fore or afterwards. Mouth movements had no effect on hand motor cortex excitability. Thus, the changes in the excitability in the hand area of both motor cortices were language related. This study provides neurophysiological evidence that the nondominant hemisphere is involved in the process of recovery from post-stroke aphasia. The activity of the nondominant hemisphere may be integrated into the cerebral network subserving language processing following ischemic stroke of the language-dominant hemisphere.

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Analysis of fine motor control deficits following head trauma. S. Buhmann, J. Hermsdörfer, C. Marquardt, Neuropsycholgie Krankenhaus München Bogenhausen on behalf of the Entwicklungsgruppe Klinische Neuropsychologie/DFG-Graduiertenkolleg Neurotraumatologie und Neuropsycholgische Rehabilitation GRK 688

Introduction: After head trauma via fall or car accident most patients show deficits concerning motor coordination and sensory motor control even if gross force remains. Incidence of head trauma is thus followed by hand function deficits in about 40 % of all cases including plegia and paresis. So far correlation of primary traumatic insult and fine motor control deficits have not been described in more detail. This is why we analysed and quantified sensory motor performance as well as the severity of functional deficits using the following methods.

Methods: Elementary finger force and movement control: For the examination of basic abilities/disorders of finger force control we measured maximum grip force and fast force changes in a precision grip (device FCA); sensory function was assessed by resistance to perturbation (device FS).

Handwriting: To analyse more complex capabilities we measured handwriting movements using a digitising tablet (device CS).

Functional force control: To analyse grip force during daily object manipulation we used an instrumented hand-held object supplied with force and acceleration sensors (device GF).

Results: We analysed two patients (both male, 24 and 22 years, right hand affected, right handed) with head trauma after car accident and two healthy sex- and age-matched control subjects.

On the elementary control level (FCA) both patients showed an age-related normal maximum finger force, but doing fast force changes both showed slowness and decoordinated force production in the affected hand. Sensory function was not affected. In handwriting (CS) both patients were slowed writing a test sentence and also showed clear deficits during isolated sub-movements which are part of normal writing.

When both patients held the instrumented object (GF) stationary and subsequently performed cyclic movements with increasing speed-levels, they produced greater grip forces than the control subjects during both tasks (up to 100 % increased) and grip force was not well coordinated with the load in the movement-task.

Conclusion: The patients yield preserved capabilities in basic tasks but seem to be increasingly impaired in more complex tasks.

The patients produced uneconomically elevated grip forces during both stationary and dynamic tasks. This might represent a more general control strategy when the output of motor commands is suboptimal.

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Rehabilitation of hand functions after brain trauma. R. Wenzelburger, S. Kienke, H. Stolze, A. Frenzel, B.-R. Zhang, J. Raethjen, G. Deuschl, Universitätsklinik Kiel (Kiel, D)

Patients suffering from traumatic brain injury (TBI) often show severe disturbances of motor control, especially of dexterity, although the underlying mechanisms remained unclear. Our aim was to quantify manual dexterity and to gain further insights in force coordination. Pegboard and picking-up tests, a reach-to grasp movement and lifting of a small, instrumented object were assessed early after coma and during rehabilitation in 21 patients.

Clinical scores revealed an early recovery of dexterity within 2 months in most of the patients and the performance in the pegboard and picking-up tests also recovered early. Patients were still handicapped in the picking-up test if deprived from vision even after discharge from the rehabilitation unit. The peak velocity of reaching-to grasp was decreased, and patients tended to segment the movement. Terminal movement time was increased in the initial examination only. Early phases of the grip-lift cycle were prolonged (related to grasp preparation), but a later phase was not affected (related to object lifting). The prolongation of grasp preparation recovered early. Initially grip force was increased excessively and recovery was incomplete during 8 months of follow-up.

The disturbance of terminal parts of the reaching-to grasp and of early phases of the grasping-to lift movement suggests a reduced effectiveness of central sensorimotor in TBI, that might underlie impairments of dexterity of the hand. Although the speed-related parameters recovered, recovery of dexterity was incomplete. This might follow persistent abnormalities in the scaling of grip force. A stable grasp was obtained at the expense of increased grip force, even after more than half a year after head trauma. This work is supported by the Deutsche Forschungsgemeinsschaft, Verbund Neurotrauma Kiel – Restitution von Hirnschäden. BMBF (01KO9811/7).

Poster Sessions

Poster Session 1

Cerebrovascular disorders

P246

Cervical spinal cord infarction due to spontaneous vertebral artery dissection. D. Felten, C. Rousseau, L. Guilloton, Y. Billaud, J. Le Berre, A. Drouet, Hôpital Desgenettes (Lyon, F)

Vertebral artery (VA) dissection is a well-known cause of stroke. Common findings are neck pain associated with ischaemic brain stem, cerebellar or occipital stroke. Rarely, spinal cord infarction may be the sole manifestation. We report a patient in whom spontaneous VA dissection presented with an ipsilateral ischaemic cervical myelopathy. This previously healthy 34-year-old man was admitted with sudden onset numbness and weakness of the left side. He reported two weeks before a left sided neck pain. There was no history of neck trauma nor chiropractic manipulation but he daily practiced weightlifting. Neurological examination disclosed a mild weakness of the left arm and leg. Deep tendon reflexes were normal and plantar responses were flexor. Cranial nerve functions were normal. He had dysesthesia and abnormal touch sense on the left side, sparing the face. Magnetic Resonance Imaging (MRI) showed an ischaemic lesion in the spinal cord at the level C1. MRI and Magnetic Resonance Angiography (MRA) were consistent with a left vertebral artery dissection from the level C6 to C2. He was treated with anticoagulants. Two months later motor deficit had involved but left side numbness persisted. This left vertebral artery dissection can be considered as spontaneous. There are no evidence of risk factors such as hypertension or fibromuscular dysplasia and no traumatic event. However, practice of weightlifting may be a trivial but precipitating event. Spinal manifestations as presenting symptoms of VA dissection are rarely reported. Among 111 patients seen at the Mayo Clinic for VA dissection Crum et al. identified two patients with a cervical epidural haematoma and a cervical radiculopathy respectively. In a review of the literature they only found seven patients with spinal ischemia. An eighth additional case was reported by Weidauer in 1999. Spinal cord infarctions are often located in the anterior spinal artery territory. Central area of the spinal cord is the highest vulnerability site to ischemia. Unilateral like bilateral cervical infarctions may be associated with ipsilateral as well as bilateral VA dissection. Nevertheless, such ischaemic lesions are rarely observed because of frequent variations in arterial supply and a complex pial collateral network. MRI is today a reliable non-invasive method for diagnosis. In case of acute spinal symptoms in young adults spinal ischemia and vertebral artery dissection must be systematically researched.

P247

High plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in patients with acute ischemic stroke. A. Echaniz-Laguna, M-C. Fleury, C. Tranchant, J-M. Warter, Clinique Neurologique (Strasbourg, F)

Background and purpose: Arial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP) play a role in the pathophysiology of several cardiovascular diseases. However, the role of BNP has never been studied in ischemic stroke (IS) and only limited data exists on the role of ANP in IS. We planned a prospective clinical study to test whether plasma levels of ANP and BNP increase in early IS and whether ANP and BNP plasma levels correlate with initial neurological status, prognosis or stroke aetiology.

Methods: We measured ANP and BNP plasma levels with a radio-immunologic assay method in 10 consecutive patients with acute IS (mean

disease duration: 19 hours [3–45h]) and in 10 sex- and age-matched control subjects. Clinical stroke severity was assessed on admission and three weeks after stroke with the National Institutes of Health Stroke Scale (NIHSS). The subtype of IS was determined according to the Trial of ORG 10 172 in Acute Stroke Treatment (TOAST) classification.

Results: ANP and BNP levels in patients were increased in comparison with controls (ANP, patients:41.4 ± 12.4; ANP, controls:16.7 ± 6.8, pg.ml–1, p = 0.04 and BNP, patients:218.3 ± 120.4; BNP, controls:35.4 ± 22.2, pg.ml–1, p = 0.03). A correlation was found between the ANP and BNP levels and initial NIHSS score (ANP, r = 0.65 and p = 0.04; BNP, r = 0.76 and p = 0.01). There was no correlation between ANP and BNP levels and NIHSS score three weeks after IS. Interestingly, BNP levels were higher in IS of cardioembolic origin in comparison with IS of other origin (BNP, cardioembolic stroke:463.6 [16.3–1087] and BNP, non-cardioembolic stroke:22 [3.7–49.7], pg.ml–1).

Conclusions: This preliminary results suggest: 1) an increase in ANP and BNP plasma levels in patients with acute IS, 2) a correlation between ANP and BNP plasma levels and initial clinical stroke severity, 3) higher BNP plasma levels in IS of cardioembolic origin in comparison with non-cardioembolic IS, indicating that increased BNP plasma levels may constitute a marker of cardioembolism in IS.

P248

Stroke during sleep. S. Santos, L. Pascual, C. Iñiguez, E. Mostacero, C. Tejero, J. Lopez del Val, University Clinical Hospital (Zaragoza, E)

Background: Stroke symptoms may be appeared when patient is sleep or awake. Our objective is characterized these strokes that occurred during sleep.

Methods: We prospectively review all ischemic stroke patients (transient ischemic attacks were not included) admitted consecutively to the Department of Neurology of our hospital during a year. We analyzed age, sex, neurological deficit, mortality, vascular risk factors, length of hospital stay, post-stroke complications and pathogenic mechanism. In 84 patients (23,7 %) stroke occurred when they were asleep while 270 patients (76,3 %) had stroke symptoms when they were awake. The Student's Test and U-Mann-Whitney test were used for the comparison of continuous data and the chi-test was used for non-contiguous data. A multivariate analysis was also used. Statistical significance was inferred for P less than 0.05.

Results: A total of 354 cases of brain infarction were considered (192 men; 73,45 years; DS: 10,17). Significant variables associated with stroke during sleep were pathogenic mechanism (lacunar infarct; p = 0.000), mortality (p = 0.026) and neurological deficit (p = 0.004). A multivariate analysis estimated that patients with lacunar infarct were less likely to have symptoms when they were awake (p = 0.000; OR: 0.33).

Conclusion: These data show that patients with a stroke occurred during sleep had milder symptoms and a lower risk of mortality. The mechanism of stroke (lacunar infarct) was confirmed as independent predictor.

P249

Cerebrovascular disorders in elderly hypertensive patients. T. Bobrova, V. Shmyrev, Kremlin Medical Center (Moscow, RUS)

Background and Purpose: The clinical significance of leukoaraiosis found on magnetic resonance images in elderly patients is questionable. We evaluated cerebral blood flow and cerebrovascular reactivity of elderly hypertensive patients and control subjects to study influence of hypertension on cerebral hemodynamics, status white matter and clinical disorders in elderly patients.

Methods: Magnetic resonance imaging (MRI) of the brain was performed in 40 elderly patients with a long duration (> 5 years) of hypertension and 30 age- and gender-matched healthy controls. We measured the flow velocities and the Gosling pulsatility index (PI) of middle cerebral artery in rest and after rebreathing tests (apnea and hyperventilation) using transcranial doppler (TCD). Flow values were correlated with the scores for leukoaraiosis and clinical neurological disorders.

Results: Patients with hypertension had leukoaraiosis and asymptomatic lacunes significantly more often (100 % and 40 % versus 75 % and 5 %) than those without hypertension. The mean blood flow velocity and PI in the middle cerebral arteries of hypertensive patient (56,3 ± 4,2 cm/sec, 0.93 ± 0,13) was not significantly different from that of controls (60,8 ± 5,4 cm/sec, 0,87 ± 0,15). Hypertensive patients had significantly lower the breath-holding index (BHI) than normotensive. Clinical disorders and flow values in hypertensive patients were not significantly correlated with the severity of leukoaraiosis.

Conclusions: This study suggest that hypertension is risk factor of leukoaraiosis in old age in spite of no difference in cerebral blood flow in hypertensive and normotensive elderly patients. Leukoaraiosis in elderly patients does not worsen the neurological functions.

P250

The relationship of insulin-receptor gene polymorphism to ischemic stroke. Yd. Zhang, Nanjing Brain Hospital (Nanjing City, CHN)

Objective: To investigate the role of mutation of insulin-receptor (INSR) gene on the development of ischemic stroke.

Methods: The base-variations at exon 17 and 20 of INSR gene, by means of PCR-SSCP, were determined in the 68 cases of atherothrombotic cerebral infarction (ACI), 81 cases of lacunar infarction (LI) and 62 healthy controls (HC). Other biochemical markers including plasma glucose (Glu), total-triglyceride (TG), cholesterol (CHO), low-density lipoprotein (LDL), high-density lipoprotein (HDL), apolipoproteinB (apoB) and apolipoprotein A-I (apoA-I) were also measured.

Results: There were two alleles of T and C at exon 17 of INSR gene. The prevalence of mutative T allele in ACI patients was more common than that in the controls. The blood pressure and the parameters of lipid metabolism in the patients with mutant were higher than those in the controls with wild-type gene. The correlative analysis showed that, however, the polymorphism of INSR gene was not related statistically to the blood pressure. No base-variation at exon 20 was found in the study population.

Conclusions: The mutation at exon 17 of INSR gene, by promoting the development of atherosclerosis, maybe participate in the occurrence of ischemic stroke. The logistical regressive study indicated that the risk factors for ACI were ranked as CHO, Glu, TG and LDL in order, and the protective factors as ApoA-I and HDL.

P251

CT angiography versus digital subtraction angiography in a patient with transient ischemic attacks caused by Takayasu arteritis – a noninvasive diagnostic approach. J. B. Sommer, B. Tomandl, J. Heckmann, B. Neundörfer, University of Erlangen-Nürnberg (Erlangen, D)

A 34-year-old female outpatient presented with a 4-week history of vertigo and amaurosis fugax of her right eye. Physical examination revealed arterial bruits in both subclavian regions, and reduced pulses of both radial and brachial arteries and right carotid artery. There was no significant blood pressure difference between arms. Erythrocyte sedimentation rate was 23 mm/hour. White blood cell count was 15000/mm3. Funduscopy showed no retinal or optic disk changes. Extracranial duplex ultrasonography revealed signs of middle to high grade stenoses of the brachiocephalic trunk and left subclavian artery. There was no arteriosclerosis. "Systolic deceleration" was found in both vertebral arteries, and right common, internal and external carotid artery. Finally, CT angiography (CT-A) of the aortic arch revealed a 70 % stenosis of the brachiocephalic trunk and two consecutive 40 % stenoses of the left subclavian artery. Additionally, digital subtraction angiography (DSA) was performed but yielded no further information. Brain MRI showed no structural lesions. The diagnosis Takayasu arteritis was made according to the 1990 classification criteria of the American College of Rheumatology. A treatment with high dose prednisolone 500 mg/day was started and then tapered by an oral dosage. The patient is still on medication, and except for a short episode of right arm weakness there were no neurological deficits up to now. Retrospectively, the DSA would not have been necessary in our patient.

Diagnosis of Takayasu arteritis is based on clinical features and radiological findings. Conventional angiography has been considered the best imaging method but may produce serious complications like ischemic stroke or local bleedings. As in our patient, CT-A as a noninvasive diagnostic procedure has been shown to detect reliably luminal and mural changes of the aortic arch and its major branches. Furthermore, CT-A allows repeated noninvasive assessment of medical or surgical treatment efficacy. Thus, CT-A may replace DSA in the diagnosis and follow-up of Takayasu arteritis.

P252

Smoking increases risk of asymptomatic carotid stenosis in patients with peripheral vascular disease. S. Toncev, G. Toncev, B. Milicic, Clinical Hospital Center Kragujevac (Kragujevac, YU)

Background: Smoking is well-established risk factor for coronary disease but there are some controversies for cerebrovascular disease.

Objective: The aim of this study is to investigate relationship between smoking and asymptomatic carotid artery stenosis in patients with pe-

ripheral vascular disease and define its relation to the degree of carotid stenosis, as well to patients' sex and age.

Methods: Duplex ultrasound screening of the carotid arteries were performed in 168 patients with peripheral vascular disease (104 male, mean age 66.2 ± 8.62 and 64 female, mean age 68.41 ± 5.11). Degree of carotid artery stenosis was determined and four groups were formed: stenosis < 49 %, stenosis from 50–69 %, stenosis from 70–99 % and total occlusion.

Results: Internal carotid stenosis of > 50 % was found in 39.29 % of patients with peripheral vascular disease. Among these there was 370 % stenosis in 17.86 % of patients. There was no patient with occluded carotid vessel. Smokers were significantly younger than non-smokers (p = 0.003). Male smokers had a higher prevalence of carotid stenosis but there was no difference in degree of stenosis in male and female group (p = 0.023).

Conclusion: These results suggest that smoking increases the risk of asymptomatic carotid stenosis and consequently the risk of cerebral ischemic event in patients with peripheral vascular disease.

P253

Neurological aspect and susceptibility to stroke in children with sickle cell disease. W. Fadel, H. Mourad, M. Rowisha, Tanta University Hospital (Tanta, EGY)

This study was done on 20 children with sickle cell disease (SCD), diagnosed both clinically, haematologically and confirmed by hemoglobin electrophoresis. There were divided into two groups, group I with sickle cell disease in steady state and group II with sickle cell disease in thrombotic crisis. Ten healthy children with matched age and sex were taken as a control group for laboratory investigation. Clinical, brain C. T. and or MRI and electroencephalographic (EEG) studies were done for all patients. HLA typing, class II (HLA-DR), was also done. Haemostatic system was also investigated in the form of thrombin-antithrombin III complex measurement (TAT) and fibrin degradation products (FDPs). Results showed that ischemic brain infarction was evident in-group II that was documented by C. T. and or MRI and most of these children showed EEG activity. The stroke children showed association with HLA-DR at locus *0301 and *0302 which were found in children at high risk for stroke. Protective association were found at HLA-DR *1501 and *1502 locus in children without stroke. Abnormalities of the coagulation system showed decrease in the TAT complex where as abnormalities of the fibrinolytic system showed decrease in the FDPs in both groups but were more significant in group II.So, neurological assessment, HLA typing and haemostatic system may play an important role in identifying children with SCD at a high risk for stroke.

P254

Cervical artery dissection – presentation of five cases and discussion of clinical findings and therapeutic options. C. Bocksrucker, R. Resch, N. Albrecht, W. Grabmair, Krankenhaus der Barmherzigen Schwestern Linz (Linz, A)

Dissection of the cervical arteries is an important cause of ischemic stroke in young patients. The appearence can be spontaneous, minor precipitating events or chiropractic manipulation can go ahead. The clinical symptoms range from pain to severe brainstem infarctions.

Oral anticoagulation is the widely used therapy, also operative treatment can be necessary.

Results: From 5/01 until 12/01 3 cases of carotid artery dissection and 2 cases of vertebral artery dissection were admitted to our Department of Neurology, Hospital Barmherzige Schwestern Linz, Austria.

In 2 cases the dissection was spontaneous, in 1 case a severe trauma, in 1 case a minor trauma, and in another case a chiropractic manipulation caused the dissection.

The clinical occurence differed. The first patient (17 years) was asymptomatic, the second patient (25 years) suffered from severe brainstem infarction, the third (44 years) acquired a cerebellar and pontine infarction, the fourth patient (38 years) acquired a hemispheric stroke and the fifth patient (34 years) showed recurrent ischemic events and an Horner syndrome.

4 patients were treated with oral anticoagulation, 1 patient needed acute operative intervention on the internal carotid artery.

Conclusion: These 5 case reports show that young patients with symptoms of cerebral ischemia, especially in connection with possibly mild trauma, might suffer of dissection of the cervical arteries. In these cases it has proofed that a good cooperation of neurologists and surgeons is important to avoid severe complications.

P255

Initial experience with the flow reversal technique for prevention of embolic complications during carotid angioplasty. H. Sievert, K. Rabe, W. Pfeil, C. Rubel, H. Lißmann-Jensen, K.-F. Beykirch, R. Theis, Cardiovascular Center Bethanien, Bethanien Hospital (Frankfurt, D)

Background: Reversal of blood flow in the internal carotid artery during angioplasty and stenting has been suggested to prevent embolization of arteriosclerotic debris.

Patients: Carotid angioplasty and stenting under flow reversal was attempted in 34 patients (age 68 ± 9). 16 patients had a previous ipsilateral TIA and or stroke. Diameter stenosis ranged from 60 to 99 % (79 ± 10), the length of the lesion ranged from 1 to 24,6 mm. At least 4 lesions contained fresh thrombus. Two patients had a contralateral stenosis of > 50 % and one patient had a contralateral occlusion.

Methods: Reversal of blood flow in the internal carotid artery was achieved by occlusion of both the common and the external carotid artery during the procedure using the Arterial device. During the procedure the blood flowing back into the guiding catheter was re-transfused into the femoral vein via a filter. Conventional wires and balloons where used. A Wall-Stent was implanted in 24 patients. 7 patients received a Precise-Stent, 2 patients a Smart-Stent and 1 patient a Tetra-Stent.

Results: The device could easily be introduced into the common carotid artery. Balloon occlusion of the common carotid artery as well as the external carotid artery was achieved in all patients. The occlusion time ranged between 4 and 37 min (15 ± 8) and was tolerated reasonable in all patients except one, in whom the balloon had to be deflated repeatedly during the procedure. Two patients experienced transient neurological symptoms during balloon occlusion without need for interruption of the procedure. In all patients angiographic success was achieved without immediate complications. In one patient a TIA occurred several hours later. Macroscopic debris was found in the filter in 32/34 patients.

Conclusions: Flow reversal in the carotid artery for protection of embolism during carotid angioplasty is feasible in the majority of patients. Atherosclerotic debris is kept back efficiently. If the balloon occlusion is not tolerated, the procedure can be completed by deflating the balloon intermittently. As in any other embolic protection device, late ischemic events can not be avoided.

P256

Anterior cerebral artery infarction secondary to a fat embolism syndrome. A. Mariscal, R. Diez, J. C. Martinez-Castrillo, Hospital Ramón y Cajal (Madrid, E)

Background: Fat embolism syndrome (FES) is present in 1–5 % of all fractures. The diagnosis is clinical. The main criteria are neurological symptoms and a petechial rash. Less frequent is a FES with prominent neurological manifestations without respiratory symptoms. Minor criteria are tachycardia, pyrexia, retinal changes, jaundice, and renal changes. Neurological features range from drowsiness and confusion to coma, due to diffuse patchy lesions throughout the brain, most commonly in the white matter and subcortical grey matter.

Objective: To describe a patient wit a FES who suffered an infraction of a large cerebral artery.

Patient. A 30 year-old man suffered a motorcycle accident that resulted in fractures of the femur, fibula and tibia. He had no neurological symptoms at that time, Glasgow scale was 15. Thirty hours later, the patient had a progressive worsening of his level of consciousness. There was a petechial rash over the thorax and neck, fever and tachycardia. Laboratory studies disclosed anaemia, thrombocytopenia, hypocalcaemia, and a high erythrocyte sedimentation rate. A CT scan showed a hypodense lesion of the right frontal lobe. An angiography showed an occlusion of the right anterior cerebral artery (ACA). There was no respiratory symptoms nor hypoxemia. Tracheal intubation, mechanical ventilation, and support measures were performed. On day 10th a new CT scan and an MRI confirmed the infarction of the right ACA. A chest and a transesophageal echocardiogram was normal. On day 20th an angiography showed a recanalization of the ACA. Support therapy was suspended on day sixth. At discharge the patient was almost normal except from a mild bradypsychia.

Conclusion: This patient fulfilled the criteria of FES. The singularity of this case is the association of FES to an infarction of a large artery such the ACA. This association has not been previously described. The infarction was unexplained by other causes, and FES may be the explanation.

P257
Cerebral hemodynamics and white matter metabolism in patients with a symptomatic internal carotid artery occlusion. D. R. Rutgers, M. J. P. van Osch, L. J. Kappelle, W. P.Th. M. Mali, J. van der Grond, University Medical Center Utrecht (Utrecht, NL)

In patients with a symptomatic internal carotid artery (ICA) occlusion, the presence of metabolic damage in cerebral white matter as measured with proton magnetic resonance (MR) spectroscopy comprises a high risk of future stroke (Klijn et al. Stroke 2000;31:3001). In the present study we investigated whether such metabolic damage is related to cerebral hemodynamic status.

Twenty patients (age 60 ± 9 years, mean ± SD; 17 m, 3 f) with an angiographically (n = 18) or ultrasonographically proven symptomatic ICA occlusion were investigated on average 4 months (± 2) after symptoms occurred (diagnoses: retinal ischemia n = 4, transient ischemic attack n = 6, minor stroke n = 10). Reference values were obtained in age matched controls. The Human Research Committee of our hospital approved the study protocol. Informed consent was obtained.

In normal appearing white matter in the centrum semi-ovale, choline, creatine and N-acetyl aspartate (NAA) concentration were measured with MR spectroscopic imaging (SI) using the cerebral water signal as an internal reference (Christiansen et al. MRI 1993;11:107). In selected SI voxels, cerebral blood flow (CBF) and volume (CBV) were determined with quantitative bolus-tracking perfusion MR imaging. Cerebral CO2 reactivity, expressed as the relative change in blood flow velocity in the middle cerebral artery after carbogene inhalation, was determined with transcranial Doppler sonography.

In the hemisphere on the side of the symptomatic ICA, NAA concentration (9.1 ± 1.7 mM) was significantly lower than in the contralateral hemisphere (10.5 ± 1.7 mM, $p < 0.05$) and controls (10.5 ± 0.9 mM, $p < 0.01$; n = 24), CBV significantly higher (4.5 ± 1.4 ml/100 ml) than in controls (3.5 ± 1.2 ml/100 ml, $p < 0.05$; n = 9) but not compared with the contralateral hemisphere (4.1 ± 1.3 ml/100 ml), and CO2 reactivity (14 ± 19 %) was significantly lower than in the contralateral hemisphere (48 ± 21 %, $p < 0.001$) and controls (51 ± 14 %, $p < 0.001$; n = 30). No significant differences were found in choline and creatine concentration nor in CBF. In a linear regression analysis, NAA concentration was significantly related to the presence of an ipsilateral symptomatic ICA occlusion ($p < 0.05$) and not to CBF, CBV or CO2 reactivity.

A reduced NAA concentration, regarded as an indicator of neuronal damage, can be demonstrated in patients with a symptomatic ICA occlusion but is not related to cerebral hemodynamic status in a subacute/chronic stage.

P258
Smokers show no preventive benefit from healthy food intake and sports in early atherosclerosis. Results from a health study in Pomerania. U. Schminke, J. Luedemann, K. Berger, M. Piek, S. N. Willich, U. John, C. Kessler, Ernst Moritz Arndt University, Westfaelische Wilhelms-University, Humboldt University (Greifswald, Munster, Berlin, D)

Background and Purpose: Physical activity, dietary and lifestyle pattern reduce the risk of premature death and cardiovascular disease. Their relationship to stroke and atherosclerosis of the carotid arteries, however, is not clear. The objective of this study was to investigate the association between those behavioral vascular risk factors and asymptomatic atherosclerosis of the carotid arteries in a population of former "East-Germany", which may reflect specifically regional health problems after the reunification between former East and West-Germany.

Methods: The Study of Health in Pomerania (SHIP) is a cross-sectional survey in the northeast of Germany including adults with an age range of 20–79 years randomly selected from population registers. In a sample of 1632 participants 45 to 70 years of age, high resolution B-Mode ultrasound was used to assess the intima-media thickness (IMT) by averaging the measurements of the right and the left common carotid artery. Plaques and stenoses occurrence were also recorded to define a status of severe asymptomatic carotid atherosclerosis (ACA). Physical activity, dietary patterns, cardiovascular and sociodemographic risk factors were assessed in face to face interviews using standardized scales. Physically active participants with optimal dietary patterns were classified in the optimal lifestyle group, those inactive with unfavorable diet in the unfavorable group.

Results: After adjustment for gender and age, significant differences in IMT in never-smokers with moderate compared to those with unfavorable lifestyle patterns were observed (0.7332 vs. 0.7653 mm; $p < 0.0101$). No difference was seen in smokers (0.7599 vs. 0.7670 mm; $p < 0.5861$). After controlling for age, gender, hypertension, diabetes and smoking status, regression analysis revealed an increased risk of severe asymptomatic carotid atherosclerosis in subjects with an unfavorable lifestyle pattern compared to those with an optimal pattern (Odds Ratio 2.64, 95 %CI [1.12, 6.24]), following a significant linear trend.

Conclusions: Physical activity and optimal diet are associated with a reduced risk of early atherosclerosis in never-smokers, while no benefit of an otherwise optimal life style is observed in smokers.

Child Neurology

P259
The neurologic examination of the infant with cerebral palsy and the prognosis for the neurologic abnormality. L. Zikou (Pireas, Athens, GR)

Introduction: Goniometry is the most valuable examination in the neurologic examination of the newborn and infant. The use of the reflex hammer is less reliable than evaluation of tone and posture.

AIM: The assessment of the neurologic examination of the infants, the comparison between subsequent neurologic examinations and the prognosis for the progression.

Methods: 25 infants with cerebral palsy(CP) aged between 3 to 10 months were examined. The follow-up period was 18 months. The Infant Neurologic International Battery (Infanib) Scale was used for the neurologic assessment. The evaluation of neonates up to age 4 months was estimated also with the Neo Neuro & up scoring sheet. All the infants were included in physical therapy program.

Results: The degree of normality and abnormality was estimated, based on the score for three corrected gestational age divisions: less than 4 months, 4 to 8 months and 8 months or more. The mild hypotonias were included in transient neuromotor abnormalities. Infants with transient and abnormal neurologic examination were identified. The first neurologic examination in 10 infants was considered transient and 15 infants had abnormal neurologic examination. Children who had abnormal first neurologic examination remained abnormal on the subsequent follow-up examinations. Serial examinations of the infants with transient first neurologic examination revealed transient or normal neurologic examination. Children with transient neuromotor abnormalities improved and 'outgrowed' Cerebral Palsy.

Conclusion. The Infanib provides a quantified and reliable instrument for the identification of neurological prognosis in Cerebral Palsy.

P260
Pediatric pseudotumor cerebri-diagnostic and therapeutic difficulties. P. Krsek, B. Petrak, T. Belsan, P. Pochop, M. Tichi, V. Komarek, Charles University, 2nd Medical School (Prague, CZ)

Objective. Idiopathic intracranial hypertension (pseudotumor cerebri, PC) in children population often represents a diagnostic problem because its clinical presentations differ from adult patients. Owing to a wide spectrum of clinical features and prognoses, it is difficult to standardise therapeutic approaches. We present a study on a group of paediatric patients with PC.

Methods. Seventeen children aged 4–17 years who met the diagnostic criteria of PC have been thoroughly examined and observed. Clinical data including results of different diagnostic tests as well as therapeutic strategies and their outcomes have been analysed.

Results. The typical habitus (obese woman) found in adult population was not encountered among prepubertal children. Symptomatology differed in some features from adults (e. g. absence of tinnitus or frequent upper meningeal signs). Increased opening pressure in lumbar puncture was not confirmed in four out of 17 children probably because of fluctuations in intracerebral pressure. An essential role in setting the diagnosis was played by MRI as the exclusion of cerebral venous thrombosis (finally diagnosed in two children with clinical features of PC) and the proof of indirect signs of elevated intracranial pressure were of key importance. Acetazolamide and methylprednisolone therapy (with or without repeated lumbar punctures) helped in 14 out of 17 patients. In the remaining three children with refractory PC, optic nerve sheath decompression and lumboperitoneal shunt represented the treatment strategies of choice. In spite of vigorous therapy, two patients experienced an irreversible impairment of vision.

Conclusions. Based on our experience and reviewing the literature, we suggest diagnostic and treatment guidelines including special MRI studies in patients with suspected PC. Emphasis is put on thorough assessment of visual functions using perimeter, visual evoked potentials, ultrasonography of the optic nerves, and photodocumentation of the papilloedema. Criteria for the timing of the surgical interventions in patients with PC are discussed.

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P261
Long-term efficacy and tolerability of three new antiepileptic drugs in childhood epilepsy. M. Mazurkiewicz-Beldziñska, A. Matheisel, B. Mañkowska, Medical University of Gdansk Poland (Gdansk, PL)

The long-term efficacy and tolerability of the medication are very important especially in epilepsy which is a chronic disorder. Since 75 % of first epileptic seizures occur before 18 years of age it is important to have an idea which drug might have the greatest overall chance for success in children population.

A retrospective charts review was conducted to include epilepsy patients from our departments who were on Lamotrigine (LTG)(157 patients), Vigabatrin (VGB)(79 patients) and Topiramate (TPM)(101 patients) add-on therapy.

We calculated retention rates for each antiepileptic medication using Kaplan-Meyer analysis, the correlation between good therapeutic effect and type of epilepsy, the age of onset, aetiology and concomitant antiepileptic treatment was performed.

Mean time of observation was 21 months. We noticed that after one year of treatment 69 % of patients stayed on TPM, 68 % on LTG and 48 % on VGB therapy. After two years the retention rates were 57 %, 61 % and 30 % respectively. The seizure free rates after first year of treatment were 39 % for TPM, 28 % for LTG and 22 % for VGB.

There was strong correlation between good LTG effect and absence of CBZ in concomitant therapy as well as presence of generalized seizures. For VGB between the presence of psychomotor retardation and better seizure outcome. For TPM we noticed better outcome in patients with symptomatic or cryptogenic epilepsies.

Our results show that new antiepileptic drugs can serve as a good treatment strategies for many childhood epilepsies. They can provide seizure freedom or significant seizure reduction. They might be considered (in many cases) as a first-line antiepileptic medications.

P262
A late presentation of dystonia in 18p- syndrome. G. Gorman, O. Hardiman, Beaumont Hospital (Ireland, IRL)

18p- Syndrome, first described in 1963, by de Grouchy, is a frequently occurring autosomal deletion syndrome. The male to female ratio is 0.67.The degree of severity is diverse, hence, the pattern of dysmorphism may not be striking at birth. It has been associated with speech delay, ptosis, hypotonia, cardiac anomalies, mental retardation as well as autoimmune diseases. Consequently, many cases of 18p- syndrome remain undiagnosed until late childhood.

We report the case of a 42 year old previously undiagnosed woman presenting with a one year history of deterioration in mobility and progressive ataxia, on a background history of mild mental handicap, speech delay, mild pulmonary stenosis and hypothyroidism with atypical white matter changes on MRI. Karyotyping revealed an unbalanced whole arm translocation resulting in monosomy for the short arm of chromosome 21:45XXder(18;21)(q10;q10).

The primary clinical feature on examination of our patient was that of dystonia, rather than ataxia. In the previously reported cases of 18p- presenting with dystonia, the average age of onset has been 12–17 years. Diagnosis of 18p- has not been previously reported over 30 years of age.

The findings in our patient suggest that in cases of dystonia with associated dysmorphic features and mental handicap, karyotyping is indicated, irrespective of age. Furthermore, the association between 18p-and dystonia merits further attention.

P263
The use of glatiramer acetate in childhood and juvenile onset multiple sclerosis. B. Kornek, G. Bernert, C. Balassy, D. Prayer, J. Geldner, M. Feucht, University of Vienna (Vienna, A)

Introduction: Multiple sclerosis is a chronic inflammatory disease of the central nervous system of putative autoimmune origin. The disorder usually starts in early adulthood, however, onset before the age of 16 and even in childhood has been reported. Currently there are several immune modulatory drugs available aimed to reduce relapse rate, clinical progression as well as MR-activity. However, the use of these compounds in childhood and juvenile onset multiple sclerosis has not been studied in detail yet. Patients and methods: Three patients with childhood-onset (< 12 years of age) and four patients with juvenile onset (< 16 years of age) relapsing-remitting multiple sclerosis (median age of onset: 14,2 years; range 9,6–15,7) were treated with daily subcutaneous injection of 20 mg glatiramer acetate (GA, Copaxone) for a period of 2,3 years (range 1,8–2,6 years, respectively). Male/female ratio was 2/5. All patients included fulfilled the criteria of clinically definite multiple sclerosis according to Poser. The annual relapse rate, the EDSS before onset of therapy and on follow-up were documented. In addition, serial MRI was performed before onset of therapy and on follow-up.

Study design: observational survey

Results: In our cohort of juvenile patients treatment was initiated after a median disease duration of 2,4 years (range 0,4–7,9) and an annual relapse rate of 1,67 (range 0,5–4,8). Median EDSS before onset of therapy was 2 (range 1–3,5). > In all patients glatiramer acetate was well tolerated. After onset of therapy, three out of seven patients remained relapse free (43 %) and the median relapse rate was reduced (0,67; range 0–2). Clinical disability as assessed by the EDSS remained stable in four patients (57 %), but clearly increased in three patients. Major side effects of GA, known as immediate postinjection reaction were observed in one patient.

Conclusion: Treatment with GA in our cohort of childhood and juvenile onset multiple sclerosis was well tolerated and showed a certain benefit. Therefore, our findings are in concordance with studies on the use of glatiramer acetate in adult-onset multiple sclerosis. However, due to the small number of patients conclusions regarding the efficacy of this drug in childhood and juvenile onset multiple sclerosis have to be interpreted with caution.

Clinical Neurophysiology

P264
Sympathetic skin response in dialysis and renal transplanted patients. H. Ayromlou, H. Argani, M. Raisi, Tabriz University of Medical Sciences (Tabriz, IR)

Introduction: Neurological disorders, especially autonomic neuropathy, are among the most bothersome complications in renal failure. Scarce studies with conflicting results about skin sympathetic involvement in dialysis and renal transplanted patients exist.

Materials and Methods: We evaluated sympathetic skin response (SSR) of lower and upper limbs in three groups: 17 chronic haemodialysis (HD) patients, 18 patients with good function renal transplantation (RT) and 20 healthy controls (CT). Time of latency and amplitude voltage of SSR of median and tibialis nerves were registered by TOENNIES Neuroscreen® Plus machine, after biphasic electrical surface stimulation. Also, correlation between SSR with haemoglobin (Hb),calcium (Ca), phosphorus (Po4), cholesterol (Chol), triglyceride (Tg) and protein catabolic rate (PCR) was studied. Mann – Whitney U test and Pearson coefficient were used for analysis. Statistical significance was assigned at $p < 0.05$. The mean age of HD and RT groups was 46.8 ± 18 and 37.2 ± 11 years, respectively. Male to female ratio was 10/7 and 11/7 in HD and RT groups, respectively. Patients with diabetes mellitus or amyloidosis were excluded.

Results: In the HD group, the average of latency time of SSR in both limbs was 2.03 ± 0.37 seconds. It was significantly longer than 1.85 ± 0.32 and 1.64 ± 0.22 seconds in RT ($p = 0.008$) and CT ($p = 0.007$), respectively. Differences of voltage amplitude of SSR between the three groups were even more significant; it was 1160.6 ± 375.8 in HD, 1940 ± 1102 in RT and 2487 ± 1253.1 microvolt in CT groups ($p < 0.001$). It was a positive linear correlation between Hb concentration with better SSR. Although age and months of dialysis, as independent risk factors, had clear negative impacts on SSR, the other variables including of PCR, Ca, Po4, Chol and Tg had not this effect.

Conclusion: We conclude that in HD sympathetic nerve of skin, as the other organs, is involved. The sluggish and weak response would be improved after RT.

P265
Heavy acute alcohol intoxication aggravates the neurophysiological changes in mild traumatic brain injury. E. Lapina, U. Luchanok, L. Luchanok, Polotsk Regional Hospital, Vitebsk State Medical University (Polotsk, Vitebsk, BLR)

Background. In 15–60 % patients with mild traumatic brain injury (MBI) an accident takes place on the background of acute alcohol intoxication (AAI). AAI in MBI patients complicates the interpretation of main symptoms and the distinction between the traumatic and toxic effects. However

the character of concomitant AAI influence on mechanisms of MBI and recovery after the trauma remains obscure and requires further study. Dose-depend effect of AAI on central nervous system (CNS) functioning was shown in experiments.

Objective. To analyse the influence of heavy AAI on the mechanisms of CNS functioning' impairments in case of MBI by assessment of Contingent Negative Variation (CNV).

Method. This study embraces 46 males with MBI aged from 16 till 39. In 15 patients an accident took place on the background of heavy AAI (blood alcohol intoxication no less than 3.0 pro mille on the moment of the trauma). AUDIT, CAGE and RAPS were used to exclude alcohol abusers from the study. The quantitative analysis (duration/intensity) of main symptoms was carried out. The CNV was studied in the first 2–4 days and in the 2–3d week after the trauma. We used a simple sensory-motor reaction time task and Go/NoGo S2 choice paradigm with 1.5s S1-S2 interval. The amplitudes of five CNV components (each 200 ms) were analyzed.

Results. We revealed a more significant decrease ($p < 0.001$) of the CNV amplitude in MBI patients with AAI in the first 2–4 days after the trauma in both series (especially in frontal areas and in Go/NoGo task) then in MBI patients without AAI. Also we observed a delayed normalisation of the CNV parameters in the 2nd week in MBI patients with AAI.

Average headache duration in MBI patients with heavy AAI appeared to be longer then in non-intoxicated patients (respectively 7.9 ± 2.4 and 6.6 ± 2.8 days, $p < 0.05$) as well as the severe headache duration (respectively 3.4 ± 1.4 and 2.8 ± 2.6 days).

In MBI patients with heavy AAI the quantity and duration (7.4 ± 2.6 vs. 5.6 ± 2.8 days; $p < 0.05$) of subjective symptoms of autonomic dysfunction were significantly increased in comparison with MBI patients without AAI.

Conclusions. Heavy AAI aggravates a CNS functioning' impairments in case of MBI, increases the duration/intensity main clinical features and may lead to the remote recovery after the trauma. While managing the patients with MBI physician must take into account the presence and the degree of concomitant AAI.

P266

Evaluation of autonomic nervous system (sympathetic skin response) in patients with stroke. B. Labuz-Roszak, K. Pierzchala, Silesian School of Medicine (Zabrze, PL)

Background: Dysfunction of the autonomic nervous system (ANS) is often in patients with stroke. Impairment of autonomic centres manifests as dysregulation of respiration and circulation or can cause milder complications (sudomotor, urinary, bladder, bowel, cardiovascular etc).

The aim of our study was to evaluate ANS in patients with brain infarction using neurophysiological method – sympathetic skin response (SSR).

Material and Methods: The examined group consisted of 20 patients with stroke confirmed by computed tomography (mean age: $66{,}61 \pm 10$ years). The control group consisted of 27 healthy volunteers.

SSR was recorded bilaterally from the palms and soles using surface electrodes. The amplitudes and latencies of SSR were measured. SSR was regarded as abnormal if at least one parameter differed more than 2 SD from the mean values in the control group.

Results: SSR was normal only in one patient. Bilaterally abnormal SSR was recorded in 18 patients (90%); with clear asymetry between sides in 11 (55%) and without asymmetry in 7 persons (35%). In one patient the abnormal values of SSR were recorded only on the hemiparetic side. The most often observed abnormality was decreased amplitude of the response.

Conclusions: Observed reduction of amplitude of SSR provide evidence for autonomic disorders in patients with stroke. We did not notice any dependence between stroke localization and abnormal values of SSR. SSR is a useful method in testing ANS in patients with stroke.

P267

Diabetic central and peripheral nervous system complications, one or variant pathology. W. Fadel, M. Rabie, D. Ezzat, Tanta University Hospital (Tanta, EGY)

This study was done on ninety patients with type 2 diabetic and thirty healthy normal control and divided into 4 groups as follows Group I: patients with diabetic neuropathy Group II: diabetic patients developed ischemic stroke. Group III: uncomplicated diabetic patients. Group IV: normal healthy non diabetic patients. All patients were subjected to clinical and neurological examination, brain CT, motor and sensory conduction velocity of median and common peroneal nerves and laboratory investigations in the form of glycated hemoglobin percent HbAIc%, total radical trapping antioxidant Capacity of plasma "T. R. A. P." 'tissue plasminogen activator level in the plasma "t-pA level" and lipid profile.

The results showed that there is significant increase of neuropathy in diabetic patients with stroke. Also, diabetic neuropathy affects the sensory nerve fibers more than the motor nerve fibers and the nerves of the lower limbs more than the nerves of the upper limbs and these patients showed significant increase of HbAIc%. There is significant increase in serum cholesterol, triglycerides and LDL in all diabetic patient groups.

Furthermore, there was significant decrease in the level of T. R. A.P in group I and II. Moreover, there was significant increase in the level of"-pA" in Group II. So in conclusion neuropathy is not uncommon in diabetic stroke patient and sural nerve conduction is a sensitive test for its early detection. Diabetic neuropathy develops among patients with poor diabetic control. The antioxidant capacity decreases in diabetic patients regardless to the type of their complications whether central or peripheral. Disturbed fibrinolytic system is more encountered in the pathogenesis of diabetic macrovascular complications including cerebrovascular strokes and has minor role in the micro vascular complications including diabetic neuropathy.

P268

Application of independent component analysis to ictal electroencephalographs of a patient with occipital lobe epilepsy. H. Nam, T.-G. Yim, S. K. Han, J.-B. Oh, S. K. Lee, Seoul Municipal Boramae Hospital, Chungbuk National University, Seoul National University (Seoul, Cheongju, KOR)

Purpose: Independent component analysis (ICA) has been successfully applied to the ictal electroencephalograph (EEG) of medial temporal lobe epilepsy and the interictal EEG. We wanted to apply this method to ictal EEGs of a neocortical epilepsy for the extraction and the characterization of the earliest ictal components.

Methods: We analyzed four ictal EEGs from one patient with occipital lobe epilepsy (OLE). Digital EEG signal was recorded according to the international 10–20 system with additional T1, T2, Fz, Cz and Pz tracings. These tracings were analyzed by ICA algorithm into 20 independent components, and those with changing wave characteristics and evolution were regarded as ictal components. Their waves and the topographic maps were reviewed.

Results: In EEGs 1 and 2, ictal changes started at the right occipital area with 5–7 Hz rhythmic theta waves and in EEGs 3 and 4, with 11–15 Hz activities. After application of ICA, EEGs 1 and 2 were decomposed into 20 components, each with more or less prominent one early ictal component. The frequency of each wave was that of the original EEG. Each of the decomposed EEGs 3 and 4 also had the earliest ictal component and its shape is clearer than that of the original EEG with additional low-amplitude fast beta portion that was not noticed in the original EEG. Topographic maps of the earliest ictal components of EEGs 1, 3, and 4 indicated right occipital positive maximum which suggested the location of the sources.

Conclusions: ICA can separate ictal components in the ictal EEGs of neocortical epilepsy. We regard these components maintain a less distorted shape as the artefact components are separated out. Their distributions can give us a hint for the source localization.

P269

Abnormalities of central motor conduction time (CMCT) in amyotrophic lateral sclerosis (ALS) 7 weeks before denervation could be detected by electromyography (EMG). W. Verslegers, P. De Deyn, AZ Palfijn (Antwerp, B)

A 59-year old man developed difficulties in climbing stairs and walking. Neurological examination 7 weeks later showed increased reflexes of all limbs, paresis of both legs (4/5- Medical Research Council-MRC) without sensory problems, focal muscular atrophy or fasciculations. EMG with conduction studies of both legs was normal without denervation activity. Blood, internal, immunological and CT scan examination of the brain were normal. MRI of the spine revealed minimal spondylosis deformans. Sensory evoked potentials showed normal peripheral sensory conduction velocity (45 m/s) and normal cortical responses. Motor evoked potentials (MEP) demonstrated abnormalities of the CMCT: increased latencies of 50–56.4 msec (normal range 40–45 msec), low amplitude (less than 0.05 mV), dispersion of the central evoked compound muscle action potential, increased stimulation level of the corticospinal tracts:80–90% (normal between 50–60%). Normal responses could be measured from the peripheral nerve and lumbosacral plexus.

One week later, he developed a global paresis of his right arm (4/5). Examination of the cerebrospinal fluid (protein concentration, cell count,

electrophoresis and isoelectrofocusing, IgG-index, viral culture and polymerase chain reaction) were normal. One month later, he showed for the first time generalised fasciculations of the upper limb girdle, myopathic gait, falls, patella clonus, Hoffmann-Trömner with normal plantar reflex of both feet without sensory abnormality. Control MEP, one month after the first, showed total blocks of the CMCT for all limbs, with preserved peripheral evoked responses.

EMG, 7 weeks after the first, demonstrated now a marked denervation activity in the muscles of all limbs: insertion, spontaneous fibrillations, positive sharp waves, large fasciculation potentials and decreased motor recruitment. The diagnosis of ALS was made. Treatment was started with riluzole 100 mg, daily. Fast neurological deterioration was suggested by the rapid alterations MEP and EMG. During the following months, he developed the classical progression of ALS and died one year after his initial complaints.

Conclusion. We could demonstrate that in ALS central MEP can be abnormal before any EMG abnormality can be detected, so at that peculiar stage EMG is not always the neurophysiological golden standard. Physicians should be aware that at some stages EMG can not always exclude ALS.

P270

Perceptual interference between electrical and mechanical stimuli. Correlation with long-latency somatosensory-evoked potentials. M. Veciana, J. Valls-Solé, A. Cervera, Hospital St Boi, Hospital Clinic (Barcelona, E)

A stimulus of one sensory modality attenuates the perception of a stimulus of another modality delivered at the same time or after a short delay. The physiology of this effect probably involves gating mechanisms between the two stimulus modalities. We hypothesized that cognitive processes triggered by the stimulus might be apparent at least in part in long latency somatosensory evoked potentials (LLSEPs). We investigated the effect of a mechanical stimulus on the LLSEPs generated by electrical stimuli applied to the third finger, and evaluated the conscious perception of the stimulus intensity by the subjective report on a visual analogue scale (VAS). The study was carried out in 9 healthy volunteers, aged 26 to 49 years. Surface recording electrodes were attached over Cz with reference to both ears interconnected. Mechanical stimuli were delivered with a sweep-triggering hammer to the first dorsal interosseous space at random intervals between 8 and 10s. Electrical stimuli were applied to the digital nerves of the third finger with a pair of ring electrodes at an intensity of 2 to 3 times the perception threshold. The electrical stimuli were triggered between 0 and 800 ms after the mechanical stimulus. The subjects were asked to evaluate the composition of the trial and the intensity of the stimuli applied by way of a VAS.

LLSEPs were obtained to either electrical and mechanical stimuli. Mechanically induced LLSEP's amplitude and latency were not different in control and test trials. However, electrically induced LLSEPs obtained from trials in which mechanical and electrical stimuli were combined showed different degrees of reduction. Electrically induced LLSEPs were completely absent at intervals of less than 50 ms, to begin a progressive increase in amplitude afterwards. The electrical stimulus was not perceived at all or just minimally at ISIs of 50 ms or less. Perception increased progressively with increasing the ISI. VAS for the intensity of mechanical stimuli was reported always in a similar range regardless of the ISIs. In our study, we have found a significant decrease of perception of the electrical stimuli when delivered together with mechanical stimuli, and a parallel progressive recovery of the perception and of LLSEPs, with increasing separation between the two stimuli. Our results suggest that the amplitude of the LLSEPs reflects the perceptual interference between mechanical and electrical stimuli.

P271

Sonographic analysis of laryngeal elevation during swallowing. V. Kuhl, B. M. Eicke, M. Dieterich, P. P. Urban, University of Mainz (Mainz, D)

Background: Swallowing disorders are a common symptom in many neurological diseases. Since incomplete laryngeal elevation is assumed to be one of the major mechanisms in neurogenic dysphagia, we analysed vertical laryngeal excursion during swallowing non-invasively using ultrasound sonographic techniques.

Methods: Data were obtained from 42 healthy volunteers (mean age: 57 ± 19 years) and 12 patients (mean age: 63 ± 8 years) with neurogenic dysphagia due to stroke (n = 5), amyotrophic lateral sclerosis (n = 2), multiple sclerosis (n = 2), parkinsons'disease (n = 2) and myasthenia gravis (n = 1) using a 7.5 MHz linear array probe, which was placed in longitudinal position above the larynx. This allowed visualization of the contour and the acoustic shadow of the hyoid bone and the thyroid cartilage. The distance between the hyoid bone and the upper end of the thyroid cartilage during laryngeal elevation was assessed by video-mode function.

Results: In healthy subjects we found a mean distance of 220 (± 30) mm at rest; the shortest distance during swallowing of 10 ml water was 85 (± 11) mm and represents a reduction of 61 % (± 3) under physiological conditions. The mean relative laryngeal elevation in the patients with neurogenic dysphagia was reduced to only 41 % (± 10) [$p < 0.0001$]. Statistical analysis revealed no significant difference in regard to gender or age (3 subgroups: < 30, 30–60 or > 60 years).

Conclusions: Ultrasound is a viable and non-invasive method in the investigation of laryngeal elevation during swallowing. It allows direct visualization of impaired laryngeal motion in patients with neurogenic dysphagia.

Dementia and Higher Functions disorders

P272

Mini-mental state examination (MMSE) and working memory assessment. Proposing a dual-task paradigm for a useful clinical tool. L. Pascual, S. Santos, T. Fernandez, P. Saz, C. Iniguez, C. Tejero, J. Mauri, C. Ríos, E. López, E. Mostacero, A. Lobo, T. Casadevall, Hospital Clinico Universitario Zaragoza (Zaragoza, E)

Background: The item ''recall" of the MMSE is a free-recall task after a short time delay. During this delay the patient performs other items. In this way a correct recall in MMSE implies encoding, storage and recall in a Short-Term period across an interference task. This could be related to Working Memory. However in the literature of cognitive screening this relationship has received few attention.

Objective: to present a test of Working Memory assessment during the MMSE application.

Methods: Two new items of registration-recall are incorporated to the MMSE. The second registration is presented after the first recall is performed. Naming, repetition and command are applied in the usual way. The second recall is requested after command is completed. The third registration item is applied now before reading. The third recall is requested after copy design. In each new registration item is possible to introduce 3 new words if the previous recall was correct (3) or repeat the previous words. In this way a broad spectrum of learning capacities could be demonstrated: from the patient whose recall is 0 in the three trials (0–0–0) to the patient who remember 3 new words in each trial (3–3–3).

Results: Scoring System: each word is scored 3 if retrieved in first trial, 2 if retrieved in repetition, 1 if retrieved in double repetition and 0 if not retrieved. The global score range from 0 to 27.

Conclusions: This global score reflex the learning capacity and could be a measure of Working Memory.

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Interaction of the H63D mutation of the hemochromatosis gene (HFE) with the APOE e4 allele modulates age at onset of Alzheimer's disease. O. Combarros, M. Garcia-Roman, A. Fontalba, J. L. Fernandez-Luna, J. Llorca, J. Infante, J. Berciano, University Hospital Marques De Valdecilla, University of Cantabria (Santander, E)

Background: The H63D mutation of the hemochromatosis gene has recently been considered as a risk factor in Alzheimer's disease (AD) by advancing the age at onset of the disease. Objective: We attempted to replicate these findings by examining the role of H63D mutation relative to age at onset, both independently and interactively with the APOE gene. Methods: The study included 328 patients (68 % women; mean age 75.5 ± 8.9 years; range 50–98 years) who met the NINDCS/ADRDA criteria for probable AD. Genotyping of H63D and APOE were performed by PCR followed by restriction endonuclease digestions. Results: The mean age at onset in mutant H63D allele carriers and non-carriers was the same. In the presence of one or two copies of the mutant H63D allele, patients who were APOE e4 homozygotes had a significant ($P = 0.019$) 6 years earlier onset than APOE non-e4 carriers (66.8 ± 9.7 years versus 72.9 ± 10.7 years). Conclusions: The mutant H63D allele in isolation is not powerful enough to influence age at onset of AD. However, there was a significant evidence of a synergistic effect of the APOE and H63D genotypes on age at onset.

P274
Differential neuropsychological performance in Alzheimer's disease and vascular dementia. S. Santos, C. Rios, E. Lopez, M. Garces, O. Fabre, T. Casadevall, University Clinical Hospital Lozano Blesa (Zaragoza, E)

Neuropsychological and neuroimaging differences between patients with ischemic vascular dementia (IVD) or Alzheimer's disease (AD) were examined. Methods: a consecutive series of patients who met either criteria of the DSM-IV for probably AD or IVD were included in the study. Thirteen consecutive patients with probable AD were matched for age, sex and Mini-mental state examination with 24 consecutive patients with probable IVD. Patients underwent a neuropsychological assessment and CT-imaging. Results: patients with IVD showed significantly more severe anosognosia ($p < 0.05$) and emotional lability ($p < 0.03$). IVD patients showed significantly more deficits in tests of verbal fluency ($p < 0.01$) as well as ischemic leukoencephalopathy in CT-scan ($p < 0.01$). Conclusions: patients with IVD showed a relatively more severe dysfunction of the frontal lobes as expressed in specific psychiatric and neuropsychological changes than AD patients matched for age, sex and severity of dementia.

P275
Prevalence of stroke in 85-year olds and its relation to dementia. M. Liebetrau, G. F. Hamann, I. Skoog, Klinikum Grosshadern, Sahlgrenska University (Munich, D; Gothenburg, S)

Background and Purpose: Stroke and dementia are major health problems in the elderly. We examined the prevalence of stroke and its relation to dementia in a representative sample of 494 85-year olds from Gothenburg, Sweden, who were followed up to age 88.

Methods: The study included neuropsychiatric, and physical examinations, close informant interviews, and comprehensive laboratory examinations. Dementia was defined according to the Diagnostic and Statistical Manual of Mental Disorders (third edition, revised). Information on stroke was elucidated from a computerized inpatient register system, self-report and key informants.

Results: The prevalence of stroke was 5.6 % (n = 25) by self-report, 13.2 % by key informants (n = 52) and 12.4 % (n = 61) by the hospital linkage system. The correlation between these sources of information was moderate. The overall prevalence of stroke was 17.6 % (n = 87, women 19.1 %, men 14 %). The prevalence of dementia was 56.3 % in 85-year-olds with stroke and 24.1 % in those without stroke (OR 4.0; 95 % CI 2.5–6.8). Stroke at baseline was related to an increased mortality rate, but not to dementia during follow-up. New strokes during the follow-up period were related to an increased incidence of new cases of dementia. Dementia at baseline was not related to an increased incidence of stroke during follow-up.

Conclusion: One fifth of 85-year-olds had a history of stroke, and more than half of those had dementia. It is necessary to use several sources of information to detect stroke in this age group. New strokes at follow-up, but not stroke at baseline, increased the incidence of dementia at follow-up, suggesting that non-demented 85-year-olds with stroke may have protective factors for dementia.

P276
Early-onset Alzheimer's disease with presenilin–1 M139V mutation. A. J. Larner, Walton Centre (Liverpool, UK)

Objective/Methods: To report the clinical and neuropsychological findings in a patient with early-onset Alzheimer's disease (AD) with the M139V point mutation in the presenilin–1 (PS–1) gene, and to compare the findings with those of previously reported patients carrying the same mutation.

Results: A previously healthy Caucasian male presented at age 48 with a two year history of forgetfulness, word-finding difficulties, a tendency to become lost in unfamiliar locations, declining work performance, and behavioural change with aggressive outbursts. He had noted deterioration in spelling and numeracy. Family history was negative for dementia. Neurological examination was normal: neither spontaneous nor induced myoclonus was observed. Neuropsychological assessment, approximately three years after disease onset, showed marked intellectual loss, particularly affecting non-verbal abilities. All measures of auditory and visual memory for immediate and delayed recall were severely impaired. Naming was relatively spared (Graded Naming Test 19/30). There was severe impairment copying the Rey figure, indicating visuospatial problems. Impairment on the Stroop test indicated problems with divided attention. The profile was consistent with AD. Neurogenetic testing detected the M139V mutation in the PS–1 gene. Cholinesterase inhibitors (donepezil, rivastigmine) were not beneficial. The patient died aged 50 from a myocardial infarction, four years after disease onset.

Discussion: This patient shares some features with previously reported M139V early-onset AD cases (Fox et al., Brain 1997;120:491–501; Hull et al., Eur Arch Psychiatry Clin Neurosci 1998;248:123–129) such as the relative sparing of naming. However, there was no speech production impairment. Deficits in visual memory and visuospatial function were prominent at an earlier stage. Myoclonus and seizures, prominent and early features in previous reports, were not observed, although this may simply reflect the restricted period of follow up.

Conclusion: This case confirms the phenotypic heterogeneity seen in AD patients with the M139V PS–1 mutation, and hence the likelihood of phenotype modulation by genetic and/or epigenetic factors. The absence of both myoclonus and a positive family history does not exclude a genetic basis for early-onset AD.

P277
Dementia with Lewy bodies as differential diagnosis of Creutzfeldt-Jakob disease. B. Mollenhauer, I. Zerr, D. Varges, M. Bartl, K. Körtner, L. Cepec, S. Poser, Georg-August-University (Gottingen, D)

The aim of the study is to differentiate dementia with Lewy bodies (DLB) from Creutzfeldt-Jakob Disease (CJD) to precise the diagnoses.

Since 1993 until May 1999 846 patients, who were suspected to have CJD have been notified to the nationwide German Surveillance Unit for CJD in Göttingen. 269 patients did not fulfil the classification criteria for CJD (established by WHO 1998 and the BOMED–2 study 1998) for "possible" or "probable" CJD and were therefore classified as "other disease". In an additional group of 1414 patients with rapid progressive dementia determination of 14–3–3 proteins in cerebrospinal fluid was requested as a screening test to be performed in the centralized laboratory. These patients were not seen by the study-group, but detailed clinical information was available to classify them as "other disease".

Alzheimer's disease was the most frequent diagnosis followed by DLB. Out of 769 evaluated patients 41 patients had DLB according to the classification criteria for DLB by the Consortium on Dementia with Lewy Bodies. All were at least classified as "probable DLB", 3 patients got neuropathological verification.

In comparison with CJD-patients, the disease duration in DLB was longer (28 months versus 8 months), cognitive decline was fluctuating, extrapyramidal signs were more often (100 % to 78 %) but myoclonus was less often (49 % versus 88 %). A comparison of clinical symptoms and signs and the results of technical investigations to differentiate CJD from DLB will be presented.

P278
MEG/MRI correlation analyses differentiate AD and LBD patients. D. Iacono, A. Thomas, R. Franciotti, S. Della Penna, V. Pizzella, A. Di Rollo, M. Onofrj, Neurophysiopathology, Itab (Pescara, Chieti, I)

Patients with Alzheimer's Disease AD) and Lewy Bodies Dementia (LBD) present different clinical, neuropsychological and neurophysiological characteristics. Recent studies, associated fluctuating cognition (FC), important clinical symptom in LDB (80–90 %), with fluctuating EEG-activity in very short intervals, second -to-second (4 sec). We investigate the EEG/MEG activity correlations in AD LBD patients and specificity of MEG data for AD and LBD respectively.

We studied 10 AD patients (67.4 ± 5.3 y. o), 6 LBD (68,2 ± 4.9y.o) patients and 11 controls 6.9 ± 2.3y.o) using EEG/MEG techniques during spontaneous activity and mental tasks. Patients were classified according to the NINCDS-ADRDA criteria and consensus guidelines for LBD. 5 LBD patients had visual hallucinations and 1 patient suffered by psychosis. Patients did never take treatments like inhibitors of cholinesterase, L-dopa, dopaminoagonist or antipsychotics.

All patients performed complete neuroradiological (TC/MRI) and neuropsychological evaluation to exclude, focal cortical or subcortical lesions and no typical cognitive deficits present in AD and LBD at onset.

MEG was performed by a 165-multichannels whole head-helmet during spontaneous activity (15 min) with open and closed eyes and phonic stimulation at different frequencies (5–15 and 30 Hz). The MEG activity was performed during a mental task (auditory odd-ball paradigm). All patients underwent quantitative-EEG recording and event related potential recordings (P300). All AD and LBD patients and controls successfully performed EEG/MEG and P300 sessions: two LBD patients had a 90 % of successful responses at odd-ball auditory paradigm.

Results: EEG/MEG/MRI recordings in AD patients showed an alpha activity reduction in temporal and frontal areas with low frequency increasing for the response to mental tasks.

In LBD patients no specific brain regions were interested in the alpha activity reduction. The recording showed a diffuse abnormal signal in spontaneous and mental performances. Furthermore, in LBD patients MEG analysis showed fluctuating activity which occurs continuously on a 4 sec basis. The comparative analysis between AD/LBD patients and controls showed a substantial difference in the alteration of the MEG signal.

We suggest a different underlying pathophysiological mechanism in AD and LBD which can be differentiated by MEG/MRI correlation analysis, a sensitive measure, that could be useful during treatment evaluation.

P279

Evaluation of glycohydrolases and ras in fibroblasts from patients with Alzheimer's disease. An. Orlacchio, L. Racanicchi, T. Kawarai, S. Latorraca, S. Sorbi, G. Bernardi, P. St George-Hyslop, A. Orlacchio, C. Emiliani, Laboratorio di Neurogenetica, IRCCS Santa Lucia, Dip.Sc.Bio. e Biot.Mol., U.Perugia, CRND, University of Toronto, Dip.Sc.Neu. e Psi., U.Firenze, Lab.Neurogenetica, IRCCS Santa Lucia (Rome, Perugia, I; Toronto, CAN; Florence, I)

Background: Previous studies have suggested that up-regulation of the lysosomal system is involved in the molecular pathology of Alzheimer's disease (AD). There are evidence of an up-regulation of ras in brain of AD patients; ras seems to be also involved in the expression and targeting of lysosomal enzymes.

Objective: To investigate the molecular mechanisms responsible for the up-regulation of the lysosomal enzymes in AD and to determine biological factors involved.

Methods: Fibroblasts were analyzed in familial cases of AD characterized by a mutation in either Presenilin–1, Presenilin–2, or Amyloid Protein Precursor genes. In addition, sporadic AD patients and healthy controls were also investigated. The expression of the lysosomal glycohydrolases alfa-mannosidase, beta-hexosaminidase, and beta-galactosidase was evaluated by fluorimetric enzymatic assays and RT-PCR. Expression of ras was also evaluated by RT-PCR. Results: We detected an up-regulation in the expression of all the three acidic glycohydrolases in the fibroblasts of all AD patients tested. Up to a six-fold increase was observed for alfa-mannosidase activity. RT-PCR experiments have demonstrated an increased level of transcription of alfa-mannosidase gene in fibroblasts of AD patients. The increased transcription of alfa-mannosidase closely correlates with the increased transcription of ras.

Conclusions: Up-regulated enzymatic activity of lysosomal glycohydrolases investigated in this experiment and ras up-regulation are unique feature independent of mutations in current known AD causative genes and are not confined to the CNS.

Epilepsy

P280

Unusual rhythmic electroencephalographic discharges mimicking epileptogenic activity. P. Masnou, V. Bouilleret, CHU de Bicêtre (Le Kremlin-Bicêtre, F)

In the Eighteens, adult patients with subclinical rhythmic electroencephalographic (EEG) discharges (SREDA) have been reported. This is a rare non-epileptogenic epileptiform activity of unknown pathophysiology, which might be misdiagnosed as epilepsy.

We report on 3 patients considered as epileptic because of persistent epileptiform EEG activity. In the first case, a diagnosis of absence seizures was made at the age of 9 years and antiepileptic drug treatment was followed during 8 years. In the second case, status epilepticus was suspected after a typical syncope. In the last case, antiepileptic drug was prescribed during 7 years after a single provoked convulsive seizure. In all cases SREDA has been recorded on the EEG. This rhythm consisted in frequent trains of rhythmic slow activity (range frequencies from 3 to 5 Hz) lasting 5 to 30 seconds, disappearing with eyes opening and during intermittent light stimulation. Such EEG abnormalities occurred without any clinical symptoms and predominated on the left temporo-occipital region in the first case, the right temporo-occipital region in the second patient and the right parietal region in the last case. Anti-epileptic drugs were interrupted and further EEG recordings showed the same persistent epileptiform activity in all patients, without any clinical epileptic symptoms.

In conclusion SREDA must be recognized as benign EEG variant without relationship with epilepsy.

P281

Efficacy and tolerability of Levetiracetam in the treatment of focal and generalized epilepsy. J. Reis, S. Knake, H. M. Hamer, W. H. Oertel, F. Rosenow, Philipps-University Marburg (Marburg, D)

We assessed the efficacy and tolerability of levetiracetam (LEV) as add-on treatment for refractory focal and generalized epilepsy.

Patients and methods: In a retrospective study of 44 patients with chronic, refractory partial or generalized epilepsy, we assessed epilepsy syndrome, aetiology, seizure types and frequency, prior anticonvulsant therapy and co-medication during the first 6 months of LEV therapy. Primary endpoints of the 6-months-follow-up were efficacy, evaluated by change in mean seizure frequency and rate of patients who were seizure free for at least 3 months. Furthermore, frequency and severity of adverse effects were analysed. The retention rates during the first 6 months were estimated using Kaplan-Meier survival analysis.

Results: 44 patients (21 men, 23 women) with a mean age of 43 ± 15 years were treated with LEV as add-on therapy. Epilepsy was classified as focal 77 % and as generalized in 23 % of the patients. Aetiology of seizures was symptomatic in 63.6 %, idiopathic in 18.2 % and unknown in 18.2 %. Prior to LEV treatment the most common drug regimens included carbamazepine, lamotrigine and valproate, given alone (43.2 %) or in combination with other AEDs (54.5 %). The most frequently given combinations were LTG/VPA and CBZ/LTG.

Within 6 months of treatment 35.3 % of the patients with generalized epilepsy and 39.4 % with focal epilepsy became seizure free for at least 3 months. Mean seizure frequency increased in 9.1 %, decreased in 65.9 % and remained unchanged (baseline seizure frequency ± 10 %) in 25 % of the patients. Although 68.2 % of the patients had adverse effects (mainly somnolence, vertigo)discontinuation of LEV was only necessary in 22.7 % of the cases. Up to a dose of 3000 mg/day tolerability appeared not to be dose-dependent.

Conclusions: The results of this study indicate that add-on LEV-therapy is highly effective and usually well tolerated in everyday clinical practice. This was true for patients with focal and generalized epilepsy including children. Efficacy of LEV in this setting appears to exceed that found during regulatory trials [1] likely because doses could be adjusted on an individual basis. Phase III studies regarding the efficacy of LEV treatment in generalized epilepsy and in children should be initiated.

Reference

1. Grant R, Shorvon SD (2000) Efficacy and tolerability of 1000–4000 mg per day of levetiracetam as add-on therapy in patients with refractory epilepsy. Epilepsy Res 42:89–95

P282

Clinical, biochemical and experimental study on the role of free radicals and antioxidants in primary generalized tonic clonic seizures. W. Fadel, M. Rabie, W. Awara, A. Menaisy, Tanta University Hospital (Tanta, EGY)

This study was carried out on epileptic patients and experimental epilepsy model. Patient study included 60 epileptics with primary generalized tonic clonic seizure divided into 3 groups: non-medicated patients, patients under mono-therapy (phenytoin, PHT or carbamazepine, CBZ) and patients under polytherapy. Erythrocyte glutathione peroxidase (PGX),superoxide dismutase (SOD), plasma lipid peroxides (measured as malondialdehyde, MDA) and nitric oxide (measured as nitrite) were assessed in all subjects. Excessive free radicals production was found with more disturbances of enzymatic antioxidants in epilepsy especially with frequent fits, monotherapy especially PHT and polytherapy regimen. Therefore, excessive lipid peroxidation is involved in epileptogenesis as well as recurrence of seizures and assessment of free radicals scavenger enzymes and antioxidants therapy may be of clinical benefits in epilepsy. Experimental study was conducted on albino mice. Seizures were induced by i. p. injection of pilocarpine. Mice were divided and treated with different specific drugs 30 minutes before pilocarpine as follows: L-arginine (group III), L-nitro-arginine methyl ester [L-NAME] (NOS inhibitor, group IV), PHT (group V) and vitamin C (group VI). Group II received pilocarpine only, while group I served as a control group. Each group was observed for the number of convulsing mice, seizure latency and mortality, 3 hours after pilocarpine injection, blood was withdrawn for estimation of the same biochemical parameters and brain tissue was collected for histopathological study. We found that groups II, IV, and V were exposed to marked stress indicated by mortality rate, increased MDA (lipid peroxidatin), decreased in GPX, decreased serum nitrite and marked tissue injury and necrosis. So we conclude that lipid peroxidation is a dominant feature in experimental seizure. Nitric oxide may have an endogenous anticonvulsant effect. Phenytoin caused marked disturbance of the oxidant-antioxidant balance. Exogenous

antioxidants, including vitamin C may be of therapeutic benefit in management of epilepsy.

P283

Overweight induced by Topiramate. A. Hamad, S. Kamran, T. Sokrab, H. Ayman, H. Al Hail, Hamad General Hospital (Doha, QA)

Introduction: With Topiramate weight loss is frequently reported while psychosis is rare. Overweight was not reported before.

Methods: We report a case with significant weight gain and compulsive eating after initiating topiramate therapy.

Result: Twenty four year old patient epileptic since age of 5. Her physical examination was normal, with mild subnormal mentality and bouts of abnormal behaviour. In 1998 she had episode of compulsive water drinking, aggressiveness and destructive behaviour, which was controlled with thioridazol 50 mg tid, Carbamazepene and Primodone. Because of her frequent seizures she was referred to neurology clinic. At that time her EEG was severely abnormal, normal brain MRI and weight 50Kg. Topiramate was slowly built up to 100 mg bid on April 2001. Her seizures significantly reduced. Six months later patient had uncontrolled appetite, eating continuously and her weight went up to 75Kg. Finally she became aggressive, restless, wandering, not sleeping in addition to her compulsive eating. She was admitted to the psychiatry ward, topiramate was reduced by 50 mg/week. Lamitrogine was added slowly. Four months after discontinuing Topiramate, her compulsive eating and aggressive behaviour subsided and weight reduced to 55Kg.

Conclusion: The compulsive eating behaviour and weight gain which was started after topiramate and subsided with it's discontinuation is clearly related to Topiramate. In patients with history of psychotic behaviour Topiramate should be added cautiously and under frequent medical supervision.

P284

Memory abilities in patients with temporal mesial epilepsy. É. Baeta, Hospital Garcia de Orta (Almada, P)

Background and Methods: The assessment of patients with temporal lobe epilepsy (TLE)includes the investigation of memory deficits. Several methods showed to be poorly sensitive and discriminative to the specific problems of these patients. The California Verbal Learning Test (CVLT) can afford us the quantification of several components of verbal learning and memory. The aim of this study is to identify, by the CVLT, deficits and strategies that differentiate three groups of individuals: normal controls (NC) ($n = 43$), patients with left mesial epilepsy (LME) ($n = 19$) and right mesial focus (RME) ($n = 20$).

All the individuals were right handed. The epilepsy origin was determined by means of electroencephalogram and MRI scan. They did not differ in demographic variables and, patients were similar in epilepsy characteristics. All were submitted to CVLT according to standardized instructions. Fifteen raw scores as well as ten indices were obtained. Data was submitted to statistic analysis.

Results and Conclusions: Several raw scores showed to be sensitive to temporal epilepsy effects on verbal memory. The LME group was more impaired in total immediate recall ($F = 4.127$, $p = 0.020$), short term and long delay recall ($F = 10\,266$, $p = 0.000$ and $F = 11\,661$, $p = 0.000$ respectively), and recognition task ($F = 13\,444$, $p = 0.000$). RME group showed a deficient capacity of discriminability ($F = 5.334$, $p = 0.007$) comparing to NC and LME groups. Percentage of middle recall seems to discriminate RME from LME (post-hoc Tukey HSD $p = 0.032$; RME superior to LME).

The present study provides clear evidence that CVLT is an excellent measure to enhance TLE effects on memory. In fact, it points out the codification incapacity of LTE group by the difficulty to learn, retrieve and recognize new information. On the other hand, CVLT may also discriminate RME from LME patients. To our knowledge there are no other studies on primacy, middle and recency strategies in TLE patients. Our study demonstrates that RME group seems to rely on a different learning strategy, showing advantage to retain items from the middle of the word list. Due to these results CVLT rises above other memory tests to distinguish and evaluate TLE patients and shows to be a useful tool to investigate human memory.

P285

Duration of status epilepticus and survival; minimal effect beyond 10 hours. F. W. Drislane, M. R. Lopez, A. S. Blum, D. L. Schomer, Harvard Medical School, Rhode Island Hospital (Boston, Providence, USA)

Background: The outcome of patients with status epilepticus (SE) depends strongly on etiology. Duration of SE may also be predictive, but beyond 1 to 2 hours, duration of SE has not been shown to influence outcome.

Objective: to determine the influence of duration of SE on outcome in critically ill patients and to compare this influence with that of other factors.

Method: We reviewed the clinical course and outcome in 119 patients diagnosed with both clinical manifestations and EEG evidence of SE. Patients were divided into 8 groups of approximately equal numbers of patients according to duration of SE. Outcome was assessed according to survival (even when there were persistent deficits, as with stroke) vs. death or vegetative state. Also examined were the effects of age, type of SE (focal or generalized), level of consciousness, and diagnosis of anoxia or earlier epilepsy as the cause of SE. Results were analyzed by Chi square or Fisher's exact test for categorical data.

Results: Median duration of SE was 48 hours in this group. Survival was greater when duration of SE was 10 hours or less (69 % vs. 31 % for longer duration; $p < 0.02$), but beyond this time longer durations of SE did not have a significant effect on outcome. An earlier diagnosis of epilepsy was a favourable sign ($p < 0.01$), although many older epilepsy patients developed additional life-threatening illnesses precipitating SE. Overall mortality was high, 65 %, but 10 patients survived SE lasting over 3 days. Patients with focal SE (usually caused by stroke) did better than those with generalized SE ($p < 0.05$). Coma and SE caused by anoxia were unfavourable factors. Other causative diagnoses and age were not predictive.

Conclusions: A duration of 10 hours or less was associated with better outcome in SE, but beyond this time duration was not a predictive factor. Prolonged SE is not necessarily fatal. Aetiology of SE is still the primary determinant of outcome, with prior epilepsy a relatively good sign and anoxia a terrible one. A higher level of consciousness and focal SE were also relatively good signs but are probably related to aetiology.

P286

Initial manifestation of MELAS as confusional state due to focal status epilepticus. B. Feddersen, S. Arnold, A. Bender, S. Noachtar, University of Munich (Munich, D)

The hallmark of mitochondrial encephalomyopathy, lactic acidosis, and stroke like episodes (MELAS) is the occurrence of episodes that result in hemiparesis, hemianopia, cortical blindness, and lactic acidemia. Other common clinical features include recurrent migraine-like headache, vomiting, short stature, hearing loss, muscle weakness, and epileptic seizures. Status epilepticus is a major cause of death in MELAS.

We report two patients with status epilepticus characterized by confusion and inadequate behaviour, in whom the status was secondary to MELAS. The status epilepticus was confirmed by EEG and regional ictal SPECT hyperperfusion. In one patient the status epilepticus was the initial clinical manifestation of MELAS. The status ceased with rapid administration of phenytoin in both patients. No sequelae of the status were noted.

Common aetiologies of confusional state include psychiatric or metabolic disorders and non-convulsive status epilepticus. Usually the therapeutic regimen is less aggressive in non-convulsive status epilepticus as compared with convulsive status. Focal status epilepticus leads to regional increase of energy consumption. Rapid therapeutic intervention maybe crucial to prevent further neuronal damage in these patients, because MELAS is a mitochondrial disease with insufficient cellular energy consumption.

P287

Attacks of abdominal cramps as the only manifestation of temporal lobe epilepsy. W. Verslegers, P. De Deyn, AZ Palfijn (Antwerp, B)

Case. A 10-year old boy complained since two years of unprovoked attacks (between 2–4 monthly) of abdominal cramps and diarrhea, followed some minutes later by holocranial headache. They appeared during day time as well as during sleep. Over the last two years, he was investigated extensively up to five times by several paediatricians, who could not find any internal, metabolic, structural or psychiatric disease. Neurological examination was normal. During some attacks, consciousness appeared a little diminished.

The electroencephalography (EEG) during normal awareness showed a global slowed background activity of 3-Hz delta waves posteriorly. During rest conditions as well as during provocation (hyperventilation) typi-

cal paroxysmal epileptic (spike wave, spike on wave) discharges were registered, in epoches of 6 seconds and simultaneously over both hemispheres up to 200 microvolt and with an evoked response on 17 Hz light stimulation. During several registrations it was impossible to find a hemispheric predominance of this epileptic activity or to locate the beginning of an epileptic seizure in one hemispheres. Magnetic resonance imaging was normal.

Abdominal epileptic attacks were presumed and treatment with carbamazepine 150 mg, twice a day was started. During the following years, the attacks ceased gradually.

Two year later, the EEG showed a less slowed background activity with epileptic discharges only during hyperventilation. After two years of treatment, all attacks disappeared with a daily dose of 400 mg. EEG's were taken yearly. Since the age of 12 all his clinical attacks disappeared, however, the EEG normalised only at the age of 17. At this age, carbamazepine was gradually tapered and stopped after six weeks. At the age of 20, he was still without clinical attacks and the EEG remained normal without recurrence of epileptic activity.

Conclusion. In this boy, abdominal and cephalic pain was the only manifestation of epilepsy. The frequency of painful sensation in epileptic seizures is estimated between 0.3 and 2.8 %. The pain can be unilaterally and contralateral to the epileptic origin, cephalic or abdominal. The seizure origine can be located in the temporal or parietal lobe and pathology of the thalamus has been proposed based on observations in some cases. In nearly all reported cases, antiepileptic drugs were successful in treating the symptoms.

P288

The effects of nicergoline in the electroconvulsive seizure model in mice. O. Ozdemir, O. O. Erdinc, B. Sirmagul, K. Erol, G. Ozdemir, Eskisehir Osmangazi University (Eskisehir, TR)

Objective: Nicergoline (NCG) is a semisynthetic derivative of ergoline and is used in dementia to improve the cognitive functions. The aim of our study was to evaluate the effects of this drug in maximal electroshock seizure (MES) model in mice.

Material and Methods: Forty-three male albino mice were used. Three groups were formed according to the daily dose of NCG: 5, 15 and 30 mg/kg. NCG has been given for 3 days prior to the MES test. The control group received placebo. The electroconvulsive shock (ECS) with a frequency of 50 Hz, duration of 0.2 msec and intensity of 40 mA was performed via ear electrodes. The tonic extension of the hindlimbs was taken into consideration. Statistically x2 test was performed in SPSS pocket.

Results: The number of mice showing tonic hindlimb extension in 15 mg NCG group was found statistically higher than the control group ($p < 0.05$). The mortality was also higher in the same group when compared with the other groups and controls ($p < 0.05$).

Comment: Drugs found efficient in ECS often block voltage dependent Na channels. NCG binds highly to serotonergic (5-HT1A) and adrenergic (alpha–1) receptors. ECS changes several serotonin (5-HT) receptor subtypes in the central nervous system. It is reported that ECS increases sensitivity to 5-HT in 5-HT3 receptors in the hippocampus, resulting in an increase in release of neurotransmitters such as glutamate and gamma-amino butyric acid. Among the neurotransmitters 5-HT seems to affect the voltage gated Na channels more than the other amines.

Conclusion: The change in the number of seizures and mortality due to different doses of NCG seems to occur as a result of interaction between 5-HT and Na channels.

P289

Levetiracetam is effective in all generalised seizure types. G. L. Krauss, B. Abou-Khalil, G. Bergey, Johns Hopkins University (Baltimore, Vanderbilt, USA)

Objective: Not all generalised seizure types; tonic clonic, myoclonic and absence, respond to individual antiepilepsy drugs (AEDs). Some AEDs may even provoke worsening of generalized epilepsy and conversion to more severe seizure types. We evaluated the response of patients with drug-resistant epilepsy to levetiracetam (LEV), a new AED, to determine whether all seizure subtypes responded and whether any patients developed more severe seizure types.

Methods: Patients with generalised epilepsy received an open label trial of LEV 0.5 mg to 3 g/day. Seizure frequencies were compared between 12 week baseline and 12 week treatment periods. Patients had generalised seizure types, generalised spikes and both normal EEG background and MRI. Patients had baseline seizure frequencies of > 1 seizure/month and had previously failed > 1 prior AED.

Results: Overall, 44 % patients became seizure-free, 69 % were responders (> 50 % reduction), 12 % discontinued due to dizziness/drowsiness. All seizure types responded: 5/7 with tonic clonic on awakening, 10/13 with juvenile myoclonic epilepsy (JME) and 3/5 with juvenile absence. Two of 20 patients with tonic clonic seizures worsened (1 with JME, 1 with tonic clonic on awakening). No patients converted from absence or myoclonic to tonic clonic seizures.

Conclusions: AEDs may only treat a subset of generalised seizure types and some may worsen generalised seizures. Preliminary results from our series, however, show that LEV appears to be beneficial for treating absence, myoclonic and tonic seizure types without provoking new seizure types in patients with drug-resistant generalised epilepsy.

Parkinson's disease and Extrapyramidal disorders

P290

Improvement of levodopa-induced psychosis and dyskinesia in Parkinson's disease patients with low-dose olanzapine. J. J. Lin, Chushang Show-Chwan Hospital (Nantou/Taiwan, CHN)

Sixteen consecutive patients with Parkinson's disease (PD) complicated by levodopa-induced psychosis were treated with low-dose olanzapine (OLZ). This started at 2.5 mg daily and slowly increase in 2.5-mg increments as needed. Their psychotic symptoms were rated by the Scale for the Assessment of Positive Symptoms (SAPS). The Visual Hallucinations item (number 9) form the SAPS and the Brief Psychiatric Rating Scale (BPRS) were used as the behavioural outcome measures. Furthermore, the Unified Parkinson's Disease Rating Scale (UPDRS) motor and activity of daily living (ADL) subscales were used for measuring their Parkinsonian symptoms. The Modified Dyskinesia Rating Scale (MDRS) was used for measuring their dyskinesias induced levodopa. A comparison of these rating scales was made before and three months after the treatment. OLZ could significantly reduce SAPS total scores by 65.9 %, SAPS subscores for the specific visual hallucination items by 60.5 %, and BPRS total scores by 42.9 % in these PD patients with psychosis. Furthermore, this drug could also significantly reduced the mean score for dyskinesia by 51.4 %. Although treatment with OLZ could slightly worsen the UPRDS motor and ADL subscales, the degree of worsening was not significant. Overall, there was no significant increase in levodopa dose in this study. In conclusion, the results of our study revealed that treatment with low-dose OLZ could improved levodopa-induced psychiatric symptoms and dyskinesias without worsening motor function in PD patients with psychosis.

P291

Repetitive trans-cranial magnetic stimulation in Parkinson's disease: a prospective study of 33 cases. C. Mhiri, F. Belahsen, M. Jaballi, I. Feki, F. Choyakh, N. Zouari, Habib Bourguiba Hospital (Sfax, TN)

Efficacy of repetitive trans-cranial magnetic stimulation (r-TMS) of motor cortex remains controversial. We undertaken a double blind prospective study to evaluate the efficiency of r-TMS in Parkinson's disease.

Thirty three patients (17 men et 16 women) are affected by Parkinson's disease (UKPDSBB criteria). They were admitted to hospital for a period of 2 to 5 days. They were randomly divided within 3 sub-groups:
sub-group A: treatment continued and r-TMS;
sub-group B: withdrawal of treatment and r-TMS and
sub-group C: treatment withdrawal without r-TMS (fictitious stimulation).

Repetitive evaluation by Unified Parkinson Disease Rating Scale (UPDRS) was done (at admission, 24 hours after treatment withdrawal, and 1, 6 and 24 hours after r-TMS).

In sub-group A, the r-TMS induced an improvement of the motor UPDRS score. This improvement is observed within one hour after stimulation (the score dropped from 36.8 ± 11.1 to 30.2 ± 10.7) and lasted until the 24th hour.

For the sub-group B, the UPDRS motor score decreased since the first hour (score passed from 37.5 ± 8.1 to 29 ± 8; $p < 0.01$). This improvement persisted at least 24 hours after the r-TMS.

For the sub-group C, there is a significant increase in the score (worsening).

The r-TMS induces a significant improvement of UPDRS motor score. This improvement appears since the first hour, it is maximum at the 6th hour and persists at least until the 24th hours. It is observed as well in patients under medical treatment as in patients in whom the treatment was withdrawn.

P292
Health status perception evaluated by SF–36 questionnaire in patients affected by Parkinson's disease. A. Coretti, L. Capone, Regional Hospital (Bolzano, I)

Objective: To assess the health status perception of patients suffering from Parkinson disease.

Background: A good level of "quality of life" has become today the principal objective of many medical treatments, particularly in patients affected by chronic diseases. Therefore, new methods, like questionnaires, are introduced in the clinical practice to evaluate outcomes of medical care.

Methods: The SF–36 Health Status Survey Questionnaire is a self-administered questionnaire including 36 items that assesses 8 health domains. For each variable item scores are coded, summed and transformed on to a scale from 0 (worst possible) to 100 % (best possible).

Materials: The Italian and German version of the SF–36 Health Survey questionnaire was administered to 27 patients (13 females, mean age 75.4, 18 Italian-speaking patients) affected by Parkinson disease, chronically treated with Levodopa and dopaminoagonists by the same neurologist.

Results: Male and females have a similar profile of their health status perception, with slightly lower scores in the Physical Role (PR) scale for male patients. Low values were also found in Mental Health (MH) scale for both groups. No significant difference was found between German- and Italian speaking patients' profile, although the first group had lower scores in all scales.

Comment: Lower score in the MH scale corresponds with the high prevalence of depression in Parkinson patients. The low PR scale results can be explained like effect of motor disability on their quality of life. The SF–36 questionnaire is a simple and useful method to evaluate the health status perception, considering the general consensus about the importance of the patient's point of view in monitoring medical care outcomes.

P293
The novel transdermally applied dopamine receptor agonist Rotigotine CDS in early Parkinson's disease treatment – Efficacy and safety results. J. Bianchine, K. Poole, F. Woltering, Schwarz BioSciences for the Rotigotine CDS SP 506 Trial Team

Background: Dopamine agonists (DA) are recommended as first choice treatment in early IPD as they can delay the onset of motor fluctuations. This is hypothesized based on different factors such as a more continuous dopaminergic stimulation compared to L-dopa. The novel selective DA Rotigotine CDS (constant delivery system), which is applied transdermally and provides constant plasma levels, was investigated.

Methods: A double-blind, randomized, placebo-controlled, multicenter phase IIb-trial was performed worldwide at 51 sites. 316 IPD patients were treated either with the Rotigotine CDS patch (4.5, 9.0, 13.5 or 18.0 mg) once daily or placebo for a treatment period of 3 month in total. The primary variable was the change in UPDRS parts II + III from baseline to the end of treatment. Other variables included safety and tolerability.

Results: Mean age of patients was 60.3 years; mean time since diagnosis of IPD was 1.42 years; mean UPDRS was 7.4 ± 4.03 in part II and 20.5 ± 9.47 in part III at baseline. A dose dependent improvement in UPDRS II+III was observed. Statistically significant differences were measured in the 9.0 mg (mean = –4.47; $p = 0.0063$), 13.5 mg (mean = –6.25) and in the 18.0 mg group (mean = –6.29) (both $p < 0.0001$), but not in the 4.5 mg group (mean = –3.49; $p = 0.0393$) compared to placebo (mean = –1.39) (based on a closed test procedure with one-sided p-values; many to one comparisons with a predefined hierarchy). The responder rate (decrease of > 20 % in UPDRS II+III) was 29 % in placebo patients, 38 % in the 4.5 mg, 45 % in the 9.0 mg, 57 % in the 13.5 mg and 53 % in the 18.0 mg group. Adverse events (AE) tended to increase slightly at higher doses and occurred as following: Nausea, dizziness; somnolence; insomnia; headache; vomiting; fatigue. Orthostatic hypotension, collapse and hallucinations were rare. Only two subjects reported sleep attacks. Application site reactions were mild and transient in all treatment groups including the placebo group. Subjects withdrawn from the trial due to AE were 5 % in placebo and 8 % in Rotigotine CDS treated subjects.

Conclusions: This study demonstrates good efficacy, tolerability and safety of the first transdermal DA applied once daily to patients with early IPD. There was a clear dose-response relationship with a ceiling effect between 13.5 and 18.0 mg/day; 9.0 mg /day was the lowest effective dose. The safety profile of the Parkinson's patch Rotigotine CDS is similar to other dopaminergic drugs.

P294
Subthalamic nucleus lesioning with deep brain stimulation electrodes: case report. M. Pilleri, F. Valldeoriola, J. Rumià, J. Poblete, C. Cardiel, E. Tolosa, Hospital Clínic (Barcelona, E)

Background: deep brain stimulation (DBS) leads can be damaged, bound or infected. In such cases, removal of the electrodes is required even in case of satisfactory clinical therapeutic effect.

Objective: to demonstrate that it is safe to make a subthalamic lesion connecting a radiofrequency generator with DBS leads before to their removal in order to maintain the clinical effect achieved by chronic stimulation

Case report: a 65 years-old woman with Parkinson's disease who had undergone bilateral subthalamic stimulation three years before, developed skin infection over the DBS hardware in the skull. Infection was not resolved after intensive antibiotic therapy and surgical removal was indicated. A bilateral subthalamic lesion was done under local anesthesia with a radiofrequency generator (Radionics) using a bipolar connection on the DBS lead. The lesion was performed stimulating at 40 mA during 70 seconds with impedances oscillating between 300–800 ohms in two different poles. A magnetic resonance after lesioning confirmed the size and placement of the lesions. Transitory dyskinesias were seen immediately after the procedure in one side but no other adverse effects were observed. The patient had a favourable outcome with improvement of parkinsonism.

Conclusion: Subthalamic lesions can be safely performed through DBS leads achieving therapeutic benefit.

P295
The effect of N-methyl-norsalsolinol on serotonin metabolism in the rat caudate-putamen. A. Thümen, A. Benecke, F. Qadri, A. Moser, Universitätsklinikum Lubeck (Lubeck, D)

The TIQ derivative N-methyl-norsalsolinol (2-methyl–6,7-dihydroxy–1,2,3,4-tetrahydro-isoquinoline, NMNSal) was identified in parkinsonian lumbar cerebrospinal fluid. Recently, we could demonstrate that NMNSal is able to pass through the blood brain barrier of the rat brain.

In vivo microdialysis in conscious, freely-moving rats was applied to investigate the effect of intraperitoneal injection of various NMNSal concentrations (20/40 mg/kg) on serotonin metabolism in the rat caudate-putamen. Stereotaxic surgical procedures were used to implant guide cannulae aimed at the rat caudate-putamen of male Wistar rats. At least 2 days later, artificial cerebrospinal fluid (aCSF) was perfused with 2 µl/min. After a 2 hr stabilization period, three 20 min samples were collected and NMNSal was injected via an intraperitoneal cannula. Serotonin metabolites [hydroxyindole acetic acid (HIAA), 5-hydroxytryptamine (5-HT)] were measured by HPLC/ECD analysis during the subsequent 180 min period as well as after 24 and 48 hours.

After intraperitoneal injection of 20 resp. 40 mg/kg NMNSal, HIAA concentrations in the dialysate markedly increased to 900 % resp. 1300 % of basal levels (= 100 %) 90 min after application. After 48 hours, HIAA concentrations continuously decreased to 50 % of basal values. In contrast to HIAA, 5-HT concentrations were nearly constant during the whole perfusion period. Additionally, the caudate-putamen contralateral to cannulae implantation was removed 48 hours after intraperitoneal NMNSal injection and serotonin metabolites were analyzed in homogenate preparations. The HIAA/5-HT ratio was significantly reduced to 70 % resp. 20 % by 20 resp. 40 mg/kg NMNSal.

These findings indicate that NMNSal interfere with the serotonin metabolism in the rat caudate-putamen in vivo. However, since NMNSal was discussed to inhibit monoamine oxidase, the early effect on HIAA outflow was unclear.

P296
The prevalence of primary dystonia in the general community. J. Müller, S. Kiechl, G. Wenning, K. Seppi, J. Willeit, J. Wissel, T. Gasser, W. Poewe, University Hospital Innsbruck, Ludwig-Maximilians University (Innsbruck, A; Munich, D)

Objective: The prevalence of primary dystonia in the general community is unknown. Recent service-based studies suggest that the disorder may be underdiagnosed. We investigated the prevalence of primary dystonia in the general community. Methods: The present study was based on standardized examinations of a random population sample of individuals aged 50 and over that were participants of the Bruneck study, a prospective survey of stroke risk factors in South Tyrol. On-site examinations were performed by a neurologist experienced in movement disorders and videotape recordings of suspected dystonia cases were independently reviewed by

three movement disorder specialists. Definite primary dystonia was diagnosed when all reviewers agreed on the diagnosis and secondary dystonia was excluded according to published criteria. Seven hundred seven subjects were examined. Results: Initially, a total of 15 cases with sustained involuntary muscle contractions were identified at the on-site examination. Nine of the 15 cases (60 %) were excluded from the study for the following reasons: Eight cases were classified as tardive dyskinesia according to Jankovic (1993) and one case had blepharospasm associated with probable progressive supranuclear palsy (PSP). Definite primary dystonia was present in six cases (four with dystonia of the cranial and/or cervical region, one with spasmodic dysphonia, one with writer's cramp; median age at onset 50.5 years) resulting in a prevalence rate of primary dystonia in the general community aged 50 and over of 732 per 100,000 (95 % CI 319–1564). Assuming a zero prevalence of primary dystonia in the age-group from 0–49 the minimal standardized prevalence rate for the whole population was calculated as 225 per 100,000 (95 % CI 98–481). Only two of the six primary dystonia cases (33 %) had been previously diagnosed although all four undiagnosed cases experienced dystonia-related disability. Conclusion: Our results suggest that the true prevalence of primary dystonia is significantly above previously published rates, since many patients in the general community remain undiagnosed. This work has therefore implications with regard to medical education, research and service provision, with a need to train general physicians to recognize dystonia and refer patients to neurological centres with experience in movement disorders for work-up and adequate therapy.

P297

Evaluation of movement disorders in patients suffering from Wilson's disease. W. Hermann, P. Günther, T. Villmann, A. Wagner, Leipzig University (Leipzig, D)

Introduction: Extrapyramidal motor symptoms of varying degrees are part of the symptoms of Wilson's disease. The aim of therapy is to reduce or even prevent these symptoms. Follow-up is performed to spot any changes in findings.

Methods: Fine motor functions of 19 patients with Morbus Wilson (10 patients with a neurological form, and 9 with a non-neurological form) were measured. Kinematic parameters (changes in speed, changes in acceleration, frequency) were measured on a Zebris movement analysis system by recording alternating movements (diadochokinesis and index-finger tapping). Computer-assisted movement analysis proved to be more sensitive than assessing the extrapyramidal motor symptoms with a clinical score.

Results: A rise in acceleration changes was the most common finding, causing movement to slow down. Altogether, the disorders in the kinematic parameters reflected a reduced degree of movement automation. Despite clinical improvement under therapy, both a significantly reduced degree of automation in movement control and indications of an irreversible lesion were observed in the neurological patients. The main factor was the limited cerebellar function; the reduced basal ganglion control was less pronounced. Some of the non-neurological patients also exhibited disorders in their kinematic parameters, providing early indication of transition to a neurological form.

Conclusion: Clinical assessment during follow-up should be augmented by measuring fine motor movements, which may register changes more sensitively.

P298

Presynaptic parkinsonism in multiple system atrophy mimicking Parkinson's disease: a clinicopathological case study. J. Berciano, F. Valldeoriola, I. Ferrer, J. Rumià, J. Pascual, C. Marín, M. J. Rey, E. Tolosa, University Hospital Marqués de Valdecilla, Hospital Clinic (Santander, Barcelona, E)

Only 5 % of patients with multiple system atrophy with parkinsonian features (MSA-P) show obvious response to levodopa after 5 years therapy. Furthermore deep brain stimulation usually fails to improve the parkinsonian motor disturbances of MSA-P. We describe the clinicopathological findings in an MSA-P patient aged 63 years at death who developed, at age 55 years, levodopa-responsive parkinsonism with no atypical features. A diagnosis of idiopathic Parkinson's disease (PD) was made. During the clinical course fluctuations and dyskinesias appeared. Eight years after onset he was successfully treated with subthalamic nucleus stimulation, but died three weeks postoperatively from pulmonary embolus. Brain autopsy showed marked neuronal loss and gliosis in the substantia nigra and locus coeruleus. The pons, inferior olivary nuclei and cerebellum showed either mild neuronal loss and demyelination or normal findings. In spite of this, there was profuse microglial proliferation and numerous oligodendroglial (GCI) and neuronal cytoplasmic inclusions and neuropil threads, the highest GCI-density being localized in the pons and cerebellar white matter, where they ranged between 300 and 600 mm2. Striatum and subthalamic nuclei were normal. No Lewy bodies were observed. We conclude that nigral, presynaptic parkinsonism may occur in multiple system atrophy, which even in the long run can be indistinguishable from PD. Putaminal and subthalamic nuclei preservation accounts for good response to both levodopa therapy and subthalamic nucleus stimulation. The presence of high GCI-density areas and even florid microglial proliferation does not necessarily imply either neuronal loss or development of signs or symptoms.

P299

HLA-DR2 and DQA1/DQB1 typing does not predict REM sleep behaviour disorders. A. Thomas, D. Iacono, A.L Luciano, G. D'Andreamatteo, A. Di Rollo, M. Onofrj, Neurophysiopathology (Pescara, I)

Parkinson's disease (PD) is now considered as burdened by psychiatric and cognitive disturbances. Hallucinosis and hallucinations might be related to sleep disturbances and linked to REM Sleep Behaviour Disorder (RBD) that has high prevalence in PD and in other parkinsonism (MSA) and it is characterized by the loss of motor inhibition during REM Sleep. Another REM Sleep disturbance is characterized by the sudden onset of REM sleep, without, however, the loss of motor inhibition: this condition, known as narcolepsy, is characterised by an almost exclusive HLA pattern.

In the Caucasians, the DR2 association is as high as 90–95 %, even if the HLA-DQB10602 is the major HLA susceptibility allele for narcolepsy across all ethnic groups. 90–100 % of narcolepsy patients with definite cataplexy share HLA-DQA10102/DQB10602 and this evidence confirms a primary role of DQA1 and DQB1 in disease susceptibility.

We selected 24 patients with L-DOPA responsive parkinsonism for at least 6 years. 12 patients had never complained of hallucinosis or RBD despite all had severe motor fluctuations with peak dose or dyphasic dyskinesias and 12 patients had described hallucinations and/or RBD 1- 3 years after the introduction of L-DOPA or dopaminoagonists treatments and received a current treatment for the disturbance (atypical antipsychotic drugs). Mean age, daily L-DOPA and dopaminoagonists intake, UPDRS motor scores, MMSE scores were statistically overlapping in the two groups of patients. NPI scores and UPDRS mental scores were slightly different in the two groups of patients.

The method used for typing HLA antigens was a serological-based complement dependent cytotoxicity assay in which viable lymphocytes are exposed to a large panel of HLA monoclonal and alloantibodies. Antigens were assigned based on the pattern of serologic reactivity.

The statistical evaluations included c2 Fisher test with Yates correction.

The results showed that HLA patterns were equally distributed in the two groups of patients without a significant correlation with any HLA subtype.

In our study familial-parkine synucleine positive patients were also excluded. Previous studies considers RBD hallucinations concordance and did not exclude familial parkinsonism.

The lack of specific correlation for HLA-DR2 and HLA-DQA10102/DQB10602 in PD-RBD/Hallucinator patients is the first evidence of a REM Sleep Disturbance lacking of specificity for the examined HLA types.

Multiple Sclerosis

P300

Influence of pulsed methylprednisolone therapy on cognitive functions in patients with multiple sclerosis. I. Uttner, C. Zinser, M. Maier, S. Süßmuth, A. Claus, E. Elitok, D. Ecker, H. Tumani, University of Ulm (Ulm, D)

Although there is strong evidence that elevated glucocorticoid levels can cause cognitive impairment, as yet only few data exist on that association in multiple sclerosis (MS) patients treated with corticosteroids. Our study addresses the questions (1) whether high-dose corticosteroid treatment can cause such cognitive deficits and (2) whether the cognitive performance is dose-dependent.

Sixteen patients (11 females, 5 males; mean age 33 ± 9.34 years) with relapsing-remitting MS in early disease stage and eight healthy controls matched for age, gender and IQ underwent a comprehensive clinical and neuropsychological investigation. Using a double-blind, randomized study design, one half of the patients was treated with 500 mg/d methylprednisolone (MP) over five days, the other half received 2000 mg/d MP. Neu-

ropsychological investigations were made before (day 0), and 6 and 60 days after treatment.

Results show impairment of free and cued retrieval of declarative memory in the patients at day 6 compared to day 0 ($p < 0.05$). These cognitive deficits recovered completely at day 60. All other functions were unaffected. In contrast, the untreated controls showed a slightly improvement in their declarative memory at day 6. No differences were found between the profile and severity of the cognitive impairment of the two dose groups.

Our findings suggest that high-dose treatment with MP can induce selective, but reversible impairment of the declarative memory-recall in MS-patients. This deficit seems independent of the administered MP-dose.

P301

Fatigue in multiple sclerosis is related to dysfunction of the sympathetic nervous system. A. Rufer, P. Flachenecker, C. von Hippel, K. Reiners, K. V. Toyka, J. Kesselring, Rehabilitation Center, Julius-Maximilians-Universität (Valens, CH; Wurzburg, D)

Fatigue is one of the most common disabling symptoms in patients with multiple sclerosis (MS), but the mechanisms of this complex impairment remain to be determined. Dysfunction of the autonomic nervous system is also frequent in MS, but its causal association to fatigue is not clear. Therefore, we evaluated cardiovascular autonomic function in MS patients with (MS-F) and without fatigue (MS-NF).

Patients and methods: 36 patients (28 women, 8 men) with relapsing-remitting (n = 19), secondary progressive (n = 14), or primary progressive MS (n = 3), aged 41.7 ± 11.3 years, median EDSS 4.0 (range 1–6.5) were studied by parasympathetic (heart rate responses to Valsalva manoeuvre, deep breathing and active change of posture, HR-post) and sympathetic function tests (blood pressure responses to active change of posture and sustained handgrip, BP-grip) as well as by measures of heart rate variability during rest and standing in the time- and frequency-domain (low-frequency power, LF, and high-frequency power, HF). Results were compared to those obtained in 36 age-matched healthy volunteers (21 women, 15 men, age 39.4 ± 10.0 years). Fatigue was assessed by Krupp's Fatigue Severity Scale (FSS), with a score > = 4.0 indicating fatigue.

Results: 21 MS patients (58 %) revealed abnormal results in at least one autonomic test, predominantly in those reflecting sympathetic function (44 % vs. 14 % in healthy volunteers, $p < 0.01$). Median HR-post (1.25 vs. 1.38, $p < 0.003$) and BP-grip (11 vs. 18 mm Hg, $p < 0.0001$) were significantly lower in MS patients than in controls, as were measures of heart rate variability. 27 MS patients (75 %) complained of fatigue. The median LF/HF ratio (indicating sympathetic activity) was lower in MS-F than in MS-NF patients (standing: 8.9 vs. 15, $p < 0.05$, rest: 2.1 vs. 3.3 $p = 0.09$), and FSS was inversely related to BP-grip ($r = -0.40$, $p < 0.02$) and LF power ($r = -0.38$, $p < 0.05$). Worsening of symptoms with heat ("Uhthoff's phenomenon") was reported by 22 patients (61 %). These patients demonstrated higher fatigue scores (5.4 vs. 4, $p < 0.01$) and lower heart rate variability than those without this symptom, particularly during standing.

Conclusions: The results of this study confirm the high prevalence and pattern of abnormalities in cardiovascular reflex tests in MS patients as a whole and suggest that sympathetic nervous system activity may be particularly reduced in MS patients with fatigue.

P302

The natural course of multiple sclerosis: predictive value of lesion volume in T2-weighted brain MRI. A. Czaplinski, P. Freitag, E. W. Radü, L. Kappos, University of Basel (Basel, CH)

Background: Magnetic resonance imaging (MRI) is a powerful procedure for the diagnosis of multiple sclerosis (MS) and delineating its natural history. MRI-evident disease activity (new or enlarging lesions on the T2-weighted images and enhancing lesions on the short TR/short TE images) occurs more frequently than is detectable on clinical grounds.

Objective: To determine whether an increase in T2-lesion volume correlates with an increase in disability in "treatment naive" patients. We were also interested in the relation between initial and subsequent T2-lesion volume.

Patients/Methods: Our patients had to fulfil the following criteria: definite MS [Poser 1983], no immunosuppressive or immunomodulatory therapy other than steroids for relapses, at least two MRI separated by > 2 years and performed in a relapse free period, complete independent clinical follow-up including documentation of relapses and Expanded Disability Status Scale (EDSS)-assessment. Computer-assisted volume measurements were performed by a single observer blinded to the clinical data. We compared lesion volume in T2-weighted brain MRI at baseline with clinical progression in the EDSS and lesion volume at the end of follow-up.

Results: 51 patients were included. The mean follow-up was 3 years and the mean disease duration at baseline was 11 years. The mean EDSS at baseline was 3,5 and 4,0 at the end of follow-up. In our group the volume of T2-lesions at entry did not allow prediction of change in EDSS but we found that MRI lesion load at entry predicts lesion load at follow-up.

Conclusions: That we did not detect a relation between T2-lesion volume and clinical disease progression in the EDSS is probably related to our short follow-up period and to the group of MS patients we studied being relatively stable clinically. However, previous studies also demonstrated only poor or no correlation between abnormalities seen on brain MRI and clinical status [Filippi 1994, van Walderveen 1995, Truyen 1996, Molyneux 1998, Sailer 1999]. Several factors can contribute to this clinicopathologic paradox. One possible explanation for the lack of a closer relation between MRI activity and disability is that not all abnormalities seen on T2-weighted images are clinically significant. Inflammation, oedema, gliosis, demyelination and axonal loss are all represented as areas of high intensity on T2-weighted MR-images.

P303

Characterization of the astrocytic scar in chronic multiple sclerosis plaques. N. J. Gutowski, J. E. Holley, D. Gveric, J. Newcombe, Royal Devon and Exeter Hospital, Institute of Neurology (Exeter, London, UK)

Introduction: In chronic multiple sclerosis (MS) plaques the astrocyte scar inhibits tissue repair. Animal work has shown that the antigenic phenotype of the most abundant cell type in the brain, the astrocyte, varies depending on astrocyte type and location. Characterisation of human astrocytes in MS tissue may identify markers of scarring seen in chronic lesions.

Methods: Astrocytic phenotype was investigated in sub-ventricular white matter by immunocytochemistry and supported by Western blotting. Snap-frozen tissue from normal controls (n = 4), MS normal appearing white matter (n = 5) and lesions [acute (n = 7), sub-acute (n = 7) and chronic (n = 13)] was studied. Western blots compared control white matter, normal appearing white matter and chronic plaques.

Results: As expected, glial fibrillary acidic protein, vimentin and tenascin-C and -R expression was elevated in areas of astrocytic scarring. There was also increased expression of nestin, embryonic neural cell adhesion molecule, epidermal growth factor receptor and nerve growth factor. Amongst the factors not increased was connective tissue growth factor which can be involved in wound repair.

Conclusion: The scar astrocyte phenotype in chronic MS lesions has been characterised by changes in expression of several proteins. Factors which may produce this phenotype can now be assessed. In addition, the role of proteins associated with development, growth factors and growth factor receptors in glial scar formation and tissue repair is the subject of further investigation.

P304

Serum beta–2 microglobulin in multiple sclerosis patients before and after interferon beta therapy. A. Sena, R. Pedrosa, V. Sena, M. Morais, R. Couderc, Hospital dos Capuchos (Lisbon, P)

Background – Interferon beta has been shown to induce the expression of beta 2 micro globulin (b2 mic). This biological effect could suggest the potential use of serum b2mic levels as a marker for monitoring interferon beta therapy in multiple sclerosis (MS) patients.

Aim – This work was intended to investigate the potential utility of measuring serum b2 mic levels as a marker of MS severity and clinical response to interferon beta therapy

Patients and Methods – The levels of b2 mic were measured in sera from 85 patients with relapsing-remitting or secondary progressive MS before and after 12 months of interferon beta therapy (n = 37 with Betaferon; n = 28 with Rebif; n = 20 with Avonex). The correlations of these levels with the clinical variables were investigated including the onset and duration of the disease, the expanded disability status scale (EDSS) score, the relapse rate, and the progression index (EDSS/Duration). b2 mic was determined by using an immunometric assay (DPC). The c2 and t-tests, an ANOVA and regression analysis were used.

Results – There was a slight non-significant increase of the mean b2 mic concentration after treatment (1.51 ± 0.36 vs. 1.75 ± 0.45 mg/L). There were no alterations in b2 mic levels related to the different interferon beta preparations and no significant correlations of these levels with the clinical variables.

Conclusion – Our results do not suggest that serum b2 mic levels could represent a useful marker for monitoring the clinical response to interferon beta therapy in MS patients.

P305
Multiple sclerosis in Kuwait: relationship of onset and clinical exacerbations to seasonal factors. Y. M. Ayad, A. Alshubaili, Ibn Sina Hospial (Safat, KWT)

Introduction: Multiple Sclerosis is a chronic inflammatory disease of the central nervous system.

Many studies and observations over the years demonstrated environmental influence on Multiple Sclerosis occurrence and clinical relapses together with genetic factors. The environmental effect is thought to be due to, though not definitely 'factors such as hours of sunshine, atmospheric temperature, pollution and possibly other factors.

Aim and methods: This study was done to evaluate the relationship between onset and exacerbations (relapses) of multiple sclerosis in Kuwait and seasons, hours of sunshine and atmospheric temperature

A total of 207 patients diagnosed as clinically definite MS in the period between January 1995 till end of December 2000 were included in the study. there were 78 males and 129 females.

The date of onset of the disease as well as subsequent relapses during this 6 years period were retrospectively studied from the hospital files of these patients. The number and date of the relapses were plotted against the month of the year, temperature, and hours of sunshine.The meteorological data was obtained from the National Kuwait Meteorological department which holds accurate weather records for the last 40 years for kuwait

Results: The total number of clinical events recorded was 371.The onset of MS and relapses had a clear seasonal pattern with more events in summer '182 out of 371 (45 %) and least during spring 67 out of 371 events (18 %) p value(< 0.001). In relation to the other two factors; the curve showed a steady increase in relapse rate with the increase in mean hours of sunshine except for the range of 6 to 8 hours were the curve plateaus (p value < o.o5) On the other hand, it was more or less a V shaped curve in relation to extreme atmospheric temperature with least clinical events in moderated temperature ranges between 20 to 30 C.

Conclusion: In Kuwait, the onset and relapses of Ms show an uneven frequency across the seasons with a stastitically significant highest incidence in summer and lowest in spring. Together there was also a statistically significant correlation of clinical events with hours of sunshine and positive correlation with both extremes of atmospheric temperature. Our study had clearly demonstrates an influence of environmental factors on MS onset and exacerbations, the mechanism of which is unclear.

P306
High dose interferon beta1-A tolerance. Paralen study. Prelimary results. M. Hernández, Hospital Universitario Nuestra Señora de la Cander for the PARALEN Study Group

Background: The higher clinical and Magnetic Resonance Image (MRI) efficacy of Interferon beta–1a three times per week (tiw) at the approved dose (44 mcg x3) on Relapsing-Remitting Multiple Sclerosis (RR-MS) has been described. However, it has not been tested yet if patients previously treated with beta interferon (IFN-beta) undergo similar tolerance when they are treated with this high dose Interferon beta–1a compared to those who are treated for the first time with such a dose.

Objective: We evaluate whether the IFN-beta–1a 44 mcg tiw dose-increasing schedule, shows equivalent tolerance and safety as the full dose starting schedule that can be administered to patients previously treated with beta interferon. Expanded Disability Status Scale (EDSS) has been evaluated too. Methods. An observational, comparative, prospective study has been designed in 38 centers. 191 patients have been already recruited, 54 of them have received an IFN-beta–1a 44 mcg tiw dose-increasing schedule (slow schedule, SSG) as they were interferon beta naïve patients. 137 patients have been treated with the full dose from the beginning (fast schedule, FSG) (132 mcg, tiw subcutaneous injections) as they were previously treated with other low dose IFN-beta. Tolerance, safety and EDSS data are evaluated before treatment, at 3, 6 and 12 months after the high dose IFN-beta–1a treatment has started. Data have been analysed by Pearson and Fisher association tests, Student t-test and the analysis of variance for repeated measures.

Results: There were no statistical difference in age and sex distribution between the two groups. Statistical significance was found in EDSS, p = 0.0006 (2.5 SSG vs 3.4 in FSG) and number of relapses in the previous 3 months, p = 0.011 (0.6 in SSG vs 0.9 in FSG). At 6 months, adverse reactions were described in 24 patients (44.4 %) of the SSG and in 53 patients (38.7 %) of the FSG, although only a 10 % and 11 % of them were considered severe in the SSG and FSG respectively, although only 5 dropouts were found. There were no statistical differences referred to adverse reactions between the two groups. The 6-month EDSS score decreased significantly in the SSG (p = 0.023). The decrease was close to reach statistical significance in a subgroup of patients previously treated with interferon-beta1b (p = 0.062).

Conclusions: Both high dose IFN-beta–1a 44 mcg tiw schedules show similar tolerance and safety, although a longer follow-up is needed to state final conclusions.

P307
The black hole in SPMS: longitudinal observations using magnetization transfer imaging. I. Redmond, C. Tench, L. Blumhardt, Queen's Medical Centre Nottingham (Nottingham, UK)

Hypointense lesions ("black holes") on T1-weighted magnetic resonance imaging (MRI) represent areas of focal tissue damage and are of particular importance in multiple sclerosis (MS). Total black hole volume estimates correlate more strongly with disability than T2 lesion volumes, thus partially resolving the "clinico-radiological paradox" and providing a potential surrogate marker of disability. Manual contouring of lesions involves a large error of reproducibility and the natural history of individual lesions remains unknown. The purpose of our study was firstly, to define black holes using magnetization transfer ratio (MTR) histograms and secondly, to delineate the natural history of individual lesions in secondary progressive MS (SPMS).

Methods. 12 patients with SPMS were imaged with T1-weighted spin-echo (T1-SE) and MTR; MTR was repeated at 12 and 24 months and the images co-registered with baseline. Lesions were identified on the baseline T1-SE and a region of interest (ROI) defined such that the whole of each lesion was encompassed by the ROI. Lesion volume was determined by the number of voxels within the ROI having MTR below a threshold value derived from normal controls. The volume of the lesions identified at baseline was then estimated at month 12 and 24 using the baseline ROI on the co-registered MTR images, thus the same ROI was used to estimate lesion volume at each timepoint.

Results. 172 lesions were identified at baseline, median volume 95mm3 (IQR 24 to 236mm3). 98/172 lesions (57 %) increased in volume to 103 mm3 (IQR 33 to 247mm3, p = 0.0006) at month 12 and to 152mm3 (IQR 76 to 348mm3, p < 0.0001) at month 24. 137/172 lesions (80 %) showed a volume increase compared to baseline at month 24. 3 lesions identified at baseline were undetectable at month 24.

Discussion. We used baseline ROIs on serially co-registered MTR images to study individual lesions longitudinally. Lesions were not redrawn and therefore, with accurate patient repositioning and co-registration, the coefficient of variation for our technique of serial lesion volume estimation was necessarily zero. We were able to define lesions using a quantitative MRI technique sensitive to tissue damage and demonstrate that in the majority of lesions such damage increased over the 2-year period.

P308
Enhanced interleukin 10 production by in vitro immunoglobulin in multiple sclerosis patients. D. Reske, S. Schoppe, H. F. Petereit, University of Cologne (Cologne, D)

Multiple Sclerosis is a chronic inflammatory disease with a predominance of T-helper type 1 cells. Therefore, pro-inflammatory cytokines are upregulated and the anti-inflammatory cytokines are reduced. As demonstrated previously, immunomodulatory drugs like immunoglobulins reduce the pro-inflammatory cytokine response in healthy controls. Here, we target the anti-inflammatory cytokine interleukin 10 and its response to immunoglobulin exposure in vitro. Therefore, we recruited 10 untreated MS patients in the stable phase of a relapsing-remitting course of the disease and 10 healthy volunteers as controls. We analysed the production of interleukin 10 in peripheral blood lymphocytes by flowcytometry. In vitro immunoglobulin increased the interleukin 10 production in lymphocytes in the patient group (p = 0.005). The effect was not MS specific since it was also seen in the control group of 10 healthy volunteers (p = 0.005). In summary, in vitro immunoglobulin increases the production of the anti-inflammatory cytokine interleukin 10 in blood lymphocytes of relapsing-remitting multiple sclerosis patients and controls, indicating immunomodulatory properties of immunoglobulin.

P309

The cortex metabolic alterations in multiple sclerosis (MS) patients – the role in pathophysiology of disease. A. Ilves, L. Prakhova, G. Kataeva, M. Roudas, N. Totolian, A. Petrov, I. Stoliarov, Institute of the Human Brain, State Medical University (St.Petersburg, RUS)

Introduction: MRI is the most powerful imaging technique in managing patients with MS. However, MRI show nonspecific abnormalities weakly correlated with clinical impairments and progression of disease. Positron emission tomography (PET) unlike MRI assesses real biochemical and physiological process in the cortex and subcortical brain structures in vivo. So this technique offer better characterisation of the pathophysiology of neurologic disability in MS.

Objective: to study the association between the regional cerebral metabolic rate of glucose (rCMRglu) and neurologic disability in MS.

Methods: 55 relapsing-remitting and secondary progressive MS patients and 13 healthy volunteers as control were studied with FDG-PET. All patients were assessed using the Expanded Disability Status Score (EDSS) and Functional Systems (FS) Score. RCMRglu differences were evaluated by Mann-Witney U-statistics, and the relationships between PET and clinical data – with Spearman's rank correlation coefficients.

Results: significant reduction of rCMRglu in patients' group was found in the frontal cortex (Brodmann areas 44,45,9,8) and supramarginal gyrus of the left hemisphere ($p < 0.01$) and relatively elevated metabolism in visual cortex bilaterally. Negative correlations between FS2 and glucose metabolism were found for the right and left cerebellar hemisphere ($r = -0.51$, $p < 0.01$). Positive correlation between EDSS and rCMRglu were found for the left inferior temporal gyrus and left putamen.

Conclusion: Our data support the contention that the metabolic alterations at the cortical level seem to play an important role in the pathophysiology of neurologic impairments in MS. So the measurement of cerebral metabolism in MS has the potential to be an objective marker for monitoring disease activity and to provide prognostic information.

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P310

Expression of chemokine receptor CXCR–3 on cerebrospinal fluid T-cells is related to active MRI lesion appearance in patients with relapsing-remitting multiple sclerosis. E. Sindern, T. Patzold, L. Ossege, J. P. Malin, Ruhr-University (Bochum, D)

Objective: The aim of this study was to investigate the relationship of chemokine CXCR–3 receptor expression on cerebrospinal fluid (CSF) T-cells and of IP–10 levels in the CSF to multiple sclerosis (MS) disease activity as defined by magnetic resonance imaging(MRI).

Background: Immunohistological studies of autopsy brain sections containing active MS lesions showed that interactions between CXCR–3 and its ligand IP–10 might mediate trafficking, retention and activation of T-cells in MS lesions.

Methods: Paired blood and CSF samples were collected from 21 consecutive relapsing-remitting MS (RRMS) patients undergoing diagnostic lumbar puncture short after Gadolinium (Gd)enhanced MRI examination. The expression of CXCR–3 receptor was studied on CD3+ T-cells in blood and CSF using flow cytometry. IP–10 was measured by an ELISA (R&D systems). 21 sex and age matched healthy volunteers served as controls for blood investigation.

Results: CXCR–3 expression was increased in the CSF compared to blood as reported recently by Sorensen et al.($p < 0{,}0001$). 12/21 RR-MS patients exhibited active Gd-enhancing lesions on MRI. They had higher CXCR–3 expression and higher levels of IP–10 in the CSF compared to patients without active lesions ($p < 0{,}05$). In the blood no changes were found.

Conclusion: These data further support in vivo a pathogenic role of CXCR–3 and its ligand IP–10 during active RRMS and suggest that these chemokines could represent a potential target for therapeutic interventions.

P311

The prevalence of depression in a community-based population with multiple sclerosis and its effect on patient rated scores of disease impact. C. McGuigan, A. McCarthy, M. Hutchinson, St. Vincents University Hospital (Dublin, IRL)

Objective: To identify the prevalence of depression in a community-based population with multiple sclerosis (MS) and assess its effect upon patient rated measures of disease impact.

Background: Depression is common in MS with a lifetime prevalence as high as 50 %. Affect is known to influence perception of general well being, however a recently reported patient rated measure of the physical impact of MS, the Multiple Sclerosis Impact Scale (MSIS–20), has not been analyzed for this effect.

Design/Methods: In an epidemiological study 125 patients with clinically definite or probable MS (Poser criteria) were identified in County Wexford, Ireland and 84 of these patients agreed to take part in the study. Demographic information was recorded. Kurtzke Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC) scores were assessed as well as Beck's Depression Inventory II (BDI-II), MSIS–20, Multiple Sclerosis Psychological Impact Scale (MSIS–9), London Handicap Scale (LHS) and Modified Social Support Survey (MSSS).

Results: Of the 84 patients, 73 completed all assessments. On the BDI-II, 21 (28.8 %) scored between 20–63 indicating moderate or severe depression and 52 (71.2 %) scored below 20 indicating minimal or mild depression. Both groups showed similar characteristics for age, level of education, marital status, age at onset of MS, years since onset of MS, disease course, relapse rate and treatment regimes including interferon therapy. No significant difference existed between the EDSS and MSFC scores for the two groups. The MSIS–20 score was significantly worse in the more depressed group: $t = 2.34$, $p = 0.022$. As expected the MSIS–9 average was also significantly worse in this group: $t = 3.15$, $p = < 0.001$. The more depressed individuals also rated poorer social support on the MSSS form, despite receiving more community support in comparison with their less depressed controls.

Conclusions: Depression, measured by BDI-II, significantly affects patients interpretation of the physical impact of MS as measured by the MSIS–20 whereas observer rated measures of physical impairment do not show such a relationship. Further longitudinal studies on the relationship between mood and the MSIS–20 are indicated.

P312

Multiple sclerosis disease impact: The relationship between observer and patient assessed impact. C. McGuigan, A. McCarthy, M. Hutchinson, St. Vincents University Hospital (Dublin, IRL)

Objective: To compare the results obtained from observer and patient rated measures of disease impact in a community-based population with multiple sclerosis (MS).

Background: In an attempt to produce a reliable scale, sensitive to change, for use in clinical trials and epidemiological studies on patients with MS many outcome measures have been developed. The more commonly recorded measures are the Kurtzke Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC). Both these scales are observer rated, not addressing the patient's views of the disease impact on their daily functioning. Therefore the Multiple Sclerosis Impact Scale (MSIS–20), a patient rated disease specific measure of the physical impact of MS has been developed as an alternative or additional outcome measure.

Design/Methods: A population of 125 patients with clinically probable or definite MS (Poser criteria) was identified during the course of an epidemiological study; 84 patients agreed to participate in the study. The EDSS and MSFC were assessed and the MSIS–20 and London Handicap Scale (LHS) satisfactorily completed by 70 patients.

Results: The study group of 70 patients had a mean age of 47.2 years; male to female ratio of 1:2.7; average age at onset of MS – 33.1 years. The mean scores (range) for each scale were as follows: EDSS 4.32 (0–9); MSFC –1.3 (–6.55 535–0.7739); MSIS–20 37.54 (0–85) and LHS 0.655 (0.359–1). As expected the EDSS scores correlated strongly with the MSFC scores: $r = 0.762$, $p = < 0.001$ ($r2 = 0.5807$). The MSIS–20 results correlated strongly with the patient rated LHS: $r = 0.825$, $p = < 0.001$ ($r2 = 0.6808$). A moderate correlation existed between the EDSS scores and the MSIS–20 scores: $r = 0.694$, $p < 0.001$ ($r2 = 0.4815$). A weaker but still significant correlation was demonstrated between the MSFC scores and the MSIS–20 results: $r = 0.568$, $p = < 0.001$ ($r2 = 0.323$). Both observer rated scales correlated less well with the non-disease specific LHS, with EDSS $r2 = 0.2805$ and with MSFC $r2 = 0.1949$.

Conclusions: The strong correlation of the MSIS–20 with the LHS indicates that the MSIS–20 is more useful in assessing the patient's perception of social impairment than burden of disease as measured by the MSFC and EDSS. Further longitudinal studies on the relationship between these measures are required.

P313

A null mutation in the ciliary neurotrophic factor (CNTF)-gene is not related to susceptibility and clinical characteristics in patients with multiple sclerosis (MS). V. Hoffmann, S. Schimrigk, D. Pöhlau, C. Lukas, K. Hellwig, N. Brune, M. Rieks, C. Hardt, Ruhr-University Bochum, Kamillus-Klinik Asbach, Medical School Hannover (Bochum, Asbach, Hannover, D)

Increasing evidence indicates that axonal degeneration and impaired remyelination may account for progressive disability in MS patients. CNTF takes part in survival, proliferation and maturation of neuronal cells. Additionally protection against tumour-necrosis-factor (TNF)-a induced cytotoxicity has been demonstrated. We therefore analysed the frequency of a CNTF null mutation in 349 MS with respect to their clinical presentation and in comparison to 434 healthy controls. Both groups had been HLA-DRB1*15 typed previously. The CNTF gene was amplified by polymerase chain reaction (PCR). The wildtype and mutant alleles were discriminated by Allele-Specific-Oligonucleotide (ASO) hybridization. Genotype frequencies of the CNTF mutation were similar in MS patients and controls (genotype 0101–74.8 % versus (vs) 71.7 %, 0102–22.3 % vs. 26.5 %, 0202–2.9 % vs 0.10.8 %). Similar genotype frequencies were obtained after stratification for the HLA-DRB1*15 allele. Additionally, no significant correlation of the CNTF genotype to age at onset, clinical course and disease severity was detected. We conclude that requirement of CNTF activity in myelogenesis and differentiation may be bypassed by a second ligand or functional redundancy of other neurotrophic factors.

P314

Situation of medical care of patients with multiple sclerosis in North-eastern Germany. T. Krüger, U. K. Zettl, M. Schulz, Clinic of Neurology, University of Rostock (Uckermunde, Rostock, D)

Until now the state of medical care, rehabilitative medical care and sociomedical care of multiple sclerosis (MS) patients in Germany has not been subject of a study. Aim of this study is to obtain a general view of this situation in north-eastern Germany. The study is based on a structured questionnaire containing 64 items in the following categories: epidemiological-medical, psychological and socio-medical. Included in the investigation are also services of support groups of the German Multiple Sclerosis Society.

Data of 128 questionnaires were retained for this study. Mean age of patients was 47.4 years (range 22 to 80 yrs). The 33 male patients were younger with a mean age of 43.1 years (range 27 to 68 yrs) than the enrolled 95 female patients having a mean age of 49.0 years (range 22 to 80 yrs). Mean age at onset was 30.4 years (range 10 to 60 yrs). The mean interval between onset and diagnosis was 4.6 years (range 0.1 to 28 yrs). Even though a majority of patients was informed about the nature of their illness in hospital (60.9 %) or by a neurologist (21.1 %), 48.4 % expressed total dissatisfaction with the information obtained. Patients predominantly felt desperate and were anxious after having been diagnosed with multiple sclerosis. However, 20 patients declared that they felt relieved.

Among 128 patients enrolled in the study 43 had primary relapsing/remitting MS, 62 secondary progressive and 21 primary progressive MS (2 no indication). 62.9 % of the patients with primary relapsing/remitting and secondary progressive disease received drugs preventing exacerbations or treatment according to an escalation schedule(Austrian-German-Swiss Multiple Sclerosis Therapy Consensus Group). 8 patients declared receiving permanent steroid therapy. The majority of drugs for causal treatment was initially prescribed at the hospital (75.8 %). However, 24.2 % of all patients declared that they initially received a causal oriented drug by their neurologist. After that, drugs preventing exacerbations (79.2 %) are mostly prescribed by general practitioners. An overall majority of patients (93.7 %) urgently suggests the establishment of special multiple sclerosis clinics. A mean interval of 4.5 months between visits at a special MS clinic is wanted.

P315

Cerebrospinal fluid isoelectrofocusing in a large cohort of multiple sclerosis and other neurological disease patients. A. Bourahoui, J. de Seze, J. Guttierez, B. Onraed, B. Hennache, D. Ferriby, T. Stojkovic, P. Vermersch, Chu H Mondor, CHRU (Creteil, Lille, F)

Background: The presence of oligoclonal immunoglobulin G bands restricted to CSF is one of the most consistent laboratory abnormalities for the diagnosis of multiple sclerosis (MS).

Aim of the study: To confirm the diagnostic value of isoelectrofocusing (IEF) in a large multiple sclerosis cohort and to evaluate the various neurological diseases likely to present the same profile.

Methods: The cerebrospinal fluid of 1000 patients with neurological diseases was studied by IEF. The affections without microbiological confirmation and/or not fulfilling the classically definite diagnostic criteria for the various neurological diagnoses were excluded. After a follow up of 2 to 36 months, 407 patients were diagnosed as MS and 593 patients as others neurological diseases.

Results: The best sensibility and specificity was obtained with 3 oligoclonal bands. 385 patients had oligoclonal bands including 335 with MS and 50 with other neurological disease. Our results showed a sensitivity of 82.5 % and a specificity of 91.5 %. The positive and negative predictive values were 87 % and 90 % respectively. Inflammatory and infectious disorders of the central nervous system represent the main affections associated with oligoclonal bands in particular Sjögren syndrome, HIV encephalitis and Lyme disease.

Conclusions: IEF of the CSF is a reliable method for the diagnosis of MS with both good sensitivity and specificity. CSF is therefore of particular interest after a first neurological event.

P316

Magnetic resonance imaging of the spinal cord in multiple sclerosis: a novel quantitative T1 relaxation time mapping approach. L. Vaithianathar, C. R. Tench, P. S. Morgan, C. S. Constantinescu, University of Nottingham (Nottingham, UK)

The cervical spinal cord is a common site of predilection in multiple sclerosis (MS). Pathology within this region is likely to contribute significantly to locomotor disability due to the concentration of pyramidal pathways. Previous studies have found a significant relationship between clinical disability and the development of cervical cord atrophy in MS, but not with cord T2 lesion load. We aimed to study cervical cord pathology, for the first time, using quantitative T1 relaxation time (T1) mapping, which shows histopathological specificity for tissue damage in cerebral lesions and normal appearing white matter.

Method: Cervical cord T1 was compared in 15 MS patients (8 relapsing-remitting (RR), 7 secondary progressive (SP)) and 6 healthy controls, and related to normalised upper cervical cord area (UCCa), cerebral white matter T1, cerebral T2 lesion load and disability measures including the Expanded Disability Status Scale (EDSS), ambulation index (AI) and timed 25-foot walk. T1 maps of the brain and cervical cord were acquired using a high-resolution, 3-dimensional fast low-angle shot sequence. Dual-echo sequences were also performed.

Results: Median cervical cord T1, cerebral white matter T1 and UCCa were significantly different in MS patients compared to controls ($p = 0.0001$, $p = 0.008$, $p = 0.045$ respectively). On subgroup analysis, median T1 in the cervical cord was significantly greater in both the RR ($p = 0.006$) and SP groups ($p = < 0.0001$) than controls, and in SP vs. RR patients ($p = 0.002$). UCCa was smaller in the SP vs. RR ($p = 0.02$) and control groups ($p = 0.03$), but not between RR patients and controls. Median cervical cord T1 correlated significantly with cerebral white matter T1 ($r = 0.7$, $p = 0.0046$), UCCa ($r = -0.87$, $p < 0.0001$), but not cerebral T2 lesion load or disease duration. Both median cervical cord T1 and UCCa correlated significantly with the EDSS ($r = 0.55$, $p = 0.03$; $r = -0.54$, $p = 0.04$ respectively), AI ($r = 0.77$, $p = 0.001$; $r = -0.60$, $p = 0.02$ respectively) and timed 25-foot walk ($r = 0.56$, $p = 0.03$; $r = -0.55$, $p = 0.04$). Cerebral white matter T1 did not correlate with disability measures or UCCa.

Conclusion: Cervical cord T1 mapping detects pathology in early MS patients and distinguishes between clinical phenotypes. It is also a sensitive surrogate marker of clinical disability. The relationship of cervical cord T1 to cerebral white matter T1 suggests that cord pathology maybe influenced by tissue damage upstream, possibly through wallerian degeneration.

P317

A genome wide linkage disequilibrium screen in Scandinavian multiple sclerosis patients shows association to chromosome regions at 1q (D1S1601) and 11q (D11S1986). H. F. Harbo, P. Datta, A. Spurkland, L. P. Ryder, S. Sawcer, E. G. Celius, H. Modin, E. Akesson, M. Sandberg-Wollheim, K.-M. Myhr, O. Andersen, J. Hillert, P. Soelberg Soerensen, A. Svejgaard, A. Compston, F. Vartdal, A. Oturai, The National Hospital, Copenhagen University Hospital, Addenbrooke's Hospital, Ulleval University Hospital, Huddinge University Hospital, Lund University Hospital, Haukeland Hospital, Gothenburg University Hospital, Addenbrookes Hospital (Oslo, N; Copenhagen, DK; Cambridge, UK; Huddinge, Lund, S; Bergen, N; Gothenburg, S)

Objective: This study attempts to identify gene regions encompassing putative susceptibility genes in multiple sclerosis (MS) in the genetically homogenous Scandinavian population.

Materials and methods: Linkage disequilibrium mapping of the genome was performed by analysing two pools of DNA from MS patients (n = 199 and n = 201) and two pools from healthy controls (both n = 200). These pools which contain equal amounts of DNA from each individual were analysed in two separate screens using the same 6000 microsatellite markers evenly spaced throughout the genome. Differences in microsatellite allele image patterns between one MS pool and one control pool were identified in each screen. Furthermore, data from both screens (i. e. from 400 patients and 400 controls) were analysed together. A few selected markers which displayed significant deviations were reanalysed in both sets of pools.

Results: A total of 4212 markers were successfully analysed, when data from both screens were analysed together. The HLA markers D6S2447 and D6S2444 are among the markers displaying association in this analysis. Fourteen markers appeared to be significantly associated with MS in both screens when analysed separately. Among these the D1S1601 marker at 1q and the D11S1986 marker at 11q were confirmed to be associated with MS in a repeat experiment.

Conclusion: Two novel genetic regions (1q and 11q) which seem to contribute to the genetic susceptibility to MS were identified. More susceptibility gene regions are expected to be identified when this study is included in a European meta-analysis in the Genetic Analysis of Multiple sclerosis in EuropeanS study (GAMES).

P318

Expression and function of toll receptors on human glial cells. A. Jurewicz, M. Matysiak, K. Selmaj, Medical Acdemy of Lodz (Lodz, PL)

Objective: To assess expression and function of Toll receptors (TLRs) on human oligodendrocytes (hOLs) and microglia (Mi).

Background: Toll receptors are recently characterized class of "patern recognition receptors" (PRRs) involved in response to lipopolysaccharid (LPS), other non-protein bacterial antigens and CpG palindrome DNA sequences. TLRs have been shown to be critically involved in induction of innate immune responses and development. Their stimulation leads to increased release of proinflammatory cytokine or generation of apoptotic signal. The intracellular signaling events following TLRs activation are largely unknown but involve adaptor molecule MyD88, IRAK and Tollip. Expression of TLR in CNS might contribute to enhancement of local inflammation and immune mediated injury of CNS cells.

Methods: The expression of TLR 1,2,3,4 and 5 was assessed on hOLs, hMi and mononcytes (Mo) by immunocytochemistry (IH) and Western blot (WB). hOLs and hMi culture were prepared from brain specimen obtained during neurosurgical procedures. For IH cells were slightly fixed with acetone and stained with polyclonal anti-TLRs antibodies followed by ABC technique. For WB cells were lysed, subjected to electrophoresis and immunoblotting with the same anti-TLRs antibodies. TLRs expression was assessed in non-stimulated and IFN?, TNFa, GM-CSF and IL–4-stimulated cells. LPS-induced hOLs death was assessed by annexinV-FITC and PI staining and flow cytometry analysis and LPS-induced cytokine production by Mi was assessed by ELISA assay. MyD88 expression was assessed by WB.

Results: hOLs expressed TLR1 and 2 whereas hMi expressed TLR1,2,4. Low level of TLR3 expression on hMi was detected by IH. Cytokines, IFNg and TNFa, did not influence TLR expression on hOLs whereas TNFa significantly enhanced TLRs expression on hMi. Human monocytes expressed, as expected, TLR1,2,4 and 5. The presence of TLR3 on hMi might be of revelance to potency of these cells to develop into dendritic cells. MyD88, the major adaptor molecule in TLR signaling has been detected in hOLs, hMi and Mo. LPS induced hOLs death after 24 hours of exposure.

Conclusions: TLRs are expressed on hOLs and h Mi. TNFa enhances expression of TLRs on hMi. LPS induces hOLs death which is probably mediated by TLRs. TLRs expression on glial cells might contribute to generation of immune responses in autoimmune conditions and recognition of non-protein antigens.

P319

MTR discloses subtle changes in the normal-appearing tissue from relatives of patients with MS. M. Siger-Zajdel, M. Filippi, K. Selmaj, Medical Academy of Lodz, University Ospedale San Raffaele (Lodz, PL; Milan, I)

Background: Relatives of patients with MS have a higher risk of developing MS than the general population. MRI can show asymptomatic focal white matter lesion in relatives of patients with familial MS, which are undistinguishable from those of the affected siblings.

We performed this study to quantify and compare, using magnetization transfer (MTR) histogram, the extent of normal- appering brain tissue (NABT) damage in asymptomatic first-degree relatives of patients with familial and sporadic MS.

Patients and Methods: We studied 15 first-degree asymptomatic relatives of patients with familial MS, 15 first-degree asymptomatic relatives of sporadic MS, 15 MS patients with familial MS, 15 MS patients with sporadic MS and 15 healthy volunteers. In all participants conventional (dual- spin echo, repetition time [TR]= 4.5000ms, echo time [TE]= 22/90 ms, 25 slices with slice thickness = 3mm, interslice gap = 0.5mm, matrix size = 190x256 and field of view [FOV]= 250x250 mm) and 2D gradient-echo (GE) (TR = 800 ms, TE = 10ms, 25 thickness = 3mm, interslice gap = 0.5 mm, matrix size = 192x256 and FOV = 250x250) with and without saturation pulse were performed. In postprocessing step in NABT-histogram were obtained and for each histogram the following parameters were estimated: the average MTR, the relative peak height and the peak position.

Results: NABT MTR histogram-derived metrics from patients with MS were all significantly lower than the corresponding quantities from healthy volunteers. Compared to their relatives, MS patients also had significantly lower mean NABT-MTR, whereas a significance trend was found for MTR histogram peak position. The MTR histogram peak height from relatives of MS patients was significantly lower than that from healthy volunteers. MTR histogram peak height from asymptomatic relatives of patients with familial ($p = 0.01$) and sporadic ($p = 0.001$) MS were both lower than the corresponding quantities from the controls. When compared to the corresponding group of MS patients, only the mean NABT MTR from asymptomatic relatives of patients with familial MS showed a significance trend ($p = 0.02$), whereas all the other NABT-MTR histogram-derived metrics did not differ significantly.

Conclusion:This study suggests a reduction of truly normal NABT in asymptomatic relatives of patients with MS

Muscle disorders

P320

Primary myoadenylate deaminase deficiency with severe muscle weakness and atrophy: novel phenotype caused by the C34T mutation in the AMPD1 gene. M. Castro del Rio, M. Seijo-Martinez, M. Mouriño Sestelo, J. Arenas, C. Navarro, M. Puig-Saez, Complexo Hospitalario de Pontevedra, Complejo Hospitalario de Pontevedra, Hospital 12 de Octubre, Hospital do Meixoeiro, Complexo Hospitalario Pontevedra (Pontevedra, Madrid, Vigo, E)

Introduction: Myoadenylate deaminase (MAD) is an enzyme of the purine nucleotide cycle that converts AMP into inosine monophosphate and ammonia during muscle exercise. MAD deficiency (MADD) is a common, heterogeneous, and usually benign, metabolic myopathy that usually is asymptomatic or may manifest variable exertional fatigue or myalgias. Primary MADD, in the Western population, is usually caused by a nonsense C34T mutation in the second exon of the AMPD1 gene. Secondary MADD is found in association with other neuromuscular diseases, especially in advanced stages. There is a recent publication of a patient with primary MADD and compound heterozygous missense mutations in the AMPD1 gene, presenting with muscle weakness and atrophy. We report the first patient with primary MADD manifesting progressive and severe muscle weakness and atrophy, harbouring a homozygous C34T mutation in the AMPD1 gene.

Material and methods: Case report.

Results: A 47 year-old patient, with chronic effort-induced myalgias, presented an 8-year history of progressive weakness of upper arms and shoulder girdle muscles. His parents were non-consanguineous, and family history was negative. Severe weakness and muscle atrophy affected biceps, triceps, forearm, and less in shoulder girdle, and hamstring muscles. Muscle-CT scan showed atrophy and fat substitution of paravertebral, arms, posterior thigh, and medial and posterior compartment muscles of lower limbs. Serum creatine kinase level were elevated normal x10. The ischemic lactate-ammonia test showed a normal increase in lactate, without increase in the ammonia level. Electromyographic studies manifested a myopathic pattern in proximal muscles. A muscle biopsy showed scattered ragged-red fibers, with other non-specific pathologic findings. Immunohistochemical staining showed MADD. Respiratory chain studies were normal. DNA analysis confirmed a C34T mutation (homozygous) in the AMPD1 gene.

Conclusion: We present a patient with primary MADD and a C34T mutation, presenting with severe muscle weakness and atrophy. This phenotype has not been previously described. The clinical spectrum of MADD deficiency may be wider than presently assumed.

P321

Polymyositis: a disease entity disputed. I. M. Bronner, M. F. G. van der Meulen, J. E. Hoogendijk, H. Burger, W. J. van Venrooij, A. E. Voskuyl, H. J. Dinant, W. H. J. P. Linssen, J. H. J. Wokke, M. de Visser, Sint Lucas Andreas Hospital, University Medical Center Utrecht, University of Nijmegen, Free University Hospital Amsterdam, University Medical Center Amsterdam (Amsterdam, Utrecht, Nijmegen, NL)

Objective: According to the Bohan and Peter criteria (1975), dermatomyositis (DM) is differentiated from polymyositis (PM) only by typical skin changes. More recent criteria also include the histopathological characteristics enabling the distinction between PM and DM, and the differentiation of sporadic inclusion body myositis (s-IBM) from PM. However, the Bohan and Peter criteria are still widely used. We investigated the applicability of broadly accepted diagnostic features for diagnosing PM and DM.

Methods: Inclusion criteria: 1) a previous diagnosis of myositis; 2)subacute onset of symmetrical, proximal muscle weakness; 3) presentation between 1977 and 1998 in one of 3 third-line referral centres. Exclusion criteria: 1) s-IBM, muscular dystrophies, rhabdomyolysis, and exposure to myotoxic drugs; 2) clinical data or muscle biopsy not available for revision. We reviewed the clinical charts of all included patients (n = 165) and we re-examined 111 patients (67 %)

Results: The diagnoses at presentation according to pre-defined criteria were as follows: PM 9(5 %), DM 54(33 %), unclassifiable myositis 38(23 %), possible myositis 29(18 %), myositis with CTD 32(19 %), myositis with malignancy 3(2 %). At follow-up, 5 of the 9 PM patients had typical s-IBM features. Although the remaining 4 patients (2 %) fulfilled criteria for PM, none of them complied with the assumed typical picture of this disease.

Conclusions: 1) PM must be disputed as a specific disease entity. 2) At presentation, almost half the patients can not be diagnosed as PM, DM, myositis with CTD or myositis with malignancy applying generally accepted diagnostic features.

P322

A rare paternal transmission of congenital myotonic dystrophy having a lower Ctg repeat size. D. Tessarolo, M. Liguori, R. Luna, E. Zachara, C. Blundo, S.Camillo Hospital (Rome, I)

Aim: The congenital form of myotonic dystrophy is reported to be almost exclusively maternally transmitted disease. Paternally transmission is rare, but possible. Myotonic dystrophy (DM) paternally transmitted shows a more benign course and onset later than birth. In many reports the affected by congenital DM of paternal inheritance are young adults mentally retarded and with muscular weakness. Our young adult congenital DM with only 500 CTG repeats was inherited by a father with classical form of DM. This is the first report of congenital DM having the lower CTG repeat until described (Redman et al.,1993).

Clinical Findings: The patient affected by congenital DM is a male young adult of 24 years old. His parents referred about a neonatal suffering, feeding difficulties, walking at 24 months. Characteristic facial appearance such as high forehead and carp mouth were noted until early childhood as mental retardation. Muscular weakness with atrophy of the extremities and myotonia were present. The patient was submitted to MRI of the brain (Philips Gyroscan NT 1.5 MR Unit on T1 and T2 weighted sequences), transthoracic echocardiography and neuropsychological evaluation. His father of 45 years old is affected by a classical DM with muscular weakness and atrophy, myotonia, cataracts, balding, facial diplegia and onset about 30 years old.

Results: MRI of the congenital DM showed enlarged ventricles and severe hypoplasia of corpus callosum as described in previous reports. Echocardiography was in accord with dilated cardiomyopathy. Neuropsychological evaluation was compatible with mild mental retardation.

Discussion: This is the first report of congenital DM with a lower CTG repeat until described. The clinical features (mental retardation and muscular weakness) and MRI findings (enlarged ventricles and severe hypoplasia of corpus callosum) are in accord with a congenital DM. The paternal transmission confirmed the relatively more benign course until young present life. The possibility of paternal transmission of congenital DM should be always considered when counselling DM patients and their families.

P323

A new mutation in the poly (A) binding protein 2 (PABP2) gene in a family with oculopharyngeal muscular dystrophy. H. Miura, T. Kubodera, H. Shimamura, T. Matsuoka, I. Nishino, I. Nonaka, K. Ishikawa, H. Mizusawa, Tokyo Medical University, National Institute Neurology and Psy, Tokyo Medical and Dental University (Inashiki, Ibaraki, Tokyo, JP)

Objective: To describe a new mutation in the poly (A) binding protein 2 (PABP2) gene found in a Japanese family with oculopharyngeal muscular dystrophy (OPMD).

Case report: The proband of this family, a 65-year-old man has been suffering from dysphagia and blepharoptosis from age of fifty. Neurological examination showed severe blepharoptosis, slight external ophthalmoplegia, and dysphagia. There were slight weakness in the proximal lower limbs and gait disturbance. CK was moderately increased, and EMG showed myogenic changes. Muscle biopsy showed a few fibers with rimmed vacuoles.

Methods: DNA was isolated from peripheral blood. The portion of exon 1 containing the GCG repeat in PABP2 gene was amplified by Polymerase chain reaction (PCR) method. The PCR products were cloned into plasmid vector, and the relevant insert of plasmids were sequenced.

Results: Molecular genetic analysis revealed an unusual GCA (GCG)3 insertion mutation followed by six GCG triplets in this patient. This type of variation was reported by Scacheri et al., and Schober et al.

Conclusions: The clinical phenotype in this case is similar to that of French-Canadian patients, however, a new insertion mutation in PABP2 gene was identified in this case.

P324

Adult polyglucosan body myopathy. A. Kaminska, C. Lamperti, A. Mickielewicz, A. Fidzianska, S. DiMauro, Medical University of Warsaw, Columbia University, Polish Academy of Sciences (Warsaw, PL; New York, USA)

Abnormal accumulation of polyglucosan deposits may occur in various tissues and organs or may be confined to a particular tissue such as skeletal muscle. Both in generalized and isolated myopathic form of the disease defects of glycogen branching enzyme or phosphofructokinase have been found in some patients. The aetiology of the syndrome still remains unexplained in a substantial proportion of cases.

We report on a sporadic late-onset case of progressive myopathy manifesting as a moderate weakness of proximal and distal leg muscles. EMG, nerve conduction velocity and somatosensory evoked potentials as well as ECG and echocardiography were normal. The muscle biopsy revealed vacuolar myopathy. The vacuoles contained basophilic strongly PAS-positive material which was only minimally digested by diastase and displayed myophosphorylase activity. Electron microscopy showed the vacuoles to contain filamentous material mixed with glycogen granules. The deposits were not membrane-bound and were often located adjacent to numerous mitochondria, some of which contained paracrystalline inclusions. Biochemical studies did not reveal any specific abnormality in muscle glycogen pathway enzymes.

The morphological hallmark of this myopathy is excessive vacuolar accumulation of granular and filamentous material corresponding to polyglucosan bodies. A biochemical study, however, excluded specific enzymatic defects known to cause the accumulation of polyglucosan bodies in muscle fibers. Thus, our patient represents the case of polyglucosan body myopathy in which a specific enzyme abnormality is not yet known.

P324

Alternative splicing of the dystrophin rod-domain in normal human tissues and in DMD/BMD skeletal muscle. M. Sironi, R. Cagliani, A. Bardoni, G. P. Comi, U. Pozzoli, N. Bresolin, IRCCS E. Medea, Associazione La Nostra Famiglia, IRCCS Ospedale Maggiore Policlinico (Bosisio Parini, Milan, I)

The DMD gene, located on Xp21, codes for dystrophin, a rod-shaped 427 kDa protein. Alternative splicing provides a mean for dystrophin diversification: the 3' region of the gene undergoes alternative splicing resulting in tissue-specific transcripts, while 12 patterns of alternative splicing have been described in the 5' region of the gene in skeletal muscle.

Mutations in the dystrophin gene are responsible for either Duchenne or Becker muscular dystrophy (DMD and BMD). A major hot spot for DMD/BMD deletions has been identified around exons 45–55. We analysed splicing patterns in the gene region encompassing exons 17 through 58. Human skeletal muscle, heart and brain tissues from healthy subjects were analysed. A total of 16 alternative transcripts were identified, the majority of them being present in the three tissues. Yet, tissue-specific splice vari-

ants were also detected. Alternative products displayed a great variability with respect to the number of missing exons with some of them skipping up to 13 exons. The widest range of different dystrophin gene products was detected in brain, maybe reflecting the higher complexity of this tissue. Transcript analysis was extended to 14 muscle biopsies of DMD/BMD deleted patients. When possible, two or three patients carrying the same deletion were analysed. Surprisingly, in some instances, short deletions were found to abolish splicing variants that longer and overlapping deletions did not. These data suggest that secondary structure formation on dystrophin pre-mRNAs plays no or little role in directing alternative splicing events. In two cases patients carrying the same exonic deletions displayed different splicing behaviours with respect to the loss or preservation of alternative transcripts. Most interestingly, we carried out transcript analysis on autoptic tissues from a DMD patient with a 45–52 exon deletion: a different pattern of alternative transcript was detectable in muscle, heart and brain.

Our data indicate that alternative splicing events are differently regulated in different organs and that equal deletions can determine diverse splicing behaviours in different patient or even in different tissues of the same individual. In this view, allelic differences and tissue-specificity of splicing factors should be regarded as possible determinants of disease expression and differential organ involvement.

P326

Chronic progressive external ophthalmoplegia – a case with uncommon course and cause of death. G. Lehrieder, H. Molitor, W. Roggendorf, Juliusspital, University/Neuropathologie (Wurzburg, D)

Chronic progressive external ophthalmoplegia (CPEO), the most frequent manifestation of mitochondrial myopathies, is a disorder characterized by slowly progressive paralysis of the extraocular muscles. Patients usually experience bilateral, symmetrical, progressive ptosis, followed by ophthalmoparesis months to years later. It may occur in the absence of any other clinical sign, but usually it is associated with skeletal muscle weakness.

We present the case of a 70-year-old woman, who was admitted to the internal department for treatment of pneumonia and cardiac decompensation. History revealed that at the age of 20 – after the birth of her daughter – she experienced progressive bilateral ptosis and oculomotor disturbances. Tarsorraphy did not have a persistant success. No further neurological symptoms occurred in the following 50 years except for a mild, not disabling muscle weakness and exercise intolerance. Family history was negative, so clinical features indicated sporadic chronic progressive external ophthalmoplegia (CPEO). Chest X-ray showed a bilateral symmetrical diaphragmatic eventration. Laboratory results were normal except a mild lactic-acid-dehydrogenase elevation. Lactic and pyruvic acid were normal, no abnormalities in cerebrospinal fluid were found. Myasthenia gravis-testing and acetylcholine receptor antibody testing were negative. Tensilone was given without any effect. Imaging studies of the brain were normal. Electromyography showed myogenic and neurogenic changes. Muscle biopsy detected "ragged red fibers" and proved diagnosis of mitochondrial myopathy. Further ultrastructural examination and electron microscopy showed large accumulations of mitochondria and numerous crystallin inclusions in mitochondria. There were no clinical signs for different kinds of mitochondrial encephalomyopathy, especially no retinal degeneration or heart block as expected in Kearns-Sayre-Syndrome. Six months after confirmation of the diagnosis of CPEO patient was readmitted due to recurrent pneumonia. Despite sufficient antibiotic therapy with disappearing pneumonic infiltrations and cardiac recompensation weaning from respirator-therapy was not possible and patient died from respiratory failure. We present clinical and neurophysiological findings, histological pictures and electron-micrographs. Molecular genetic analysis was not done. We discuss the patient's death as late progression of the mitochondrial myopathy with involvement of the respiratory muscles.

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The post-polio syndrome: experience from a tertiary neurology referral centre in Ireland. G. Gorman, O. Hardiman, Beaumont Hospital (Dublin, IRL)

Up to 5000 Irish people continue to experience the effects of the polio epidemics of the 1940s and 1950s. The sequelae of this disease are now recognised to be potentially progressive in nature, with a percentage originally affected beginning to experience new symptoms after 20–40 years. The development of these new symptoms has been termed post polio syndrome and include increased cold intolerance, fatigability, joint pain and in some instances progressive muscle weakness and wasting. The proportion of Irish patients who experience such symptoms is currently unknown. Our aim is to characterise the population of patients in Ireland who exhibit the late effects of polio.

Method: A database was established of patients attending the Neuromuscular clinic. All patients had been fully evaluated clinically and neurophysiologically. Analysis of 100 consecutive(n = 100; male:female = 39:61)medical records was performed. Details of age, gender, occupation, symptoms, age and weakness at onset, residual weakness, initial rehabilitation, use of callipers/mobility aids at initial diagnosis, surgery, current status and new onset of symptoms and concomitant disease were included.

Results: Of the 100 patients analysed 5 had been wrongly diagnosed at initial presentation. The correct diagnoses were transverse myelitis (3), and isolated mononeuropathies (2).The mean age of the poliomyelitis patient population is 53 ± 3 years. 55 % of those affected were between 0 to 5 years at the time of exposure to the virus. Notably 6 cases were linked to vaccination. 75 % had no recollection of the onset of symptoms. 15 % of patients required respiratory support during the acute illness. New symptoms reported included limb weakness (n = 38), fatigue (n = 40), increased cold sensitivity (n = 4), joint pain (n = 48), low back pain (n = 27),falls (n = 26), reduced exercise tolerance (n = 31),dysphagia (n = 4), respiratory symptoms (n = 5) and documented muscle weakness and wasting.

Conclusion: This preliminary analysis is likely to broadly reflect the overall population of patients who are experiencing late effects of polio and attend the Post-polio Clinic. The observation that 5 % of this cohort had been misdiagnosed at presentation underscores the necessity to fully investigate patients who give a history of childhood poliomyelitis. Furthermore, 18 % of those who described new symptoms had documented new weakness, suggesting that post polio spinal muscle atrophy is common in this selected population.

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Focal muscle involvement in polimyositis or focal myositis? C. Rodolico, A. Mazzeo, A. Toscano, M. Gaeta, A. Migliorato, C. Messina, G. Vita, Policlinico Universitario (Messina, I)

Focal myositis is a rare condition with a wide clinical spectrum. Affected patients may rarely develop a polymyositis. Response to steroid is dramatic. We describe three patients: a 18-year-old man with a focal inflammatory involvement of calf muscles, a 25-year-old woman with an orbital myositis and a 52-year-old woman with an isolated impairment of cervical paraspinal musculature. Standard laboratory tests, EMG, MRI were performed in all patients. MRI displayed diffuse increased signal involving muscles clinically affected. Two patients underwent muscle biopsy (in one of them, a clinically unaffected muscle was examined), with immunocytochemistry of inflammatory markers, which evidenced mononucleate cells infiltration, necrosis and myophagia. In all cases there was a favourable response to steroids. MRI findings well correlated with severity of both clinical and histological manifestations, providing an helpful noninvasive test for diagnosis and follow-up. Histological evidence of inflammation at clinically spared muscles suggests that focal myositis may represent a clinical manifestation of a diffuse polymyositis.

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Dysferlin expression pattern in human primary muscle cultures. S. Salani, S. Lucchiari, F. Fortunato, F. Locatelli, S. Corti, M. Crimi, N. Bresolin, G. Scarlato, G. P. Comi, Università degli Studi di Milano (Milan, I)

Dysferlin is a skeletal muscle protein whose deficiency causes distal and proximal forms of muscular dystrophy, recessively inherited, designated Miyoshi myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B), respectively. The protein product of Dysferlin gene is a novel molecule of 230 kD localised to the muscle fibre membrane. Despite the accumulation of knowledge about dysferlin role in muscle pathophysiology, the function of this protein is not defined yet. In order to better understand the expression of dysferlin during development, we examined by immunocytochemical, genetic and Western Blot analysis myoblasts and myotubes of human control muscle cultures, in the attempt to relate dysferlin pattern in vitro to well known developmental patterns of desmin, dystrophin and alfa-sarcoglycan. These studies showed that dysferlin is expressed at a very early stage of myoblast differentiation in human culture. Furthermore, genetic dissection performed on cultured cells and whole normal and pathological tissues revealed the presence of a splice-variant of dysferlin mRNA, resulting from perfect skipping of exon 17, which seemed to be developmentally regulated, since it was more expressed in myoblasts than in myotubes and re-expressed by human muscles affected by polymiositis, a human autoimmune disorder, and absent in normal

muscle tissue. These data suggest alternative splicing of exon 17 of the dysferlin gene is operating during myogenesis and that the acquisition of a mature cell phenotype results in a tighter control of dysferlin messenger RNA splicing.

Recently, dysferlin expression was investigated in peripheral blood mononuclear cells evidencing it only in CD14+ monocyte fraction. On the basis of these results, we analysed, with a simple, non quantitative PCR, the dysferlin mRNA in CD14+ cells for the presence of the alternative spliced isoform, revealing that both forms, the wild type and the shorter one, were expressed at the same intensity level. To further discern our findings about the additional transcript, we also tested human control bone marrow at different conditions. We evidenced in all samples both transcripts, raising in intensity from uncultured cells to cells cultured for 10 days. These data indicate that both in human muscle and bone marrow-derived cells the dysferlin gene undergoes to a complex pathway of expression, whose relationship with the clinical phenotypes remains to be investigated.

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A novel splice-site mutation in a LGMD–2B family causing activation of a cryptic site and total dysferlin absence. R. Cagliani, M. Sironi, A. Toscano, S. Lucchiari, F. Fortunato, A. Prelle, L. Tancredi, S. Salani, M. Sciacco, C. Zecca, G. Comi, N. Bresolin, IRCCS E. Medea, Associazione La Nostra Famiglia, Università degli Studi di Messina, IRCCS Ospedale Maggiore Policlinico (Bosisio Parini, Messina, Milan, I)

Dysferlin is the protein product of the DYSF gene, mapped at 2p31, which mutations cause limb-girdle muscular dystrophy type 2B (LGMD–2B) and Myoshi myopathy. The dysferlin gene is constituted of 55 exons and is translated as a 8.5 Kb major mRNA expressed strongly in skeletal muscle and heart. The protein product, with a molecular weight of 230 kDa, is supposed to be a vescicle-associated membrane protein involved in fusion of large vesicles and membrane docking. Up to date, less than 20 mutations have been described in the dysferlin gene. Here we present the case of two sisters affected by LGMD–2B carrying a new mutation in the gene.

The proband is a 36 year-old woman born from healthy first cousin parents. The 38 year-old sister is similarly affected. The proband presented a progressive weakness at the lower limbs with frequent falls since the age of 20 years. In the following years she also manifested upper limb girdle involvement. The neurological examination showed distal hypotrophy, muscle strength was decreased at the tibialis anterior, ileopsoas and glutei muscles, tendon reflexes were absent, anserine gait with bilateral foot drop. CK was constantly higher than 3,000 U/l. Dystrophic changes were present at the muscle biopsy. Dysferlin was absent both by immunohistochemistry and Western blot analysis. The other tested muscle proteins were normal, including calpain 3.

The patients were revealed to carry a 3 bp deletion involving exon 45 donor splice-site. The mutation was present in a homozygous status, consistent with the notion that the alleles are identical by descent. Transcript analysis was performed in order to determine the effect of the mutation on mRNA processing: the only detectable product derived from activation of a cryptic splice-site located in exon 45. The aberrant splicing event determines a shift in the reading frame and thus the transcript is predicted to be translated into a truncated dysferlin protein.

Here we have report a novel mutation in the dysferlin gene causing a somewhat atypical phenotype in that both limb-girdle and distal muscle compartments were affected.

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Correlations Between Cardiac Involvement And Ctg Repeat Amplification In Myotonic Dystrophy Tipe 1. V. Rakocevic-Stojanovic, D. Savic, S. Pavlovic, D. Lavrnic, M. Grujic, S. Romac, S. Apostolski, Institute of Neurology, Institute of Cardiology, Biological Faculty (Belgrade, YU)

Objective: Myotonic dystrophy type 1 (DM1) is a multisystemic disease caused by the expansion of a CTG repeat, located in the 3' untranslated region of dystrophia myotonica protein kinase (DMPK) gene. The number of CTG repeats broadly correlates with the overall severity of the disease. However, the connection between the number of CTG repeats and the presence and severity of cardiac abnormalities is still unclear. In this study the number of CTG repeats detected in blood cells of 50 DM1 subjects was correlated with the presence and severity of cardiac disorders.

Methods: Fifty DM1 patients (29 males and 21 females), age between 19–51 years, (meanSD: 3615) were studied. All patients underwent 12 lead standard electrocardiogram (ECG), M-mode and two-dimensional echocardiogram (Echo) and His-bundle electrogram (hissography). All subjects were studied by both polymerase chain reaction (PCR) and Southern blot analyses. DNA was extracted from nucleate blood cells using a standard phenol chloroform protocol. We classified all the patients in three groups according to the CTG repeat number. Nine patients had a CTG repeat number </ = 500 and belonged to group A, 21 patients had > 500 and < 1000 CTG repeats (group B) while 20 patients with a CTG repeat number >/ = 1000 belonged to group C.

Results: The CTG repeat number ranged from a minimum of 63 to a maximum of 1663. Cardiological abnormalities were detected in 84 % of our patients. ECG abnormalities were present in 78 % (group A), 48 % (group B) and in 55 % (group C). The most prevalent ECG changes were sinus bradycardia and low P wave amplitude. Echo abnormalities were found in 55 % (group A), 38 % (group B) and in 40 % (group C). The most common Echo changes were mitral valve prolapse and septal fibrosis. Hissography detected cardiac conduction defects in 78 % (group A), 71 % (groupB) and 75 % (group C) of our patients.

Conclusion: In 50 investigated DM1 patients we found a significant correlation between the number of CTG repeats, age of onset and muscular disability. However, the presence or severity of cardiac abnormalities were not related to the number of CTG repeats. These findings suggest that mechanisms leading to heart disorder may be different from those responsible for neuromuscular disturbances in DM1 patients.

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The effectiveness of home exercise program in myophatic patients(1 year follow up). S. Aksu, M. Kilinç, E. Tan, Hacettepe University (Ankara, TR)

This study was made to investigate the functional level and muscle strength in 1 year followed up patients. 9 myophatic patients; 3 man, 6 woman, ages ranged from 16 to 52 (mean 26.5) were included to the study. 3 of this patients was limb girdle muscular dystrophy, 2 was inclusion body myositis,1 herediter myophaty, 1 charcho marie tooth, 1 becker muscular dystophy and 1 fascio scapulo humeral muscular dystophy, and duration of the illness is 2–16 years. Home exercise program including breathe exercise,upper and lower extremity active exercise(theraband, active joint motion), streching exercise, strenght exercise and functional mobility training was recommended to the patients. Home exercises were thought both to the patient and his/her family and also standart exercise form was given to the patients. As inviting in every 6 montht muscle strenght and functional assessment were done. To shoulder flexors, shoulder abductors, elbow flexors, elbow extansors, hip flexors, hip extansors, knee flexors, knee extansors and dorsi flexors muscle strenght evaluation was done manually in Dr. Lovett's recommended test position according to 0–5 point degree system. Rolling, siting, crawl position, kneeling and half kneeling, stair, climbing and walking activities were assessed according to 0–3 points degree system.(0: unable, 1: Dependent, person or device, 2: Independence but supervision is needed, 3: Completely independence). As a result there was not significant increase between muscle strenght and functional assessment in the evaluation made in 6 and 12 th months ($p > 0,5$). In conclusion, we have found that home exercise program is sufficient and necessary in myophatic patients to maintain the functional level.

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Inhibitory interhemispheric visuo-visual interaction: fMRI and psychophysics. E. Marx, T. Stephan, S. Bense, M. Dieterich, T. Brandt, Center of Sensorimotor Research (Munich, Mainz, D)

Objective: In an earlier fMRI study (Brandt et al. Neuroreport 2000; 11: 2803–9) we showed that coherent motion stimulation of the right or left visual hemifield elicits a significant visuo-visual interhemispheric interaction: a) activation of motion-sensitive area MT/V5 and b) deactivation of the primary visual cortex, both contralateral to the stimulated hemisphere. The latter inhibitory transcallosal visuo-visual interaction would theoretically allow attention to be shifted between the two hemispheres (two visual hemifields) by raising the perceptual threshold in the visual hemifield with the currently less relevant input. A psychophysical study was therefore conducted on object motion perception with and without motion pattern stimulation of the contralateral hemifield.

Methods: Object motion perception was tested in 14 healthy volunteers (8 females, 6 males; ages 20–52 yr; mean age, 31.6 yr). Volunteers sat on a chair with a head rest in darkness while fixating a stationary target straight ahead (red LED, diameter 0.6°). A second target, a projected white dot (diameter 0.9°), was presented throughout the experiments in the right or left hemifield located 10°horizontally beyond the vertical meridian. The eccentric dot started to move with random latencies at a constant velocity of

0.4°/s in the horizontal or vertical direction at random. In a second condition, an additional coherent motion pattern was projected on the contralateral hemifield. Horizontal eye movements were recorded by electronystagmography to monitor fixation of the stationary target.

Results: Mean detection times for horizontal target motion were 0,499 ± 0,188s without concurrent visual motion stimulation and 0,609 ± 0,218s with concurrent visual motion stimulation. Mean detection times for vertical target motion were 0,527 ± 0,188s without concurrent visual motion stimulation and 0,722 ± 0,336s with concurrent visual motion stimulation. Analysis of the data by ANOVA revealed a significant increase ($p = 0.015$) in detection times during concurrent pattern stimulation in the hemifield contralateral to target motion.

Conclusion: Object motion perception in one visual hemifield was impaired during motion pattern stimulation of the contralateral hemifield. Thus the inhibitory interhemispheric visuo-visual interaction found in fMRI is associated with a decrement of visual perception.

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Changes in cerebellar activation pattern during two successive runs of saccades. A. Nolte, T. Stephan, A. Mascolo, T. A. Yousry, S. Bense, T. Brandt, M. Dieterich, Center for Sensorimotor Research, Queens Square (Munich, D; Pavia, I; London, UK; Mainz, D)

Objective: The differential effects of two successive runs of familiar and identical visually guided to-and-fro saccades on the cerebellar activation pattern were compared in 12 healthy volunteers.

Materials and Methods: Subjects were scanned under two visual conditions using MRI-compatible video glasses. Fixation of a stationary target straight ahead (diameter 1.2°) served as the rest condition and was compared to visually guided voluntary saccades with an amplitude of 24°at a frequency of 1Hz. Functional images were acquired on a standard clinical scanner (Siemens Vision, Erlangen, Germany) at 1.5 Tesla using echo planar imaging (EPI, TE = 60 ms, voxel size 3.75 x 3.75 x 4 mm3, matrix 64 x 64, interscan interval 2.5 s). The images were realigned, spatially normalized and smoothed prior to statistical group and single subject analysis using SPM99 implemented in Matlab.

Results: Group analysis showed significant activations during both runs in the cerebellar hemispheres (simple lobule, inferior semilunar lobule, superior semilunar lobule) and the cerebellar vermis (uvula, tuber, folium, declive).

Direct statistical comparison of the activation patterns of run 1 and run 2 showed a significant decrease of BOLD signal in the second run in the biventer lobule, inferior semilunar lobule, and simple lobule of the left cerebellar hemisphere, superior semilunar lobule bilaterally, as well as in the uvula, the left tonsil, the pons, and in the substantia nigra.

Conclusion: Group and single subject analyses revealed a constant activation of the paramedian cerebellar vermis (uvula, tonsils, tuber, folium/declive), which reflects constant ocular motor activity in both runs. The significant decrease in activation of the cerebellar hemispheres found in the second run is best explained by either a decrease in attention or the effects of motor optimisation and learning. These significant, systematic changes of the cerebellar activation pattern in two successive runs were not expected, because the ocular motor task was simple, familiar, and highly automated. Our findings indicate that similar effects may bias other cerebellar activation studies, in which sensorimotor tasks are repeated in a single session.

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New candidate genes for stem cells. L. Cova, A. Ratti, J. Sassone, I. Fogh, R. Fantozzi, L. Mantegna, V. Silani, Univ. of Med. School, IRCCS Osp. Maggiore, Univ.of Milan,IRCCS Ist. Auxologico (Milan, I)

Stem cells are multipotent cells able to divide indefinitely and/or to differentiate into many cell types, through the generation of progenitors cells with a limited proliferative capability. They can be found in several tissues of the body as an expandable reserve, which may be activated and differentiated into the required cell type. In particular stem cells could be used for the reconstitution of damaged cell populations selectively lost in neurodegenerative disorders such as Amyotrophic Lateral Sclerosis, Parkinson and Alzheimer's diseases. The existence of common genetic programs among different tissue-specific stem cells and their wide plasticity "in vivo" and "in vitro" have enhanced the prospects of regenerating organs with adult stem cells of different origin. Unfortunately, their selection is difficult since they lack of specific markers and their gene expression profile is still far to be understood. Molecular mechanisms of stem cell behaviour probably relay on the existence of unique gene patterns.

We analyzed the expression of some genes suspected to play a pivotal role in stem cell proliferation: the murine acetyltransferase Querkopf, its human counterpart MORF, Limd1 and other brain-derived Expressed Sequence Tags (EST). Acetyltransferases are involved in transcriptional activation of genes and in maintaining chromatin accessible through acetylation of histones. Human LIMD1 gene seems to be involved in tumourigenesis, a process which shares common features with stem cell proliferation. Gene expression was studied by Northern blot and RT-PCR assays in several tissues such as brain, spinal cord, liver, heart, muscle, kidney and lung. In addition we analyzed their expression in stem cells of different lineages (neural, mesenchymal and hematopoietic) and in a time-course assay during the differentiation from neural stem into specialized cell phenotypes, such as astrocytes, neurons and oligodendrocytes. Three mouse ESTs, differentially expressed in neural stem cells, were further characterized and the full-length transcripts were isolated by cDNA library screening. We found relevant differences in the expression patterns of stem cells in comparison with completely differentiated cells /tissues. Our data may help in the comprehension of the complex and precisely regulated molecular mechanisms which underlay the stem/progenitor cell proliferation and plasticity.

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The response of brain endothelial cells to H2O2-induced apoptosis. K. Voigt, R. Lyck, J. Kraus, P. Oschmann, B. Engelhardt, University Hospital Giessen, MPI for Physiological Research (Giessen, Bad Nauheim, D)

Background: The induction of apoptosis in brain endothelial cells has been suggested as a potential mechanism for increased molecular permeability of the blood-brain barrier. It may be at least partially involved in neurologic disease like the occurrence of immunosuppressant-induced encephalopathy and enhancement of HIV–1 neuroinvasion by cocaine. Apoptosis can be modulated by oxidants such as H2O2 influencing signal transduction pathways into the cell.

Objective: We examined whether presence or absence of ICAM–1, which plays a crucial role in transendothelial migration of T-cells across the blood-brain barrier, affects the response of brain endothelial cells to H2O2-induced apoptosis.

Methods: A brain endothelial cell line derived from ICAM–1 knockout mice, bEndalfI1.1, which lacked ICAM–1 expression, and a reconstituent of the same cell line that had been successfully retransduced with a plasmid containing wild type ICAM–1, bEndalfI1.1+wt, were generated. Both cell lines were cultured to confluency in growth medium for two weeks before the monolayers were exposed to concentrations of 150, 300, 400, 500, and 1000 microM H2O2 for 1 hour and 22 hours respectively. After exposure, the cells were harvested and stained with propidium iodide. FACS analysis was applied to determine the percentage of apoptotic and necrotic cells.

Results: After exposure to H2O2 for 1 hour, at all concentrations the bEndalfI1.1+wt reconstituents expressing ICAM–1 showed a higher percentage of apoptotic and necrotic cells than their bEndalfI1.1 knockout counterparts. However, there was no correlation between H2O2 concentration and the percentage of apoptotic or necrotic cells. After 22 hours exposure to H2O2, no clear difference between the two cell lines could be established. Controls that had not been exposed to H2O2 showed a higher percentage of both apoptotic and necrotic cells for the bEndalfI1.1+wt reconstituents than bEndalfI1.1.

Conclusion: the results indicate that retransduction of ICAM–1 into a brain endothelial ICAM–1 knockout cell line increases apoptosis and necrosis in these cells. This is independent of H2O2 concentration and could rather result from the retransduction itself. Therefore, H2O2-induced apoptosis seems not to play a major role in brain endothelial cells in vitro and is not influenced by the presence or absence of ICAM–1. At longer exposure times effects other than those examined in the experiments may play an additional role.

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Long-term use of the potential neuroprotective agent creatine is well tolerated and safe in humans and mice. A. Bender, T. Ruthsatz, K. Gempel, I. Bieger, M. Elstner, J. Schmidt, T. Gasser, T. Klopstock, University of Munich, GSF, Schwabing Hospital (Munich, D)

Creatine (Cr) is a natural compound of the cellular energy homeostasis system and serves in its phosphorylated form (PCr) as an energy donor in order to maintain high levels of ATP. Beyond its use as an anabolic agent, Cr exerted highly significant neuroprotective effects in several animal models of neurodegeneration, e. g. Parkinson syndrome. While Cr is well tolerated and safe in the short term, long term studies are still lacking despite reports on potential nephrotoxic and tumorigenic side effects. We

have therefore launched an investigation of long term Cr supplementation in patients with Parkinson disease (PD) and in aged mice.

Twenty-two patients with PD received either Cr or placebo. Blood and urine samples were drawn after 1, 3 and 6 months. Twenty aged C57Bl/6 mice (1 year old) received either a Cr supplemented or an equicaloric diet and were repeatedly weighed. Cr in blood and urine was measured after 3 and 6 months by mass spectrometry. After 6 months the animals were sacrificed and evaluated by an animal pathologist.

Cr was well tolerated by all patients. No specific side effects were reported. There was no significant difference in alpha–1-microglobulin, albumin and protein content in the urine and in serum urea between groups. The only significant difference ($p < 0,05$) was observed in the serum creatinine levels which were elevated in the verum group ($1,16 \pm 0,12$ mg/dl; $n = 8$) but not in the placebo group ($0,95 \pm 0,17$ mg/dl; $n = 4$). Correspondingly urine creatinine levels in the verum group were also higher (1,12 mg/dl vs. 0,68 mg/dl).

None of the mice showed evidence of malignant disease at the pathological examination. In the verum group ($n = 10$) two animals had hydronephrosis whereas only one animal in the placebo group ($n = 10$) was affected (not significant). Serum levels of Cr after 3 months and 6 months were significantly higher ($p = 0,003$ and $p = 0,0001$) in the verum group.

Cr might prove a powerful neuroprotective agent in neurodegenerative disease if given long term. Preliminary results of a clinical trial and an animal model imply that the 6 month oral use of Cr is safe and well tolerated and leads to significantly higher serum levels. An increase in serum creatinine is accompanied by an increase in urine creatinine and might reflect an increased degradation of the exogenous Cr rather than renal impairment.

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Inflammatory and anti-inflammatory influences to the astroglial Syncytium. D. Smikalla, D. Hinkerohe, D. Szlachta, D. Krause, P. M. Faustmann, R. Dermietzel, Ruhr-Universität Bochum (Bochum, D)

Astrocytes in the central nervous system (CNS) form an extensively coupled astroglial syncytium (AgSy) by connecting individual cells with gap junction (GJ). The predominant gap junction protein is connexin 43 (Cx43). Inflammatory processes influence the extend of gap-junctional-coupling and the membrane properties through cytokines released by activated microglia.

We tested the response of the AgSy to the cytokines Interleukin–1-b (IL–1-b), TGF-b and LPS with respect to the coupling efficiency and changes of membrane resting potential (MRP) by patch clamp techniques.

Goal of our study was to verify the hypothesis whether inflammatory processes influence the degree of intercellular coupling and exert on influence on the MRP of astrocytes.

Primary astrocyte cultures of newborn rats were co-cultured with 5 % microglia and incubated with LPS (1 mg/ml) or Il–1-b (5000 U/ml) for 24 hours. Results were compared to those incubated with phosphat buffered saline (PBS).

Microglial activation was investigated using the monoclonal anti-ED1 and the polyclonal anti-Cx43 antibodys to study the astroglial Cx43 expression with immunofluorescence microscopy. MRP was recorded in single cells using patch clamp (whole cell) mode. Functional coupling of astrocytes was evaluated by monitoring the transfer of intracellular injected Lucifer Yellow dye into neighboring cells under patch clamp conditions.

To examinate the effect of TGF-b we co-cultured astrocytes with 30 % microglia and incubated with TGF-b (5ng/ml and 10ng/ml). Data were compared with control (PBS) samples.

LPS and IL–1-b have significant effects on the AgSy. First, MRP moved from –44,8 mV (PBS) to –20,6 mV after LPS incubation ($p = 0,0260$) and to –28,1 mV after IL–1-b incubation ($p = 0,0079$) median, degree of dye coupling was affected in both cases. LPS reduced coupled cells about 50 %. Second, IL–1b affected the coupling even stronger (> 75 %). The fraction of activated microglia increases while the CX43 expression falls as compared to PBS.

Third, TGF-b affects the AgSy in a reverse fashion. Dye coupling was found to be doubled as compared to PBS. The MRP median increased from –16,3 mV (PBS) to –29,7 mV ($p = 0,2247$) after incubation with 5 ng/ml and to –36,5 mV ng/ml ($p = 0,0249$) at 10 ng/ml.

The TGF-b experiments shows that an inflammatory enviroment with a high percentage of activated microglia is partly reversible in vitro, which seems to exert a protective function on the stability of the AgSy.

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Modulated generation of neuronal cells from bone marrow by expansion and mobilization of circulating stem cells with in vivo cytokine treatment. S. Corti, F. Locatelli, S. Strazzer, S. Salani, R. Del Bo, D. Soligo, P. Bossolasco, N. Bresolin, G. Scarlato, G. Comi, Università degli Studi di Milano, IRCCS Eugenio Medea, Fondazione Matarelli (Milan, Bosisio Parini, I)

The aim of the present study was to determine whether the expansion and mobilization of circulating bone marrow (BM) stem cells by in-vivo treatment with Granulocyte Colony-Stimulating Factor (GCSF) and Stem Cell Factor (SCF) increase the amount of BM-derived neuronal cells in mouse brain. Stem cell transplantation is a potential strategy for treatment of neurodegenerative diseases and central nervous system injury. Intravascular transplantation of marked mouse BM demonstrated that BM cells migrate into the brain and differentiate in cells expressing neuronal antigens. A 250fold increase of the BM stem cell population characterised as Lin-,c-kit+,sca1+ results from the administration of GCSF and SCF in mice. This fraction is responsible of long term BM repopulation and it has been indicated as the BM cell compartment that contributes also to the regeneration of non-hematopoietic tissues.The presence of BM-derived cells in the brain was traced by transplanting into lethally irradiated adults and newborns adult BM from transgenic mice ubiquitously expressing enhanced green fluorescent protein (GFP). After 4 weeks transplanted mice were injected s. c. with GCSF 200 ug/kg/day and SCF 50 ug/kg/day for 5 days. 1 month after cytokine treatment the animal forebrains and olfactory bulbs were analysed. The number of BM derived cells that shared neuronal phenotype was evaluated by coexpression of GFP and nuclear neural specific antigen (NeuN), neurofilament (NF), glial fibrillar acidic protein (GFAP) with laser confocal microscope. As further control of donor derived GFP+ cells in brain, FISH for Y chromosome were done. FP+ and Y+ donor-derived cells were present in several brain areas of all treated mice (cortical and subcortical areas, cerebellum, olfactory bulb). The presence of NeuGFP+ cells in cortical forebrain and olfactory bulb was higher in GCSF-SCF treated groups ($p < 0.05$, analysis of variance, post hoc). Overall the amount of GFPNeu+ cells was higher in animals treated at birth than in adults, and in OB than in forebrain areas ($p < 0.05$). Temporal cortical areas of cytokine-treated adult animals revealed a mean threefold increase in the number of GFP+ cells expressing NeuN. Our results indicate that GCSF and SCF administration modulates the availability of GFP+ cells in the brain and enhances their capacity to acquire neuronal characteristics. Cytokine stimulation of autologous stem cells might be seen as a new strategy for neuronal repair.

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Tau-protein levels and S–100B levels in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. L. Cepek, P. Steinacker, B. Mollenhauer, C. Werner, M. Bartl, B. Ciesielczyk, J. Wiltfang, W. Schulz-Schaeffer, H. Kretzschmar, S. Poser, M. Otto, University of Gottingen, University of Munich (Gottingen, Munich, D)

Background: S–100B and tau-protein have a high differential diagnostic potential for the diagnosis of Creutzfeldt-Jakob disease (CJD). So far there was only limited information available about the dynamics of these parameters in the cerebrospinal fluid (CSF). Especially as there is an interest to find biochemical markers to monitor disease progression.

Patients and methods: We analysed serial CSF samples of 28 patients with sporadic CJD. If possible S–100B and tau-protein were analysed for each patient. Tau-protein and S–100B were measured with commercially available assays. All patients were neuropathologically verified. For nine patients the prionprotein-type was also available.

Results: Follow up times ranged between five and 306 days. Tau-protein levels increased in 15 patients and decreased in 9 patients. S–100B levels increased in 20 cases and decreased in one case. Levels mainly stayed above the diagnostic cut-off level. Even if both markers increased, there was no strong correlation between the relative increase of both parameters. In some cases tau-protein decreased wheras S–100B increased. For the prionprotein subtype analysis a similar pattern was observed. For the individual patient the level of S–100B and tau-protein did not predict survival time.

Conclusion: Both makers might represent different pathological features. The level of tau-protein may reflect neurodegeneration, whereas S–100B might reflect astroglial activation and/or destruction. So far the analysis for both markers gives only limited information in the follow-up, as the individual variation is very high.

Neurorehabilitation

P341
Rehabilitation of peripheral neuropathies. Indications for a diagnostic-rehabilitation strategy. G. Frazzitta, C. Fundarò, A. La Manna, E. Magnani, P. L. Sgromo, R. Casale, 'S.Maugeri' Rehab. Inst. Montescano (Montescano, I)

The increased incidence of occupational neurological disorders has led, in recent years, to the development of new specialities in neurorehabilitation for the recovery of deficits of central nervous system (CNS) lesions. This same development has not occurred for damage to the peripheral nervous system (PNS), the treatment of which is still based on empirically applied rehabilitation techniques. This is due to the fact that the peripheral neuropathies comprise a vast group of disorders caused by a huge variety of etiological factors; in order to identify the exact cause of a PNS lesion and thus be able to differentiate rehabilitation techniques it is necessary to classify them. We have developed an integrated therapeutic rehabilitation strategy which is based on meticulous diagnosis and the use of pharmacological and physical treatments aimed at reducing or eliminating symptoms of pain in order to facilitate mobilization and thus avoid the pain becoming chronic. Finally, our strategy, including various different rehabilitation techniques, offers the possibility of partial or total recovery of the motor deficit so that the patient can return to employment and successfully carry out his or her working activities.

P342
Rehabilitation treatment of Parkinson's disease. G. Frazzitta, C. Fundarò, A. La Manna, E. Magnani, P. L. Sgromo, R. Casale, "S. Maugeri" Rehab. Inst. Montescano (Montescano, I)

Parkinson's disease (PD) is one of the commonest neurological disorders in adults. Pharmacological treatment has improved the quality of life of many patients with PD, although side effects can diminish the benefits and in some cases drastically reduce patients' autonomy. Rehabilitation therapy can improve autonomy and quality of life in the Parkinsonian patient. However most of the rehabilitation programs for patients with PD are quite aspecific, dealing with general scores such as "improving mobility".

We have developed a therapeutic program for PD specific for each patient. The program comprises a series of exercises and advice about life habits which differ according to the stage of the disease.

So far we have enrolled 12 patients (9 Female, 3 Male; age 75.8 ± 6.1 years; duration of disease 16.6 ± 5.1 years) into this project. According to Hoehn and Yahr's classification, 4 have stage 4 disease, 8 have stage 3 disease. All the patients were evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) at admission to and discharge from the Unit.

The total UPDRS score in stage 3 patients was 49.3 ± 9.7, in stage 4 patients was 76.5 ± 13.9.

The patients underwent rehabilitation treatment that was specific for their stage of disease and remained in the Unit for 47 ± 6.8 days. The patients' pharmacological treatment was not changed during their admission; only occasionally patients who suddenly developed "off" symptoms were administered 125 mg of dispersible levodopa.

At the end of the rehabilitative treatment the clinical picture of all the patients had improved. In particular, the total UPDRS score in stage 3 patients was 29.9 ± 10.9, which was a statistically significant improvement ($p < 0.0001$), while in stage 4 patients was 46.2 ± 8.2 ($p < 0.05$).

The patients in both stage 3 and stage 4 had a statistically significant improvement in the items of the UPDRS concerning activities of daily living ($p < 0.0005$ and $p < 0.05$, respectively) and motor evaluation ($p < 0.0005$ and $p < 0.05$), while there was no change in the items evaluating complications of pharmacological treatment. Furthermore, patients in stage 3 also had a statistically significant improvement in items concerning behaviour and mood ($p < 0.05$); this change was not found in patients with stage 4.

The above data, which represent the first results of our rehabilitation protocol, show that rehabilitation treatment gives significant benefits even in the most advanced forms of Parkinson's disease.

P343
Interest of levodopa/benzerazide and bromocriptine in brain anoxia. S. Debette, O. Kozlowski, M. J. Launay, M. Steinling, M. Rousseaux, CHRU Lille (Lille, F)

Background: Secondary and late motor and especially cognitive consequences of postanoxic encephalopathy are often severe. Little is known about the effectiveness of oral medications.

Objective: To present data suggesting partial improvement upon levodopa/benserazide and bromocriptine.

Methods: After observing partial benefit in one case, each further patient admitted to rehabilitation following brain anoxia was treated with levodopa/benserazide (200/50 to 400/100 mg/day), then bromocriptine (15 mg/day).

Results: In the first patient, brain anoxia was severe, with secondary agitation, quadriparesis, hypertonia, involuntary movements, inattention and communication disorders. Other therapies (antiepileptic, anticholinergic, antispastic drugs) were ineffective. Introduction of levodopa/benserazide resulted in reduction of agitation and involuntary movements and improvement of communication, thus facilitating care and rehabilitation efforts. A weaning test resulted in rapid worsening. The patient returned home nineteen months after anoxia. The four following patients also presented with anoxia of variable severity. Marked improvement was observed in case 2, presenting with agitation, loss of orientation, amnesia, postural disorders, involuntary movements and dysphagia, with a withdrawal test resulting in immediate re-enhancement of symptoms. Modest improvement was observed in patient 3, who had hypokinesia, rigidity, adynamia, impaired attention, and reduced verbal fluency. Patient 4 presented with memory disorders without motor difficulties, mild improvement was observed in tests, with discrete benefit in daily life. In patient 5, who had more severe memory disorders, no benefit could be documented. In each case, bromocriptine was introduced 3–4 weeks following levodopa, but without additive effect. Furthermore, both treatments could be interrupted after a few months (2–13), without worsening. Bilateral cerebral blood flow reduction (HMPAO), predominating on the frontal lobes, could be documented in each case.

Conclusions: Levodopa and benserazide can be of interest in the few months following brain anoxia, especially on motor disorders and apathy. The benefit is inconstant and modest on memory disorders. Anoxia could alter dopaminergic mesencephalic systems, which activate the striatal and mediobasal frontal cortex, and resulting disorders could be partially reversible upon medical treatment.

P344
Computer-assisted neurorehabilitation in severely cognitive impaired patients – preliminary results. T. Kraus, R. Schmidt, W. Schupp, Fachklinik Herzogenaurach (Herzogenaurach, D)

Objective: Sufficient activation and stimulation of severely cognitive impaired patients often needs hospitalization and admission to special rehabilitation centres. Relatives who decide to care and train the patient at home wish to have more tools and support that makes their work easier and more effective. The Entertainer is an interactive computer program developed in an European Community research project, that allows to present emotional relevant contents in form of images, texts and music pieces with connection to actual experiences in the life of the patients. A preliminary study was performed to test if this computer-assisted method of neurorehabilitation could improve basal cognitive functions and could support the caring person.

Method:10 patients severely impaired in basal cognitive functions due to cerebral infarction were repeatedly instructed and assisted in applying The Entertainer. A multimedia PC with a touch-screen was installed. Before and after the sessions certain basal cognitive parameters like vigilance, level of activity, mood, memory and locomotion were checked using semi quantitative scales.

Results: We found prominent improvements of vigilance, activity state, mood and locomotion. The patients spoke about the percepted contents and wished to continue with the sessions.

Discussion: Computer programs like The Entertainer using emotionally stimulating sources seem to be effective in improving severe basal cognitive deficits. Moreover, they might be appropriate tools for occupating the patients. Relatives who care patients at home could get temporary support by others who can easily run the computer program together with the patient. The main care person thus could be relieved for a certain time. Hence, computer-assisted programs like The Entertainer might become an important place in future home care strategies. They should be further improved and evaluated in clinical studies.

P345
Quality management in early neurological rehabilitation. T. Belian, U. Bruer, A. Friedo, S. Bamborschke, Brandenburg Klinik (Bernau, D)

Early neurological rehabilitation plays a crucial role in the treatment process of patients with severe neurological impairments. While patients show severe neurological deficits, one must also consider frequent medical

complications as a result of their critical condition. Therefore substantial and qualified resources (staff and equipment) for neurological rehabilitation and intensive care are necessary. To cope with this special interface between acute and rehabilitative medicine effective quality management is of great concern.

Structural quality: The field of early rehabilitation is structured as a combination of intensive neurological rehabilitation and intensive care with appropriate diagnostic tools to provide permanent control of vital functions and allow specific treatment of complications. The presentation will give a more detailed description of the structure of early neurological rehabilitation.

Quality of outcome: From 726 patients, who were admitted to the early neurological rehabilitation department of the Brandenburg Klinik Bernau-Waldsiedlung between 1997 and 2001 (phase B corresponding to the phase model of the Bundesarbeitsgemeinschaft für Rehabilitation) 589 patients could be evaluated. The approximate length of stay was 43 days, depending on the diagnose. The average age of the patients was 59,6 years (60 % more or equal 65 years). Men were admitted more frequently (65 %). Of the admitted patients 38 % had an ischemic stroke, 29 % an intracerebral hemorrhage, 10 % a hypoxic/toxic encephalopathy, 4 % an intracerebral tumour, 3 % a peripheral neuropathy and 2 % each a cerebral inflammation, a cerebral degenerative disorder or a spinal disease.

To evaluate the outcome of rehabilitation we used the Frührehabilitation-Barthel-Index (Schönle, FRBI) and the kind of discharge. The overall initial FRBI was –44 and on the day of discharge –2 accounting for an average improvement of 42 points. 42 % of the patients could be discharged home with 50 % of these being mainly independent. The outcome depended on age and diagnosis of the patient. 27 % of the patients treated in phase B of early rehabilitation were transferred to a nursing home. 29 % had to be treated again in a hospital. In these latter cases it was a matter of complications appearing regularly in patients with severe neurological or medical conditions. Strikingly the proportion of early transfer (within the first 10 days after admission) was fairly high, especially in older patients (35 %).

P346

The perception of affective prosody in patients with right-hemisphere lesions. H. Pihan, Inselspital (Bern, CH)

Introduction: Healthy individuals are able to infer affective speaker attitudes from the speech signal, either explicitly from the meaning of words, such as "I am happy (sad etc)", or implicitly from the speakers' tone of voice. This speech component is referred to as 'affective prosody'. From lesion studies, the neural mechanisms underlying the processing of prosodic speech components have not been identified yet (for a review see Baum, 1999). Accordingly, it has not been clarified to which degree left and right hemisphere (RH) lesions affect nonverbal communication skills relevant to a sufficient social functioning and, thus, essential for a successful rehabilitative outcome. Distinct left and right hemisphere mechanisms of prosody processing have been demonstrated in a previous study analysing evoked potentials (Pihan et al., 2000).

Objective: This study will evaluate the effects of RH lesions on discrimination of various degrees of emotional expressiveness from the tone of voice. It will also investigate possible impairments arising from a processing failure of spectral and temporal signal properties. Furthermore, the possible role of left hemisphere neural networks in affective speech processing is explored. Patients performing overt speech during stimulus discrimination are expected to improve in discrimination of emotional expressiveness.

Methods: The same stimulus set, which has been validated in experiments with normal subjects is used. Patients with RH lesions discriminate pairs of declarative sentences with either happy, sad or neutral intonation. Each stimulus pair comprises two identical original utterances that, due to digital signal manipulations, slightly differ in fundamental frequency (F0) range or in duration of stressed syllables. Patients are asked, first, to denote the original emotional category of each sentence pair and, second, to decide which of the two items displayed stronger emotional expressiveness. In a second run participants are advised to repeat the utterances by overt speech during stimulus presentation in addition to the discrimination task.

Latest Results of this ongoing study will be presented. Performance of RH lesioned patients and normal controls will be contrasted. Effects of brain lesions on (i) categorical emotional identification, (ii) dimensional evaluation of varying expressiveness, and (iii) acoustic signal processing will be discussed.

P347

Upper limb immobilization induces motor cortex hyperexcitability. A transcranial magnetic stimulation study. S. Tamburin, A. Fiaschi, P. Manganotti, A. Forgione, G. Zanette, Hospital GB Rossi University of Verona (Verona, I)

Objectives. Plasticity of the sensorimotor cortex has been described in response to changes in somatic afference or motor output. The study of neuroplasticity secondary to disuse, such as in long-term limb immobilization, yield conflicting results. For this reason, we studied 8 subjects, who underwent upper limb immobilization with a splint for unilateral wrist fracture. Data were compared to 10 normal controls.

Methods. The subjects were examined immediately after the removal of the splint. Cortical representation of abductor pollicis brevis, flexor carpi radialis, biceps and deltoid muscles were mapped with single pulse transcranial magnetic stimulation (TMS). Resting motor threshold (RMT), central motor conduction time (CMCT), motor evoked potential (MEP) amplitude and MEP recruitment curve were examined for each muscle. Paired pulse TMS was used to study the changes in intracortical excitation and inhibition. In 3 subjects the recording was repeated after 1 month. H-reflex and F-wave were recorded to document if any changes took place at spinal level.

Results. RMT and CMCT did not differ significantly between immobilized and free sides. The area of cortical maps was not different between the two sides, while the volume was significantly larger on the cortex contralateral to the immobilized sides. On this side the recruitment was significantly larger. The study of cortical excitation and inhibition showed a significant prevalence of excitatory networks on immobilized sites. No side-to-side differences were detected in controls. H-reflex and F-wave data suggested that hyperexcitability is mainly sustained by cortical mechanisms. After 1 month side-to-side differences tended to disappear in all 3 subjects.

Conclusions. Our data document that no map expansion or restriction takes place in the motor cortex following long-term immobilization of upper limb. Rather, neuroplastic hyperexcitability takes place inside the representation of single immobilized muscles, due to an imbalance between excitation and inhibition at the cortical level. These hyperexcitable changes seems to be reversible. These data may be applied in the field of rehabilitation to improve recovery after prolonged immobilization. Moreover this study may contribute to a better understanding of the mechanism of 'constraint-induced therapy'.

Pain and Headache

P348

Dose escalation of intrathecal drugs for intractable pain. S. Kamran, Hamad General Hospital (Doha, BH)

Introduction: Various medications have been used intrathecally for pain control. There are few studies describing the dose escalation over variable duration. The purpose of this study was to see the dose escalation over a fixed period of time. The data obtained should help define some parameters when using intrathecal medications.

Patients and methods: We reviewed our pump database for non-malignant pain and selected forty-two consecutive patients. The dose escalation was calculated over a period of fifty-one weeks. The statistical analysis was performed and mean, median, standard deviation and dose range was calculated.

Results: There were 27 men and 15 women with age range of 39 to 73 years. All implants were for non-malignant pain. The drugs used were morphine/marcaine (n = 32) and dilaudid (n = 10). For morphine/marcaine the mean increase was from 1.046 mg/day at week 1 to 5.85 mg/day at week 51. The dose range was from 0.25 to 3.0 mg/day at week 1 to 1.0 to 15.0 mg/day at week 51.

For dilaudid the mean increase was 0.25 at week1 to3.10 at week 51. The dose range was 0.25 to 1.88 at week 1 and 0.27 to 6.0 at week 51. Sufficient data regarding patients previous narcotic intake was not available to correlate dose escalation to previous narcotic intake. However, a trend in rapid dose escalation was observed in patients with prolonged history of narcotic use or multiple narcotic use.

Conclusion: Our data indicates a dose escalation that was significant over approximately one year period. This may reflect tolerance to the medication and unpredictable narcotic dosing for a given patient. Although data is insufficient a trend towards rapid dose escalation in chronic oral narcotic use indicates development of significant tolerance.

P349

Botulinum Toxin A reduces neurogenic flare but not mechanical hyperalgesia in humans. H. H. Kraemer, C. Angerer, F. Erbguth, M. Schmelz, F. Birklein, Johannes Gutenberg University, Friedrich-Alexander University (Mainz, Erlangen, D)

Botulinum toxin A (BTX A) has been used therapeutically to treat muscular hypercontractions and sudomotor hyperactivity. During the last years there is increasing evidence that BTX A might also have analgesic properties, in particular in headache. In the present investigation we tested the commonly cited hypothesis that BTX A-induced analgesia can be attributed to inhibition of neuropeptide release from nociceptive nerves.

In 15 healthy volunteers BTX A (5, 10, 20 mouse units BOTOX) or saline (contralateral side) was injected intracutaneously on the volar forearm. We repeatedly elicited pain, mechanical hyperalgesia and neurogenic flare by transcutaneous electrical stimulation before and 1,2,3,7 and 14 days after injection simultaneously on the BTX A and saline treated side. Before each session, sweating and local anhydrosis was assessed by iodine starch staining.

BTX A suppressed sweating as early as from the second day after injection ($p < 0.001$). The size of electrically induced flare was smaller on the BTX A treated arm (BTX A side: 21.46 cm§ ± 3.58, saline side 24.80 ± 3.46, $p < 0.005$). Similarly, electrically-induced pain was reduced ($p < 0.001$). However, mechanical hyperalgesia and allodynia after electrical stimulation were unchanged.

In conclusion our results indicate, that peripheral neuropeptide release could be attenuated by BTX A, while the spinal release of neuropeptides or excitatory amino acids seems to be unaffected. We assume that other mechanisms must be more important for BTX A induced pain relief in different pain syndromes.

P350

Normalization of high interictal cerebrovascular reactivity in migraine without aura by treatment with flunarizine. B. Dora, S. Balkan, E. Tercan, Akdeniz University (Antalya, TR)

Alterations of intracranial vessel tone have been proposed to be an important pathophysiological factor in migraine and cerebrovascular reactivity (CVR) to changes in arterial pCO2 has been shown to be impaired in the interictal phase. There are only few studies questioning the effect of treatment on impaired CVR in migraine.

CVR to hypercapnia was evaluated in 12 patients with migraine without aura (MWOA) interictally and 11 healthy controls by Transcranial Doppler (TCD) recording using the breath holding index (BHI). This index is obtained by dividing the percentage increase in mean flow velocity occurring during breath holding by the time (seconds) subjects held their breath. The BHI's of three consecutive periods of breath holding were averaged to calculate the mean BHI for each individual.

Patients were started on prophylactic treatment with flunarizine 10 mg/day and measurements repeated at the end of every month for a period of 3 months. Headache was evaluated by a headache index (HI). HI, BHI, systolic, diastolic and mean blood flow velocities (BFV) and pulsatility index (PI) measurements were recorded on every session.

The baseline BHI (1,58 ± 0,36) was significantly higher in the migraine group compared to the controls (1,25 ± 0,36) ($p < 0,05$). No difference was found in systolic and mean velocity and PI between both groups.

The pretreatment HI was 13,0 ± 7,2 and after 3 months of treatment it decreased to 4,3 ± 3,9. The change in HI was significant ($p = 0,02$) showing a beneficial effect of flunarizine.

After 3 months of treatment with flunarizine the BHI decreased to 1,26 ± 0,23. The improvement in BHI was significant ($p < 0,01$) and there was no difference between the posttreatment BHI and the control group after 3 months. There was no significant change with treatment in the other TCD parameters.

We have demonstrated that there is a high CVR in patients with MWOA interictally and that flunarizine is effective in normalizing CVR. Our finding of unchanged BFV but normalized CVR after treatment support that the mechanism of action of flunarizine in migraine is not by a vasodilatatory effect on cerebral vessels. It is possible that flunarizine acts on CVR by its antihypoxic properties or through an action on centres of autonomic vascular control in the brainstem altering this hypersensitivity to hypercarbia. The exact beneficial mechanism of action of flunarizine on both headache and CVR in migraine remains to be determined.

P351

Generalized hyperresponsiveness to substance P in complex regional pain syndrome. S. Leis, M. Weber, A. Isselmann, M. Schmelz, F. Birklein, Neurologische Universitätsklinik, Institut für Physiologie (Erlangen, Mainz, D)

Background: Pain, vasodilation and edema are characteristic symptoms of acute complex regional pain syndrome (CRPS), thus resembling inflammation. Recently, we have been able to demonstrate facilitated neurogenic inflammation on the affected limb. The present study was conducted to elucidate the underlying mechanisms.

Methods: Dermal microdialysis was employed (1) to apply exogenous substance P (SP) in ascending concentrations (10 –9 M, 10 –8 M, 10 –7 M, 10 –6 M) in CRPS patients on both the affected and unaffected side, and (2) to perform electrical C-fibre stimulation (= endogenous neuropeptide release) on the unaffected limb to complete our previous study. The respective protein extravasation was measured photometrically.

Results: In healthy controls, SP at concentrations of 10 –8 M or higher lead to plasma protein extravasation. However, in CRPS patients significant protein extravasation was found with SP 10 –9 M on the affected (98.4 ± 8.4 % of baseline, $p < 0.05$, MANOVA) and on the unaffected limb (104.4 ± 5.6 %, $p < 0.005$; controls: 72.8 ± 4.4 %, n. s). In contrast to the affected limb, electrical C-fibre stimulation on the unaffected side did not provoke protein extravasation (91.1 ± 4.3 %; controls: 88.8 ± 10.1 %, n. s).

Conclusions: We conclude that there is a constitutively increased sensitivity to SP in CRPS patients, which leaves them asymptomatic under normal conditions. However, in the inflammatory process following a local trauma with consecutive upregulation of endogenous neuropeptides it might lead to exacerbation and spreading of the inflammation as clinically seen in CRPS.

P352

Calcitonin gene-related peptide (CGRP) in complex regional pain syndrome. M. Weber, M. Schmelz, S. Schifter, B. Neundörfer, F. Birklein, Neurologische Uniklinik Erlangen, Institut für Physiologie Erlangen, University of Copenhagen, Neurologische Uniklinik Mainz (Erlangen, D; Copenhagen, DK; Mainz, D)

The clinical picture of Complex regional pain syndrome (CRPS) with oedema, swelling and vasodilatation strongly resembles neurogenic inflammation, in the consequence of nociceptor activation. Having provided the first evidence for a facilitated neurogenic inflammation in CRPS recently, in this study we focussed on the release of neuropeptides from the primary afferents.

Methods: 19 patients with acute CRPS fulfilling the IASP diagnostic criteria and a group of 16 healthy control subjects were included. 10 of the patients and 10 controls underwent intradermal microdialysis on a previous day. At that time protein extravasation was measured photometrically and vasodilatation by using Laser-Doppler imaging after strong transcutaneous electrical stimulation. Now in all 19 patients serum was collected from the affected, in 13 additionally from the unaffected sides, before and 9 months after therapy ($n = 9$). Plasma calcitonin gene-related peptide (CGRP) concentrations were measured with a radioimmunoassay (RIA) for human CGRP.

Results: The patients who underwent microdialysis showed protein extravasation and increased vasodilatation, suggesting a facilitated release of neuropeptides from the primary afferents. Accordingly in CRPS patients CGRP levels were increased ($p < 0.03$). There was no difference between affected and unaffected sides. However, in those 9 patients reinvestigated 9 months later a reduction of serum CGRP was measured ($p < 0.005$); absolute CGRP levels then no longer differed from controls. Increased serum CGRP was correlated to the incidence of nerve lesions, CGRP levels in CRPS II were higher than in CRPS I ($p < 0.02$) and the severity of the trauma ($p < 0.007$). Also serum CGRP was higher in patients with markedly hyperhydrosis ($p < 0.04$). But absolute CGRP serum levels did not correlate to other clinical symptoms, duration of CRPS or pain. However, normalization of CGRP after therapy was accompanied by clinical improvement of local inflammatory signs, but not by pain reduction.

Conclusions: In the acute stage of CRPS systemic CGRP levels are increased, corresponding to the findings of protein extravasation and vasodilatation in CRPS. These results suggest neurogenic inflammation as a pathophysiologic mechanism contributing to vasodilatation, oedema and increased sweating. However, pain and hyperalgesia, in particular in chronic stages, seem to be independent of increased neuropeptide concentration.

P353
Pseudomigraine with pleocytosis: two new cases. M. Castro del Rio, M. Seijo-Martinez, M. Mouriño Sestelo, F. Vazquez, J. Brasa, M. Puig-Saez, Complexo Hospitalario Pontevedra, MEDTEC-Hospital Xeral-Cies (Pontevedra, Vigo, E)

Introduction: Pseudomigraine with pleocytosis (PMP)is a rare,autolimited clinical syndrome, with well characterized diagnostic criteria. The etiology and pathogenesis are presently unknown, but it is probably postinfectious in nature, with secondary meningeal inflammation and vasomotor phenomena. PMP usually affects young adults, and presents recurrent multifocal central nervous system symptoms. Despite its spectacular clinical presentation, it is a benign syndrome. Clinical suspicion is important for early diagnosis. Usually meningoencephalitis is suspected, but the clue is the finding of normal neuroimaging studies.

Material and methods: Review of the Neurology Service clinical histories.

Results: Two patients fulfilled criteria for PMP. A 38 year-old male presented with fluctuating intense right hemicranial headache, and 3 episodes consisting in both left and right-sided motor and sensitive deficits and dysphasia. The headache lasted for 2 weeks. Neuroimaging studies, including angio-magnetic resonance, were normal. Cerebrospinal fluid studies showed lymphocytic pleocytosis, which persisted for more than two months. IgG and IgM titres for cytomegalovirus (CMV) were elevated. The second patient was a 24 year-old female with intense, excruciating headache, presenting an epileptic fit and rich brainstem signs with cranial nerve dysfunction. The disease lasted 5 days. Lymphocytic pleocytosis under increased pressure was present. The neuroimaging findings were normal.

Conclusion: Our results disclose a positive serology for CMV and prolonged pleocytosis in one patient. Brainstem manifestations with cranial nerve dysfunction (probably nuclear) have not been, to our knowledge, previously described.

Peripheral Neuropathy

P354
The endogenous pentapeptide QYNAD induces acute nerve conduction block in vitro. F. Weber, R. Rüdel, P. Aulkemeyer, H. Brinkmeier, German Air Force Institute of Aviation Medicine, University of Ulm (Fürstenfeldbruck, Ulm, D)

Reversible block of sodium channels by endogenous substances was claimed to account for the fast relapses and remissions seen in demyelinating autoimmune disorders. The pentapeptide QYNAD, isolated from the CSF of MS or GBS patients, blocked Na+ channels in various types of cultured cells. To explain the fast symptom changes in MS and GBS, we extended our studies of QYNAD effects from those on sodium channels functionally expressed in test cells to those on the compound nerve action potential (CNAP) of isolated rat sciatic nerve, a model that is closer to the in vivo situation.

100 µM QYNAD bath-applied to isolated rat sciatic nerve causes a decrease of amplitude and area as well as an increase in CNAP latency. After 60 min the decline of amplitude of the action potential caused by QYNAD was more than 50 %. On average, it took about 20 min of incubation with 100 µM QYNAD to see an inhibitory effect on amplitude and area of CNAPs and an increase of latency. After 60 min, the amplitude and the area were decreased to 61 and 68 %, respectively, of their initial values, whereas the latency was increased to 130 %. Washout reverses the changes in part.

The endogenous pentapeptide QYNAD may have an anti-excitatory effect on intact myelinated axons and nerves in vivo and may contribute to the fast symptom changes in MS and GBS.

P355
Small-fiber polyneuropathy in leprosy without skin changes. M. De Freitas, O. Nascimento, A. Oliveira, M. Hanh, Universidade Federal Fluminense (Niterói, BR)

Leprosy is a chronic disease predominantly of skin and nerves. It is caused by a infection with Mycobacterium leprae. Leprosy is one of the most common disease of the peripheral nerves in the developing countries in the world. It is believed to affect 300 thousands Brazilians. There is a pure neuritic form without any skin lesions (3–10 % of leprosy).The isolated polyneuropathy is rare. It has often a distal stocking and glove distribution with thermal and pinprick anaesthesia. Preservation of proprioception and vibration sense is common. No objective motor sign may be detectable. The tendon reflexes are usually preserved until late advanced stages. The nerves may be normal although with time there is a slowly and symmetrical enlargement.

We study from January 1995 through May 2001, 16 patients with small-fibre polyneuropathy probably due to leprosy without skin and systemic lesions. There were no muscle weaknesses. All patients had distal temperature and pain anaesthesia with different individual variations. The tendon reflexes were normal, decreased or absent. In seven cases there was a moderate uniform thickening of peripheral nerves. The nerve conduction was normal in two patients. In the other fourteen cases the amplitude of the sensory potentials were absent in the nerves of the lower and the upper limbs. In six of them the amplitude of motor potentials were reduced in the nerves of the lower and upper limbs.

The pathological findings in the biopsy of the sural nerves showed in all cases: 1) extensive inflammatory infiltrates consisting of macrophages and lymphocytes; 2) presence of vacuolated "foamy cells"; 3) severe fibrosis of endoneurium, perineurium and epineurium; 4) partial or total loss of nervous fibers, 5) large number of bacilli in the perineurial, endothelial cells and particularly in the Schwann cells.

Our results allowed us to confirm the diagnostic of pure neuritic and multibacillary leprosy in all our 16 cases with small-fibre polyneuropathy without cutaneous manifestations. We concluded that nerve biopsy is an obligatory procedure in cases with small fibre polyneuropathy in the countries were leprosy is frequent.

P356
Higher incidence of Bell's palsy during the NATO strike attacks against Yugoslavia. B. Milicic, S. Perovic, A. Gavrilovic, S. Toncev, G. Samardzic, G. Toncev, Clinical Hospital Center Kragujevac, Health Center Kragujevac (Kragujevac, YU)

Introductions: Idiopathic facial palsy (Bell's palsy) is the commonest cause of acute facial paralysis. It is well known that an incidence of Bell's palsy varies between 14 and 25 cases per 100,000 inhabitants per year. The origin is still unknown, but infectious, immunological and genetic factors have been suggested to play a role in the pathogenesis of the disease.

Objective: The aim of this study was to investigate incidence of Bell's palsy in 45 months periods, including the war period.

Methods: In retrospective study from March 24th 1998 to December 23rd 2001, 387 Bell's palsy patients (136 male and 251 female) were analyzed (in region with 350,000 inhabitants). The 15 periods of three months were made, including the air strikes period, and those periods coincided with seasons (spring, summer, autumn and winter). Data were analyzed according to age, gender, and seasonal distribution of cases.

Results: The significantly highest incidence of Bell's palsy was found during the NATO air strike period, from March 24th to Jun 23rd 1999 (77 patients or 19,9 % of all cases, $p = 0.000$). Women were significantly more sensitive to appearance of Bell's palsy than men (65.1 % vs. 34.9 %; $p = 0.000$) in total Bell's palsy group but there was no difference in sex distribution between different seasonal periods ($p = 0.783$).

Conclusions: We suggest an unexpectedly high-intensity stress and an unusual life conditions during the air strikes (basements, cold, draught, humidity) as factors predisposing possible viral infection may be including in Bell's palsy appearance.

P357
Assessment of the severity of chemotherapy-induced neuropathy: comparison between clinical, neurophysiological and quantitative sensory testing results in a single-center study. M. Piatti, G. Giussani, P. Villa, A. Rotondi, R. Ferraro, G. Bogliun, L. Marzorati, S. Cundari, C. Zanna, A. Buda, A. Galbussera, A. Zincone, G. Cavaletti, University of Milan "Bicocca", S. Gerardo Hospital, Sigma-Tau SpA (Monza, Pomezia, I)

Chemotherapy-induced neuropathy (CIN) is potentially a severe and dose-limiting side effect of the current treatment of cancer, particularly in the case of the schedules which include platinum-derived drugs, taxanes and vinca alkaloids. However, it is still unclear the real correlation existing between the subjective and objective clinical findings and which is the role of the instrumental methods used to support the diagnosis. We performed this prospective study in order to examine the correlation existing between a well-established symptom scale (NSS), a composite score already validated for diabetic neuropathy (TNS), the amplitude of the sural nerve SAP and the findings obtained by quantitative vibrametry (VDT). The patients belonged to a series of women affected by uterine cervix carcinoma treated with a chemoterapy regimen based on the combination of cisplatin and paclitaxel. So far, a total of 23 patients are evaluable and a total of 45 visits are

available for the comparison. All the clinical and instrumental evaluations were performed under standard conditions by members of our staff specifically trained to study CIN.

A significant correlation was observed between TNS and VDT (Pearson's correlation test $r = 0.848$, $p < 0.0001$) and between TNS and sural nerve SAP ($r: -0.518$, $p = 0.0003$). Moreover, also the correlation between VDT and sural nerve SAP was significant ($r = -0.434$, $p = 0.0029$). The correlation between the symptoms reported by the patients and the instrumental evaluation was less strict, although VDT results were positively correlated with the NSS results ($r = 0.336$, $p = 0.023$). The use of VDT, a method which can be more simple to be used than electroneurography, has been frequently suggested as a reliable surrogate of the neurophysiological investigation. The formal comparison between the different instrumental methods and their correlation with validated clinical scores is still, however, to be established. Our results, obtained in a very homogeneous and selected single-center cohort of patients examined in a neurological department by specifically trained persons, evidence that VDT, as well as sural nerve SAP, can be a reliable tool to assess the severity of CIN induced by cisplatin and paclitaxel. It is still, however, to be proven that VDT is equally reliable in different settings (multicenter trials, exams performed by oncologists, different chemotherapy regimens,.) when the possibility of a technical bias is higher.

P358

Guillain-Barré syndrome and hallucinations. E. Le Rhun, J. de Seze, T. Stojkovic, D. Ferriby, P. Vermersch, Hopital R. Salengro (Lille, F)

Background: Guillain-Barré syndrome (GBS) are related to peripheral nervous system. However, in Miller-Fisher syndrome, a variant of GBS, central nervous system (CNS) may be involved.

AIM of the Study: To report 3 patients with GBS associated with CNS manifestations including hallucinations and onirism.

Methods: We retrospectively studied 3 patients with GBS and CNS manifestation. All patients had CSF analysis, viral and bacterial serologies, electromyogram and electroencephalogram analysis. Brain MRI was also performed in all cases.

Results: Two men and one woman aged 64, 49 and 52 years, respectively, presented with GBS secondary to Epstein-Barr virus (EBV) in the last case. In the 2 other cases no infectious origin was found. The CNS clinical manifestations appeared at the end of the period of progression and was sustained a mean of 3 weeks and associated mainly onirism and hallucinations. They spontaneously resolved followed by motor improvement. Electromyography showed typical features of GBS. CSF analysis showed protein increase in all cases and a pleocytosis in the case with EBV infection. Electroencephalogram was abnormal in all cases with features suggestive of encephalitis without epileptic pattern. Brain MRI was normal in all cases.

Conclusion: GBS may be associated with CNS involvement mimicking delirium tremens. These manifestations should be secondary to infectious encephalitis or post-infectious. Although a large cohort is necessary CNS involvement in GBS do not appear associated with a poor prognosis.

P359

Comparison of surface and near nerve needle electrodes recordings with myelinated fiber density in nerve biopsies of patients with peripheral neuropathy. I. Mori, G. Said, Dokkyo University School of Medicine, University Hospital of Bicetre (Tochigi, JP; Paris, F)

We investigated 32 patients (men/women 16/16, mean age 61 [range 15–91]) with clinical signs of peripheral neuropathy by nerve biopsy and nerve conduction study (NCS). Clinically affected sural or superficial peroneal nerve (SPN) were selected for Biopsy and NCS performed beforehand. To investigate the influence of distance between nerve fiber and recording electrode, we studied both by surface and needle electrode at the same recording point. Supramaximal stimulation was performed 14 cm proximal to the recording electrode. First, we compared the density of large myelinated fiber (DLM) with sensory nerve action potentials (SNAP) in 20 patients. In 6 patients SNAP was obtained both by surface and needle electrode (Surface: median 4.9 microvolt [range 2.6–12], Needle: median 3.7 microvolt [range 1.9–15]), in 7 patients SNAP was obtained only by needle electrode (median 2.1 microvolt [range 1.5–2.7]), and in 7 patients SNAP was not excitable by either electrode. SNAP by surface electrode well correlated with SNAP by needle electrode (= 0.89 p = 0.01). The correlation between DLM and SNAP did not reach the statistical significance.

SNAP of 23 patients (72 %) was excitable by surface or needle electrode. In patients with Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), conduction velocity (CV) of SPN ranged from 20 to 44 m/s (SNAP: median 3.9 microvolt [range 3.5–6.1]). In patients with axonal neuropathy, SNAP of SPN nerve ranged from 1.5 to 2.7 microvolt (CV: median 36 m/s [range 30–48]). Electrophysiological examination was limited for the severe neuropathy (DLM < 2000 /mm2) In 9 of 32 patients (28 %) SNAP was not excitable and diagnosed pathologically as CIDP, amyloidosis, and ischemic neuropathy (DLM 380–1100 /mm2). In patient with foot oedema, SNAP was only elicited with needle electrode (SNAP/CV 2.7 microvolt 46 m/s). Pathological findings were slight axonal degeneration (DLM 3360 /mm2). SNAP obtained with surface electrode reflects the density of large myelinated fiber. However, the distance between electrode and nerve fiber is different in each patient, which results in the individual variation of SNAP. DLM itself is variable in normal control. Moreover, Surface electrode is not useful in severe neuropathies. We suggest that the application of NCS with needle electrode and Nerve biopsy is essential for the diagnosis of severe neuropathy.

P360

Sensory ataxic neuropathy associated with anti-GD1b antibodies and positive serology for Campylobacter jejuni. D. Ulbricht, R. L. Humbel, R. J. Metz, Centre Hospitalier de Luxembourg (Luxembourg, LUX)

Objective: to describe the association of a subacute sensory ataxic polyneuropathy (PNP) with anti-GD1b antibodies and recent Campylobacter jejuni infection.

Introduction: Following recent progress in the differentiation of the different variants of Guillain-Barré-Syndrome, a number of associated antibodies have been described. This is especially true for the sensory variants, which are associated with antibodies against GD1b-, Sulfatide- or GM2-epitopes.

Case report: a 44-year-old woman complained of both hands "falling asleep" for 3 days in a progressive fashion. She was especially frightened as she experienced a similar episode 23 years ago, which left her bedridden for 2 weeks but from which she fully recovered. Her past medical history was unremarkable but for a Beta-Thalassemia minor. At admission, there was a nearly abolished positional sense in both hands, to a lesser degree in both legs, with strongly diminished vibrations sense. Her march was moderately ataxic. Those symptoms worsened strongly with eyes closed. Reflexes were diminished, but there was only a slight paresis of toe elevation bilaterally. Furthermore, the patient presented her symptoms in a rather demonstrative fashion evoking the differential diagnosis of somatisation disorder. In the diagnostic work-up there were (1) slightly slowed motor nerve conduction and dispersion of the F-waves; (2) a normal cervical MRI excluding posterior ectopic myelogenesis; (3) significantly elevated serum titres for antibodies against GM1 and GD1b. In the clinical course, there was worsening within a week with prominent sensory ataxia and slight respiratory trouble but rapid resolution in the following 10 days. At follow-up 2 months later, the patient had no more subjective complaints but kept a slight ataxia at the right leg.

Discussion and Conclusion: The anti GD1b antibody is thought to affect specifically the dorsal root ganglia entry zone and even its central projections. Outside Japan, this antibody has rarely been described, especially with an associated recent C. jejuni infection. This case emphasizes the thoroughly search for an underlying autoimmune pathology in subacute polyneuropathy of unknown origin.

Poster Session 2

Cerebrovascular disorders

P361

The effect of thymus ubiquitin complex on neuropathological changes within the brain of pregnant rabbits with experimental model of antiphospholipid syndrome. P. Nowacki, J. Ossowicka-Stepinska, E. Ronin-Walknowska, Pomeranian Academy of Medicine (Szczecin, PL)

Aim of study: present study was designed to assess an impact of thymus ubiquitin complex (TUC) on morphological changes within the central nervous system (CNS) in pregnant rabbits with experimental model of antiphospholipid syndrome (APS). We have also compared the intensity of neuropathological appearance and serological markers of the APS treated with the TUC.

Material and method: postmortem neuropathological investigations

were done in 47 female New Zealand rabbits. The material was divided into 4 groups: Group I – 23 pregnant animals with APS; Group II – 7 pregnant rabbits with APS, treated with TUC; Group III – 7 pregnant rabbits without APS, treated with TUC; Group IV (the control one) – 10 pregnant animals without APS, untreated with TUC. The APS was induced by subcutaneous injections of cardiolipin.

Results: there were two main abnormalities within the CNS of pregnant rabbits, which could be a result of the APS: the thrombo-necrotic foci of nervous tissue, and perivascular or meningeal inflammatory infiltrates. It turned out that TUC application reduced the morphological abnormalities, but it hasn't eliminated them entirely. The number of cases with thrombo-necrotic changes has been reduced by approximately 18 %, while perivascular infiltrates by 36 % respectively. The TUC application hasn't influenced the meningeal infiltration. The platelet count significantly increased ($p < 0.001$), the activated partial thromboplastin time shortened ($p < 0.001$), and the number of immunised animals, demonstrating positive immunofluorescence test significantly decreased after the TUC administration.

Conclusions: The inflammatory changes within the CNS are the integral component of the experimental model of APS in pregnant rabbits. The TUC may decrease the inflammatory component of the APS in the CNS. The inflammatory infiltrates seem to be more responding to TUC application and parallel to APS serological improvement after treatment, then necrotic changes.

P362

Infratentorial strokes: testing the clinical utility of early diffusion-weighted MR imaging. S. Engelter, S. Wetzel, E-W. Radü, A. Steck, P. Lyrer, University Hospital Basel (Basel, CH)

Objective: In supratentorial strokes, early diffusion-weighted MR imaging (DWI) has a proven usefulness as adjunctive tool to predict outcome and to determine stroke etiology. For infratentorial strokes, the clinical utility of DWI is widely unknown.

Design: prospective cohort study

Study population: Twenty-two consecutive patients (61 ± 13 yrs) with acute infratentorial strokes and DWI within 17.9 ± 12.1 hrs.

Methods: Blinded comparison between volume, number, and pattern of acute DWI lesions versus initial NIH Stroke Scale score (NIHSSS), functional outcome after 3 months (modified Rankin score (mRS), Barthel-index (BI)) and versus stroke etiology (TOAST classification).

Results: Acute infratentorial DWI lesions were detected in 95 % (21/22) of the patients. Lesion volume (7.39 ± 10.42 ccm) was not correlated with NIHSSS (6.5 ± 5.0) ($p > 0.5$). After 3 months, 50 % (11/22) of the patients according to mRS and 63.6 % (14/22) according to BI had recovered. However, DWI lesion volume and outcome scores were not correlated (each $p > 0.05$). Thirteen patients (59 %) had single lesions, while 8 (36 %) had multiple lesions. Number of DWI lesions and outcome scores were not correlated, too (each $r = 0.4$, $p > 0.05$). In 7 patients (32 %) DWI lesions were restricted to the brainstem, 7 patients had pure cerebellar lesions and in another 7 patients DWI lesions involved the brainstem plus the cerebellum or additional supratentorial areas. The latter patients had a significantly lower BI score after 3 months than those with pure brainstem or pure cerebellar lesions ($p = 0.037$). The number of DWI lesions was significantly correlated with stroke etiology ($r = 0.6$, $p = 0.03$): Among the 8 patients with multiple lesions, 5 (63 %) had a cardioembolic stroke cause, which in turn did not apply for the 13 patients with a single lesion ($p = 0.003$). Three out of 5 patients (60 %) with cardioembolic stroke had clinically silent DWI lesions in the anterior circulation in addition to their infratentorial lesions, whereas none of the 17 patients with other etiologies showed this pattern ($p = 0.008$).

Conclusion: For infratentorial infarcts, volume and number of early DWI lesions were not correlated with clinical outcome parameters. However, a lesion pattern of multiple lesions not restricted to either brainstem or cerebellum seemed to indicate a less favourable outcome. Multiple lesions and clinically silent lesions in the anterior circulation suggested a cardioembolic stroke etiology.

P363

High blood pressure in acute phase of stroke. F. F. A. Figueira, V. S. Santos, F. C. Silva, Hospital da Penitência (Rio de Janeiro, BR)

Background. Whether previously hypertensives or not, about 85 % patients with stroke entering Emergency Room (ER) present with high blood pressure (BP) levels at acute phase, with a spontaneous trend towards normalization as long as process evolves. Rational therapy requires correct understanding of these adaptative mechanisms, as they suggest a kind of response, in order to provide hemodynamic adjust to an acute ischemic situation. To address this question we studied retrospectively the files of Stroke Study Group, a standard protocol for early primary care to non-selected consecutive stroke patients at ER, introduced in our Hospital by Department of Neurology in September 1992. Complete protocol is available on line at www.ffigueira.net.

Methodology. From a cohort of 1423 patients consecutively admitted and submitted to protocol, final diagnosis was confirmed in 1226. All them were submitted to CT scan and ultrasonology study and stratified according to stroke subtypes. Estimates of stroke volume were defined thru imaging as small, moderate and large lesions, by the same observer to avoid inter-observer variation. BP was monitored every hour at first phase and every 4-hour at phase–2, and corrected as outlined in protocol.

Results. As much as 92 % patients presented with high BP levels at entry and more than 75 % had normal or near normal values at 15^{th} day, with no regular medication, whether or not previously hypertensives. There was a clear correlate between stroke volume and mean BP variation on large vessel disease and cardioembolism: larger strokes had a trend to higher BP variation throughout acute phase of protocol, with higher levels at entry and a trend to spontaneous normalization after 10^{th} day, whereas smaller ones and lacunae did not.

Conclusion. Acute stroke pathophysiology involves a sequence of events at cellular level triggered by ischemia which final step is cell death. Despite controversy, rationale for hemodynamic adjustment at acute ischemic insult aim to provide regional perfusion, directly or thru collateral channels, and BP levels are cornerstone for both. A correlate between stroke volume and BP levels variation as well as spontaneous trend to BP normalization after acute phase suggest a kind of compensatory mechanism: proper knowledge of it is fundamental for optimal care in stroke treatment.

P364

Recurring sub-dural hematoma revealing acquired hemophilia. I. Bonnaud, H. Broux, C. Guérois, E. Mercier, D. Saudeau, B. De Toffol, A. Autret, Hopital Bretonneau, Hopital Trousseau (Tours, F)

Background: Acquired hemophilia is a rare condition characterized by spontaneous haemorrhagic complications, which can be fatal in 15 to 20 % of cases. Neurological symptoms rarely reveal or complicate this coagulation disorder. We report the case of a patient with recurring sub-dural haematoma revealing an acquired haemophilia.

Case report. A 82-year-old man was on oral anticoagulant treatment for a cardiac arrhythmia.

He presented with headaches of abrupt onset and drowsiness, and a spontaneous acute left sub-dural haematoma was diagnosed. Abnormal preoperative haemostasis tests were noted and attributed to anticoagulant treatment.

Two weeks after surgery and after disruption of anticoagulant drugs, the patient was admitted again for seizures and a right hemiplegia. The CT scan showed a recurrence of the left sub-dural haematoma and the surgical evacuation was performed. Activated partial thromboplastin time (aPTT) remained abnormally prolonged.

After a week, voluminous sub-cutaneous and muscular haematomas appeared. APTT was prolonged, factor VIII:C (FVIII) levels were 2 %, and a FVIII inhibitor was detected, with a title of 4.4 Bethesda units. There was also a severe anaemia.

In spite of treatment with recombinant human factor VII (rFVIIa) infusion, prednisone (1 mg/kg per day), and cyclophosphamide (2 mg/kg per day), clinical and biological condition worsened and the patient was admitted in intensive care unit. Intravenous immunoglobulin treatment was initiated (30 g per day during six days). A week after the end of this treatment, FVIII level was 43 % and FVIII inhibitor was 0.72 Bethesda units. No causal disease was found associated with this acquired haemophilia.

Two months after, there were no residual haemorrhagic symptoms, haemostasis and coagulation tests were normalized, with degressive corticosteroids therapy alone.

Discussion: Acquired haemophilia is a severe and rare coagulation disorder causing sub-cutaneous and muscular bleeding. It may arise in association with auto-immune diseases, lymphoproliferative malignancy, pregnancy, and as a drug reaction. It can also occur in the oldest patients, without any associated disease.

Only a few cases of neurological complications have been reported in this disease.

Conclusion: Coagulation disorders such as acquired haemophilia should be considered, in case of recurrent intracranial haematomas.

P365
Imaging of post-ischemic hyperperfusion at the subacute stage of stroke with [11C] -Flumazenil PET. I. Bonnaud, L. Spelle, A. Autret, G. Rancurel, Y. Samson, Hopital Bretonneau, SHFJ. CEA, Hopital de la Salpêtrière (Tours, Orsay, Paris, F)

Background: [11C]- Flumazenil(CFLU) PET is used in various neurological disorders, because it allows to measure cerebral blood flow (CBF) variations and benzodiazepine receptors (BZR) density, providing a functional and structural reflect of cortical changes. It can be used in the subacute stage of stroke to monitor CBF changes and to evaluate permanent neuronal damage. Using this method, we studied one patient in the subacute stage of an hemispheric stroke, and four months later.

Case Report: A 47-year-old man was admitted with an aphasia of Broca's type and a right hemiparesis (NIHSS at admission: 16). The CT scanner examination at admission showed a slight hypodensity in the left superficial middle cerebral artery territory. Clinical improvement began early, and the patient was evaluated seven days after the onset of symptoms with clinical scores (NIHSS: 10; Barthel score: 85), standard MRI and CFLU PET. The PET examination was compared with those of ten normal subjects, and showed no CBF decrease ($p < 0.01$), but a large hyperperfusion in the clinically affected territory. This hyperperfusion was co-localized with BZR loss traducing neuronal damage (extent: 529 voxels, $p < 0.01$). Four months later, recovery was nearly perfect (NIHSS: 2, Barthel: 100), and the PET study disclosed no abnormal CBF variations. BZR density decrease, traducing permanent neuronal damage, was found ($p < 0.01$) in a less extensive cortical region (323 voxels) which appeared normal in the MRI T2 weighted images.

Conclusion: This PET study confirms that early post-ischemic hyperperfusion in ischemic regions with neuronal damage could be predictive of better outcome. In the subacute stage, BZR loss found in hyperperfused regions, may correspond not only to neuronal loss but also to other pathophysiological disturbances, such as reorganization of GABA inhibitory circuits. CFLU PET shows that such reorganization may occur late after stroke. Final BZR loss reflects permanent neuronal damage, and the small final structural abnormalities are correlated with the total recovery.

P366
Obstructive sleep apnea and extracranial atherosclerotic disease. A. Nachtmann, E. Wondzinski, A. Scharff, Y-M. Wang, A. F. Thilmann, FRR (Essen-Kettwig, D)

Introduction: Obstructive sleep apnoea (OSA) is suspected to be an independent risk factor for ischemic stroke. Several underlying pathomechanisms are currently discussed: one possible mechanism is a worsening influence on atherosclerosis. Thus, atherosclerosis should be detectable in a higher amount in obstructive sleep apnoea patients than in controls. To determine atherosclerotic burden, the ultrasonographically measured intima-media thickness (IMT) is an adequate parameter.

Methods: In 96 consecutive patients (mean age 60,5 ± 10,5 years, range 33 to 82 years, 74 male, 22 female) referred to diagnostic for sleep disordered breathing (SDB) three to four weeks after ischemic stroke, measurements of the IMT in the common carotid artery (CCA) were undertaken. Three blinded examiners measured the IMT offline in three different spots in the CCA on both sides, so that finally 18 single values formed a mean value per patient. If screening for SDB was positive or doubtful, full polysomnography was performed. Patients were then divided into three groups: severe OSA (respiratory disturbance index (RDI) > 20/h, n = 30), light to moderate OSA (RDI between 5 and 20/h, n = 18) and no OSA (RDI < 5/h, n = 36). All OSA patients were previously undiagnosed and untreated. Conventional risk factors (body mass index (BMI), hypertension, diabetes, smoking and hyperlipidemia) were recorded. Multiple regression analysis was performed using SPSS software.

Results: 12 patients, in whom only one carotid artery could be measured due to low picture quality or extended plaques, had to be excluded from further analysis. Mean IMT was 0,87 ± 0,16 mm in patients without OSA, 0,94 ± 0,15 in patients with light to moderate OSA and 0,96 ± 0,16 in patients with severe OSA. The difference between patients with severe OSA and asymptomatic controls was statistically significant ($P < 0,03$), even after adjustment for age, sex, BMI and conventional risk factors. Smoking, as measured in pack years ($p < 0,002$), age ($p < 0,04$) and prevalence of hypertension WHO grade II ($p < 0,02$) were significantly correlated with IMT too.

Discussion: A higher IMT in patients with severe OSA compared to controls supports the hypothesis of a possible atherogenic mechanism of OSA. As OSA is a treatable disease, a reduction of atherogenic impact and therefore reduction of the risk of stroke and myocardial infarction may be possible, but this has yet to be proven by further studies.

P367
Vigilance impairment caused by occlusion of the Pecheron artery: description of four cases. R. Gentile, L. Capone, R. Pentore, R. Schoenhuber, Regional Hospital (Bolzano, I)

Four patients affected by bithalamic stroke caused by occlusion of the Percheron's artery (or thalamo-perforating artery) are reported. The first patient (male, 33 years old) migrainous, was found comatous with anisocoria right < left and a light facial paresis right. The second (female, 87 years old), became suddenly stuporous and presented anisocoria right > left. The third one (male, 55years old) suffering from arterial hypertension, complained headache followed by memory impairment, sopor and a minimal facial paresis right. The fourth one (male 52 years old) was found comatous and with anisocoria left > right.

All patients were investigated to exclude metabolic and toxic causes. A computer tomography made immediately was negative in all cases. A following neuroradiologic control showed a bithalamic infarction in all patients. In all patients but one the consciousness improved and they complained a mesencephalic syndrome with ptosis and diplopia. Comment: In 30 % of population the vascularization of both thalami is supported by only one thalamo-perforating artery. The occlusion of this artery can be an unusual cause of sudden vigilance impairment with poor neurological focal signs.

P368
Stroke and depression: does the etiology count? S. Pires-Barata, I. Henriques, Hospital do Espirito Santo (Évora, P)

Introduction and purpose: Stroke patients suffer from depression but the relationship between stroke etiology and depression is not well known. We studied the association between stroke etiology and depressive simptomatology and looked for a prevalent depressive criteria.

Methods: We interviewed 22 stroke patients (11 men and 11 women) using the DSM-IV criteria for major depression. Patients were observed 2 to 12 months after stroke. We excluded patients with global aphasia, previous stroke and those who were unable to perform the interview. Age varied between 36 and 78 years.

Results: From 11 patients with hemorrhagic stroke, 5 were localized in the left hemisphere. Seven of the 11 isquemic strokes were also localized in the left hemisphere. Depressive symptoms were present in 59 % of the patients (23 % in hemorrhagic stroke and 36 % in isquemic stroke). Lost of interest in diary activities or life in general was present in 50 % of the patients and in 75 % of patients with depressive simptomatology. 28 % of the patients had previous criteria for depression, being all of them women that suffered an isquemic stroke.

Discussion: Depressive simptomatology is common after stroke. In our sample we found that the isquemic stroke patients were more likely to have depressive simptomatology. Lost of interest in diary activities was the most prevalent depressive symptom, so it might be used for early detection and treatment decision in stroke depression.

P369
Intravenous tissue plasminogen activator treatment in a patient with acute ischemic stroke related to bilateral internal carotid artery dissection. S. Busse, A. Khaw, M. Kirsch, C. Kessler, U. Schminke, University of Greifswald (Greifswald, D)

Intravenous (IV) tissue plasminogen activator (tPA) is considered an effective treatment in acute ischemic stroke within the first 3 hours after onset of symptoms. However, only scarce data exist on the safety of tPA treatment in patients with carotid artery dissections (CAD). Many clinicians concern that tPA might worsen the intramural hematoma, and therefore, they refrain patients from thrombolysis if a ICD is suspected on admission.

We report on a 46 year old Caucasian, otherwise healthy woman without any cardiovascular risk factors who presented to our stroke unit with complete right sided hemiplegia, global aphasia and bilateral ptosis. A few days prior to the event, she experienced an upper respiratory tract infection with bilateral neck pain. Initial computerised tomography (CT) scan revealed subtle early signs of an infarction restricted to the left basal ganglia. CT angiography of the intracranial vessels showed an occlusion of the left intracranial portion of the internal carotid artery (ICA), and additionally, an occlusion of the M1 segment of the left middle cerebral artery (MCA). Treatment with IV 0,9 mg/kg tPA within 3 hours after onset of symptoms resulted in a complete recanalization of the MCA occlusion as demonstrated by transcranial colour-coded duplexsonography. During further clinical work-up, bilateral CAD was suspected by extracranial color-coded sonography showing an occlusion with a tapered lumen in the

left ICA, and increased blood flow velocities in the right ICA about 3 cm distally to the bifurcation. The diagnosis was confirmed by magnetic resonance imaging (MRI) demonstrating intramural hematoma in both ICA at the level of the scull base. Under therapy with anticoagulants, the occluded ICA recanalized within 2 weeks. Clinically, the aphasia and the paresis of the lower extremity completely resolved, whereas the right arm remained severely paretic.

In conclusion, the present case report is consistent with other anecdotal reports supporting the hypothesis that IV thrombolysis can be performed safely in patients with acute ischemic stroke related to carotid artery dissection.

P370

Characterization of novel 5'-sequences of the murine glutamate transporter EAAT2 and regulation in a mouse model of hypoxia. C. Münch, B. Zhou, A. Leven, A. C. Ludolph, M. W. Riepe, T. Meyer, University of Ulm, Humboldt-University (Ulm, Berlin, D)

A reduced expression of the excitatory amino acid transporter 2 (EAAT2) has been described in ischemia and hypoxia. EAAT2 is the main carrier protein of glutamate uptake and serves to maintain extracellular glutamate below excitotoxic concentrations. In hypoxia, a loss of EAAT2 has been previously reported, however the mechanism of EAAT2 downregulation is unknown.

We report two novel splice variants (named mEAAT2/5 UT6 and mEAAT2/5 UT7) of the mouse EAAT2 encoding different 5'-untranslated sequences. In the murine CNS we found a region specific pattern of the novel 5'-splice variants of EAAT2 as shown by in situ-hybridization, northern blotting and competitive RT-PCR (GeneAmp rTh Reverse Transcriptase RNA PCR, Perkin Elmer). Furthermore we performed an expression study of all known EAAT2 5'-splice variants in a mouse model of chemical hypoxia generated by the treatment of 3-nitropropionic acid (3-NP). In the cerebellum, hippocampus and cortical regions we found a time and region-dependent alteration of expression of three splice variants (mEAAT2/5 UT3–5) from 24h to seven days following the administration of 3-NP.

We conclude that changes of quantitative expression of EAAT2 5'-sequences are part of the pathogenesis in the studied model of acute neurodegeneration and may contribute to the transporter dysfunction reported in ischemia and hypoxia.

P371

Disappearance of essential tremor after pontine stroke. O. Lermen, M. J. M. Dupuis, G. Picard, P. Jacquerye, N. Misson, Clin. St Pierre (Ottignies, B)

Background: Only two similar cases of essential tremor disappearance following posterior fossa strokes are reported. The accumulation of such observations may lead to more clinicoradiological observations and to the better understanding of essential tremor.

Case report with video presentation: A 75 year old diabetic and hypertensive man suffered from essential tremor for 6 years, partially responsive to Primidone. His father suffered from essential tremor at the age of 94. In January 2000 he was admitted to hospital for sudden mild right hemiparesis and dysmetria with unsteadiness and dysarthria. MRI showed a small left paramedian pontine stroke. After regression of the right hemiparesis and cerebellar syndrome, disappearance of the essential tremor of the right arm was noted and the patient appreciates the two years persisting functional improvement.

Conclusions: We interpret this case as an interruption of an afferent cerebellar pathway (on the fronto-ponto-cerebellar pathway before decussation) inducing the disappearance of essential tremor. Further such observations are useful to better understand the loops involved in essential tremor. The fact that two of the three cases observed are reported by our team may be explained by chance but may reflect also, that if enough interest is brought to strokes and movement disorders, many more informative clinicoradiological cases would be published. This may lead to a better understanding of the physiopathology of essential tremor.

P372

Cervical artery redundancy and dissection. S. Vassilopoulou, A. Tavernarakis, N.-M. Alexandri, P. Papageorgiou, I. Kaskarellis, C. Potagas, N. Matikas, Evangelismos Hospital (Athens, GR)

Dissection of cervical arteries is a frequent cause of stroke especially in young patients, but so far, the role of arterial morphologic abnormalities in its pathogenesis has not been clarified.

The aim of this study is to evaluate the relationship between redundant arteries and dissection.

We studied 35 consecutive patients (25 males and 10 females) 22 to 58 years old (mean age 42.1), hospitalised for angiographically-diagnosed dissection of cervical arteries. Morphologic abnormalities were observed in 23 patients (65.7 %). Redundancies concerned 39 vessels, 31 internal carotids and 8 vertebral arteries, and were classified as loops, kinks and coils.

The prevalence of dissection in carotids with coils or kinks (more severe redundancies) seems to be significant ($p = 0.05$), while there were no statistically significant results in the group of dissected vertebral arteries.

Factors such as sex, tobacco smoking, hypertension and hypercholesterolemia were not found to be related to frequency and type of redundancies. However, age was considered to be an important factor as we found that redundancies were more frequent in the elderly ($p < 0.02$). Since our study showed that coils and kinks are more often observed in patients over 42 years of age, we reached the conclusion that the age of patients also plays a role in the type and severity of morphologic abnormalities ($p < 0.05$).

P373

Cerebral protection with filter devices during carotid artery stenting. Our experience on 120 consecutive procedures. F. Vecchio, E. Menegazzo, C. Fattorello S, C. Cernetti, B. Reimers, P. Pascotto (Padua, Venice, I)

Objective: purpose of this prospective study was to determine periprocedural complications and short and medium-term outcomes in a cohort of patients (pts) treated with carotid stent implantation routinely using cerebral protection devices.

Materials and Methods: Stent implantation was attempted in 114 consecutive pts (mean age 70.8 ± 14 years; 70 % males) presenting significant stenosis (> 70 %; mean 82,8 % ± 9 %) in 120 lesions of the extracranial carotid artery. Fifty pts (43.8 %) presented previous stroke or transient ischemic attacks related to ipsilateral hemisphere. Cerebral protection was performed using filter devices in 120 lesions treated. Cerebral protection was performed using 3 different types of distal filter protection devices: Angioguard filters 90 % (108/120), Neuroshield filters 5 % (6/120), FilterWire EX filters 5 % (6/120). In 80 % (96/120) of filters, there was macroscopic evidence of debris. Collected material consisted of lipid-rich macrophages, fibrin material and cholesterol clefts.

Self expandable stents (mesh-wire 60 %; nitinol 40 %) were successfully implanted in all lesions.

Results: Neurological complications during the procedure and in-hospital, occurred after 3 procedures (2.5 %). These were 1 major stroke (1 %: amaurosis of ipsilateral eye) and 2 transient ischemic attacks (1.7 %).

During a follow-up of 9.3 ± 3.5 months (minimum 3 months) further neurologic events did not occur. Ecocolor-Doppler TSA at 6 months after the procedure was available in all lesions treated; restenosis in-stent > 50 % was found in 3 lesions (2.5 %). Major adverse cardiac events during follow-up occurred in 2 pts (1.8 %) and these were 1 fatal and 1 non fatal myocardial infarction.

Conclusions: Incidence of procedural complication during carotid artery stenting with routine use of cerebral protection appeared low. During the follow-up further neurological events did not occur and the frequency of the restenosis was low.

P374

Dissection of cervical arteries: factors that contribute to the severity of clinical outcome. P. Papageorgiou, A. Tavernerakis, N.-M. Alexandri, S. Vassilopoulou, C. Potagas, N. Matikas, Evangelismos Hospital (Athens, GR)

Severe disability and handicap frequently follow stroke due to dissection of cervical arteries.

The aim of this study is to view the relationship between possible risk factors and clinical outcome in dissection of cervical arteries.

We studied 43 consecutive patients (30 males, 13 females) 22 to 60 years old, hospitalised for cervical dissection. Patients were divided in two groups depending on the severity of clinical outcome. In the first group patients suffered either transient ischemic attack, local symptoms or had mild disability and in the second group patients had severe neurologic deficits (severe hemiplegia, tetraplegia or aphasia). Sex, age, hypertension, tobacco smoking, site and multiplicity of dissections were studied in both groups.

In the group with severe clinical outcome the frequency of double dissection, especially bilateral carotid dissection, is significantly higher ($p = 0.01$). We found no remarkable relation between other parameters and clinical outcome.

P375
Endothelial dysfunction in ischemic stroke. A case-control study. B Fuentes, E Díez Tejedor, M.C Garcés, J Gómez Cerezo, A. Fernandez Pavón, P Barreiro, University Hospital La Paz (Madrid, E)

Introduction: Endothelial dysfunction has been implied in acute coronary disease and related with prognosis. Our objective was to analyse if endothelial dysfunction markers are also present in stroke patients.

Methods: Prospective case-control study including patients with ischemic stroke diagnosis as cases and emergency room patients with non-ischemic diseases as controls pared by gender, age and vascular risk factors. Blood samples were taken on emergency department both in cases and in controls, and von Willebrand factor (vWF)and tissular factor (TF) were determined as endothelial dysfunction markers.

Results: 38 ischemic stroke patients and 22 controls were included. Mean vWF and TF values were higher in stroke patients (193.9 (vWF) and 451.2 (TF) pg/ml vs 145.2 (vWF) and 298.2 (TF) pc/ml; $p < 0,05$). 3 moths follow up blood sample analysis in stroke patients revealed still higher vWF and TF factors (152.0 and 501.7 pg/ml respectively).

Conclusions: Plasmatic levels of some endothelial dysfunction markers as vWF and TF are increased in acute stroke patients and remains high at three moths of follow up. These findings are not present in other acute, non-ischemic patients. These data support the current hypothesis that endothelial dysfunction markers could be not only a lesion marker but a risk marker. Further prospective studies are necessary to confirm this point.

P376
A case of multiple brain infarctions associated with Erysipelothrix rhusiopathiae endocarditis. S.B Ko, D.E Kim, J.K Roh, Seoul National University (Seoul, KOR)

Background: Human infection of Erysipelothrix rhusiopathiae is rare and its intracranial manifestation is rarely described. Case report: A 63-year-old woman was admitted to our hospital because of fever and coma. She was a heavy drinker. One month before admission, she cut her fingers with a sickle during work but kept on digging out a shellfish at the estuary. Twenty days before admission, she developed headache and fever. Nine days before admission, fever aggravated, so she admitted to our hospital. On examinations, she was comatous and body temperature was 38.5 degree centigrade. Cardiac auscultation revealed diastolic murmur. Transthoracic echocardiography revealed vegetations in aortic valve. Brain MRI revealed multiple high signal intensities on T2-weighted images at bilateral thalamus, basal ganglia and cortico-subcortical areas. Corresponding regions were high signal intensities on Diffusion-weighted images (DWI) and low signal intensities on Apparent Diffusion Coefficient (ADC) map. Gradient-Echo (GE) images showed multiplicity of lesions more accurately as low signal intensity. She was diagnosed as multiple hemorrhagic infarctions associated with bacterial endocarditis and the pathogen was later identified as Erysipelothrix rhusiopathiae. Penicillin G (18 million units per day in six divided doses) and ceftriaxone (2 g twice a day) improved her mental status and fever in 6 weeks. Discussion and comment: There are some interesting points in our case. In our knowledge, it is the first report precisely describing intracranial manifestation of Erysipelothrix rhusiopathiae endocarditis. There is one case report describing intracranial manifestations of Erysipelothrix rhusiopathiae infection briefly as hemorrhagic infarction. Our case described hemorrhagic infarctions using DWI, and GE image revealed the lesion more accurately because of its hemorrhagic tendency. She worked with a wound in her hand at the estuary, where the pathogen are rich, and our patient was a heavy drinker and found to have liver cirrhosis during work-up, these played some role in provoking endocarditis and hemorrhagic infarctions in this case. Conclusion: We report a case of multiple hemorrhagic infarctions associated with Erysipelothrix rhusiopathiae endocarditis and its location is more accurately revealed on GE images. Heavy drinking and liver cirrhosis played some role in the intracranial manifestation.

Clinical Neurophysiology

P377
Idiopathic scoliosis:a transcranial magnetic stimulation study. V. K. Kimiskidis, M. Potoupnis, S. Papagiannopoulos, G. Dimopoulos, G. Kapetanos, A. Kazis, Aristotle University of Thessaloniki (Thessaloniki, GR)

Background: Idiopathic scoliosis (IS) is a deformity of the spine of unknown aetiology. Previous studies associated IS with pathological asymmetries of the cerebral cortex and the brain stem at the level of the corticospinal tracts.

Goals of the study: To investigate the motor system of scoliotic patients with transcranial magnetic stimulation.

Methods: 21 female patients with right IS (mean age = 12.7,scoliotic curves:20–40o) and 20 normal subjects (mean age = 13.8) were studied. Stimulation was performed with a figure of 8 coil for upper limbs (recording:1st dorsal interosseous) and a double cone coil for lower limbs (recording: abductor hallucis).Lower (LT), upper (UT) and mean (MT) threshold were defined at rest according to the method of Mills & Nithi. Other parameters included UT-LT range, central motor conduction time (CMCT, F-wave method), cortex to muscle latencies (Cx-M resting and facilitated),F- and M-wave latencies, silent period (SP) duration (at 130 % MT stimulus intensity),amplitude and area of MEPs. For all parameters asymmetries between the two hemispheres were calculated. Electrophysiological data were correlated with the degrees of the scoliotic curve and the Perdriole and Nash & Moe indexes.

Results: In upper limbs, patients had a right hemisphere (R Hem) MT of 40.4 ± 7.9 (vs. 43.7 ± 8.5 in controls), a left hemisphere (L Hem) MT of 39.8 ± 7.8 (vs. 43.4 ± 5.5) and an MT asymmetry of 4.4 ± 2.4 (vs. 3.8 ± 3.5). R Hem SP duration was 124.2 ± 32.5ms (vs. 124.05 ± 32.5), L Hem SP duration was 130.8 ± 36.9 (vs. 137.4 ± 35.9), R Hem CMCT was 3.8 ± 0.6ms (vs. 3.6 ± 0.6) and L Hem CMCT was 3.8 ± 0.8 (vs. 3.8 ± 0.7). None of the examined parameters differed from those of the control group. In lower limbs, asymmetry of facilitated Cx-M was 1.4 ± 0.75ms in IS (vs. 0.71 ± 0.47 in controls) and correlated significantly with Nash & Moe and Perdriole indexes (Spearman's $r = 0,554$ and 0.575 respectively, $p < 0.05$).Other parameters did not differ from the control group.

Conclusion: IS is associated with increased asymmetry of facilitated cortex to muscle latencies to lower limbs. This novel finding is correlated with measures of the rotational deviation of the spine.

P378
Fosphenitoin-methylprednisolone neuroprotection during cardiac surgery. A. Sehic, E. Austin, T. Yeh, S. Pollock, H. Edmonds, University of Louisville, Norton and Kosair Childrens Hospital (Louisville, USA)

This study was a retrospective analysis of the neurologic complications following adult and paediatric cardiac surgery in 759 patients during the years 2000 –2001.

Methods: In all cases, multi-modality neuromonitoring was performed which included bihemispheric cerebral oxymetry (INVOS 5100, Somanetics, Troy, MI, USA), transcranial Doppler (Companion, Nicolet Vascular, Golden, CO, USA) and computer-processed 4 channel EEG (A–1000, Aspect Medical, Newton, MA, USA). Persistent signs of regional cerebral ischemia (brain O2 desaturation > 20 % and/or > 50 % decline in relative alpha or total EEG power) were often treated with fosphenytoin 15 mg/kg + methylprednisolone 10 mg/kg (F+M).

Results: Noteworthy EEG changes occurred in 44 (5.8 %) of the cases. In 34 of these cases, F+M was administered following termination of cardiopulmonary bypass. In no case was the 20-minute fosphenytoin infusion associated with hypotension or myocardial depression. There were no neurologic complications in this group. In contrast, F+M was not administered to 10 patients with EEG changes. Subsequently, 9 (90 %) of them developed major neurologic complications ($P < 0.001$). One of 716 (0.1 %) patients without sustained EEG changes experienced a new major neurologic complication during initial recovery from anaesthesia.

Discussion: Fosphenytoin has been shown to exert neuroprotective effects in animal models of cerebral ischemia (1). Here, we make the first report of an apparent reduction in the post-cardiac surgery stroke rate associated with EEG and oxymeter-based fosphenytoin + methylprednisolone administration. The neuroprotective action may be related to fosphenytoin inhibition of apoptosis by reduction of sodium and calcium flux through non-inactivating ion channels (2). In the absence of pharmacologic neuroprotection, the computer-processed 4-channel EEG combined with cerebral oxymetry was a highly predictive of developing brain injury. References:1.Chan SA, Reid KH, Schurr A et al. Fosphenytoin reduces hippocampal neuronal damage in rat following transient global ischemia. Acta Neurochir 1998;140:175–80. – 2.Taylor CP. Sodium currents that fail to inactivate. Trends Neurol Sci 1993;16(11):455–60.

P379

Eye torsion after blinks reveals vestibular imbalance. E. Schneider, S. Glasauer, M. Dieterich, Ludwig-Maximilians Universität, Johannes-Gutenberg Universität (Munich, Mainz, D)

In a recent study we found that blinks in healthy volunteers triggered ocular torsion (OT) quick phases during head rotations in roll [1]. On the basis of this observation we hypothesized that blinks in patients with a vestibular tone imbalance would have the same effect on OT.

Using video-oculography with a fixation target, we recorded the OT of the left eye of 27 participants while they made voluntary blinks once every 10 sec. The participants were recruited from 3 groups: A) healthy volunteers ($n = 9$, mean 33 ± 4 SD years of age); B) healthy age matched volunteers ($n = 9$, 64 ± 13 a); C) patients with a unilateral vestibular disorder such as vestibular neuritis or Menière's syndrome ($n = 10$, 55 ± 18 a).

In normals (groups A and B) blinks triggered no or only small quick phases of 0.1 ± 0.1 and 0.2 ± 0.1 deg, respectively. In the patients (group C) blinks always triggered quick phases with significantly higher amplitudes of 2.1 ± 1.3 deg ($p < 0.0005$). They were followed by exponentially shaped slow phases. The direction of quick phases was (counter-) clockwise in patients with a disorder of the left (right) side. By coincidence, we had recorded the OT of one patient prior to his acute vestibular disorder and had not observed any effect of blinks.

We conclude that blinks are able to trigger torsional quick phases in patients with a unilateral vestibular disorder. Thus, OT recordings during blinks can be used as a clinical bedside test for a vestibular tone imbalance. The side of the impairment can be determined from the direction in which the eye is rotated after a blink.

This study was supported by the Deutsche Forschungsgemeinschaft (Br 639/5–3; DI 379/4–1) and Fritz Thyssen-Stiftung.

Reference

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P380

Quantification of the interferential electromyographic pattern (IEP) by using a normative area defined by the maximal and the mean value of the turns/amplitude ratio. B. Zeevaert, F. C. Wang, University of Liège (Liège, B)

In this paper, we propose an easy, fast and reproducible method to quantify the IEP without muscular straight measurement.

Normative data were collected from 50 healthy volunteer subjects (mean age: 38 ± 17 years). The tibialis anterior muscle was studied. In each subject, 66 concentric needle (uptake area: 0,003 mm§) EMG recordings epochs of 1 msec were obtained during 6 to 10 sec-periods of active dorsiflexion of the ankle with progressive rising force. These data were analysed by using the automatic IEP decomposition software, developed by Stalberg (Keypoint).

In the present study, from the 66 calculated turns/amplitude (T/A) ratios, we considered the maximal (Max T/A) and the mean (Mean T/A)values.

Results were reproducible. In fact, coefficients of variation for Max T/A and Mean T/A were 7 and 11 % respectively. The mean MAX T/A in the 50 control subjects was 0.98 ± 0.24 (upper and lower limits of normal: 1.44 and 0.52) while the mean of the 50 Mean T/A values was 0.57 ± 0.14 (upper and lower limit of normal: 0.84 and 0.31)

Retrospective determination of the Max T/A and Mean T/A values in a myopathic population ($n = 27$, mean age 39 ± 16 years) indicated a significant ($p < 0.0001$) increase in both variables (Max T/A: 1.71 ± 0.52; Mean T/A: 1.02 ± 0.35). Conversely, in patients with neuropathies ($n = 30$; mean age $= 49 \pm 11$ years), there was a significant ($p < 0.0001$) decrease of both Max T/A (0.46 ± 0.22) and Mean T/A (0.24 ± 0.11).

The relationship between Max T/A and Mean T/A showed a highly significant correlation ($r = 0.78$, $p < 0.0001$) defined by the following equation $1/y = 0.209+1.52/x$. The association of the prediction interval of this relationship with the normative values defined above gave us normative area. The application of this area to the myopathic and the neuropathic population enable us to discern abnormal quantitative pattern in 77 % and 82 % of the subjects.

P381

Catecholamine release in human skin – a microdialysis study. S. Drenkhahn, S. Leis, C. Arnolt, A. Bickel, M. Schmelz, F. Birklein, University of Erlangen, University of Wurzburg, University of Mainz (Erlangen, Wurzburg, Mainz, D)

Introduction: Nowadays, investigation of catecholaminergic neurons comprises variable vasoconstrictor reflexes or indirect measurements of skin temperature. Dermal microdialysis, however, might be a promising tool to directly investigate peripheral sympathetic neurons.

Methods: Dermal microdialysis ($n = 21$) was performed on distal limbs in 14 healthy subjects. 4 microdialysis fibres (200 µm diameter, cutoff 5 kDa) were inserted intradermally to a length of 1.5 cm and perfused with saline (flow rate: 4 µl/min). After baseline (1 hour) the perfusion was changed to tyramine for 13 min (stimulation). Tyramine concentrations varied from 0.195 to 200 /ml. Finally, the system was perfused with saline again for further 13 min (washout). Blood samples were taken to control systemic catecholamine levels. Dopamine (DA) and Noradrenaline (NA) concentrations were assessed by HPLC-ED. Control experiments were performed in homogenised human skin samples with and without tyramine incubation.

Results: NA in the dialysate increased from baseline of 36.3 ± 10.2 pg/ml to 84.4 ± 18.4 pg/ml during stimulation ($p < 0.001$) and declined again to 57.1 ± 13.2 pg/ml during washout (n. s). DA increased more than 50-fold during tyramine (baseline 105.2 ± 36.5 pg/ml, stimulation 7162.4 ± 3972.4 pg/ml; $p < 0.001$) and decreased to 1369.7 ± 666.7 pg/ml during washout ($p < 0.001$). Tyramine induced NA- and DA-release was dose dependent (NA: $r = 0.438$, $p < 0.05$; DA: $r = 0.894$, $p < 0.001$). Plasma catecholamine levels were in the normal range. In homogenised skin, NA and Adrenaline (A) after incubation with tyramine (NA: 726.2 ± 13.8 pg/ml, A: 130.2 ± 3.7 pg/ml) did not differ from before (NA: 754.0 ± 11.4 pg/ml, A: 126.6 ± 2.8 pg/ml). DA concentrations, however, were about 30-fold higher after tyramine. (387.0 ± 34.8 pg/ml, control: 13.2 ± 2.4 pg/ml; $p < 0.05$).

Conclusion: Our experiments show that dermal microdialysis is able to measure NA release from sympathetic neurons in human skin. Intradermal dopamine transformation from tyramine is independent from neuronal mechanisms.

P382

Short-latency postural reflexes in patients with bilateral vestibulopathy. K. Bötzel, J. Fischereder, Ludwig-Maximilians-Universität (Munich, D)

A tap with a reflex hammer applied to the forehead can evoke a reflex in the neck muscles similar to a loud click sent via headphones. We applied forehead-taps to 15 standing subjects with bilateral vestibulopathy of different causes, which were mostly complete. We recorded the electromyographic responses of lower leg muscles and averaged these responses after rectification. The same tests were applied to a control group. We found that tap evoked leg muscle responses were easily obtainable from both the healthy subjects and those with vestibulopathy. These data show that tap-evoked leg muscle response are reliably recordable in healthy subjects and that they are probably not of vestibular but proprioceptive origin (neck muscle receptors).

P383

Central motor conduction in acute relapsing-remitting versus chronic progressive multiple sclerosis. A. M. Humm, A. Truffert, M. R. Magistris, K. M. Rösler, Inselspital, HUG (Berne, Geneva, CH)

Background: Multiple sclerosis (MS) can induce both a deficit of central motor conduction and an increase of central motor conduction time (CMCT).

Objective: To analyze central motor conduction in patients with relapsing-remitting MS (RR-MS) and with primary or secondary progressive MS (P-MS).

Methods: We studied 81 patients with definite RR-MS and 44 with definite P-MS. In each patient, the central conduction of the clinically most affected limb was chosen to compare the two groups. Presence or absence of muscle weakness and pyramidal signs (hyperreflexia, Babinski and Hoffman signs, spasticity) of that limb were noted. The triple stimulation technique (TST) was used to measure the conduction deficit (Magistris et al., 1998, 1999). The TST combines transcranial magnetic stimulation with a peripheral collision that allows eliminating the effects of discharge desynchronisation of the target motor neurons. The amplitude of the TST response allows a quantification of the proportion of conducting central motor neurons. Conventional motor evoked potentials were used to measure

the CMCT. Recordings were taken from abductor digiti minimi (n = 69) or abductor hallucis (n = 56). To allow combined analysis of upper and lower limbs, TST amplitude and CMCT were expressed as percentage of the respective mean values of healthy controls.

Results: TST amplitude was significantly reduced in weak sides (mean TST amplitude without paresis 80.3 %, with paresis 60.1 %; p = 0.006). It was the same in RR-MS and P-MS (corrected for presence or absence of muscle weakness and/or pyramidal signs; p > 0.05). CMCT was independent of muscle weakness and pyramidal signs (p > 0.05). It did not correlate with disease duration. CMCT was however markedly longer in P-MS (175.9 % of the mean normal value) than in RR-MS (111.3 %; p < 0.0001).

Discussion: The TST measurement of conduction deficit related well to the clinical muscle weakness. It did not differ in RR-MS and P-MS, suggesting similar motor deficit in our two groups.

Despite this similarity, the CMCT was markedly longer in P-MS than in RR-MS. The CMCT difference was not related to the presence of spinal cord lesions (which had the same frequency in the two patient groups), and not to disease duration. Thus, our results suggest that marked central conduction slowing may relate to the type of lesion in P-MS. We hypothesize that it may be linked to restoration phenomena, and result from slow conduction along remyelinated or unmyelinated fibres.

P384

Impaired excitatory and inhibitory cortical circuits in patients with corticobasal ganglionic degeneration. A. Kühn, T. Trottenberg, B.-U. Meyer, S. A. Brandt, A. Kupsch, Charité, Campus Virchow-Klinikum (Berlin, D)

Previous TMS-studies on patients with corticobasal ganglionic degeneration (CBGD) revealed decreased cortical excitability1 and a shortened silent period2. Others3 described an enhanced excitability and a larger extension of the cortical map obtained from the responses in hand muscles to TMS of the hemisphere contralateral to the most affected side correlating with a prominent alien hand syndrome in CBGD. By systematically measuring cortical excitability and transcallosal inhibitory effects we tried to identify specific electrophysiological parameters correlating with distinct clinical features of CBGD.

10 probable CBGD patients and 10 age-matched controls were examined. Five patients had a myoclonus of the dominantly affected upper limb. TMS was performed over both motor cortices with 80 % of max. stimulator output. Excitatory (motor threshold, CMAP onset latency and amplitude) and inhibitory stimulation effects (onset latency and duration of transcallosal inhibition – TI and postexcitatory inhibition – PI) were recorded bilaterally from the tonically contracted first dorsal interosseus muscle.

Contralateral motor responses (cMEP) could be elicited in all patients with normal onset latencies. Interestingly, patients without myoclonus had a significantly higher threshold (60,9 % ± 18,5) compared with those with myoclonus (39,1 % +/– 8,0) and controls (39,7 % ± 5,9). PI was significantly shorter in patients (117,8ms ± 52,3) than in controls (182,5ms ± 48,5). TI occurred in 10 out of 20 muscles partly with a shorter duration, a lower degree of inhibition and increased transcallosal conduction time. Ipsilateral excitatory motor responses (iMEP) were present in four of five patients with myoclonus in hand muscles of the predominantly affected side. Mean onset latency of the iMEP was 8,4 ± 1,7ms longer compared with cMEP evoked in the same muscle by stimulation over the contralateral hemisphere.

CBGD patients showed a decreased excitability of corticospinal neurones and of neurones being involved in the generation of TI and PI. We observed a systematic difference of motor cortex excitability in patients with and without myoclonus, suggesting a pathologic hyperexcitability of the motor cortex in those with myoclonus. This may be due to a loss of inhibitory neurones, which is reflected in the shortened PI and TI. Furthermore, iMEP might indicate a disinhibition of pre-existing ipsilateral motor pathways as it has been discussed for patients after stroke. Alternatively, transcallosal activation of the contralateral motor cortex could be responsible. We conclude that CBGD with and without myoclonus differ in their electrophysiological parameters characterizing motor cortex excitability and transcallosal inhibition.

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P385

Examination of central and peripheral motor pathways by standardized magnetic stimulation during voluntary contraction of the contralateral homonymous muscles. H. Takada, M. Ravnborg, Iwaki National Hospital, Rigshospitalet (Aomori-Namioka, JP; Copenhagen, DK)

Facilitation to transcranial magnetic stimulation by standardized voluntary contraction of ipsilateral muscles has been widely used for evaluation of central motor pathways in various neurological disorders. However, it is difficult to obtain ipsilateral facilitation effects in some cases. The aim of the present study, therefore, established normal values for motor evoked potential (MEP) examinations using contralateral facilitation effects. MEPs were recorded from 6 muscles bilaterally in 60 healthy volunteers aged 12 to 81 years. The mean height was 170.7 cm ranging from 154 to 197 cm. Facilitation was effectuated by maximum isometric voluntary contraction of the contralateral homonymous muscles. The target muscles were: the brachial biceps (BB), the radial carpal flexor (FCR), the first dorsal interosseus of the hand (FDI), the medial vastus of the quadriceps muscle (VM), the anterior tibial (TA) and the abductor hallucis muscles (AH). The parameters used were the conduction times and the amplitudes of the MEPs elicited by brain and root stimulation. The central conduction time (CMCT) was calculated by subtraction of the peripheral conduction time (PCT; MEP latency by root stimulation) from the total conduction time (TCT; MEP latency by cortical stimulation). MEPs could be recorded from all muscles in all but one subject in whom both of the cortical and root stimulations were unsuccessful in one VM, one TA and one AH. There was no significant difference between parameters of the two sides. The average conduction times or amplitudes of the two sides were consequently applied for statistical analysis. Height and PCTs or TCTs were significantly correlated in all target muscles, while height and CMCTs were not correlated in BB, FCR or FDI. Regarding amplitudes, the correlations with height were inconsistent. There was no significant correlation between age and conduction times except for PCTs in VM, TA and AH. Negative correlation was found between age and amplitudes in MEPs elicited by root stimulation, not by cortical stimulation.

P386

Motor potentials in acute traumatic brain injury: a prospecitve one year follow-up. H. Wiese, P. Stude, K. Nebel, H.-C. Diener, M. Keidel, Universitätsklinikum Essen, District Hospital of Bayreuth (Essen, Bayreuth, D)

Background: Focal brain lesions due to traumatic brain injury (TBI) do not only lead to functional deficits in the lesion area, but also disturb the structurally intact neuronal network connected to the lesion site. Therefore, a deficit in the neuronal motor network after frontal TBI is hypothesized. The motor potential (MP) is an EEG-measure related to voluntary movement. It is divided into an early, slow rising negativation from up to 1800 ms to about 300 ms before movement onset (Bereitschaftspotential, BP), and a later, more rapidly rising phase from about 300 ms to the time of movement onset (Negative Slope, NS). MPs reflect the local neuronal activity at a particular electrode position, that largely depends on interrelations of the network's single components.

Goal: Therefore the aim of our prospective longitudinal study was to demonstrate alterations and recovery in the movement-related cortical network after TBI (MRI-defined contusion of the left frontal cortex) by comparing the temporal and topographical pattern of the patients MPs to those of a healthy control group.

Methods: EEG of 22 patients (41 ± 14.6 years) 6 weeks and one year after TBI and of 28 normal subjects (34 ± 9.8 years) was recorded from 30 electrodes according to the 10–20-system. In relation to movement onset (self-paced, brisk abduction of the right index finger), EEG-data were segmented, filtered and averaged.

Results: In normal subjects the BP (1750–300 ms before movement onset) was observed followed by the NS-component, with a maximum shortly after the onset of finger movements over fronto-central and central midline leads and a preponderance over the hemisphere contralateral to the movement. In the initial phase after TBI, the onset of BP was delayed, starting at about –1200 ms. NS was less pronounced and showed a decreased peak negativity in central and fronto-central midline leads. One year after TBI the initially observed less pronounced negativity recovered and exceeded normal controls in left central and fronto-central leads. Further, a more distinct negativation in the patient group after movement onset was evident in left, central and right EEG recordings.

Conclusion: The results demonstrate a deficient neuronal activity of the involved motor network prior to voluntary movement in the initial phase after frontal TBI. This deficit recovered during one year. Finally, an increased neuronal activity in the contralateral motor cortex and adjacent areas was observed before movement onset. We suggest that, in addition to

other methods, the analysis of the temporal and topographical pattern of MPs represents a possibility to investigate alterations and recovery of the neuronal motor network after TBI.

P387
Denial in acute stroke. L. Caeiro, J Ferro, R. Albuquerque, L. Figueira, Hospital Santa Maria Dpt. of Neurology (Lisbon, P)

Background and purpose: Denial is a frequent psychological defect in acute stroke and may have a negative influence in the care of patients. The aim of this study was to investigate the presence and correlates of denial in acute stroke. Patients and methods: Between April 2000 and June 2001 we assessed denial in a sample of 218 consecutive inpatients with an acute (< 5 days) stroke (28 subarachnoid haemorrhages (SAH), 48 intracerebral haemorrhages (ICH), 142 cerebral infarcts (CI)) with the Denial of Illness Scale (DIS), and related the presence and intensity of denial with clinical, imaging and neuropsychiatric data. Results: 57 (31 %) patients presented denial (mean DIS scores = 4, SD = 2.2, range 0 to 10), of mild (16 %), moderate (18 %) and severe (7 %) degree. Denial was more frequent after SAH (OR = 2.1, p = 0.04) or after a right hemispherical (OR = 2.69, p = 0.02). Neglect was more frequent (OR = 4.84, p = 0.0001) in patients with denial. DIS scores were associated with depressed mood (p = 0.0001), feelings of guilt (p = 0.008), apathy (p = 0.0001) and hyperemotivity (p = 0.0001). Conclusions: Denial is a frequent finding in acute stroke and appears to be related with neglect, depressive symptoms and specific lesion sites (right and basofrontal).

Dementia/Higher function disorders

P388
Cognitive decline associated with stroke. I. Barbov, I. Petrov, V. Petrova, A. Popovski, Medical Center, Clinic of Neurology (Strumica, Skopje, MK)

Background: The causes and characteristics of cognitive impairment after stroke and the risk factors related to poststroke dementia are still not well identified.

Purpose: to evaluate the cognitive capacities in a cohort of ischemic/hemorrhagic stroke survivors and to identify the clinical determinants of poststroke cognitive decline.

Methods: 185 consecutive patients admitted to a Stroke Unit with a ischemic (141) or hemorrhagic (44) stroke were evaluated 6 months after the stroke with a neuropsychological battery that included a screening battery (the Mini Mental State Examination, tests for the assessment of memory, the Hamilton Depression Scale and the Hachinski Ischemic Score) and a comprehensive battery administrated to those who had a low score in the MMSE or in the memory screening test. Vascular dementia was defined according to the DSM IV criteria.

Results: 185 patients were evaluated. Six months after the stroke 87 (47 %) patients had no cognitive impairment; 50 (27 %) had deficits in cognitive domains other than memory; 13 (7 %) had focal memory deficits; 15 (8 %) had memory deficit and impairment in one other cognitive domain; 11 (6 %) had cognitive deficits compatible with dementia. 9 (5 %) patients were not possible to classify because they had severe aphasia. Demented patients were older than non-demented. Patients with memory deficits were also older than patients without memory dysfunction and had a lower education level. Memory dysfunction was associated to alcohol consumption (x§ = 4.85; p = 0.027). Lesion type, side and localization of the demented group were heterogeneous (9 ischemic stoke, 2 hemorrhagic stroke; 5 left side lesion, 3 right side lesion, 3 bilateral infarctions; 6 subcortical lesions, 3 cortical, 2 cortical and subcortical lesion).

Conclusions: Our data suggests that impairment in cognitive domains other than memory are the most frequent deficits found six months after the stroke. Memory deficits were associated with age, low education and alcohol consumption. The causes of poststroke dementia seem to be multiple, including strategic lesion location, multiple lesions and aging.

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The 129 codon polymorphism of the prion protein gene influences cognitive performance in sown Syndrome subjects. R. Del Bo, G. P. Comi, R. Giorda, M. Crimi, F. Locatelli, F. Martinelli-Boneschi, U. Pozzoli, E. Castelli, N. Bresolin, G. Scarlato, Università degli Studi di Milano, I. R. C. C.S. E. Medea (Milan, Bosisio Parini, I)

Prion Protein gene (PRNP) presents a common polymorphism at codon 129 encoding either methionine (M) or valine (V); homozygosity at this locus predisposes to sporadic or iatrogenic forms of Creutzfeldt-Jakob disease. Recently, variability at codon 129 has been evaluated in elderly people, in subjects affected by non-familial forms of Alzheimer's disease (AD) and in sporadic inclusion-body myositis. This polymorphism can be considered an interesting marker of potential genetic variability and can be a suitable candidate for an association with AD, a disorder characterised by neuronal degeneration and synaptic loss. Down Syndrome (DS) is associated to mental retardation and development of Alzheimer-like brain abnormalities. To determine the potential role of PrP in processes leading to neurodegeneration, we studied the influence of genetic variability of the PRNP gene at codon 129 on cognitive performance in 122 DS subjects (56 males and 66 females; mean age: 17.5 ± 8.9 yrs, ranging from 5 to 49 yrs) living in the North of Italy. Allele frequencies of DS subjects did not differ from general population (MM 44.3 %, MV 41.8 %, VV 13.9 %). No significant difference in genotype frequencies was found between DS patients with either severe and profound (FIQ < 50) or moderate and mild retardation (FIQ > = 50), although V+ carriers have a higher risk to be severely mentally retarded according to a multivariate logistic regression model adjusted for age and sex (OR:2.17; 95 %CI: 0.54–8.75; ref. MM). However, a significant inverse correlation between age and IQ scores was detected only in the subgroups of DS subjects carrying at least one V allele (MM: r:–0.23; MV: r:–0.35, p < 0.05; VV: r:–0.69, p = 0.001, Pearson's correlation). We found a significantly faster rate of decline in intellectual ability – expressed as mean value of FIQ points' loss/year – in the subgroup of DS patients carrying at least one V allele compared to the M/M DS subjects (MM: –0.43 ± 0.77 vs VV: –1.71 ± 1.24; p < 0.05). An additive deleterious effect of apolipoprotein E e4 allele was detected after stratifying by APOE gene status (MV/VVe4-: –0.63 ± 1.25 vs MV/VVe4+: –1.64 ± 1.30; p < 0.05). Our results evidence that variability of the PRNP gene at codon 129 in DS subjects may affect their intellectual performance: in particular, Valine phenotype may play a role in influencing cognitive abilities in DS subjects – alone or in combination with e4 allele – mainly by affecting progression of mental deterioration.

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Tc 99m-HMPAO SPECT in the evaluation of progress of cognitive dysfunction in various types of dementia. W. Lojkowska, T. Jedrzejczak, D. Ryglewicz, H. Jarosz, S. Minc, T. Jakubowska, A. Bochynska, I. Kozlowicz, Institute of Psychiatry and Neurology, Institute of Oncology (Warsaw, PL)

Cholinesterase inhibitors (ChE) are widely approved in the symptomatic treatment of patients with mild to moderate Alzheimer's disease (AD). There is also an increasing evidence to suggest that patients with vascular dementia (VaD) exhibit a cholinergic deficit and good response to ChE treatment could be observed. The MMSE has been criticized for the lack of sensitivity, especially in patients with mild AD. Some studies indicate that there is a relationship between various aspects of cognitive function impairment and regional Cerebral Blood Flow (rCBF). SPECT permits to assess decrease of cortical perfusion and could potentially be useful for diagnosis of dementia and for evaluation of ChE therapy effects. The aim of this study was to assess the relation between effects of cholinesterase inhibitors therapy and rCBF disturbances in SPECT.

Material & methods: Out of 41 patients with mild to moderate dementia, in 33 patients AD (NINDS ARDRA criteria) and in 8 patients VaD (NINDS-AIREN criteria) were diagnosed. In all patients, after clinical assessment (CT or MRI and a battery of neuropsychological tests) SPECT examination was performed. ChE therapy was introduced in 25 patients with AD and in 8 patients with VaD, while 8 patients refused ChE treatment. At a 12 month follow-up a control neurological examination, neuropsychological tests and SPECT were repeated in all patients. In SPECT semiquantitative analysis was performed over the cerebrum and the cerebellum using circuit regions of interests (ROIs). Subjects were injected with 550 MBq of Tc–99m HMPAO.

Results: In the group of ChE-treated patients the control clinical and neuropsychological examination revealed only a slight impairment of cognitive function, on the average 1.3 point decrement by a MMSE in contradistinction to non-treated patients in whom a more marked decrease in cognitive function, on the average 3.3 points decrement in the MMSE, together with a decline in Barthel Scale were observed. The SPECT examination correlated with clinical state of the patients. In the group of treated patients the difference between rCBF in the first and second SPECTs was not statistically significant. Among untreated patients a decrease in rCBF especially in temporo-parietal areas was observed.

Conclusions: SPECT examination can be a useful tool for objective evaluation of ChE therapy effects. Treatment with ChE slows down the natural course of Alzheimer's disease and vascular type of dementia.

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Script knowledge in Huntington's disease. C. Verny, P. Allain, G. Aubin, D. Bonneau, F. Dubas, D. Le Gall, Centre hospitalier universitaire, EA2646-Université (Angers, F)

Scripts are knowledge representations necessary for the storage of familiar plans of actions (Schank et Abelson, 1977). Grafman (1989) has proposed that various aspects of script knowledge are stored as basic units of managerial knowledge in the frontal lobes. Sirigu et al. (1995, 1996) have found impairments in script information processing in patients with focal lesions of the frontal lobes. As recent neuropsychological data have suggested that cognitive deficits in early Huntington's disease (HD) include executive impairments (Lawrence et al., 1996) which often are linked with frontal-striatal system dysfunction, this study aimed to investigate how patients with HD could manipulate scripts.

The sample included a group of 9 HD patients early in the course of the disease (mean motor score on the Unified Huntington's Disease Rating Scale = 38.2 ± 23.3; mean duration of symptoms = 3.2 ± 3 years; mean score on the Mini Mental State Examination = 26.4 ± 1.7; mean score on the Mattis Dementia Rating Scale = 131 ± 8.9) and 9 normal control (NC) subjects matched by age and education. Patients and NC subjects were requested to re-establish the sequential order of series of actions belonging to 4 scripts. Two scripts contained distractor elements which were actions belonging to trivial scripts.

HD patients, relative to NC subjects, committed significantly more errors in script sequencing ($p < 0.001$): the mean numbers of sequencing errors across all scripts were 9.9 ± 2.8 for HD patients and 0.5 ± 0.9 for NC subjects. However there was no significant difference in performance between HD patients and NC subjects in inhibiting irrelevant actions ($p < 0.30$): the mean number of intrusion errors were 0.8 ± 0.4 for HD patients and 1 ± 0.5 for NC subjects.

These results suggest that early HD patients exhibit a precocious impairment in their ability to produce temporally coherent sequences without deficit in their ability to eliminate distractors in the action domain. This dissociation of performance fits with what is known about the neuropathological progression of HD in which neuronal loss progresses in a dorsal-to-ventral direction and with what we have shown in patients with circumscribed frontal lobe damage (Allain et al., 2001). In our study, impairment in script sequencing was related to lesions in the lateral prefrontal regions and impairment in inhibiting irrelevant script actions was related to orbitofrontal lesions.

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Adult onset dementia and retinitis pigmentosa in two sisters due to mucopolysaccharidosis III-C. E. G. Plantinga, J. A. L. Vanneste, J. E. M. Groener, M. van Schooneveld, Sint Lucas Andreas Ziekenhuis, Leids Universitair Medisch Centrum, Universitair Medisch Centrum Utrecht (Amsterdam, Leiden, Utrecht, NL)

Objective. To describe two sisters with adult onset dementia combined with retinitis pigmentosa due to mucopolysaccharidosis type III-C (Sanfilippo C syndrome).

Background. Mucopolysaccharidosis type III-C (MPS III-C), is an autosomal recessive disease due to a deficiency of the lysosomal enzyme acetyl-CoA: alpha-glucosaminidase-N-acetyltransferase leading to storage of heparan sulfate in some organs. MPS III-C commonly presents with progressive cognitive decline during infancy. Dementia and retinitis pigmentosa due to MPS III-C, presenting during adulthood, is a very rare condition.

Methods. Review of the clinical data, neuropsychological assessment, ophthalmologic investigations, and profile of enzyme deficiency in two sisters presenting with their first neurological symptoms and signs during the third decade of life.

Results. Two sisters presented at the age of 31 and 36 with slightly progressive cognitive decline of the subcortico-frontal type, and nasal speech. Their parents were not consanguineous. Metabolic screening revealed a heparansulfaturia and a diminished activity of acetyl-CoA: alpha-glucosaminidase-N-acetyltransferase in leucocytes respectively 4.1 and 1.4 nmol/mg 0.17 hours (normal range: 13–46 nmol/mg 0.17 hours), the enzyme activity in fibroblasts of the youngest sister was 5.7 nmol/mg 0.17 hours (normal range: 76–175 nmol/mg 0.17 hours). These results were consistent with the diagnosis MPS III-C. The two patients had no signs of other organ involvement such as hepato-splenomegaly or facial coarsening. Ophthalmologic examination showed retinitis pigmentosa. MRI brain showed only slight non specific cerebral atrophy. During the following years mental deterioration and cognitive decline progressed further, necessitating admission to a nursing home 10 years after the first symptoms. The oldest sister died at the age of 48 due to extreme malnutrition.

Conclusion. These two sisters illustrate that when young adults present with progressive mental deterioration and retinitis pigmentosa, the differential diagnosis should include MPS III-C.

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Verbal fluency and SPECT in Alzheimer's disease. S. Ochudlo, J. Siuda, A. Gorzkowska, G. Opala, Silesian Medical Academy (Katowice, PL)

Background: Dysfunction of frontal lobe is noted in many types of dementia including Alzheimer type. Impaired verbal fluency is a classic feature of frontal lobe dysfunction. SPECT imaging is useful for estimation of frontal lobe dysfunction in early stages of dementia.

Objective: We estimated twelve patients (8 women and 4 men) aged 51–87 with dementia of Alzheimer type diagnosed according to NINDS-ADRDA.

Methods: All patients were estimated by MMSE (mean score 18.9 (SD8.3)), verbal fluency test (semantic and letter initial) and SPECT (Single Photon Emission Tomography) using 99m-Tc-HMPAO. We values 99m-Tc-HMPAO up-take in superior and inferior frontal regions using cerebellar up-take as referential.

Results: All patients have significantly lower verbal fluency (semantic mean score 6.4 (SD5.5); letter-initial mean score 5.3 (SD4.2)). Letter fluency was more impaired than semantic. In SPECT all patients has decreased 99m-Tc-HMPAO up-take in examined regions. In superior frontal region it was 0.79 (SD0.6) and in inferior frontal region 0.47 (SD0.6).

Conclusions: Dysfunction of cognitive domain under the control of frontal lobe shown by neuropsychological test is confirmed by impaired blood flow in frontal regions estimated by SPECT. It seem that both methods are sensitive for frontal lobe disturbances due to Alzheimer disease.

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A new case of progressive aphasia due to Pick's disease. A. Danek, M. Neumann, I. Uttner, F. Willoch, A. Drzezga, U. Wahlländer-Danek, H. A. Kretzschmar, Neurologische Klinik LMU, Institut für Neuropathologie LMU, Neurologische Universitätsklinik, Nuklearmedizinische Klinik TU, Ludwig-Maximilians-Universität (Munich, Ulm, D)

Ever since Mesulam (1982) delineated progressive aphasia has its nosological status been debated. It is presently viewed as one subtype of frontotemporal lobar degeneration. We report a clinico-pathological observation with typical Pick's disease at post mortem.

A housewife had presented at the age of 60 with depression, originally felt to explain her slight difficulties in verbal expression. We followed her until death seven years later. Progressive aphasia was diagnosed when the patient demonstrated severe anomia and some echolalia at age 62. Depression had remitted completely. MRI showed left temporal atrophy and FDG-PET showed foci of hypometabolism in the left hemisphere: anterior temporal lobe, inferior frontal gyrus, inferior parietal lobule, and the frontal midline. At age 65 speech output was reduced to echolalia, empty phrases and perseverations. In addition, dyslexia, dysgraphia, dyscalculia and apraxia had appeared. The next year, the patient was completely dependent. Cranial nerves, reflexes, strength, sensation and coordination had remained normal, but verbal communication was impossible. Repetitive, ritualistic behaviours had developed. She neglected her personal care and showed hyperphagia.

The patient died suddenly of an undetermined, probably cardiac cause (brain autopsy only was permitted). Gross pathological findings were consistent with the earlier PET findings in the distribution of atrophy. Histopathological examination revealed extensive neuronal loss and astrocytic gliosis in the temporal and frontal cortex. Numerous tau-positive intracytoplasmatic inclusions (Pick bodies) were detectable within the granule cells of the dentate gyrus and in layers II, V and VI of the frontal, parietal, temporal, insular and cingulate gyrus. Moreover, several ballooned neurons (Pick cells) were present in the deeper cortical layers.

This case adds to the evidence that progressive aphasia is non-specific with respect to aetiology. Typical Pick's disease may be one of several underlying processes, that in other cases have been identified as Alzheimer's disease, as "dementia lacking distinctive histopathology", and as tau-negative, ubiquitin-positive inclusions. At present, differentiation is only possible with histology. Since treatment will eventually depend upon the individual pathology, our observation stresses the need for non-invasive techniques of aetiologic diagnosis in progressive aphasia and other frontotemporal lobar degeneration syndromes.

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Chemokin and cytokine produktion in Alzheimer's disease patients treated and untreated with achetylcholine-esterase inhibitors (AchEI). C. Iarlori, M. Reale, G. De Luca, F. Gambi, A. Salone, L. Toma, A. Di Iorio, F. Ferro, A. Lugaresi, D. Gambi (Chieti, I)

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by the accumulation of plaques containing beta-amyloid fibrils, reactive astrocytes, activated microglia. Inflammatory molecules may be involved in a number of key steps in the amyloid-driven cascade. A-beta activated astrocytes and oligodendrocytes upregulate chemokine expression, in particular MCP–1 and RANTES, which serve as in vitro microglial and macrophage chemoattractants. Acetylcholinesterase (AchE) colocalizes with amyloid-beta peptide and accelerates beta-amyloid formation and deposition in Alzheimer's brain. In addition, beta-amyloid peptide regulates AchE expression, assembly and glycosylation. As a result, AchE, expressed and accumulated around neuritic plaques, influences beta-amyloid formation. AchE inhibition may influence amyloid precursor protein (APP) processing and release and consequently beta-amyloid deposition. Acetylcholine-esterase inhibitors (AchEI) are now considered the first choice treatment for AD. Goal: to assess the effects of AchEI treatment on proinflammatory molecule production (RANTES and IL–1) and on IL–4 level in AD patients. Methods: we studied 13 patients with clinical diagnosis of AD according to DMS IV-R and NINCDS-ADRDA. Only AD patients without clinical signs of inflammation were included. All patients underwent blood withdrawal before and after 3 months of AchEI treatment. Peripheral blood mononuclear cells (PBMC) were purified by Ficoll-Hypaque density gradient centrifugation. PBMCs were cultured with or without PHA. RANTES, IL–1 and IL–4 levels in 24-h supernatants were measured with commercially available ELISA kits. Statistical analysis was performed using Wilcoxon test. Results: RANTES and IL–1 levels were significantly lower in AD patients treated with AchEI, both in unstimulated or PHA stimulated PBMC cultures. IL–4 production was significantly higher after AchEI treatment in unstimulated and PHA stimulated cultures. Conclusion: PBMC from AD patients display an increased peripheral "active state"; proinflammatory cytokines in conjunction with other molecules, appear to play a primary role in the pathogenesis of chronic degenerative alterations of AD brain. Our results suggest that the AchEI-induced increase in IL–4 production and the proinflammatory cytokine reduction might favourably modify the inflammatory process present in AD and possibly contribute to delay disease progression.

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Predominantly visual dysnomia after an ischaemic stroke. R. Cruce, A. Venneri, M. Milders, S. Della Sala, University of Medicine and Pharmacy of Craiova, University of Aberdeen (Craiova, RO; Aberdeen, UK)

We report the case of a 67-year-old patient, NB, who suffered an ischaemic stroke in the territory of the posterior cerebral artery in September 2000.

We assessed the neuropsychological profile of the patient using standardized tests and a battery of 20 objects for testing his naming and gesture abilities.

NB developed a naming deficit for visually presented stimuli, that was significantly more severe than for naming from palpation($p < 0.0009$), from typical sounds ($p < 0.0009$) or from verbal definitions ($p < 0.0001$). Many of the visual naming errors were perseverative or semantically related to the target and he demonstrated a typical "homing in" behaviour in naming. Although he behaved in many respects like a visual agnosic, he performed within the normal range on the first part of the Birmingham Object Recognition Battery (BORB)and, unlike visual agnosics, he experienced difficulties in naming from touch (60 %) and from verbal definitions (70 %).

NB was able to discriminate famous faces from unfamiliar faces (100 %), but could hardly specify a person's occupation (46.8 %) and named correctly only 4.1 %; he could provide more information if he was presented only the name of a person (83.3 %).

His access from vision to semantics appears to be severely – but not totally – impaired. While he could perform correct gestures from auditory cues(99 %), he encountered problems in naming from auditory cues (70 %), suggesting a potential deficit from semantics to naming.

The T14 test from BORB revealed that the deficit was significantly more severe for structurally similar (SS) items than for structurally dissimilar items (SD)($p = 0.0225$). For SS items, NB also produced significantly more semantic errors($p = 0.0167$). A deficit for SS items was disclosed by a test of visual differences (De Renzi and Luchelli, 1994), which operates with verbal stimuli ($p = 0.0309$). A possible explanation for these findings might be offered by the less firm interconnections between perceptual and functional features in the case of living entities.

We discuss the case in the light of the model proposed by Sitton et al. (2000)for optic aphasia, supporting the idea of a continuum of neuropsychological syndromes affecting visual naming.

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Weather conditions and transient global amnesia. N. Maalikjy Akkawi, C. Agosti, B. Borroni, L. Rozzini, A. Padovani, University of Brescia (Brescia, I)

Transient global amnesia (TGA) has been described for the first time by Adames and Fishers as a loss of short-term memory characterised by an incapacity to form new memories, repetitive queries, retrograde amnesia and absence of other neurological signs and symptoms. In this study we investigate the implication of climatic or meteorological factors, such as temperature, humidity, or barometric pressure in triggering off the pathogenetic mechanism of TGA. This study was initiated after observing a high number of admitted TGA patients admitted to our department in the cold days.

Materials and Methods: The study was conducted in the Department of Neurology, Civil Hospital of Brescia (Italy). Two hundred and twenty-five cases of TGA sequentially admitted to our Department over a period of five years (from January 1996 to December 2001) were studied and were controlled to 225 patients with transient ischemic attacks (TIA) matched by age and sex, admitted to our Department over the same period.

The parameters were recorded at the meteorological station of the Pastori Agriculture Technical Institute in Brescia during the study period. The following parameters were recorded: Maximum temperature (Tmax), Minimum temperature (Tmin), Mean temperature (T = [T recorded at 8 am + T recorded at 7 pm + Tmin + Tmax]/4), Excursion temperature (ÄT = Tmax – Tmin), Mean Atmospheric Pressure reduced to sea level (P), Mean Relative Humidity (RH), Mean Water Vapor Pressure (e).

Results: There was no statistically significant correlation between TGA events and the following parameters (P, RH and e) whereas a significant relationship was present with Tmin, Tmean, Tmax and ÄT (the mean values of temperatures was significantly lower for TGA patients than TIA patients).

The difference of frequency of TGA and TIA with respect to the mean temperature classified in quartiles is highly significant ($p < 0.02$). The frequency of TGA decreases progressively with higher temperatures.

Conclusion: We demonstrated a significant relationship between the frequency of a TGA episodes and low temperatures. However, the other atmospheric conditions, such as barometric pressure and humidity do not influence the incidence of TGA.

Epilepsy

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Newly identified seizures in the elderly in hospital data registry. K. Niedzielska, M. Baranska-Gieruszczak, W. Lojkowska, E. Slusarska, S. Pilip, B. Koziol, D. Ryglewicz, Institute of Psychiatry and Neurology (Warsaw, PL)

Background: In recent years an increase in the incidence rates of epileptic seizures in the elderly has been reported. Since elderly people constitute an increasing proportion of the population, there is a need for a more extensive knowledge about clinical features and aetiology of seizures in this age group. The aim of the study was firstly to assess the incidence of first epileptic seizures in hospitalised elderly patients and secondly to determine their possible aetiology.

Material & Methods: Out of 4021 patients admitted to the Neurological Departments of the Institute of Psychiatry and Neurology, 231(5.7 %) had their first ever epileptic seizure. In this group there were 92 (39.8 %) patients (45 male, 47 female) aged 60 years or older (60- 98, mean age 71 yrs). In all patients CT/MRI and repeated EEGs were performed.

Results: Out of 92 patients with newly diagnosed seizures, in 62 (67.4 % of cases) single seizures and in 30 (32.6 %) status epilepticus (SE) were identified.

In the group of 62 patients with single seizures, in 16 cases partial seizures with or without secondary generalization were observed, in 4 – generalized tonic-clonic seizures, and in 2 cases – myoclonic seizures. Symptomatic seizures were diagnosed in 60 patients (97.8 % of cases): vasogenic origin in 39 (62.9 %), tumour in 9 (14.5 %), metabolic disorders in 6 (9.7 %), head injury in 4 (6.4 %), and Alzheimer's disease in 2 (3.2 %) patients.

In the group of 39 patients with seizures subsequent to vascular lesions neuroimaging scans revealed: multifocal lesions in 28 patients (71.8 %),

and single lesions in 11 cases (28 %). In the group of 30 patients with SE, in 15 partial SE, in 2 generalized convulsive SE, and in 13 cases nonconvulsive SE were identified on the basis of clinical and EEG examination. A cause of SE could be identified in 28 (93 %) patients: vascular origin in 23 (76.7 %) tumour in 3 (10 %), and metabolic disorders in 2 (6.7 %). In cases with vascular aetiology CT/MRI scans revealed multiple lesions in 15 (65.2 %) patients, and single lesions in 8 (34.8 %).

Conclusions: In our study a considerable proportion of the first ever epileptic seizures occurred in patients aged > 60 years. A relatively common manifestation is de novo status epilepticus. The main reason for so high incidence of seizures in elderly patients is the number of symptomatic cases. Multiple, recent or old vascular brain lesions are the most common cause of seizures.

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The characteristics of epilepsy in the elderly. P. H. Polychronopoulos, A. Economou, P. Theodoropoulos, J. Nilas, Th. Papapetropoulos, University Hospital of Patras (Patras, GR)

The aim of this study was to evaluate the clinical features of elderly patients with seizures and clarify the risk factors and seizure precipitans in this age group.

Methods: We prospectively studied 74 consecutive elderly hospitalised patients (> 60 years old) with seizures. Clinical data (past history, family history of epilepsy, age of onset, seizure types, risk and precipitating factors, treatment and seizure control) were collected by experienced neurologists using a detailed questionnaire. EEG and neuroimaging studies (CT and/or MRI) were performed to all patients. After discharge follow up was continued by outpatient epilepsy clinic.

Results: The mean age of 74 patients was 70.16 and females slightly outnumbered males (males 36 – females 38). The syndromic classification of seizures according to ILAE revealed localization related epilepsies 70.27 %, generalized epilepsies 5.41 %, unclassified epilepsies 12.16 % and special syndromes 12.16 %.

Partial seizures were mainly symptomatic (94.2 %) and just 5.8 % cryptogenic. The most frequent risk factor was stroke in 56.75 %, followed by tumors (9.46 %) and dementias of non-vascular origin (8,11 %). The most common seizures precipitans were drugs that have been reported to cause seizures (21.62 %), followed by sleep (18,91 %), sleep deprivation (6.75 %) and emotional stress (5.40 %). In 36,48 % of our patients multiple factors were contributed to seizures but in 14,86 % no aetiology was found. Seventy-five per cent had monotherapy and carbamazepine was the most frequently used AED.

Conclusions: Our results showed that seizures in the elderly patients were partial or secondary generalized type mostly symptomatic. Stroke was the most significant risk factor. Sleep and drugs lowering seizure threshold were the most common seizure precipitants. In a significant number of patients no aetiology was identified. Although these patients had good therapeutic response to monotherapy AED selection should be done carefully considering the other medications used for other health problems in this group of elderly patients.

P400

Epileptic seizures in Behçet's disease. E. Aykutlu, B. Baykan, P. Serdaroglu, A. Gökyigit, G. Akman-Demir, University of Istanbul (Istanbul, TR)

Purpose: To outline the clinical characteristics of epileptic seizures in our large series of Behçet's Disease patients with neurological involvement.

Methods: All files of 223 patients with neuro-Behçet's Disease were evaluated retrospectively and the group with clearly documented seizures was included in the current study. Clinical characteristics, EEG, neuroimaging and CSF findings were evaluated and the seizures were classified according to the new proposed criteria of the International League Against Epilepsy. The seizures that appeared during a neurological exacerbation were noted. We also analyzed the possible role of seizure provoking factors.

Results: Epileptic seizures were seen in 10 of 223 patients (%4.48). There were 1 female and 9 male patients. In 5 of the patients, seizures occurred during neurological exacerbations. In the remaining 5 patients the seizures were not related to neurological attacks. The predominating seizure type was generalized tonic-clonic convulsions accompanied by focal motor seizures. Some provoking factors for the seizures were found in half of the patients. It is remarkable that 4 patients died 1 to 5 years after the onset of the seizures.

Conclusions: Our study showed that epileptic seizures are rare in Behçet's disease. Some interventions and drugs could provoke the seizures. The occurrence of seizures seems to be associated with a higher mortality rate when compared with the patients without seizures.

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Memory deficits and depression in patients with chronic epilepsy. J. Rösche, C. Uhlmann, R. Weber, W. Fröscher, ZfP Die Weissenau (Ravensburg-Weissenau, D)

Introduction: In patients with depression verbal and non-verbal memory deficits have been described (1). In patients with epilepsy (PWE) memory deficits are found especially in correlation to temporal lobe lesions. Since depressive comorbidity occurs in up to 65.7 % of PWE (2) there might be a correlation of depressive symptoms with memory deficits as well. Mild symptoms of depression may be a response to chronic disability. In this retrospective study we tested the hypothesis that PWE with moderate to major depression have more severe memory deficits than PWE with mild depression or none depression. Patients and Methods: 99 patients with chronic epilepsy (48 male, 51 female; age mean 40.06 years) were studied with the Self-Rating-Depression Scale (SDS) (3) and a neuropsychological-screening-battery (4) the day after admission on a specialised ward for PWE. For this study the data from the Memo-Test for verbal memory and the Benton-Visual-Reproduction-Test for non-verbal memory were taken into account. The results of patients without depression, patients with minor depression and patients with moderate to major depression were compared with the student-T-Test. Results: 33 patients had a normal score in SDS, 35 patients had a score indicating minor depression and 31 Patients showed symptoms of moderate to major depression in SDS. There were no significant differences in age or age at onset of epilepsy between these groups. The only significant differences in memory performance were found between patients with minor depression and patients with moderate to major depression on immediate recall ($p = 0{,}0074$) and continuous long term retrieval ($p = 0{,}011$) in the Memo-Test. Patients with minor depression tended to do even better than patients without depression on immediate verbal recall ($p = 0{,}095$) Discussion: Our data suggest only a mild verbal memory deficit in patients with moderate to major depression when compared to patients with minor depression. Memory deficits in PWE and depression were not more pronounced than in PWE without symptoms of depression. References: 1. Beblo T, Herrmann M: Fortschr Neurol Psychiat 2000; 68, 1–11; 2. Rösche & al: Nervenheilkunde 2001; 20: 456–60; 3. Zung WWK & al: Arch Gen Psychiat 1965; 13: 508–515; 4. Rösche & al: Akt Neurol 2001; 28: 455–459

P402

Genetically proven myoclonus epilepsy with ragged red fibers syndrome and hypolipidemia: a case report. G. Sahin, K. Uluc, O. Kursun, S. Erdem, C. Kocaefe, G. Nurlu, E. Tan, S. Saygi, Hacettepe University (Ankara, TR)

Myoclonus epilepsy with ragged red fibers (MERRF) syndrome is one of the causes of progressive myoclonus epilepsy and differentiation from the other mitochondrial cytopathies is not always possible with clinical signs. Definitive diagnosis depends on muscle biopsy and molecular genetic analysis. We present the first case of genetically confirmed MERRF syndrome in Turkey and we will discuss its association with hypolipidemia which is not established in the literature.

A 24-year-old left-handed male patient was admitted with jerks and generalized tonic-clonic convulsions which were begun at the age of 13. It was learnt that clonazepam controlled his other convulsions but not the myoclonic ones. His complaints continued increasingly and fallings were added to his clinical findings three years ago. In his medical history, diarrhoea and weight loss for 1 year was obtained. His mother and father were cousins. His mother had the same symptoms, which were begun at the age of 29, and she died 16 years later after the onset of her signs. In the neurological examination, there were bilateral optic atrophy, hearing loss, cerebellar and pyramidal signs and, proximal dominant quadriparesis. The electroencephalography revealed active epileptiform abnormality and slowing of the basal activity suggesting progressive myoclonus epilepsy. On this basis, laboratory analysis was directed towards the etiology of progressive myoclonus epilepsy. Routine laboratory tests were normal except for the low levels of total cholesterol, HDL, VLDL and triglyceride. The cranial magnetic resonance imaging showed cerebellar atrophy. Polyneuropathy with severe axonal involvement in sensory nerve fibers and myopathic involvement were found in the electroneuromyography. Due to the high levels of lactate in the cerebrospinal fluid and serum, muscle biopsy was performed and ragged red fibers and cytochrome-c oxidase negative fibers were reported. In the analysis of muscle DNA mt8344 mutation that is specific for MERRF was obtained. Concerning the etiology of hypolipidemia all tests including intestinal biopsy were normal. As a consequence, although MERRF syndrome is a rare disorder, in clinical suspicion, definitive diagnosis could be done by DNA analysis and in these patients lipid biometabolism must be investigated.

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Paroxysmal hyperhydrosis, mydriasis, tachycardia, and hypertension with frontotemporal atrophy: 'Paroxysmal sympathetic storm?' K. Uluc, S. Saygi, I. A. Yilmaz, G. Nurlu, Hacettepe University (Ankara, TR)

Autonomic paroxysmal alterations of the central nervous system like hyperhydrosis, mydriasis, blood pressure and heart rate variability have been described with several disorders. Any lesion of the central autonomic network (CAN) can be the cause. The underlying mechanism can be the 'release phenomenon' at the level of the brain stem and diencephalon secondary to the loss of cortical and subcortical control. The paroxysmal nature of the autonomic attacks can make an evidence for an epileptiform cause. The term 'diencephalic epilepsy' (paroxysmal sympathetic storms) have been used to clarify these attacks, but this phenomenon have not been supported by an electroencephalography (EEG) during attacks, and anticonvulsant therapies are not successful in many patients. We describe a patient with paroxysmal sympathetic attacks with clinical, laboratory, radiologic, and electrophysiologic findings.

A 22-year-old male patient without any remarkable medical history except a febrile convulsion was admitted with episodic attacks up to 30 times a day which were started at the age of 2. Mydriasis without pupillary reaction to the light, hyperhydrosis, tachycardia and increased blood pressure without impairment of consciousness were the components of the attack. All attacks were lasting longer than 30 seconds, usually up to 5 minutes. The attacks were not responding to anticonvulsant treatments, and all the EEG's were normal. His physical, neurological examination and routine laboratory work-up including serum and urine hormone levels were unremarkable. The continuation of the suspected simple partial convulsions 30 times a day for nearly 20 years without any transformation into another convulsion type and with no response to anticonvulsant drugs made the diagnosis of epileptiform attacks impossible. Also, the findings of normal interictal and ictal EEG's, presence of no hyperperfusion in the ictal single photon emission computed tomography (SPECT) and no rise in the serum prolactin level which normally arise in the postictal period, were the other inappropriate findings for epileptic attacks. Episodic, autonomic nature of the attacks made the necessity of differential diagnosis of the 'paroxysmal sympathetic storms', and magnetic resonance imaging (MRI) of the brain revealed pathology in the high order zone of the CAN; mild left frontotemporal opercular focal atrophy was detected. A partially respond to clonazepam and clonidine was obtained.

P404

Epidemiological study of epilepsy among children in Belarus. H. Navumava, A. Naumov, O. Klimonenkova, Clinical Research Institute for Radiation Medicine (Vitebsk, BLR)

Some epidemiological studies of epilepsy have been conducted in Belarus during the last decades. They were based on the information obtained from outpatient departments of psychoneurologic clinics, which reflect the prevalence rate of the most severe forms of epilepsy accompanied by psychiatric disorders and dementia. Other forms of epilepsy have not been taken into consideration in spite of their rather high prevalence rate.

We have performed a population-based case ascertainment of all available sources of medical care from 1986 to 2000. Children younger then 15 were analysed.

The incidence rate of epilepsy (newly-diagnosed registered patients) among children suffering from Chernobyl disaster in 1987–2000 varied from 53.6 to 118.4 per 100,000 of population, while the incidence rate of epilepsy in the control group ('noncontaminated' areas of Belarus) varied from 37.2 to 79.1. We consider, that the comparatively high incidence rate of epilepsy (692.0 per 100,000 of population) in 1986 among children subjected to low doses of ionised radiation exposure could result from obligatory universal clinic system for such children, which had been initiated since that time. From our point of view it may be evident, that not all patients with epilepsy turn for help to a specialist in spite of generally available and free medical assistance in Belarus. It is also confirmed by the following facts: 1. According to the data obtained from anonymous questionnaires, 19.8 % of parents did not turn for medical assistance after the first seizure in their child. 2. In spite of the fact, that epilepsy patients in our country receive anticonvulsants free of charge, 5 % of all parents refused this kind of help, because they did not want have the diagnosis of epilepsy registered in case history of their child.

The prevalence rate of epilepsy among children suffering from radiation exposure in 1987 was 130.8 and in 2000–200 per 100,000 of population. The prevalence rate of epilepsy in the control group in 1986 was 109.7 and in 2000–143.1.

Anticonvulsants in Belarus are free of charge for the patients suffering from epilepsy. But only 76.25 % of patients receive these medicines regularly.

Phenobarbital was chosen as the basic anti-epileptic medicine in 78.63 % of patients.

Monotherapy was prescribed in 64.60 % of patients.

P405

Epileptogenesis after experimental status epilepticus. Analysis of functional changes in vitro after electrically induced limbic status in vivo. M. Holtkamp, K. Buchheim, H. Siegmund, H. Meierkord, Charité,Humboldt-University Berlin (Berlin, D)

Background: Persistent functional alterations after complex-partial status epilepticus (SE) in patients are controversially discussed. After experimental limbic status epilepticus in vivo rat brains were examined in vitro for pathological changes.

Methods: 5–7 days after electrically induced self-sustaining limbic status epilepticus in vivo lasting 5 minutes combined entorhinal cortex-hippocampus slices were prepared. Seizure-like activity was induced by omission of Mg++ from the artificial cerebrospinal fluid. Using intrinsic optical signals (IOS) spread onset, propagation and velocity were analysed. With ion sensitive microelectrodes activity-dependent changes of the extracellular potassium concentration and of the field potential were measured. The results were compared to sham-operated controls.

Results: 64 seizure-like events of 5 slices after status epilepticus were compared to 54 seizure-like events of 6 control slices. Latency to the onset of activity as well as duration and frequency of seizure-like events did not differ. The extracellular K±concentration in the SE rats was 10.6 mM and thus significantly higher compared to the control animals (8.2 mM; $p < 0.0001$). The change of the field potential after SE was increased as well (1.7 mV vs. 1.3 mV; $p < 0.0001$). After SE the seizure-like activity invaded the dentate gyrus in 3 of 5 slices, in the control rats this structure was involved in one slices only.

Summary: Our data show that limbic status epilepticus in vivo results in altered function in vitro. The activity-dependent increased extracellular potassium may indicate an impaired buffering of potassium by glial cells. The higher field potential and possibly the higher amplitude of the IOS may indicate an increased excitability. After SE the dentate gyrus is more often invaded than in slices of sham-operated animals, which was never seen in naive animals. Our experimental findings may give reason for a rapid and consequent proceeding in the therapy also of complex partial status epilepticus.

P406

Sleep epilepsy in adults. A. Karlovassitou, E. Dimitrakoudi, P. Armentsoudis, S. Boufidis, G. Rizos, T. Karapanayotidis, P. Hamlatzis, S. Baloyannis, Aristotle University of Thessaloniki (Thessaloniki, GR)

Sleep epilepsy (SE) is characterized by the occurrence of seizures exclusively during sleep. Although some epileptic syndromes with nocturnal seizures, as the partial idiopathic epilepsy with centrotemporal spikes, the autosomal dominant frontal nocturnal epilepsy and the frontal lobe epilepsy have already been recognized, there are many epilepsies with nocturnal tonic-clonic seizures whose nature as partial or generalized, idiopathic or cryptogenic remains to be elucidated.

We present in a retrospective study the clinical EEG and neuroimaging characteristics as well as the triggered and prognostic factors of seizures of patients with SE who have been under examination in our Outpatients' Clinic of Epilepsy during the last 10 years (1991–2000).

We examined 46 patients presented more than one attacs exclusively during sleep (25 M and 21 F; 6.71 % in a total of 685 patients with epilepsy). All patients had a waking EEG, a CT and a MRI examination. Additionaly, 1 patient had a video-EEG monitoring and 6 patients had a polysomnographic recording.

29 patients had GTCS, 9 had TS, 7 had confusional states (CPS) and 1 had confusional states and sleep wandering (CPS). The duration of epilepsy varied between 6 months to 15 years. EEG findings: 20 normal, 18 focal abnormality in frontotemporal regions and 8 generalized abnormality with bilateral discharges. CT and MRI findings: 34 normal and 12 abnormal. Sleep apnea syndrome: 6 patients. We classified 12 patients as symptomatic and 1 as autosomal dominant nocturnal frontal epilepsy.

32 patients were treated with CBZ or OXBZ, 6 with VPA, 4 with CZP and 4 with OXBZ and TPM. 42 patients were free of seizures for more than 2 years with monotherapy. However, withdraw of treatment in 10 patients free of seizures for 3 to 5 years and normal EEG and MRI examination, provoked recurrence of seizures.

Patients with SE represent the 6.71 % of total epileptic patients. GTCS are the most frequent seizures but TS are also frequent. Symptomes like parasomnia may represent epileptic syndromes that respond to antiepilep-

tic drugs. Normal EEG and normal neuroimaging are often findings. Triggered factors as sleep apnea should be evaluated in refractory seizures. Many epileptic syndromes during sleep are probably lifelong. SE is an heterogeneous epilepsy and in the majority of cases their nature as idiopathic or cryptogenic have to be elucidated.

P407

Dynamic CT perfusion imaging in a patient with a postictal paresis. P. Gallmetzer, J. Spatt, G. Pelzl, P. Samec, B. Mamoli, L. Boltzmann Institute for Epilepsy, NKR (Vienna, A)

Background: The postictal paresis is a well known phenomenon occurring after seizures. Although it was first described in 1827, its underlying pathophysiological mechanisms are still unclear.

Methods: We performed a dynamic CT perfusion study in a 30-year-old woman with a right-sided non-lesional TLE. She was admitted to our department following a generalized tonic clonic seizure and showed a postictal paresis of the left arm and leg at that time. The CT perfusion was performed approximately one hour after the seizure when a slight weakness of the left arm and leg was still present. CT perfusion scans were obtained using a single-section perfusion technique by injection of 50 ml of iodinated contrast medium (injection velocity = 10 ml/sec). The parameters chosen for evaluation were cerebral blood volume (CBV) and cerebral blood flow (CBF). A control scan was performed after the resolution of the postictal paresis.

Results: Perfusion CT scan showed an increased CBV and CBF in the region of the right basal ganglia, which was most developed in the right head of the caudate nucleus and nucleus lentiformis and in a smaller degree also in the right thalamic region. The control CT scan, which was performed after the resolution of the paresis, showed a complete normalization of the perfusion changes seen in the previous scan.

Conclusion: A hyperperfusion of basal ganglia structures could be observed in our postictal CT perfusion study. Our data do suggest that the basal ganglia may play a role in the development of postictal phenomena like Todd's paralysis, possibly through seizure propagation to these structures. To our knowledge, this is the first report of a postictal perfusion study demonstrating basal ganglia involvement in an adult patient with a postictal paresis.

P408

Cortical focal dysplasia, stereoelectroencephalographic, neuroimaging and histologic correlations. F. Beuvon, F. Chassoux, E. Landré, B. Devaux, F. Brahmi, P. Varlet, C. Daumas-Duport, Sainte Anne Hospital (Paris, F)

Focal cortical dysplasia (FCD) described by Taylor and colleagues in 1971 consists in the neocortical developmental lesions cause of intractable epilepsy of early onset.

FCD manifests clinically by partial seizure, semiology is stereotyped for each patient and is clearly related to the location of FCD. Aquired neurological deficit and mental impairement are frequently associated and depend also on location of the lesion.

Neuroimagnig is playing an important role of FCD detection but changes are subtle. MRI findings are: localized broad gyrus, gyral abnormalities or global increase in the cortical volume, increased signal on T2-weighted images with blurring of the demarcation between grey and white matter, abnormal signal in the underlying white matter on prolonged T2 relaxation.

As we have demonstrated in a precedent study (Brain 2000), stereoelectroencephalography (SEEG) provides opportunity for obtaining direct intralesional recordings and shows intralesional interictal activity characterized by a continuous rythmic or pseudorythmic spikes. The site of maximal rythmic spike discharges, in term of rapidity and frequency, correlated with the location of FCD

In this study, we have analysed a serie of 11 patients operated during the years 1992–2000 and correlated neurolophysiological (SEEG) data with histological finding and MRI. The results have emphasized strength of correlation between MRI images, SEEG and pathological changes in accurately assessing the extent of the FCD. The aim is to delimit precisely surgical resection for the best outcome, because post surgical prognosis depend on the total removal of the dysplastic lesion and the complete resection of the epileptogenic zone

P409

The place of levetiracetam compared to other antiepileptic drugs in adults with mental retardation. M. O'Rourke, Beds. & Luton Community NHS Trust (Clapham, UK)

Introduction: People with Mental Retardation or Learning Disabilities have a much higher incidence of epilepsy than the general population. Their seizure classifications show a bias to partial onset seizures and the more severe generalised epilepsies

Methods: This paper looks at antiepileptic drugs (AEDs) used in a population of adults with mental retardation (n = 97) attending a seizure clinic and draws some conclusions based on the range of medications used in their treatment. Credit for the improvement in seizure control is given to the add-on AED in the analysis regardless of combinations. In calculating the effects noted figures were corrected for the number of patients on the database taking the particular AED as mono- or combination therapy to provide a degree of context in the findings.

Results: Comparing Lamotrigine (LTG), Topiramate (TOP), Gabapentin (GBP) and Levetiracetam (LEV) our findings were as follows: LTG achieved 21 % seizure free and 25 % > 50 % reduction in seizure frequency and was used for all seizure types; TOP achieved 7 % seizure free and 29 % > 50 % reduction and was used for all seizure types; GBP achieved 11 % seizure-free and 22 % > 50 % reduction and was used only for partial onset seizures; LEV achieved 11 % seizure-free and 50 % in addition > 50 % reduction and was used for all seizure types. The LEV figure is artificially lowered by the number of new patients in titration, allowing for this the corrected percentages are as follows: LEV 14 % seizure free and 64 % > 50 % reduction.

Conclusions: Our clinical experience of treating people with mental retardation in the UK, using AED medication from when generally available, shows LEV to have an efficacy (seizure free and > 50 %reduction) that exceeds the other main newcomers of the past ten years. Only LTG showed a higher seizure free percentage. The LEV group results are the more impressive for representing patients previously tried on LTG and other AEDs. No patient with mental retardation should be considered to have intractable seizures until the available AEDs have been tried, and LEV should be considered an early option.

Disclosure: The author has received educational support from the manufacturers of all of the drugs cited in this abstract over the past ten years.

P410

A microdialysis study of the novel antiepileptic drug Levetiracetam: extracellular pharmacokinetics and concurrent amino acid neurotransmitter effects in rat hippocampus and frontal cortex. P. N. Patsalos, X. Tong, Institute of Neurology (London, UK)

Background: Levetiracetam (LEV) is a new antiepileptic dug (AED) with a desirable therapeutic index and favourable pharmacokinetic characteristics. Its exact mechanism of action is unknown. In this study we have investigated the temporal kinetic inter-relationship of LEV in serum and brain extracellular fluid (frontal cortex and hippocampus) following the systemic administration of LEV. Concurrent neurotransmitter amino acid concentrations were also determined with a view to enhancing our understanding of the mechanism of action of LEV.

Methods: In this study, we used a freely moving and behaving rat (Sprague Dawley) model. Under halothane anaesthesia, a catheter was placed in the internal jugular vein for blood sampling and microdialysis probes were implanted stereotactically into the hippocampus and frontal cortex for monitoring of the extracellular fluid. LEV and amino acid concentrations were measured by High Performance Liquid Chromatography (HPLC) using ultra violet and florescence detection, respectively.

Results: After administration (40 or 80 mg/kg), LEV rapidly appeared in both serum (Tmax, 0.4–0.7 h) and extracellular fluid (Tmax, 2.0–2.5 h) and concentrations rose linearly and dose-dependently, suggesting that transport across the blood-brain barrier is rapid and not rate-limiting. The kinetic profiles for the hippocampus and frontal cortex were indistinguishable suggesting that LEV distribution in the brain is not brain region specific. However, t1/2 values were significantly larger than those for serum (mean range, 3–3.3 h v 2.1–2.3 h) and concentrations did not attain equilibrium with respect to serum. LEV (80 mg/kg) was associated with a significant reduction in taurine in the hippocampus and frontal cortex. Other amino acids were unaffected.

Conclusion: LEV readily and rapidly enters the brain without regional specificity. Its prolonged efflux from and slow equilibration within the brain may explain, in part, its long duration of action that has been reported clinically. The concurrent changes in taurine may contribute to its mechanism of action.

Parkinson's disease and Extrapyramidal disorders

P411

Agitation and psychosis during cholinesterase inhibitor (CEI) therapy in patients affected by Parkinson's disease and dementia (PDD). A. Thomas, G. D'Andreamatteo, D. Iacono, A. L. Luciano, A. Di Rollo, M. Onofrj, Neurophysiopathology (Pescara, I)

Background: Recent studies demonstrated the beneficial effect of CEIs on hallucinations, delirium or psychosis in patients affected by Lewy body disease (LBD) or by PDD

Method/patients: We selected 16 patients (6F/10M) affected by PDD, mean age 73.2 ± 0.77 S.E, mean duration of disease 7.67 ± 0.67 S. E, mean UPDRS subscale III score 39.8 ± 1.2 S.E, mean Hoehn/Yahr stage 3–4, mean MMSE score 15.25 ± 0.95. All patients were on stable medication regime: L-DOPA (620.83 ± 35.6 mg) and dopaminoagonist (6 patients: ropinirole 11.50 ± 3.02 mg; 4 patients: pramipexolo 2.99 ± 0.44 mg; 1 patients 8 mg cabergoline; 1 patients 3 mg pergolide). All patients suffered form mental decline in the last 12 months without psychotic symptoms, such as hallucination and delusions. During the titration period the patients received 5 mg of donepezil for 15 days and then 10 mg throughout the following 6 months. UPDRS, MMSE, laboratory analysis, vital signs, caregiver interview, ADL were recorded at baseline and at the end of the study.

Results: Only 8 patients completed the study, MMSE scores, UPDRS III subscale score registered a minimal but statistically not significant improvement, respectively 14.05 ± 0.85 and 37.1 ± 0.9 S. E. Caregivers reported an increased attention. 6 patients were withdrawn from the study because of behavioural and psychiatric symptoms: 3 patients complained persistent hallucinations, 2 patients reported nightmares and REM sleep behaviour disorder, 1 patients had severe agitation and 2 further patients dropped out because of nausea and vomiting during titration period.

Discussion: We hypothesized that CEIs increase AChE in the striatum regulating/increasing dopamine release and consequently induce "potentially L-DOPA" side effects in patients previously non affect by psychotic symptoms and on the other hand patients who presented psychotic symptoms in course of LBD or PDD ameliorate these symptoms during CEIs treatment because of changes of consciousness.

P412

Amantadine for dyskinesia and motor fluctuations in patients. C. Paci, A. Thomas, G. D'Andreamatteo, A. L. Luciano, D. Iacono, A. Di Rollo, M. Onofrj, Neurophysiopathology (Pescara, I)

Although levo-dopa continues to be the gold standard of symptomatic efficacy in the drug treatment of Parkinson's Disease (PD) it also induces dyskinesias and motor fluctuations in the long term. (MD).We describe a double-blind study performed tin a 12 months period in order to understand whether the beneficial effects of amantadine on levodopa-induced dyskinesias are transient or long-lasting.

The patients were treated for 8 ± 2 years with levodopa (800 ± 122 mg) and dopaminoagonists (ropinirole 16 mg ± 2 mg/day, bromocriptine 18 ± 6 mg/day) and their symptoms were characterised by peak-dose and/or dyphasic dyskinesias that occasionally were associated with pain. The dyskinesias were assessed using the UPDRS subscale IV (complications of the therapy), the Dyskinesias Rating Scale (DRS). The Investigator Global Assessment of dyskinesias was also utilised to evaluate changes of dyskinesia. Statistical analysis was performed with use of Wilcoxon's signed-rank test and Student's t test. All 43 patients received tablets of amantadine – chlorhydrate (100 mg) or of placebo titrated to 1 capsule three times per day (tid). After 15 days of amantadine treatment there was a significant reduction in motor fluctuations and in the total dyskinesias scores. UPDRS subscale IV mean score was 5.40 (SD = 1.26, $p < 0.0001$); DRS scores had a mean value of 7.50 (SD = 1.65, $p < 0.0001$); IGA for dyskinesia was rated 2.10 (SD = 0.88, $p < 0.0001$). At the 30 day-control UPDRS, DRS and IGA values were statistically overlapping with those obtained 15 days after the introduction of treatment. Therefore at month 1 three patients experienced psychosis characterized by delusional jealousy and so they interrupted the study. During placebo treatment motor fluctuations and dyskinesias scores tended to be higher than amantadine group and were unchanged during the entire study. Patients did not complete the study because of the increase of dyskinesias in intensity and duration so after 8 months we decided to interrupt the trial.

Our results have demonstrated that 300 mg amantadine reduces dyskinesias in PD by approximately 36 % but this benefit is transient and disappears after 1–2 months; therefore we think that amantadine can not be used for the treatment of levo-dopa induced dyskinesias but only for the treatment of Acute Akinetic Syndrome. Amantadine stimulates a receptor that is an alternative dopaminergic structure and seems to be refractory to physiologic stimulation.

P413

Neurophysiological identification of the subthalamic nucleus in Parkinson's disease by Power Spectral Density analysis of neural signals from intraoperative microrecordings. M. Rohr, A. Priori, A. Pesenti, M. Egidi, P. Rampini, F. Tamma, M. Locatelli, E. Caputo, V. Chiesa, S. Cerutti, A. Bianchi, G. Baselli, S. Barbieri, Politecnico di Milano, IRCCS Ospedale Maggiore di Milano, Ospedale San Paolo (Milan, I)

Objectives: To test a new tool for the neurophysiological identification of the human subthalamic nucleus (STN) during stereotactic surgery for the implantation of deep brain stimulation (DBS) electrodes, we analyzed off-line the intraoperative signals recorded from patients with Parkinson's disease.

Methods: We estimated the power spectral density (PSD) along each penetration tract (8 patients, 13 sides) and determined the spatial correlation of the PSD with the target location estimated from neuroimaging procedures ("anatomical target"), and with the final target location derived from standard intraoperative monitoring procedures (microrecordings and stimulations) for STN localization ("clinical target"). The PSD was estimated by calculating the Periodogram for 6-seconds epochs of neural signal.

Results: When the electrode tract crossed the STN, the PSD in the 0.25–2.5 KHz band increased, peaking on average < 0.05 mm (0.04 ± 0.72 mm (mean ± SD)) cranial to the point determined by standard neurophysiological procedures ("clinical target"), and 1.00 ± 1.51 mm. caudal to the target location calculated from the neuroimaging data ("anatomical target"). When the tract was outside the nucleus the PSD remained unchanged. Even on recordings with a low signal-to-noise ratio, off-line PSD analysis of neural signals reliably, rapidly and quantitatively indicated the site were the surgical team, using data obtained with standard intraoperative monitoring techniques, implanted the final electrode.

Conclusions: On-line intraoperative estimation of the PSD may represent a simple, reliable, rapid and complementary or even alternative approach to electrophysiological monitoring during STN surgery for Parkinson's disease. By shortening operative time and improving target location it should also make surgery safer for the patient and reduce hospital expenses.

P414

Changes in cerebral blood flow detected in the middle cerebral arteries, in patients affected by Idiopathic Parkinson's disease, during on-off phenomena. A transcranial color Doppler study. L. Curatola, S. Sanguigni, G. Malferrari, T. Carboni, R. Gobbato, C. Paci, Azienda Sanitaria USL12 Madonna del Soccorso Hospital, Az.Osp. (San Benedetto del Tronto, Reggio Emilia, I)

More than 50 % of patients affected by Parkinson's Disease(PD) receiving levodopa treatment, developed motor response fluctuations. Most typical features are the on-off phenomena: abrupt response swings not related to the timing of medication, with fast worsening of symptomatology so as to make speech and gait impossible. The aim of this study was to assess the cerebral blood flow in PD patients during motor fluctuations, by transcranial colour Doppler (TCCD).12 subjects (10 males,2 females, aged from 47 to 70,mean 61.4 ± 6.7),affected by advanced Dowered examined by TCCD (Acuson 128 XP10)during on and off periods. Right and left middle cerebral arteries(MCA),in M1 segment, were studied by a 2-MHz128 channels hand-held probe. Peak Systolic Velocity(PSV)and Peak End Diastolic Velocity(PEDV)were evaluated. Blood pressure and oxygen saturation were monitored. Statistical evaluations included Student's test and paired Wilcoxon test between on and off stages. In both MCA we found differences statistically highly significant between on and off blood flow. In right MCA mean PSV:1.12 ± 0.13 m/sec in on stage;0.83 ± 0.09 m/sec in off ($P < 0.001$).Mean PEDV:0.47 ± 0.09 m/sec in on stage;0.33 ± 0.07 m/sec in off($P < 0.001$).Similar results were obtained in left Macaw have no cognition of other papers about neurosonologic assessment during motor fluctuations in PD. Some PET studies have been published about the cerebral blood flow in PD patients at rest (Eidelberg et al 0.1994)or when subjects were asking to perform a motor task (Jahanshahi et al 0.1995).Our data suggest that in some stages of advanced PD the cerebral blood flow could have important changes independent from systemic blood pressure and oxygen saturation. Further studies are needed to elucidate the intracranial blood flow pathophysiology in PD and the TCCD contribution.

P415

c 0.255del A parkin gene mutation in Spanish patients with autosomal recessive parkinsonism. E. Munoz, J. Campdelacreu, P. Pastor, M. J. Martí, F. Valldeoriola, R. Oliva, E. Tolosa, Hospital Clinic (Barcelona, E)

Background: Autosomal recessive juvenile parkinsonism is a neurodegenerative disorder associated with mutations in the parkin gene.

Objective: To search for the presence of parkin gene mutations in Spanish patients with Parkinson's disease (PD) and characterise the phenotype associated with these mutations.

Methods: Thirty-seven PD patients with either early-onset or autosomal recessive pattern of inheritance were screened for parkin gene mutation throughout PCR amplification of the exons 1 to 12 followed by single strand conformation polymorphism analysis. The PCR products with an abnormal pattern of motility were sequenced.

Results: We identified parkin gene mutations in 7 patients. The c 0.255delA mutation was found in 4 unrelated patients. In these patients, the age at onset varied from 30 to 41 years. The disease began with postural tremor on the upper-limbs, mimicking essential tremor, in 2 patients; feet dystonia in 1 patient; and lower body parkinsonism in 1 patient. Two patients did not require levodopa treatment because they presented a good long-term response to dopamine agonists.

Conclusions: c 0.255delA is the most frequent mutation found in Spanish patients with early-onset PD. The phenotypes associated to this mutation show the presence of an inter-patient variability.

P416

Progressive multifocal leucoencephalopathy (PML) presenting with parkinsonism. S. O'Riordan, C. McGuigan, M. Farrell, M. Hutchinson, St Vincent's University Hospital, Beaumont Hospital (Dublin, IRL)

Background: In PML, a demyelinating disease caused by the JC virus, clinical features reflect its predominantly white-matter location. Although the basal ganglia circuitry may be involved in the pathology of PML, movement disorders are exceedingly rare as presenting features.

Case Report: A 77 year old right-handed woman was admitted with lower-limb cellulitis. She gave a two-month history of bilateral, asymmetric, upper-limb tremor. This was most noticeable at rest. Her mobility had decreased in the preceding months. In 1994 she had been diagnosed with CLL which had not required treatment.

On examination she was bradykinetic with reduced facial expression. There was cogwheel rigidity and a coarse resting tremor in her upper limbs, worse on the right. Mild cognitive impairment was noted. Eye movements were normal. Power, reflexes and sensation were normal in her limbs. Plantar responses were flexor. Walking was slowed but limited by her cellulitis. Parkinson's Disease was diagnosed. Treatment with low-dose levodopa and selegiline was commenced.

Arrangements were made for out-patient CT brain and neurology review.

She was readmitted seven weeks later. Her mobility had lessened and she had become withdrawn. Examination revealed significant deterioration. She was bradyphrenic and had a mild expressive dysphasia. Prominent echolalia was noted. She has right hemi-inattention and was markedly dyspraxic. Once again, asymmetric upper-limb rigidity and resting tremor were noted.

Investigations: There was a peripheral lymphocytosis. Evidence of non-specific cerebral dysfunction was present on electrencephalogram. CT brain showed hypodense lesions within the deep white matter. T2-weighted cranial MRI revealed widespread high-signal abnormalities in the white-matter. Cerebrospinal fluid analysis (CSF) was normal. JC virus was not detected in CSF by polymerase chain reaction. She developed a progressive right hemiparesis with a right extensor plantar response and became progressively more demented. She died four months after her initial presentation.

The diagnosis of PML was confirmed at post-mortem.

Lesions affecting bilateral frontal and parietal lobes and the left striatum and thalamus were seen. The papova JC virus genome was detected using in-situ hybridisation techniques.

Summary: PML rarely presents with a movement disorder. We describe the clinical, radiological and pathological findings in a case in which PML presented with parkinsonism.

P417

Early-onset parkinsonism is not associated with mutations in the pantothenate kinase gene PANK2. T. Klopstock, T. Gasser, D. Wassilowsky, F. Asmus, T. Meitinger, K. Hörtnagel, University of Munich, GSF (Munich, D)

Hallervorden-Spatz syndrome (HSS) is a rare autosomal recessive neurodegenerative disorder leading to extrapyramidal dysfunction. It may serve as a model for Parkinson disease since many HSS patients suffer from parkinsonism and both conditions lead to iron accumulation in the basal ganglia. Mutations in the pantothenate kinase 2 gene (PANK2) have recently been identified as a cause of HSS, including atypical cases with early-onset Parkinson disease. We found no mutations of the PANK2 gene in 76 Parkinson patients (31 cases of parkin-negative recessive parkinsonism and 45 cases of early-onset Parkinson disease). Thus, PANK2 mutations are not a major cause of autosomal recessive or early-onset Parkinson disease.

P418

Subthalamic nucleus stimulation improves choice more than simple reaction time in Parkinson's disease. H. Kumru, C. Summerfield, F. Valldeoriola, J. Valls-Solé, Hospital Clinic (Barcelona, E)

Patients with idiopathic Parkinson's disease (IPD) show a dramatic improvement of their symptoms and signs with repetitive electrical stimulation of the subthalamic nucleus (DBS-STN). In order to have neurophysiological evidence of the change in akinesia and bradykinesia, we recorded the EMG activity and the wrist movement related to simple reaction time (SRT) and choice reaction time (CRT) in 8 IPD patients in conditions of 'on' and 'off' DBS-STN 1 year after electrode implantation. The patients were 7 males and 1 female with a mean age of 62.8 ± 8.5 (range, 51–76 years). Their mean Hoehn and Yahr stage was 3.7 ± 0.4 in 'off' condition before surgery, and 2.6 ± 0.4 in 'on' DBS-STN. Reaction time parameters used for comparison between conditions were onset latency of EMG activity (onsetEMG), task execution (TASK), and the number of bursts of EMG activity between onsetEMG and TASK (burstsEMG). Reaction time shortened in 'on' with respect to 'off' DBS-STN. The percentage shortening was 22.16% in onsetEMG, 17.6% in TASK, and 38.6% in burstsEMG for SRT, and 20.02% in onsetEMG, 25.1% in TASK, and 63.2% in burstsEMG for CRT. The improvement was significant ($p < 0.01$) for the number of bursts in both conditions and for TASK in CRT. Our results suggest that performance of PD patients in reaction time paradigms improve with DBS-STN. The improvement is more marked in CRT paradigms which involve a larger degree of attentional processes. Reduction of the number of tremor bursts between onsetEMG and task execution is likely to contribute to the improvement of reaction time.

P419

Posterior Ct guided approach for botulinum toxin injection into spinal psoas. P. Garcia Ruiz, A. Perez Higueras, R. Escorihuela, F. Castillo, Fundacion Jimenez Diaz (Madrid, E)

Over the last few years, Botulinum toxin A (BTA) has been used for the treatment of lower limb spasticity due to cerebral palsy and other conditions. In the majority of cases, BTA is injected in gastrocnemius, tibialis posterior, hamstrings and hip adductors, depending on the pattern of spasticity. These muscle groups are easy to inject, however some deep muscles do not permit an easy approach, particularly the spinal psoas.

We have used a posterior, CT guided approach to inject the spinal psoas in cases of severe flexion-adduction contracture of the hip.

Case 1. A 10 year-old boy with Sanfilippo syndrome (mucopolysaccaridoses III) was referred for extremely painful spastic hip subluxation that was resistant to conservative measures. Hip mobilization was very painful due to severe contracture. Under light sedation we injected 100 u BTA (Allergan) into the spinal left psoas by posterior approach (level L4) with CT guide. After three days, the hip contracture improved and the pain disappeared. His left leg could be passively extended. He has been injected with the same method every 4 months.

Case 2. A 9 year old girl with cerebral palsy was referred for spastic hip subluxation that did not respond to conservative nor surgical measures. We injected 100 u BTA (Allergan) into spinal psoas (CT guided) with similar results observed in case 1. In both cases, the procedure was well tolerated.

In summary, spinal psoas can be easily injected with posterior, CT guided approach. This method can be useful in cases of severe spastic contracture of the hip

P420

Dentatorubropallidoluysian atrophy in a familial Spanish case: clinical and radiological evolution. J. Campdelacreu, E. Muñoz, B. Gómez, E. Tolosa, C. Gaig, C. Pascual, Hospital Clínic Provincial (Barcelona, E)

Background: Dentatorubropallidoluysian atrophy (DRPLA) is a neurodegenerative disease with an autosomal dominant inheritance causing ataxia, chorea, epilepsy, behavioural disorders and dementia. There are few radiological studies showing brainstem atrophy and cerebral white matter signal alterations.

Objective: To describe the clinical and radiological findings after 5 years of follow-up of a Spanish patient who had been diagnosed of dentarorubropallidoluysian atrophy.

Patients: At first examination the patient presented severe ataxia with upper and lower limb dysmetria, marked gait instability, slight dysarthria and was demented. She also presented occasional slight choreic head movements. Cranial MRI showed atrophy of the cerebellum, brainstem and cortex and subcortical high intensity lesions in T2 weighted images. Genetic testing confirmed the diagnosis. Five years later the patient presents severe uncontrolled head movements associated to severe bruxism and tetraparesis, abnormal limb movements, and can hardly speak or eat. She is also deeply demented. MRI shows severe diffuse cerebral white matter alterations in T2 weighted sequences.

Conclusion: These patients can be initially misdiagnosed of Huntington's disease or olivopontocerebellar atrophy, but with atypical clinical and radiological features. In our patient the clinical worsening seems to correlate with the spreading of white matter lesions, thus suggesting that the structures altered on MRI are responsible for the clinical symptoms. Neuroimaging can be useful to support the diagnosis and to explain the clinical worsening.

Neurogenetics

P421

A novel lamin A/C mutation in autosomal-dominant Emery-Dreifuss muscular dystrophy and low penetration. F. Hanisch, M. Wehnert, S. Zierz, G. Bonne, Martin-Luther-University, Institut of Human Genetics (Halle/Saale, Greifswald, D)

Autosomal-dominant Emery-Dreifuss muscular dystrophy (AD-EDMD) is characterized by the clinical triad of early onset contractures of elbow, Achilles tendons, and cervical spine, slowly progressive humeroperoneal muscle wasting and weakness, and life-threatening cardiac involvement with conduction blocks manifesting in the third decade. AD-EDMD is due to mutations in the LMNA gen affecting the nuclear envelope proteins Lamin A and C. There does not seem to be a correlation between phenotype and genotype.

We represent a 16-year old German boy with typical muscular involvement and contractures, mild creatine kinase (CK) elevation, and normal echocardiography. 24-hour Holter ECG demonstrated sinusrhythm, repeated polymorphic ventricular premature beats (Lown III), and salves of atrial premature beats. Muscle biopsy revealed mild myopathic pattern and normal immunolabeling for antibodies to Emerin and Lamin A/C. Neurological and cardiological examination of parents and siblings suggested a sporadic case. However, mutational analysis in the LMNA gen revealed the new missense mutation R401C in exon 7 that was present not only in the index patient but also in his both clinically asymptomatic 40-year old mother and 12-year old sister.

The data of this family suggests a lower penetrance of muscular and especially cardiac symptoms than previously supposed. Because of the high incidence of sudden cardiac death regular ECG assessment of apparently unaffected mutation carriers is recommended.

P422

Two novel mutations in the spastin gene in a family with hereditary spastic paraparesis and in one patient with apparently sporadic spastic paraplegia. B. Alber, G. Rothmund, A. C. Ludolph, T. Meyer, University of Ulm, Charité University Hospital Berlin (Ulm, Berlin, D)

Introduction: Hereditary spastic paraparesis (HSP) is a clinically and genetically heterogenous neurodegenerative disorder characterised by progressive spasticity of the lower limbs. 40–50 % of cases with an autosomal dominant HSP are caused by mutations in the spastin gene. The gene consists of 17 exons spanning a region of approximately 90kb on chromosome 2p21–22. The gene is encoding a polypeptide, which is a member of the AAA protein family (ATP-associated proteins with various cellular activities). The goal of our study was to search for mutations in the spastin gene in patients with a HSP and sporadic spastic paraplegia (SSP).

Material and methods: We investigated 12 patients who showed a HSP and 18 patients with a SSP. The genomic DNA of the patients was purified from EDTA-blood using QIAGEN DNA Blood Midi Kit. The exons including the flanking parts of the introns were amplified by polymerase chain reaction using recombinant taq-DNA-polymerase. The PCR products were directly sequenced.

Results: We found two novel mutations in the spastin gene. The first mutation was found in a family with three effected female individuals in three generations showing a pure form of HSP. The underlying mutation is a nonsense mutation in exon 5 [871C-G, Ser-Stop] leading to a truncated protein. – The second mutation was found in a patient with an SSP. This patient shows a pure form of the disease as well. The underlying mutation is a missense mutation in exon 9 [1342T-C, Ile-Thr].

Discussion: We describe two novel mutations in the spastin gene encoding different gene products (truncated protein and amino acid change, respectively). Both mutations are associated with a pure form of the disease. Interestingly, we identified the 1342T-C mutation in a patient with an SSP. We conclude, that SSP at least in part represents a spastin associated disorder. Furthermore it will be of interest to study the prevalence of spastin mutations in the sporadic disease group and to determine the diagnostic value of spastin mutation screening in patients with SSP.

P423

Clinical, electrophysiological and sensorineural deafness in Charcot-Marie-Tooth disease with Connexin 32 mutation. W. Fadel, T. Mehalwi, H. Mourad, Tanta University Hospital (Tanta, EGY)

This study was done on 17 patients with Charcot- Marie-Tooth disease (CMT) and 14 healthy subjects with normal hearing. All subjects were subjected to clinical, audiometric tests (pure tone audiometry and immittancemetry) and electrophysiological tests (Motor nerve conduction velocities of the median, ulnar and common peroneal nerves and auditory brainstem response). Molecular genetic analysis of connexin32 gene was also performed to the studied groups. Males with CMT were more affected than females. Distal muscle wasting and weakness, sensory loss, areflexia, high arched palate and pes cavus were the dominant clinical signs. Our results showed that there was reduction of the motor nerve conduction velocity (MNCV) and reduction of compound motor action potential amplitude (CMAP) especially for the peroneal nerve. Sensorineural deafness ranged from mild to moderate hearing loss was observed in 3 patients (17.6 %). High frequency Sensorineural hearing loss in the 4–8KHz was observed in 3 patients (17.6 %). Abnormal ABR was found in 8 out of 17 patients (47.05 %) that ranged from prolonged waves III & V and interwave latencies I-III and I-V to absent ABR waveform, indicating that the lesion must be localized to the auditory nerve or brain stem. Point mutation A 142Q was observed in the patients complaining of hearing loss, while point mutation A 142 W was found in other patients with auditory abnormalities. So, the connexin32 gene mutation at the codon 142 could play an important role in the auditory pathway in CMT disease patients.

P424

Nicastrin gene is not a susceptibility locus for Alzheimer's disease. An. Orlacchio, T. Kawarai, E. Paciotti, A. Stefani, E. Rogaeva, A. Orlacchio, P. St George-Hyslop, G. Bernardi, IRCCS Santa Lucia, CRND, University of Toronto, University of Perugia, University "Tor Vergata", IRCCS Santa Lucia (Rome, I; Toronto, CAN; Perugia, I)

Background: The Presenilins (PS1 and PS2) play a central role in the pathogenesis of Alzheimer's disease (AD). Nicastrin (NCT) is a Type I transmembrane glycoprotein and a component of the PS1 and PS2 complexes. Mutations in the coding and in the non-coding region including promoter, which regulates the expression level of NCT, could cause a crucial effect in the neuronal cells of Alzheimer's disease patients. Objective: To test the hypothesis that NCT might be genetically associated with AD by linkage analysis, by direct nucleotide sequencing of the entire open reading frame of this gene and by association analysis of two single nucleotide polymorphisms in the coding region and one in non-coding region of the gene. Methods: The study was performed in an Italian population. The linkage analysis included 28 pedigrees, the mutation analysis 20 subjects with familial AD and 10 subjects with sporadic AD and the association study 403 patients (71 % females; mean age 72.3 ± 8 years; range 49 ± 96 years) who met the NINCDS/ADRDA criteria for probable AD, and 395 control subjects (71 % females; mean age 74.3 ± 7.7 years; range 51 ± 97 years) with Mini Mental State Examination scores greater than 28, which were verified

by at least one subsequent annual following up assessment. Genotyping of NCT and APOE polymorphisms were performed by PCR followed by restriction endonuclease digestions. Results: We found no pathological mutations in the NCT gene and no differences in allele or genotype frequency between AD cases and controls of the polymorphisms examined. We split the data based upon APOE carrier status and there was not significant association between the polymorphisms examined and the risk of AD, in either APOE epsilon4 carriers and non-APOE epsilon4 carriers. The same results held when our data set was stratified by age or gender. Conclusions: The results obtained indicate that NCT is not likely to be a major AD susceptibility locus.

P425

Association study of the 5-HT6 receptor gene in Alzheimer's disease. An. Orlacchio, T. Kawarai, E. Paciotti, A. Stefani, A. Orlacchio, S. Sorbi, P. St George-Hyslop, G. Bernardi, IRCCS Santa Lucia, CRND, University of Toronto, University of Perugia, University "Tor Vergata University of Florence, IRCCS Santa Lucia (Rome, I; Toronto, CAN; Perugia, Florence, I)

Background: Serotonergic (5-hydroxytryptamine; 5-HT) transmission has been implicated in the pathogenesis of Alzheimer's disease (AD). Objective: A coding single nucleotide polymorphism (SNP) 267 (C/T) in the 5-HT6 receptor gene was previously reported as a susceptibility factor for AD. An extensive replication study was performed using our data set including sporadic and familial cases. Methods: The study was performed in an Italian population. A total of 403 subjects were included in this study. We have analysed the above-mentioned polymorphism in 303 AD patients meeting the NINCDS-ADRDA criteria for probable AD: 127 patients with sporadic AD (age at onset 69.1 ± 7.2, mean ± SD) and 110 patients belonging to 110 autopsy-proven FAD families [50 LOFAD subjects (mean age 73.2 ± 3.9) and 60 EOFAD subjects (mean age 55.7 ± 8.0)]. These familial cases were without mutations in the Amyloid Precursor Protein (APP), Presenilin–1 (PS–1) and Presenilin–2 (PS–2) genes, but probably with other unknown mutations. We have also analyzed the 5-HT6 receptor polymorphism 267 C/T in the affected subjects carrying pathological mutations in the APP, PS–1 and PS–2 genes, including PS–1 Met146Leu mutation, PS–2 Met239Val mutation and APP 717 Val Ile mutations. In addition, we have also studied 100 normal controls (mean age 71.2 ± 34.2). The polymorphism was analyzed by PCR-RFLP analysis. Results: No significant association between the 5-HT6 receptor gene and AD was obtained with or without the stratification of ApoE epsilon4 status. Conclusions: Our result suggests that the 267C allele of the 5-HT6 receptor gene may not be a genetic risk factor for AD.

P426

Incidence of apolipoprotein E alleles in Greek patients with familial and sporadic Parkinson's disease. S. Veletza, E. Dimoula, S. Bostatzopoulou, I. Iakovakis, R. Divari, G. Hadjigeorgiou, A. Papadimitriou, University of Thessaly (Larissa, GR)

The apolipoprotein E (APOE) gene polymorphism has been studied in sporadic and familial Parkinson's disease (PD) in different ethnic groups with conflicting results. A recent study showed significant association of sporadic PD with a polymorphism within alpha-synuclein gene and APOE (E4 allele) while this association was not confirmed in a much larger sample of histopathologically proven PD.

The frequency of APOE alleles E2 (5.3 %) and E4 (6.5 %) has been reported to be lower in Greek general population than frequency in North European countries due to a North-South gradient in Europe.

The incidence of APOE alleles in Greek patients with familial (n = 49) and sporadic (n = 105) PD has been investigated. Thirteen patients with familial PD carried the G209A mutation in alpha-synuclein gene. Although the E2 allele was found to be more frequent in familial (7.1 %) and less frequent in sporadic (3.8 %) PD patients in compare to Greek general population, these findings did not reach statistic significance. The E4 allele appeared more frequently in familial (11.2 %) PD patients than in Greek general population and this difference was more clearly pronounced (19.2 %)and statistical significant (p = 0.015) among patients with familial PD who also carried the G209A mutation in alpha-synuclein gene. Our data need more extensive investigation in order to clarify the role of APOE genotype in familial PD patients who carry the G209A mutation.

P427

A novel form of autosomal recessive pure hereditary spastic paraplegia maps to chromosome 13q14. S. Bohlega, C. A. Hodgkinson, S. N. Abu-Amero, E. J. Cupler, M. Kambouris, B. F. Meyer, V. A. Bharucha, King Faisal Specialist Hospital & Re (Riyadh, SA)

Hereditary spastic paraplegia(HSP)is a clinically and genetically heterogeneous disorder. The disorder is characterized by progressive weakening and spasticity of the lower limbs; a variety of neurological symptoms can accompany this including, occasionally, disordered pigmentation and deafness. HSP is classified according to the presence or absence of neurological symptoms and by the mode of its inheritance. Currently, seventeen loci have been linked to the various forms of HSP. We have identified a family that displays an autosomal recessive form of HSP. Five out of eight of the children in the sibship have had difficulty in walking since early childhood and are severely spastic. None of these individuals displays any mental retardation or visual deficit. Three of the paraplegic children and two of their siblings have sensory-neural deafness, although the deafness and paraplegia segregate independently. Using genome scanning, we have been able to link the locus for paraplegia to chromosome 13 and confirm that the trait for deafness is independent of the paraplegia. No HSP locus (autosomal dominant or recessive) has been linked to chromosome 13, and therefore this family exhibits a novel form of autosomal recessive pure HSP.

P428

A Tunisian family with cerebellar ataxia and oculomotor apraxia caused by a whole deletion of the aprataxin gene. M. Zouari, G. El Euch-Fayache, M. Kefi, R. Amouri, S. Belal, F. Hentati, National Institute of Neurology (Tunis, TN)

Objective: To report the clinical findings, biological data, nerve biopsy studies and the mutation analysis of a family with an autosomal recessive cerebellar ataxia associated to oculomotor apraxia.

Background: An autosomal recessive cerebellar ataxia associated to oculomotor apraxia (AOA1), has been recently described in Japanese and Portuguese families. This form of cerebellar ataxia is characterized by an early-onset with oculomotor apraxia, peripheral neuropathy associated to hypoalbuminemia and hypercholesterolemia; the gene responsible has been mapped to chromosome 9p13 and encodes a protein called aprataxin.

Methods: Four patients belonging to a Tunisian family and affected by an early-onset cerebellar ataxia associated to oculomotor apraxia with a peripheral neuropathy were selected. All patients had hypoalbuminemia with hypercholesterolemia. Nerve biopsy study was done in one patient. Genetic linkage analysis confirmed the linkage of this form of cerebellar ataxia to the locus 9p13.

Results: The mean age of onset was 5 years. The four affected members of this family showed stereotyped clinical features with cerebellar ataxia, oculomotor apraxia and peripheral neuropathy affecting the four limbs. There was no pyramidal signs, no hearing impairment, no optic atrophy and no mental retardation. All patients had hypoalbuminemia with hypercholesterolemia. Nerve biopsy study showed a severe axonal neuropathy. Mutation analysis showed a large deletion of the whole aprataxin gene.

Conclusion: The family reported here showed the same clinical, biological and nerve biopsy studies as the cerebellar ataxia with oculomotor apraxia linked to the locus 9p13 with a large deletion of the whole aprataxin gene.

P429

An alternative genetic epidemiology research design for the identification of germline mutations involved in the development of glioma. M. P. W. A. Houben, R. H. Osborne, C. C. Tijssen, J. W. W. Coebergh, C. M. van Duijn, Erasmus Medical Center Rotterdam, University of Melbourne, St. Elisabeth Hospital, Comprehensive Cancer Centre South (Rotterdam, NL; Melbourne, AUS; Tilburg, Eindhoven, NL)

Only few germline mutations are known to be involved in the development of malignant brain tumors. The search for genetic causes of gliomas has been complicated by the rarity of the disease, a limited number of families with multiple affected relatives and the short survival time of patients. For these reasons, traditional genetic epidemiological strategies like linkage or sib-pair analysis are less useful in the research for germline mutations. However, there has been growing interest in identifying disease genes through association studies using population-based patient series. This method is particularly suitable for genetically isolated populations where the variety of genetic risk factors will be reduced as a consequence of genetic drift and where patients are more likely to be descended from one common ancestor. We evaluated the feasibility of such studies for glioma.

From the Eindhoven Cancer Registry, 12 patients were identified in a recently isolated population in the Netherlands who were diagnosed with glioma between 1988 and 1998. A neuropathologist reviewed this diagnosis. By extensive genealogical research a pedigree was constructed connecting 9 of the 12 patients to one common ancestor. In addition, further intermarriages occurred in more recent generations, leading to a consanguineous marriage of the parents of 6 patients. Seven patients suffered from a grade IV astrocytoma and two patients had a grade II astrocytoma which reoccurred as grade III and IV tumors. Five of the patients were male, the median age at diagnosis was 60 years (range 24 to 73 years) with a median survival time of 10 months.

The nine patients appeared to be related within 7–12 generations, suggesting a common genetic origin of the tumors. A germline mutation may be present in one of a pair of chromosomes manifesting as a first 'hit' in the neoplastic transformation of an astrocyte. Because consanguinity was seen in most patients, an autosomal recessive mutation may be involved. The features of this pedigree thereby provide an opportunity for homozygosity mapping, a method to identify a recessive disease locus with only a very small number of inbred patients. Although this pedigree does not prove a common genetic origin, these patients and others identified from the same region provide an exciting opportunity for investigating the genetic susceptibility of glioma.

Multiple sclerosis

P430

Demographic and clinical findings in familial multiple sclerosis: a hospital-based study. M. Eraksoy, N. Turan, M. Kurtuncu, G. Akman-Demir, A. Kiyat-Atamer, Z. Yapici, H. Ozcan, Istanbul University (Istanbul, TR)

In this study, demographic and clinical findings of 159 patients with familial multiple sclerosis(MS) in a hospital based cohort from Istanbul were described. The results were compared with 1486 sporadic MS patients. The familial frequency of MS was 4.4 % of the total 1645 patients with MS at January 2002.

The familial MS patients were the members of 73 families, and this group was divided into the following three groups: sibling pairs, parent-child pairs and the other collateral relatives. Consanguinity was found in fourteen families.

The age at the onset of the disease was 30.1 years. Female/male ratio was 1.6/1. Most of the patients(41.3 %)were seen from onset of the disease. The most common initial symptoms were sensory(44.6 %), diplopia (17.6 %)and optic neuropathy(14.4 %). According to Poser and co-workers' criteria, 93 % of the patients was clinically definite MS, and the rest of the patients were clinically probable MS(4.4 %)and laboratory-supported definite MS(1.8 %). Relapsing-remitting course was seen in 53.4 % of 159 patients. The mean duration of disease was 11.2 years, Kurtzke's score was 3.3 and the mean progression index was 0.3 at the last follow-up. The mean duration of follow-up was 10.2 years.

Of 159,42(26.4 %) patients have been receiving immunosupressive and immunomodulatory therapy. However,37(23.2 %)out of 159 familial MS patients reached the Kurtzke's score of 6.0 mean 13.2 years after the onset of the disease.

In conclusion, familial MS patients resembled those remaining sporadic in both clinical, demographic characteristics and outcome, although the subgroup analysis of the parent-child group revealed that the onset of the disease was earlier in children.

P431

Clinical, cerebrospinal fluid and neuroimaging findings of opticospinal involvement in the spectrum of inflammatory demyelinating diseases. M. Eraksoy, N. Turan, G. Akman-Demir, Z. Yapici, E. Deniz, C. Bayindir, H. Ozcan, Istanbul University (Istanbul, TR)

The selective involvement of optic nerve(s) and spinal cord may be encountered in the spectrum of inflammatory demyelinating diseases. There has been some debate on the classification and the naming of this group of diseases.

The objective of this study was to determine the clinical characteristics, outcome and laboratory findings of 25 patients with inflammatory demyelinating disease presented with opticospinal involvement. The findings of these patients were compared with the clinically definite multiple sclerosis(CDMS)patients presented with uni- or bilateral optic neuropathy(ON/BON) or transverse myelopathy(TM)/partial spinal cord syndrome.

This study revealed that most of the patients in this group developed multiphasic Devic's neuromyelitis optica(DNO), a small group of patients had monophasic DNO, and the remaining patients had a transitional form between multiphasic DNO and opticospinal MS at the last follow-up. Mean interval between first and second relapses was shorter in multiphasic DNO than CDMS patients with the onset of ON/BON or TM. The prognosis of multiphasic DNO group is relatively poor compared with the other two multiple sclerosis(MS)groups.

However, statistically significant difference was not found between three groups in terms of reaching the Kurtzke's score of 6.0.

Consequently, the occurrence of opticospinal involvement was a result of different aetiopathogenetic factors. Some of the clinical and laboratory clues showed that there has been a close relationship between inflammatory demyelinating diseases, vasculitis and DNO showing opticospinal presentation. The genetic and environmental factors which modify the acuteness and tempo of the process seemed to play a role in the differences of the syndrome presented with opticospinal involvement.

P432

Mitoxantrone-induced immunological changes in MS patients – ex vivo studies on proliferation and cell death of peripheral blood leukocytes. F. X. Weilbach, A. Chan, K. V. Toyka, R. Gold (Wuerzburg, D)

Mitoxantrone is a highly effective immunosuppressant for the treatment of active multiple sclerosis (MS). Despite proven clinical efficacy, only few data are available concerning immunological mechanisms. In leukaemia cells mitoxantrone in vitro and in vivo induces apoptosis. In this study we investigated the effects of mitoxantrone on leukocytes from MS patients ex vivo. Peripheral blood derived mononuclear cells (MNC) were obtained from 23 active MS patients (mean age 38.8 yrs., m:f 1:1.4) before and immediately after 1h mitoxantrone infusion. Isolated MNC were cultured for 24h with and without phytohemagglutinin activation (PHA, 5 microgram/ml). Proliferation was measured by 3H-thymidine uptake. Cell death was analysed flow-cytometrically using Annexin-V/propidiumiodide double staining (Ann/PI). Mitoxantrone decreased proliferation of MNC in 21/23 patients in comparison to control MNC from the same patient before mitoxantrone application (58 ± 22 % of controls, $p < 0.001$). Mitoxantrone induced late apoptotic/necrotic changes in MNC of 19/23 patients ($p < 0.001$, Wilcoxon), increasing the proportion of Ann/PI + cells by 30 % ($p < 0.001$, t-test). Subpopulation analyses (CD3, CD8, CD14, CD19, CD25, CD56) performed in 10 patients so far revealed no significant differences in susceptibility towards apoptosis. Our data indicate that already a short 1h in vivo exposure to mitoxantrone induces a profound suppression of proliferative responses in MNC of MS patients. This suppression appears to be mediated by induction of apoptotic/necrotic cell death.

P433

Lack of evidence for a role of the myelin basic protein gene in multiple sclerosis susceptibility in Sardinian patients. E. Cocco, C. Mancosu, E. Fadda, M.R Murru, G. Costa, R. Murru, M.G Marrosu, University of Cagliari (Cagliari, I)

Introduction. Susceptibility to multiple sclerosis (MS) is genetic in nature, as demonstrated by the fact that familial clustering of the disease is due to gene sharing rather than environmental factors. The myelin basic protein (MBP) gene is one attractive candidate for conferring disease susceptibility, as its product is a potential MS autoantigen. A link between MBP polymorphism and MS has been reported in some populations but not in others. Sardinia, a Mediterranean Island, has one of the highest incidences of MS in Europe. Sardinian population is genetically homogeneous with a genetic structure different from other Europeans, because it results from the fixation of alleles and haplotypes which are rare or absent elsewhere.

Materials and methods. We analyzed two polymorphisms in the 5' flanking region of the MBP exon 1 gene in MS patients from the founder population of Sardinia. Using the transmission disequilibrium test (TDT), MBP polymorphisms were analyzed in 363 singleton MS families.

Results. No distortion in transmission of the tetranucleotide repeat (ATGG)12 and of the 1116–1540 nt alleles was found. Moreover, we discovered no epistatic effect of the MBP gene on the HLA/MHC DRB1,DQB1, DPB1 loci or on alleles defined by D6S1683 marker found to be associated with MS in Sardinians.

Conclusion. Our results prove that the (ATGG)12 and the 1116–1540 polymorphisms in the 5' flanking region of MBP exon 1 gene are not associated with susceptibility to MS in Sardinia. Present findings firmly exclude that the MBP gene play a role in Sardinian MS, but they do not reject the possibility that genes involved in disease susceptibility might differ in ethnically different populations.

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P434

The independent comparison of interferon (INCOMIN) trial: analysis of the MRI activity. E. Verdun, P. Barbero, M. Bergui, A. Ghezzi, M. Zaffaroni, E. Montanari, L. Durelli,. INCOMIN Study Group, University of Turin, Civil Hospital (Turin, Gallarate, Fidenza, I)

Objective: To compare and analyze the effect of two IFN beta preparations on MRI activity in MS. BACKGROUND: Controlled trials have demonstrated efficacy of once-a-week IFN beta–1a or of on-alternate-day IFN beta–1b compared to placebo. Recently, we compared the clinical effacing of the two drugs, and some MRI parameters. We evaluate here the effect of the two treatments on different types of MRI activity. Methods: Prospective 2-years follow-up of 188 consecutive RR MS patients randomized by 15 MS centers to receive IFN beta–1a (30 mcg i. m. once a week) or IFN beta–1b (8 MIU s. c. on alternate days). 149 patients have performed baseline and annual pre- and post-gadolinium (Gd) axial T1-weighted (TR: 600–700; TE: 15–25) and dual-echo PD/T2 weighted (TR: 2000–2400 msec; TE: 20–40/80–100) brain MRI scans. Outcome measures were the mean number of new PD/T2 lesions, of new PD/T2 lesions with concomitant gadolinium enhancement, of lesions that were new PD/T2 lesions without concomitant enhancement, of enhancing lesions and of enhancing lesions that were not new lesions on PD/T2 scans. Scans were repeated once a year for two years. All types of active lesions were counted on each yearly scan (compared to baseline) and their mean number calculated on all the scans. Neuroradiologists completely blind as to the treatment and patients clinical characteristics evaluated the scans.

Results: Baseline outcome measures were similar in both groups. At the end of the 2-years of the study follow-up in the IFN beta–1b group, the mean of number of new PD/T2 lesions was 1.6 ± 2.6 in the IFN beta–1b and 3.9 ± 4 in the IFN beta–1a group ($p = 0.0001$). Other outcome measures were: mean number of new PD/T2 lesions with concomitant enhancement, 0.3 ± 0.9 for IFN beta–1b and 0.9 ± 1.6 for IFN beta–1a group ($p = 0.01$); mean number of lesions that were new PD/T2 lesions without concomitant enhancement 1.3 ± 2.2 in the IFN beta–1b and 3 ± 3 in the IFN beta–1a group ($p = 0.01$); mean number of enhancing lesions 0.9 ± 2.2 in the IFN beta–1b and 1.8 ± 2.9 in the IFN beta–1a group ($p = 0.04$); and mean number of enhancing lesions that were not new lesions on PD/T2 scans in the IFN beta–1b 0.6 ± 1.7 and 0.8 ± 1.4 in the IFN beta–1a group ($p = n. s$).

Conclusion: The results of MRI analysis showed that IFN beta–1b reduced signs of disease activity more effectively than IFN beta–1a and confirmed the clinical results. The effect of IFN beta–1b was slightly more pronounced on PD/T2 than on gd-enhanced MRI activity.

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Post marketing survey for multiple sclerosis centres by year/person approach: fourth year data. G. Iuliano, R. Napoletano, M. Tenuta, A. Esposito, Ospedali Riuniti di Salerno (Salerno, I)

Background: Italian district Multiple Sclerosis Centers treat with interferons (IFN) patients (pts) with 1 or more relapse/year for 2 years, and EDSS up to 5.5, and/or secondary progression up to EDSS 6.5. Since 1998 we are performing a survey by a simple year/person registry. Last update (december 2001) is reported in this paper.

Methods: years/person approach is the standard method to evaluate little groups, with different observation periods, often with previous therapies, sometimes switching from drug to drug.

We included in the survey only patients with complete history, so to avoid different relapse risks, and grouped them in: 0 = pts without therapy; 1 -pts with IFN1b; 2 -IFN1a (i. m 0.1/w); 3 -azathioprine (AZA); 4 -IFN1a (22 mg s. c 0.3/w); 5- IFN1a (44 mg s. c 0.3/w).

Patients usually start or switch therapy when they have at least 1 relapse/year for two years.

Results: From 51 patients (age onset 18–49, mean 28.34) we obtained 420 years (group without therapy = 67, patients before therapy = 219, IFN1b = 26, IFN1a 1/w = 42, IFN1a 3/w = 22, AZA = 44).

Group 0 has lower year relapse rate (RR) (0.343) and is excluded from further evaluation; RR is similar for the years before treatment in groups 1–2–3–4 (mean 0.927, SD.817), so we made a single control group. During therapy, for IFN1b RR is 0.667 (SD.877), for IFNIa 1/w 0.595 (0.828); for IFN Ia 3/W.909 (0.971); for AZA.467 (0.757). Overall Kruskal-Wallis test is significant ($p = 0.000501$), and so Neuman-Keuls multiple comparisons ($p < 0.05$) for all groups. Stratification till the fourth year don't show significant differences in RR, or in EDSS, but a trend to progressive reduction of relapse rate is evident for IF1b and AZA and not for IF1a (but there are no data about IF44 U), highly suggestive for further survey.

As to side effects, besides 1 allergic reaction to AZA; the most common was protracted fever after injection (with IFN1b, 11 yrs, 12 with IF1a 1/week, 3 with IF1a 3/week); 2 depressions with IF1b, 1 site reaction; with IF1b and 1 thyroid disturbance with imIF1a.

Dropouts were 2 IFN 1b, and 1 each IFN 1a im and AZA. Switching occurred in 6/26 yrs for IFN 1b, 9/42 for i. m. IFN 1a, 7/44 for AZA, 5/22 for s. c. IFN1a.

Conclusions: A periodically updated epidemiological monitoring of disease modifying groups in district SM centers adds to the main trials longitudinal data and, above all, deals with practical managing of the drugs.

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Disability in familial multiple sclerosis. A clinically based study on Sardinian patients. M.G Marrosu, E. Cocco, M. Pischedda, M. Lai, G. Spinicci, S. Massole, G. Marrosu, A. Vannelli, P. Contu, University of Cagliari (Cagliari, I)

Background. Familial cluster of multiple sclerosis (MS) is due to gene sharing rather than environmental factors. In addition to affecting susceptibility, genes might also contribute to determining disease outcome. Whether or not the clinical course of the disease is influenced genetically can be deduced by the presence of a similar course in relatives having the same MS status.

Methods. We estimated disability risk, defined by the time required to reach EDSS score 6, in a large cohort of patients with 1^{st} -degree, 2^{nd}- degree and without (sporadic) MS affected relatives. All patients came from Sardinia, a Mediterranean island having high disease incidence and prevalence of the disease. Disability risk was calculated using Kaplan-Meier life table methods in 1,258 (991 sporadic, 78 with 2^{nd}-degree and 189 with 1^{st}-degree affected relatives) consecutive MS patients, all frequenting the MS clinic at the University of Cagliari (Italy). Risk factors associated with disability were analysed according to the following variables: gender, age at MS onset, age at EDSS 6 and disease course categorised into relapsing-remitting/secondary progressive (RR-SP) or primary progressive (PP). The joint relationship of these covariates with disability risk was subsequently analysed using the Cox Regression Model and calculating proportional hazards.

Results. Despite similarity in onset age, the mean time required to reach EDSS 6 was less in familial 1^{st} (19 years, CI 95% 17–21) than in sporadic and familial 2^{nd} patients (25 years, CI 95% 22–28, P = 0.0196). Cox proportional hazard analysis showed that the risk of reaching EDSS 6 was not influenced by gender, whereas PP course conferred a risk 1.37 times (CI 95% 1.04–1.80, P = 0.249) higher in the familial than in the sporadic group. Having PP course determined in familial patients a risk 5.30 times (95% CI 4.11–6.82, P = 0.0001) higher than RR-SP course.

Conclusion. The high rate of disability in patients with a high genetic load, due to the excess of individual with PP MS, suggests that genes influencing familial aggregation might be involved in the outcome of the disease.

Acknowledgments. The authors thank the patients and their relatives for their kind cooperation in our study

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Status epilepticus revealing fulminant exacerbation of multiple sclerosis: efficacy of plasma exchange. I. Bonnaud, V. Gissot, V. Caillé, A. Autret, D. Perrotin, Hopital Bretonneau (Tours, F)

Background: Only a few cases of generalized status epilepticus (SE) have been reported in multiple sclerosis (MS). Moreover, fulminant exacerbations occurring in relapsing-remitting forms of MS are rare. We report a patient with fulminant exacerbation of MS, leading to a comatose state, resistant to corticosteroid therapy, and requiring intensive immunomodulating treatments. This acutisation was revelled by a SE.

Case report: A 26-year-old woman had a six -year history of relapsing-remitting MS, which had been treated with beta-interferon during several months in 1999. The last neurological manifestation was a generalized seizure in October 2000. EDSS was 0. Three months after a normal childbirth in October 2001, she experienced several generalized seizures and was treated by sodium valproate. During the following days she developed frontal dysfunction and apraxia of increasing gravity. In November 2001 a generalized status epilepticus occurred and she was admitted in an intensive care unit, treated with sodium valproate, carbamazepine, barbiturates, and a mechanical ventilation was required. After the end of seizures and cessation of sedative therapy, the patient remained comatose and mechan-

ical ventilation could not be withdrawn. EDSS was 9.5. Cerebral MRI showed hyperintense T2-weighted lesions, in periventricular regions, cerebellum and brainstem. Some of them were enhanced after IV injection of Gadolinium. CSF examination was normal. Intravenous prednisolone (1 g /day during five days) did not modify the clinical status. Plasma exchange (PE) was initiated. Dramatic improvement begun after the 4th one. Seizures completely stopped with phenobarbital alone. A week after the 8th PE, the patient was able to speak and walk, there were only an apraxia and a frontal dysfunction. EDSS was 4.5.Cerebral MRI showed an important decrease of extent of hyperintense lesions with less contrast enhancement.

Discussion: SE is an exceptional feature in MS, traducing the development of acute cortico-subcortical demyelinating lesions. Fulminant exacerbation of MS revealed by SE is an exceptional clinical presentation. Intensity of the demyelinating process after a long remission had probably been favoured by the immune changes following pregnancy.

Conclusion: PE remains controversial in progressive forms of MS, but this observation confirms its dramatic efficacy in acute fulminant forms(Weinshenker et al., annals of Neurology, 1999).

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Risk factors in multiple sclerosis: results of a case-control study. M. Geilenkeuser, W. Firnhaber, K. Griesenbeck, K. Lauer, Klinikum Darmstadt, Elisabethenstift Darmstadt (Darmstadt, Gross-Gerau, D)

Objectives: To assess the role of environmental variables during childhood and few genetic variables in MS. – METHODS: A case-control study in 538 MS patients (364 females, 174 males; mean year of birth [YOB] 1952, SD 15.0 years) and 102 hospital controls with minor surgery (68 females, 34 males; mean YOB 1957, SD 10.5 years) was performed. The MS cases were part of a period prevalence material collected in 1979–1998. The controls were interrogated in 1998. The probands were unmatched, and basic variables (YOB; gender) were controlled in the analysis. All interviews were made by trained physicians. Odds ratios (OR), 95 % confidence intervals (CI) and p-values based on chi2-test or Fisher's test were calculated in a bivariate fashion, and all significant variables ($p < 0.05$), YOB and gender were entered in a stepwise multivariate logistic regression model.

Results: The following variables were significantly more frequent in Ms patients in multivariate analysis: measles (OR = 6.4; 95 % CI: 1.8–23.1; p = 0.005); frequent (3 once per year) tonsillitis (OR = 2.5; 95 % CI: 1.0–6.6; p = 0.054); animal fat consumption (OR = 6.6; 95 % CI: 1.4–31.5; p = 0.019); vegetable fat consumption (OR = 26.5; 95 % CI: 4.9–142.0; p = 0.0002); dental caries (OR = 5.0; 95 % CI: 1.6–14.9; p = 0.005); familiar MS (OR = 9.7; 95 % CI: 1.6–14.9; p = 0.0114); coal heating (OR = 2.9; 95 % CI: 1.2–7.3; p = 0.022); and contact to mice (OR = 3.8; 95 % CI: 1.4–9.9; p = 0.007). Diphtheria and polio vaccination, sinusitis, egg consumption, dental fillings, and intestinal worms were significantly less frequent in MS patients.

Conclusions: The independent role of measles, familiar MS and animal fat consumption is in agreement with earlier findings. The other variables are more controversial, or shown for the first time to be risk factors, and should be tested in subsequent studies.

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Multiple sclerosis and diabetes mellitus. Do they share a common pathogenesis? M. Gedizlioglu, E. Özerkan, P. Çe, S. Yalin, B. Karaca, A. Çavusoglu, SSK Izmir Teaching Hospital, SSK Tepecik Teaching Hospital (Izmir, TR)

Multiple sclerosis (MS) has an increased association with autoimmune diseases more than just coincidental. Observations on relationship of MS and diabetes mellitus (DM) have led hypothesis of a common pathogenesis between two diseases. In this study we looked for an abnormality of glucose metabolism in MS patients.

Subjects: 24 MS patients (11 males, 13 females) and 15 healthy controls (4 males, 11 females) were recruited for the study. Of the patients 22 had relapsing-remitting and 2, secondary progressive definite MS. Body mass indexes (BMI) of subjects were calculated. Blood sugar, insulin and c-peptide levels have been measured at 0–60–90–120th minutes during oral glucose tolerance testing (OGTT). Type 2 DM indexes (glucose/BMI, c-peptide/BMI, glucose/c-peptide) were calculated. Anti-islet cell antibodies (AICA) and anti-insulin antibodies (AIA) were estimated.

Results: AICA and AIA were negative in all cohort. There was no statistical difference between ages and BMIs of groups.

Two MS patients had overt DM, and two, fasting glucose abnormality (American Diabetes Association criteria). During OGTT, glucose and insulin levels, c-peptide/BMI, glucose/c-peptide indexes were statistically not different in both groups. However, c-peptide values on 60 and 90th minutes, and glucose/BMI index were meaningfully high in MS group (p = 0,028, p = 0,013 and p = 0,0002 respectively).

Any association between glucose metabolism abnormality and medications (beta interferon, azathiopirine, steroids) could not be observed.

Conclusions: In this study, higher c-peptide levels, glucose/BMI index abnormality and presence of 4 diabetic patients in MS group support existence of a pathology of glucose metabolism, compatible with type 2 DM. There are some other clues pointing to an association between MS and DM. Both type 1 and 2 DM are proposed to have a link to MS. According to this hypothesis, both MS and DM may be the result of a kind of pancreatopathy experienced in very young ages. Although epidemiological studies support this view, no direct proof exists. Our study is aimed to find some laboratory evidence pointing to any relationship between the two conditions. It has failed to find any proof in favour of type 1 DM. However, the results point to an apparent abnormality of glucose metabolism in type 2 DM fashion. Further studies are needed to ascertain this hypothesis.

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Cytokine profile in multiple sclerosis (MS) patients before and after reducing the dose of interferon (IFN) beta. A. Ricci, E. Verdun, P. Barbero, A. Oggero, A. Cucci, M. Clerico, A. Bosio, A. Pipieri, L. Durelli, University of Turin (Turin, I)

Objective: To evaluate the immunological profile in MS patients who have reduced the dose of IFN beta.

Background: Many trials have demonstrated the efficacy of IFN beta–1a at the dose of 30 mcg intramuscularly (i. m) once a week or of IFN beta–1b at dose of 8 million international units (MIU) on alternate days subcutaneously (s. c), compared to placebo. The chronic administration of a drug on alternate days reduce the compliance of patients and encourage the decision to reduce the IFN beta dose. A study of the correlation of the immunological, clinical and MRI effects of IFN beta dose reduction in MS patients is needed.

Methods: Ten MS patients, after 3 years of IFN beta–1b treatment at 8 MIU on alternate days s. c., without any clinical and MRI signs of disease activity (no relapses or progression at EDSS = / > 1 for at least 2 years, no new T2 or gadolinium-enhancing lesions in last two yearly scans), were gradually switched to IFN beta–1a 30 mcg i. m. once a week. Before and one year after the IFN reduction we examined the levels of interleukin (IL)–4, IL–10, IL–12, tumour necrosis factor (TNF)-alfa and IFN-gamma in supernatant of stimulated peripheral blood mononuclear cells (by ELISA), and neutralizing interferon antibodies (NAb) (by an anti-viral assay) in serum.

Results: One year after IFN reduction 9 out of 10 (90 %) patients had a resumption of disease activity, defined as the occurrence of clinical relapses, sustained EDSS worsening or lesional activity on brain MRI scan. Two patients (20 %) were Nab positive before IFN reduction (titre > 60) and still one year after (with lower titres). One year after dose reduction IFN-gamma levels were significantly higher than baseline in all patients (p = 0.019). IL–10 levels in 9 patients with disease activity were similar or lower than baseline; only in the patient without disease activity the IL–10 level was higher than baseline. No significant differences were found in IL–4, IL–12, TNF-alfa levels.

Conclusion: The reduction of IFN-beta dose was associated with the reactivation both of the clinical as well as of the immunological response in most patients. IFN-gamma, a pro-inflammatory cytokine, increased in all patients (90 % of whom had increased clinical disease activity). IL–10, an anti-inflammatory cytokine, increased in the only patient who had not clinical reactivation.

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The effect of intravenous immunoglobulins on quantities derived from MT MRI in secondary progressive multiple sclerosis. M. Filippi, G. Iannucci, M. P. Sormani, F. Fazekas, X. Lin, O. R. Hommes, G. Comi, Scientific Institute and University HSR, Karl-Frenzen University, Queen's Medical Centre, European Charcot Foundation (Milan, I; Graz, A; Nottingham, UK; Nijmegen, NL)

Magnetization transfer (MT) magnetic resonance imaging (MRI) can provide in vivo markers reflecting the severity of irreversible, multiple sclerosis (MS) brain damage occurring within and outside T2-visible lesions. Cross-sectional and longitudinal studies have found that MT MRI abnormalities are more evident in patients with a more disabling disease course and tend to worsen at a greater pace in secondary progressive (SP) MS than in all other MS clinical phenotypes.

In this study, we investigated whether intravenous immunoglobulin (IVIG) treatment at the dose of 1 g/kg/body weight monthly is effective in

reducing the accumulation of MT MRI-measured damage of the normal appearing brain tissue (NABT) and T2-visible lesions in patients with SPMS.

Seventy SPMS patients from 10 centers participating into the European, multi-center, double-blind, placebo-controlled trial of IVIG in SPMS (ESIMS) underwent brain T2-weighted, T1-weighted, and MT MRI at baseline and every 12 months for two years. MT MRI scans were post-processed and analyzed to obtain average MT ratio (MTR) from the NABT and T2-visible lesions.

At baseline, the placebo (n = 34) and treated (n = 36) patients did not differ significantly in terms of demographic, clinical, and MRI characteristics. No statistically significant difference between treated and placebo patients was found for both average NABT MTR and average lesion MTR in terms of "treatment x time" interaction. Weak to moderate correlations were found between MTR quantities and T2 lesion volume, T1 lesion volume, brain parenchymal fraction and clinical measures of disability (r values ranging from 0.23 to 0.55).

This study suggests that IGIV treatment does not favorably modify the mechanisms leading to intrinsic tissue damage in patients with SPMS. Nevertheless, this study was based on a relatively small sample of patients and, as a consequence, its results should be regarded as preliminary.

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Cervical cord damage in patients with clinically isolated syndromes suggestive of multiple sclerosis: a study with MTR histogram analysis. M. Bozzali, M. Rovaris, V. Martinelli, M. Rodegher, A. Ghezzi, G. Comi, M. Filippi, Scientific Institute and University HSR, Ospedale di Gallarate (Milan, Gallarate, I)

Patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS) often present brain magnetic resonance imaging (MRI)-visible abnormalities, whose burden predicts the subsequent development of clinically definite MS. Previous studies showed conflicting results regarding the presence of cervical cord damage in CIS patients.

Using magnetization transfer (MT) ratio (MTR) histogram analysis, we evaluated the extent of cervical cord damage in patients with CIS and whether such damage was more severe in patients with a higher risk of evolution to definite MS, as identified by the fulfillment of ad hoc MRI criteria (Barkhof's criteria).

Twenty-three patients with CIS (mean age: 28.6 years) and 11 sex- and age-matched healthy controls were studied. All patients had had a CIS suggestive of demyelination within the three months preceding MR acquisition. Median patients' expanded disability status scale score was 0.5 (range: 0.0–2.0). In a single session, the following sequences were acquired: A) Brain: dual-echo turbo spin echo (SE) (TR/TE = 3300/16–98); post-contrast (gadolinium-DTPA, Gd) T1-weighted conventional SE (TR/TE = 768/14)(number of axial slices: 24, contiguous, 5-mm thick); B) Cervical cord: Fast-short tau inversion recovery (TR/TE/TI = 2.288/60/110; number of sagittal slices: 8, 3-mm thick); 2D gradient echo (GE) (TR/TE = 640/10; number of axial slices: 20, contiguous, 5-mm thick), with and without MT pulse. The number and location of brain T2-hyperintense, T1-hypointense, Gd-enhancing, and cervical cord hyperintense lesions were evaluated and the fulfillment of Barkhof's MRI criteria for MS diagnosis was assessed. Cervical cord MTR maps were derived and histogram analysis of MTR values was performed.

Thirteen CIS patients fulfilled Barkhof's criteria and 6 patients showed one or more cervical cord hyperintense lesions. No significant differences between CIS patients and controls were found for any of the MTR histogram-derived quantities, albeit the histogram peak height, which reflects the amount of truly normal tissue, was lower in the former group. No significant group differences were found between patients who fulfilled Barkhof's criteria and those who did not, nor between patients with and without MRI-visible cervical cord lesions.

MTR histogram findings indicate that there is no overt structural damage in the cervical cord of CIS patients, independently of the burden of brain MRI-visible lesions.

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The Italian version of the Chicago Multiscale Depression Inventory: translation, adaptation and testing in people with multiple sclerosis. A. Solari, National Neurological Institute Carlo Besta (Milan, I)

Background. Depression represents the most frequent psychiatric disturbance in people with multiple sclerosis (MS), with rates higher than in the general population and other chronic diseases. Timely identification and treatment of depression is thus important. However, accurate assessment of depressive symptoms can be biased by somatic symptoms, which are part of both MS and depression. The Chicago Multiscale Depression Inventory (CMDI) is a tool developed specifically to assess depression in MS and other chronic diseases. It consists of a total score and three subscales assessing mood, vegetative, and evaluative symptoms (Nyhenius 1995).

Objectives. To translate and adapt into Italian the CMDI. To test the questionnaire in outpatients with MS, healthy controls, and people with major depression (MD).

Methods. The CMDI was translated and adapted into Italian employing a standardized methodology. The Italian CMDI was then tested in 213 MS outpatients, 213 individually matched healthy controls, and 32 MD outpatients.

Results. Mean completion time was 11.8 minutes (SD 3.9), and in no instance was assistance asked to complete it. Ninety percent of people with MS, and 93 % of controls completed all CMDI items. Internal consistency reliability, and test-retest reliability were overall good. The CMDI total score and mood subscore correctly classified 96.4 % and 90.6 % of people with MD, respectively.

Nine percent of healthy controls and 15.5 % of people with MS were impaired on CMDI mood (p = 0.04). The corresponding figures for CMDI evaluative were 11 % vs. 18 % (p = 0.04), and for CMDI vegetative 6 % vs. 21 % (p < 0.0001). We found a higher risk for depressive symptoms in people with MS compared to healthy controls, with odds ratio (OR) for impaired CMDI mood 1.85, 95 % confidence interval (CI) 0.99–3.45. The OR for impaired CMDI evaluative was 1.66, 95 % CI 0.92–2.99, and for somatic symptoms (impaired CMDI vegetative) 4.36, 95 % CI 2.20–8.67. After excluding first degree relatives from controls, the risk for impaired CMDI mood (OR 2.60, 95 % CI 1.04–6.53) and CMDI vegetative (OR 8.14, 95 % CI 2.43–27.27) increased further.

Conclusions. The Italian version of the CMDI is characterised by reliability parameters and results in different populations (healthy controls, people with MS and MD) that closely resemble those of the original. These findings support the use of the CMDI as a clinical and research tool with Italian people with MS.

Neuro-oncology

P444

Multiple brain metastases of melanoma, 11 years after the primary facial localization. W. Verslegers, P. De Deyn, AZ Palfijn (Antwerp, B)

Case. A 59-year old woman developed at the age of 48 a melanoma inferior to the right lower eye limb, treated with resection and irradiation. Eleven years later, she developed gradually paresis and irradiating pain from the neck into the right arm, instability, nausea, dizziness and headache. Internal and haematological investigation were normal. Near the border of the old resection zone, brown pigment could be seen. CT scan of the brain with and without contrast enhancement demonstrated numerous tumours (at least thirty one supratentorial) and seven in the fossa posterior (also in the cisternae between mesencephalon and vermis). All symptoms disappeared with methylprednisolone 125 mg daily.

Anatomopathological examination of a left frontal located and macroscopic dark brown metastases revealed tumour cells with high mitotic activity and intracytoplasmatic brownish pigment, which was positive for Fontana, S–100 and monoclonal mouse anti-human–45, confirming melanoma. She dead three weeks later.

After a symptom free period of eleven years, the cerebral metastasises were probably linked to the original facial localisation. Very late reappearance of such localisations exist because the blood brain barrier (BBB) does not protect the invasion of the central nerve system (CNS) by circulating metastatic cells. Trophic factors promote BBB invasion by enhancing the production of basement membrane degrading enzymes. CNS-metastatic melanoma cells responding particular to nerve growth factor and neurotrophin–2. The ability to form metastasises in the CNS dependent on tumour cell responses to autocrine and paracrine factors that influence their growth and survival in the CNS. The cells from brain metastases have a slower growth rate and exhibited lower metastatic potential than cells from visceral metastasises. Brain metastasises are likely to originate from a unique subpopulation of cells within the primary neoplasm. Treatment of leptomeningeal gliomatosis is discouraging but clinical improvement and clearance of neoplastic cells from the cerebrospinal fluid have been seen in patients treated with intrathecal interleucin–2 and lymphokine-activated killer cells.

Conclusion. Some questions remain: after which symptom free period patients can be considered cured, what is the value of repeated investigations in the absence of disease modifying treatments when metastasises appear.

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Serial MR imaging of lymphomatoid granulomatosis: punctate and linear enhancements preceding hemorrhage. H. Shimamura, H. Miura, E. Hatao, T. Matsuoka, Tokyo Medical University (Ami, Inashiki, Ibaraki, JP)

Background: Lymphomatoid granulomatosis (LG) is a rare lymphoproliferative disorder that involves the lung, skin, nervous system. There have been few reports, however, on serial changes seen on MR images during the follow-up period of LG. We report a case of LG who presented the pulmonary and central nervous system (CNS) involvement. Serial MR images of CNS showed multiple punctate and linear area with gadolinium enhancement followed by hemorrhage.

Case report: A 28-year-old male was admitted to our hospital complaining of persistent cough and sputa. Chest X-rays detected diffuse interstitial infiltrates. Hypersensitive pneumonitis was diagnosed, and treatment with corticosteroids gave marked clinical improvement. Four months later, he was readmitted because of paraparesis and dysesthesia below the level of Th 6. MR images of spinal cord showed swelling and abnormal signal intensities extending from the lower cervical to the upper thoracic vertebrae. MR image of the brain with gadolinium enhancement showed multiple punctate and linear areas. He was treated with corticosteroids, which gave some clinical improvement. Three months after onset of paraparesis, he suddenly experienced right hemiparesis due to small hemorrhage in the upper pons. Repeated corticosteroid therapy improved some neurological symptoms. Eight months after pneumonitis, remaining lesion of the lung was taken under thoracoscopic surgery. This lung tissue showed a perivasucular infiltrate of lymphoid cells, together with occasionally histiocytes, and eosinophils. No angiodestractive feature or obstruction of the vessels was present. An immunohistochemistry assay with CD45RO monoclonal antibodies revealed that many of the infiltrated lymphoid cells were T cells. The pathological diagnosis was LG. On follow-up MR images 13 months after onset of paraparesis, multiple new lesions were seen in the basal ganglia, pons, and corpus callosum, but the spinal lesion had completely disappeared.

Conclusion: The lesion showing punctate and linear enhancement on T1-weighted imaging preceded the hemorrhage in this case. We speculate that the affects on the small vessels, shown by punctate and linear enhancement, led to hemorrhage in a course of the disease. Moreover, spinal cord involvement, rarely observed previously in LG, also was seen on MR images.

P446
Primitive neuroectodermal tumor (PNET) in a 60-year-old man. A case report and review of the literature. A. Miliadou, M. Balafouta, J. Kouvaris, D. Kolokouris, Areteion Hospital, Aeginition Hospital (Athens, GR)

Purpose: We report the first case of primitive neuroectodermal tumor (PNET) presented in the age of 60s, we review the literature, and the management of this tumor is discussed.

Case report: A 60-year old man is presented with a cerebral PNET. The symptoms at the time of diagnosis were: intense headache, Broca's aphasia and left hemiparesis. Only an open biopsy was performed. Irradiation of the primary tumor was the main treatment (total tumor dose 59.8 Gy) because of serious hematological side effects due to chemotherapy. The patient tolerated radiation therapy extremely well, and his neurologic symptoms were improved. One month after completion of radiotherapy (RT), magnetic resonance imaging (M. R. I) showed no regression of the tumor. Recurrence was observed ten months after the initial diagnosis and the patient died 2 months later.

Conclusion: PNET is rare in adults. The survival seems to be longer than that in children. Multimodal treatment is necessary. The initial therapy is surgical bulk reduction whenever possible. Irradiation to the cerebro-spinal axis is justified as a routine treatment but, due to the radioresistance of the tumor, the addition of multi-regiment chemotherapy appears to improve survival.

P448
Temozolomide and cisplatinum combination as a second line systemic regimen in recurrent glioblastoma patients: a phase II study. A. Silvani, M. Eoli, A. Salmaggi, A. Boiardi, Istituto Nazionale Neurologico C. Besta (Milan, I)

We report a phase II trial of temozolomide and cisplatinum combination in recurrent glioblastoma patients.

The DNA repair protein O(6)-methylguanine-DNA methyltransferase (MGMT) is important in glioblastoma resistance to alkylating antitumor agents such as the methylating drug temozolomide (TMZ). Cisplatin (CDDP) decreases in vitro MGMT activity in a time-and dose-dependent manner, with maximal suppression (50 %) observed 24 h after treatment.

In view of these considerations 16 glioblastoma patients were treated at recurrence or progression with combination of oral TMZ (200 mg/sqm/day) daily for 5 consecutive days together with iv CDDP (75 mg/sqm) on day 1 (4 h after TMZ) every 4 weeks.

All patient had been previously treated by surgery followed by radiotherapy and our standard nitrosurea-cisplatin-based chemotherapy before recurrence. At recurrence patients were not judged suitable of repeated surgery. The primary endpoint of the study was six-month progression-free survival assessed by NMR and clinical criteria. Secondary endpoints included radiological response and toxicities

Sixteen patients received a total of 49 courses (median 3 range 2–5). Complete responses were not observed, partial responses determined by gadolinium-enhanced magnetic resonance imaging scans were 25 %, with an additional 62 % of patients, having stable disease.

Progression-free survival at six months was 50 %. The six-month survival rate was 60 %. The principal toxicities of the regimen were: neutropenia (1/16 WHO 4 grade, thrombocytopenia (2/16 WHO grade IV), nausea, and vomiting. Only one out of patients was hospitalized for treatment with parenteral antibiotics, granulocyte-colony stimulating factor, and platelet transfusions. Cisplatinum ad Temozolomide has been shown to be a safe treatment with moderate activity that may lead to temporary long-term stabilization in recurrent glioblastoma patients.

P449
A false diagnosis: primary central nervous system lymphoma presenting as multiple sclerosis. R. Clerici, M. De Riz, A. Micco, M. Tiriticco, I. Guidi, G. Conti, P. Baron, E. Scarpini, G. Scarlato, IRCCS Ospedale Maggiore (Milan, I)

Primary central nervous system lymphoma (PCNSL) is a relatively uncommon disease in which spontaneous remission is exceedingly rare. The clinical presentation is variable, but consists, mostly, of headache, motor dysfunction, memory and behavioural disturbances.

We report the case of a 32 year-old woman, previously healthy with the exception of an isolated episode of vertigo, who developed a partial motor seizure. A brain MRI, demonstrating enhancing and non-enhancing white matter lesions, the CSF exam (presence of oligoclonal bands) and visual evoked potentials (delayed latency) were compatible with the diagnosis of multiple sclerosis (MS). Moreover, the chemistry and viral screening were normal and the search of neoplastic cells in CSF was negative.

After three years of health, she developed headache, temporal and spatial disorientation and memory disturbance. The MRI lesions were similar to the previous scans, but the lumbar puncture showed many B lymphocytes with abnormal morphology, the laboratory exams demonstrated increased LDH and the bone marrow biopsy was not pathological.

The final diagnosis was "Primary central nervous system B-cell lymphoma" and the patients was treated with high-dose methotrexate and steroids, with a transient remission. She died six months after the diagnosis.

We think that this case is instructive for the clinical practice. We must consider two different possibilities: the PCNSL might have mimicked MS regarding clinical aspects, laboratory exams and spontaneous regression or a demyelinating disease might have preceded, and possibly heralded, the development of a primary central nervous system lymphoma.

Neuro-ophthalmology – Neurovestibular disorders

P450
Evaluation of the medical care of patients with benign paroxysmal positional vertigo. M. von Brevern, F. Lezius, K. Tiel-Wilck, T. Lempert, Charité, Campus Virchow (Berlin, D)

Background: Benign paroxysmal positional vertigo (BPPV) is the most common vestibular disorder which can be easily diagnosed. The evolution of highly effective positioning manoeuvres has made BPPV the most successfully treatable cause of vertigo.

Objective: To evaluate the medical care of patients with BPPV in Berlin/Germany.

Methods: Patients with BPPV were evaluated retrospectively with regard to past medical history and disease-related diagnostic/therapeutic procedures. Forty-two patients were recruited from a specialised dizziness-clinic and a further 29 patients from a neurological practice.

Results: The mean duration of the disease was 3.2 years with an aver-

age of 2.4 episodes lasting typically several weeks to months. More than half of the patients felt severely disabled by BPPV and 25 % were temporarily unfit for work. On average, three different medical specialities were consulted. Audiometry (49 %), caloric testing (46 %), cerebral imaging (42 %) and carotid Doppler ultrasonography (34 %) was performed more often than diagnostic positioning (28 %). Most patients received ineffective or no therapy and only 4 % were treated with a specific therapeutic positioning manoeuvre.

Conclusions: BPPV is a long-lasting and frequently recurrent disease which leads to significant morbidity and medical costs. The recent progress in the diagnosis and therapy of BPPV has not yet been widely established in medical practice in Germany.

P451

Does the vertical semicircular canal influence the subjective visual vertical and the vection? M. Iida, Tokai University School of Medicine (Isehara, JP)

The aim of the present study is to evaluate the influence of vertical semicircular canals on the subjective visual vertical (SVV) and the vection of self-motion perception in patients with benign paroxysmal positional vertigo(BPPV). SVV was measured on conditions with or without the rotatory stimulus in a head-tilted position, 60 deg. back-ward and then rotated 45 deg. either to the right or left. By this procedure, it was possible to evaluate the SVV elicited by the excitability of vertical semicircular canals [1]. Vection was measured while the patient was tilted backward until the head was both turned and hanging (Dix-Hallpike manoeuvre). SVV was abnormal on the condition with the rotatory stimulus, especially, which was deviated on the opposite side of the excited posterior canal. We conclude that the vertical semicircular canal influences the spatial orientation such as the SVV [2]. Rollvection was appeared during the patient had vertigo, which was displaced to the affected (excited) ear. Rollvection mainly agreed with the direction of rotatory nystagmus elicited by the excited posterior semicircular canal, which might be a postural compensation.

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P452

Cranial nerve palsies: herpes simplex virus type 1 and varicella zoster virus latency. D. Theil, T. Derfuß, M. Strupp, D. Gilden, V. Arbusow, T. Brandt, Klinikum Grosshadern, University of Colorado (Munich, D; Denver, USA)

Reactivation of HSV–1 in human geniculate (GG), vestibular (VG) and spiral ganglia (SG) is assumed to cause distinct and separate cranial nerve palsies, such as Bell's palsy, vestibular neuritis, and sudden hearing loss. In contrast to HSV–1 infection, reactivation of VZV in the GG usually causes a combined palsy of the facial and vestibulo-cochlear nerves (Ramsay Hunt syndrome, RHS). The following questions therefore arise with regards to the involvement of the vestibulo-cochlear nerve in RHS: is it due (1) to concomitant infection in all three temporal bone ganglia, (2) to a coreactivation of HSV–1 in the VG and SG? or, (3) to an extension of the inflammation from the GG to the neighbouring vestibular and cochlear nerves?

After anatomical preparation of 20 human temporal bones of ten individuals (ages ranged from 4 months to 58 years), the GG, VG, and SG were tested using a multiplex nested PCR assay for HSV–1 and VZV infection. A dual infection with

HSV–1 and VZV was detected in four individuals. Three of them had a double infection in the GG and one a double infection in the VG. VZV latency without HSV–1 infection was found in the GG, VG, and SG of only one individual. HSV–1 DNA was detected more frequently (seven individuals).

The detection of VZV predominantly in the GG without concomitant involvement of the other ganglia does not support the view that the multiple nerve involvement in RHS is caused by reactivation of VZV in these ganglia. The frequent association of VZV infection and HSV–1 infection in the GG theoretically makes it possible that VZV reactivation in GG induces a reactivation of latent HSV–1 in the VG and SG. However, the most likely explanation is that inflammation spreads from the GG towards the neighbouring ganglia or directly to the labyrinth and the cochlea, since it is known that VZV infection triggers a strong inflammatory response that affects adjacent tissue and vascular structures.

P453

Actual and imagined locomotion suppress spontaneous vestibular nystagmus. K. Jahn, M. Strupp, T. Brandt, Ludwig-Maximilians University (Munich, D)

Vestibulo-ocular and vestibulo-spinal motor responses use common vestibular input and partially overlapping neuronal networks. It is not known if and to what extent these responses are linked functionally or if they operate separately.

Therefore, slow-phase velocity (SPV) of spontaneous nystagmus was measured during standing and walking in patients with acute unilateral vestibulopathy due to vestibular neuritis (n = 6). To avoid interference between the physiological vestibulo-ocular reflex and the spontaneous nystagmus, the differential effects of imagined standing, walking, and running on spontaneous vestibular nystagmus were also evaluated (n = 10; mean age 49 years, range 30–74 years, 2 females).

We found that in patients with acute vestibulopathy due to vestibular neuritis spontaneous vestibular nystagmus was suppressed both during actual and imagined locomotion. Recordings by video-oculography in six patients showed that the mean peak SPV of the horizontal nystagmus was 14.0 ± 5.8°/s while standing upright in complete darkness; this decreased by 26 % to 10.5 ± 4.8°/s during locomotion (ANOVA, $F(1,5) = 10.2$; $p = 0.02$).

Mean peak SPV of the horizontal nystagmus was 11.1 ± 5.8°/s during actual standing and 10.8 ± 5.8°/s during imagined standing at a bus stop. During the imagination of slowly walking down a country lane, SPV decreased by 26 % to 8.2 ± 4.7°/s and by 42 % to 6.3 ± 2.8°/s during the imagination of running down a grassy hill (Bonferroni: standing vs. imagination of running $p < 0.003$).

A functional link was demonstrated between vestibulo-ocular and vestibulo-spinal mechanisms. Patients suffering from vestibular neuritis benefit from the suppression of spontaneous nystagmus for it alleviates the disturbing impression of movement of the visual scene (oscillopsia) caused by involuntary eye movements.

P454

Horizontal head and gaze paresis following infarction in the ipsilateral superior colliculus. V. Agnetti, M. D'Onofrio, M. Deidda, P. Galistu, A. Pala, K. Paulus, G. Sechi, University of Sassari neuro-ophthalmology

Introduction. Gaze paresis may be caused by brainstem lesions. Contralateral eye deviation occurs in these cases, whereas head turning is not usually seen. Experimental studies indicate that neurons in the caudal portion of the superior colliculus facilitate combined eye-head gaze shift, but no report is available in humans. We present a patient with left gaze palsy and right eye-head deviation followed a discrete midbrain infarction in the left superior colliculus.

Case Report. Few hours after sudden dizziness a 82 year-old man showed mild proximal right arm paresis, unsteadiness with retropulsion, forced right eye-head deviation and upward gaze paresis. Both voluntary eye and head movements could not cross the midline. Early CT scan showed an extensive infarct in the rostral part of the left cerebellar hemisphere involving the superior and antero-inferior cerebellar artery territories. A small lesion appeared in the left dorsal midbrain. Cerebellar lesions were confirmed by MRI which showed in the brainstem only a very small infarct in the caudal portion of the superior colliculus. Right arm paresis resolved quickly. Eye-head deviation recovered three days after onset, but voluntary eye movements to the left were still slow and hypometric after ten days. Left arm ataxia and left lateropulsion, absent at onset, appeared after few days and persisted.

Comment. Brainstem control of horizontal gaze is attributed to ipsilateral abducens nucleus and paramedian pontine reticular formation. No pontine lesion was documented in our patient. Paralysis of gaze to the side of the infarcted cerebellar hemisphere or eye deviation to the opposite side are described in cerebellar infarctions. Worsening of the hemispheral cerebellar syndrome when the eye-head impairment tended to recover does not support cerebellar damage as explanation of eye-head impairment in our patient. In spite of high incidence of cerebellar infarcts, their association with eye-head palsy and turning is absolutely uncommon. Stimulation studies in primates suggested that the caudal superior colliculus may contribute to eye-head movements. In fact, neurons in the caudal colliculus project: a) to long-lead burst neurons which are more concerned with shifting gaze to a new visual target, and b) to spinal neurons facilitating a combined eye-head shift. The present case suggests that the lesion in the

superior colliculus may had caused the head-gaze palsy with their combined deviation to the right.

P455
Efficient immunosuppressive therapy in a patient with bilateral vestibulopathy and antibodies against the inner ear structures. O. Schüler, M. Strupp, V. Arbusow, T. Brandt, Ludwig-Maximilians University (Munich, D)

Background: Some types of bilateral vestibulopathy seem to arise from systemic autoimmune processes, e. g. lupus erythematosus, polychondritis, Cogan's syndrome, or rheumatoid arthritis. About 20 % of bilateral vestibulopathies remain idiopathic despite extensive diagnostic workup. We previously demonstrated antilabyrinthine antibodies in the serum of 8 of 12 patients with "idiopathic" bilateral vestibulopathy. Although the pathogenicity of these antibodies remains unclear, their appearance seems to indicate organ-specific immune dysregulation. Here we report on a patient with bilateral vestibulopathy who recovered after immunosuppressive steroid therapy. The recovery correlated with a disappearance of serum autoantibodies against inner ear structures.

Patient: In 1995 a 55-year-old man was admitted to the hospital with sudden attacks of rotational vertigo, lasting for 30–60 seconds. Caloric irrigation (44°C) showed a reduced maximum slow phase velocity of horizontal nystagmus of 8°/s on both sides. Serum autoantibodies against the inner ear structures, the cochlea and the vestibular organ, were positive (> 1:100). Assuming an immune dysregulation as the cause of the bilateral vestibular dysfunction, we treated the patient with glucocorticoids for 6 weeks, beginning with 100 mg/day methylprednisolone. A follow-up examination after the end of the therapy showed improvement of vestibular function on both sides with a slow phase velocity of 14°/s after caloric irrigation (44°C). Serum autoantibodies remained positive. In 2002 the patient was seen for another follow-up examination 6 years after the immunosuppressive steroid therapy. Caloric vestibular testing showed a complete recovery of vestibular function with a maximum slow phase velocity of 25°/s (44°C) on both sides. Serum autoantibodies against the cochlea and the vestibular organ had disappeared.

Conclusion: Some of the so-called idiopathic vestibulopathies may be due to autoimmune inner ear disorders. Immunosuppressive steroid therapy may have a delayed therapeutic effect in patients with incomplete, autoimmune-induced bilateral vestibulopathy. Therefore, we recommend determining inner ear autoantibodies in such cases, since incomplete autoimmune bilateral vestibulopathy may be responsive to immunosuppressive therapy.

P456
Dissociation of ocular torsion and tilt of subjective visual vertical in superior semicircular canal dysfunction. M. Strupp, T. Eggert, A. Straube, S. Glasauer, T. Brandt, Ludwig-Maximilians University (Munich, D)

The complete ocular tilt reaction is characterized by ocular torsion (OT), skew deviation, tilt of the subjective visual vertical (SVV), and head tilt. Complete OTR or skew torsion indicates a vestibular tone imbalance in the roll plane. It is caused by either a unilateral peripheral vestibular or a unilateral lesion of ''graviceptive" brainstem pathways from the vestibular nuclei to the interstitial nucleus of Cajal in the rostral midbrain. The tilt direction of the SVV and the direction of the OT are correlated in peripheral- and central-vestibular disorders. Although the tilt of SVV increases with larger angles of ocular torsion, there is no exact quantitative correspondence between the net tilt angle of both. Nevertheless, one may assume that the tilt of the SVV was simply caused by the OT.

We report on a 53-year-old patient with an exceptional dissociation of OT and SVV caused by an isolated unilateral dysfunction of a superior semicircular canal (sSCC). The patient who was suffering from an ''inner perilymph fistula" due to a superior canal dehiscence syndrome underwent surgical patching of the sSCC. This caused vertigo and spontaneous rotatory-vertical nystagmus due to an isolated dysfunction of the left sSCC, which was documented by a search-coil 3D-analysis of the nystagmus and vestibulo-ocular reflex. Otolith function was tested by brief, high-acceleration lateral translations (''heaves") and appeared to be intact. Before surgery, the patient had neither an OT nor a displacement of the SVV. Five days after surgery, when the patient was able to visually suppress his spontaneous nystagmus, we found a significant OT toward the side of the affected labyrinth (16 degs of the ipsilateral eye), but no displacement of the SVV or skew deviation. Two weeks later OT had disappeared.

This dissociation suggests that isolated dysfunction of a sSCC can cause OT without an associated tilt of the perceived vertical. In contrast, an association of displacement of OT and tilt of the SVV indicates a combined SCC and otolith or ''graviceptive" pathway dysfunction.

P457
Rollvection vs. linearvection: comparison of brain activations in PET. A. Deutschländer, S. Bense, T. Stephan, M. Schwaiger, M. Dieterich, T. Brandt, Ludwig-Maximilians-University, J-Gutenberg-University, Technical University, Johannes Gutenberg-University Dpt. Neurology (Munich, Mainz, D)

Objective: To investigate the differential activations and deactivations during large-field visual motion that induces the sensation of apparent linear or circular motion.

Background: In an earlier PET study using visual motion stimulation that induced vection in roll we found bilateral activations of a medial parieto-occipital brain area and simultaneous deactivations of the posterior insula and retroinsular regions (the parieto-insular vestibular cortex) [Brandt et al. Brain 1998].

Methods: 11 healthy male volunteers (29 to 60 yrs) were examined in a Siemens PET scanner using O–15 water-PET. For visual stimulation a display was mounted (FOV: 100 x 60 deg). Four conditions were presented: A) stationary dots (rest); B) dots accelerating in radial directions away from a focus of expansion (forward linearvection); C) dots rotating counter clockwise (clockwise rollvection); D) dots moving in different directions (no vection). Prior to random effects statistical group analysis ($p = 0.001$, uncorrected), data were analysed using SPM99.

Results: During rollvection (C-A) bilateral activations were seen in the visual cortex including PO (BA 17–19; 5105 voxels) and in the motion-sensitive area MT/V5. Deactivations were found in the middle temporal gyri bilaterally and in the right posterior insula. Linearvection (B-A) also induced bilateral activations in the visual cortex including PO (BA 17–19; 9725 voxels) and MT/V5.Simultaneously rCBF decreases occurred in the cingulate gyri bilaterally, in the right inferior parietal lobule (BA 40), and in the right posterior insula. The comparison B-C showed bilateral activations in the lower visual cortex (BA 17/18). In the comparison C-B the largest cluster was in the superior parietal gyrus (38 voxels), smaller clusters were in the precuneus; there were no activations in the occipital gyri. When linearvection or rollvection was compared to condition D MT/V5 and BA 19 showed no activations.

Conclusions: Linearvection and rollvection during large-field visual motion stimulation led to activations of neighbouring, partially overlapping visual areas including PO. These activations were larger and more significant during linearvection. Thus the mediation of rollvection and linearvection was represented in partially overlapping visual cortical areas. Both stimuli led to deactivations of the posterior insula as described earlier for roll motion, indicating an inhibitory interaction between the visual and the vestibular system.

Neurorehabilitation

P458
Rehabilitative cognitive treatment of hemiglect syndrome secondary to stroke of the right hemisphere. D. Ruma, M. Ciancio, C. Melita, A. Pappalardo, C. Di Vincenzo, A. Reggio, F. Patti, Institute of Neurological Science, Policlinico, University of Catania (Sicily, Italy)

Aim: to evaluate the efficacy of a cognitive rehabilitative treatment of patients with either paresis or palsy of left limbs and associated hemineglect syndrome.

Methods: Patients:14 pts (7 M and 7 F) mean age 69 years, right handed with a middle-high education level affected by stroke lesions of the right emisphere (fronto-temporo-parieto-occipital cortex in the majority of cases) underwent a complete neurological examination and an extensive neuropsychological assessment 30 days after the stroke event. Neuropsychological evaluation. Albert, bisection of lines reading and writing, Corsi test, and Rey figure were the measures used to test hemineglect syndrome. Mini mental state examination (MMSE) was used to not include patients with abnormal thinking and other cognitive deficits.Disability measure. Functional Independence Measure (FIM) was also used to measure disability patients as means of functional independence level.

Patients were furtherly reevaluated at months 3,and 6 following the beginning of the rehabilitative treatment.

Patients were divided into two groups of 7 each one. One group was tretaed with a cognitive approach for the hemineglect syndrome plus the conventional physiotherapy; the control group was treated with the only conventional physiotherapy.

Rehabilitative treatment: paper and pen,the sitting position, and the principles of cognitive therapy plus the training for the re-learning of walking or tasks with upper limbs constituted the plot of the rehabilitative treatment. Passive motion and stretching were also used.

Results. Patients tretaed with the combination regimen therapy (cognitive plus conventional) significantly improved their functional independence in the sections which measure self-care and transfers ($p = 0.04$ in both).

Conclusions: this study seems to confirm that patients with motor disabilities associated with cognitive impairment benefit of a rehabilitative treatment based on a neuropsychological approach.

P459

Process and outcome during early inpatient rehabilitation after brain injury. R. J. Greenwood, M. Edwards, J. McNeil, Homerton University Hospital NHS Trust (London, UK)

Purpose: To describe aspects of process and outcome during early inpatient rehabilitation of younger adults after single incident brain injury.

Method: Analysis of a database of 905 patients discharged from an inner-city hospital-based inpatient rehabilitation unit for younger adults after single incident neurological events, 95% after brain injury, between 1985 and 1999, with particular emphasis on admission and discharge dependency measured by the Barthel Index (BI) and Functional Independence Measure (FIM), in the 290 patients discharged since 1995.

Results: Vascular brain injury (VBI) accounted for 47% of admissions, traumatic brain injury (TBI) for 40% but only 14% of female admissions. Patients were significantly younger after TBI (37 vs 47 $p < 0.001$). 32% of admissions were non-Caucasian. Mean time from injury to admission was 130 days (SD:98) and length of stay (LOS) was 124 days (SD:72). Mean admission BI and FIM scores of 9/20 and 71/126 changed by a mean of 4 and 20 during the admission. Neither admission dependency nor change scores differed significantly by diagnosis, gender or ethnicity, but the change scores and LOS correlated with the level of dependency on admission (both $p < 0.001$).

Failure to record improvement in 15% of patients was related to the floor and ceiling effects of the instruments. The BI was a slightly better predictor of LOS than the FIM. A useful regression equation was produced relating length of stay to Barthel score on admission. 70% of patients returned home. These data remain stable by year over the 14 years surveyed.

Conclusions: These data emphasise that admission dependency is a major determinant of care and treatment costs during early inpatient rehabilitation after single incident brain injury. They confirm the similarity of the needs of many younger patients after both TBI and VBI, particularly in relation to family reintegration and work. The stability over time of LOS in rehabilitation suggests that LOS will only shorten significantly if there is major change in levels of care, rehabilitation, and rehousing available in the community.

P460

Gait analysis in lower limbs spasticity. M. Coletti Moja, U. Dimanico, V. Cavaciocchi, L. Tallone, P. C. Gerbino Promis, E. Grasso, S Croce Hospital (Cuneo, I)

Lower limbs spasticity treatment by botulinum toxin plays an important role in planning therapeutic decisions and rehabilitation projects. The proper management of this drug requires objective techniques and hallmarks aimed at supporting physicians for the decision of using the toxin, the selection of muscles to be treated, the choice of the dose of drug to be injected in each muscle, the quantification and documentation of the outcomes and, finally, for planning follow-up forthcoming treatments. Among its clinical applications, gait analysis allows for obtaining an objective quantification of spasticity in the upper motoneuron syndrome. Nonetheless a complete study of gait through 3D sterophotogrammetric systems is not justified in this specific application, which requires a trouble-free testing protocol yielding results easy to be interpreted directly by the physician himself and to be translated into immediate clinical decisions. Our aim is to propose a simplified experimental protocol effective in helping the management of the patients suffering from distal focal lower limbs spasticity. From January 1998 to October 2001 we included patients having an equino-varus gait pattern. Herein we report the data concerning a group of 10 patients with post-stroke spasticity. Every patient underwent clinical evaluation (gait velocity, Ashworth modified scale grade and range of movement) video recording of gait and gait analysis by EMG electrodes from tibialis anterior, peroneus longus, medial gastrocnemius and tibialis posterior, knee and ankle angles and basography. This evaluation was carried out prior to the first treatment, one month after and three months following each successive treatment. In 3 patients out of 10, gait analysis demonstrated muscular retraction thus providing ground for excluding these patients from the therapy. In all the other patients we documented an improvement in gait-related clinical parameters; only 3 patients required a second treatment to obtain objective results. In conclusion, dynamic EMG allowed us to demonstrate objectively muscles hyperactivation, either phasic or tonic and modifications of the activation pattern of leg muscles, thus supporting the choice of muscles to be treated by botulinum toxin and making it possible to document and quantify the benefits.

P461

Visual restitution training for patients with damage to visual cortex. B. Sabel, Otto-von-Guericke University (Magdeburg, D)

Partial blindness after brain injury has been considered non-treatable for several years. In several independent clinical trials we showed that a computer-based visual restitution training (VRT) increases the size of the intact visual field [see e. g. Nature med., 1998, Vol. 4, 1083].

Methods: Patients with homonymous visual field defects (VDF) were evaluated before and after a visual restitution training. For evaluation the automated static High Resolution Campimetry (program "NovaVision status") was used. In contrast to other perimetric procedures this test measures areas of residual vision by 5 repeated measurements in a given field location in the visual field. It also measures the reaction times. All patients had stable homonymous VFDs due to cerebral ischemia or haemorrhage (lesion age > 1 yr). The patients carried out the NovaVision Visual Restitution Training (VRT) on their computer at home daily for one hour over a period of six months. Training parameters were regularly adjusted to the individual pattern of residual vision for each patient.

Results: The correct responses were counted in the central and in the total visual field after VRT. Most patients showed an improvement of visual field size after the training procedure. After VRT, reaction time significantly increased. During the 6 months of training, fixation abilities improved in many patients.

Conclusions: Computerized visual field training can lead to an enlargement of the visual field in many patients. Fixation artefacts are unlikely to contribute to the apparent visual field improvements. Furthermore, the extent of visual field enlargements are variable among patients, but do not correlate with improvements in reaction times. Faster reaction times were found to be highly correlated with subjective improvements of vision. Thus, plasticity of neuronal processing in space (visual field enlargements) and in time (reaction time) seem to be independent parameters, both of which contribute to restoration of vision following VRT.

P462

A new picking up test for sensory deficits and its application in traumatic brain injury. R. Wenzelburger, C. Trockel, A. Frenzel, H. Stolze, S. Peters, J. Kuhtz-Buschbek, M. Gölge, M. Illert, G. Deuschl, Neurologie des Universitätsklinikums, Physiologisches Institut der CAU (Kiel, D)

Deficits of sensorymotor functions of the hand following traumatic brain injury (TBI) can lead to severe deficits of dexterity. Our aim was to apply a new picking-up test for monitoring of the rehabilitation process in TBI and its validation in a large group of healthy controls.

We analysed 105 controls and compared the age-matching subjects with 11 patients with moderate to severe TBI early after coma and during 8 months of rehabilitation. A bowl was filled with 30 small and 10 big steel balls. The subjects were asked to pick up as many big balls as possible within 30 seconds and put them to a second bowl. The test was performed with and without sight. The number of correct balls was counted and the time for completion of the task was measured.

We found a considerable restriction of fine motor functions in TBI even though the clinical examination revealed no paresis in most of the patients. The number of correctly sorted balls was significantly reduced in the non-vision condition at the first visit and three months later with a gradual remission of performance in the follow-up (mean (SD) TBI first visit 6.7 (1.7), controls 8.1 (1.5), $p < 0.05$). The time needed to complete picking-up in the vision condition was increased in TBI at the first and second visit (mean (SD) TBI second visit 12.8 (2.1) s, controls 10.2 (1.8) s, $p < 0.05$).

We speculate that the Picking-up test measures aspects of motor co-ordination different from the purdue pegboard test. It could additionally reveal a disturbance of dexterity due to deficits in the sensorymotor integration of afferent information from the hand.

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P463
Post-traumatic syringomyelia. F. Parker, J. F. Lepeintre, N. Aghakhani, M. C. Lacour, D. Adams, M. Tadié, CHU Bicêtre (Kremlin Bicêtre, F)

We report on a retrospective study of 42 patients (89 % males) with post-traumatic syringomyelia (PTS) operated between 1984 and 1999 (median age at the diagnosis of PTS: 42.3 years). The mean time between the traumatism and the diagnosis was 14.7 years.

31 patients (74 %) have been operated on. A total amount of 44 surgical procedures have been done. 11 patients have been operated on twice and 2 others have been operated on three times. No post-operative mortality was observed. The complication rate was 11 %.

We analysed the results according to the type of the first operation: group D (derivation, n = 21), group SSR (Subarachnoid Space Reconstruction, n = 10). The rate of re-intervention was 43 % in a mean time of 39 months in the group D (36 months mean follow-up) and 20 % in the SSR Group (31 months mean follow-up).

In early postoperative stage, we reported 24 % of posterior cordonal sensibility worsening for the group D versus only 10 % for the group SSR.

The long term clinical results analysis showed statistically significant improvement of pain upper and under the lesion (respectively $p = 0.05$ and $p < 0.02$) after surgery. The analysis of the Frankel motor score (F) and Functional Independence measurement score (FIM) showed 77 % of stabilisation for the F score and 76 % for the FIM score. This functional results (F and FIM) and the post-operative decrease of the pain syndrome were not statistically different between the two group.

The morphological results analysis on MRI showed significant decrease of the Vaquero Index (VI) ($p = 0{,}01$). There is no significant differences concerning the VI between the patients who have been operated on by D or SSR.

An MR velocity study was performed in 7 patients. Cyst velocities correlated in the preoperative course with the clinical status of the patients. In the postoperative course, cyst velocity decreased ($p = 0.017$) and velocity of the subarachnoid space increased.

On the whole, the SSR operations are associated with a lower rate of re-intervention and low frequent postoperative posterior cordonal syndrome, with the same functional and morphological results.

P464
Neglect and hemianopia superimposed and improvement by visual restitution training. E. M. Müller-Oehring, M. Arnold, T. Schulte, E. Kasten, B. A. Sabel, Institute of Medical Psychology Otto-v.-Guericke University Magdeburg (Magdeburg, D)

In patients with posterior-parietal brain damage it is often difficult to determine whether left-sided omissions in perimetry are due to primary visual loss or due to visual neglect. Thus, we investigated 11 patients with combined neglect/hemianopia and 11 patients with pure hemianopia.

In a first study, visual fields measurement in neglect patients showed that left-sided omissions within the visual field were dependent on the spatial eccentricity of the stimulus. Moreover, in neglect-hemianopic patients visual field performance improved significantly with repeated measurements in contrast to pure hemianopic patients, who showed highly stable results. One patient with chronic neglect-hemianopia was trained using visual restitution training (Kasten et al., Nature med., 4, 1998, 1083–87). After two months of training, the patient showed a considerable improvement in the contralesional visual field. The cortical activation by the contralesional stimulus might be weakened by backward projections from (lesioned) parietal areas to striate cortex. The observed training-induced improvement may be due to a strengthening of the activity in striate and extrastriate areas in the lesioned hemisphere and the stimulus might, in consequence, be perceived consciously.

In a second study we used a bilateral summation paradigm with redundant targets. The redundant target effect (RTE) was calculated to test whether RTs were faster for stimulus pairs (one stimulus in the intact and one in defective visual field) than single stimuli. A redundant targets effect (RTE) was found in neglect patients with superimposed hemianopia, indicating unconscious processing of left-sided stimuli. Surprisingly, RTE was not correlated with the visual field defect in these patients. The neural mechanisms underlying unconscious visual processing in neglect-hemianopic patients probably occurs at the colliculus and visual cortical areas, i. e. at early visual processing stages.

In sum, these results suggest that neglect may cover intact visual functioning in those patients having apparently superimposed visual field defects.

P465
Percutaneous dilatational tracheotomy (PDT) in neurologic rehabilitation patients. S. Graumüller, S. Dommerich, H. Mach, A. Eich, Rostock University, Neurologic Rehabilitations Center (Rostock, Waldeck, D)

Today, we find more patients with a tracheostoma in the early rehabilitation. Long term ventilated ICU-patients commonly require tracheotomies, most of them will get a PDT. In the past we examined 271 patients with a tracheostoma in the early rehabilitations center Waldeck. Our study included the examination of the tracheostoma, a endoscopic view through the stoma down to the carina and up to the larynx with a rigid 70 degree optic. We described the method of tracheotomy, diagnosis, aspiration, phonation and late complications. Late complications, like granulations in the area of the stoma, in the subglottic area of the trachea and difficulties changing the cannula are more frequent in patients with percutaneous dilatated tracheostomas. Our examination to the choice of the tracheootomy method showed, decisively is the time the tracheostoma is needed and the contraindications of every method. Besides the indisputable advantages of tracheostomas, disadvantages in the rehabilitation process, such as a reduction and problems in the gustatoric and olfactoric function, in the swallow process, in the phonation and so in the communication and in the flexibility of the patient, have to be taken into consideration.

P466
Evaluation of electrical muscle stimulation in management of Bell's palsy. S. A. S. Tawfik, Alexandria University (Alexandria, EGY)

This study was conducted on twenty patients with Bell's palsy of grade V or VI and complete degeneration of the facial nerve as demonstrated by the minimal excitability test. These-patients were divided randomly into two groups, 10 patients each. Group I (control or untreated group), and Group II (treated group) who were treated by electrical muscle stimulation (3 sessions per week). After observation for 4 months, the study revealed that both the treated and the untreated groups showed significant recovery. However, on comparing the two groups by further statistical analysis, no significant difference in recovery between the two groups was observed at the end of the fourth month. It is possible that a significant difference in recovery might need a longer duration of treatment and follow-up to be apparent, but yet, this leaves the value of electrotherapy in management of Bell's palsy controversial.

Peripheral neuropathy

P467
Carpal tunnel syndrome: effects of treatment with steroid injections into the carpal tunnel. L. Gogovska, R. Ljapcev, Clinic of Neurology (Skopje, MK)

Objective: To assess the effectivenes of local injections of steroids into the carpal tunnel in patients with carpal tunnel syndrome (CTS).

Background: Should all patients with CTS undergo steroid injections first or surgical therapy as a treatment of choice? Steroid injections have been accepted as a conservative treatment modality in CTS patients, despite of controversies concerning the indications, dose and type of steroid to be administered, therapeutic regimen, safety.

Method: We prospectively studied 40 patients with idiopathic CTS diagnosed on the basis of both clinical and electrodiagnostic findings. The severity of the disease (according to clinical features, electromyography and nerve conduction studies) was graded on a 3-point scale (mild, moderate and severe). The patients were treated with steroid injections (1 ml Betamethasone) into carpal tunnel up to three times at 2–3 day intervals. We followed the effects of treatment clinically and electrophysiologically every month up to 6 months after the last injection.

Results: At first follow-up (month 1) all patients with CTS achieved improvement in both clinical and electrophysiologic parameters (reduction of pain and paresthesiae or numbness in the hand, reduction in DML of median nerve and improvement in motor and sensory nerve conduction velocity), but the electrophysiologic parameters returned to normal in only 10 % of patients injected. At second follow-up (month 2) complete relief of symptoms and normal electrophysiologic parameters were achieved in 85 % of CTS patients. The improvement was sustained until the last follow-up in patients with mild and moderate CTS, and there was no need for repeat injections. Patients with severe CTS experienced only temporary benefit (mean duration of 6 weeks). There were no side effects of treatment, except for mild local pain during injection.

Conclusion: Steroid injections into carpal tunnel can be effective in the treatment of patients with CTS. The outcome of treatment depends mostly on CTS severity. Almost complete relief of symptoms and improvement of electrophysiologic parameters should be expected in patients with mild and moderate CTS. In patients with severe CTS only temporary benefit after steroid injections occurs and surgical therapy should be considered. Larger and longitudinal studies are needed to define the long-term efficacy, type and dose of steroid to be administered and safety of the repeat steroid injections.

P468

Different pathogenesis of thalidomide neuropathy in multiple myeloma. G. Isoardo, D. Cocito, P. Barbero, P. Ciaramitaro, M. Bergui, M. Boccadoro, B. Bergamasco, L. Durelli, Università di Torino (Turin, I)

Objective. To determine if thalidomide neuropathy had MRI feature of a ganglionopathy.

Background. In the past few years thalidomide became one of the most interesting chemotherapic drugs in the treatment of multiple myeloma. However a predominantly sensory neuropathy is a well-known side effect of thalidomide in a substantial amount of patients. Peripheral nerve damage resulted to be at lest partially reversible only in 50 % of cases suggesting a possible toxic effect on dorsal root ganglion neurons. Spinal cord MRI was indicated as a useful tool in the diagnosis of sensory ganglionopathy. We describe MRI findings in 6 patients with thalidomide neuropathy and multiple myeloma.

Patients. Six patients (4 men, 2 women, mean age 61.2 ± 8.6 years) were included: two had non-secretory, 3 osteolytic and 1 osteosclerotic myeloma. Thalidomide was administered orally at a dose of 200 mg/day in 4 patients, and at a dose of 100 mg/day in 2. All patients where asymptomatic for peripheral neuropathy before treatment. Five of them were previously treated with vincristine and 4 with cisplatin, both at low doses. Positive sensory symptoms developed 6 to 19 months after treatment beginning: all patients had paresthesiae 2 had pain in stocking and glove distribution. One patient developed sensory ataxia. On nerve conduction studies, all patients had decreased or absent sensory action potential both at upper and lower limbs.

Methods. Cervical spine MRI was performed in all patients with a 1 T system, with sagittal T2 FSE spin echo (TR/TE 3909/112), axial gradient echo (630/22/30), T1 SE (550/12) -weighted images.

Results. Cervical spine MRI was normal in 5 patients. In 1 patient, however, MRI disclosed T2-weighted high signal intensity in the posterior columns.

Discussion. Our results suggest that thalidomide could have different toxic effect on peripheral nervous system, either on dorsal root ganglion neurons or axons. This could explain discrepancy in the degree of recovery observed in previous studies.

P469

Peripheral neuropathy in hepatitis C virus infection with and without cryoglobulinaemia. L. Sanvito, R. Nemni, A. Quattrini, M. Camerlingo, G. Santuccio, N. Canal, Don C. Gnocchi Foundation, S. Raffaele Scientific Institute, Ospedali Riuniti (Milan, Bergamo, I)

Introduction: Approximately 50 % of patients with chronic hepatitis C virus (HCV) infection show detectable cryoglobulinaemia (CG). Peripheral neuropathy (PN) is present in most of the patients with symptomatic CG and it is thought to be due to ischaemia resulting from inflammatory vascular destruction caused by a hypersensitivity reaction or from intravascular deposition of cryoglobulins. Recently some HCV+ patients with PN and persistent negativity for CG have been reported. HCV RNA in homogenates of nerve biopsy has also been reported. These studies suggested a possible direct role of HCV in the pathogenesis of PN. Aim of the study: We studied 51 HCV+ patients to determine the prevalence of CG and to clarify the role played by HCV in determining the PN. Methods: All patients were studied clinically and electrophysiologically, 28 of them underwent sural nerve biopsy. Morphological and morphometric evaluation of the biopsy was performed. Results: Cryoglobulins were found in 40 of 51 cases (78 %). Of the 40 CG+ patients, 18 had polyneuropathy (45 %), 16 had mononeuritis multiplex (40 %), 3 had cranial neuropathy (7.5 %), and 3 had a combined peripheral and cranial neuropathy (7.5 %). Nerve biopsy was performed in 25 CG+ patients: Epineurial vasculitis was present in 8 patients (32 %), differential fascicular loss of axons was found in 10 (40 %), signs of both demyelination and axonal degeneration were present in 7 (28 %). Of the 11 CG- patients, 5 had cranial neuropathy, 4 had mononeuritis multiplex, 1 had polyneuropathy, and 1 had a combined cranial and peripheral neuropathy. 3 of the 11 CG- patients underwent sural nerve biopsy: 2 had epineurial vasculitis and 1 showed a differential fascicular loss of axons. Conclusions: Our results indicate that the prevalence of CG in HCV+ patients with PN is higher than in overall HCV+ population (78 % vs 50 %). HCV+ CG- patients more frequently develop well defined mononeuritis multiplex (10 of 11, 90 %) when compared with HCV+ CG+ (22 of 40, 55 %). Morphological findings in the sural nerve from HCV+ CG- are consistent with an ischaemic mechanism of nerve damage and are against a direct role of the virus in causing the associated PN.

P470

A novel splice-site mutation in the SPTLC1 gene causes HSN type I in a Spanish family. A. Pou-Serradell, J. Zabala, K. Verhoeven, E. Nelis, V. Timmerman, P. De Jonghe, Hospital del Mar, Universitat Autonoma, Interuniversity for Biotechnology (Barcelona, E; Antwerpen, B)

Background: HSN I is an autosomal dominant (AD) neuropathy characterized by progressive sensory loss. HSN I is genetically linked to chromosome 9q22.1-q22.3. Recently, mutations in Serine Palmytoiltransferase, long chain base subunit 1 (SPTLC1) were identified as underlying HSN I. We report the phenotype of a HSN Spanish family with a novel SPTLC1 mutation.

Case History: Clinical and electrophysiological studies were performed in two sisters, aged 28 and 22 years-old respectively, with bilateral plantar ulcer developed in the second decade of life. They never experienced spontaneous pains. X-Ray examination documented osteomyelitis which led to the amputation of the 2nd metatarsal. Neurological examination shows foot deformities, plantar hyperkeratosis and a plantar ulcer. Impaired acrodistal sensation in the lower limbs and absence of the ankle reflexes were detected Electrophysiological studies demonstrated signs of mild, exclusively sensory neuropathy in the lower extremities. The older sister is the mother of a 4 y-o-boy who is asymptomatic. The affected 54 years old mother denies any abnormality but she had an operation at the left foot at the age of 35 years for an arthropathy. Her mother who died at age of 76 years also had trophic abnormalities at the feet.

Mutation: A splice-site mutation at position c. 781–6A > G in intron 8 of the SPTLC1 gene was found in both sisters and in the son of the elder sister who is six years old and asymptomatic. Both women inherited the mutation from their mother.

Conclusion: A novel mutation in the SPTLC1 gene is responsible for an AD HSN I neuropathy. The clinical phenotype of our family differs from other phenotypes of HSN I previously reported because, clinically, the neuropathy remains limited and relatively mild, the progression is very slow if not existent and there is no history of pain attacks. So this clinical feature should be taken with care.

P471

Thermal sensitivity in type 1 and type 2 diabetes. E. A. Gryz, P. Szermer, D. Galicka-Latala, J. Sieradzki, A. Szczudlik, Jagiellonian University, College of Medicine (Krakow, PL)

Background: It remains unclear whether there are specific differences in presentation of diabetic neuropathy between patients with type 1 and type 2 of diabetes. The quantitative temperature sensation testing is an approved method for assessment of small nerve fibers in diabetic neuropathy.

The aim of this study was to investigate whether there are any differences in thermal sensitivity between type 1 and type 2 diabetes patients.

Material and methods: Sixty two patients with type 1 of diabetes and 33 patients with type 2 of diabetes entered the study. The exclusion criteria were: uremia, alcohol abuse, radiculopathy and use of hypotensive and antyarrhytmic drugs. Control group consisted of 35 healthy volunteers. All patients and subjects in control group underwent quantitative temperature sensation testing in upper and lower extremities.

Results: In the patients with type 2 of diabetes the cool and cold thresholds in upper extremities were significantly lower comparing to type 1 diabetes group (20.49 ± 6.28 and 24.45 ± 4.02; p = 0.0028 for cool threshold, 17.15 ± 5.99 and 20.19 ± 5.20; p = 0.017 for cold threshold). The differences between type 1 and type 2 diabetes patients were also noticed in warm and heat thresholds in upper extremities being higher in type 2 diabetes (38.23 ± 4.60 and 40.78 ± 5.82; p = 0.013 for warm threshold, 42.18 ± 4.48 and 45.17 ± 4.17; p = 0.001 for heat threshold). In lower extremities only the warm threshold differed significantly between type 1 and type 2 diabetes (39.70 ± 4.31 and 41.51 ± 4.73; p = 0,037).

In patients with type 2 of diabetes the abnormalities in temperature sensation were recorded in 23 cases (70 %), and in type 1 diabetes patients in 25 cases (40.3 %) (p = 0,0064).

Conclusions: The abnormal thermal sensitivity similarly to nerve con-

duction studies was more often present in patients with type 2 of diabetes indicating that damage of small fibers is more pronounced in this type of disease. Small fibers dysfunction occurs early in subclinical neuropathy and presented findings could be related with incidence of hyperglicemic states that often precede the type 2 of diabetes for many years.

P472

The relationship between risk factors for diabetic neuropathy and criteria of its diagnosis. E. A. Gryz, P. Szermer, D. Galicka-Latala, J. Sieradzki, A. Szczudlik, Jagiellonian University, College of Medicine (Krakow, PL)

Background: It is difficult to establish risk factors for diabetic neuropathy because no generally accepted criteria of its diagnosis exist. In previous investigations risk factors profiles differ markedly.

The aim of this study was to assess risk factors for diabetic neuropathy in relation to different criteria of its diagnosis.

Material and methods: Ninety-five diabetic patients entered the study. The exclusion criteria included uremia, alcohol abuse, radiculopathy and use of hypotensive and antyarrhytmic drugs. Control group consisted of 43 healthy volunteers. All patients underwent the clinical assessment, instrumental evaluation of superficial and deep sensation, tests of cardiovascular autonomic function and nerve conduction studies. According to the performed assessment patients were classified into following groups: without neuropathy, suspicion of neuropathy, neuropathy confirmed in clinical examination, neuropathy confirmed in electrophysiological testing, autonomic neuropathy.

Results: Analysis (logistic regression model) showed that the most important risk factors in patients with subjective symptoms were type 2 of diabetes, diabetes duration and age of patients. When neuropathy was diagnosed according to the clinical examination, risk factors included type 2 of diabetes and duration of the disease. In the cases of neuropathy confirmed by electrophysiological studies and autonomic neuropathy only the diabetes duration still appeared to be significant risk factor.

Conclusions: Our study demonstrated that risk factors for diabetic neuropathy varied in relation to different diagnostic criteria and most important risk factor for all forms of neuropathy is duration of diabetes. This result indicates for the need of frequent screening tests in patients with long duration of the disease irrespective of its metabolic control, patients' age or type of diabetes.

P473

A case of idiopathic bilateral diaphragmatic paralysis. J. Valls-Solé, M. Solans, Hospital Clinic, Hospital Mataró (Barcelona, E)

Involvement of the phrenic nerve has been reported in some patients with unilateral or bilateral idiopathic brachial neuritis. Here, we report the case of a patient who had isolated bilateral phrenic nerve involvement of unknown origin. He was a 41-year-old man with well controlled chronic bronchial asthma but no personal or family history of neurological disease. His first symptoms were dyspnea and pain in the neck and chest of subacute onset. Pain lasted for some 10 days, while dyspnea became worse and led him to have mechanical ventilation when lying. He was diagnosed with bilateral diaphragmatic paralysis based on clinical inspection of the breathing pattern and transdiaphragmatic pressure recording. After a few days, he was able to breath with no extenal aid when standing but needed to use a portable bi-level positive airway pressure apparatus (BiPAP) when lying or sitting. He was carrying the BiPAP apparatus with him in a hand bag for use when he felt drowsy.

Needle electromyography showed profuse fibrillation potentials and positive waves in the diaphragm, more abundant on the right than left side, no response to right phrenic nerve stimulation, and a small delayed response to left phrenic nerve stimulation. Other muscles were not involved. Motor and sensory nerve conduction velocity was normal en upper and lower limb nerves. Follow-up examinations, performed at 9 and 12 months after onset of paralysis, demonstrated a slow but progressive improvement of the patient's respiratory function, together with the appearance of reinnervation potentials in the diaphragm, and polyphasic, long-latency responses to phrenic nerve stimulation.

The subacute onset of the paralysis associated with local pain, and its subsequent recovery, suggest bilateral proximal lesions in the phrenic nerves. In the absence of traumatic or metabolic causes, these findings indicate that the phrenic nerve can be a target in idiopathic neuritis.

P474

Autonomic function in different patterns of chronic inflammatory demyelinating polyneuropathy. D. Cocito, G. Isoardo, P. Ciaramitaro, S. Maule, R. Quadri, B. Bergamasco, L. Durelli, U. O. A. D.U. Neurologia I, Università di Torino, U. O. A. Neurochirurgia Ospedale CTO (Turin, I)

Among chronic autoimmune demyelinating polyneuropathy (CADP) three different patterns are distinguishable: chronic inflammatory demyelinating polyneuropathy (CIDP), distal acquired demyelinating symmetric neuropathy associated with IgM-paraproteinemia and anti-MAG antibody (DADS-M) or not (DADS-I). These types of polyneuropathy have different clinical and electrophysiological feature and response to treatment. Few studies investigated autonomic dysfunction in CADP and none differentiated among CIDP, DADS-M or DADS-I.

We evaluated 12 patients with CADP for dysautonomia: 7 CIDP-I, 4 DADS-M and 1 DADS-I.

None of them was affected with diabetes mellitus, or other disease associated with dysautonomia.

In all we performed deep breathing test, lying to standing, Valsalva ratio, change in blood pressure with tilting. Each test was scored between 0 and 2, and a summed score higher than 4 was considered suggestive of dysautonomia.

Only one patient affected with DADS (8.3 %) had autonomic dysfunction, particularly decrease in blood pressure with tilting.

Our preliminary results confirmed previous studies indicating a low incidence of autonomic dysfunction in patients with CADP.

P475

Axonal Guillain-Barré syndrome subsequent to mycoplasma infection. K. Susuki, N. Yuki, K. Hirata, Dokkyo University School of Medicine (Tochigi, JP)

Backgrounds and goals: Guillain-Barré syndrome (GBS) subsequent to Mycoplasma pneumoniae infection was reported to be associated with antibody to galactocerebroside (GalC), a major glycolipid in the myelin of the peripheral nerve. Sensitisation of GalC to rabbit can induce demyelinating polyneuropathy. GBS subsequent to M. pneumoniae infection may be demyelinating type, but we had a case of axonal GBS subsequent to M. pneumoniae infection. We here report the detailed serological findings of the patient.

Case report: A 29-year-old man developed weakness of his four limbs. During two weeks before the onset of neurological symptoms, he suffered from fever and dry cough. Deep tendon reflexes were decreased without pathological reflexes. High titres of antibody against M. pneumoniae as well as cold agglutinin were detected. Cerebrospinal fluid showed elevated protein levels (69 mg/dl) with slightly elevated cell count (12 /μl). Nerve conduction study showed decreased compound muscle action potentials without evidence of demyelination. GBS was diagnosed and he was successfully treated by intravenous immunoglobulin therapy.

Materials and methods: Serum was obtained during the acute phase of the illness. Anti-glycolipid antibodies were assayed by enzyme-linked immunosorbent assay. High titres of both IgM and IgG antibodies against GM1 and GalC were detected. Absorption studies were performed to determine the cross-reactivity of these antibodies. Antibody reactivity was confirmed by thin-layer chromatogram (TLC) with immunostaining. Serum from the patient and demyelinating polyneuropathy rabbit sensitised with GalC were examined.

Results: High titres of anti-GM1 IgM (4,000) and IgG (4,000) antibodies were detected as well as those of anti-GalC IgM (8,000) and IgG (8,000) antibodies. GM1 absorbed both anti-GalC IgM and IgG antibodies, whereas GalC absorbed both anti-GM1 IgM and IgG antibodies: This suggests the cross-reactivity of these antibodies. TLC-immunostaining revealed strong reactivity of anti-GalC IgG antibody in serum from demyelinating polyneuropathy rabbit. In contrast, anti-GalC antibodies were not detected in serum from the axonal GBS patient. Anti-GM1 IgM antibody was clearly detected in the patient's serum, whereas anti-GM1 IgG antibody was not.

Conclusion: Axonal GBS subsequent to M. pneumoniae infection is associated with anti-GM1 IgM antibody, and the anti-GalC IgM antibody may be caused by the cross-reaction.

P476

Passive transfer by intraneural injection in axonal Guillain-Barré syndrome. M. Kamijo, N. Yuki, Chubu Rosai Hospital, Dokkyo Medical University (Japan, JP)

Backgrounds and goals: Anti-GM1 IgG antibody can be detected in acute phase sera from patients with axonal Guillain-Barré syndrome (GBS). On

sensitisation with a bovine brain ganglioside mixture or isolated GM1, rabbits developed flaccid limb weakness of acute onset with high anti-GM1 IgG antibody titers which resembles to human axonal GBS (Yuki et al., Ann Neurol 2001;49:712–20). Induction of clinical and pathological disease by passive transfer of anti-GM1 IgG antibody is required to establish an autoimmune aetiology for axonal GBS. Materials and methods: Galactocerebroside or the ganglioside mixture including GM1 with keyhole limpet hemocyanin in Freund's complete adjuvant was injected to Japanese white rabbits several times. Anti-galactocerebroside or anti-GM1 plasma was obtained from each rabbit that showed flaccid paralysis. Control plasma was obtained from rabbits before the inoculation or by sensitisation with keyhole limpet hemocyanin in Freund's complete adjuvant. Twenty microliters of each plasma was injected with a microsyringe and 30-gauge needle through the perineurium into the proximal tibial branch of sciatic nerve. Fifteen microliters of Purified IgG from a patient with axonal GBS, which has anti-GM1 activity was injected with 5 microliters of normal human plasma as the source of complement. Normal human IgG was used as the control. Six sciatic nerves were evaluated on each group. Seven days after intraneural injection, sciatic nerve was dissected and evaluated morphologically. Results: Intraneural injection of rabbit anti-galactocerebroside plasma produced focal demyelinative lesions in rat sciatic nerves, whereas injection of rabbit anti-GM1 plasma induced predominant axonal degeneration. Any control plasma could not induce these pathological changes. Purified IgG from a patient with axonal GBS, which has anti-GM1 activity, produced predominant axonal degeneration when homologous complement was given. Both rabbit anti-GM1 plasma and human IgG with anti-GM1 activity induced degenerative mitochondria accumulation in the nodes of Ranvier in sciatic nerves. Conclusion: Passive transfer of axonal degeneration was induced by intraneural injection of rabbit plasma and human IgG with anti-GM1 activity. Although further studies by intraneural injection of monoclonal anti-GM1 IgG antibody or by systemic transfer will be required, our results indicate that anti-GM1 IgG antibody play a key role in the development of axonal GBS.

P477

Excitability parameters in median motor and sensory and in peroneal motor axons of normal subjects. P. Lozeron, M. Moldovan, C. Krarup, Rigshospitalet (Copenhagen, DK)

Threshold tracking was used to test excitability of median motor and sensory axons at the wrist and peroneal motor axons at the ankle and knee in 30 normal subjects. The original protocol for recording multiple excitability parameters of motor axons was also used for sensory axons to allow direct comparison [1].

A surface cathode for stimulation was placed over the median nerve at wrist and the anode at a 10-cm more proximal site; the compound muscle action potential (CMAP) was recorded from the abductor pollicis brevis muscle and the compound sensory action potential from digit III via surface electrodes. The peroneal motor axons were stimulated at the fibular head and at the ankle, and the CMAP was recorded from the extensor digitorum brevis muscle. Temperature was kept at 35–36 degrees C. Motor fibers of the median nerve had shorter strength-duration time constant, higher rheobase, greater accommodation during depolarization, less inward rectification during hyperpolarization, shorter refractory period and more pronounced supernormality. Significant differences were found between the motor axons of the median and peroneal nerves. The excitability properties of the peroneal at knee appeared mainly similar to those of the median nerve at wrist. These differences in excitability measures suggest that the distribution of ion-channels varied between motor and sensory fibers, between different motor nerves and between proximal and distal sites. The findings are in agreement with previous studies where results from the same subjects were, however, not compared [2, 3].

Supported by a grant from the European Neurological Society. Present address: Service de Neurologie, Le Kremlin-Bicêtre, France

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P478

Chronic inflammatory demyelinating polyneuropathy (CIDP) in diabetic patients -diagnosis and response to treatment. T. de Greslan, V. Planté-Bordeneuve, D. Adams, J.-Y. Méar, C. Lacroix, P. Rondot, G. Said, Hopital de Bicetre, Université Paris-Sud (Le Kremlin Bicetre, Paris, F)

CIDP, which is often associated with diabetes, poses specific diagnostic and therapeutic problems in this population. In order to learn more on the management of CIDP in diabetic patients, we reviewed the clinicopathological and follow-up data of diabetic patients with CIDP seen in our service from 1996 to 2001.

Patients and Method: Diabetic patients with a subacute sensorimotor deficit that affected all four limbs and predominated on large fibre function, with electrophysiological and nerve biopsy findings compatible with CIDP, and no other cause of demyelinating polyneuropathy than diabetes. After initial work-up and treatment, the patients were examined monthly during at least one year. Ten diabetic patients (8 type 2 and 2 type 1), 7 men and 3 women, aged 39 to 75 years (mean 64 y-o), out of the 188 diabetic patients with peripheral neuropathy referred during that period of time, were included. The average duration of diabetes was 12.6 years (range 0–31 yrs). The first neurological manifestations had started 3 to 24 months before referral. Patients 1–7 had severe alteration of proprioception with ataxia and paresthesiae in both feet that progressed to a sensorimotor deficit more marked distally in the lower limbs. Patients 8–10 manifested progressive symmetrical weakness in both feet that extended proximally in the lower limbs, along with moderate proprioceptive ataxia. Nerve biopsies showed active demyelination and variable loss of axons in all cases. In some patients it was difficult at the first examination to diagnose CIDP because of the severe underlying diabetic neuropathy (Patients 2 & 10).

The neurological condition of the 8 patients who were initially given intravenous immunoglobulins (1 to 2 g/Kg) continued to deteriorate to the point that 6 of them became bedridden within a month. Methylprednisolone was then given intraveinously (500 mg/day) for 5 days, followed by oral prednisolone (1 mg/kg/day) for 6 weeks. Improvement of the neurological deficit occurred within 2 to 16 weeks, in 7 patients, with partial recovery of their walking ability. One patient (10) noticed improvement of sensory symptoms only. The two patients (4 and 6) who received oral prednisone (1 mg/Kg/day) as a first line treatment also improved. In two patients (7 and 10) corticosteroids had to be discontinued after one month because of side effects. While on corticosteroids, insulin had to be started in two type 2 diabetic patients. At tapering of corticosteroids, 5 patients had one or more relapses within 6 months with a favourable response to the subsequent increases of dosage in 3 of them.

In this series the diagnosis of CIDP was difficult to establish in some patients because of pre-existing diabetic neuropathy. Treatment with corticosteroids gave better results than IVIgs but the long-term prognosis remains uncertain because of relapses and side effects of treatment.

Poster Session 3

Cerebrovascular disorders

P479

The function of the adrenocortical axis, and the effect of glucocorticoids on the neurological outcome following focal cerebral ischemia. J. Weidenfeld, N. Gai, A. Teichner, A. Itzik, R.R Leker, H. Ovadia, Hadassah Hospital, University of Rome La Sapienza (Jerusalem, IL; Rome, I)

The role of glucocorticoids (GC) in the outcome of stroke is still controversial.

We characterized the effect of acute ischemic stroke (IS) on the activation of the hypothalamic-pituitary-adrenal (HPA) axis and evaluated the role of endogenous and exogenous glucocorticoids on the post-IS clinical outcome and ex-vivo production of brain prostaglandin E2 (PGE2). Male spontaneous hypertensive rats underwent permanent middle cerebral artery occlusion (PMCAO) by craniotomy and electrocoagulation resulting in a well-defined cortical infarct. At 1 and 4 hours post-PMCAO or sham operation the serum levels of ACTH and corticosterone were elevated 3 and 6 fold respectively as compared to intact controls. At 24 hours post-surgery the levels of these hormones returned to basal values. PMCAO or sham operation also caused a significant depletion of corticotropin releasing hormone (CRH–41) at 4 hours post surgery. In animals that underwent PMCAO the ex-vivo production of PGE2 at the region of the brain infarct significantly increased and was further enhanced in rats lacking circulating GC following bilateral adrenalectomy (ADEX) as compared to rats with PMCAO without ADEX.

In ADEX rats the degree of motor disability was similar to that of sham ADEX animals. However, in dexamethasone-treated ADEX rats, a significant reduction in motor disability was observed. Similarly, infarct volumes were significantly reduced in ADEX rats treated with dexamethasone as compared to the respective controls. Importantly, sham-operated animals

treated with dexamethasone did not show a reduction in motor disability or infarct volumes as compared with vehicle.

The results suggest: 1. The activation of the HPA axis following PMCAO is due to the general effects of stress induced by surgery rather than to the presence of the brain infarct per-se. 2. This activation is mediated by a mechanism, which involves the release of CRH–41 from the hypothalamus. 3. Stroke is associated with increased production of brain PGE2 and GC attenuates this response. 4. Absence of endogenous GC may not alter motor or pathological parameters in the acute stage following PMCAO. In contrast, administration of dexamethasone improves the outcome after focal cerebral ischemia in ADEX animals.

P480

Sarcoidosis presenting with stroke and meningoencephalitis. S. Cagirici, Dr.Lutfi Kirdar Kartal Education and Research Hosp (Istanbul, TR)

Sarcoidosis involves the nervous system in approximately 5 % of cases. The most common presentation of neurosarcoidosis is cranial neuropathy, usually facial. The involvement of cerebral vessels in sarcoidosis was showed from pathologic studies, but stroke like events was showed very rare. Meningoencephalitis are extremly rare too.

We describe a case of sarcoidosis in a young women who presented meningoencephalitis with seizures and followed by stroke resulting from a subacute infarction

Case Report: A 37 year-old woman with sarcoidosis was admitted to the hospital for sudden unconsciousness, generalized tonic-clonic seizures and agitation. The patient was biopsy-proven sarcoidosis with pulmoner involvement ten years ago. She had recurrent corticosteroid treatment for ten years. General physicial examination revealed temperature of 38,5˚C, an arteriel blood pressure of 90/60 mmHg and agitation. Neurological examination except positive meningial irritation finding was normal. Complete blood count showed leucocytosis, ESR 50 mm/hr, CRP 73 mg/L. Cerebrospinal fluid analysis demonstrated a sterile fluid with total protein of 108,2 mg/dl, glucose of 36 mg/dl, serum glucose of 153 mg/dl and CSF pressure was elevated. There were 30 cell/mm3. Our diagnosis was meningoencephalitis and started cephtriaxon therapy (4 gr/day). Her consciousness state recovered slowly. On seventh day, at neurological examination, meningial irritation finding was negative. On tenth day, at neurological examination was found mild left hemiparesia and left hemihipoestesia. Her gait was ataxic. There were no abnormal findings of cranial computed tomography(CT). Cranial MRI with and without contrast showed that subacut infarction at the posterior of the right parietooccipital region and minimum leptomeningial contrast absorbtion of the supratentorial region. At the time the patient stayed in the hospital, she had two TIA attacks. She was symptoms-free after 1-month. She had no neurological findings.

Stroke and concomittant meningoencephalitis are very rarely complications of sarcoidosis. Several different mechanisms can be responsible for stroke and meningoencephalitis in this patient: granulomatous infiltration of the meninges and underlying parenchyma, small-vessel granulomatous vasculitis;or large-vessel inflammation resulting in artery-to-artery embolization, stenosis, or oclussion.

P481

Wallenberg's syndrome: a review of 15 cases. R. C. Ginestal, J. C. Alvarez-Cermeño, J. C. Martínez-Castrillo, Hospital Ramón y Cajal (Madrid, E)

Introduction: Lateral medullary infarction, Wallenberg's syndrome, is more often secondary to an intracranial vertebral artery occlusion and afterwards to a posterior inferior cerebellar artery occlusion. We present a retrospective study of the cases admitted to Ramón y Cajal hospital in the last seven years. Epidemiological, clinical, radiological and prognosis data are shown.

Patients: Patients admitted to neurology service with a final clinical diagnosis of Wallenberg's syndrome between January 1995 and December 2001. It was also required a radiological (computed tomography, magnetic resonance imaging or both) confirmation of the lateral medullary infarction. A total of 15 patients with a clinical and radiological Wallenberg's syndrome were found.

Results: Lateral bulbar syndrome is a condition more frequent in late middle aged men with an average of 64,2 (49–79) years of age. The main risk factor was arterial hypertension (60 per cent), followed by diabetes and smoking. The commonest symptom was dizziness (52 per cent) whereas the most frequent finding on physical examination was an ataxic gait (60 per cent). Other symptoms were crossed sensory loss or numbness (46 %), nausea and vomiting (46 %), headache (26 %), diplopia (26 %), dysphagia (20 %), hoarseness (20 %) and disphonia (13 %). Other examination findings were Horner syndrome (53 %), ipsilateral ataxia of limbs (46 %), crossed sensory loss (46 %), and Nystagmus (40 %).

The most common outcome complications during hospitalization were respiratory tract infections (two patients) and gastrointestinal haemorrhages (two patients). In most cases the prognosis was good. The main sequels were an ataxic gait (40 %) and one-sided or crossed sensory loss (40 %).

Conclusions: Our results are similar to those in the literature. Nevertheless some findings, like diabetes as the second more common risk factor of lateral medullary infarction, or the disphonia being less frequent in the clinical presentation than expected, make the difference between our patients and other series in the literature.

P482

Epileptic seizures associated with benign post-partum angiopathy. D. Felten, S. Fresse, L. Guilloton, P. Ehre, R. Legros, A. Drouet, Hôpital Desgenettes (Lyon, F)

Peripartum seizure is a serious disease with eclampsia and venous stroke as the most common causes. Post-partum cerebral angiopathy (PCA) is a less common event that develops shortly after a normal pregnancy. It is characterized clinically by headaches, vomiting, seizures and, less often, focal neurological deficiency. Cerebral angiography reveals segmental and multifocal narrowing of cerebral arteries. We report the case of a 22-year-old woman who was admitted for generalized epileptic seizures, 8 days after spontaneous delivery of normal twins. Pregnancy had been uncomplicated. Bromocriptine was prescribed after delivery to suppress lactation. After six days she experienced frontal unusual headache and vomiting. The first neurological examination was normal. Her blood pressure was165/100 mmHg. Laboratory results were normal. Brain computed CT scan and cerebrospinal fluid (CSF) were normal without brain nor subarachnoid haemorrhage. A first magnetic resonance imaging (MRI) revealed T2 hyperintense lesions involving cortical areas. After six days MRI was normal again. MR angiography (MRA) showed segmental arterial narrowing. The patient remained headache and seizure free with valproate and clobazam. Bromocriptine had been stopped at admission. Blood pressure was controlled by calcium inhibitor. Three months later, blood pressure was normal without treatment and a control MRA was normalized. This woman has typical clinical signs, radiological patterns and benign outcome of PCA. In the event of post-partum headache and seizures, dural sinus thrombosis, arterial or venous stroke and subarachnoid haemorrhage have to be first excluded. Another cause is eclampsia, where cortical MRI T2 hyperintense lesions are frequent. Similar abnormalities can be observed in dural sinus thrombosis and in benign PCA. MRA precises the vascular abnormalities. In eclampsia, MR angiograms may show narrowing of the major vessels constituting the circle of Willis that resolve after some weeks. Such segmental vasospasms are observed in PCA. PCA may be promoted by vasoconstrictive drugs like bromocriptine and criteria of toxaemia are usually absent. Nevertheless, it is sometimes difficult to differentiate late eclampsia and benign PCA. According to other authors the question may be asked of different illness or different manifestations of the same underlying process.

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Dysphagia in acute stroke: a simple bedside swallowing evaluation. R. Pentore, M. L. Lugli, M. Santangelo, M. Baratti, G. Greco, Hospital, Regional Hospital (Carpi, Bolzano, I)

Background: Swallowing abnormalities are a common functional impairment of acute stroke. Its prevalence ranges from 25 % to 32 %. Dysphagia and aspiration may result in various medical complications like pneumonia, dehydration, delay of recovery and death.

Objectives: to detect dysphagia, to prevent medical complications and to improve quality in stroke care. Subjects and Methods: 124 acute stroke patients admitted at our neurological department in one year were examined. Neurological examination and neurological scales (Glasgow coma scale, Scandinavian Neurological Stroke Scale, Barthel Index) were performed and risk factors for dysphagia (dysphonia, dysarthria, impaired pharyngeal gag reflex, oral apraxia) were investigated. Swallowing ability was assessed at time of admission by asking the patients to drink 50 ml water from a beaker or a big syringe. Patients without risk factors for dysphagia and those unconscious were excluded. All patients were tested initially with smaller volumes of water. If the patient choked, they were allowed to rest for a few minutes and the test was repeated a second time, using then thickened liquids in those who choked. Dysphagia was defined as the inability to drink 50 ml water or choking more than once while attempting to drink 50 ml water on two occasions. They were managed preparing an appropriate food including thickened liquids or positioning a nasogastric tube. All patients were investigated for symptoms of aspira-

tion pneumonia (cough, fever, signs of infection at clinical or radiological examination). Results: In 10 patients, unconscious at admission and after 24 hours, was positioned a nasogastric tube. 34 out of 124 (16 woman, 19 men; median age: 74.5, range 61–89) were tested with the bedside swallowing evaluation; 27 (21.7 %) patients had dysphagia. 13 patients received an appropriate diet including thickened liquids and in 14 patients was positioned a nasogastric tube. 5 (4 %) patients died. One patient had signs and symptoms of aspiration pneumonia just at admission and a nasogastric tube was immediately positioned. Conclusion: In our acute stroke patients group 37 (29.8 %) had difficulty in swallowing at admission. No clinical or radiological findings of aspiration pneumonia were found in our patients. The bedside swallowing evaluation is a simple method to detect dysphagia, to improve acute stroke patients care and to prevent medical complications.

P484

Transient ischemic attack (TIA): a clinical model of ischemic tolerance. I. Petrov, V. Petrova, I. Barbov, Clinic of Neurology, Medical Center (Skopje, Strumica, MK)

Background: It has been shown in animal models that short duration ischemic episodes reduce the cerebral damage originating from a later persistent ischemia.

Methods: This study was designed to compare the intensity of the neurological lesion (rated using the Canadian Stroke Scale- CSS measured on admission, at 48 hours, 7 days and 3 months- and by the size of the infarct measured using a CT carried out between the fourth and seventh day following admission) in two groups of patients with cerebral infarction: one with TIA in the seven days before (n = 94) and the other without a history of ischemia (n = 94), admitted consecutively to each patient selected in the first group (n = 94). The results from the CSS are expressed as a median and a range.

Results: In 30 patients the TIA occurred in the area ipsilateral to the infarct and during the 72 hours before it. In this sub-group of patients the CSS on admission (7; 2.5- 9), 48 hours (7.5; 2- 9), 7 days (9; 2- 10) and 3 months (9.5: 3- 10) were significantly higher ($p < 0.0001$) than that recorded in the group without TIA: CSS on admission (5; 1.5- 10), 48 hours (3.5; 1.5- 10), 7 days (5; 1.5- 10) and 3 months (7.5; 3- 10). The percentage of patients with early neurological deterioration ($p < 0.0001$) and the size of the infarct ($p < 0.001$) was greater in the group of patients without TIA. The patients with contralateral TIA or with more than 72 hours until infarct did not give statistically different results to those obtained in the group of patients without TIA.

Conclusion: A history of ipsilateral TIA in the preceding 72 hours is associated with cerebral infarctions with reduced neurological lesions, possibly owing to the induction of an ischemic tolerance mechanism.

P485

Elective stenting in a severe basilar artery stenosis. J. Izquierdo, J. Roquer, A. Rodríguez Campello, A. pou-Serradell, L. Soler Singla, L. Guimaraens, Hospital Universitari del Mar, Hospital General de Catalunya (Barcelona, E)

Background: Severe stenosis of the basilar artery often has a bad prognosis with an high rate of ischemic lesions, and recurrences. Medical treatments using antiplatelets, anticoagulants or both sometimes are ineffective. With the new techniques and materials, the stenting of basilar artery has been postulated as an alternative in such patients. We report a case of a patient who was successfully treated with basilar stenting after suffering recurrent episodes of sudden tetraparesis unresponsive to different medical treatments.

Case report: A 70 year-old woman, with hypercholesterolemia as unique vascular risk factor, suffered in July 01 a bilateral stroke of the posterior cerebral artery more extended in the left side, with a residual quadranopia. She was treated with aspirin, but three months later she experienced a reversible episode of vertebrobasilar ischemia featured by tetraparesis and anarthria. The angio-MRI showed a severe stenosis of the proximal basilar artery. The same clinical symptoms recurred despite the clopidogrel treatment and the combination of anticoagulant and antiplatelet treatment. A cerebral angiography was performed and confirmed the findings of the MRI. In the same procedure a basilar stenting was performed, with no complications, showing a complete recanalisation of the artery. Patient was discharged with a modified Rankin Scale of 0 and under clopidogrel and aspirin treatment with no recurrences in the following months.

Conclusion: Stenting of the basilar artery could be considered as a good option in patients with proximal stenosis who don't respond to pharmacological treatment.

P486

Has age an influence on stroke recovery in the early phase? M. Manz, P. Lochner, T. Altenhöner, Ch. Kugler, A. Ferbert (Kassel, D; Meran, I; Bielefeld, D)

Age is the most important risk factor for developing a stroke. Less clear is the influence of age on functional outcome once stroke has occurred.

To answer this question we retrospectively analysed data of 11 968 acute stroke patients from the quality assessment registry of the stroke study group Hessen in the years 1999 and 2000. We included patients with acute ischemic stroke treated on stroke units. We excluded patients with a Barthel Index score less than 100 before stroke onset. A study group of 2219 patients remained. Solely for calculation of the age dependent in-hospital fatality rate we formed a second study group. Activities of daily living was assessed by Barthel Index score on admission, 6 to 8 days after admission and at discharge and correlated those with six different age groups.

There was a significant trend of older patients having less increase in Barthel Index score. This effect was not very strong. Whereas there was an impressing correlation between age and fatality: The fatality of the age group over 85 years increased almost ten times compared to the patients younger than 44 years.

We conclude that age has a strong significant influence on acute stroke fatality.

There is only a weak impact of age on stroke recovery in the early phase.

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A clinical case of midbrain lacunar infarct (Claude's syndrome with pupillary sparing): anatomical and neuroradiological correlation. M. Liguori, D. Tessarolo, M. R. Fele, M. Panzera, A. Pingi, S.Camillo Hospital Neurological Service, Neuroradiological Service (Rome, I)

Aim: To demonstrate that a careful clinical and neuroradiological study allows to detect very uncommon midbrain infarcts limited to oculomotor nerve fibres.

Introduction: In 1912 H. Claude described for the first time a complete paresis of the third cranial nerve on the right associated to a left hemiataxia, scanned speech without hemiparesis and sensitive deficit (Rev. Neurologique, 1912). Claude's syndrome is very unusual and in our case the presence of pupillary sparing is interesting about the intra-extra axial fascicular organization of the oculomotor nerve.

Clinical Findings: The patient is a male of 77 years old, affected by diabetes. He presented a sudden balance deficit associated to left ptosis. The neurological examination showed left third nerve cranial palsy limited to ocular muscles and contralateral cerebellar ataxia. The patient was submitted in emergency to CT scan brain, echocolordoppler of epi-aortic vessels and otorhinolaryngologist evaluation. Subsequently an MRI brain study was performed and images obtained by Philips Gyroscan NT 1.5 MR Unit on axial planes on T1 and T2 weighted sequences.

Results: CT scan brain, echocolordoppler of epi-aortic vessels and otorhinolaryngologist evaluation resulted normal. MRI images of the brain on T2 weighted sequences showed a focal hyperintense signal localized in the rostral ipsilateral midbrain with involvement of red nucleus and oculomotor fibres for ocular movements.

Discussion: A careful clinical and neuroradiological study allows to detect very rare brainstem syndrome as that described by Claude for the first time. It is very important to underline that the ipsilateral localization of the ischemic lesion in the midbrain is in accord with the exclusive involvement of oculomotor fibres for ocular movements and with pupillary sparing, since the oculomotor fibres for extraocular movements are located in the middle of midbrain (Saeki et al., 2000).

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Early CT findings in acute middle cerebral artery ischemia. M. Mohamed, R. Boguslawska, R. Poniatowska, G. Rejnowski, R. Krawczyk, T. Mendel, P. Kozlowski, Institute of Psychiatry and Neurology (Warsaw, PL)

Introduction: It has been stated in the literature that during the first hours after an acute ischemic attack (a. i.a) CT usually shows no abnormalities. The aim of the study was to assess the reliability of the detection of early acute ischemic brain changes, the frequency of early CT signs of acute cerebral ischemia and to predict final infarct extension and topography.

Material and Method: CT studies of 50 patients admitted within 12 hours of onset of ictus and a follow-up study within 7 days were analyzed. CT was performed using 512x512 matrix with 5mm slices in the posterior fossa and 8 mm supratentorally. Results: On the first CT early signs of ischemia were a hyperdense middle cerebral artery (HMCAS), hypoattenu-

ation of the lentiform nucleus (ALN), loss of insular ribbon (LIR) and hemispheric sulcar effacement (HSE). Early CT was abnormal in 90 % of cases, there was correlation between the incidence of early signs and the time of CT ($p < 0.001$ for ALN, $p < 0.33$ for LIR, $p < 0.0035$ for HSE, $p < 0.011$ for HMCAS). At 3 hours the most frequent sign was effacement of cerebral sulci (45 %), ALN(18,2 %), LIR (27,3 %). At 9 hours percentages were: 100 % ALN, 100 % HSE, 85 % LIR. Presence of one, two or three signs was associated with massive MCA infarct ($p < 0.001$),ALN with deep MCA infarct ($p < 0.0001$), positive HMCAS correlated with massive MCA infarct ($p < 0.001$).

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Cardioembolic risk factors in AIT. S. Escalante, E. Díez Tejedor, M.V Mejías, University Hospital La Paz (Madrid, E)

Introduction: TIA is considered secondary to large vessels arteriosclerosis. We analyse the presence of cardioembolic risk factors (RF) in these patients in order to evaluate its diagnostic and therapeutic implications.

Methods: We performed an observational and sequential study from our stroke data bank during 1994 to 1999, analysing RF for cerebral ischemia. According to the presence or absence of cardioembolic RF (atrial fibrillation, valvulopathy, ventricular aneurysms or diskynesis), patients were assigned to group A (presence of cardioembolic RF) or group B (absence). Statistical anaysis: t-student, chi-square.

Results: 3003 stroke patients were attended during the study period, 505 with the diagnosis of TIA. 158 (31,3 %) patients had cardioembolic RF (Group A), while 347 (68,7 %) were assigned to group B. In 30 patients (18,9 %) cardioembolic RF were detected during hospital stay. Not significant difference in gender distribution (male/female) (A: 53,2 %/46,8 %; vs B: 38,3 %/61,7 %) was found. An older age (A: 69,6 ± 10, B: 65,9 ± 11; $p < 0,01$) and longer length of stay (A: 9,8 ± 5,4; B: 8,4 ± 5,4; $p < 0,01$) were demonstrated in group A.

Conclusions: Cardioembolic risk factors are present in a third of TIA patients. The hospitalary procedures contribute to its identification in an important way. These data suggest that TIA is not an homogeneous group and cardioembolism must be considerd as a TIA etiologic subtype. This should be taken in account in diagnostic and therapeutic attitude.

P490

Autoregulation monitoring in patients with stenosis of the middle cerebral artery. C. Haubrich, R. Diehl, A. Klemm, C. Klötzsch, RWTH Aachen, Krupp Krankenhaus Essen (Aachen, Essen, D)

Spontaneous oscillations in cerebral blood flow velocity (CBFV) and arterial blood pressure (ABP) are appropriate parameters to describe cerebrovascular autoregulation as a high pass filter function. This function can be altered for instance by a severe stenosis or occlusion of carotid artery. The purpose of the present study was to evaluate spontaneous oscillations in patients with a stenosis of the middle cerebral artery (MCA). Using bilateral continuous transcranial Doppler monitoring (TCD) we examined 14 controls and 20 patients (11 male, 9 female; age 60 ± 10 years) with a MCA-stenosis of different degree witch were detected by transcranial colour-coded duplexsonography. Peak systolic flow at the side of the stenosis ranged between 141 and 180 m/s in low-grade and 181 and 220 in moderate and > 220 m/s in high-grade stenosis. CBFV in both MCA and the ABP were monitored in supine and head-up position (80°tilt). The data underwent power- and cross-spectral analysis for B-waves (0.5–3 Hz) and M-waves (3–9 Hz). Coefficients of variation of both frequency bands did not differ between in patients with a MCA-stenosis did and controls. Yet, the phase relation between ABP and CBFV was significantly ($p < 0.05$) altered in patients with high-grade stenosis of the MCA: M-wave phase angle shifts were decreased (14.4 ± 15.4°supine, 19.3 ± 7.6°head-up) indicating a loss of autoregulatory capacity. In contrast to controls, B-waves showed a clear phase relation between CBFV and ABP with a significantly smaller variance in phase relation (22.7 ± 12.0°supine, 24.2 ± 17.0°head-up). This phase relation was the same for M-waves as well as for B-waves that usually are not related to oscillations of ABP. We conclude that CBFV in high grade MCA stenosis passively follows ABP modulations which can be considered as indication of an altered cerebrovascular autoregulation. Results not only suggest an impaired function of the cerebrovascular high pass filter but point also to an altered signal transduction of B-waves due to MCA stenosis.

Clinical Neurophysiology

P491

Trigemino-cervical reflex in patients with multiple sclerosis. D. Bogdanova, University Hospital of Neurology 'St. Naum' (Sofia, BG)

Neurophysiological studies have shown abnormal activity of some brainstem nuclei in patients with multiple sclerosis (MS).

A further opportunity for neurophysiological examination of the brainstem and its central control is the trigemino-cervical reflex, utilising connections from the face to the neck motoneurons. The preliminary data suggest that it may be more sensitive in disclosing brainstem lesions than the blink reflex.

We studied the trigemino-cervical reflex in 25 patients with MS. In all patients the response was abnormal, as compared with the healthy persons, or absent. The results are compared with the clinical and neuroradiological data.

We conclude that the trigemino-cervical reflex may be useful for detecting and localizing lesions of the lower brainstem. It is of a little use for the diagnosis but is helpful as a clue to a better understanding of the alterations of the brainstem neuronal connections in patients with MS.

P492

Movement interferes with the generation of the cutaneomuscular reflex. G. Lauria, J. Valls-Solé, C. Ciano, M. Veciana, National Neurological Institute (Milan, I; Barcelona, E)

Repetitive electrical stimulation of the digital nerves of the index finger induce a reflex response in the voluntarily activated first dorsal interosseous (FDI), known as the cutaneomuscular reflexes (CMR). The CMR is composed by a short latency and a long latency component, which are believed to represent the modulatory effects of sensory inputs on motor circuits at a spinal and cortical levels, respectively. We hypothesized that the influence of sensory inputs at the cortical level would be different depending on the requirements of motor activity. Therefore, we investigated the effect of different types of voluntary movement on the CMR.

Twelve healthy volunteers (23 to 51 years of age) participated in the study. Electrical stimuli were delivered to the index finger through ring electrodes at 3 times the sensory perception threshold. Electromyographic activity (EMG) was recorded from FDI. We averaged and rectified 200 sweeps time-locked to the stimulus. The recordings were done twice at each of the following conditions: 1) holding a pen in the position to begin writing (baseline); 2) writing a standardized short sentence in the subject's own language (writing); 3) holding a pen as in the baseline condition, and performing a regular flexion-extension phasic wrist movement (moving wrist) or elbow movement (moving elbow). We measured peak latency of each CMR wave in ms, and peak amplitude, in percentage of the background EMG activity.

Baseline CMR showed a short-latency component, with an excitatory (E1; mean latency 38 msec) and an inhibitory (I1; mean latency 55 msec) phase, followed by a long-latency excitatory (E2; mean latency 65 msec) phase. In 9 of 12 subjects, a further inhibitory phase (I2; mean latency 110 msec) was recognizable. Writing and moving wrist conditions induced a significant ($p < 0.01$) decrease in the size of I1, E2, and I2 waves with respect to baseline condition. E1 remained unchanged (120 % vs 125 % at baseline). The effects induced on the CMR by writing were not different from those induced by moving. No significant effect was detected in the condition moving elbow.

Our results suggest that the reflex effects of sensory inputs on active motoneurons are inhibited during performance of phasic voluntary movements. This effect, which would serve the purpose of preventing unwanted reflex responses, is likely to occur at a cortical level and could be comparable to the 'gating' effect described on somatosensory evoked potentials.

P493

Neurophysiological diagnosis of acquired chronic sensory ganglionopathies. G. Lauria, D. Pareyson, A. Sghirlanzoni, National Neurological Institute (Milan, I)

Sensory ganglionopathies are caused by the primary impairment of T-shaped sensory neurons of dorsal root ganglia (DGR). Early symptoms, namely ataxia and sensory disturbances in all extremities, suggest that the impairment of sensory fibers occurs in a fashion that is not length-dependent. However, patients, particularly when the disease has a chronic course, are often diagnosed as having an axonal sensory neuropathy. Neurophysiological findings could support the clinical suspicion of ganglionopathy. We reviewed the electrophysiological data of 26 patients with

chronic ganglionopathy. Neurophysiological tests included: motor and sensory nerve conduction studies (NCS), needle electromyography (EMG), quantitative sensory testing (QST), somatosensory evoked potentials (SEP), and blink reflex examination. In all patients, cervical spine magnetic resonance imaging (MRI) showed T2 hyperintensity in the posterior columns. First neurophysiological evaluation was performed 1.4 yrs after onset. Upper or lower limb sensory nerve action potentials (SNAP) were undetectable in more than 50 % of patients and were all absent in 27 % of cases. Decrease in compound motor action potential (CMAP) amplitudes was observed in 13 % of tested nerves and was more severe in paraneoplastic cases. Follow-up NCS was performed at 4.3 yrs on 18 patients: mean SNAP and CMAP amplitudes did not significantly change. EMG showed rare spontaneous activity and mild chronic changes in 15 % of cases; most patients showed an incomplete interference pattern on maximal voluntary contraction likely related to impaired sensory input from denervated spindles and Golgi tendon organs. SEP were absent in 85 % of cases by stimulating either median or tibial nerves and severely decreased in amplitude in the remaining cases. QST showed increased vibratory and cooling threshold at hands in 88 % of patients and at feet in 64 % of cases. Blink reflex was normal in 6 of 8 patients. Ganglionopathies have distinct electrophysiological findings, dominated by not length-dependent decrease in SNAP amplitudes. This pattern, characterized by global rather than distal sensory NCS impairment, distinguishes them from axonal neuropathies and should be considered the electrophysiological hallmark of ganglionopathies. Concomitant involvement of central sensory pathway, which localizes the pathological process to DRG, was better confirmed by MRI hyperintensity in the posterior columns rather than by SEP abnormalities.

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Effects of subthalamic nucleus (STN) stimulation on motor cortex excitability. J. Däuper, T. Peschel, C. Schrader, C. Kohlmetz, G. Joppich, W. Nager, R. Dengler, J. Rollnik, Neurologische Klinik (Hannover, D)

Background: Deep brain stimulation of the internal global pallidus (GPi) and the subthalamic nucleus (STN) has become an alternative treatment in PD. While the effects of GPi stimulation have been examined recently, we know only little about STN stimulation effects on motor cortex excitability.

Methods: The effects of STN stimulation have been studied in eight PD patients using paired-pulse transcranial magnetic stimulation (TMS) in comparison to healthy controls. Motor evoked potentials (MEPs) following paired-pulse TMS (inter-stimulus interval 3 ms to test for corticocortical inhibition vs. 13 ms for facilitation) have been recorded from the extensor carpi radialis (ECR) and its functional antagonist, the flexor carpi radialis (FCR) muscle. In addition, silent period (SP) was determined. Patients were examined under four conditions: medication OFF/stimulator OFF vs. medication ON/stimulator OFF vs. medication OFF/stimulator ON vs. medication ON/stimulator ON.

Results: While the mean values for intracortical inhibition (ICI) were not significantly different, data variation was smaller and levels of significance higher with the STN stimulator switched ON, indicating that ICI was more pronounced. Further, SP was prolonged with the STN stimulator ON. Motor performance (peg-board test, UPDRS) was significantly better with dopaminergic medication and further improved with StimON.

Conclusions: Our results suggest a disturbance of intracortical inhibitory mechanisms in PD which may be compensated by STN stimulation. This hypothesis could explain a more pronounced MEP depression following inhibiting paired-pulse TMS, a prolongation of the SP, and a reduction of akinesia and rigidity leading to a better motor performance in STN stimulated patients.

P495

Symmetry of neurography. F. C. Wang, A. Horward, CHU (Liège, B)

To document side-to-side differences, motor and sensory nerve conduction measurements were collected from 30 healthy subjects (mean age 22 ± 2 years).

The protocol consisted of: motor nerve conduction studies of median, ulnar, peroneal and tibial nerves bilaterally for measurement of amplitude (CMAP amplitude), terminal latency, minimal F-wave latency, and calculation of motor conduction velocity (CV) and F-wave persistance; sensory nerve conduction studies of median, ulnar, radial, lateral and medial cutaneous, sural and superficial peroneal nerves bilaterally for measurement of amplitude (SNAP amplitude) and calculation of sensory CV.

Side-to-side relationships indicated a highly significant correlation ($r^2 >/= 0.8$) only for minimal F-wave latencies and radial SNAP amplitude (with minimal side-to-side percent differences). Side-to-side differences in CMAP amplitudes were greater in lower limbs (on average 14 % and 18 % for tibial and peroneal nerves) than in upper limbs (on average 10 % and 11 % for median and ulnar nerves). The smallest side-to-side difference in SNAP amplitude was observed for radial nerve (on average 11 %) and the largest one for the medial cutaneous nerve (on average 34 %). Side-to-side differences in parameters evaluating the conduction velocity ranged on average from 2 % (lateral cutaneous nerve CV) to 7 % (tibial nerve motor terminal latency). At least, the smallest side-to-side difference calculated in the present study was for F-wave persistance from tibial nerve (0 %). The limits of symmetry were determined for each variable from distinct nerves.

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Cortical somatosensory representation in patients with solitary thalamic infarction. B. Taskin, F. Blankenburg, J. Jungehülsing, J. Ruben, A. Villringer, University Hospital Charité (Berlin, D)

The capability to reorganise its representational maps in response to altered afferent information patterns is a basic property of the somatosensory system as shown by several studies on primates with experimental nerve lesions as well as in patients after limb amputation. In contrast to peripheral deafferentation less is known about the processes following impairment of sensory input at a central level. Lesions of the thalamus – the final relay site to primary somatosensory cortex – represent a central type of partial deafferentation. We investigated four right-handed patients (60–68 yrs) with non-acute solitary unilateral thalamic infarctions exhibiting contralateral hypaesthesia. Localisation of lesions revealed an involvement of the ventral posterior lateral nucleus of the thalamus (VPL). Event-related fMRI (1.5 T) was performed applying a BOLD-sensitive T2*-weighted echoplanar sequence (TR 2 s, TE 60 ms, voxel size 4 x 4 x 5 mm, 16 slices) while electrical current pulses trains (4 pulses at 7 Hz, single pulse duration 200 µs, mean amplitude 7.6 mA) were delivered in a randomised order to the right and left index finger (60 presentations each). Imaging data was analysed using SPM99. In the group analysis, stimulation of the non-hypaesthetic side led to highly significant activations in the contralateral primary somatosensory cortex (S1) and bilaterally in the secondary somatosensory cortex (S2). Stimulation of the hypaesthetic side was associated with a smaller volume of activation in S1 than for stimulation of the non-hypaesthetic side. A reduced activation within contralateral S1 in response to stimulation of the hypaesthetic side is presumably caused by an impairment of functionally active thalamocortical relay projections. However, the volume of activation in contralateral S2 was larger compared with the activation in S2 for stimulation of the non-hypaesthetic side though associated with a reduced activation in S1. Following the notion of a hierarchical organisation and sequential information processing in the somatosensory system (VPL-S1-S2) reduced activation in S2 could have been expected as well. Most probably the observed activation pattern reflects a lesion-induced functional reorganisation of the somatosensory system at a chronic stage of thalamic infarction. The underlying changes of brain activity might be mediated by an altered state of cortico-cortical interaction between S1 and S2 or influenced by direct thalamocortical projections.

P497

Kinematics of reversal movements of the wrist: discrepancy with kinematics of pointing movements. S. Dondlinger, M. Manto, G. Van Campenhoudt, O. Camut, M. Pandolfo, G. Cheron, M. Duchene, ISEPK – ULB, FNRS Neurologie, Ergotherapie ULB, Neurologie Erasme (Brussels, B)

It is currently thought that kinematics of distal single-joint movements for flexion pointing tasks (monodirectional) and for reversal tasks (flexion pointing movements followed by an immediate return to the starting position) share similar features for the flexion phase.

So far, there is no study comparing these two fundamental movements for the wrist.

We compared fast single-joint distal movements in 7 healthy subjects (mean-age: 23 ± 2 years). We analysed ballistic-pointing tasks towards an aimed target located at 30, 20, 10 degrees from the starting position. The same targets were used for reversal movements. Kinematics were analysed with a selspot system (Selcom). Planar velocities were computed. We found a discrepancy between pointing movements and reversal movements for the 30 degrees experiment. Mean of peak velocities were 1385.3 ± 209.5 mm/sec for the flexion task and was 1617.8 ± 192.7 for the flexion component of the reversal movement ($p < 0.001$). This discrepancy was absent for low amplitude movements. Mean of peak velocities were 636.4 ± 166.1 for the monodirectional movement and were 673.0 ± 162.0

for the flexion part of the bidirectional movement (p = 0,126). Interestingly, for reversal movements the mean of the peak velocities for the flexion phase divided by the peak velocities for the extension phase decreased from 1.158 (aimed target: 30 degrees) to 1.023 (aimed target: 10 degrees) ($p < 0.001$). This study demonstrates that peak velocities are higher for the flexion component of the reversal task as compared to monodirectional movements. The drop in the ratio of peak velocities associated with flexions divided by peak velocities associated with extension is an additional argument in favor of a distinct neural control for monodirectional and reversal tasks. Our results show that reversal tasks are not under the control of a superposition of elementary motor plans.

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Effects of proximal fatigue on terminal oscillations associated with fast goal-directed distal single-joint movements. A. El Bali, M. Manto, G. Van Campenhoudt, O. Camut, M. Pandolfo, G. Cheron, M. Duchene, ISEPK – ULB, FNRS – Neurologie, Ergotherapie – Erasme, Neurologie Erasme (Brussels, B)

Whether a proximal fatiguing task has consequences upon distal rhythmic components associated with fast movements remains undetermined.

We analysed the terminal oscillations associated with performance of distal single-joint movements before and after a fatiguing task of a proximal joint ipsilaterally.

Our aim was to test the hypothesis that a fatigue of shoulder muscles changes the frequency characteristics of terminal oscillations associated with fast goal-directed wrist flexions.

Methods: Kinematics of wrist movements on the right side were studied using a Selspot System (Selcom, Sweden) in 10 right-handed subjects (mean age: 23.7 ± 2.1; 6 women) before and after fatigue. The fatiguing procedure was a 30-minutes static abduction of the right shoulder. Right wrist was kept relaxed during the fatiguing procedure. Movements were ballistic flexions towards an aimed target located at 30 degrees from the start position. We recorded 123 movements in the basal condition and 115 movements after fatigue. The peak velocities in the horizontal plane, the frequency of the oscillations (FFT, Acknowledge Software), the power spectral density and the integrals of spectral density curves from 0 to 20 Hz were analysed. Terminal oscillations were studied during the period of 640 msec following the first zero-crossing of the velocity curve.

Results: Before fatigue, mean of peak velocities was 1278.7 ± 220.7 mm/sec. After prolonged abduction, mean of peak velocities was 1266.8 ± 236.0 mm/sec ($p = 0.33$). Mean of peak frequencies was 5.04 ± 3.78 Hz before fatigue and was 5.07 ± 3.48 Hz after fatigue ($p = 0.91$). Mean power spectral densities was 4.37 ± 4.62 $(mm/Hz)^2$ and 5.03 ± 5.96 $(mm/Hz)^2$ in the basal condition and after fatigue, respectively ($p = 0.066$). Integrals of the spectral curves showed a statistically significant increase from 29.9 ± 18.4 mm^2 to 34.8 ± 25.8 mm^2 ($p = 0.001$).

Conclusions: Our study shows that the peak frequencies of terminal oscillations associated with fast goal-directed distal movements remain unchanged after a prolonged fatiguing task of a proximal joint. However, integrals of spectral data show an increase, indicating an unstability of the neural mechanisms controlling distal movements. This is the first study demonstrating a "remote effect" of proximal fatigue upon terminal rhythmic components associated with ballistic wrist flexions.

P499

Intracortical inhibition of the leg muscles in normal subjects: differences between sitting and standing. J. Valls-Sole, P. A. Shanahan, J. C. Rothwell, Hospital Clinic, Sobell (Barcelona, E; London, UK)

Intracortical inhibition and facilitation of motor evoked potential (MEP) amplitude can be demonstrated using paired-pulse transcranial magnetic stimulation (TMS). Short interstimulus intervals (ISIs) of 1–5ms result in inhibition, and longer ISIs (10–15ms) produce facilitation of the MEP. This inhibition and facilitation is reduced during voluntary contraction of the target muscle. This effect is thought to be due to reduced activity in inhibitory cortical neurons during muscle contraction. We compared the effects of postural and voluntary activation on this intracortical inhibition and facilitation.

Methods: 10 healthy volunteers aged 23–50 were studied. Baseline MEPs were recorded from tibialis anterior and soleus. Paired stimuli with ISIs of 1–15ms were then delivered to the vertex, and the resultant MEP sizes recorded. The measurements were performed with the subjects seated at rest, and then repeated while sitting and plantar-flexing the foot (voluntarily activating soleus), and then again with the subjects standing. MEP amplitudes were expressed as a percentage of the unconditioned MEP for each subject and posture. For analysis the ISIs were averaged into blocks: Block 1 was the 1ms interval alone, and block 2 consisted of the 2–5ms ISIs. Block 3 consisted of ISI of 6–9ms (where a transition from inhibition to facilitation could be expected) and block 4 was 10–15ms (the expected facilitatory ISIs). Changes in MEP size were analysed using a repeated-measures analysis of variance (ANOVA) technique, with posture and ISI as the within-subject factors and muscle (TA or soleus) as the between-subject factor.

Results: At rest, the MEPs showed inhibition at intervals of 1–5ms and facilitation at intervals of 10–15ms. Inhibition, though not facilitation, was significantly reduced in soleus when the test was performed during ankle plantar flexion ($F(3,27) = 31\,268p < 0.001$), as well as during standing ($F(3,27) = 31\,268$, $p < 0.001$). There was no significant difference, however, between the reduction seen during voluntary or postural activation ($F(3,27) = 0.551$, $p = 0.652$). In tibialis the posture*time interaction did not reach significance ($F(6,54) = 1.372$, $p = 0.243$). There was no significant difference in the effect of posture on soleus and tibialis ($F(6,108) = 1.80$, $p = 0.106$).

Conclusion: These results suggest that activation of leg muscles causes a similar reduction in intracortical inhibition regardless of whether the activity is related to voluntary or postural tasks.

Dementia – Higher Functions disorders

P500

Treatment of Alzheimer patients with donepezil after nootropic (non-cholinergic) pre-treatment: results from the 2nd German Post Marketing Surveillance (PMS) study. L. Froelich, H. Hampel, T. Klinger, M. Winkel, C. Goebel, F. Berger, University of Frankfurt, Ludwig-Maximilian-University Munich, Klinikum St. Georg, Input GmbH, Pfizer GmbH, Eisai GmbH (Frankfurt, Munich, Leipzig, Aachen, Karlsruhe, D)

Background: In Germany there is a long history for using nootropic agents in dementia patients. The selective cholinesterase inhibitor donepezil (Aricept (R)), an effective and well-tolerated treatment specifically targeting the cholinergic deficit in Alzheimer's disease, recently became available.

Objectives: To compare – in a "real world" setting – the effect of different nootropic pre-treatments on the observed efficacy of donepezil.

Methods: 913 patients were enrolled in the 2nd German PMS study with donepezil. 709 patients (77.7 %) had been pre-treated with nootropics, mainly piracetam, ginkgo and memantine. In the majority of cases (> 80 %), this pre-medication was discontinued when donepezil therapy was initiated. Cognition was evaluated by the Mini-Mental State Examination (MMSE) before the start of donepezil treatment and after the observation period of 3 months. Influence on quality of life (QoL) was assessed by the investigators on a three-point scale (improved/unchanged/worsened). Tolerability was evaluated by analysis of adverse event (AE) reports.

Results: After 3 months of donepezil therapy, MMSE score improved by +2.5 points in nootropic-naïve "N–" patients (n = 183). We compared this reference cohort to patients with discontinued nootropic pre-medication. In patients treated with donepezil instead of piracetam, MMSE improved by +2.4 points (n = 206). If donepezil was used instead of ginkgo, MMSE improved by +2.1 points (n = 129). If donepezil followed memantine, MMSE improved by +1.4 points (n = 61).

QoL was judged "improved" in 70 % and "worsened" in 2.6 % of all patients, with only minor differences between pre-treatment cohorts. Donepezil was very well tolerated. AEs were reported in 85 of 913 patients (9 %).

Conclusions: In a routine clinical setting reflecting daily life conditions, donepezil improved cognition and QoL in Alzheimer patients, with little influence of pre-existing nootropic treatment.

P501

Effects over 12 months of galantamine in probable vascular dementia and Alzheimer's disease with cerebrovascular disease. A. Kurz, T. Erkinjuntti, S. Lilienfeld, S. Schwalen, Technische Universitat, Helsinki University Central Hospital, RW Johnson Pharmaceutical Research, Janssen-Cilag GmbH (Munich, D; Helsinki, FIN; Raritan, USA; Neuss, D)

Background: Galantamine (Reminyl®; GAL) is a cholinergic treatment for dementia with a novel dual mode of action. To date, GAL has shown efficacy for maintaining cognitive function in patients with mild-to-moderate Alzheimer's disease (AD) in both short- and long-term studies. Furthermore, GAL recently became the first cholinergic agent to demonstrate efficacy for maintaining cognitive function in patients with probable vascu-

lar dementia (VaD) or AD with cerebrovascular disease (CVD). We report data from a 6-month, open-label extension to this 6-month, double-blind, placebo-controlled study.

Objective: To assess cognitive function in patients with VaD or AD+CVD who were treated with GAL over a 12-month period.

Methods: Patients with confirmed VaD or AD+CVD were eligible to enter the 6-month, open-label extension study if they had completed an earlier double-blind phase (6 months randomized to GAL 24 mg/day or placebo [PLA]). All patients in the open-label study received GAL 24 mg/day. Cognitive function at baseline and during 12 months of follow-up was assessed using the 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog/11).

Results: In all, 459 patients entered the open-label phase, of whom 195 had probable VaD. 73 % of PLA/GAL and 86 % of GAL/GAL patients completed 6 months of open-label treatment. At the end of 6 months of double-blind treatment, ADAS-cog/11 scores had significantly improved over baseline in the GAL group ($p < 0.001$). After a further 6 months of GAL (12-month follow-up), ADAS-cog/11 scores were still better than baseline (-0.9 ± 0.45), but not significantly so. PLA patients had deteriorated significantly during the double-blind phase, but their ADAS-cog/11 scores returned to baseline after 6 months of open-label GAL (-0.3 ± 0.68).

Conclusion: By maintaining cognitive function at baseline levels, GAL benefits patients with probable VaD or AD+CVD for at least 12 months. Furthermore, cognitive function returned to baseline in patients who received GAL for 6 months after 6 months of PLA.

P502

Three-year follow-up of galantamine therapy for Alzheimer's disease: efficacy and tolerability in open-label extension studies. G. Wilcock, L. Truyen, University of Bristol, Janssen Research Foundation (Bristol, UK; Titusville, USA)

Background: Galantamine (Reminyl®; GAL) is a novel, dual-action, cholinergic agent. In double-blind clinical trials it has demonstrated cognitive efficacy and good tolerability for at least 6 months in patients with mild-to-moderate Alzheimer's disease (AD). In order to assess long-term efficacy, many patients entered open-label extension studies. We present data from patients receiving GAL for a total of 3 years.

Objective: To assess whether GAL remains effective and well tolerated during long-term treatment of AD.

Methods: Patients completing international- or USA-based double-blind, placebo-controlled clinical trials (3–6 months duration) were eligible to enter open-label extension studies. If they completed 12 months of treatment, they could enter a further 24-month open-label study (36 months total treatment). All patients received GAL 24 mg/day during open-label periods. Changes in cognitive function were measured with respect to baseline using the 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog/11). Adverse events are reported for the 24-month extension period.

Results: Almost two thirds of the 818 patients who entered the 24-month extension study completed 36 months of therapy (60.6 %). Over 36 months, patients' cognitive function declined by a mean of 12.2 ADAS-cog points in the international trial and by 10.2 points in the US trial. This represents a considerably slower rate of decline than that predicted for untreated patients by the Stern equation (22.0 ADAS-cog points over 36 months) and by extrapolating 12-month placebo data (18.7 points over 36 months). Adverse events were in line with those expected in an elderly population (e. g. falls, depression, insomnia). In the international study, 11.6 % of patients discontinued GAL due to adverse events, as did 13.1 % of patients in the US study.

Conclusion: Long-term GAL therapy has clinical value in AD. GAL delayed deterioration in cognitive function compared with predicted rates of decline for untreated patients with AD, and was well tolerated.

P503

The virtual synaptic cleft – a model to illustrate the dual mode of action of galantamine. H. Geerts, L. Finkel, A. Spiros, M. Lazarawicz, R. Carr, C. Grantham, In Silico Biosciences, Janssen Pharmaceutica (Lexington, Philadelphia, USA; Beerse, B)

Background: Galantamine (Reminyl®; GAL) has a unique dual mode of action – it is both an acetylcholinesterase (AChE) inhibitor and an allosterically potentiating ligand of nicotinic acetylcholine receptors (nAChRs). This dual mechanism may contribute to the broad-spectrum efficacy that GAL has demonstrated in treating dementia associated with Alzheimer's disease (AD) and dementia associated with cerebrovascular disease, but it also means that the effect of GAL on neurotransmitter pathways is complex.

Objective: To achieve better understanding of the dual mechanism of action of GAL using a specially-designed computer simulation of the cholinergic synapse.

Methods: Recently recorded neuroanatomical and neurophysiological data have allowed the development of a computer model that simulates the cholinergic synapse. The model mimics alpha4beta2 and alpha7 nAChRs in their full spectrum of transition states and incorporates the allosterically potentiating ligand effect at the alpha2beta2 nAChR in a quantitative manner. Furthermore, the interaction between dopaminergic cholinergic neurons is modelled using appropriate firing characteristics.

Results: Introducing neuropathology data from tissues affected by AD into the model allowed the cholinergic deficits associated with the condition to be simulated. It was then possible to compare the effects of conventional AChE inhibitors with GAL in patients with mild-to-moderate AD. For example, the model suggests that overly potent inhibition of AChE results in desensitization of nicotinic receptors, particularly if the synapse is under phasic activation. This counteracts the beneficial effects of increasing ACh levels. The model was also used to simulate the effect of cholinergic agents on 'cross-talk' interactions between cholinergic and dopaminergic pathways in the striatum. GAL was observed to have unique effects on dopamine levels.

Conclusions: The virtual synaptic cleft is a useful tool that enables the effect of drug molecules on complex neuronal pathways to be assessed. It will allow a reference database to be developed and its web-based nature facilitates global usage.

P504

Beneficial effects of galantamine on patient behaviour and caregiver distress in Alzheimer's disease and dementia associated with cerebrovascular disease. D. Kaufer, S. Lilienfeld, S. Schwalen UPMC Montefiore, RW Johnson Pharmaceutical Research, Janssen-Cilag GmbH (Pittsburgh, Raritan, USA; Neuss, D)

Background: Patients with dementia often exhibit aberrant behaviour that can be very distressing for caregivers (e. g. aggression). In long-term clinical trials involving patients with Alzheimer's disease (AD), galantamine (Reminyl®; GAL), a novel cholinergic agent, has demonstrated benefits in function and behaviour, as well as cognition. GAL may confer such benefits in a broader range of dementia syndromes.

Objective: To assess (a) the effect of GAL on behaviour in patients with mild-to-moderate AD, vascular dementia (VaD) or AD with cerebrovascular disease (CVD), and (b) the relationship between behavioural symptoms and changes in associated caregiver distress.

Methods: Using the Neuropsychiatric Inventory (NPI), the behaviour of patients was assessed throughout two large-scale, double-blind clinical trials. Distress experienced by patients¡≥ caregivers was also evaluated using the NPI Distress scale (NPI-D). Study 1 involved 978 patients with mild-to-moderate AD who were randomized to GAL (8, 16 or 24 mg/day) or placebo (PLA) for 5 months. In Study 2, 592 patients with VaD or AD+CVD received GAL 24 mg/day or PLA for 6 months.

Results: In Study 1, GAL 16 or 24 mg/day prevented the deterioration of patients behaviour for at least 5 months (NPI scores remained at baseline). The behaviour of PLA-treated patients deteriorated from baseline and their NPI scores were significantly worse than those in GAL groups (change +2.3 vs. –0.1; $p < 0.05$). In Study 2, NPI scores in the GAL group were above baseline after 6 months of treatment and were significantly better than the PLA group (change –1.2 vs. 1; $p = 0.016$). In both studies, distress was reduced among caregivers of GAL-treated patients compared with those caring for PLA-treated patients. The difference in NPI-D scores between treatment and PLA groups reached significance in Study 1 patients assigned to GAL 24 mg/day ($p = 0.04$).

Conclusions: GAL is effective for delaying the emergence or deterioration of behavioural symptoms in patients with a broad spectrum of dementia – AD, VaD and AD+CVD. The favourable effects of GAL on behaviour may help relieve associated caregiver distress.

P505

Long-term response to galantamine in patients with Alzheimer's disease (AD), vascular dementia or AD with cerebrovascular disease. R. Bullock, L. Truyen, Kingshill Research Centre, Janssen Research Foundation (Swindon, UK; Titusville, USA)

Background: Galantamine (Reminyl®; GAL), a dual-action, cholinergic agent has consistently demonstrated efficacy for maintaining cognitive function in long-term studies of patients with Alzheimer's disease (AD), vascular dementia (VaD) or AD with cerebrovascular disease (CVD). Patients who 'respond' to treatment can be defined according to the degree of cognitive improvement that they experience.

Objective: To assess cognitive response rates in patients receiving long-term GAL for mild-to-moderate AD, VaD or AD+CVD.

Methods: Data from three long-term, open-label extensions to double-blind clinical trials were assessed. All patients received GAL 24 mg/day. Cognitive function was measured using the 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog/11). Response was defined as an improvement from baseline of 0, 4, 7 or 10 ADAS-cog/11 points. Study 1 was of 36 months total duration and included 327 patients with AD. Study 2 included 699 patients with AD and was conducted over 18.5 months. Finally, Study 3 lasted 12 months and focused on a population of 459 patients with VaD or AD+CVD.

Results: Data refer to patients who received GAL throughout the entire study period. After 12 months, 52 % of patients in Study 1 had improved or unchanged cognitive function (ADAS-cog/11 change 0). At 36 months, 18 % of patients were maintained at or above baseline. In Study 2, 52 % of patients remained at or above baseline for 12 months. After 18.5 months, 43 % had a 0 point change from baseline in ADAS-cog/11 score, 23 % had clinically-relevant improvements in cognition (4 point change) and more than 10 % had improved by 7 points. In Study 3, 60 % of those patients who received GAL for 12 months had preserved cognitive function and 32 % showed clinically-relevant improvements.

Conclusion: More than 50 % of patients with AD had preserved cognitive function after 12 months of GAL, with one in five retaining baseline levels for 3 years. Furthermore, nearly two-thirds of patients with VaD or AD+CVD, responded to GAL over 12 months, with one in three showing clinically-relevant improvements in cognition. As over 80 % of those attending specialist services have AD, AD+CVD or VaD, many people would benefit from long-term GAL treatment.

P506

The cognitive function of patients with 'advanced-moderate' Alzheimer's disease is significantly improved by galantamine. J. Marcusson, S. Schwalen, Linkoping University Hospital, Janssen-Cilag GmbH (Linkoping, S; Neuss, D)

Background: In major clinical trials, galantamine (Reminyl; GAL), a novel, dual-action cholinergic agent, has proved efficacious for maintaining cognitive function in patients with mild-to-moderate Alzheimer's disease (AD) over a minimum period of 12 months. In clinical practice, however, physicians are often presented with patients who have more advanced AD. They may not prescribe cholinergic agents for these patients due to a perceived lack of efficacy.

Objective: To investigate whether GAL provides cognitive efficacy in a sub-group of patients with more severe, 'advanced-moderate' AD.

Methods: We performed a post-hoc analysis using pooled data from four pivotal GAL studies. Patients were defined as having 'advanced-moderate' AD if their baseline Mini-Mental State Examination (MMSE) score was $< / = 12$ (Group A) or if their 11-item Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog/11) score was > 30 (Group B). Cognitive evaluations at baseline and 6 months were made using the ADAS-cog/11.

Results: Group A consisted of 63 GAL-treated patients and 61 placebo (PLA)-treated patients, while in Group B there were 245 GAL-treated patients and 257 PLA-treated patients. The mean MMSE score in Group A was 11 and the mean ADAS-cog/11 score in Group B was 39. In patients completing 5–6 months of treatment, the mean difference in ADAS-cog/11 scores between GAL and PLA groups was 6.7 points ($p < 0.001$) in Group A and 6.4 points in Group B ($p < 0.001$). In Group A, 27 % of GAL-treated patients compared with 3 % of PLA-treated patients improved from baseline by $> / = 4$ ADAS-cog/11 points ($p < 0.01$). In Group B, 46 % and 16 % of GAL- and PLA-treated patients experienced $> / = 4$-point improvements ($p < 0.001$). Compared with placebo, significantly better scores were evident for all 11 ADAS-cog items in Group B and for 8 ADAS-cog items in Group A.

Conclusion: Our post-hoc analysis suggests that GAL has utility in a broad clinical population, benefiting not only patients with mild-to-moderate AD, but also those with more severe illness. GAL has potential for wider use in clinical practice.

P507

Galantamine reduces caregiver time in Alzheimer's disease: a pooled analysis from two 6-month, placebo-controlled studies. M. Sano, S. Kavangh, Columbia University, Janssen Pharmaceutica (New York, USA; Beerse, B)

Background: As Alzheimer's disease (AD) increases in severity, patients not only use more formal healthcare and social services, but often require more assistance and supervision from informal caregivers (e. g. relatives or friends). The amount of time spent caring is associated with increased caregiver stress, fatigue and decreased quality of life. Furthermore, caregiver fatigue can be a factor in the decision to institutionalize a patient.

Objective: To assess the effectiveness of galantamine (Reminyl®) for reducing the time family members or friends spend caring for patients with mild-to-moderate AD.

Methods: In two large-scale, double-blind clinical trials, 809 patients received galantamine 24 mg/day or placebo for 6 months. Caregiver burden was measured using the Activity of Caregiver Time Survey, a self-administered assessment of the time spent assisting with activities of daily living (ADL) and providing supervision. Results from both trials were pooled for this analysis.

Results: At treatment endpoint, 60 % of caregivers in the galantamine group reported maintained or reduced time spent assisting with ADL compared with 50 % of caregivers in the placebo group ($2 = 6.9$; $p = 0.008$). The time during which patients could be left unsupervised was also maintained or increased in more galantamine-treated patients than placebo-treated patients ($2 = 4.1$; $p = 0.042$). For patients with moderate AD (Mini Mental State Examination score 18), the advantage of galantamine over placebo was more pronounced. In the caregivers of these patients, the time spent assisting with ADL was either maintained or reduced in 62 % of the galantamine group compared with 42 % of the placebo group ($p = 0.002$). Similarly, there were striking differences in the time patients could be left alone, with 68 % of 'galantamine' caregivers and 57 % of 'placebo' caregivers reporting that the time during which patients could be left unsupervised was either maintained or increased ($p = 0.021$).

Conclusion: The beneficial effects of galantamine on cognition and daily functioning translate into tangible reductions in the activities the caregiver has to perform and in the time they spend supervising the patient.

P508

The assessment of regional cerebral blood flow in Parkinson's disease patients with and without dementia. B. Jasinska-Myga, S. Ochudlo, G. Opala, J. Siuda, M. Pieta, M. Arkuszewski, A. Gorzkowska, M. Swiat, E. Krzystanek, S. Nowak, Medical University of Silesia (Katowice, PL)

Introduction: Dementia is more frequent in patients suffering from Parkinson's disease (PD) then in general population. The mechanism for mental deterioration in PD remains controversial.

Aim: The aim of our study was comparison of the regional cerebral perfusion quantified by single photon emission computed tomography (SPECT) in patients suffering from idiopathic Parkinson's disease with and without dementia.

Material and methods: We examined 43 PD patients: 16 PD patients with dementia and 27 PD patients without dementia. Dementia was recognized according to International Classification of Diseases – Tenth Revision (ICD–10) and Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) criteria. Cognitive functions were executed by means of the Mini Mental State Examination (MMSE) and neuropsychological assessment. The Unified Parkinson's Disease Rating Scale (UPDRS) and Modified Hoehn & Yahr Scale was used to quantify the severity of PD. SPECT was performed with Siemens Diacom single – head rotating gamma camera after intravenous application of technetium 99m hexamethylpropylene amine oxide (99mTc-HMPAO). The perfusion values were expressed as cortical or basal ganglia regions of interest (ROIs)/ cerebellum activity ratios.

Results: In the subgroup of PD patients with dementia significant hypoperfusion affecting the inferior frontal cortices was observed.

Conclusions: The hypoperfusion in the frontal lobe, which may reflect dysfunction of subcorticofrontal projection, may contribute to dementia in PD patients.

P509

The auditive oddball paradigm in subcortical cognitive impairment. B. van Harten, M. Laman, H. van Duijn, H. Weinstein, Sint Lucas Andreas Ziekenhuis (Amsterdam, NL)

Introduction: Recognition of subcortical cognitive impairment is important, because a treatable cause must be considered and educational and behavioral advices can be given to the patient as well as the caregiver. The most important features of subcortical cognitive impairment are: slowing of psychomotor functions, memory deficits with a relatively intact recognition part, problems of complex executive functions and affect lability. Recognition is difficult, therefore an objective diagnostic test could be of additional value. Many studies have investigated the value of the auditive

oddball paradigm or the p300 potential in dementia. However, most studies investigated patients with Alzheimer's disease or patients with a relatively low age. The aim of this study was to investigate the p300 latency in a group of elderly patients with subcortical cognitive impairment independent the cause of the disease.

Patients and methods: Patients were included if they were 60 years or older and if there was a clinical suspicion of subcortical cognitive impairment. The control patients were selected from the healthy partners or from patients without a brain disease. Subjects were excluded if they had cortical dementia or a severe hearing problem. As the best reference test for the diagnosis of subcortical cognitive impairment a neuropsychological investigation was performed in every subject. The different groups were obtained based on the clinical diagnosis as well as the results of the neurpsychological tests. In every subject the p300 was performed under standardized conditions. The results were analyzed by two independent neurophysiologists.

Results: 48 patients with a clinical and neuropsychlogical diagnosis of subcortical cognitive impairment and 54 controls were included The mean age was 74 ± 7 and 74 ± 6 respectively. Other demographic characteristics were also not statistically significant different between the two groups. The p300 was not interpretable in 12 patients and in 9 controls. The mean latency in the patient group was 420 ± 58 seconds and the median 404. In the control group the mean latency was 410 ± 69 seconds and the median 392 seconds ($p = 0.2$).

Conclusions: There is no statistically significant difference of the p300 latency between patients with subcortical cognitive impairment and age-matched controls. The test is not of clinical value in the diagnosis of subcortical cognitive impairment.

P510

Donepezil improves cognition in patients with early Alzheimer's disease. B. Seltzer, P. Zolnouni, M. Nunez, D. Kumar, T. Griesing, S. Richardson, Tulane University, CA Clinical Trials Medical Group, ICSL Clinical Studies, Eisai Inc, Pfizer Inc (New Orleans, Beverly Hills, St Petersburg, Teaneck, New York, USA)

Background: Placebo-controlled studies of up to 1 year in duration have demonstrated that donepezil-treated patients with mild to moderate Alzheimer's disease (AD) experience benefits in cognition, global function, activities of daily living, and behavioral symptoms. The current study was designed to evaluate donepezil in patients with early (mild) AD.

Objective: Evaluation of the efficacy and tolerability of donepezil in patients with early AD.

Design: A 24-week, randomized (2:1;donepezil:placebo), double-blind, placebo-controlled study.

Methods: Diagnostic evidence of probable AD (DSM-IV and NINCDS/ADRDA criteria) was required for enrollment. In addition, patients were required to have a Mini-Mental State Examination (MMSE) score of 21–26 and a global Clinical Dementia Rating (CDR) of 0.5 (questionable or very mild dementia) or 1 (mild dementia). Patients were randomized to receive placebo or 10 mg/d donepezil (5 mg/d for the first 42 days and 10 mg/d thereafter). The primary efficacy measure was the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog). The MMSE was included as a secondary efficacy measure. The primary analysis was based on the least squares (LS) mean change from baseline on the ADAS-cog at endpoint using last observation carried forward analysis of the intent-to-treat population.

Results: 153 patients were enrolled (57 placebo, 96 donepezil). Mean (SE) MMSE scores at screening were 24.3 (1.3) for placebo and 24.1 (1.7) for the donepezil group. In the donepezil treatment group, 33 % of patients had a CDR score of 0.5 and 62.6 % a CDR score of 1.0, while 34.5 % and 65.5 % of patients in the placebo group had CDR scores of 0.5 and 1.0, respectively. LS mean change from baseline scores on the ADAS-cog improved for donepezil at all visits and were significantly different from placebo at weeks 12, 24, and endpoint (treatment difference = 2.2; $p = 0.003$). LS mean change from baseline on the MMSE showed improvement with donepezil that was significantly different from placebo at all visits and at study endpoint (treatment difference = 1.8; $p = 0.002$). Donepezil was well tolerated with low withdrawal rates due to adverse events (placebo, 8.8 %; donepezil, 15.6 %).

Conclusions: Donepezil-treated patients with early AD demonstrated cognitive improvements on both the ADAS-cog and the MMSE. Donepezil was also well tolerated in this population. These results further support initiating donepezil therapy early in the disease course.

P511

Differential analysis of beta-amyloid peptide pattern in cerebrospinal fluid of patients with Creutzfeldt-Jakob disease. M. Otto, H. Esselmann, M. Bibl, L. Cepek, P. Steinacker, B. Mollenhauer, K. Buerger, H. Hampel, S. Paul, M. Maler, H. Kretzschmar, S. Poser, J. Wiltfang, University of Goettingen, University of Munich, University of Erlangen (Goettingen, Munich, Erlangen, D)

Background: Decreased levels of Abeta1–42 measured by ELISA are described in cerebrospinal fluid (CSF) of patients with Alzheimer's disease (AD) and Creutzfeldt-Jakob's disease (CJD). Is was supposed that decreased levels of Abeta1–42 do not exclude CJD.

Patients and methods: We have analysed cerebrospinal fluid of 20 patients with CJD, 20 patients with AD and 20 non-demented control patients (NDC) using a quantitative urea-based Abeta-SDS-PAGE/immunoblot with attomolar detection sensitivity. Following lumbar puncture CSF samples were boiled in the presence of detergent before freezing. This sample pretreatment does significantly and differentially affect the concentration of single Abeta peptide species, as compared to direct freezing. Like in AD and NDC we found a highly conserved pattern of carboxyterminally truncated Abeta1–37/38/39 in addition to Abeta1–40/42 also in CSF of CJD patients.

Results: There was no significant difference between the patients groups for the three carboxyterminally truncated Abeta1–37/38/39 and for Abeta1–40. Abeta1–42 was significantly reduced in CSF of patients with AD in comparison to the NDC and the CJD group. Abeta1–42 was significantly reduced in CSF of patients with CJD, but was not as pronounced as in patients with AD.

Conclusion: We conclude that by using the urea-based Abeta-SDS-PAGE/immunoblot CJD and NDC patients can be effectively differentiated from patients with AD. We suppose that the slightly different results with regard to Abeta1–42 for the ELISA and Abeta-SDS-PAGE/immunoblot are due to differences in epitope detection and cold precipitation.

Epilepsy

P512

Effect of levetiracetam on resistant juvenile myoclonic epilepsy. T. Betts, L. Greenhill, H. Yarrow, Birmingham University Seizure Clinic (Birmingham, UK)

Introduction: Juvenile Myoclonic Epilepsy (JME) is a common syndrome of early morning myoclonic jerks, absences and tonic clonic seizures, usually treated by sodium valproate or lamotrigine. Not all patients fully respond, however, and valproate is relatively contraindicated in women of childbearing potential. Levetiracetam (LEV) is closely related to piracetam, effective in resistant myoclonias, and therefore might be effective in resistant JME: we have been studying its use in this condition in an open study in our department.

Method: The notes of 40 patients with resistant JME exposed to treatment with LEV in its usual dose escalation were reviewed for evidence of reduction in seizure frequency and drug related side effects.

Results: 60 % of these patients became, and remained, totally seizure free and some have withdrawn from concomitant medication: only 8 % had no effect at all. The drug (LEV) seems particularly effective in abolishing myoclonic jerks and concomitant photo or pattern sensitivity. A total daily dose of 4 grams seems useful in some patients: beneficial results do not fade with the passage of time.

Conclusion: This is an impressive result in a group of patients resistant to conventional treatment and suggests that a formal trial of LEV in JME is urgently required.

P513

Dramatic response to levetiracetam in patients with severe myoclonus. P. Kinirons, K. Murphy, N. Delanty, Beaumont Hospital (Dublin, IRL)

Background: Leveteracetam, an analogue of piracetam, is a new anticonvulsant licensed for use in partial epilepsy. Its mode of action is unknown but animal studies suggest it may have a broad spectrum of anticonvulsant activity. Here we describe a dramatic response to this medication in two patients with severe myoclonus of different aetiologies, one with genetically confirmed Unverricht-Lundborg disease (ULD), and the other with post-anoxic myoclonus after a near fatal drowning incident.

Methods: The first patient was a thirty two year old lady who was referred to our service with a background history of progressive myoclonic

epilepsy of unknown aetiology. At admission she had severe action and stimulus induced myoclonus necessitating a wheelchair. Several anticonvulsants had previously been tried without success. She was commenced on levetiracetam 500 mg b. i.d, increased to 1.5 mg b. i.d over two weeks.

The second patient was a nineteen-year-old man who developed severe myoclonus after a near fatal drowning incident resulting in cerebral anoxia. He was commenced on 500 mg b. i.d and increased to 1 g b. i.d after one week.

Results: Both patients showed dramatic response to levetiracetam. The first patient was able to walk with the aid of a rollator for the first time in twelve years and her speech became significantly more intelligible. Genetic testing revealed mutations in both cystatin B genes, consistent with a diagnosis of ULD (the first genetically confirmed case to be described in Ireland). The second patient also had a clinically significant response. Benefit has been sustained at follow up in both cases and neither patient experienced significant side effects.

Discussion: Levetiracetam markedly improved the clinical condition and quality of life in two patients with severe myoclonus of different aetiologies. This supports other recent case reports in the literature. We feel reports such as this are important, as individual cases are relatively rare making larger clinical trials unfeasible.

P514

Levetiracetam treatment of experimental status epilepticus. C. G. Wasterlain, A. M. Mazarati, H. Klitgaard, R. A. Baldwin, UCLA School of Medicine, UCB (Los Angeles, USA; Brussels, B)

Levetiracetam has a unique spectrum of anticonvulsant activity, a very high therapeutic index, and neuroprotective properties, and these properties make it a potentially interesting agent in the treatment of status epilepticus. Here we report its efficacy in an animal model of self-sustain8ing status epilepticus (SSSE).

We used a rat model of SSSE induced by perforant path stimulation (PPS) for 30 min. in awake animals. LEV or diazepam were injected iv 10 min. before or 10 min. after the end of PPS. Seizures and spikes were recorded continuously and analyzed by Harmonie software.

When injected before PPS, LEV (50 mg/kg) reduced total seizure time from 606 min. to 7 min., and higher doses reduced it further. Post-PPS treatment required higher doses): i. v. administration of LEV 200 mg/kg 10 min after the end of PPS attenuated SSSE cut total seizure time to 322 min., LEV 500 mg/kg reduced it to 22 min. and 1000 mg/kg to 10 min. ($p < 0.05$). Diazepam suppressed spikes immediately after administration, however, after 5 hrs a rebound was observed, while Levetiracetam irreversibly suppressed spikes. As expected, after 70 min. of stimulation and/or seizures, diazepam became less effective in treating SSSE, while LEV in doses of 500 and 1000 mg/kg continued to be effective.

Treatment of SSSE with levetiracetam, at the 40 min. time point, reduced serum neuron-specific enolase (NSE), from 26.8 ± 3 U. to 8.2 ± 2.1 U, a level which did not differ from controls (5.4 ± 0.4), suggesting a marked reduction in seizure-induced neuronal death.

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Parkinson's disease – Extrapyramidal disorders

P515

Interference of N-methyl-norsalsolinol with the metabolism of dopamine in vivo. A. Moser, K. Mende, O. Jöhren, J. Bürmann, J. Scholz, A. Thümen, Universitätsklinikum Lübeck (Lubeck, D)

Increased concentrations of N-methyl-norsalsolinol (NMNorsal) have been measured in the brain and the cerebrospinal fluid of patients with Parkinson's disease (PD). Even though NMNorsal shows structural analogy with 1-methyl–4-phenyl–1,2,3,6-tetrahydropyridine (MPTP), its involvement in the degeneration of dopminergic neurons in the substantia nigra remains to be established. In the present study, we compared the effects of NMNorsal and 6-hydroxydopamine (6-OHDA) on the metabolism of dopamine (DA) in the substantia nigra and the caudate-putamen of the rat. NMNorsal or 6-OHDA was stereotaxically injected into the left medial forebrain bundle. At 3, 7, 21 days following the injection, the concentrations of DA, its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined by high performance liquid chromatography and electrochemical detection. In situ hybridization and Western blot were used to assess the expression of tyrosine hydroxylase (TH), the key enzyme in catecholamine synthesis. In contrast to 6-OHDA, NMNorsal induced only a slight decrease of DA over the time course of 3 weeks. Increased concentrations of DA metabolites indicated an enhanced turnover of the neurotransmitter both after NMNorsal and 6-OHDA. TH expression was reduced moderately in animals injected with NMNorsal, whereas injection of 6-OHDA led to a marked decrease in TH mRNA and protein concentration. Our results demonstrate the interference of NMNorsal with the synthesis and the metabolism of DA in vivo. Consequently, NMNorsal does not represent an inert by-product of biochemical alterations in PD but rather has direct impact on DA metabolism. The extent of changes as determined in our animal model is compatible with the chronic course of PD and does not mirror the pattern of alterations seen after injection of the exogenous neurotoxin 6-OHDA.

P516

Neurophysiological study of essential tremor in children and adolescents. C. Fusco, J. Valls-Sole, C. Iturriaga, J. Colomer, E. Fernandez Alvarez, Ospedale Maggiore, Hospital Clinic, Hospital San Joan de Deu (Parma, I; Barcelona, E)

Surface electromyography and accelerometry provide the most essential information about the neurophysiological characteristics of essential tremor (ET). There are many reports on neurophysiological features in adult onset ET, but to our knowledge there are no similar investigations of ET in paediatric age. We have conducted a neurophysiological study in 9 children with definite ET, subdivided into two groups according to their age: "children group" consisted of patients from 7 y. 5 m. to 12 y. 3 m. of age, and "adolescent group" consisting of patients from 14 y. 10 m. to 16 y. 10 m. of age. With arms extended, the mean tremor frequency was 7.3 Hz (SD = 2.2 Hz), which increased to 7.6 Hz (SD = 1.6 Hz) when we added a mass of 300 grs. In the finger-to-nose condition the mean frequency was 6.8 Hz (SD = 1.6). The amplitude of tremor was 14.2 microV (SD = 8.8 microV) with upper limbs outstretched, 28.3 microV (SD = 27.7 microV) during finger-to-nose movement and 17.3 microV (SD = 23.6 microV) with added mass. In the 'children group', the peak of the mean frequency was 5.3 Hz (SD = 0.5 Hz) with upper limbs outstretched, 6.3 Hz (SD = 1.6 Hz) with finger-to-nose, and 8.2 Hz (SD = 1.5 Hz) with added mass. In the 'adolescent group', the figures were 9.0 Hz (SD = 1.4 Hz), 7.2 Hz (SD = 1.7 Hz), and 7.2 Hz (SD = 1.8 Hz), respectively. Addition of a mass caused a significant increase ($p < 0.05$) in tremor frequency in the 'children group' but not in the 'adolescent group'. Our results suggest that the central oscillators and the peripheral structures might play a different role in tremor genesis at different ages. While in adults the central oscillators are directly responsible for the genesis of ET, our data support that in children and adolescents, peripheral structures play an important role. ET and physiological tremor might be intermingled in some children.

P517

Delayed-onset Meige-Brueghel syndrome after a large vertical brain stem haemorrhage. W. Verslegers, P. De Deyn, AZ Palfijn (Antwerp, B)

Case. A 51-year old man developed a large oblong haemorrhage from the mesencephalon to the lower pontine level causing: diminished consciousness, quadriparesis +3/5 (according to the Medical Research Council), dysarthria, dysphagia, extreme dizziness, vertiginous sensations and elevated masseter reflex. Extensive internal, hemostatic, cardiac, vascular and neurological investigations revealed only increased arterial tension and cholesterol levels. Magnetic resonance imaging and CT-scan didn't revealed basal ganglia lesions.

He showed a mild neurological improvement of speech, swallowing and strength of all limbs (4/5). Especially because of limb and gait ataxia, he remained mostly bound to wheel chair.

One year later he developed progressively a complex movement disorder: involuntary cervical dystonia, blepharospasms, sudden contractions of the forehead, brusque opening and closure of the mouth, spastic dysphonia and elevation of the shoulders, high monotonic speech, protrusion of tongue and lips. Although his face was rich of dystonic contractions his visage remained poor of emotional expression.

Single fiber electromyography of facial muscles revealed no abnormalities. Cinematographic examination could record all these movements. His movement disorder became more pronounced and was resistant to all kind of treatments: benzodiazepines (even clonazepam), muscle relaxants, levodopa, baclofen, dantrolene sodium, tizanidine hydrochloride, tetrabenazine, lithium, phenytoin and phenobarbital. Blepharospasms responded to botuline toxine A, the cervical dystonic movements didn't respond to injection of 150 units in the sternocleidomastoideus, platysma and splenius.

Comment. We believe that this patient fulfilled the criteria of Meige or

Brueghel syndrome, the latter because of the similarity of the grotesque grimace to that of a subject in a Brueghel painting namely "De Gaper". We examined extensively the accepted masterpieces from the thirteenth thill the nineteenth century and found only one additional masterpiece. The similarity between our patient and the boy by El Greco ("Boy blowing on smouldering coals."-around 1573) is striking. Such comparisons between patients and painting as by El Greco and Brueghel, however, are of limited value in view of the fact that paintings seldom depict real medical pathology.

P518
Writer's cramp treated with hand immobilization. S. Badarny, T. Drori, S. Zivziner, S. Honigman, Carmel Medical Center (Haifa, IL)

Introduction: Writer's cramp is a focal occupational dystonia characterized by involuntary muscle contraction that interferes with writing as a specific motor task. Available treatments as anticholinergic drugs, benzodiazepines and anticonvulsive drugs are not efficient. Injections of botulinum toxin into involved muscles improve the writer's dystonia only partially.

Objective: To assess the efficacy of hand immobilization by a supporting plastic splint for a period of 6 weeks in patients with writer's cramp and other focal dystonia.

Methods: Motor performance and severity of dystonia were assessed in 5 patients with writer's cramp and one patient with other hand dystonia using a arm disability scale and self rating score. Patients were assessed before immobilization and one, 4, 8 and 12 weeks after removal of the splint.

Results: Over half of the patients showed significant improvement of the writing task without serious side effects. Detailed data will be presented.

Conclusion: we suggest that immobilization of the hand in patients with writer's cramp can be effective and should be considered as an alternative treatment for this type of dystonia in selected cases.

P519
Which factors influence the body image in patients with Parkinson's disease? E. A. Spottke, P. Strate, M. Reuther, O. Athen, R. Koehne-Volland, W. Schreiber, J. C. Krieg, W. H. Oertel, R. Dodel, Philipps University Marburg, Metronomia (Marburg, Munich, D)

Objectives: The first aim was to evaluate the body image of Parkinson's Disease (PD) patients. Second aim was to identify factors which have an impact on the body image.

Methods: 51 patients with PD (mean age: 67.2 ± 9.4; male:31; female:20) were included. The questionnaire of body image (Fragebogen zum Körperbild; FKB 20) has been used consisting of two subscales. The first subscale called "negative body assessment" (Ablehnende Körperbewertung; AKB) measures the appearance, body-related satisfaction and well-being. Higher scores indicate a negative body assessment. The second subscale called "vital body dynamic" (Vitale Körperdynamik; VKD) assesses the subjective impression of activity and potency of the body (10 items). Lower scores indicate a reduced vitality and activity. The Beck Depression Inventory (BDI) has been used for measuring depressive symptoms. The UPDRS II-IV was used to assess PD symptoms. Disease specific quality of life was measured by using the PD Questionnaire 39 (PDQ–39). The mean scores with standard deviation and the pearson's correlating factor were calculated.

Results: The total mean score of the AKB was 20.5 ± 6.5 according to the 60. percentile of a healthy control group and to the 30 percentile of psychiatric patients. The total score of the VKB was 23.9 ± 8.1 according to the 5 percentile of the healthy control group and to the 30 percentile of psychiatric patients. The overall score of the UPDRS II-IV correlated with the AKB (0.59 $p < 0.0001$) as well as the VKB (–0.41 $p < 0.0025$). The activities of daily living correlated with the AKB 0.53 ($p < 0.0001$) and with the VKB (–0.35 $p = 0.0097$). The motor impairment had a strong correlation with both subscales (AKB: 0.60 $p < 0.0001$, VKB:–0.42 $p = 0.0021$). No significant correlation has been found for the UPDRS IV. The PDQ–39 had a higher correlation with the AKB (0.47 $p = 0.0004$) compared to the VKB (–0.40 $p = 0.0033$). The correlation of the BDI (AKB: 0.54 < 0.0001, VKB: –0.49 $p = 0.00023$) was nearly as high as the correlation with the UPDRS III.

Discussion: In PD patients the body assessment (AKB) is comparable to a healthy population. In contrast, the vitality and dynamic score (VKB) is significantly reduced compared to healthy persons as well as psychiatric patients. Both subscales are markedly influenced by the motor impairment. The second important factor however, which impairs the body image and the vitality in PD patients seems to be the occurrence of depressive symptoms.

General Neurology

P520
Small fibre neuropathy in patients with restless legs syndrome. S. Happe, J. Zeitlhofer, University of Gottingen, University of Vienna (Gottingen, D; Vienna, A)

Introduction: The restless legs syndrome (RLS)is often associated with periodic leg movements (PLM). The pathophysiology of RLS is presently unknown. A reduction of dopaminergic activity in the central nervous system is favoured as underlying path mechanism. However, there is evidence of peripheral axonal neuropathy of the small fibers which is usually not detected under routine conditions.

Patients and methods: We assessed small fiber sensory function by psychophysical estimation of cutaneous thermal thresholds (warming, cooling, heat pain) on the lower leg using the Marstock thermostimulator method in 22 patients with idiopathic RLS and 40 healthy controls. Severity of RLS was rated with the questionnaire of the International Restless Legs Study Group (IRLSSG). Intake of RLS specific medication, pathological nerve conduction, and any severe additional neurologic, medical, and psychiatric disease were exclusion criteria.

Results: Twenty-two RLS patients (56.4 ± 13.7 years, 16 female) with moderate to severe idiopathic RLS (mean IRLSSG score 16.8 ± 3.2, range 11–21) and a mean disease duration of 16.2 ± 11.2 years were compared to 40 healthy subjects (51.6 ± 11.7 years, 20 female). 36 % of the patients had a positive family history with at least one affected first-degree relative, 59 % reported an early onset (< 45 years of age) of RLS. 32 % of the patients and 10 % of the controls showed pathological values in at least one of the three thermal thresholds ($p = 0.04$). Thresholds for coldness were significantly reduced ($p = 0.035$). Thresholds for warmth and pain were slightly but not significantly increased in patients with RLS as compared with the control group ($p = 0.096$ and $p = 0.086$, respectively). There was no significant association of severity and duration of RLS as well as age of onset with thermal thresholds. Cold thresholds were significantly lower ($p = 0.038$) and warm thresholds were significantly higher ($p = 0.038$) in patients with a negative family history.

Conclusion: A subgroup of patients with idiopathic RLS might have a neuropathic disorder which affects only those unmyelinated fibers involved in the perception of temperature and pain. Since patients without a family history showed significantly more abnormal values of thermal thresholds we agree to the suggestion that there are two different etiologic subtypes of idiopathic RLS, regardless on age of onset one familial type without neuropathy and one sporadic type with small fiber neuropathy.

P521
Function of the OPG/RANKL cytokine complex system – on the basis of an Albers-Schonberg disease case report. J. Domanski, J. Opalko-Barcinska, Bielanski Hospital (Warszawa, PL)

Osteopetrosis (OST) is a rare genetic disorder in which the function of osteoclasts is defective resulting in impaired bone resorption.Autosomal dominant OST(ADO t II)-also known as Albers Schonberg disease is characterised by sclerosis predominantly involving the scull base, spine,cranial deformation and secondary impaired nervous system,especially cranial nerves,increased intracranial pressure(ICP) and even cerebral arterial disturbances (occlussion)At the same timein osteopetrotic (op/op) mice cranial deformation is produced by a deficiency of osteoclasts and a subseqent defect of bone resorption.By linkage analysis the presence on chromosome 1p21 and 16p13.3,of a gene causing ADO tII is suggested. Numerous growth factors and cytokines are known to modulate bone turnover. Although multiple hormones and cytokines regulate various aspects of osteoclast formation, there was recently discovered an important-involved in osteoclastogenesis – the osteoprotegerin/osteoprotegerin-ligand (OPG/OPGL/RANKL/) cytokine complex-which is produced by osteoblasts.RANKL (receptor activator of nuclear factor kappaB ligand)is an essential factor for osteoclast formation by cells. The activity of RANKL appears to be a balance between interaction with its receptor RANK and its antagonist binding protein OPG.OPG is a naturally secreted protein that decreases bone resorption by inhibiting osteoclast differentiation and activation while promoting osteoclast apoptosis.Excess OPGL increases bone resorption, whereas excess OPG inhibits resorption. The authors described 37- year- old male patient with ADO t II-confirmed by CT scan (revealed large skull sclerotic hypertrophy with narrowing of all foramina with venticular dilatation) – and cerebellar syndrome and cranial nerves pulsy.

Conclusions: Recent evidence for the role of tumor necrosis family members in the coupling of cellular function during skeletal homeostasis suggests that these may also be involved in the regulation of skeletal repair.

The identification of the OPG/RANKL/RANK system as the dominant, final mediator of osteoclastogenesis represents a major advance in bone biology. Pathophysiological associations and therapeutic applications of cytokines in cranial nerves decompression or influence on ICP changes were discussed.

P522

Acute disseminated encephalomyelitis treated by intra venous immunoglobulins – Two reported cases. N. Chausson, S. Stefanizzi, A. Ameri, N. Mamane, N. Woets, F. Chédru, Hôpital de Meaux (Meaux, F)

Acute disseminated encephalomyelitis (ADEM) is a presumed immune-mediated demyelinating disease of the central nervous system (CNS) which is usually treated by high dose intravenous corticosteroids. Recent reports indicate that Intra Venous Immuno Globulins (IVIG) is another valuable therapeutic modality. We describe 2 patients (a 35 year old woman, a 38 year old man) with rapidly progressing ADEM in whom Magnetic Resonance Imagery (MRI) showed massive asymmetrical white matter lesions of both hemisphere. There was no response from a 3 days course of high dose intravenous methylprednisolone: neurological conditions were deteriorating (including major consciousness disturbances) and extensive MRI changes were noted. The patients were treated with IVIG (400 mg/kg/day during 5 days). Both patients dramatically recovered within 3–6 weeks. With the exception of mild neuropsychological signs, they return to their previous conditions and resume their work. This good outcome suggests that IVIG could be proposed as a first line therapy.

P523

Diffuse aseptic arachnoïditis following epidural anaesthesia. F. Klapczynski, T. Faillot, P. Oubary, A. Malka, A. Ameri, F. Chédru, Centre Hospitalier de Meaux (Meaux, F)

Serious neurological deficits related to lumbar epidural anaesthesia are exceptional. We report the clinical and neuroradiological features of a diffuse arachnoiditis and its evolution after surgical treatment. A previously healthy 24 year-old woman had a vaginal delivery under epidural anaesthesia. After she received 10 ml of a 0,25 % bupicaine solution (added to 10 microgramms fentanyl), paresthesiae extending to the trunck and the upper limbs were noted which resolved over a few hours period. Two months later, the patient progressively developed bilateral weakness and numbness of the legs with sphincter dysfunction. Neurological examination showed a pyramidal syndrome and a somato-sensory deficit with a T6 upper limit. A Magnetic Resonance Imaging showed multiple intraspinal cysts, with an irregular septate aspect, compressing the thoracic and lumbar spinal cord. The cord was thin and irregular. Surgical treatment consisted of T6–8 laminectomy and wide opening of the subarachnoid cysts compressing the spinal cord. Pathological examination of the cyst walls revealed fibrosis. Bacterial examination of intra-cystic fluid was negative. Neurological function markedly improved after surgery and remains stable until now (3 months follow-up) with oral corticotherapy. Spinal cord arachnoiditis may occur as a delayed complication of epidural anaesthesia or introduction of other drugs into the subarachnoid space. In the present case, arachnoïditis can be considered as an adverse reaction to the anaesthetic drugs (and/or their preservatives) that had entered the subarachnoïd (or the epiarachnoïd) space. The outcome reported in the literature is poor, from progressive spastic paraparesis to being wheel-chair bound. Very few cases were reported with surgical treatment, and even if some improvement occurs, follow-up is necessary to detect delayed recurrence.

P524

The use of "screening dysarthria test" for detection of dysarthria types in various neurological diseases. B. Tomik, I. Gatkowska, M. Tutaj, A. Pichor, M. Bala-Slodowska, M. Kusiak, M. Rudzinska, Z. Tarkowski, A. Szczudlik, Orator Foundation (Cracow, Lublin, PL)

Background: The assessment of dysarthria types in the neurological clinical examination is difficult. There is a need for a simple method designed to better detect dysarthria in clinical practice. The current study proposes the simple screening test for detection and characterising the dysarthria features in different neurological diseases.

Material and methods: The study was performed in 78 dysarthric patients diagnosed with amyotrophic lateral sclerosis (n = 28), extrapyramidal disorders (19), cerebellar disorders (11), multisystem atrophy (6), multiple sclerosis (7), neuropathy (4) and myasthenia gravis (3) in the Department of Neurology in Cracow 2000–2001 yr. The presence of dysarthria and its characteristic were assessed by means of a semiquantitative method, as is "screening dysarthria test" (SDT). The SDT is based on short -time assessment of four dysarthria features as: respiratory control, articulation, phonation and prosody during the spontaneous speech, loud counting, reading and singing. The results were scored in 4-points scale and compared with results of Robertson's Dysarthria Profile Test (DPT) and clinical sings.

Results: Mild shortening of respiratory cycle (92.9 %), disturbances of phonation (92.9 %), articulation (71.4 %) and well preserved prosody occurred in patients with spastic dysarthria (14 out of 78 patients). Pronounced shortening of respiratory cycle (70.6 %), abnormalities of phonation (58.8 %) and articulation (47 %) were typical for patients with flaccid dysarthria (17/78). Dysprosody (86.7 %) occurred predominantly in patients with ataxic dysarthria (15/78), although slight disturbances of respiratory cycle, articulation and phonation were observed. The abnormalities of phonation (86.7 %) and dysprosody (80 %) were dominant in patients with hipokinetic dysarthria (15/78), loss of respiratory control and small changes in articulation also occurred in these patients. The significant loss of respiratory control (100 %) and dysprosody (75 %) occurred in patients with hieprkinetic dysarthria (4/78) while phonation was merely preserved. All of dysarthria features measured were abnormal in patients with mixed dysarthria (13/78), though, loss of respiratory control (92.3 %) and abnormal articulation (76.9 %) were dominant. The details of these results will be presented.

Conclusion: Our results demonstrate the practical usefulness of SDT in detection and classification of dysarthria types which occur in different neurological diseases.

P525

Lhermitte-Duclos disease and multiple cutaneous lesions. A possible new phakomatosis. A. Verdelho, C. Morgado, A. Lima, J. Pimentel, Hospital Santa Maria (Lisbon, P)

Background and purpose: Lhermitte-Duclos disease (LDD) is a rare lesion of the cerebellum, considered to be hamartomatous in origin. Cowden syndrome (CS) is a rare autosomal dominant disorder characterised by mucocutaneous lesions, systemic hamartomas and high incidence of several malignancies. The description of LDD associated with CS suggests that these two entities could be part of the same disease. We present a patient with LDD and multiple cutaneous lesions not fulfilling clinical criteria of CS.

Case report: A 38-year-old male, with multiple skin lesions since the age of fifteen (sebaceous cysts, sclerotic fibroma and viral papilloma diagnosed after several surgeries) and familiar history of skin lesions was admitted in our hospital with intracranial hypertensive syndrome and macrocephaly. A cerebral MRI showed a non-enhancing cerebellar mass suggesting LDD. Surgery was performed with total gross resection of the lesion and pathological examination confirmed the diagnosis. During the two-year follow-up period multinodular goiter was diagnosed, with no further complications, and no recurrence from the cerebellar lesion. Clinical criteria of CS were not present.

Discussion: Reported cases of patients with LDD and CS are relevant as they allow early search and detection of cancer in patients with LDD. The presence of LDD and multiple skin lesions in this patient suggests a neurocutaneous disease (other than Cowden disease). This fact is relevant as the possible association with other benign and malign lesions can have clinical implications in the management of those patients.

P526

Description of a case of meningeal granulomatosis as unique expression of Wegener's disease. P. Sola, J. Mandrioli, G. Ficarra, L. Mavilla, A. Zanasi, C. Manzini, P. Nichelli, Università di Modena (Modena, I)

Wegener's granulomatosis is a systemic vasculitis, characterized in the classical form by the involvement of the respiratory tract and the kidneys Wegener's granulomatosis (WG). Ophthalmic and neurological involvement are common (22 % and 54 % respectively). Regarding to the nervous system, the commonest finding is peripheral neuropathy, commonly as multiple mononeuritis. Meningeal involvement in WG is exceptional: we describe a case of meningeal granulomatosis as unique expression of the disease.

A 53-year-old man was admitted to the Neurological Clinic of the university of Modena on October 2001, for a five days history of diplopia and frontal cephalalgia, with abrupt onset.

When he was 23 years old, a Hodgkin's lymphoma was diagnosed, and successfully treated without any relapse. In 1999 he was admitted because of a spontaneous D1 spinal hematoma, in absence od neuroradiologically documented vascular malformations, with complete recovery.

On examination, a left sixth cranial nerve palsy was found, in absence of other neurological signs. All metabolic or vascular cause of mononeuritis were excluded with proper tests. Brain, cervical and dorsal MRI revealed diffuse thickening and enhancement of the dura mater, consistent with hypertrophic pachymeningitis, and a nodular granulomatous lesion near the left pons. Erythrocyte sedimentation rate and serum C-reactive protein were mildly increased, as well as other unspecific inflammatory markers. Serum angiotensin converting enzyme and the test for cytoplasmic antineutrophil cytoplasmic antibody were in the normal range. Cerebrospinal fluid (CSF) analysis revealed only mildly increased total proteins, and mild mononuclear pleocytosis (12 lymphocytes/mmc). All viral, retroviral, bacterial and fungal investigations were negative both in the blood and CSF.

Dural biopsy was performed and histopathological examination showed unspecific arachnoid nests with whirling aspect. After a two week therapy of 50 mg/daily prednisolone, the patient's conditions recovered, the diplopia disappeared and erythrocyte sedimentation rate and serum C-reactive protein were in the normal range.

After one month brain MRI was repeated, showing the disappearance of the granuloma near the left pons and a slight reduction of the hypertrophic pachymeningitis.

It has been hypothesized that the previous spinal hematoma was caused by vasculitis in course of WG.

P527

Idiopathic intracranial hypertension: diagnosis and management. E.-S. M. Tag El-Din, M. S. A. Moussa, M. El-Mahallawy, Tanta University (Tanta, EGY)

Idiopathic intracranial hypertension (IIH) or pseudotumour cerebri, is a syndrome characterized by; an elevated intracranial pressure (intracranial pressure more than 200 mm H2O), in the absence of a focal lesion or infective process, normal or small ventricles and normal cerebrospinal fluid (CSF) composition. The aim of this work is to evaluate and properly treat either medically or surgically the patients diagnosed as having IIH. Thirty patients with IIH were included in this study, collected according to Dandy criteria. Magnetic resonance imaging (MRI) of the orbit and brain was done for all cases. The MR imaging disclosed flattening of the posterior sclera in 70 %, distension of the perioptic subarachnoid space in 50 % of the patients, vertical tortuosity of the orbital optic nerve in 30 %, intraocular protrusion of the prelaminar optic nerve in 26.6 % and empty sella in 20 % of the patients. Regarding the therapy, it was found that 18 cases (60 %) of the 30 patients improved by medical treatment in the form of Prednisone, acetazolamide and removal of 25 ml of cerebrospinal fluid. During follow up of the cases, two (6.6 %) of 18 cases suffered from recurrence of symptoms and signs. Finally 14 cases out of the 30 cases were candidate for lumbo-peritoneal shunting. Follow up of cases with medical treatment for 2 years revealed no evidence of recurrence or deterioration except for one case with chronic papilledema, which ended up with optic atrophy inspite of surgical treatment for this case. we can conclude that elevated intracranial pressure produces a constellation of MR imaging signs that can assist in establishing the diagnosis of IIH in 90 % of cases.

We propose to perform lumboperitoneal shunt if medical treatment failed at the first onset of IIH or in case of severe visual loss or recurrence.

Neurogenetics

P528

Hereditary cerebral and cutaneous cavernous angiomas are caused by mutation in the gene CCM1 encoding KRIT1 at the chromosome 7q21: Analysis of a Spanish family. A. Pou-Serradell, Hospital Universitari del Mar (Barcelona, E)

Cerebral capillary malformations (CCM), also known as cerebral cavernomas, are vascular malformations of the brain. These malformations are usually multiple which tend to grow in size and often show familiar aggregation and genetic linkage has been established to three chromosome loci, 7q21 (CCM1), 7q13 (CCM2) and 3q25 (CCM3). CCM1 mutations are not restricted to cerebral vasculature but can also cause cutaneous cavernomas.

We studied longitudinally five members belonging to one large Spanish family with cerebral cavernous malformations and cutaneous cavernomas inherited in a dominant form and which genetic analysis has demonstrated a 7q11.2-q21/KRIT1 mutation with probable loss of function of this protein. We report here the most relevant features of the disease in those members in whom the clinical status has been controlled for many years, till the death of two of the patients. All the members affected presented multiple encephalic cavernomas preferably located at the protuberantial, thalamic and left subcortical levels. Two brothers died, at 39 and 37 years of age respectively. The death was related to the growth effect of the brainstem and thalamic cavernomas (operated one of them). A third brother overcame a locked-in syndrome related to a bleeding cavernoma being at present rather good. Finally, the mother and an aunt of these brothers are old aged women whose brain MRI have shown plenty of asymptomatic cerebral cavernous angiomas. All these patients presented skin lesions consistent of more or less convoluted dermal capillary-size channels which histological aspects are similar to those proceeding from the neurosurgical intervention.

Identification of mutations in CCM1 gene encoding KRIT1 (Krev–1 interaction Trapped 1) has provided the first clue to the molecular mechanisms causing CCM1.

P529

Spontaneous cervical artery dissection – Exclusion mapping as an approach to elucidate the underlying connective tissue disorder. U. Müller, I. Hausser, B. Moormann, O. Busse, A. Grau, T. Brandt, C. Grond-Ginsbach, University of Heidelberg, City Hospital Minden (Heidelberg, Minden, D)

Background and purpose: Spontaneous cervical artery dissection (sCAD) is an important cause for ischemic stroke in young adults. An underlying arteriopathy presumably related to an extracellular matrix defect is often suggested. Moreover the observed ultrastructural dermal connective tissue abnormalities in sCAD patients are inherited in some families.

Material and Methods: Skin biopsy studies followed by independent linkage analysis and in two families with at least one family member affected by sCAD were performed. SCAD's in patients were confirmed by MRI, angiography and/or Doppler sonography. Neither patients nor relatives showed skin, joint and/or skeletal abnormalities characteristic of a known hereditary connective tissue disease.

Results: We observed ultrastructural dermal alterations in skin biopsies of both index patients and six out of ten first and second degree relatives, comparable to those found in patients suffering from Ehlers-Danlos Syndrome type III (EDS III).

Hence the alterated morphologic pattern is considered an electron microscopic phenotype for carriers of a mutated gene. In a genetic linkage analysis we excluded 50 obvious candidate genes encoding for extracellular matrix components with LOD scores < -2. This LOD value is accepted as a sufficient exclusion criterion assuming a monogenic trait with complete penetrance and no phenocopies.

Conclusions: Even though exclusion of these candidate genes is still restricted to the two families there is strong evidence that none of the classical candidate genes are responsible for the underlying connective tissue alterations and therefore for the arteriopathy. Taken this into consideration, future linkage analysis in larger families and "genome wide" searches for candidate genes may enlighten the etiopathology of a possible heterogeneous disease.

P530

A novel mtDNA tRNA-tryptophan mutation in a severe neurodegenerative disorder with progressive ataxia, dementia and axonal neuropathy. M. Crimi, S. Galbiati, A. Bordoni, M. P. Perini, M. Monferini, M. Sciacco, I. Bianno, G. Ferrari, M. Moggio, G. Scarlato, G. P. Comi, Università degli Studi di Milano, ITBA, Ospedale di Ivrea (Milan, Ivrea, I)

An enlarging number of mitochondrial DNA (mtDNA) point mutations have been associated with extremely different phenotypes. Here we present evidence for the causative role of a novel tRNA Tryptophan (Trp) mutation in a female patient affected with a sporadic neurodegenerative disorder. We identified a G to A transition at position 5,540 of mitochondrial tRNA-Trp in association with progressive ataxia, mental deterioration and axonal neuropathy. The proband was born from non-consanguineous healthy parents. She was the only affected child: her four brothers remain healthy well beyond the age of proband's death. She presented since age 6 years progressive bilateral hearing loss and few years later recurrent muscle cramps. Since age 30 years, she developed progressive cognitive impairment, dysarthria, dysphagia and severe difficulties in walking with worsening ataxia and incoordination. Examination of cognitive functions, which were clearly impaired, was extremely difficult because of hypoacusia and dysarthria. She presented severe lactic acidosis and mild glucose intolerance. At age 35 years she presented progressive cachexia with severe muscle wasting. EMG showed distal axonal mainly sensitive polyneuropathy. EEG revealed bilateral generalized irritative discharges. MRI of brain showed a severe diffuse cerebral and cerebellar atrophy; focal areas of altered signals were present both in supra- and infratentorial white matter

and in basal ganglia and occipital cortex. At age 40 years, muscle biopsy showed some ragged-red fibers. The histochemical reaction for cytochrome c oxidase (COX) was absent in numerous fibers. She died at age 43 years for bronchopneumonia.

Southern blot analysis of muscle-derived DNA and the most common mtDNA point mutations were negative. By sequencing the entire mtDNA, we detected a G to A transition at position 5,540: this substitution is almost homoplasmic in the muscle and heteroplasmic in the blood (39%). The mutation was absent in the blood-derived DNA of her healthy sister, as well as in 41 control samples. Single muscle fibre analysis demonstrated segregation of higher percentages of mutated genomes in COX-negative RRF compared with COX-normal fibers. The identified mutation affects a conservative mtDNA position and is likely to impair the tRNA-Trp anticodon stem secondary structure. The association of this de-novo mtDNA mutation with a severe neurogenerative disorder awaits confirmation form other cases.

P531

The first maternally-inherited mutation of mitochondrial tRNA-His gene results in retinitis pigmentosa and neuro-sensorial hypoacusia. M. Crimi, S. Galbiati, A. Bordoni, S. Strazzer, G. Malferrari, M. Sciacco, I. Biunno, F. Tiberio, N. Bresolin, G. Scarlato, G. P. Comi, Università degli Studi di Milano, ITBA (Milan, I)

We identified a new heteroplasmic mutation at mitochondrial DNA (mtDNA) nucleotide 12,183 in the tRNA Histidine (His) gene, in three subjects sharing different degrees of visual, neurosensorial and muscle impairment. The different clinical phenotypes seems to correlate with the level of heteroplasmy for this new mutation.

The proband is a 30-year-old male patient: the patient was born after uncomplicated pregnancy and delivery to healthy nonconsanguineous parents. At age 7 years subacute bilateral visual loss and cataract in both eyes was noticed. Since age 11 years he developed progressive bilateral hearing loss. Dysarthria, retinitis pigmentosa, proximal muscle weakness with hypotonia and diffuse muscle hypotrophy were observed at age 20 years. He also presented short stature and hypogonadism. The cognitive function was normal. The proband's mother had retinitis pigmentosa and developed at age 41 years bilateral cataract. An older sister was affected since the age of 7 years with neurosensorial hypoacusia and since 23 years with progressive visual due to retinitis pigmentosa. Another brother died immediately after birth.

The proband's laboratory tests showed lactic acidosis and decreased levels of testosterone with normal Luteinizing and Follicle-Stimulating Hormone. The EMG showed mild myopathic features. Seum CK level was normal. The EEG was dysrithmic with diffuse irritative activity. Brain MRI showed bilateral paramagnetic signals in the caudate and thalamic nuclei and a mild vermis atrophy.

Muscle biopsy revealed numerous COX negative fibers by histochemistry. Southern blot analysis of muscle-derived DNA and the most common mtDNA point mutations were negative. Sequence analysis of the mitochondrial genome revealed a G to A transition at position 12,183 in the tRNA-His: this substitution was almost homoplasmic in the muscle and heteroplasmic in the blood (47.3%) of the proband, was present in the sister's (degree of heteroplasmy: 24.8%) and mother's (13.2%) blood DNA, but was absent in 41 healthy controls.

The mutated site is conserved among higher and lower species during evolution and is located in the tRNA variable Loop, therefore leading to uncorrect tRNA structure's formation. This is the first pathogenic, maternally-inherited mutation involving the mitochondrial tRNA-His gene.

P532

Carpal tunnel syndrome in three generations of a German family. M. Elstner, T. Gasser, T. Meitinger, T. Klopstock, Klinikum Grosshadern, GSF/Technical University Munich (Munich, D)

Carpal tunnel syndrome (CTS) is a frequent and usually sporadic disorder. Inherited CTS may be the manifestation of a systemic disease (e. g., mucopolysaccharidosis, amyloid neuropathy) or of a disorder of peripheral myelin (e. g., Charcot-Marie-Tooth disease type 1A, hereditary neuropathy with liability to pressure palsies). Isolated familial CTS (FCTS) is a rare autosomal dominant disorder with a hitherto unknown gene locus. We report on a pedigree of three generations in which seven individuals had clinical symptoms of CTS, five of whom required uni- or bilateral CTS surgery. Two more family members had delayed median motor latency without clinical symptoms. All affected subjects were female and the onset of symptoms was between thirty and fifty years of age. Duplications and deletions in the peripheral myelin protein 22 gene were excluded as well as mutations in the transthyretin gene. This is one of the largest FCTS pedigrees reported to date. Linkage analysis, however, is hampered by the so far insufficient number of affected individuals and by the high prevalence of CTS in the general population.

P533

Polymorphisms of the angiotensin converting enzyme, endothelial nitric oxide synthase and interleukin–6 genes in the lacunar stroke. M. Revilla, V. Obach, A. Cervera, A. Chamorro, Hospital Clínic Provincial (Barcelona, E)

Background and objective: we compared the prevalence of I/D angiotensin converting enzyme (ACE), glu298asp endothelial nitric oxide synthase (eNOS) and –174G/C interleukin–6 (IL–6) polymorphisms in a well defined population of lacunar stroke and an age- and sex- matched cohort of asymptomatic controls.

Method: eighty-two patients with lacunar stroke and 82 asymptomatic controls of the same European white ancestry and geographical area were prospectively assessed and genotyped for the ACE, glu298asp eNOS and –174G/C IL–6 polymorphisms. Demographics and vascular risk factors were recorded in both groups.

Results: we found no significant differences in ACE and glu298asp eNOS polymorphism distribution. When we analyzed –174G/C IL–6 polymorphism, the prevalence of CC genotype (18.3% Vs 7.3%, $p < 0.03$), and the frequency of C allele (42.7% Vs 31.1%, $p < 0.03$) were significantly higher in patients than in controls. A logistic regression model showed that independent variables associated with lacunar stroke included history of hypertension (OR 7.02, 95% CI 3.11–15.81), diabetes (OR 5.37, 95% CI 1.52–18.89), hyperlipidemia (OR 3.43, 95% CI 1.04–11.25), smoking (OR 5.84, 95% CI 2.15–15.84), and CC genotype of –174G/C IL–6 gene (OR 4.28, 95% CI 1.22–15.00).

Discussion: these findings suggest that lacunar stroke might result from genetic susceptibility to inflammation-mediated damage in concert with atherosclerotic risk factors.

P534

Two novel mutations in the myophosphorylase gene in a patient with McArdle disease. M. Deschauer, K. Hertel, S. Zierz, University Halle-Wittenberg (Halle/Saale, D)

Defects of the muscle-specific isoform of glycogen phosphorylase cause a metabolic myopathy that is called McArdle disease (glycogenosis type V). This glycogen storage disease is inherited in an autosomal recessive trait. We performed molecular genetic analysis in a 33-year-old women with McArdle disease. The patient has complained of exertional fatigue with muscle cramps since childhood but never had myoglobinuria or "second-wind-phenomenon". Neurological examination revealed a mild proximal limb weakness and a mild weakness of the neck muscles. Ischemic forearm work test showed no rise in venous lactate, but a normal increase in ammonia. Muscle biopsy showed accumulation of glycogen and histochemical analysis absence of glycogen phosphorylase activity. Biochemical analysis of the muscle homogenate revealed no detectable activity of myophosphorylase. The presence of the common R49X mutation was excluded by restriction fragment length polymorphism. In Europe this mutation is found in 32% to 81% of the alleles of patients with McArdle disease. By direct sequencing of the myophosphorylase gene two novel mutations were identified. The patient was compound heterozygous for a nonsense mutation at codon 84 changing tyrosine to stop codon (Y84X) and for a missense mutation at codon 93 changing arginine to tryptophan (R93W). To our knowledge these mutations are the first described in exon 2 and they expand the genetic heterogeneity in patients with McArdle disease. Genotype-phenotype correlation in McArdle disease remains enigmatic. The phenotype of our patient does not differ form patients with the common R49X mutation.

P535

Study of five large autosomal-dominant parkinsonian families originating from Southern Poland. A. Krygowska-Wajs, Y. Tsuboi, R. J. Uitti, M. J. Farrer, Z. K. Wszolek, Jagiellonian University, Mayo Clinic (Krakow, PL; Jacksonville, USA)

Objective: To report clinical data on five parkinsonian families (PL-Krakow 1–5) originating from a small geographical region in Southern Poland and molecular genetic data related to known parkinsonian loci/mutations.

Background: Studies of familial Parkinson ± fs disease (PD) have led to the identification of several mutations and loci. There are still another

group of parkinsonian kindreds whose genetic characteristics are unknown.

Design/Methods: Systematic prospective genealogical, clinical and molecular genetic studies of 5 large Polish families have been carried out. Examination of affected (n = 18) and at risk (n = 117) individuals were performed. Using DNA from 15 affected persons, presently sampled and given a common founder for disease, power analysis suggests an 1 % probability of identifing significant linkage (LOD > 3.0).

Results: Family members from all five families reside in small geographical region in southern Poland. PL-Krakow 1 contains 77 family members with 9 affected individuals. PL- Krakow 2 contains 47 family members with 6 affected individuals. PL-Krakow 3 contains 14 family members with 2 affected individuals. PL- Krakow 4 contains 72 members with 5 affected individuals. PL-Krakow 5 contains 11 family members with two affected individuals and one 21- year-old individual with postural and resting tremors. All affected family members present the cardinal symptoms of PD. Resting tremor is usually an initial sign. There is a good response to levodopa therapy with the occurrence of long-term levodopa complications. Mean age of symptomatic onset for PL-Krakow 1 is 53 (range: 45–65), PL-Krakow 2 is 54 (range: 37–73), PL-Krakow 3 is 43 (range: 29–58), PL-Krakow 4 is 53 (range: 47–60) and for PL-Krakow 5 is 50 (range: 43–58). Molecular genetic studies demonstrated negative linkage to known parkinsonian loci/mutations in families PL-Krakow 1–2. This negative data and the preliminary results from a full genome search are presented.

Conclusions: Large, multiply affected families from homogeneous isolates are powerful method to map new genes and mutations in PD. These families are the first to report inherited parkinsonism in Polish population. Negative data to date on known genetic risk factors confirm parkinsonism is genetically heterogeneous. However, it is evident that novel loci/mutations associated with a phenotype commonly seen in sporadic cases of PD will be identified using and extended family-based approach in the near future.

P536

X-linked recessive bulbo-spinal muscula atrophy (Kennedy's syndrome): a report of five cases. P. Banfi, E. Vitelli, L. Faggi, Ospedale Maggiore Lodi (Lodi, I)

Patients- Five cases of bulbo-spinal muscular atrophy are reported; three of them are familar and two are single cases with no similar male affected relatives. Methods – The patients underwent routine blood examination with creatine chinase (CPK) and sexual hormones assay; electromyography (EMG) was performed in different muscles (mentalis, deltoideus, biceps brachii, interosseus dorsalis, psoas); motor nerve conduction velocity (MNCV) was measured in the peroneal, tibial, ulnar and median nerve and sensory nerve conduction velocity (SNCV)in the sural, ulnar and median nerve; somatosensory evoked potentials (SEPs) were obtained from stimulation of the tibial nerve; cerebrospinal fluid (CSF) examination and muscular biopsy were performed in one case. Molecular genetic test was performed by polymerase chain reaction (PCR) amplification of the CAG repeat region within the androgen receptor (AR) gene (Xq11-Xq12). Results – The main age at observation was from the fifth to the sixth decades of life; prominent features were weakness and fasciculations of facial muscles and tongue; muscle weakness in the limbs was mainly proximal with wasting of distal muscles in upper limbs; dysphonia and dysphagia were reported in two cases; tendon reflexes were absent. Four patients presented gynecomastia; in two cases elevated levels of circulating folliculus stimulating hormone were found; CPK was slightly elevated in all cases. EMG showed the features of denervation even in clinically unaffected muscles. MNCVs were normal and in all cases we observed small or unrecordable sensory action potentials. P36 in the cortical SEPs was undetectable in 2 cases and prolonged in 3; lumbar SEPs couldn't be recordered. Muscular byopsy was neurogenic and CSF examination was normal. Molecular genetic test confirmed in all cases the expansion of the CAG trinucleotide (> 35 CAGs) in the AR gene. Conclusions- The clinical features of Kennedy's disease are distintive; a striking feature is the presence of facial fasciculations and wasting and fasciculation of the tongue preceding the onset of bulbar symptoms. The neurophysiological features are consistent with a neuronopathy indicating the involvement of the lower motor neurons and the primary sensory neurons. Our pedigree is consistent with a recessive X-linked inheritance; single cases are likely to occur in any X-linked recessive disorder and must be described, the recognition of such patients being important for genetic information.

P537

Identification of a novel mutation in a patient with acute intermittent porphyria characterized by late onset of severe neurological symptoms. G. Wekerle-ten Bruggencate, L. von Brasch, P. E. Petrides, K. Jacob, H. Brueckmann, C. Siebold, T. Klopstock, Juedisches Krankenhaus, Internistische Praxis, Klinikum Grosshadern (Berlin, Munich, D)

We report the case of a 46 year old female patient who was admitted after having suffered two generalized epileptic seizures. A few days prior to admission, she had complained about nausea and mild abdominal pain. Within the next days, she developed oculomotor signs, visual field defects, severe dysfunction of the autonomic nervous system and subacute predominantly motor neuropathy with general muscle weakness leading to tetraplegia. MRI of the brain revealed multiple lesions in both occipitoparietal regions, MR angiography demonstrated irregular beading appearance of the large brain vessels and transcranial doppler study showed increased flow, both suggesting CNS vasculitis. EMG revealed severe axonal damage. CSF was normal. Levels of urinary aminolevulinic acid and porphobilinogen were massively elevated. Apart from chronic constipation, this patient had never suffered any serious health problems. There was no family history for porphyria.

Mutation analysis by PCR-DGGE (denaturing gradient gel electrophoresis) revealed a novel T to C mutation in the porphobilinogen deaminase (PBG-D) gene (33+2 T to C). This is another exon 1 splicing defect typical for acute intermittent porphyria (AIP). Using this technique, more than 120 mutations have been identified in the PBG-D gene.

AIP is the most common dominantly inherited disease of porphyrin metabolism. Acute porphyria attacks can occur in gene carriers when the biosynthesis of heme is increased by drugs, low calorie intake, alcohol consumption or infections. Under these conditions, PBG-D cannot convert the precursors adequately so that porphobilinogen and delta-aminolevulinate accumulate. This may lead to neurovisceral symptoms and neurological complications which are potentially life threatening as seen in this patient. Mutation analysis by PCR-DGGE is becoming increasingly important since it also permits rapid identification of their presymptomatic relatives. When identified, the family members are informed about their genetic predisposition and are taught how to prevent porphyric attacks.

P537a

Estimation of penetrance in transthyretin (TTR) related familial amyloid neuropathies (FAP) of French and Portuguese origin. V. Planté-Bordeneuve, A. Fereira, C. Bonaiti-Pellie, M. Misrahi, D. Adams, G. Said, CHU Bicêtre (Paris, F)

Transthyretin amyloid neuropathies are autosomal dominant devastating affections reported mainly in Portugal, Sweden, Japan and occasionally in France. The Val30Met is the only pathogenic variant identified in Portugal and Sweden whereas TTR-mutations are heterogenous in Japan and in France. Depending on the geographic origin, the average age of onset (AO) ranges from the 3rd to the 6th decade. The disease duration seldom exceeds 10 years and, so far, liver transplantation is the sole promising treatment. Predictive molecular diagnosis became recently accessible in at risk relatives of families. It requires precise genetic epidemiological information to support genetic counselling. Based on segregation analysis, penetrance of FAP is incomplete, but might differ in the different foci. The purpose of this study was to calculate the penetrance in Portuguese and French FAP using a method derived of Kaplan-Meier corrected for ascertainment bias.

Methods: 81 unrelated kindreds were studied, including 34 of Portuguese and 47 of French ancestries. For subjects older than 16 years, date of birth and death, if appropriate were collected. For patients, FAP history was recalled with special attention to the AO. The Val30Met was previously searched in several Portuguese individuals as part of presymptomatic tests. In French kindreds, genotyping was performed on DNA of consenting at risk members over 18 years of age, following a protocol approved by the local ethic committee. Penetrance was calculated, in each population, as a cumulative risk of being affected in a gene carrier. The risk was estimated in age classes defined from 16 to 80 y-o. A carrier probability of " or , was attributed to non genotyped subjects according to their relationships with the patients. Index cases were excluded to account for selection of families through an affected individual.

Results: 319 individuals of the Portuguese families were assessed. Of them, 119 had the Val30Met, including 92 affected cases, with a good estimation of their AO. The penetrance at 25, 35, 50 and 80 years was respectively 13.4 %, 48.7 %, 58.1 % and 71.1 % in men and 2.2 %, 33.3 %, 63 % and 74.6 % in women. In the French kindreds, 464 individuals were included. Of them, 156 had a pathogenic TTR variant including 71 patients with available data on AO. The penetrance rate at 35, 50 and 80 years was respectively, 9.9 %, 27.1 %, 70.7 % in men and 1.7 %, 19.3 %, 59.5 % in women.

In both samples, it was significantly higher in men in the first class of age ($p < 0.01$).

Conclusions: The penetrance is actually incomplete in Portuguese and French FAP with lower values in the latter. In both populations, we observed a trends towards a higher penetrance in men, of unclear significance. Such data are of importance in the management of at risk members of families and to adjust the indication of liver transplantation, accordingly.

Multiple sclerosis

P538

Geography-based hypotheses on multiple sclerosis. G. Iuliano, Ospedali Riuniti di Salerno (Salerno, I)

Introduction: After the latitude assessments by Kurtzke, most of the studies on geographic distribution of multiple sclerosis (MS) seem to appreciate better genetic and infectious variables. A few papers are dedicated to what is commonly called "pollution", either atmospheric or in the soil, and in particular with pH of the soil.

Methods: There are available very good recent reviews about worldwide prevalence of Multiple Sclerosis (MS). We correlate 213 worldwide prevalence data about MS with a series of variables, divided in geographical (latitude, hemisphere, continent, nation) economic (life expectance for male and female, childhood mortality, Gross Domestic Product (GDP); energetic consume) and environmental (climate, urbanization, acid rains, water pollution, desertification, CO2 emissions, SO2 emissions).

Results: In a first level analysis by multiple regression, latitude, acid rains and GDP were selected for further analysis, as the best correlated with prevalence.

Multiple regression among latitude, acid rains and GDP showed all the variables significantly linked to MS prevalence (latitude $p = 0.001$; acid rains $p = 0.000$; GDP $p = 0.002$.

If data about not known levels of acid rains ($pH > 5$) are excluded, multiple regression ($N = 116$) shows significance only for acid rains (latitude $p = 0.134$; acid rains $p = 0.001$; GDP $p = 0.573$).

Further stratifications are made to screen confusing variables. Stratification for latitude bands, either comprising or excluding acid rains over pH 5, in many bands there is significant correlation with acid rains and not with GDP or even latitude (30–35 degrees acid rains $p = 0.004$; 25–30 dgr $p = 0.000$). In 50–55 and 55–60 bands there was significant correlation either for acid rains or for GDP. As to continents, in Europe there is still a significant link with acid rains ($p = 0.000$), without correlation with latitude.

Stratifications for urbanization and climate also show significant correlations for acid rains and prevalence of MS independently from latitude, so that these variables does not seem to be confused.

Discussion: Acid rains and variables linked to them are not in contrast either with genetic or infectious aetiologies: as example, environment could also account for a different virus diffusion. We believe that at present hypotheses linked to environmental factors cannot yet be rejected.

P539

Normalized regional brain atrophy measures in multiple sclerosis. R. Zivadinov, L. Locatelli, B. Stival, A. Bratina, A. Grop, D. Nasuelli, 0. Brnabic-Razmilic, M. Zorzon, Neurological Clinic (Trieste, I; Heilbronn, D)

Background. Recently, normalized measures of whole brain atrophy that correct for head size and may also minimize the effect of patient positioning in the scanner have been introduced. This issue is of great importance as there is still a controversy regarding the optimal regional brain atrophy measurement for multiple sclerosis (MS) studies.

Objectives. The aim of this study was to establish whether, in a cross-sectional study, normalized measures of regional brain atrophy correlate with MRI defined regional brain lesions better than an absolute measure of regional brain atrophy.

Methods. We assessed 45 patients with clinically definite relapsing-remitting (RR)- MS (median disease duration 12 years). T1- and T2- lesion load (LL) of frontal lobes and pons were measured using a reproducible semiautomated technique. The regional brain parenchymal volume (RBPV) of frontal lobes and pons was obtained using a computerized interactive program, which incorporates semiautomated and automated segmentation processes. A normalized measure, the regional brain parenchymal fraction (RBPF) was calculated as the ratio of RBPV to the total volume of the parenchyma and the cerebrospinal fluid (CSF) in the frontal lobes and in the region of the pons. The total fractional regional brain volume (TFRBV) was obtained after correcting the total volume of the parenchyma and the CSF in the frontal lobes and in the region of the pons for the total intracranial volume. The mean coefficient of variation (CV) for RBPF of the pons was 1 % for intra-observer reproducibility and 1.4 % for inter-observer reproducibility. The mean CV for RBPF of the frontal lobes was 1.6 % for intra-observer reproducibility and 2.1 % for inter-observer reproducibility.

Results. RBPF and TFRBV demonstrated remarkably stronger correlation with quantitative MRI lesion measures compared to RBPV: $r = -0.37$, $p = 0.011$ and $r = -0.40$, $p = 0.0005$ vs. $r = -0.18$, $p =$ N. S. for T2-LL of the pons, and $r = -0.27$, $p = 0{,}046$ and $r = -0.31$, $p = 0.04$ vs. $r = -0.09$, $p =$ N. S. for T1-LL of the pons. T1-LL of the frontal lobes was related to RBPF ($r = -0.32$, $p = 0.033$) and TFRBV ($r = -0.29$, $p = 0.05$), whereas there was no correlation with RBPV. There was no significant correlation between T2-LL of the frontal lobes and both the absolute and the normalized regional atrophy measures.

Discussion. These data suggest that normalized regional brain atrophy measures are preferable to absolute measures in cross-sectional studies.

P540

A functional MRI study of patients with clinically definite multiple sclerosis and 'atypical' conventional MRI. M. A. Rocca, E. Pagani, A. Ghezzi, A. Falini, M. Zaffaroni, B. Colombo, G. Scotti, G. Comi, M. Filippi, Scientific Institute and University HSR, Ospedale di Gallarate (Milan, Gallarate, I)

Using fMRI, we evaluated the pattern of cortical activations during the performance of simple motor tasks in patients with clinically definite MS (CDMS) and 'atypical' MRI of the brain. We also obtained diffusion tensor imaging (DTI) to quantify the tissue damage of the normal appearing white (NAWM) and grey (NAGM) matter.

We investigated 12 right-handed patients with CDMS (mean age = 38.0 years, median disease duration = 2.5 years, median EDSS = 1.5) and 12 matched right-handed healthy controls. Patients were included if they had three or fewer lesions on T2-weighted scans of the brain.

We acquired: 1) fMRI (during flexion-extension of the last four fingers of the right and left hands). 2) dual-echo turbo spin echo sequence and 3) pulsed-gradient spin-echo sequence. FMRI data were analyzed using statistical parametric mapping (SPM99). Lesion volumes on dual-echo scans were measured using a local thresholding segmentation technique. Mean diffusivity (MD) histograms of NAWM and NAGM were produced.

In CDMS patients, the mean T2-weighted lesion load was 0.3 ml. MS patients had lower MD histogram peak height ($p < 0.0001$) and higher histogram peak position ($p = 0.03$) of the NAGM when compared with healthy subjects. Compared to controls during right-hand movement, CDMS patients showed more significant activations of the contralateral superior temporal gyrus and thalamus and of the ipsilateral supplementary motor area (SMA) and superior frontal sulcus. On the contrary, CDMS patients had significantly reduced activation of ipsilateral primary sensorimotor cortex. In CDMS patients, the relative activation of the ipsilateral SMA was correlated with NAGM MD histogram peak height ($r = -0.88$) and position ($r = 0.87$). Compared to controls during left-hand movement, CDMS patients showed an increased activation of the contralateral precentral gyrus.

This study demonstrates the presence of abnormalities of the NAGM in patients with CDMS and 'atypical' conventional MRI scans. It also shows a different pattern of movement-associated cortical activation in this group of patients which might have an adaptive role in limiting the clinical outcome of microscopic abnormalities of the tissue appearing normal on conventional MRI scans.

P541

Short-term correlations between clinical and MRI findings in relapsing-remitting multiple sclerosis. M. Rovaris, G. Comi, D. Ladkani, J. S. Wolinsky, M. Filippi, Scientific Institute and University HSR, TEVA Pharmaceutical Industries, The University of Texas for the European/Canadian Glatiramer Acetate Study Group

Despite the extensive use of magnetic resonance imaging (MRI) to provide markers of multiple sclerosis (MS) activity and accumulated disease burden, the relationship between clinical and MRI findings in patients with established MS has not been fully elucidated yet.

We investigated the short-term correlations between clinical and MRI-measured disease activity in a large sample of patients with relapsing-remitting (RR) MS by analysing the dataset from the European/Canadian glatiramer acetate (GA) trial.

The trial was a nine-month, double-blind, placebo-controlled study, where 239 RRMS patients were randomized to receive either 20 mg GA ($n = 119$) or placebo ($n = 120$) by daily subcutaneous injections. Clinical as-

sessment included monthly neurological examinations and additional visits in case of a relapse. Dual echo, pre- and post-gadolinium (Gd) T1-weighted MRI scans of the brain were obtained at baseline and every month during the follow-up. Gd-enhancing and new T2-hyperintense lesions were counted and total T2-hyperintense and T1-hypointense lesion volumes (LV) measured.

Significant correlations were found between number of relapses during the study period and number of Gd-enhancing lesions at baseline ($r = 0.25$) and during the follow-up ($r = 0.30$) in the overall study population. When the two study arms were considered in isolation, the degree of the correlations was higher in the placebo than in the GA group. A multivariable model showed that the independent factors more strongly correlated with the frequency of relapses during the study period were the number of relapses during the two years before study entry and the number of on-trial Gd-enhancing lesions, both in the overall study population and in the placebo group. In the whole patient sample, both T2 hyperintense and T1 hypointense LV at baseline were significantly correlated with baseline EDSS. Changes of MRI lesion volumes and EDSS were significantly correlated in the whole patient sample and in the GA group. Both T2 and T1 LV at baseline were significant predictors of the amount of MRI activity during the study period. T2 and T1 LV at baseline were also significantly correlated with the lesion volume changes observed during the follow up.

In RRMS, MRI-measured inflammatory activity is only modestly, but significantly correlated with the occurrence of clinical attacks over a short-term period. Clinical and MRI assessment can provide complementary outcome measures for RRMS trials.

P542

Seasonal variation of multiple sclerosis in a Turkish MS patient population. O. Anlar, T. Tombul, O. Unal, Yuzuncu Yil University (Van, TR)

Background: To quantify and characterize seasonal variation in multiple sclerosis (MS) onset and MS exacerbations (MSE) in province of Van-Turkey.

Methods: Sixty- two patients with clinically definite relapsing- remittent MS were retrospectively reviewed. We analyzed monthly and seasonal occurrence of the beginning of the disease and the exacerbations after the onset between 1997 and 2001 in our hospital.

Results: on review of 88 exacerbations, we found that a seasonal variation was found in both the time of onset of MS and the next exacerbations. The occurrence of MS and MSE was highest in winter, lowest in autumn and moderate in spring and summer.

Conclusions: In previous studies, different seasons of peak disease activity were found. These differences may be caused by the local factors, which influence the course of the disease.The seasonal variation of the frequency of the disease manifestations is probably caused by a variation in environmental factors. In this study, the nomination of the season's occurrence is important for MS patients to determine ways to prevent excess MSE.

P543

Third ventricle volume: a surrogate marker for disability and disease burden in multiple sclerosis. B. Turner, L. Vaithianathar, C.R Tench, P.S Morgan, X. Lin, C.S Constantinescu, Queen's Medical Centre, University Hospital (Nottingham, UK)

Introduction-Magnetic resonance imaging (MRI) is used as a surrogate marker in the assessment of disease modifying therapies in multiple sclerosis (MS). Previous studies indicate that whole brain atrophy maybe a putative surrogate marker of disease severity since it reflects clinical disability, but more specific measures of atrophy such as third ventricle enlargement may also be related to clinical outcome, particularly locomotor function. We present data on disability and third ventricle size in MS patients, and explore the cause of third ventricle enlargement.

Method–70 MS patients (32 relapsing remitting, 31 secondary progressive and 7 primary progressive) and 11 controls were recruited for this cross sectional study. Third ventricle volume (IIIV) and width (IIIW) were estimated on T1-weighted three- dimensional MR images. Cerebral T2 lesion (T2) load was measured on T2-weighted MR images. MRI measures were correlated with patient age, symptom duration (SyD) and clinical disability, measured by expanded disability status scale (EDSS). In a subgroup of 30 patients and 11 controls, T1 relaxation time values of grey matter (T1G) surrounding the third ventricle were measured and correlated with IIIV and IIIW.

Results-In the overall patient cohort, the IIIV demonstrated a superior correlation with EDSS ($r = 0.44$, $p = 0.0002$), compared to IIIW ($r = 0.29$, $p = 0.0153$) and T2 load ($r = 0.25$, $p = 0.0367$). IIIV was also correlated to age ($r = 0.26$, $p = 0.0307$) and SyD ($r = 0.39$, $p = 0.0008$). In the subgroup analysis, T1G was significantly different between controls and MS patients ($p = 0.0025$), but was not related to IIIV and IIIW. However IIIV ($r = 0.40$,$p = 0.0294$) and IIIW ($r = 0.46$,$p = 0.0117$) were significantly correlated to T2 load. Conclusion-Third ventricle enlargement is significantly related to greater disease duration and disability in MS patients. Our subgroup analysis shows that third ventricle dilatation reflects severity of cerebral white matter disease, as measured by T2 load, rather than pathology in the surrounding grey matter structures, as measured by T1G. A possible pathological mechanism is that distant lesions result in wallerian degeneration of the tracts running lateral to the third ventricle, including the pyramidal pathways. This may explain the significant correlation between disability and third ventricle enlargement. We propose that the third ventricle volume is a useful surrogate marker of both disease burden and the vital clinical endpoint, disability.

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Alpha(1,3)fucosyltranspherase VII deficiency blocks lymphocyte homing into the brain and experimental autoimmune encephalomyelitis. L. Piccio, E. Scarpini, B. Rossi, D. Ciabini, L. Ottoboni, C. Laudanna, J. W. Homeister, J. B. Lowe, G. Constantin (Milan, I; Ann Arbor, USA)

Alpha(1,3) fucosyltrasferases catalyze glycosylation of glycans that ligate endothelial E- and P-selectin and are responsible for leukocyte recruitment to inflammatory sites. Recent evidences suggest that downregulation of fucosyltransferase (FucT) activity may represent an attractive target for therapeutic intervention aimed at blockade of chronic inflammatory diseases.

Objective: The goal of this study was to determine the effect of different fucosyltransferase deficiency on lymphocyte recruitment in brain venules and on the induction of experimental autoimmune encephalomyelitis (EAE).

Methods: FucT-deficient mice (FucT-/-) for FucT-IV, FucT-VII and double deficient mice for FucT-IV & FucT-VII were generated on C57Bl/6 genetic background. Intravital microscopy studies in brain microcirculation were performed in LPS- or TNF-treated mice. EAE was induced in wt or FucTs deficient C57Bl/6 mice by using MOG35–55. RESULTS: Th1 lymphocytes were produced from wt or FucT deficient mice. Lymphocytes isolated from FucT-IV-/- mice efficiently tethered and rolled in brain postcapillary venules when compared with cells isolated from wt mice. In contrast, primary adhesion of lymphocytes isolated from FucT-VII-/- or Fuc-VII-/- & FucT-IV-/- mice was drastically reduced, suggesting that FucT-VII is critical for the recruitment of Th1 cells in brain microcirculation. Actively-induced EAE was significantly inhibited in Fuc-VII-/- & FucT-IV-/- mice when compared with wt mice. The effect of single Fuc-VII and FucT-IV deficiency on the induction of EAE will be also discussed.

Conclusion: Our data unveil a critical role for FucT-VII in the recruitment of Th1 lymphocytes into the brain, and suggest that FucTs may represent novel therapeutic targets for autoimmune diseases of the brain.

P545

Experience of interferon beta treatment in relapsing-remitting and secondary progressive multiple sclerosis in Galicia, Spain. J. Romero, M. Seijo-Martinez, V. del Campo, M. C. Amigo, M. Arias, J. A. Cortes, D. Dapena, F. J. Lopez, J. R. Lorenzo, M. Marin, D. Munoz, G. Ozaita, J. M. Prieto, Hospital do Meixoeiro, Complexo Hospitalario de Pontevedra, Complexo Hospitalario Universitario, Hospital Xeral, Hospital de Ferrol, POVISA, Hospital Juan Canalejo, Hospital Xeral-Cies, Hospital Cristal Piñor on behalf of the Galician Multiple Sclerosis Study Group

Introduction: The pathogenic mechanisms of multiple sclerosis (MS) are, in large part, unknown. The present consensus holds that multiple sclerosis is a immunopathogenic mediated disease appearing in genetically susceptible individuals, and precipitated by environmental, probably infectious, factors. Clinical trials have shown that interferon (IFN) beta reduces relapse rate and delays disability progression of relapsing-remitting (RR-MS) and secondary-progressive (SP-MS) multiple sclerosis. The experience of IFN beta treatment in a population is useful to evaluate the impact of these medications on clinical practice.

Objective: To analyze the experience in daily clinical practice of interferon beta treatment in relapsing-remitting and secondary progressive multiple sclerosis in Galicia (Spain).

Patients and methods: Patients with RR-MS and SP-MS treated with IFN beta–1a and –1b between 1995 and December/2000, analyzing demographic and clinical data.

Results: A total of 313 patient were included (207 females and 106 males), with a mean age of 38,2 years at the onset of treatment. A total of

296 patients (94,6 %) were clinically defined MS and 17 (5,4 %) were laboratory supported (Poser criteria). At the start of the treatment 84,6 % of the patients were RR and 15,4 % were SP. Disease-onset affected the following functional systems: pyramidal in 49,2 % cases, sensitive in 24,9 %, visual-optic in 24 %, brainstem in 18,8 % and cerebellum in 14,1 %. The mean duration of the disease prior to treatment was 7,06 years. Betaferon was used in 52,4 % patients, Avonex in 26 % and Rebif in 21,6 %. Relapse rate was reduced in 68,8 % for the RR MS for Betaferon-treated patients, 73,3 % for the Avonex treated and 35,7 % for Rebif-treated patients. Betaferon reduced relapse rate in 50 % for SP MS. The global EDSS remained stable during the treatment period, and for the three groups of interferon. During the treatment period, 33 % of Betaferon, 60,5 % of Avonex and 54,5 % of Rebif-treated patients remained relapse-free. Treatment was suspended in 12,9 % of Betaferon, 6,2 % of Avonex, and 3 % Rebif-treated patients. The most frequent causes of treatment suspension was increase in disability and number of relapses.

Conclusions: The present study supports the benefits of treatment with IFN beta in RR-MS and SP-MS in daily clinical practice, with reduction in the number of relapses, and discapacity, good over-all tolerance and low incidence of serious adverse side-effects.

P546

Activation of T cells is inhibited by the peroxisome proliferator-activated receptor gamma (PPAR-gamma) agonist pioglitazone in patients with multiple sclerosis and in healthy subjects. S. Schmidt, E. Moric, M. Schmidt, D. L. Feinstein, G. E. Landreth, T. Klockgether, M. T. Heneka, University of Bonn, University of Illinois, Case Western Reserve University (Bonn, D; Chicago, Ohio, USA)

Background: PPARs belong to a nuclear receptor superfamily of ligand-activated transcription factors. The demonstration of PPAR-gamma mRNA in human T cells raises the possibility that PPAR-gamma may be involved in the regulation of T-cell activation. Since potent anti-inflammatory properties have been ascribed to PPAR-gamma agonists including inhibition of cytokine generation, we tested the ability of the PPAR-gamma agonist pioglitazone to modulate T cell activation and cytokine secretion in patients with Multiple Sclerosis (MS) and healthy donors (HD). Methods: Phytohemagglutinin (PHA)-induced T-cell proliferation of eight untreated MS patients, eight MS patients treated with recombinant interferon-beta or glatiramer acetate, and eight HD was investigated according to four different experimental protocols in the presence of and after preincubation with 0.1, 1, 10 and 30 mcmol pioglitazone. Cytokine secretion of Interferon-gamma (IFN-gamma), tumor necrosis-factor-alpha (TNF-alpha) and interleukin–2 (IL–2)was assessed by ELISA and intracytoplasmic cytokine staining. Results: Pioglitazone inhibits PHA-induced T-cell proliferation and cytokine secretion of IFN-gamma, TNF-alpha and IL–2 in both MS patients and HD. The most significant effects were observed after preincubation of T-cells with pioglitazone for 48 hours. Interestingly, the anti-proliferative effects of pioglitazone were more pronounced in MS patients than in HD irrespective of a concomitant immunomodulatory treatment. Conclusions: PPAR-gamma seems to be involved in the regulation of human T-cell activation suggesting a potential role for PPAR-gamma agonists as immunomodulatory agents.

P547

Methyeprednisolone pulses and osteoporosis in relapsing-remitting multiple sclerosis. M. Zorzon, R. Zivadinov, L. Locatelli, D. Giuntini, M. Toncic, A. Bosco, D. Nasuelli, M. A. Tommasi, A. Bratina, R. A. Rudick, G. Cazzato, Neurological Clinic, Mellen Center (Trieste, I; Cleveland, USA)

Background. We demonstrated in patients with relapsing-remitting-multiple sclerosis (RR-MS), that prolonged treatment with pulsed IV methylprednisolone (IVMP) slows development of T1 black holes and delays brain atrophy and disability progression. Over 5 years, osteoporosis developed in two cases but the incidence of osteoporosis was unknown since no systematic effort to identify patients with osteoporosis was made.

Objective. To determine the effects of pulsed IVMP on bone mineral density (BMD) and bone turnover in patients with RR-MS.

Methods. Lumbar spine and femoral neck BMDs were measured by dual-energy-x-ray absorptiometry (DEXA) and biochemical markers of bone turnover were assessed in 25 (18F/7M) patients who received regular pulses of IVMP (PIVMP) (1 g/day for 5 days with an oral prednisone taper) and the same treatment for relapses as required, in 18 (11F/7M) patients who received IVMP at the same dose schedule only for relapses (RIVMP) and in 61 (41F/20M) sex- and age-matched healthy controls. Patients were followed for 5 years. PIVMP was given every 4 months for 3 years and every 6 months for the subsequent 2 years. PIVMP and RIVMP patients had comparable gender distribution, age, disease duration and number of relapses. The average dose of MP was 75.4 g (SD 11.9 g) in PIVMP group and 28.6 g (SD 18.3 g) in RIVMP group ($p < 0.0001$).

Results. Mean (SD) BMD at lumbar spine and femoral neck were respectively 0.808 (0.2) g/cm2 and 1 (0.1) g/cm2 in PIVMP group, 0.790 (0.12) g/cm2 and 1.02 (0.1) g/cm2 in RIVMP group, and 0.798 (0.04) g/cm2 and 0.965 (0.02) g/cm2 in healthy controls. The differences were not statistically significant ($p = N. S$). Serum parathyroid hormone, total serum alkaline phosphatase, serum osteocalcin and renal calcium excretion were not pathologically altered in PIVMP patients in comparison with the other two groups. In Spearman rank correlation analysis the average dose of MP did not correlate with BMD either in PIVMP or in RIVMP patients.

Conclusions. BMD did not differ significantly in PIVMP patients, in RIVMP patients and in healthy controls. None of the biochemical markers of bone metabolism was abnormally altered in PIVMP group. Treatment with pulsed IVMP for 5 years did not cause osteoporosis in patients with RR-MS.

P548

Effects of glatiramer acetat treatment on T cell responses in patients with multiple sclerosis. A. Dressel, M. Gottschalk, A. Scheschonka, M. Mäder, F. Weber, University Greifswald, Max-Planck-Institut of Psychiatry, Georg August University Gottingen (Greifswald, Munich, Gottingen, D)

Background: Multiple sclerosis (MS) is considered as an autoimmune disease mediated by autoreactive T cells. Placebo controlled multicenter trials demonstrated the efficacy of glatiramer acetate (GA, Copaxone®) in the treatment of relapsing-remitting MS. Its mechanism of action, however, is only partly understood. As possible mechanism a shift in cytokine production towards a TH2 response in GA treated patients has been observed

Objective: To identify subsets of T-cells that may be responsible for the TH2 shift during therapy with GA.

Methods: Peripheral blood mononuclear cells (PBMC) are isolated before and after six month of therapy. PBMC are separated into CD4+ and CD8+ T cells by Dynabeads and stimulated with PHA. GA-reactive, CD4+ long term T cell lines are established using the split well technique before and during therapy with GA and activated by GA and irradiated MHC-class II matched PBMC. T cell subsets and T cell lines are analysed for 3H-thymidine uptake and the production of cytokines (TNF-alpha, lymphotoxin, IFN-gamma, IL–4 and IL–10) is determined in cell culture supernatants by ELISA.

Results: So far a total of 51 long term GA-reactive T cell lines of four patients have been investigated. T cell lines generated during therapy with GA showed an increase in proliferation, a reduced production of IFN-gamma and an increased production of IL–4 compared with T cell lines generated before treatment. Also, T cell lines raised during treatment tended to produce less TNF-alpha than T cell lines generated before treatment. Production of lymphotoxin and IL–10, however, were unchanged.

IFN-gamma and IL4 production by CD4+ and CD8+ T cells upon stimulation with PHA were both decreased at six month of GA therapy while no consistent effect on proliferation was observed.

Conclusion: Our results demonstrate, that treatment with GA differentially modulates the proliferative and cytokine response of GA-reactive T cells. The increase in proliferation suggests a higher proliferative capacity of GA-reactive T cells primed in vivo, which might be caused by selection of T-cells bearing a T cell receptor with high affinity for GA. A shift from TH1 to TH2 cytokines is reflected by a decreased IFN-gamma/IL–4 ratio in GA-reactive T cells raised during therapy with GA. In addition the TH1 cytokine TNF-alpha tends to be decreased. In contrast, the production of the proinflammatory TH1 cytokine lymphotoxin and the TH2 cytokine IL–10 remained unchanged.

P549

Evaluation of mitochondrial manganese in leukocyte in multiple sclerosis (MS) patients. A. Nonnato, M. A. Cucci, P. Barbero, L. Branciforte, A. Ricci, E. Verdun, A. Caropreso, G. P. Pescarmona, L. Durelli, U. O. A. Chimica Analitica, Università di Torino (Turin, I)

Objective: To measure the leukocyte mitochondrial manganese (Mn) by atomic absorption spectroscopy with graphite furnance atomizer (GFA-AAS) in MS patients and in healthy controls.

Background:Mitochondrial Manganese is moster associated with superoxide dismutase (SOD) activity. SOD converts O2– in H2O2, modulating the concentration of free radicals potentially toxic like O2–, NO, H2O2 and peroxy nitrate that with cytokines, chemokines, proteases are candidate mediators of demyelination and axonal loss.

Material and MethodS:15 MS patients of which 7 Secondary Progressive MS (SPMS), 8 Relapsing Remitting MS (RRMS) (5 male, aged 31–62 and 10 female, aged 31–46) and 15 control subjects (7 male, aged 22–51 and 8 female aged 26–37) were included in the study.

Method: separation of mitochondrial fraction after leukocyte lysis by means of differential centrifugation in buffer; determination of protein contents in mitochondrial fraction by microplate spectrophotometric method; analysis of Mn in GFA-AAS after mineralization of mitochondria in HNO3 (65 %) at 100 (1 hour).

Statistical method: means were compared with the non parametric Wilcoxon-Mann-Whitney test.

Results: The Mn content was 83.5 +/–75 microg/g protein in healthy and 37.9 +/–70.5 microg/g protein in MS patients with a significant difference ($p = 0.02$). Sixty seven per cent of MS patients had an intramitochondrial Mn value < 20 microg/g protein, against 21 % of the controls.

Within the MS patient group only 43 % of SPMS had an intramitochondrial Mn value < 3microg/g protein (disease duration between 7–27 years) while in the RRMS patients group 75 % had value < 3 microg/g protein (disease duration between 8–13 years). Mn level seems to correlate with disease duration. The mean value of patients affected for 10 years was 19.5 microg/g protein while that of those affected for more 10 years was 58.6 microg/g protein. Patients mitochondria Mn was lower in women than in men (19.2 microg/g protein versus 70.3 /g protein) while control subjects had an opposite behaviour (115.0 /g protein in men and 47.3 /g protein in women).

Conclusion: The biochemical reasons of the decrease of leukocyte mitochondrial Mn in MS patients is not clear. Further studies are in progress to correlate this reduction with other clinical immunological, and MRI markers of disease activity.

P550

Failure to confirm interferon beta efficiency in multiple sclerosis (MS) in a general neurological ward. W. Verslegers, P. De Deyn, M. Van den Kerchove, AZ Palfijn, AZ Middelheim (Antwerp, B)

Purpose. Evaluation of interferon beta efficiency (IFN-beta) in a non academic neurological ward.

Methods. During the period from December 31, 1990 until December 31, 2001, 30 de novo patients with relapsing remitting definite MS according to Poser and Mc. Donald criteria were followed prospectively and treated with IFN-beta from the moment IFN-beta was available in Belgium and as soon as they fulfilled the Belgian criteria for reimbursement (Expanded Disability Status Scale-EDSS-equal to or less than 5.5, ability to walk minimal 100 meter, age between 18–50 and minimal 2 exacerbations for which treatment with glucocorticoids was necessary.

Results. Thirty patients were enrolled, (17 females, 13 males) with a mean age at diagnosis of 40 years (woman 40.2 years, man 42 years old). The overall EDSS at the moment of diagnose was 3. The EDSS was 3.56 for 17 patients who never fulfilled the Belgian criteria and 2.73 for the 13 patients who fulfilled these criteria. IFN-beta 1a was admitted to 12 patients, IFN-beta 1b to 2 patients. Patients who never received IFN-beta developed 0.96 exacerbations (E)/year. Those who were treated developed 1.05 E/y before and 0.95 E/y during IFN-beta treatment. Those who didn't receive IFN-beta were followed for a mean of 4.4 years, those who received IFN-beta were followed during 1.48 years and 4.5 years before treatment. The mean EDSS before treatment with IFN-beta was 2.73, after treatment 3.62 and without IFN-beta treatment 2.91. In two woman, IFN-beta had to be stopped because of rapid clinical deterioration (from 2 to 4.5/1 year and from 2 to 6/2 year on the EDSS, with a pre-treatment period of respectively 10 and 6 years) and dramatic increase of MS lesions on magnetic resonance imaging. Within 2 months, they returned to baseline after cessation of IFN-beta and treatment with methylprednisolone (MP) up to 1 g/month. Four patients refused IFN-beta because of to difficult and unclear long term effect. 10/17 patients not treated with IFN-beta required MP 125–500 mg/month and 7/17 other immunomodulating drugs to control their symptoms. Also 4/13 IFN-beta treated patients required MP 125–500/month for the same reason. Three/12 IFN-beta 1a treated patients developed disturbances of thyroid function.

Conclusion. In our de novo MS population, we could not demonstrate clinical effects of IFN-beta. Our number to treat seems very high with an unclear cost-efficiency rate, compared with non IFN-beta treated patients.

P551

Axonal damage induced by cerebrospinal fluid from multiple sclerosis patients in neuronal cultures related to T1-hypointense lesions. C. Cid, J. C. Alvarez-Cermeño, J. F. Plaza, J. Masjuan, M. Gomez-C, M. Salinas, A. Alcazar, Hospital Ramon y Cajal (Madrid, E)

Background: Multiple sclerosis is the most common demyelinating disease of the central nervous system. Early diagnosis of multiple sclerosis (MS), prognosis and progression delay are focused in clinical practice. Magnetic resonance imaging (MRI) has proved to be an important tool in studying of MS. We studied the potential relationship between changes in MS patients' disability after relapse, the degree of T1 lesion hypointensity in MRI in vivo, and the neurite fragmentation induced by cerebrospinal fluid (CSF) on neuron cultures in vitro.

Methods: We included twenty-four MS patients with relapsing-remitting disease. The clinical recovery from relapse was measured by the expanded disability status scale (EDSS). T1-weighted MRI studies were done at relapse according to established standards. Primary neuron cultures from cerebral cortex from rat foetuses were used to assay the CSF from MS patients. Neuron cultures were placed and maintained in serum-free medium and the neuronal content was determined by immunocytochemistry. Neurite fragmentation was induced by treatment of neuronal cultures with CSF from patients while relapsing. Neurite fragmentation was detected in cultures treated with CSF from MS patients by immunocytochemistry with antibodies against beta-tubulin and following secondary antibody fluoresce in-conjugated. Statistical analysis between variables was assessed by nonparametric test.

Results: CSF from patients with hypointense T1 lesions caused axonal damage/neurite fragmentation, whereas CSF that did not induced such effects corresponded to patients without T1 lesions ($p = 0.0039$). Besides, a correlation was found between T1 lesion hypointensity and clinical recovery from relapse ($r = 0.57$, $p < 0.002$).

Conclusion: The recovery from an acute MS relapse is significantly worse in patients with hypointense T1 lesions in MRI and in those whose CSF damaged neurons on cultures in vitro, phenomena that closely correlated each other. These findings may be useful particularly in the early steps of MS, as well as to confirm the relevance of T1-weighted MRI findings, and when early treatment of MS can play an important role to reduce clinical progression of the disease. (Supported by BMC2001–0047).

P552

Brain atrophy and ApoE genotypes in early relapsing-remitting MS patients. M. P. Amato, M. L. Bartolozzi, B. Nacmias, V. Zipoli, M. Mortilla, E. Cellini, S. Bagnoli, L. Guidi, P. Lambruschini, G. Siracusa, S. Sorbi, A. Federico, N. De Stefano, University of Florence, S. Giuseppe Hospital, University of Siena (Florence, Empoli, Siena, I)

Objectives: To assess axonal and tissue damage in patients with early relapsing remitting (RR) multiple sclerosis (MS) and with different apoliprotein E (ApoE) genotypes.

Background: Recent studies have suggested that MS patients who carry the ApoE e4 allele (e3/e4 or e4/e4) may have a more severe disease course compared to those without the ApoE e4 allele (e3/e3). This might be related to more extensive tissue in APOE e4 carriers.

Design/Methods: We determined the ApoE genotype in 27 consecutive RR MS patients in the early stage of the disease (median disease duration = 1 year and median Expanded Disability Status Scale [EDSS]= 1.5). In order to obtain measures of cerebral volumes and central brain levels of N-acetylaspartate (NAA, a measure of axonal integrity), respectively, each MS patient underwent proton MR imaging (MRI) and MR spectroscopic imaging (MRSI) examinations. Findings of the MS patient group were compared to those of 18 demographically matched normal controls (NC) using the nonparametric Kruskal-Wallis test of variance. Differences between different patient subgroups and NC were assessed using analysis of variance (ANOVA).

Results: 20 patients carried the ApoE e3/e3 genotype and 7 the e4 allele. The two patient groups showed no significant differences in age, age at onset, EDSS and disease duration ($p > 0.5$ for all measures). Decreases in central brain NAA levels (normalized to creatine [Cr]) with respect to NC were significant ($p < 0.01$) and similar in both patient groups (NAA/Cr in e3 MS patients = 2.8 ± 0.22, NAA/Cr in e4 MS patients = 2.7 ± 0.10, NAA/Cr in NC = 3.1 ± 0.20). However, automated measurements of normalized brain volumes (NBV) showed significant decreases ($p < 0.001$) in MS patients carrying the e4 allele compared to both NC and MS patients without the e4 allele (NBV in e3 MS patients = 1605 ± 39 cc, NBV in e4 MS patients = 1523 ± 038 cc, NBV in NC = 1600 ± 39 cc).

Conclusions: Our preliminary findings do not confirm the hypothesis of more severe disease course in MS patients with ApoE e4 genotype.

Moreover, decreases in NAA/Cr, suggesting a relevant axonal damage despite the early disease stage, were similar in the two patient groups. However, significant brain volume loss was found only in patients with the ApoE e4 genotype. The e4 allele might alter the neuronal maintenance and repair in MS patients since the earliest phases of the disease.

P553

Speech-analysis in MS-patients with deep brain stimulation. B. Reuter, U. Dillmann, S. Merkelbach, H. Sittinger, J. Spiegel, J.-R. Moringlane, University of Saarland on behalf of the MS-Intention-Tremor/Ataxia Study Group (D. Pöhlau, K. Wessels, H. Gharebaghi, R. Thümler, W. G. Elias, G. Japp)

Background: Subthalamic stimulation in patients with multiple sclerosis (MS) is aimed to lower tremor. There are visible effects of the ON vs. the OFF-setting of the stimulator.

Goals: Recent studies claim the variety of disorders associated with MS. Here the influence of the stimulator setting (ON, OFF, pre-operative) on language is evaluated.

Methods: The language of 4 MS-patients is studied via corpus linguistics. This approach tries to avoid the setbacks of formal testing, e. g. the metalinguistic attitude. Accordingly interviews are recorded under ON, OFF or preoperative condition, transcribed and serve for statistical analyses. Interview duration is about 7 minutes yielding 500 tokens. The minimum record interval is 30 minutes. Evaluated parameters are: verbal diversity VD, information load (ratio of function words/content words), word-length, grammatical and textual errors, text cohesion as expressed by the use of anaphoric and cataphoric pronouns, speech pauses, articulation (easy vs. difficult phoneme-groups) and articulation errors.

Results: Under position ON, VD is reduced in all patients ranging from 64 to 104 points, going from 67 to 107 points otherwise. Information load diminishes under ON in 3 patients and in 1 patient there is no change. With 3 patients, mean word length under ON is reduced (3.9 phonemes against 4.0–4.3 phonemes for the other condition). In 1 patient the word length increases from 4.2 to 4.4 phonemes. Grammatical errors increase under ON for 3 patients: an average of 3.5 errors/100 tokens under ON vs. 1.6 errors/100 tokens under OFF or preoperative status. In 1 patient there are 1.6 errors/100 tokens under ON, 2 errors/100 tokens under OFF. Text-cohesion is lowered for all patients under ON: 3 patients have a sharp drop of the cataphoric/anaphoric pronouns ratio, in 1 patient the solely used anaphoric pronouns are reduced. For speech-pauses and more surprisingly for articulatory errors there is no common tendency shown. The same is true regarding the phoneme groups whose articulatory difficulty was scaled by means of the Lauttreppe of Möhring.

Conclusion: The stimulator in position ON diminishes the verbal diversity and the textual integration to an objective but small extent. A slight impact on articulation can be observed. On all levels studied the capability for daily communication remains intact and training by an speech pathologist is not necessary.

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P554

Multiple sclerosis and psychosis. Tx. Arbizu, E. Moral, O. Carmona, V. Casado, P. Cardona, C. Casasnovas, Ciutat Sanitària i Universitària de Bellvitge L'hosp. de Llobregat (Barcelona, E)

Background: Psychiatric symptoms are common in Multiple Sclerosis (MS), especially mood disorders, have a high prevalence in the course of the illness.However, schizophrenialike psychosis is rare, although has been reported in the literature.

Goals: To report the prevalence, range of age, concommitant aetiological factors, location of brain lesions and treatment of the psychotic illness in our MS patients and compare with those previously published.

Methods: We followed prospectively 860 patients controlled at our MS Unit for 10 years, being a part of EDMUS database and report 5 cases that presented psychotic symptoms (one or more episodes), before MS was diagnosed or during the developement of the disease. Finally we review related literature.

Results: Psychotic symptoms occur in 0.58 % of our MS patients. Drug abuse and steroid treatment seem to be an important aetiological factor in population studied. All the patients were on neuroleptic treatment, and just in one case steroids were added. MRI imaging revealed that temporal lobe and periventricular areas are the most common place for the location of the lesions. The age of onset for the psychotic illness in our patients is higher than in general population.

Conclusions: We cannot establish a clear relationship between MS and psychosis.-Neuroleptics should be considered in the treatment of psychosis in MS patients. -The use of steroids for MS outbreaks can produce psychotic symptoms.

P555

Beta endorphin levels are decreased in PBMC of patients with different subtypes of multiple sclerosis. M. Gironi, M. Rovaris, R. Furlan, M. Filippi, G. Comi, A. Panerai, P. Sacerdote, San Raffaele Hospital, University of Milan (Milan, I)

Objective: Multiple Sclerosis (MS) subtypes differ not only for clinical phenomenology, but also with respect to epidemiology, pathogenesis, genetics and neuroimaging. This study is aimed at investigating the putative role of Beta Endorphin (BE) to explain different disease forms of MS.

Background: There is growing evidence suggesting a tight cross-talk between neuroendocrine and immune systems. Opioid peptides and opiate drugs have been shown to affect multiple immune responses, among them (BE) has been reported to play a possible modulation role in autoimmune diseases such as MS. In our previous study we disclosed a low mean BE levels in MS patients (pts) compared with controls. We also showed significantly higher levels of BE during a clinical relapse and during IFN&No 61538; treatment.

Design: 48 MS pts, under no treatment, and 12 controls have been studied. At study entry pts were classified into Relapsing Remitting (RR) forms, Secondary Progressive (SP), Primary Progressive (PP) Benign (BB) and clinically relapsing (r).Peripheral blood samples were obtained from all patients and peripheral blood mononuclear cells were separated by gradient sedimentation over Ficoll-Paque After pellet sonication, BE was measured by radiommunoassay. At study entry 38 pts out of 48 underwent MRI analysis.

Results: Our study has confirmed low levels of BE in MS pts (55.5 ± 36) compared with controls (106 ± 45), shown the RR (70 ± 41) and BB (65 ± 32) forms of MS as the one with the highest levels, the progressive forms PP (53 ± 32) and SP (40 ± 23) those with the lowest. No significant difference was found between enhancing and non enhancing pts on MRI analysis.

Conclusion: Considering that BE is believed to skew TH1/TH2 balance towards TH2 subset, our findings lead to speculate that low levels of BE can be linked to mechanisms of progression of disease. By contrast the highest BE levels found in "milder" forms of MS can be read as a winning counteract mechanism to inflammatory process

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PROVIGIL(R) (modafinil): A pilot, single-centre, double-blind, placebo-controlled cross over study in the treatment of fatigue in multiple sclerosis. A. Dowson, S. Kilminster, R. Salt, King's College Hospital, Royal Surrey County Hospital (London, Guildford, UK)

Background: Fatigue is a consistent symptom of Multiple Sclerosis (MS). Modafinil is licensed for the treatment of narcolepsy. This study evaluated the efficacy and safety of modafinil in the management of MS-related fatigue.

Methods: Patients were randomised to either modafinil 100 mg OD for three weeks, followed by modafinil 100 mg BD for three weeks, or matching placebo. After a 2-week washout, patients crossed over to the other treatment arm. A power calculation using MS-FS as the primary efficacy parameter suggested enrolling 60 patients.

Results: 35 patients, mean age 45 (± 7.9) yrs, mean time since diagnosis 10.5 (± 7.7) yrs, mean Kurtzke Expanded Disability Status Scale 3 (± 2.3), mean MS-specific Fatigue Scale (MS-FS) 4.6 (± 0.9), were enrolled. 29 patients completed the study and are included in the efficacy analyses. Patient enrolment was terminated prematurely due to local logistical problems. No statistically significant differences between treatments were seen on the objective measures of sedation (Critical Flicker Fusion), $p = 0.128$, although an initial placebo effect was noted. Some patients had normal baseline CFF values, despite being subjectively sleepy.

Patients experienced mean improvements from baseline in MS-FS score on modafinil that were 0.5 greater than on placebo, at both doses – the degree of difference that the study had been powered to detect. However, due to the shortfall in numbers, this difference did not reach statistical significance. The other fatigue parameters (Visual Analogue Scale of Fatigue and MS-Quality of Life Questionnaire) showed similar trends of improvement that again did not reach statistical significance. The Epworth Sleepiness Scale (ESS) showed a trend in favour of modafinil, but when a subset of patients with significant sleepiness (ESS = 10 or more) was analysed ($n = 19$), this trend was reduced or disappeared (principally due to a placebo response).

No Serious Adverse Events were seen. The most common adverse events were headache and nausea, both occurring in 9 % of subjects on modafinil.

Conclusion: This underpowered study was inconclusive. However, the trends toward improvement in fatigue parameters suggest that further

study is warranted. The differences between the fatigue and sleepiness parameter findings (baseline, efficacy and placebo effects) strongly suggest that they are different features in this population. Future studies must address these issues. Modafinil was well tolerated.

P557

Clinical, radiological and immunological aspects of inflammatory myelopathies. P. Perini, M. Calabrese, E. Tzintzeva, M. Tiberio, F. Ranzato, P. Gallo, Multiple Sclerosis Centre (Padua, I)

Introduction. The diagnosis of inflammatory myelopathy not related to multiple sclerosis is often difficult, and the identification of the etiopathogenic process underlying the spinal cord inflammation remains sometime obscure.

Materials and Methods. Twenty-five patients (15 males, 10 females; mean age at onset: 44 yrs) were studied. Immunological and virological screenings consisted in the determination of ESR, PRC, RF, ANA, ENA, CIC, ATA, ANCA, ACA, LAC, ACE, Cryoglobulins, C3, C4, C1q, immunoelectrophoresis, lymphocyte subsets, anti-neuronal antibodies, anti-neurotropic virus antibodies, detection of viral genome by PCR. Spinal cord imaging was obtained by conventional MRI with T1, T2, DP, Gadolinium-ETA (single dose), and FLAIR sequences. Cerebrospinal fluid (CSF) examination consisted in cell count and differentiation, calculation of CSF/serum albumin ratio and IgG indexes, demonstration of IgG oligoclonal bands (IgGOB) by isoelectricfocusing, detection of antibodies to and genomic sequences of neurotropic viruses (by PCR).

Results and Discussion. The onset was monosymptomatic in 7 cases (3 pyramidal, 4 sensorial), and polysymptomatic in 18 cases. The clinical onset was acute in 14, subacute in 9, and chronic/relapsing in 2. A post-infectious origin of the myelitis was documented in 8 patients (32 %). In only one case the association with a systemic autoimmune disease was observed (thyroiditis, ATA = 2178 U/ml), while ANA, ENA and ANCA were within the normal range in all cases. In two patients the association with the HHV–6 was supposed on the base of positive virus specific IgM and/or DNA detection on biological fluids.

The involvement of other neurotropic viruses was never demonstrated. IgG OB were found in 9 patients (39.1 %) patients, bur never in the post-infectious myelopathies and in the two chronic/relapsing cases. A blood-brain barrier damage was observed in 10, and a mirror IgG pattern in 4 patients. Only one patient later developed a primary-progressive MS. The diagnosis of Devic's disease (Neuro-myelitis optica) was definite in one patient, and probable in another patient.

Post-infectious myelitis had the most extensive MRI abnormalities.

Conclusion. While confirming the large clinical heterogeneity of inflammatory myelopathies, our study suggests that immunological tests in blood and CSF and neuroimaging may allow the identification of diagnostic patterns.

P558

Vascular endothelial growth factor gene polymorphism and its association with multiple sclerosis. J. M. Partridge, A. A. Fryer, R. C. Strange, M. D. Boggild, C. P. Hawkins, Keele Multiple Sclerosis Research Group (Stoke-on-Trent, Liverpool, UK)

Introduction: Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system characterised by progressive disability. Vascular endothelial growth factor (VEGF) is a cytokine that has been implicated in other autoimmune inflammatory conditions such as rheumatoid arthritis and Crohn's disease. It induces vascular permeability and macrophage migration, increases brain expression of intercellular adhesion molecule–1 and major histocompatibility complex class I and II, and is strongly up-regulated in reactive astrocytes suggesting it may contribute to blood-brain barrier (BBB) breakdown. It is thus a good candidate cytokine in MS pathogenesis. We therefore performed a candidate gene association study to determine whether VEGF influences MS onset or severity.

Methods: 269 Caucasian patients (75 % female, 25 % male) and 206 controls of Northern European origin were recruited. Mean onset age of MS was 31.5 ± 8.7 years and mean disease duration was 12.4 ± 9.2 years. DNA was extracted from leucocytes and amplification refractory mutation system polymerase chain reaction with allele specific primers was performed to identify a C to A mutation at –2578 of the VEGF gene to identify the alleles. Outcome was assessed using Kurtzke's Expanded Disability Status Scale (EDSS) and cases were stratified into mild/moderate disability (EDSS 0–5.5) and severe disability (EDSS 6–10) after disease duration of variable years. Results were analysed using logistic regression to correct for independent covariants of age of onset, gender and disease duration. Significance levels were set at $p < 0.05$.

Results: No association was seen between MS susceptibility and possession of mutant allele (OR = 1.00, 95 % CI = 0.66–1.53, p = 0.98). Near significant association was seen between severe MS and wild type VEGF (CC) in the whole cohort (OR = 1.80, 95 % CI = 0.94–3.44, p = 0.08, n = 267). Consideration of those diseased 15 or more years, when disease outcome is clearly established, demonstrated significant association with more severe disease (OR = 3.70, 95 % CI = 1.13–12.1, p = 0.03, n = 81).

Conclusion: VEGF –2578 polymorphism is associated with severity of MS in those cases with established disease. We postulate this is due to immune modulating effects of VEGF on BBB function and leukocyte adhesion and recruitment.

P559

Liposomal prednisolone pulse therapy leads to in situ T cell apoptosis and is beneficial in treatment of experimental autoimmune encephalomyelitis. J. Schmidt, J. M. Metselaar, M. H. M. Wauben, G. Storm, K. V. Toyka, R. Gold, University of Wurzburg (Wurzburg, D; Utrecht, NL)

To investigate whether a long-circulating liposome formulation containing prednisolone is superior to methylprednisolone (MP) pulse therapy in induction of T cell (TC) apoptosis. In adoptive transfer (AT)- experimental autoimmune encephalomyelitis (EAE) ultra high doses of MP have been shown to be more efficient in induction of TC apoptosis than the "standard" dose of 10 mg/kg used in MS therapy. AT-EAE was induced in female Lewis rats by 10E7 MBP-specific TC i. v. We used long-circulating liposomes coated with polyethylene glycol, encapsulating prednisolone phosphate. 10 mg/kg prednisolone-liposomes (PL) were applied i. v. at 42 hours and 18 hours prior to sacrifice. Another group received 50 mg/kg MP i. v. at 18 hours and 6 hours before perfusion. Control rats received empty liposomes and/or saline at equivalent time points. TC or macrophages (MO) in spinal cord were detected immunohistochemically in paraffin embedded tissue and apoptosis was assesed by the TUNEL assay and by morphological criteria. The rate of TC apoptosis in spinal cord tissue was significantly augmented by PL (39.4 ± 6.8 %, $p < 0.0001$ vs. 16.1 ± 4.3 % in the control group, all data given as mean ± SD). MP as an internal control lead to a rate of 30.8 ± 8 % TC apoptosis ($p < 0.01$ vs. controls). As a result of the increase in apoptosis TC infiltration was clearly reduced by PL (45 ± 12 TC/mm2), which was statistically significant compared to controls (115 ± 51 TC/mm2, $p < 0.05$) as well as compared to MP (96 ± 19 TC/mm2, $p < 0.05$). As another aspect of inflammation the MO infiltration was significantly reduced by PL (31 ± 13 MO/mm2) compared to controls (78 ± 37 MO/mm2, $p < 0.05$) and compared to MP (66 ± 25 MO/mm2, $p < 0.05$). Even though we chose the AT model to investigate rapid mechanisms, we could observe a therapeutical benefit from PL within 42 hours, achieving a clinical score of 2.8 ± 0.2 compared to controls (3.2 ± 0.3, $p < 0.01$), which was superior to MP (3.2 ± 0.3, $p < 0.05$ vs. PL). Long-circulating PL given at 10 mg/kg augment TC apoptosis in situ rapidly and the reduced infiltration of TC and MO leads to an ameliorated disease activity of AT-EAE. As the liposomes can extravasate and accumulate in inflamed tissue with a disrupted blood-brain-barrier, PL could be a therapeutic alternative to MP, which needs a higher dosage and would therefore cause more systemic side-effects. These findings may have implications for the treatment of inflammatory autoimmune diseases of the CNS such as multiple sclerosis.

P560

Regional NAA concentration of the normal appearing white matter correlates with focal abnormalities in patients with multiple sclerosis. M. Matzke, J. Kaufmann, C. Tempelmann, H. J. Heinze, M. Sailer, O. v. Guericke Universität (Magdeburg, D)

Background: The involvement of normal appearing white matter (NAWM) in multiple sclerosis (MS) is well established whereas there remains some controversy of its origin. The altered tissue integrity may be a result of microscopic lesions in the NAWM although recently a relationship between focal lesions and remote alteration of neuronal tissue is being discussed. The aim of this study is to assess the changes in NAWM according to the amount and integrity of focal lesions. The use of magnetization transfer (MT) imaging and proton magnetic resonance spectroscopy (1H-MRS) offer the possibility to characterize the underlying pathology and provide quantitative insights in the extend of pathologic damage of brain tissue.

Methods: We studied 21 MS patients with a clinical definite diagnosis. Proton spectra were acquired in a volume of interest of 2 x 2 x 1.2 cm positioned in NAWM of the right hemisphere anterior to the central sulcus. Resonance intensities of N-acetylaspartate (NAA) and creatine (Cr) were determined. Results were expressed as the ratio NAA/Cr. Proton-density-weighted images were acquired with and without MT saturation pulses in order to calculate MTR maps. After coregistration of all scans the lesions

were outlined on PD-weighted images. MTR histograms based on segmented white matter were calculated several times while boundaries of the NAWM were varied by a simple dilation algorithm. Additionally, conventional T2- and T1-weighted images were acquired.

Results: We found a significant correlation between the lesion volumes of lesions detected on T2- and T1-weighted MRI brain scans and the NAA/Cr ratio in the NAWM. Moreover we observed a significant correlation between NAA/Cr and MT-ratio of T2-weighted lesions showing a reduction of the NAA/Cr ratios in patients with low mean MT-Ratios of T2-weighted lesions ($r = 0.502$, $p = 0.017$)

Conclusion: In this study, we combined the MT-ratio and MRSI as quantitative measures to examine the relationship between NAWM and focal lesions. The amount and severity of focal tissue damage seems to be closely related to the neural integrity of the NAWM, probably due to remote changes of axons after axonal transection in focal MS lesions. This corroborates earlier studies and underlines the importance of limiting the amount of lesions in MS patients. Quantitative measurements of axonal integrity provide insight in the progression of axonal injury in MS patients.

P561

Autoimmune thyroiditis in Sardinian multiple sclerosis patients treated with interferon beta. E. Cocco, S. Sanna, M. Matta, N. Casula, L. Fadda, P. Marchi, M. Lai, M. G. Marrosu, University of Cagliari, University of Sassari (Cagliari, Sassari, I)

Background. The association between autoimmune thyroiditis and multiple sclerosis (MS) have been recently reported in Ashkenazy MS women. In Sardinians, an insular Italian population, a very high incidence of organ specific autoimmune disease (MS and type 1 diabetes mellitus) and an incidence of antibodies against thyroid antigens higher than the other Italian regions has been reported.

Alpha and beta interferon (IFN) treatments are associated with the development of autoimmune thyroiditis, among other autoimmune diseases, in various medical condition.

Objective. The aim of our study was to evaluate which role could be played by IFN beta therapy in the occurrence of autoimmune thyroiditis in Sardinian MS patients.

Methods We assayed the serum level of free triiodothyroxine (fT3), free thyroxine (fT4), thyroid -stimulating hormone (TSH), anti-thyreoperoxidase (Ab TPO) and anti-thyreoglobulin (Ab Tg) antibodies in 140 Sardinian MS patients at basal level and every 3 months. All the patients were treated with IFN beta at least from 12 months (median duration of treatment 31,3 months). The patients were evaluated by an expert endocrinologist with a clinical visit and ultrasound examination when relevant alterations were present in the serum exams. Thyroid alterations were defined according to the criteria reported by the "Thyroid American Association".

Results. On 140 patients, 29 (20.8 %) presented at basal level some laboratory alterations (37.9 %,hormonals, 44,8 % auto Ab and 17,2 % both). Among the 29 patients 4 patients presented an autoimmune hypothyroidism. During the follow up period 50 (36 %) patients showed laboratory alterations and 14 (12.9 %) patients presented a new diagnosis of autoimmune hypothyroidism.

Conclusions. Our results demonstrated a high frequency of new diagnosis of autoimmune hypothyroidism in Sardinian MS patients during IFN treatment supporting the need of repeated assessment of thyroid evaluation in populations particularly prone to develop autoimmunity like Sardinians.

Acknowledgments. We are grateful to the patients for their kind collaboration.

Pain and headache

P562

Severe headaches in the emergency room. A prospective study of 100 cases. K. Phanthumchinda, W. Jantararotai, Chulalongkorn University (Bangkok, TH)

While many medical conditions are capable of producing headache, a select group appears responsible for majority of acute severe presentations. This is a prospective study of cases and clinical profiles of severe of headache in an emergency room. Materials and Methods. In an emergency room at King Chulalongkorn Memorial Hospital (university hospital), 100 consecutive cases of adults who presented with severe disabling headache were evaluated. Headache questionnaires, detail medical history, physical and neurological examinations had been checked by neurological residents. Appropriate investigations including blood tests, neuroimaging, cerebrospinal fluid analysis had been applied when indicated. International Headache Society criteria had been used for diagnosis of headache.

Results: Primary and secondary headache had been observed in 10 % and 90 % of cases. Primary headache included 4 % of refractory migraine and 6 % of tension type of headache and myofascial pain. Secondary headache included, cerebrovascular disease 27 % (arterial infarction 14 %, venous infarction 6 %, parenchymal haematoma 4 %, subarachnoid hemorrhage 3 %), brain tumour and granuloma 21 %, meningitis 16 %, paracranial lesion 10 %, systemic disease 7 %, cerebritis and encephalitis 6 %, subdural haematoma 2 % and pseudotumour cerebri 1 %. From analysis of clinical profiles, the most important clinical features which were helpful for an accurate diagnosis were: location of pain, clinical course and associated physical and neurological findings. Severity of pain could not be used to differentiate primary and secondary headache.

Conclusion: Patients seeking emergency room care for acute severe headache may suffer from serious life-threatening neurological or systemic illness and should be approached in an organized fashion.

P563

Effects of surgery on the pain and sensory deficits associated with syringomyelia. N. Attal, F. Parker, N. Aghakani, M. Tadié, D. Bouhassira, Hôpital Ambroise Paré, Service de Neurochirurgie (Boulogne, Kremlin-Bicêtre, F)

This long-term prospective study evaluated the outcome of the pain and sensory deficits associated with syringomyelia related to Chiari malformation (11 patients) or spinal cord trauma (4 cases) after surgical management. Fifteen consecutive patients (11 men, 4 women; mean age: 35.9 ± 10 years; mean duration of symptoms: 5.3 ± 4.6 years) presenting with clinical and radiological evidence of cervico-dorsal syringomyelia were evaluated before surgery, then at 6 months and 2 years. The extent of thermal deficits was measured using thermo-rollers. Quantitative sensory tests (QST) were used to determine the mechanical, vibration and thermal detection thresholds and the mechanical, thermal pain thresholds. MRI was performed before and after surgery to measure the syrinx dimensions. The fonctional impairment of the patients and the proprioceptive deficits, but not the magnitude of thermo-algesic deficits improved significantly after sugery. The intensity of acute pain episodes (evoked by effort/movement), but not of ongoing pain at rest, was reduced at 2 years. The syrinx collapsed in 80 % of cases, the degree of foramen stenosis and the syrinx/canal index were improved, but these were not correlated with clinical outcome. There were no correlations between the outcome of neuropathic pain, thermoalgesic and proprioceptive deficits. The effects of surgery on thermal deficits were correlated with duration of the syrinx. Notably patients whose duration of the symptoms was less than 2 years were stabilized or improved. This study shows that 1/ Neuropathic pain due to syringomyelia is not related to the magnitude of thermoalgesic nor proprioceptive deficits 2/ The surgical decompression of syrinx is more effective on symptoms of posterior fossa compression than on thermoalgesic deficits, that depend essentially on spinal cord damage. 3/ However, an early surgical treatment of syringomyelia may result in a better outcome of thermoalgesic deficits.

P564

Pregabalin effectively reduces pain and pain interference with sleep in patients with postherpetic neuralgia (PHN). A. Corbin, J. Young, L. LaMoreaux, U. Sharma, E. Garofalo, R. M. Poole, Pfizer Global Research and Development

Rationale: PHN can be classified as pain lasting more than 3 months beyond the crusting of skin lesions associated with an acute attack of herpes zoster. PHN is one of the most difficult pain syndromes to manage. Sleep problems, prevalent among patients with chronic pain, complicate pain management. Pregabalin has shown efficacy in clinical trials for another common neuropathic pain condition, diabetic neuropathy. This randomized, double-blind, placebo-controlled, parallel-group trial evaluated the efficacy and safety of pregabalin for reducing pain in PHN patients.

Methods: Patients with PHN of at least 3 months duration were randomized in this 26-center add-on therapy trial consisting of a 1-week baseline phase and an 8-week double-blind phase. Pregabalin dose was stratified to 300 or 600 mg/d, dependent on the patient's creatinine clearance, and analyzed as a single pregabalin treatment arm. The primary efficacy parameter was the endpoint mean pain score from the patient's daily pain diary. Secondary efficacy parameters included the Short-Form McGill Pain Questionnaire (SF-MPQ), daily sleep interference diary, Clinical and Patient Global Impression of Change (CGIC, PGIC), and proportion of pa-

tients with 50 % or greater decrease in endpoint mean pain score (% responders).

Results: 84 patients received placebo and 89 received pregabalin. Patients in the pregabalin group showed significant improvement in endpoint mean pain score ($p = 0.0001$) and endpoint mean sleep interference score ($p = 0.0001$) compared to the placebo group; improvements were evident by week 1 and continued for the duration of the trial. A significantly higher proportion of pregabalin-treated patients than placebo were responders (50 % vs. 20.2 %, respectively). Significant improvements were also observed for the mean SF-MPQ total and VAS scores, CGIC, and PGIC. The most common adverse events were dizziness, somnolence and peripheral edema. Thirty-two of 173 patients withdrew from the trial due to adverse events, and 6 withdrew due to lack of efficacy. Study medication was generally well tolerated: 76 % of patients completed the trial, and 72 % entered a follow-on safety trial.

Conclusions: Pregabalin produced statistically and clinically significant improvements in pain compared to placebo in patients with PHN. Pregabalin also improved sleep interference and global measures of change, and is safe and generally well-tolerated in this elderly patient population.

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P565

Moderate coffee consumption reduces the risk of post-lumbar puncture headache in women, but not in men. O. Schüler, M. Strupp, A. Straube, T. Brandt, Ludwig-Maximilians University (Munich, D)

Objective: To determine whether coffee consumption decreases the susceptibility to post lumbar puncture headache (PLPH) in a dose-dependent manner.

Material and methods: The study was a prospective investigation. After giving their informed consent, 230 patients (18–59 years old; 143 females) participated in the study. Lumbar puncture (LP) was performed with either an "atraumatic" Sprotte needle (115 patients) or a "traumatic" Quincke needle (both 22 gauge, 0.80 mm). One week after the procedure patients completed a questionnaire providing details on intake of coffee before and after the LP and about their complaints. The symptoms, especially headache, were recorded with respect to body position, delay of onset, severity (visual analogue scale), and duration. Headache was assumed to be related to LP in accordance with the definition of the International Headache Society.

Results: The average coffee consumption before and after LP was 1.7 cups/day and did not differ significantly between female and male patients. There was no difference of PLPH frequency between those who drank coffee (20.8 %) and those who did not (17.1 %). For the subgroup of females however, there was a significant difference, not only between those who drank coffee and those who did not, but also between moderate and high coffee consumption. In the subgroup of females who drank coffee the incidence of PLPH strongly depended on the amount of coffee consumed daily in a u-shaped manner. A daily coffee consumption between 0.5 and 1 cup of coffee resulted in a significantly lower incidence of PLPH than a coffee consumption of more than 1 cup per day (5.9 % vs 26.8 %, $p < 0.01$, chi-square test). In male patients coffee consumption did not correlate with the incidence of PLPH (27.2 % vs 24.9 %, $p > 0.05$, chi-square test). The same interesting u-shaped correlation was found between coffee consumption and risk of Parkinson's disease in women, with the lowest risk observed at moderate intakes.

Conclusion: We conclude that moderate coffee consumption (0.5–1.0 cups/day) before and after LP was beneficial for female patients by preventing PLPH, but not for male patients. In view of this clear benefit, moderate coffee consumption before and after LP can be recommended for females.

P566

Lhermitte sign in patient without multiple sclerosis. J. Porta-Etessam, A. Martínez-Salio, A. Berbel-García, J. Benito-León, C. Gomez Escalonilla, L. Galán, I. Garcia Morales, Hospital Universitario (Madrid, E)

To present eight patients without multiple sclerosis and Lhermitte's sign analysing the aetiology, treatment and their prognoses.

Lhermitte's sign is most prevalent in patients with multiple sclerosis, and less frequent in cervical spondylotic myelopathy, cisplatin neurotoxicity, cervical radiation injury, and neck trauma.

There were eight patients (five men and three woman) ranging in age from 19 to 65 years old. All patients had Lhermitte's sign, a shock-like or electric sensation, transmitted down the spine, which occurred during neck flexion or rotation.

Two patients had postradiation myelopathy; one was due to cis-platinum toxicity, two because of a slipped disc. One patient had a spinal cord vascular malformation, another a cervical myelopathy and the last one a cervical spinal cord compression due to a metastasis. All cases respond to a combination between carbamazepine treatment and surgical approach to the aetiology disease (spinal cord malformation, cervical myelopathy, slipped disc) or radiotherapy (spinal cord compression).

Lhermitte sign is non-specific phenomena responding to a multiple injuries. Early and aetiological treatment should be established as soon as possible. As an isolated Lhermitte phenomenon has good prognosis.

P567

Clinical study of the value of botulinum toxin-A (BOTOX) in the treatment of chronic tension-type headache with asociated pericranial muscle tenderness. M. Mata, J. J. Lopez-Lozano, R. Dorado, I. Tuduri, Clinica Puerta de Hierro Movement Disorders Unit and Headache Unit

Introduction: Chronic tension-type headache with associated pericranial muscle tenderness is a subtype of chronic tension-type headache that associates increased sensitivity of the pericranial muscles confirmed by palpation, pressure algometry, or EMG (IHS calsification, 2.2.1).

Preliminary reports suggest that infiltration of the pericranial muscles with botulinum toxin may be a promising treatment of chronic tension-type headache. However, there are no reports concerning the effects of this therapy in specific subtypes of chronic tension-type headache.

Objective: To assess the efficacy of botulinum toxin A (BOTOX) in the treatment of chronic tension-type headache with associated pericranial muscle tenderness

Methods: Ten patients that fulfilled the IHS criteria for chronic tension-type headache with associated pericranial muscle tenderness, were treated with single bilateral injection of BOTOX, into the pericranial muscles. Patients were assessed prior to botulinum toxin infiltration and at 3, 6, 9 and 12 weeks after. Clinical evaluation was based on the patient diary, focused on the frequency, intensity, and duration of pain. Intensity of pain in the tenderness muscles was assessed by manual palpation, in an analogic visual scale of 0 to 10, before and after infiltration (8 weeks).

Results: Patients showed a gradual improvement, that was maximal at week 9. A mild worsening was observed at week 12, although the beneficial effects of BTX-A therapy continued to improve at the end of follow-up. Significant decrease in frequency of pain was observed from the first evaluation, and maintained during the follow-up period (61,2 % week 9; $p < 0.05$). Intensity of pain showed significant improvement at weeks 6, 9 and 12 (68 % week 9; $p < 0.05$). Duration of pain was reduced, but changes were not statistically significant. The pain analogic scale after pressure in the tenderness muscles was reduced, mainly in Splenius Capitis (37,7 %) and Temporal muscles (32,7 %). Five patients were free of pain at week 9, 3 at week 12, and 1 patient at week 3.

Conclusions: Treatment with injection of BOTOX produced a significant improvement of headache in patients with chronic tension-type headache with associated pericranial muscle tenderness. Main improvement was achieved for frequency and intensity of pain. The results of our study suggests that BOTOX may be an effective therapy for treatment of this subtype of chronic tension-type headache.

P568

Prediction of post-traumatic cervico-cephalic pain duration following whiplash injury by means of computer-aided pressure algesimetry. K. Nebel, P. Stude, H. Wiese, C. Lüdecke, H. Diener, M. Keidel, University of Essen, District Hospital of Bayreuth (Essen, Bayreuth, D)

Background: The key symptoms of the acute cervical syndrome after whiplash injury are cervical pain and neck stiffness due to painful tension in the shoulder/neck muscles, often accompanied by posttraumatic headache. As a rule the cervico-cephalic pain resolves within 6 weeks. However, chronification of sustained neck pain and headache develops in 10–20 % of whiplash patients.

Objective: The aim of the study was to objectify pressure pain in cervical muscle sprain due to whiplash injury and to elaborate predictors for the duration of posttraumatic cervical pain (PTCP) and posttraumatic tension-type headache (PTTH). Methods: We examined 20 whiplash patients (28.8 ± 12.1 SD yrs) suffering from PTCP and from PTTH and 23 healthy controls (28.8 ± 10.4 SD yrs). Patients were investigated within the early post-traumatic phase on average 7 days (± 2.9 SD) after a vehicle collision. PTCP- and PTTH-courses were quantified by means of pain diaries. A period of six weeks after the trauma was examined. Using a computer-aided pressure algesimetry a constant pressure pain was induced in the right and left splenius and trapezius muscle while subjects continuously rated the

muscle pain intensity on a PC-display. The course of the pressure pain intensity was recorded for 3 minutes as a function of time. Pain maximum, time to pain maximum, slope and integral of the pain intensity-time function were calculated.

Results: We found an increased pressure pain of all investigated muscles for almost all pain related parameters examined in acute whiplash injury in comparison to the healthy control subjects. Pressure painfulness was more marked in the left than in the right trapezius muscle in the patient group. No side differences were observed in the splenius muscles.

Both the duration of cervical muscle pain and of posttraumatic headache days are predicted by the ratio of painfulness of the left vs. right trapezius muscle. Separate regression analyses of neck pain and headache duration revealed highly significant results for the integral ($p = 0.001$, $p = 0.02$) and slope ($p = 0.002$, $p = 0.003$) of the pain intensity-time function and for the maximal pain intensity ($p = 0.003$, $p = 0.043$) of these left vs. right trapezius muscle ratio measures.

Conclusions: We have shown a possibility to quantify increased muscle pain due to neck sprain following whiplash injury in a standardised and inter-examiner independent manner using the computer-aided pressure algesimetry. Algesimetric parameters of posttraumatic muscle pain can be of value for the prediction of individual PTCP and PTTH development. They might be useful tools to identify patients at risk for pain chronification already in the acute stage of whiplash injury.

Peripheral Neuropathy

P569

Corticosteroids treatment provides improvement in recovery of idiopathic facial palsy. S. Perovic, G. Toncev, S. Toncev, G. Samardzic, B. Milicic, Health Center Kragujevac, Clinical Hospital Center Kragujevac (Kragujevac, YU)

Background: Treatment of idiopathic peripheral facial paralysis has remained controversial in many aspects. Controversy exists as to whether the disorder should be left to run its natural course or treated with steroids.

The objective of this study was to evaluate the effect of corticosteroids in the treatment of idiopathic facial palsy.

Methods: The effect of early steroid treatment on the evolution of idiopathic facial palsy was evaluated in Health Center Kragujevac with a prospective protocol from January 1997 to December 2000. 99 idiopathic facial palsy patients treated with prednisone (a single daily dose of 1 mg/kg of body weight) for 10 days and tapered to 0 over the next 6 days. 65 idiopathic facial palsy patients had contraindications for prednisone. They were treated with pentoxifylline (1200 mg daily in three doses, per os) for 16 days and used as control. Treatment started within three days after the onset of palsy in both groups. Minimum follow-up was 3 months in all patients.

Results: Full recovery of facial motor function without sequelae occurred in 80.49 % of patients. The prednisone group demonstrated better clinical recovery than those treated with pentoxifylline ($p = 0.021$). Fewer incidences of sequelae were observed in the prednisone group compared with controls (12.12 % vs. 30,77 %).

Conclusion: Corticosteroid treatment provides a clinically and statistically significant improvement in recovery of function in complete idiopathic facial palsy. These results support early steroid treatment for idiopathic facial palsy.

P570

Schwartz-Jampel syndrome associated with sensorimotor polyneuropathy: report of three siblings. S. Nafissi, M. Soltani, Shariati Hospital (Tehran, IR)

Schwartz-Jampel syndrome (SJS) is a rare disorder characterized by myotonia, joint contracture, facial dysmorphism and growth retardation. We present three siblings (two sisters and one brother) 19, 24 and 27 years old from consanguineous healthy parents with SJS. Their clinical features were similar to those previously described. Additionally, they had distal weakness and atrophy, impaired position and vibration senses and absent deep tendon reflexes. Motor and sensory NCS were compatible with an axonal-type sensorimotor polyneuropathy. Myotonic discharges, complex repetitive discharges, myokymic discharges, positive sharp waves and fibrillation potentials were seen on EMG needle examination and MUPs were prominently neurogenic. One of the sisters had mental retardation and hypothyroidism from infancy. This is the first known report of sensorimotor polyneuropathy and hypothyroidism in SJS and the first known cases of SJS from Iran.

P571

Chronic ataxic neuropathy with cold agglutinins: expanding phenotype and treatment possibilities. K. Siddiqui, A. Cahalane, D. Meldrum, M. Keogan, N. Sheehy, O. Hardiman, Beaumont Hospital (Dublin, IRL)

A specific phenotype of chronic inflammatory demyelinating polyneuropathy (CIDP) presents with ophthalmoplegia, areflexia, sensory ataxia and minimal motor signs, and with anti-disialosyl IgM antibodies and cold agglutinins (CANOMED). We report a 53 year old man who developed unsteadiness and painful paraesthesias. He had marked gait disturbance, sensory ataxia and weakness in the distal extremities. CSF protein was elevated (85 mg%), and neurophysiology showed temporal dispersion and prolonged distal latencies in sensory and motor nerves. Serum protein electrophoresis (SPEP) was repeatedly normal, as were cryoglobulins and cold agglutinins. No other cause of neuropathy was identified.

He was treated with plasma exchange, azathioprine and steroids with initial improvement. 4 years after disease onset, his response to plasma exchange and immunosuppression declined. He was treated with intravenous gammaglobulin (IVIg) with improvement in his ataxia, muscle strength (verified repeatedly by quantitative muscle analysis (QMA)).

Infusions of 3–5 days at 4–6 week intervals were required for maximal clinical benefit.

6 years following diagnosis a decline in clinical response to IVIg was verified by QMA. A trial of plasma exchange was complicated by cryoprecipitation of the patient's blood. SPEP revealed an IgM paraproteinemia. The IgM antibodies reactived principally with NeuAc(alpha2–8), NeuAC(alpha2–3) and other epitopes characteristically associated with CANOMED, although our patients clinical phenotype was atypical.

He was treated with a CD20 antibody (Ritoximab) for 4 weeks. There was a lasting improvement in muscle strength, verified by QMA. He is currently maintained on regular infusions of IVIg.

Our patient illustrates a number of important clinical points. 1. His presentation has expanded the clinical phenotype associated with CANOMED paraproteinemia. He had normal eye movements, and significant motor weakness that responded to immunomodulatory therapies. 2. His clinical phenotype preceded the identification of a paraproteinemia with cold agglutinins by 5 years, suggesting that patients with CIDP should be tested at regular intervals for paraproteinemia. 3. We have demonstrated, using QMA, that Rituximab can rescue patients who have become unresponsive to IVIg. The use of CD20 antibodies in the management of CIDP merits further investigation.

P572

Distal polyneuropathy in normotensive type 1 diabetic patients. S. Vuckovic-Rebrina, L. Duvnjak, A. Barada, N. Car, M. Reljanovic, Z. Metelko, University Clinic (Zagreb, HR)

The aim of this study was to establish predictive factors for distal symmetric diabetic polyneuropathy (DSDP) in normotensive normoalbuminuric type 1 diabetic patients. Based on the evaluation of neurological symptoms and signs of DSDP, 110 patients were divided into two groups: patients with DSDP (G1, $n = 40$) and those without DSDP (G2, $n = 70$). Performing a battery of standard Ewing tests (heart rate variation at rest, during deep breathing, Valsalva ratio, 30/15 ratio, blood pressure response to standing up) and power spectral analysis of heart rate variation, autonomic neuropathy was diagnosed in 36 patients (33 %). Among those, autonomic neuropathy was found in 22 patients from G1 (61.1 %) and 14 from G2 (38.9 %), ($p < 0.01$). DSDP further correlated with age (G1 = 39.7y.; G2 = 31.3y.; $p < 0.0001$), longer diabetes duration (G1 = 16.6y.; G2 = 7.0y.; $p < 0.0001$), higher mean overnight systolic (G1 = 111.0mmHg; G2 = 105.5mmHg; $p = 0.004$), diastolic (G1 = 65.8mmHg; G2 = 59.9mmHg; $p = 0.0001$) and mean daily diastolic pressure (G1 = 76.6mmHg; G2 = 72.4mmHg; $p = 0.002$). There were no differences between the groups in gender, body mass index, albuminuria and HbA1c. Using multiple regression analysis longer diabetes duration, higher diastolic blood pressure at night and positive power spectral analysis were independently related to the presence of DSDP. We conclude that the prevalence of distal diabetic polyneuropathy increases with age, diabetes duration, blood pressure elevation and the existence of autonomic neuropathy.

P573

Sensory Guillain-Barré syndrome. Report of 5 cases. M. Charif, J. M. Blard, C. Vergnes, M. Pages, CHU Gui de Chauliac, CHU Arnaud de Villeneuve (Montpellier, F)

Objective To describe clinical and electrophysiological characteristics of 5 cases of acute sensory neuropathy corresponding to Guillain-Barré syndrome (GBS).

Background Motor weakness of more than one limb is one the diagnosis criteria of GBS. The concept of sensory equivalent to the classical GBS is debated and few series have been reported.

Material and Methods From a data base devoted to peripheral neuropathies, we searched for cases of sensory neuropathies with an acute and monophasic course similar to classical GBS. Patients with other possible causes of neuropathy were excluded from the study.

Results From 1995 to 2001, 5 patients were included into the study. There were 3 male and 2 female, aged from 26 to 75 years. An antecedent of infectious illness was found in 4 cases. Clinical symptoms included paraesthesias (5 cases), sensory ataxia (2 cases), hypoaesthesia (2 cases) and areflexia (5 cases). Maximum sensory deficit was reached from 3 days to 4 weeks. All patients had albumino-cytologic dissociation of CSF. Electrophysiological studies showed signs of sensory-motor neuropathy in 3 cases and isolated motor involvement in one case. Electrophysiological signs of demyelination were found in 4 patients.

4 patients were treated with intravenous immunoglobulins. In all cases, a full recovery was obtained after a course varying from 2 to 8 weeks.

Conclusion This study confirms the existence of pure sensory form of GBS. The course of the disease seems faster and much more benign than usual ascending paralysis of classical GBS.

P574

Combined immunotherapy in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with CNS involvement. I.E Markakis, E. Alexiou, A. Tsakiris, A. Tzimas, M. Xifaras, M. Ioannidou, S. Voidonikola, N. Matikas, "Ag. Panteleimon" General Hospital of Piraeus (Korydallos, Piraeus, Ambelokipoi, Peristeri, Ag. Paraskevi, GR)

Background: CIDP is an acquired disorder characterized mainly by progressive symmetrical sensorimotor defects, decreased conduction velocities, elevated CSF protein and demyelination with inflammatory infiltration of peripheral nerves. Several randomized controlled trials have suggested a therapeutic benefit from intravenous immune globulin (IVIg), according to symptoms and laboratory findings. We evaluated the efficacy of combined immunotherapy (oral prednizolone plus IVIg) vs. IVIg alone, in patients with definite CIDP and concomitant CNS involvement.

Methods: Six patients (5 women, 1 man/mean age: 45,8 yrs) suffering from CIDP with CNS involvement were studied. They were all fulfilling the American Academy of Neurology clinical and electrophysiological criteria and had a diagnostic sural nerve biopsy. Brain MRI scans were abnormal, with presence of demyelinating lesions. All patients were initially put on a 5-day trial of IVIg, at a dose of 0,5 g/kg/day and afterwards on monthly one-day trials at the same dose for a period of 12 months.

Results: Although there was a mild improvement in the disability status estimated by the modified Rankin scale and timed 10 meter walk test, findings of CNS disease deterioration were noted in 5 patients during the treatment period. Two patients presented recurrent episodes of diplopia, two developed pyramidal signs and one suffered from cramps and paraesthesias. In the above patients oral prednisolone was added to the therapeutic regimen at an initial dose of 75 mg/d and then tapering to a maintenance dose on an individual basis. Clinical findings of CNS involvement showed complete remission, whereas disability status was significantly better one year after introducing the double regimen.

Conclusions: In cases of CIDP with involvement of the CNS, double immunotherapy with IVIg and oral prednisolone should be considered from the beginning, since the prognosis is worse and the efficacy of immune globulin in controlling CNS disease seems limited.

P575

Cerebral blood flow velocity and vasomotor reactivity in patients with Guillain-Barré syndrome. S. v. Stuckrad-Barre, H. Laufs, T. Kahles, M. Sitzer, K. Kessler, Johann-Wolfgang-Goethe Universität (Frankfurt am Main, D)

Introduction: Dysautonomia such as sinus tachycardia, hypertension, and labile blood pressure assessed by standardized autonomic tests is a common and important complication in Guillain-Barré syndrome (GBS). However, very little is known whether cerebral blood flow and vasomotor reactivity (VMR) are compromised in patients with GBS. To study cerebrovascular function in GBS, we performed measurements on cerebral hemodynamics by using transcranial Doppler sonography (TCD).

Patients and Methods: Three men with GBS were included, mean age was 45 years. One patient required mechanical ventilation for nine days. VMR was tested using TCD insonating both middle cerebral arteries (MCA). Cerebral blood flow velocity (CBFV) increase after bolus injection of acetazolamide (15 mg/kg body weight) was determined immediately after admission and after clinically overt improvement (mean: 12 days) in all three patients.

Results: MCA CBFV was normal in all three subjects and comparison of mean CBFV at rest upon admission and after clinical improvement did not show significant differences (46.6 +/– 12.7 cm/s versus 43.0 +/– 14.3 cm/s). Although acetazolamide VMR was initially within normal limits in all three patients, we found a marked increase in the follow-up measurement after clinical improvement (38.3 % +/– 14.6 versus 61.3 % +/– 18.6; P = 0.056).

Conclusions: So far, information on cerebral hemodynamics in GBS is limited. Thus, preliminary results of our ongoing study provide evidence for altered cerebral VMR in the course of GBS in a small number of patients. Improvement of both motor and dysautonomic symptoms paralleled the observed increases of VMR. A larger series of patients will show whether measurements of VMR prove to be a sensitive and prognostically valuable indicator of clinical course and suspected neurovascular dysregulation in GBS.

P576

Necrotising vasculitis and isotretinoin. Y. Naegelin, A. Czaplinski, M. Tolnay, A. J. Steck, Kantonsspital Basel (Basel, CH)

A previously healthy 19-year old man was treated with Isotretinoin (10 mg/day) for 4 months for acne (vulgaris). After 10 weeks of treatment he developed a persistant pain in the distal part of the lower legs and in the left ankle region when walking. He also reported plantar sensory deficit and dysesthesia in both legs, that affected his gait. Neurological examination on admission revealed an exquisite pain caused by pressure on his lower legs and a staggering gait. Laboratory findings showed a slight leucocytosis and elevated blood sedimentation rate. C-reactive protein, liver enzymes and creatine-phosphokinase were normal, ANA, c-ANCA and p-ANCA were negative,viral and bacterial serology was negative. Protein electrophoresis and cerebrospinal fluid were normal. Electromyographie (EMG)showed the absence of neurogenic or myogenic changes. Magnetic Resonance Imaging (MRI) of the left lower leg showed a swelling of muscles innervated by the peroneal nerve that was compatible with a diffuse myositis. A biopsy of the left tibial muscle showed a subacute necrotising vasculitis of small vessels. Isotretinoin therapy was then discontinued,three weeks after the onset of symptoms and prednisone was given at 1 mg/kg body weight. The patient recovered within a few months.

Isotretinoin (13-cis-retinoic acid) is a synthetic derivative of vitamin A that modulates cell proliferation and differentiation. Its well known toxic side effects include bone lesions, seronegative spondyloarthropathies (SNSA), disseminated idiopathic skeletal hyperostosis (DISH), arthritis, myopathy and vasculitis. Retinoids are known to cause immune dysfunction and cases of vasculitis and Isotretinoin have been reported previously.

In the present case the occurence of an Isotretinoin-induced necrotising vasculitis is suspected.

To our knowledge this represents one of the rare reports of vasculitis induced by this drug that presents with neurological symptoms and adds to the variety of complaints that patients with vasculitis may present.

P577

Intravenous immunoglobulins (IVIG) in Guillain-Barré syndrome (GBS) -The Indian experience. A. Rohatgi, C. Agarwal, I. Anand, P.K Sethi, Sir Gangaram Hospital New Delhi (New Delhi, IND)

A retrospective study regarding the efficacy of IVIG in GBS was carried out at SGRH, New Delhi.

This study was carried out from 1998–2001.The inclusion criteria were severe disease(aid needed for walking),bulbar/respiratory involvement and onset of neuropathic symptoms within previous two weeks. The duration of follow-up varied from 7days to one year. The mean age of patients was 35 years and there were 28 males and 14 female patients. The outcome measures used were time to discontinue ventilation, time to recovery of unaided walking and the trend describing recovery from disability during follow-up. There was one death, three patients did not improve, five patients improved partially and one patient relapsed, rest of the 32 patients showed good improvement. In conclusion, IVIG was effective in 76 % of patients. It was not useful in patients with rapid onset and evolution of disease and early respiratory involvement.

P578

Pregabalin relieves pain and reduces pain interference with sleep in patients with diabetic neuropathy. U. Sharma, J. Moore, L. LaMoreaux, A. Corbin, E. Garofalo, R. M. Poole, Pfizer Global Research and Development (Ann Arbor, USA)

Rationale: Diabetics often experience painful peripheral nerve dysfunction, primarily distal, symmetrical polyneuropathy. Two previous clinical trials (1008–14 and 1008–29) have shown that pregabalin is effective in relieving pain in these patients. This randomized, double-blind, placebo-controlled, parallel-group trial evaluated the efficacy and safety of pregabalin 300 mg/d (100 mg TID) for reducing pain in patients with painful diabetic peripheral neuropathy.

Methods: The trial consisted of a 1-week baseline phase and an 8-week double-blind fixed-dose treatment phase in diabetic neuropathy patients for at least 1 year, but no more than 5 years. The only allowed medications were stable dosages of SSRIs for depression and acetaminophen. 146 patients were randomized to receive 300 mg/d pregabalin (100 mg TID; 76 pts) or placebo (70 pts). The primary efficacy parameter was the endpoint weekly mean pain score from patient daily pain diaries (11-point numerical rating scale). Secondary measures included the SF-McGill Pain Questionnaire (SF-MPQ), sleep interference score, Clinical and Patient Global Impressions of Change (CGIC, PGIC), and proportion of patients with 50 % or greater decrease in endpoint mean pain score.

Results: Compared to placebo patients, pregabalin-treated patients had significant improvement in the endpoint mean pain score (–1.47; $p = 0.0001$), evident at week 1 and continuing for the duration of the trial. Pregabalin-treated patients were more likely to have 50 % reduction in pain from baseline compared to placebo (40 % vs. 14.5 %; $p = 0.001$). Endpoint mean sleep interference scores, SF-MPQ total scores and mean VAS scores were significantly improved for the pregabalin group compared to placebo; significant differences were also evident by week 1. Significant improvements were also observed for the PGIC and CGIC. Ten patients withdrew due to adverse events, and 4 due to lack of efficacy. The most commonly reported adverse events were dizziness (35.5 %) and somnolence (19.7 %); however, withdrawal rates due to these events were low. Pregabalin was well tolerated: 87 % of patients completed the trial and 84 % entered a follow-on safety trial.

Conclusions: Pregabalin 300 mg/d produced statistically and clinically significant improvements in pain compared to placebo in diabetic neuropathy patients. Pregabalin also improved sleep interference and global measures of change, and is safe and well-tolerated.

P579

TNF-alpha-converting enzyme is expressed in inflammatory demyelinating disorders of the peripheral nervous system. B. C. Kieseier, A. H. K. Chan, K. V. Toyka, R. Gold, H.-P. Hartung, Heinrich-Heine University, Julius-Maximilians-University (Dusseldorf, Wurzburg, D)

Tumor necrosis factor-alpha (TNF-alpha) is a major proinflammatory cytokine implicated in the pathogenesis of inflammatory demyelinating diseases of the peripheral nervous system (PNS), such as the Guillain-Barré syndrome (GBS). Soluble TNF-alpha is released from its membrane-bound precursor by shedding through a proteinase, identified as TNF-alpha-converting enzyme (TACE; ADAM–17), a member of the ADAM (A Disintegrin And Metalloproteinase) domain family of proteins. To investigate the role this proteinase in inflammatory demyelinating disorders of the PNS the expression and distribution patterns of ADAM–17 were investigated immunohistochemically using an avidin-biotin detection system in adoptive transfer experimental autoimmune neuritis (AT-EAN), an animal model for human GBS. Immunoreactivity against ADAM–17 could be found in diseased animals with peak expression concurrent with maximal disease. By double labelling experiments invading T cells could be identified as the cellular source of this proteinase. These data were strengthened by studying sural nerve biopsies from GBS patients. Positive immunoreactivity against ADAM–17 could be detected in the biopsies, and increased protein expression was demonstrable in the cerebrospinal fluid of GBS patients in comparison with non-inflammatory controls. Our findings suggest that ADAM–17 is upregulated during AT-EAN and is expressed in GBS and therefore may contribute to the pathogenesis of inflammatory disorders of the peripheral nervous system.

P580

Pain: a frequent and often overlooked presenting symptom in Guillain-Barré syndrome. M. Carpo, A. Bersano, A. Citterio, R. Pedotti, F. Lolli, G. Scarlato, E. Nobile-Orazio, Milan University, IRCCS C. Mondino, Florence University Western Lombardia GBS Study Group

Pain is a common symptom reported in up to 70 % of Guillain-Barré Syndrome (GBS) that sometimes requires an intensive management. Pain, including paraesthesia, dysaesthesia, radicular pain, muscular discomfort following exercise, myalgia and meningism, often precedes muscular weakness by few days to one week and can persist during the course of illness. We retrospectively analysed the clinical features of pain in 184 GBS patients referred to our attention in the last 10 years. 79 % of patients complained "painful syndromes", 14 % of whom had deep and shooting low-back or dorsal pain irradiating to lower limbs or to the interscapular region, while 54 % had paraesthesia or dysaesthesia described as burning or tingling involving distal upper or lower limbs, trunk and perioral area and 32 % both symptoms. Few patients (1.3 %) complained severe headache. In almost all patients the "painful syndrome" preceded limb weakness by some days prompting the use of non-steroidal anti-inflammatory drugs (NSAIDs) with partial remission. These patients often referred to medical examination later than patients presenting with limb weakness. When pain was present, it was usually so severe to be spontaneously reported by patients presenting to the hospital. During the period of maximum functional impairment, our patients had more frequently pain than paraesthesia and required NSAIDs or steroids to allow passive or active motion; no one required opioid analgesics. Later in the course of illness, paraesthesia in stock-glove distribution was the predominant and persistent sensory symptom. In conclusion, also in this retrospective analysis of GBS patients, pain and paraesthesia/dysaesthesia were prominent symptoms often appearing before the onset of limb weakness. Their presence during the course of illness, if untreated, could interfere with early physical therapy resulting in a longer period of confinement to bed increasing the risk of related severe medical complications. In addition the recognition of pain as presenting symptom may lead to an earlier diagnosis and, possibly, therapeutic intervention in GBS.

P581

Recurrent sensory ataxic neuropathy with ophthalmoplegia: a case with three episodes over 5 decades. C. Bensa, M. Borg, J. Boucraut, E. Delpont, M. Chatel, Hopital Pasteur, Hopital La Conception (Nice, Marseille, F)

This patient, born in 1927, presented three neurological episodes:

- the first in 1948, made of flaccid tetraparesia, with oculomotor, facial and respiratory palsies. He recovered completely but kept a generalised deep tendon areflexia.
- the second, in 1976, occurred after an aspecific infectious event and associated diplopia, 4 limb and face paresthesiae, dysarthria, 4 limb motor weakness and bilateral facial palsy installed in few days; mechanical ventilation was temporally required; recovery was complete.
- the last one, in September 2001, associated bilateral VI palsy, bilateral acral paresthesiae, sensory ataxia with loss of vibration sense. Early electrophysiological features included decreased sensitive conduction velocities with an increased central conduction time revealed by somesthesic evoked potentials. Serological investigations revealed the presence of high titer of IgG anti-GQ1b, IgM anti-GD1b, but no IgG or IgM anti-GM1. Cerebrospinal fluid analysis revealed hyperproteinorachia (0,98 g/L). Campylobacter jejuni serology was negative. Brainstem MRI was normal. The patient began to improve 3 days after intravenous immunoglobulin (IV Ig) treatment and complete recovery was obtained in two weeks.

This case is remarkable by the similarity of the three episodes, separated by 25-year asymptomatic intervals. Ophthalmoplegia belonged to the three recurrent acute events and detection of IgG antiGq1b antibodies is in favor of recurrent Miller Fisher syndromes. Sensory ataxia with loss of vibration sense might be related with IgM anti-GD1b. The clinical signs were similar with those present during the chronic sensory ataxic polyneuropathy with anti-disialosyl IgM antibodies as described by Willison et al. in 1996 under the acronym CANOMAD (chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins and anti-disialosyl antibodies).

Reference

Willison, et al. (1968–1977) The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies, Brain, Vol. 124, No. 10, October 2001

P582

Chronic inflammatory demyelinating polyneuropathy (CIDP) and membranoproliferative glomerulonephritis. M. Capasso, A. Di Muzio, S. Lupo, L. Amoroso, P. Cappelli, L. Di Liberato, S. Di Stante, A. Lugaresi, Center for Neuromuscular Diseases, Clinica Nefrologica, Clinica Neurologica (Chieti, I)

Background: CIDP has been rarely reported in association with glomerulonephritis. To our knowledge only 5 cases of membranous glomerulonephritis, 2 of focal-segmental glomerulosclerosis and 1 of IgA nephropathy have been described in CIDP patients. The presence of a pathogenetic autoantibody directed to a common antigen in myelin and glomerular basement membrane has been hypothesized.

Case report: A 60-year-old man developed proteinuria (3.4 g/24 h) without clinical signs of nephrotic syndrome. Six months later he began to complain of paresthesias and progressive limb weakness. Examination showed ataxic gait, predominantly distal weakness with bilateral foot drop, glove-stocking sensory loss, decreased or absent deep tendon reflexes, and postural tremor. Electrophysiological studies showed a sensory-motor demyelinating polyneuropathy with marked axonal damage in lower limbs. CSF examination showed increased proteins, no cells. HBV, HCV and HIV markers, rheumatoid factor, ANA, ANCA, ENA were negative. Monoclonal gammopathy and cryoglobulins were absent. C3 and C4 were normal. Circulating immune complexes were 37 % (n. v. < 35). Anti-ganglioside (GM1, GM2, GA1, GD1a, GD1b), anti- sulfatide and anti-MAG antibodies were negative. Sural nerve biopsy showed small epineural and perineural infiltrates, marked loss of fibers, and no deposits of IgG and IgM or amyloid. A membranoproliferative glomerulonephritis with associated interstitial nephritis was diagnosed through kidney biopsy. Neurological and renal abnormalities improved with prednisone.

Conclusion: Here we report the first case, to our knowledge, of membranoproliferative glomerulonephritis associated with CIDP, and the sixth presenting with CIDP and glomerulonephritis. The putative common pathogenetic antigen is not represented, at least in our case, by MAG, sulfatides or gangliosides usually associated with GBS.

P583

Guillain-Barré syndrome (GBS) following Rubella. M. Capasso, A. Di Muzio, C. M. Caporale, S. Lupo, A. Uncini, A. Lugaresi, Clinica Neurologica, Center for Neuromuscular Diseases (Chieti, I)

Background: GBS has rarely been reported in association with rubella infection or vaccination with attenuated virus of different strains. Recently, anti-myelin basic protein (anti-MBP) antibodies were reported in a woman with acute demyelinating motor neuropathy after rubella vaccination (RA27/3 virus strain). Antibodies showing a cross-reactivity between MBP and a viral antigen were present in this patient.

Case report: A 20-year-old man was admitted because of weakness without sensory complaints ten days after rubella. Examination showed distal weakness of all four limbs (grade 4 MRC) and brisk tendon reflexes. He couldn't get up from squatting, walk on heels and toes. Cranial nerve and sensory examination were normal. Serological tests revealed IgG and IgM anti-rubella. CSF examination showed increased protein content (0,8 g/L). Electrophysiological examination showed partial motor conduction blocks in eight nerves. Sensory conduction was normal even across the sites of conduction block. MRI of brain and spinal cord and SEPs were normal. The patient was treated with 4 plasmaphereses and improved gradually with almost complete recovery since month 3. Anti-ganglioside (GM1, GM2, GA1, GD1a, GD1b) and anti-sulfatide antibodies (IgG, IgA and IgM) were tested through ELISA and were negative at day 1 and 15. Anti-MBP antibodies (IgG, IgA and IgM) were tested through western blotting using either a partially purified bovine CNS myelin preparation (kind gift of Dr Nobile-Orazio) also containing myelin-associated glycoprotein (MAG) or a 50 % purified bovine MBP (Sigma) as antigen. Anti-MBP antibodies were negative at day 1 and 15.

Conclusion: Results of our immunological studies indicate that cross-reactivity between viral antigens and MBP does not represent a common pathogenetic mechanism in acute polyneuropathy following rubella infection or vaccination using an attenuated virus. Exclusively motor involvement, possibly due to cross-reactivity with antigens available to antibody binding on motor fibers only, seems to be common in post-rubella polyneuropathy.

P584

Clinical and genetic study of 10 cases with early-onset demyelinating neuropathy including one with a mutation in periaxin gene. Y. Parman, M. Poyraz, I. Baris, B. Bilir, E. Battaloglu, Z. Yapici, V. Plante-Bordeneuve, A. Guiochon-Mantel, P. Serdaroglu, F. Deymeer, M. Eraksoy, Istanbul University, Bosphorous University, CHU de Bicêtre (Istanbul, TR; Kremlin-Bicêtre, F)

Dejerine-Sottas Disease (DSD) which is a severe demyelinating hypertrophic neuropathy of infancy has remained a controversial and confusing subject. Molecular genetic studies indicate that DSD may be associated with heterozygous point mutations in the peripheral myelin protein 22 (PMP 22), the myelin protein zero (MPZ) gene or the early growth response gene 2 (EGR2). Recently, it has been shown that mutations in the periaxin (Prx) gene cause an early-onset demyelinating neuropathy with DSD phenotype. The Prx gene in Schwann cells encodes L- and S-periaxin, two abundant domain proteins which play a role in the stabilization of myelin.

In order to explore further the spectrum of DSD, we studied the clinical and genetic aspects of 10 early onset demyelinating neuropathy cases with DSD phenotype born of unaffected parents. Autosomal recessive inheritance was likely in 5 cases only. Age of onset ranged from the neonatal period to 3.5 years. Presence of CMT1A duplication was excluded by both Southern and STR analyses in all. Patients were previously screened for PMP22, MPZ and EGR2 gene mutations. Further SSCP and subsequent sequencing analysis identified a point mutation in periaxin gene in one case. The patient is homozygous for the mutation which is a C ± T transition leading to R1070 ± X in exon 7 coding for the acidic domain. Although DSD phenotype is quite distinct, our results suggest that patients with this phenotype show a wide genetic heterogeneity.

P585

Neuropathy associated with biclonal and triclonal gammapathy: a study of 9 cases. E. Roze, D. Adams, C. Theodore, C. Lacroix, M. Corcia, K. Abbed, G. Said, CHU Bicetre (Le Kremlin-Bicêtre, F)

Association of a peripheral neuropathy and biclonal gammopathy has been rarely reported.

In order to define the clinicopathological profile and the prognosis of this subgroup, we reviewed the files of 9 patients with neuropathy associated with biclonal or triclonal gammopathy referred to our department over the past 12 years, including 7 males and 2 females. The mean age at referral was 62 years (range from 56 to 72).

Four patients had a distal symmetrical polyneuropathy in association with autonomic dysfunction in 1 and a multifocal neuropathy in 5. One patient had a purely sensory neuropathy but 8 a sensory-motor neuropathy which was severe in 2. Nerve biopsy showed amyloidosis in one. The neuropathy had a mixed demyelinating and axonal pattern in 4, an axonal pattern in 2 including one with asymmetrical fascicular involvement and a demyelinating pattern in 3. 6/7 patients had an increased level of protein content in CSF.

Eight patients had a biclonal gammopathy including both IgG and IgA components (2), IgG and IgM component (2), two IgM components (2), two IgG components (1), two IgA components (1) and one patient had a triclonal IgM gammopathy. Serum level of biclonal components was usually low (< 10 g/L). 4/5 patients with an IgM component had anti-MAG antibodies. Two patients had a POEMS syndrome, 2 had a Waldenström macroglobulinemia, one a solitary plasmacytoma, one a light chain (AL) amyloidosis, and 3 a biclonal gammopathy of undetermined significance.

Eight patients were treated for lymphoproliferative disorder and/or for progressive neuropathy usually with alkylating agents. Patient with solitary plasmacytoma received also local radiotherapy, AL amyloidosis was treated by high dose of melphalan. The mean duration of follow up was 5 years (range from 1 to 9 y). After therapy, the neuropathy improved in 5 patients, remained unchanged in 2 and worsened in 1. In 2/5 pts with positive response of therapy the neuropathy relapsed and responded to chemotherapy. Three patients died from: severity of the neuropathy (1), anasarca (1), unrelated cause (1). Another patient developed myelodysplasia (monosomy 7).

In conclusion, neuropathy associated with biclonal gammopathy are usually severe, and associated with various lymphoplasmacytic disorder.

P586

Matrix-metalloproneinase (MMP) expression in nerve biopsy of CIDP: a RT-PCR and immunohistochemical study. A. Boulahia, C. Lacroix, D. Adams, CHU Bicetre (Le Kremlin-Bicêtre, F)

Matrix-metalloproteinase is a large family of proteinases which are known to be essential for degradation of the protein components of extracellular

matrix. Their pathogenic role has been suspected in many inflammatory diseases including MS and inflammatory demyelinating neuropathies.

Aim of this study was to assess the expression of large number of MMP in nerve biopsy of CIDP patients in order to evaluate their potential role.

Methods: We studied samples of nerve biopsy in patients with CIDP, for expression of MMP by semi-quantitative RT-PCR and also by immunohistochemistry. Thirteen MMP were studied by RT-PCR including stromelysin (MMP3, MMP10, MMP11), gelatinase (MMP2 and 9), collagenase (MMP1, MMP8, MMP13) matrix-type (MMP14, MMP15, MMP16) matrilysin (MMP7) and metalloelastase (MMP12). Beta actin was used as internal control.

We studied patients with CIDP (n = 4) and as controls: nerve of patients with HNPP (hereditary nerve pression palsy) (n = 1) and axonal inflammatory neuropathy (n = 1) and normal sensory nerve in ALS patients (2). Glioblastoma was used as a positive control for MMP.

Results: Various MMP were detected in CIDP by RT-PCR. All 3 stromelysins were constantly and strongly expressed in CIDP. Conversely, other MMP were expressed inconstantly and at low level including matrix-type in l' pts, gelatinase in only 2 pts and collagenase (MMP–13) in 1 pt. On immunohistochemical studies, stromelysin MMP11 was expressed in endoneurial macrophages in CIDP patients and stromelysin MMP3 and MMP10 were expressed by endothelial cells in both CIDP patient and HNPP patient. There was no expression of MMP by Schwann cells. In 2 neuropathy controls, expression of MMP was more various and at low level, normal nerve expressed only collagenases.

Positive control (glioblastoma) showed high expression of all stromelysins, gelatinase and MMP1 by RT-PCR. Immunohistochemical study showed expression of stromelysins by tumoral cells and of gelatinase by microglia cells.

Conclusion: There is a strong expression of stromelysins in nerve biopsy of CIDP patients. Further studies are necessary before considering them as potential target for therapy.

Sleep disorders

P587

Long-term course of restless legs syndrome in dialysis patients after kidney transplantation. J. Winkelmann, A. Stautner, W. Samtleben, C. Trenkwalder, Max Planck Institute of Psychiatry, Krankenhaus Muenchen Schwabing, Ludwig Maximilians University, Georg August University (Munich, Gottingen, D)

Background: Restless legs syndrome (RLS) is a common cause of sleep disturbance and a frequent complaint in hemodialysis patients. Factors triggering the disease in uraemia have not yet been identified. The course of RLS symptoms after a kidney transplant has never been investigated systematically.

Methods: We investigated the clinical long-term course of RLS in haemodialysis patients who underwent kidney transplantation. Patients were investigated three times with a standardized questionnaire: at baseline and twice after their kidney transplant. Severity of RLS was rated by the patients (0 = no symptoms, 10 = very severe symptoms). The last follow-up visit was used for the description of the final outcome.

Results: 11 out of 64 haemodialysis patients with RLS (5 male, 6 female, severity of RLS at baseline 7.8 ± 2.3 [mean ± SEM]) had received kidney transplants. In all subjects RLS symptoms disappeared within 1 to 21 days after the kidney transplant. At follow-up visits, 4 patients whose transplanted kidneys still functioned well were still free of RLS symptoms up to the longest follow-up period of 9 years. In a further 3 patients, RLS symptoms gradually started again (severity 1 ± 0 [mean ± SEM]). In 3 of 11 patients, the kidney transplant failed and RLS symptoms reoccurred within 10 days to 2 months (severity 7.3 ± 2.6). RLS symptoms reoccurred in 1 patient with the failure of the transplant but disappeared again after a second successful transplant.

Conclusion: Kidney transplantation has a strong and positive influence on RLS symptoms in haemodialysis patients. Haemodialysis patients can expect a substantial improvement of RLS symptoms after a successful kidney transplant.

P588

The association between sleep apnea syndrome and stroke. B. Labuz-Roszak, K. Pierzchala, M. Tazbirek, Silesian School of Medicine (Zabrze, PL)

The association between sleep apnoea syndrome (SAS) and cerebrovascular diseases although widely investigated in last years remains still unclear. SAS is considered to be not only a risk factor but also a consequence of stroke.

The aim of our study was to determine the frequency of SAS in patients with stroke admitted to our stroke unit and to analyse the relationship between SAS and topography of stroke.

Material and Methods: The examined group consisted of 27 patients with stroke confirmed by computed tomography (mean age: 66 ± 10 years, mean BMI: 24.4 ± 4.4). In all cases a sleep study was performed in the acute phase of stroke (1–10 days) using a portable respiratory recording device (Poly Measam) which measures nasal and oral air flow, chest wall movements, heart rate, oxygen saturation and snoring.

Results: The frequency of SAS (apnoea/hypopnea index-AHI > 10/h) among patients in acute phase of stroke in our unit was 59 % (15 persons). 5 persons had an AHI > 20/h and 5 persons had an AHI > 30/h.

Mean AHI in SAS patients was 26,89 ± 4,94, mean minimal saturation of O2 (SaO2)- 71,2 ± 13,24.

We observed mostly obstructive (53.3 % of all) and mixed apnoeas (40 %). Central apnoeas constituted only 6,7 % of all recorded respiratory disorders.

We did not observe any relationship between SAS and stroke localization.

Conclusion: The frequency of SAS in high in patients with stroke. Screening for respiratory disorders during sleep should be a routine practice in every stroke unit.

P589

Mirtazapine induces confusion with hallucinations and REM sleep behaviour disorder in parkinsonism. A. L. Luciano, G. D'Andreamatteo, A. Di Rollo, D. Iacono, A. Thomas, M. Onofrj, Neurophysiopathology (Pescara, I)

Mirtazapine is a new noradrenergic and specific serotoninergic antidepressant drug. Mirtazapine is the first of the new developed drugs classified as Noradrenergic and Specific Serotoninergic Antidepressant. Its effect appear to be related to the dual enhancement of noradrenergic and serotonine 5HT1, receptor mediated serotoninergic neurotrasmission, as the drug directly blocks 5HT2 and 5HT3 receptors and apparently does not induce anticholinergic, adrenergic and serotonine related adverse events.

Shortly after the initiation of mirtazapine treatment of depression we observed the appearance of hallucinations, psychomotor agitation and cognitive changes accompanied by REM sleep behaviour disturbance (RBD) with apparent dream enactment in two male patients affected by moderate L-Dopa responsive parkinsonism and the appearance of RBD in a third male patient, with rigidity and cogwheeling in the left arm.

Polysomnography evidenced short onset REM sleep (SOREM) and lack of muscle inhibition with REM sleep during Mirtazapine treatment.

These disturbances promptly remitted after the drug discontinuation and did not reappear in the following year (patients 2 and 3) and in following 2 years (patient 1). RBD is consistently described in synucleinopathies (Idiopathic PD, Lewy Bodies Dementia, Multiple System Atrophies and Progressive Supranuclear Palsy); its appearance may precede the appearance of PD symptoms. Recently a relationship between RBD and hallucinations in parkinsonism has been postulated and the observation of degeneration of the cholinergic sub-nucleus of the Locus Coeruleus (nucleus subcoeruleus), also suggested that RBD might be linked to alteration of cholinergic structures.

Even though RBD might be linked with hallucinations and psychosis, is not described among the mental disturbances induced in parkinsonism by drug treatment. We describe the appearance of RBD after the administration of a drug lacking anticholinergic effects and its disappearance, for as much as three years, after the drug withdrawal in three patients affected by initial forms of parkinsonism.

P590

Respiratory dysfunction and Chiari malformation type I (CM I): clinico-electrophysiological correlations. V. K. Kimiskidis, E. Serasli, S. Papagiannopoulos, V. Tsiara, G. Dimopoulos, V. Katsaridis, P. Hristaki, A. Kazis, G.Papanikolaou Hospital (Thessaloniki, GR)

Background: CM I is occasionally associated with disorders of breathing and sleep.

Goal of the study: We report on a rare case of CM I with acute respiratory failure (ARF) as presenting symptom and mixed type of sleep apnoeas (SA).

Methods: A 32 year old man was admitted for investigation of intractable hypercapnia following ICU hospitalisation for ARF. Neurological examination revealed severely affected cranial nerves IX-XII and mild pyramidal, cerebellar and dissociated sensory signs. MRI scans showed

CM I with syringomyelia. There was hypoxemia with hypercapnia and polysomnography revealed severe respiratory dysfunction with mixed type of SA (Apnea Hypopnea Index 58/h,central SA total:58,obstructive SA total:12,mixed:84,minSaO2:77 %).In order to elucidate the underlying mechanisms, we studied the corticodiaphragmatic pathway with magnetic stimulation. This technique assesses the integrity of the efferent motor pathway from the cortex to the diaphragm and helps categorize causes of respiratory dysfunction. Diaphragmatic motor evoked potentials were recorded with surface electrodes placed in the sixth to eighth intercostal space. Cortical stimuli were delivered with a circular coil centered over the vertex. Phrenic nerve (PN) was stimulated with a circular coil centered over the C7 vertebra.

Results: Cortical latencies to diaphragm (17.3,17.7 ms, right, left respectively), CMCT (11.6,12.1ms) and peripheral PN latencies (5.7,5.6ms) were within normal limits. This observation rules out a malfunctioning of the corticodiaphragmatic pathway (i. e. due to compression of the respiratory center by the ectopic cerebellar tonsils or of the phrenic motoneurons by syringomyelia) as a cause of the respiratory insufficiency. We postulate that stretching of nerves IX and X causes dysfunction of upper airway musculature and vocal cord paresis, leading to occlusive SA. In addition, due to IX nerve injury 'there is carotid body denervation and a lack of functional chemoreceptor afferents which may explain central SA.

Conclusions: I may rarely present with ARF and SA. An electrophysiological investigation into the mechanism of the respiratory dysfunction is presented.

P592

Periodic limb movement (PLM) disorder: autonomic cardiac activation in relation to Cyclic Alternating Pattern (CAP). L. Ferini-Strabi, L. Riva, V. Castronovo, A. Oldani, M. Zucconi, A. Bianchi, IRCCS H San Raffaele, Politecnico (Milan, I)

The rhythm of PLM involves the EEG, the heart rate (HR), blood pressure and breathing activity. PLM periodicity recalls the physiological EEG arousal rhythm during NREM sleep described as CAP. It has been recently found in healthy subjects that the sympathovagal balance is unbalanced, during CAP, towards a sympathetic activation (Ferini-Strambi L et al., Clin Neurophysiol 2000).

Aims of this study were to evaluate the autonomic changes during CAP condition in presence or absence of PLM, and the coupling among PLM, HR variability, respiratory and EEG signals.

Eight patients (3 M, 5 F; mean age 50 yrs) with PLM disorder were evaluated. The EEG, respiration, ECG and EMG-leg signals in all sleep stage 2 NREM without artifacts were analysed. The HR variability signal (t) was derived from the ECG as the sequence of the RR time intervals as function of the beat number (interval tachogram). The respirogram synchronous with the tachogram was obtained by subsampling the signal in correspondence of each R wave (r). The EEG variability signal was evaluated in time windows corresponding to RR time intervals (e); the EMG variability signal (m) was derived with the same procedure. The coupling relationships between pairs of variability signals was quantified by means of an autoregressive spectral analysis in the bivariate form.

A synchronization of respiration and tachycardia preceding PLM (autonomic sympathetic pre-activation) in correspondence of the EEG activation has been observed by means of a time domain analysis.

A significant increase of synchronization between t and r ($p < 0.001$) was found in the passage from 2 CAP without PLM to 2 CAP with PLM, on the basis of the percentage value of the coherent power between the signals (CPtr%). This indicates an increased coupling between the signals and could be interpreted as an increased (unexpected) vagal activation. During 2 CAP with PLM, m, e, t and r signals were characterized by high synchronization with a significant ($p < 0.05$) increasing trend of percentage coherent power in the passage from 2 NCAP to 2 CAP, to 2 CAP with PLM.

In conclusion, the relationship between PLM and cardiac autonomic activity may not be correctly interpreted by the traditional parameters used for quantifying the sympathovagal balance, both in time and in frequency domain. Our results in patients with PLM show the possibility of a "common central oscillator" triggering the different systems evaluated.

P593

Chiari malformation and sleep-related – breathing disorders. V. Stal, F. Parker, N. Aghakhani, M. Tadié, P. Escourrou, P. Bourgin, Hopital Antoine Béclère, CHU Bicêtre (Clamart, Kremlin Bicêtre, F)

Patients suffering from Chiari malformation (CM) show a wide variety of neurologic, pharyngo-laryngeal symptoms and signs suggesting brainstem, spinal cord or lower cranial nerves dysfunction. The anatomical localization of respiratory centers and pathways may also explain their possible injury in CM and the presence of respiratory disturbances, in particular during sleep. Several case reports of CM related-sleep apnea syndrome have been described in the literature, but the involvement of CM in the mechanisms underlying respiratory disturbances are poorly understood.

Objectives: To determine the mechanisms and the incidence of sleep-related breathing disorders in patients suffering from CM.

Methods: 16 patients (7 females and 9 males, mean age 38,69 ± 15 years) consecutively diagnosed with a Chiari Malformation in a department of neurosurgery were included over a period of 21-months. All the patients were submitted to physical examination, MRI, lung function evaluation (including also when necessary diaphragmatic EMG and breathing challenge to CO2) and polysomnography (including oesophageal pressure recording).

Results: Central sleep apnea syndrome was observed in 4 patients, obstructive or mixed sleep apnea syndrome in 3 and central alveolar hypoventilation in one patient. All these cases were related to CM except one patient who had an increased body mass index, a pharyngeal obstruction related to a retrognathia without motor or sensitive pharyngo-laryngeal innervation. 8 patients had no sleep respiratory disturbances.

The presence of sleep breathing disorder related to CM was statistically more frequent when patients displayed cerebellar dysfunction ($p < 0.05$), cranial nerves injury ($p < 0.01$), cerebellar tonsils herniated to the superior edge of axis ($p < 0.05$). No statistical relationship to the presence of basilar impression or syrinx was observed.

Conclusion: Sleep breathing disorders in patients suffering from CM are frequent in our study and are accounted for by various mechanisms. Sleep respiratory disturbances might be a cause of mortality in CM disorders and might increase the risk of post-operative respiratory failure. Finally, these results suggest that sleep breathing disorders should be systematically screened leading to an adapted treatment in patients suffering from CM.

P594
L-dopa-responsive restless legs syndrome caused by a lesion in the dorsal medulla oblongata. E. A. Spottke, S. Nessler, J. C. Moeller, H. Pape, S. Bien, W. H. Oertel, N. Sommer, Philipps University Marburg (Marburg, D)

Introduction: Restless legs syndrome (RLS) is a common sensorimotor disorder with an estimated prevalence of 2–9 %. It is characterized by an urge to move the legs usually associated with leg paresthesias and motor restlessness (1, 2). These sensations occur almost at rest and are at least partially or temporarily relieved by activity (3).The symptoms are most pronounced in the evening and at night (4). The diagnosis of RLS is based on these four clinical features (1–4) as defined by the Int. RLS Study Group. Both primary and secondary causes of RLS have been reported. Secondary causes include, for example, iron deficiency, uremia, (diabetic) neuropathy and several drugs. Improvement in symptoms will often occur if these causes are removed. Rarely RLS is caused by spinal lesions. Dopaminergic agents are currently considered the treatment of choice for RLS.

Case report: A 60-year-old woman presented with a 3-year history of a slowly progressive left hemiparesis. At night paresthesias of her left leg occurred which improved by activity. Three months later, similar but less pronounced sensations occurred also in her right leg. The central motor conduction time was prolonged to the left limbs. The SSEPs were prolonged on the left side above the C5 level as well. MRI showed a non-enhancing lesion which was hyperintense in T2 weighting in the left dorsal medulla oblongata. During polysomnography a PLM index of 30.4 n/h, a PLMS index of 16.6 n/h and a PLMS +arousal index of 6.4 n/h was observed. REM sleep was reduced to 1 % of total sleep time. The Vit. B12 level was decreased to 112 pmol/l (130–700 pmol/l) and homocysteine level was elevated to 29,3 µmol/l. Despite a normal Schilling test, Vit. B12 was substituted leading to normalized blood levels. Electrophysiological parameters improved markedly after substitution and the clinical features and the MRI lesion were stable during 1 year follow-up. The RLS has been successfully treated with L-Dopa (200 mg/die). Conclusion: The case described above suggests that RLS was due to a CNS lesion probably caused by funicular myelosis. Although usually included in the extended laboratory examination for the differential diagnosis of RLS, to our knowledge there have been no case reports on L-Dopa- responsive RLS caused by Vit. B12 deficiency. Irrespective of the cause, the location of the lesion in the dorsal medulla oblongata points at a pathophysiological involvement of the central sensory system in (secondary) RLS.

P595
Rapid eye movement sleep behavior disorder: a case-series study of 17 patients. V. Kiriakakis, N. Tsiftsis, Lamia District General Hospital (Lamia, GR)

Rapid eye movement sleep behavior disorder (REM SBD) is a parasomnia characterized by repeated episodes of complex motor activity during periods of REM sleep. The estimated overall prevalence of this disorder is 0.5 %.

We present the demographic, clinical, aetiological and laboratory findings in 17 patients (pts) seen at the Department of Neurology and Movement Disorders clinic of our hospital. Twelve pts (70.6 %) were male. The mean age at onset was 57.2 years (range 6–77 yrs) and the mean age at the time of diagnosis was 68.4 yrs (21–81). The mean follow-up period after diagnosis was 7.1 months (range 1–17 months). Eleven pts (64.7 %) had fallen or running out of the bed suffering minor injuries during the episodes of REM SBD. The primary disorder – for which they were mainly followed – was Parkinson's disease in 8 pts, progressive supranuclear palsy in 3 pts (vascular in 2), multiple system atrophy in 2 pts, essential tremor in one male patient and depression in 2 pts (one of them also had essential tremor and restless legs syndrome and the other had a serious brain injury preceding the onset of the REM SBD). The youngest patient – with onset of the disorder at childhood – was otherwise healthy but found to be heterozygous for the Wilson's disease (WD) gene (his brother has WD). In 7 out of 13 (53.8 %) pts with parkinsonism the REM SBD developed years before the onset of parkinsonism. Neuroimagine (CT or MRI of the brain) data was available for 10 pts. In 8 of them there was cerebral and/or brainstem atrophy (with basal ganglia calcifications in 2). Clonazepam was given in 10 pts with a very good response.

REM SBD is a well-defined sleep disorder, often injurious, most frequently affecting elderly males and commonly associated with various movement disorders (mainly parkinsonism). The excellent response to clonazepam indicates the importance of early diagnosis of this sleep disorder.

Poster Session 4

Cerebrovascular disorders

P596
Influence of socio-demographic factors on poststroke cognitive impairment. D. Milewska, D. Ryglewicz, W. Lechowicz, A. Czlonkowska, Institute of Psychiatry and Neurology (Warsaw, PL)

In many studies a relationship between Alzheimer's disease (AD) and lower level of education has been found. In patients exposed to causal factors of AD, education would protect against dementia or delay its onset. In Poland rural area inhabitants generally have lower education level than those from urban areas. The aim of this study is to examine whether there is an association between environmental factors (living in urban or rural area) and cognitive impairment at 1-year poststroke follow-up.

Method: 1034 stroke patients, identified in a hospital-based stroke registry, were assessed for cognitive functions using the Mini-Mental State Examination (MMSE) a year after stroke. Cognitively impaired subjects (MMSE < 27, n = 659) were compared with those cognitively intact (MMSE 27–30, n = 375) in terms of demographic and medical characteristics and type of stroke.

Results: In total 63.7 % of examined patients were cognitively impaired one year after a stroke. Patients in the group with cognitive impairment were older (mean age 69 yrs) than those without cognitive impairment (mean age 64 yrs), $p < 0.05$. Cognitive impairment was diagnosed more often among women than men (67.8 % vs 59.7 %) and in patients living in rural areas than in urban area residents (67.8 % vs 58.9 %). Discriminant analysis has shown that the most predictive demographic factors for poststroke dementia are: age (84.9 %), living in rural area (54.2 %), and female sex (16.8 %). In a complex analysis age and living in rural areas were the most important predictors of poststroke dementia. In a logistic regression analysis the risk of dementia increased by 4.2 % for each year of age in the population aged > 65 yrs and amounted to 85.5 % for those living in rural area.

Conclusions: Cognitive impairment is common one year after stroke. Age and living in rural area are the most important predictive factors of poststroke dementia.

P597
Carotid endarterectomy in Iran. J. Lotfi, I. Fazel, M. Seyedian, Shariati Hospital, Taleghani Hospital (Tehran, IR)

Background and purpose: Previous studies demonstrated the efficacy of carotid (CEA)in reducing the risk of stroke and death in selected patients when surgery is performed in institutions with low perioperative complications. In this study we determined the incidence and risk factors for postoperative complications and determined the appropriateness of patient selection.

Methods: We retrospectively reviewed 246 consecutive CEAs performed in two hospitals in Tehran, Iran. A nine-item questionnaire was then sent to 206 neurologists about CEA and their criteria for patient selection.we determined appropriateness of selection of patients for CEA according to guidelines of American heart association.

Results: Stroke or death occurred within 30 days postoperatively in 8.5 %(21/246)of patients. Complication rate was 6.7 % for symptomatic and 7.2 % for asymptomatic patients. Risk factors for stroke or death were history of diabetes mellitus and previous surgery on contralateral carotid artery. Fifty six neurologists(27 %)answered the questionnaire.

Conclusions: With a complication rate above 6 %,CEA is appropriate only for symptomatic patients with stenosis greater than 70 %.Analysis of questionnaire showed that over 80 % of neurologists choose inappropriate patients for Cathie relatively high incidence of complication rate may be due to inappropriate selection of patients.

P598
Incidence of poststroke depression in a 1-year follow-up study. A. Bochynska, A. Graban, W. Lojkowska, W. Lechowicz, D. Ryglewicz, Institute of Psychiatry and Neurology (Warsaw, PL)

Background: Stroke patients tend not to consider their emotional disturbances as a part of depression but misinterpret them as being sequelae of stroke. Moreover stroke not only induces a high rate of emotional disturbances but also concomitant high rate of cognitive functions impairment. Probably that is why the prevalence of post stroke depression (PSD) ranges from 12 % to 64 %.

The aim of this study was to assess incidence of depression and cognitive dysfunction in patients at 3 and 12 months after stroke.

Material and methods: Seventy four consecutive patients with stroke, who were able to comunicate (34 men, 40 women, mean age 65.2 yrs ± 8.3), after discharge from Neurology Department have been followed up for 12 months. Stroke was diagnosed on the basis of clinical signs and results of CT (performed in all cases). At discharge the patients functional physical impairment was quantified using the Barhel Index. During control neurological examinations at 3 and 12 months after stroke mood disorders and cognitive function were evaluated. Depression was diagnosed when depressed mood had been experienced consistently over a 2-week period together with a score of 11 or more on the Geriatric Depression Scale (mild depression 11–20 points, major depression > 21 points). Cognitive impairment was assessed using the Mini-Mental State Examination (MMSE).

Results: During the control examination, at 3 months after stroke, depression only was diagnosed in 23 (30.7 %) patients, depression and dementia in 9 (11.6 %) cases and dementia only in 3 (3.8 %).On the next examination, at 12 months after stroke the frequency of depression and dementia was increased, depression alone was found in 30 (40 %) patients, depression and dementia in 16 (21.3 %), and dementia only in 7 (9.5 %). Only in 5 patients spontaneous recovery of PSD was observed. Dependence in daily activities living during 2–3 weeks after stroke was the most important predictor of depression diagnosed at the 12-month follow-up. Out of 46 patients 35 received antidepressive treatment, with good response after 3 to 6 weeks of therapy.

Discussion. The frequency of depressed mood has increased during the first year following stroke. If spontaneous recovery from depression does not occur during the first year, there is a high risk that depression will become chronic. Therefore, there is a considerable need for systematic intervention studies to prevent or treat depression in stroke patients.

P599

Ultra-early hyperbaric oxygen therapy as adjunct for thrombolysis in ischemic stroke patients. A pilot study. M. Reinohs, J. Berrouschot, A. Schulz, A. Wagner, D. Schneider, Universität Leipzig, Universität Zurich (Leipzig, D; Zurich, CH)

Background and Purpose: In experimental models of cerebral ischemia a benefit of hyperbaric oxygen (HBO) therapy was shown. We investigated the feasibility, safety and compatibility of a adjuvant HBO treatment in combination with intravenous thrombolysis in patients with acute ischemic stroke.

Methods: From October 2000 to January 2001 six patients (age 48–79 years) were included in this prospective pilot study. Inclusion criteria were age 18 to 80 years, sudden onset of focal neurological deficit, NIH stroke scale > 4 points, and pre-stroke modified Rankin scale 0- 2, informed consent obtained from the patient. Treatment with i. v.-thrombolysis (0,9 mg/kg BW tPA) and HBO was initiated within 3 hours after the onset of symptoms. HBO treatment was performed using a monoplace chamber (Haux, Germany) containing 100 % oxygen. The patients were maintained at 2.4 atmospheres absolute (ATA) over 90 min per session. Every patient underwent 8 HBO-treatments (3;6;12;24;48;72;96 and 120 h after onset of symptoms). Primary endpoint was to investigate the mean perfusion deficit before and after start of therapy using 99mTc-ECD SPECT. For clinical outcome NIHSS, Barthel-Index and Rankin-scale on day 90 were utilized.

Results: All HBO sessions were well tolerated. No adverse events occurred. There was a significant metabolic recovery in 99mTc-ECD SPECT in 5 of 6 patients. After 90 days 5 of the 6 patients were functionally independent.

Conclusion: HBO treatment in combination with i. v. -thrombolysis was feasible and safe. There was a trend for an improvement in neurological scores but for proving efficacy a multi-centre randomized study is necessary.

P600

The prevalence, characteristics and extensiveness of atherosclerotic changes in carotid arteries. M. Nowaczenko, I. Sarzynska-Dlugosz, B. Blazejewska-Hyzorek, A. Czlonkowska, Institute Psychiatry and Neurology (Warsaw, PL)

Background and purpose: Pathological changes of internal carotid artery (ICA) have been considered to be important pathogenic mechanisms for cerebral ischemia. Modern ultrasonographic (USG) methods allow more detailed evaluation of changes in the vascular wall. The aim of our study was to investigate prevalence, characteristics and extensiveness of plaques in common, internal and external carotid arteries (CCA, ICA, ECA) in acute ischemic stroke and sex- and age- matched control group using high-resolution B-mode USG.

Methods: The USG of carotid arteries was performed with a 7,0-MHz duplex-type scanner Acuson 128 XP/10 C. We examined: 200 patients aged 26–95 years with acute ischemic stroke, consecutively admitted to our department and 80 sex- and age- matched subjects of control group without history of cerebrovascular disease. Morphology of atheromatous plaques was determined using HSP Classification (H – Hemodynamic characteristics, S – Surface plaque, P – Plaque echogenic).

Results: The extracranial carotid disease (CCA, ICA, ECA) was found in 118 (59 %) patients and in 16 (20 %) persons in control group ($p < 0{,}001$). Plaques in ICA were seen in 94 (47 %) patients and in 9 (11,25 %) subjects in control group ($p < 0{,}001$). Bilateral plaques in ICA were found in 37 patients (18,5 %), unilateral – in 57 patients (28,5 %) whereas in control group – in 5 (6,25 %) and in 4 (5 %) subjects consecutively ($p < 0{,}05$). Together in examined group we observed 131 plaques in ICA: 28 were associated with artery occlusion, 17 with stenosis in range of 60–99 % and 86 with stenosis below 60 %. In control group we found 14 plaques in ICA ($p < 0{,}001$): 1 was associated with artery occlusion and 13 with stenosis below 60 %.

Conclusions: Atheromatous changes in CA detected using ultrasonography are statistically significant more intensified in ischaemic stroke patients than in control group. USG is a rapid and feasible method to detect vascular damage in situ and to discriminate persons with high risk of cerebral vascular events.

P601

Binocular inferior altitudinal visual field deficit as the only feature of a transverse cerebral sinus thrombosis. J. M. Callejo, J. C. Martinez-Castrillo, L. Costa, R. Ginestal, C. Sanchez Bueno, M. Caballero, Hospital Ramón y Cajal (Madrid, E)

Background. Cerebral sinus thrombosis is not an infrequent vascular disease. It has a large range of clinical presentations. Headache, usually associated to diplopia and papilloedema – intracranial hypertension signs-, drowsiness, seizures and focal bilateral signs are frequent manifestations. Besides papilloedema, other neuro-ophthalmologic signs related to a raised intracranial pressure are sixth nerve palsy, transient obscuration of vision, visual acuity loss, abnormal visual field, or an afferent papillary defect attributable to optic nerve dysfunction. They are all related to intracranial hypertension.

Objective: To describe a patient with a transverse sinus thrombosis whose only complain was a visual field deficit.

Patient. A 59 year-old man consulted because of a more or less sudden loss of his inferior visual field since two weeks before. He did not have headache, ocular pain, or other neurologic symptom. There were antecedents of hypercholesterolemia, hypertension, and paroxystic auricular fibrillation. On examination there were a binocular inferior visual field loss, bigger on the right side, and papilloedema. The rest of the exam was normal, as it were hemogram, haemostasis, biochemistry, electrocardiogram and chest Rx film. A CT scan was also normal. CSF exam disclosed a pressure of 19 cm of water, with a normal biochemical and microbiologic analysis. An MRI showed a left transverse sinus thrombosis. Angiography confirmed this diagnosis. The patient received anticoagulation with intravenous heparin for four weeks and thereafter with warfarin. An MRI two weeks after heparin onset showed a partial recanalization of left transverse sinus. At six months the sinus was completely permeable. Papilloedema resolved progressively. Inferior visual field remained equal. Despite complete studies, we did not find the cause of the thrombosis.

Conclusion. A visual field loss and papilloedema may be the only features of a cerebral venous thrombosis

P602

Ischemic stroke etiology in young adults. J. Pera, A. Slowik, A. Szczudlik, Jagiellonian University (Krakow, PL)

Background: Determination of the stroke aetiology in the young may play a pivotal role in the treatment and preventing its recurrence. Data on this subject in Poland are fragmentary. This study was conducted to gain further insight into the aetiology of ischemic stroke in young adults.

Methods: We studied consecutive ischemic stroke (IS) patients aged from 16 to 50 years, admitted to the University hospital from 1998 to 2001. They were divided into two subpopulations by age at time of ictus: A) 16–35 years, and B) 36–50 years. Differences in IS causes between genders were also determined. The IS aetiology was classified according to the modified TOAST criteria (Johnson, Stroke 1995).

Results: There were 15 patients (9 female) in group A, mean age 25.5 years and 91 in group B (38 female) mean age 45.7 years. Identification of

IS aetiology was possible in all patients aged < 35 years compared with 68.2 % of patients aged > 35 years ($p < 0.0001$). The probable IS cause was found in 11 (73.3 %) cases in group A and 39 (42.9 %) cases in group B. The possible IS cause was found in 4 (26.7 %) and 23 (25.3 %) cases (group A and B respectively). The leading IS aetiology in younger patients was haematological and cardiac – both found in one third of cases. The dominant IS causes in the older group were: cardiac (26.4 %) and atherothrombotic vasculopathy (22 %). In female (n = 47, mean age 41.8 years) probable cause was found in 26 (55.3 %) and possible cause in 11 (23.4 %). In male (n = 59, mean age 43.6 years), correspondent values were: 25 (42.4 %) and 15 (25.4 %) respectively. Haematological aetiology was determined significantly more often in female than in male (23.4 % vs. 3.4 %, $p < 0.003$) in contrast with atherothrombotic vasculopathy found in 6.5 % of female and 27.1 % of male ($p < 0.03$).

Conclusions: Determination of IS aetiology was significantly more likely in patients < 35 years of age than in patients > 35 years of age. Cardiac aetiology was one of the leading IS cause independently of age of stroke victims. The second main IS cause in female and younger patients was haematological one as opposed to atherothrombotic vasculopathy predominant in male and older patients.

P603

Fronto-caudal-thalamic disconnection syndrome in deep cerebral venous thrombosis (CVT) responding to local tPA. K. Siddiqui, A. Fulton, J. Thornton, J. Moroney, Beaumont Hospital (Dublin, IRL)

Background: Cortico-subcortical disconnection presenting with global neurobehavioural syndromes have been reported with lacunar infarction in strategic sites. Few data exists, however, on disconnection syndromes (DS) occurring with deep CVT, although blockage of thalamic venous drainage may result in fronto-subcortical disconnection. AIM: To show that deep CVT may present with a DS and early recognition can facilitate successful treatment. Methods/Results: A 21-year-old woman presented with withdrawn behaviour, fluctuating drowsiness and headache with vomiting. Examination revealed abulia, bradyphrenia and hypophonia, diffuse hypereflexia and marked frontal release signs. Brain imaging found abnormal signal in both thalami and left striatum. CSF analysis showed xanthochromia and elevated protein. Angiography revealed near complete occlusion of the straight sinus and the internal cerebral veins bilaterally. The right transverse sinus was catheterised and a 5 mg bolus and 15 mg infusion of rt-PA was administered without improvement in flow. rt-PA was then infused at 1 mg/min for 10 hours. Repeat angiography showed improved venous patency, but residual clot in the straight sinus with retrograde flow. There was a rapid improvement in her mental status post prolonged rt-PA infusion and neurological examination was normal at discharge. Repeat imaging revealed resolution of the bithalamic and striatal signal abnormality and she has returned to her premorbid functional level at follow-up.

Conclusions:The clinical features and characteristic neuroimaging appearance of deep CVT should be recognized by physicians caring for young stroke patients. Deep CVT can produce extensive venous congestion without early infarction. Our report suggests that superselective infusion of rt-PA into thrombosed intracranial venous sinuses can result in clot lysis and that excellent clinical recovery is possible.

P604

Remote video-examination in acute stroke – first experience in the emergency room. R. Handschu, M. Scibor, R. Littmann, J. Heckmann, B. Neundörfer, Friedrich-Alexander-Universität Erlangen-Nürnberg (Erlangen, D)

Introduction: In acute stroke care rapid decision making is essential which requires good clinical examination by an experienced neurologist. Telemedicine offers possibilities to bring such expertise to more patients, like those treated in smaller hospitals. We report our first experiences with remote examination of acute stroke patients in the emergency room and testing the feasibility of a new videoconferencing system based on browser technology.

Methods: Acute stroke patients admitted to our stroke unit were examined on admission in the emergency room. All patients were lying in a hospital bed or on a stretcher and were linked to continuous monitoring of ECG, blood pressure and oxygen saturation during the whole examination. Video and audio connection was established by a computer-based videoconferencing system (EVITA). Standardised examination was performed using NIH Stroke Scale (German version) by the remote examiner, who was directing the whole process. Assistance was provided by a trained medical student. A conventional bedside examination was performed afterwards by a neurologist of the stroke unit.

Results: In this ongoing study 41 patients were examined until now. Total examination time including introduction, application of NIHSS, check for Babinski's reflex and repeated check for vital signs on the monitor was 12 min on average (range 8–25 min). 56 % of all exams were classified as excellent, 34 % as good and 10 % as poor in quality and diagnostic results. Repeated testing of visual field, dysarthria or ataxia was necessary in 41 %. NIHSS-Scores ranged from 0–18 for bedside and 0–20 for remote examination and differed for maximal 3 points in any patient. In 4 cases a short interruption of the examination was made as vital signs required special therapeutic measures ordered by the remote examiner. Examples with possible pitfalls will be demonstrated.

Conclusion: Remote examination of acute stroke patients using a computer based videoconferencing system is feasible even in the acute care situation in the emergency room. Our Video-Audio system provided sufficient information on clinical status as well as about relevant monitoring data of the patient. For improvement of remote examination some basics like distance, illumination or position of the camera and angle need to be addressed. To achieve maximum of reliable information in a minimum of time a clear description and high grade of standardisation of the whole process is essential.

P605

Side effects of therapeutic transcranial ultrasound – a rat model. F. Nolle, M. Nedelmann, M. Eicke, B. Alessandri, O. Kempski, M. Dieterich, Klinikum der Johannes Gutenberg-Universität (Mainz, D)

Transcranial ultrasound for thrombolysis of the middle cerebral artery is a promising method to treat patients with ischemic stroke in the future. In previous in vitro studies we could demonstrate blood thrombus destruction by low frequency ultrasound (20 kHz). Aim of this in vivo study was to detect side effects of transcranial low frequency ultrasound in rats. The probe was placed on top of the cranium of Wistar rats. We performed 26 measurements in a total of 18 rats. Different power outputs (0, 2, 4, 6, 8, 10, 12 Watt) were tested, insonation time was 20 minutes per measurement. During the insonation the tympanal and rectal temperature were monitored. Nine animals were killed immediatly after somnification, nine rats were planed to survive 7 days to obtain histological data of the brain. We found a positive correlation of power output and tympanal temperature (0,18°C with 2 Watt, 0,2°C with 4 Watt, 0,6°C with 6 Watt, 1,75°C with 8 'Watt, 1,6°C with 10 Watt and 1,8°C with 12 Watt). In all animals the rectal temperature remained constant until the tympanal temperature reached 38°C. Then it rose to a maximum of 38,7°C. From the 9 animals which were planed to survive 5 died within 72 hours after insonation. All rats developing an increase of tympanal temperature more than 2°C died. The histological examinations showed a negative correlation between the number of surviving hippocampal and cortical cells and used power output. At present time, it is not known whether the observed clinical and histological observations are only due to temperature increase. Low frequency, high power output ultrasound is potentially hazourdous. Before applied in humans, careful and extensive animal safety studies have to be performed.

P606

Plasma levels of endothelin–1 (ET–1) and C-reactive protein (CRP) in patients with acute ischemic stroke (AS). A. Hatzitolios, M. Kosmidou, M. Karamouzis, C. Savopoulos, A. Ziakas, M. Alevizos, S. Giannopoulos, Aristotles University of Thessaloniki (Thessaloniki, GR)

Background: Endothelin–1 (ET–1), exerts a vasoconstrictive effect on cerebral vessels however there are limited data of the potential role of ET–1 in acute ischaemic stroke (AS). C-Reactive Protein (CRP), an acute phase protein, is increased in acute inflammation and ischaemic tissue damage such as AS. The aim of this study was to assess plasma ET–1 and CRP levels in patients in acute phase of ischaemic stroke and explore the correlation between them.

Subjects and Methods: In 23 consecutive patients (16 women, 7 men, mean 76,3 ± 7.02 yrs) with AS diagnosed clinically and confirmed by CT brain-scan, we measured plasma levels of ET–1 by radioimmunoassay (normal values 4–10pmol/l) and CRP on the 1st and 5th day after the onset of AS and we compared them with the levels of a control group of 10 healthy volunteers.

Results: 1. The mean plasma levels of ET–1 in AS patients the 1st and the 5th day were respectively 19 ± 6.7pmol/l and 16.5pmol/l ($p < 0.001$) compared with 3.7 ± 1.2pmol/l in the control group ($p < 0.001$ versus patients values both in 1st and 5th day). 2. The mean plasma levels of CRP in the stroke patients the 1st and 5th day were respectively 2.7 ± 4.7 mg/dl and 3.0 ± 4.4 mg/dl ($p < 0,15$) compared with 0.2 ± 0.1 mg/dl in the control group ($p < 0.05$ versus patient values both in 1st and 5th day). 3. A positive

correlation was found between the high mean values of plasma ET–1 and CRP both in 1st and 5th day, which was more profound in 5th day ($p < 0.1$ and $p < 0.05$ respectively).

Conclusions: ET–1 was found to be significantly elevated in the plasma of patients with AS during the entire acute phase. The profound correlation (statistical significant) between ET–1 and CRP in the 5th day after AS onset reflects the aggravation of the brain tissue damage due prolonged ischemia. Plasma ET–1 levels and its correlation with plasma CRP levels may be used as indicators for AS progression.

P607

Normal values for transcranial Doppler sonography of basal cerebral arteries in healthy subjects. S. Demirkaya, K. Uluc, S. Bek, O. Vural, GATA Hospital, Hacettepe University (Ankara, TR)

Transcranial Doppler sonography (TCD) enables the accurate assessment of intracranial arteries. The technology has evolved considerably, leading to new clinical and research applications. In order to achieve any informative insonation of vessels and respectful interpretation of findings, knowledge of flow characteristics of distinct vessels are necessary. Dependence of reference values on distinct age and gender groups has not been sufficiently reported in TCD studies in the past literature. The aim of this study was to determine peak systolic velocity, end-diastolic velocity, mean velocity and pulsatility index reference values for anterior, middle, posterior cerebral and ophthalmic arteries in a healthy population by colour-coded Doppler sonography via a temporal and orbital acoustic window with a 2 megahertz transcranial probe. This study was carried on 70 healthy volunteers without prior hematological or cerebrovascular condition and extracranial arterial stenosis was ruled out by carotid Doppler ultrasonography prior to the study. The range of normal reference values were determined in respect to gender and seven age groups: 0–10, 11–20, 21–30, 31–40, 41–50, 51–60, and more than 60-year-old.

P608

Aneurysmal and angiographic negative spontaneus subarachnoid haemorrhages – clinical and prognostic differences. P. Beldzinski, M. Mazurkiewicz-Beldzinska, H. Wojcik-Draczkowska, E. Pilarska, Medical University of Gdansk Poland (Gdansk, PL)

The aim of the study was to review patients with aneurysmal (aSAH) and arteriographically negative spontaneous subarachnoid haemorrhages (nSAH). We tried to find the correlations between the type of SAH, it's clinical course, complications, age and sex of the patients.

Materials and Methods: We studied 435 patients aged 7–77 years with SAH admitted to the Dept. of Neurosurgery, Neurology and Developmental Neurology between 1998–2001. The male female distribution was 34,5 %: 65,5 %. The patients with nSAH were significantly younger average age 34,7 years versus 52 years in aSAH group. The patients with aSAH were in worse condition on arrival than the patients with nSAH (average H-H scale in aSAH was 3,5 and in nSAH group 2,1). The aneurysmal bleedings often had serious complications: rebleedings in hospital 15,7 %, vasospasm in 25 %, intracerebral or/and intraventricular haemorrhages in 26,3 %. For the nSAH group there was no rebleedings, vasospasm in 8 % and intracerebral/intraventricular haemorrhages in 12 % of patients. In the group of patients with aneurismal SAH 48,2 % had a good outcome, 24,5 % fair, 7,2 % poor and 20,1 % died. In the nSAH group respectively 68,2 %, 18,3 %, 8,3 %, 5,2 %. There was no differences in clinical outcome in both groups and sex of the patients.

Conclusions: Non-aneurysmal SAH is significantly more often associated with better outcome, younger age of the patients, lower risk of rebleeding and developing vasospasm. There was no differences in clinical outcome in both groups and sex of the patients.

P609

Differences between lobar and deep cerebral haemorrhages. V. Puente, J. Roquer, A. Rodríguez Campello, M. Gomis, A. Pou, Hospital del Mar (Barcelona, E)

Objective: To analyse the differences in vascular risk factors and outcome in patients suffering spontaneous intracerebral haemorrhage (ICH) according to haemorrhage location.

Methods: We compared demographic data, vascular risk factors and outcome in a cohort of 266 successive incoming patients suffering lobar or deep ICH. Diagnosis was made in all cases by CT scan. Outcome was evaluated using modified Rankin Scale (mRS) at discharge. Statistic study was performed with SPSS package for windows 7.5.1.

Results: 1.- Demographic data: There was no difference in gender (54.1 % men in lobar ICH versus 58.3 % in deep ICH) or age (mean age: 71.2 ± 12.3 versus 71.7 ± 11.9). 2.- Vascular risk factors: no differences were found between both group related with the presence of diabetes mellitus, dyslipemia, ischemic or cardioembolic cardiopathy, previous cerebral infarcts, leukoaraiosis and previous anticoagulant or antiplatelet treatment. Arterial hypertension was significantly more frequent in deep ICH (68.3 %) than in lobar ICH (52 %), $p < 0.01$;OR: 1.95(1.17–3.24). 3.- Hospital mortality was higher in lobar ICH (25.3 %) that in deep ICH patients (19.1 %), with an OR of 1.4 (0.79–2.57) but it didn't reach a statistical significant difference. At discharge 61.5 % of lobar ICH patients had a good outcome (mRS < 3) versus 47.5 % of deep ICH patients, $p < 0.05$;OR: 1.77(1.01–3.08)

Conclusions: 1.- There are no differences in age, gender and vascular risk factors other than arterial hypertension ($p < 0.01$;OR: 1.95(1.17–3.24) in patients according to lobar or deep haemorrhage location. 2.- Mortality rate is higher in lobar patients (OR: 1.4, p = NS) but patients suffering deep cerebral haemorrhage remained more disabled ($p < 0.05$;OR: 1.77(1.01–3.08).

P610

Alexithymia in chronic, mildly impaired cerebrovascular patients. C. Rossi, S. Di Legge, G. Bruti, E. Vicenzini, M. Altieri, V. Di Piero, G. L. Lenzi, University La Sapienza (Rome, I)

Background: Anxiety and depression are a common sequela after stroke. Alexithymia, which is poor ability to experience and express emotions, has been found strictly connected with depression.

Objective: To evaluate if the alexithymic features may influence mood and behavioural patterns of patients with ischemic cerebrovascular disease (CVD).

Methods: 51 consecutive mildly-impaired ischemic CVD outpatients and 60 controls were studied. Inclusion criteria were: i) absence of dementia, according to DSM-IV; ii) no aphasia and iii) good recovery (Barthel Index > = 70). All subjects were investigated with the 21-item Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory (STAI), the State-Trait Aggressiveness Scale (STAS), the 20-item Toronto Alexithymia Scale (TAS–20). TAS is divided in three factors: difficulty in identifying feelings (DIF), difficulty in describing feelings (DCF) and externally oriented thinking (EOT). Patients with TAS > 60 and BDI > 9 were defined alexithymic and depressed, respectively.

Results: CVD patients did not differ in age, gender and education from controls. Patients were 33 M and 18 F, mean age was 63.8 ± 10.6 yrs. By MANOVA, CVD patients showed higher scores in BDI (14.0 vs 6.4; p = 0.004), STAS 'trait' (29.8 vs 25.9; p = 0.05) and TAS–20 (62 vs 52.4; p = 0.003) than controls. Among CVD patients, alexithymic were more depressed (21/27 vs 12/23; chi-square; p = 0.05). By MANOVA, alexithymic also showed significantly increased scores in anxiety 'trait' (48.4 vs 44.5; p = 0.03) and both aggressiveness 'state' (20.8 vs 16.9; p = 0.04) and 'trait' (31.6 vs 26.4; p = 0.01) than noalexithymic. Depressed CVD patients showed increased difficulty in identifying feelings (20.4 vs 15.8; p = 0.02) and difficulty in describing feelings (15.2 vs 13.2; p = 0.04) scores. In CVD patients, increased externally oriented thinking scores positively correlated with increased anxiety 'trait' scores (beta = 0.46; p = 0.002).

Conclusions: In a population of ischemic CVD patients with good recovery, a high percentage of alexithymic subjects was observed. Alexithymia was associated with self-rated depression and aggressiveness. These findings suggest that alexithymia may contribute to the mood and behavioural patterns of CVD patients, regardless of the degree of functional recovery, and might have a role in their subjective perception of quality of life

P611

Cerebral arterial thrombosis in paroxysmal nocturnal hemoglobinuria. S. v. Stuckrad-Barre, J. Berkefeld, D. Steckel, M. Sitzer, Johann-Wolfgang-Goethe Universität, Institute of Neuroradiology (Frankfurt am Main, D)

Background: Cerebral vascular thrombosis predominantly in the venous but also in the arterial system is a severe complication in paroxysmal nocturnal hemoglobinuria (PNH). PNH is an acquired stem cell disorder characterized by intravascular hemolysis, hypercoagulability with predilection for the portal-splenic and cerebral system, and relative bone marrow failure. Few cases, mainly postmortem, of PNH-associated cerebral arterial thrombosis (CAT) have been reported.

Case-report: We present the case of a 35-year-old female with a two-day history of rotatory vertigo, right-sided clumsiness and bradydiadochokinesia of sudden onset during sleep. Prior to this she had been under study

due to anaemia and recurrent abdominal pain. Emergency computertomography of the head showed an ischaemic stroke of the right posterior inferior cerebellar artery (PICA). Symptomatic CAT due to PNH-associated hemolysis was documented by digital subtraction angiography and typical laboratory findings. Diagnostic testing for other causes e. g. atherosclerosis, dissection, vasculitis, and venous thrombosis were negative, and diagnosis of PNH was confirmed by means of Ham's test and expression of the GPI-linked antigen CD 59 on red cells. Antithrombotic therapy with acetylic acid (100 mg/d) was instituted rapidly and maintained before changing to coumadin therapy 4 weeks after symptom onset.

Conclusion: This case report illustrates that (1) although PNH is, in itself, a rare disorder, it should be in the differential diagnosis especially in young adults with otherwise unexplained stroke both venous and arterial; (2) features of hemolytic anemia with evidence of intravascular hemolysis can serve as an important surrogat marker for PNH; (3) currently lifetime risk of thrombosis must be balanced against the burden of lifelong anticoagulant therapy based on individual patient-oriented decision.

P612

Systemic mechanisms of hereditary disposition to stroke. V. Kuznetsov, I. Glazovskaya, D. Shulzhenko, Institute of Gerontology (Kiev, UKR)

Objective: Various levels of the formation and realization of the hereditary disposition to stroke.

Subjects and Methods: Relatives of stroke patients 1st and 2nd kinship degree aged 20–65 years (RSP, n = 210) and control subjects (C, n = 150) without cerebrovascular pathology in their genealogy were examined by using an ultrasound dopplerography of major neck and head vessels (Logidop 5, Germany), an EEG frequency-integrative analysis, and lipid metabolism determination.

Results: The constitutional EEG types, being characterized by a specific distribution of the coefficients of delta and alpha rhythms decomposition, were seen in RSP. In the latter, there were structural-functional changes of the extracranial (EC) and intracranial (IC) sinus carotid arteries (27 % and 12 %, respectively, while in C they were found in EC carotid arteries in only 10 % of cases. In RSP of all age groups from 20 to 79 years, the linear blood flow velocity (LBFV) in common carotid artery (CC) and in medial cerebral (MC) artery was lower, compared to C, while at 50–59 years, it corresponded to LBFV, which is typical of stroke patients (54.0 ± 6.7 and 51.2 ± 8.8 cm/s, respectively). At 50–59 years, marked atherosclerotic changes of cerebral vessels were diagnosed in 25 % of RSP (10 % in C). Blood cholesterol level exceeded the norm (> 6.6 mM/l) in 38 % of RSP (in 15.3 % in C). Beginning after 20–29 years of age, the apoA1concentration was lower in RSP than in C (1.4 ± 0.2 mg/ml versus 2.28 ± 0.1 mg/l). Correlation coefficients between apoA1 and HDL contents of stroke patients and their relatives were 0.87 and 0.75.

Conclusion: The specifics of cerebral hemodynamics and lipid metabolism should be considered as the systemic manifestations of a hereditary disposition to stroke.

P613

Knowledge of ischemic stroke among Italian high stroke-risk population. L. De Dominicis, E. Pucci, G. Marchegiani, V. Moretti, S. Sanguigni, G. Giuliani, AUSL 9, I. N. R. C.A, AUSL 12 (Macerata, Fermo, S. Benedetto del Tronto, I)

Background: Risk reduction and decreasing the time from stroke onset to hospital presentation depend on the knowledge of stroke in patients and in general population.

Objective: To assess the knowledge of people with high risk of cerebrovascular accidents (CVA) about risk factors, presentation and management of stroke. Participants and methods: 195 consecutive subjects referred to 3 Neurosonology Services (period: November 2000 – April 2001), without severe aphasia, dementia or recent CVA (< 2 weeks), were identified as persons with high stroke risk using a Scoring System (Coppola et al., Br J Gen Pract 1995). They were asked to respond to an ad hoc questionnaire (mean time for interview: 10'). Responses were collected in written form by trained interviewers. Categorisation in items of respondents' answers was carried out through a consensus among interviewers and two of us (LD and EP).

Main results: 84 participants (43 %) did not know that the brain is the organ affected in a stroke; 85 (43.5 %) were not able to report at least one risk factor; only 55 % would call for immediate hospitalisation; 76 % of the patients with hypertension did not report that hypertension is a risk factor. Headache and vertigo/dizziness were the symptoms reported as the most common at the onset of an ischemic stroke. Discussion: Morbidity and mortality due to stroke can be reduced by identification and subsequent intervention on people with high risk of CVA. The early identification of clinical presentation reduces time of diagnosis and possible emerging CVA treatments like thrombolysis.

Conclusions: There is a significant lack of knowledge about stroke in people with high stroke risk. This population is an important target for improved educational efforts.

P614

Connective tissue diagnostics of patients with spontaneous cervical artery dissections (sCAD) – methods, indications, interpretations and limitations. C. Grond-Ginsbach, M. Besselmann, U. Müller, F. Stögbauer, J. Rauterberg, I. Hausser, T. Brandt, University of Heidelberg, University of Munster (Heidelberg, Munster, D)

Background and purpose – The morphology of connective tissue elements was found to be aberrant in the majority of skin biopsies from patients with sCAD lacking clinical stigmata of a known connective tissue disorder. In this paper we evaluate the method, the benefits and the limitations of a routine morphologic analysis of skin biopsies from patients with sCAD.

Methods – We describe and analyze a standardized method for the collection of a skin biopsy and for its light and electron microscopic evaluation. Special attention is given to the indication for this invasive diagnosis and to diagnostic problems, ambiguities and pitfalls. Data from over hundred patients with cerebrovascular diseases and from 20 healthy relatives of patients were presented.

Results – Main indications for the performance of this invasive connective tissue diagnosis among patients are 1) the suspected presence of a known connective tissue disorder, 2) the exclusion of trauma as the pathogenetic cause, 3) scientific studies. Moreover, in skin biopsies from healthy relatives of patients with a connective tissue phenotype we observed the aberrant phenotype in about 50 %. These latter relatives are considered as carrier of an inherited predisposition for sCAD. The extend of connective tissue aberrations in patients does not seem to predict the prognosis, outcome or severity of the disease.

Conclusions – Connective tissue diagnosis is valuable for a subset of patients with sCAD. It should be performed after informed consent according to standardized guidelines.

P615

Familial history of coronary heart disease and/or stroke as risk factors of ischemic stroke subtypes. A study based on the Lausanne stroke registry. L. Urbano, J. Bogousslavsky, CHUV (Lausanne, CH)

Background and purpose. Inconclusive data have addressed the importance of familial history in the occurrence of ischemic stroke. The conflicting results may be, at least partially, due to the variability of etiological mechanisms determining brain ischemia. Besides, these different explanatory mechanisms have important clinical implications. The aim of present study was to determine the relative importance of familial history of coronary heart disease (CHD) and stroke in the occurrence of different subtypes of ischemic stroke.

Methods. We selected 4086 patients with first ischemic stroke (39 % women, aged 63.5 ± 15.1 years) from 4499 patients enrolled between 1979 and 1999 in the Lausanne Stroke Registry. Individuals with transient ischemic attack or cerebral hemorrhage were excluded. Diagnoses in our study were performed by neurologists based on clinical features and ancillary tests. Causes of ischemic stroke were classified according the TOAST criteria.

Results. Cardioembolism was the most common cause of stroke (n = 1005, 24.6 %), followed by small-vessel disease (n = 964, 23.6 %), stroke of undetermined origin (n = 905, 22.1 %) and large artery atherosclerosis (n = 844, 20.7 %). Sex, age distribution, and major risk factors were unevenly distributed among stroke subtypes ($P < 0.05$, respectively). Patients with familial history of CHD were significantly younger than patients without familial history of CHD or stroke (59.9 ± 13.1 versus 63.9 ± 15.3 years, respectively; $P < 0.01$). Middle-aged patients (aged 45 to 70 years) with macroangiopathy showed more frequently positive familial history of stroke than the other stroke subtypes globally considered (12.2 % versus 5.5 %, respectively; $P < 0.05$).

Conclusions. Our study emphasizes the probable role of familial history of stroke as risk factor in the subset of middle-aged individuals with large artery atherosclerosis. However, the definitive importance of familiarity in subtype-specific ischemic stroke occurrence should be clarified by a population-based study.

P616

Artificial neural networks based algorithm for the analysis of velocity profiles in middle cerebral artery obtained using transcranial Doppler. R. C. Sá, M. Manto, N. Abou-Azar, M. Pandolfo, S. Jeangette, Université Libre de Bruxelles (Brussels, B)

We describe an Artificial Neural Network (ANN) based algorithm, built to analyse blood velocity profiles of the Middle Cerebral Artery (MCA), obtained by Transcranial Doppler (TCD). Velocity profiles on the MCA were recorded bilaterally in 12 normal, healthy subjects (non-smokers, no history of migraine, no medication, aged 33 ± 8 years) using Nicolet EME's pioneer TCD. Probes (2MHz) were fixed using a head probe-holder, with depth set to 56mm. Velocity was recorded for 5mn, at a sampling rate of 100Hz.An ANN was taught to recognise events in these curves, namely the onset of the rise after each heart beat. Events scored by a human expert were presented to the ANN as learning examples, and the ANN learned to recognise similar events in unseen examples. From this basis, the algorithm extracts from the original signal the diastolic and systolic velocity (Vdia and Vsys) for each heart-beat "i" and the time Tdia and Tsys. Periodicity (T), mean velocity (Vmean) and pulsatility index (PI) are computed on a cycle per cycle basis. However, these parameters tell us little about the velocity profile itself, about the steepness of the rise in velocity induced by each heart beat, nor about the decay of the artery response to this repetitive stimuli. We introduced 3 additional variables that quantify these effects, namely the percentage of rise time, %Tup = %(Tsys(i)-Tdia(i))/(Tsys(i+1)-Tsys(i+1)), the acceleration of rise (Arise) and decay (Adecay). A constant acceleration from Vdia(i) to Vsys(i) and an exponential velocity decay from Vsys(i) to Vdia(i+1) (V(t) = a+b.exp(-t/Adecay)) were considered. These parameters are indirect measures of elastic properties of the arteries in the vicinity of the section measured. We found the following results (mean ± SE): Right MCA: Vsys 78.9 ± 2.91cm/s, Vdia 30.9 ± 1.20cm/s, Period 1.1 ± 0.10s, %Tup 12.8 ± 0.89 %, Arise 437.2 ± 53.5cm/s2, Adecay 0.42 ± 0.07s, PI 1.01 ± 0.04. Left MCA: Vsys 77.9 ± 3.23cm/s, Vdia 31.5 ± 1.64cm/s, Period 1.1 ± 0.10s, %Tup 14.5 ± 0.87 %, Arise 376.8 ± 44.25cm/s2, Adecay 0.30 ± 0.07s, PI 0.96 ± 0.03. Left-right differences for each subject showed no significant different ($p > 0.05$) for all variables. This study presents the feasibility and effectiveness of using an artificial neural network based algorithm to analyse velocity profile curves of MCA. This method will allow quantification of changes in the velocity curves and can be used to compare a population of normal subjects with a group of stroke patients.

P617

Neurologic complications following radiosurgical treatment of brain arteriovenous malformations. A. Hartmann, P. Marx, A. Schilling, T. Pietilä, H. Mast, University Hospital Benjamin Franklin, BG Kliniken Bergmannstrost (Berlin, Halle, D)

Purpose: To investigate the frequency of permanent neurologic deficits after radiosurgical therapy of brain arteriovenous malformations (AVMs).

Methods: A systematic review of the literature available in the National Library of Medicine (PubMed) was used to identify relevant articles. Selection criteria were (1) publication date 1990 or later, (2) prospective study design, (3) at least 30 patients included in the study, (4) length of clinical follow-up stated, (5) rate of permanent neurologic complications stated or computable.

Results: From the 111 retrieved articles, 16 studies reporting on 3854 patients fulfilled the search criteria. The mean follow-up time was 52 months. Gamma knife treatment was used in 9 studies (56 %), linear accelererator in 5 reports (31 %), and Bragg peak radiation in 2 publications (13 %). The malformations were categorized as large AVMs in 2 studies, as inoperable AVMs in another 2 publications, and as AVMs located in the motor cortex in one investigation. The remainder (11 publications, 69 %) reported on unselected AVMs. Prior to irradiation, partial surgical resection was performed in 9 % of the patients, and endovascular treatment in 18 %. The mean rate of treatment-related permanent neurologic deficits was 6.2 % (95 % CI 5 % to 8 %), regardless of severity. Nine studies reported additional reversible neurologic deficits in 6.4 % (95 % CI 3 % to 10 %). Obliteration rates, completeness and type of follow-up greatly varied between the studies.

Conclusions: The frequency of neurologic complications from radiotherapy of brain AVMs is similar to the complication rate from AVM surgery and endovascular AVM treatment.

P618

Cardioembolic risk factors in lacunar infarction. M. V. Mejías, E. Díez Tejedor, S. Escalante, University Hospital La Paz (Madrid, E)

Introduction: Nowadays, within the current stroke classifications, lacune infarction is considered secondary to small vessel disease Our objective was to analyze the possible etiologic role of cardioembolism in lacune infarction.

Methods: We performed an observational and sequential study from our stroke data bank during 1994 to 1999, analysing the risk factors (RF) for cerebral ischemia. According to the presence or absence of cardioembolic RF (atrial fibrillation had a longer length of stay (A: 10,05 ± 4,9 days; B: 8,1 ± 4,7 days; $p < 0,0001$). A higher, valvulopathy or ventricular dyskinesia) patients were assigned to group A (presence of cardioembolic RF) or group B (absense). Statistical analysis: t-student, chi-square.

Results: 3003 stroke patients were attended during the study period, 604 with the diagnosis of lacune infarction (20,1 %). 77 (12,7 %) patients had cardioembolic RF (group A) while 527 (87,2 %) were assigned to group B. There were no differences in gender in both groups (male/female 66,6 %/30,7 % Group A, and 63,4 %/36,5 % Group B). Patients in group A were older than group B and frequency of coronary arterial disease was found in group A ($p < 0,0001$), without any difference in other RF.

Conclusions: The presence of cardioembolism risk factors is important in a subgroup of lacune infarction, being this ethnology underestimated. Coronary arterial disease would have to be considered as an embolism risk factor, besides to its atherothrombotic condition. This fact should have to be considered in future etiologic classifications of lacunar infarction. Should have also important diagnostic (more cardiological studies performed) and therapeutic (more anticoagulant drugs prescribed) implications

P619

Patent oval foramen and cerebral ischemia. Is a disorder as benign as assumed? S. Monteagudo, J. Gracia, B. Fuentes, P. Barreiro, E. Díez Tejedor, University Hospital La Paz (Madrid, E)

Introduction and objectives: The relationship between patent oval foramen (POF) and cerebral ischemia of cardioembolic origin is well-known, but its consequences probably infravalued. We analyzed the size of infarcts and disability degree in patients with cerebral ischemia and POF.

Methods: Patients with cerebral ischemia and POF diagnosis were included since 1990 until 2001. The FOP was confirmed by transesophagic echocardiogram and by necropsy in one case. We analysed the size of the infarct in TC and neurological and functional state at admission and at discharge by means of Canadian scale (CS) and modificated Rankin scale (mRS). Protrombotic factors study was performed in 15 cases.

Results: In 30 patients with cerebral ischemia a FOP was diagnosed. An increase in the diagnosis of cases in the last 6 years was observed. 10 patients presented TIA, 4 lacunar infarcts and 16 territorial ones. 5 patients have had a previous cerebral ischemia. CS at admission was > 8.5 in 5 patients, 6,5–8 in 10, 3,5–6 in 2 and < 3 in 3 patients. CS at discharge was > 8,5 in 15 patients, 6,5–8 in 3 and < 6,5 in 1. mRS to the discharge: 6 patients (2–5), 13(0–1), a subject died. The TC objetived infarct in 73,3 %: < 1,5cm: 28,5 %; 1,5–3cm:38 %; > 3cm:33,5 %; of these last 71.4 % had CS < 6,5 at admission.

Conclusion: The FOP is a disorder not as benign as it has been considered when it is associated to cerebral ischemia. It can cause large brain infarctions (33,5 %),as well as marked functional dependency (Rankin > 2) up to 20 % and death in 3.3 % of the cases. This potential severity of cerebral ischemia related to the FOP must be considered and contemplated the most effective and safe therapies.

P620

Color Doppler flow imaging and power Doppler imaging in patients with cerebral aneurysms 0.10 cases reports. N. Artemis, M. Karadrakonti, T. Arida, D. Karakostas, I. Mavromatis, I. Milonas, Ahepa Hospital, Aristoteles University (Thessaloniki, GR)

Purpose: To indentify specific ultrasonographic characteristics with color doppler flow imaging (CDFI)and power doppler imaging(PDI) and to compare the results of the methods to recognize abnormal flow indicating aneurysms.

Material and method: We examined nine patients with intracranial aneurysms(one with bilateral middle cerebral artery(MCA) aneurysms) and one with aneurysm in the extracranial part of internal carotid artery.Recognition of the cerebral arteries was based on the anatomical location and blood flow characteristics with each of the two techniques.

Results: Regions with red and blue color separated with black line were observed in the region of the aneurysm with CDFI.On the other hand examination with PDI revealed ubnormal oval or round shaped regions in the course of the main trunk of the MCA

Conclusion: Cerebral arteries aneurysms more than 2 mm in diameter have specific sonographic characteristics the knowledge of which may permit the distinction of patients who need more investigation from these who did not.PDI seems to be more reliable technique in the recognition of such anatomical abnormalities than CDFI which on the other hand give more haemodynamic details.There is a need of examining more patients in order to estimate the sensitivity of the two methods in the recognition of aneurysms in MCA and in the other cerebral arteries.

Parkinson's disease-Extrapyramidal disorders

P621

A prevalence of primary dystonia in the Szczecin and Gdansk Regions – Northern Poland. A. Potemkowski, J. Slawek, J. Stankiewicz, A. Fabian, Pomeranian Academy of Medicine, Medical Academy, Regional Hospital (Szczecin, Gdansk, PL)

The aim of the study was to determine the prevalence of primary dystonia in Szczecin Region total population of 995 000 individuals)and Gdansk Region(total population of 149 0000 individuals), the similar of epidemiological point of view Regions of Northern Poland. Diagnosed cases ascertained by adult neurologists with specialist movement disorder clinic. We identified on the prevalence day 31.12 2000- 98 patients with primary dystonia in Szczecin Region(SR)and 130 in Gdansk Region(GR)and crude rate of 98 per million(181–121 CI)in SR and 87 CI –71–108)in GR. The rates per million for the main types of dystonia were as follows: focal: in SR(n = 84) 84(CI- 69–105),in GR(n = 125)84(CI–68–104), segmental:in SR(n = 8)8(CI-4- 16), in GR (n = 5) 3(CI–1–9)and multifocal: in SR(n = 6)(CI–3–13). The prevalence rates per million for the more common types of dystonia were: cervical dystonia: in SR 44(CI–33–66),in GR 50(CI 38–669), blepharospasm: in SR 22(CI–15–34), in GR 27 CI–18–39) writer's cramp:in SR 10 (CI –5–19), in GR – 4 (CI–2–10)laryngeal:in SR – 8(CI–4–16), in GR –3 (CI–1–8). The female prodominance was been noted for all subtypes of focal dystonia in both regions. In focal dystonia mean patient's age at onset was: for cervical dystonia in SR – 37.86, in GR –39.53, for blepharospasm in SR – 54.00, in GR – 57.44, for laryngea dystonia in SR – 53.12, in GR–66.25 and for writer's cramp in SR – 24.50, in GR–34.75. Our study provide the first data on the prevalence of primary dystonia and its subtypes in two similar Regions in Poland.

P622

Delayed re-administration of COMT inhibitor entacapone in Parkinson's disease patients treated with levodopa. L. Bet, S. R. Bareggi, A. H. Schapira, A. H. V. Schapira, J. Salvucci, M. Gervasoni, G. Meola, University of Milan, R. F. H. School of Medicine (San Donato, Milan, I; London, UK)

We performed this study in order to determine three major endpoints: 1) Does entacapone leads to chronic dopaminergic stimulation in different clusters of Parkinson's disease (PD) patients? 2) Is chronic dopaminergic stimulation better with a combination of levodopa and entacapone or levodopa controlled release and entacapone? 3) Is chronic dopaminergic stimulation better with a single entacapone dose or with a supplementary dose designed to increase further the area under the curve of plasma levodopa levels?

Patients were recruited as follows: 10 PD patients who have never received levodopa. 10 PD patients who have been on levodopa for more than 3 months but do not have motor fluctuations. 10 PD patients who have been on levodopa for more than 3 months and do have motor fluctuations.

All patients received their last dose of dopaminergic agent (agonist or levodopa) the evening before the study. The study days were carefully standardised for timing of dose and for dietary intake. In the first day of the study, all patients received a single dose of 125 mg of levodopa/carbidopa and at the same time a 200 mg of entacapone. In the second day all patient received the same treatment with an additional dose of 200 mg of entacapone after 1 hour. The third and the fourth days the protocol was the same but patients received 200 mg of levodopa/carbidopa CR. Blood samples were taken just prior to the oral dose and then at 30, 60, 90, 120, 150 minutes and 3, 4, 5, 6, 7, and 8 hours after the original dose. UPDRS scale was measured at the same times. Samples were processed by HPLC using already described methods to detect levodopa, dopamine, 3-OH-metyldopa and HVA.

We measured the Area Under the Curve (AUC) defined by the values of levodopa during the time expressed as μg/ml/hour. AUC is significantly ($p < 0.03$) increased in the group of patient receiving levodopa/carbidopa CR with a second dose of entacapone (5630 ± 2211) when compared to the AUC of the same patients when treated with levodopa/carbidopa CR associated to a single entacapone dose (4274 ± 1898). No significant differences were found in the three groups of patients. A good correlation was found between UPDRS score and the plasma levels of levodopa. Our preliminary results (18/30 patients) show that the repeated entacapone administration with levodopa/carbidopa CR leads to an improved plasma profile for levodopa and the potential for more continuous dopaminergic stimulation.

P623

Immunosuppressive potential of dopamine receptor agonists in vitro and in vivo. F. Gronen, S. Nessler, C. Stadelmann, W. Brück, A. Bittner, W. Oertel, B. Hemmer, N. Sommer, University of Marburg, Charité (Marburg, Berlin, D)

Dopamine receptor agonists (DAs) are increasingly used in chronic diseases of the nervous system, above all Parkinson's disease (PD). Usually patients have to be treated continuously for many years. Nevertheless, the known immunosuppressive potential of the classical DA bromocriptine (BCT) has had little influence on the clinical use of these drugs. Especially, the immunosuppressive potential of newer DAs has received little attention.

In this study we compared the influence of the ergot-derivative DAs BCT, and pergolide (PGL) and the non-ergot DA pramipexole (PPX) on lymphocyte culture in vitro and in vivo in a murine relapsing experimental autoimmune encephalomyelitis (EAE), a prototypic neuroimmunological disease model.

EAE was markedly suppressed with once daily doses of 20 mg/kg BCT. By contrast, biologically equivalent doses of PGL (5 mg/kg) or PPX (4 mg/kg) did not lead to a significant reduction of EAE. Only when PGL was increased to 20 mg/kg, EAE was significantly reduced. Treatment effect correlated with suppression of prolactin serum levels. In vitro, the 3 DAs had only minor effects at high concentrations (10 micromol) on lymphocyte proliferation and cytokine production in vitro.

In conclusion, DAs have dose-related immunosuppressive properties. Inhibition of prolactin is probably one important mechanism in this respect. Nevertheless, our data suggest that the different DAs have a different immunosuppressive potential which cannot simply been explained by pharmacological properties such as relative potency and biological half life. We suggest that the various clinically available DAs should be further investigated in patients with movement disorders, because some DAs might lead to unwanted immunosuppressive side effects.

P624

Dopaminergic neurons in patients with mitochondrial disorders. M. Minnerop, C. Kornblum, A. Joe, K. Tatsch, M. Reinhardt, U. Wüllner, University Bonn (Bonn, D)

Decreased activity of complex I of the mitochondrial electron transport chain and mitochondrial DNA damage have been detected in tissue samples of Parkinson's disease (PD) patients. In addition, several compounds that inhibit complex I activity induce a parkinsonian syndrome in humans and non-human primates. Thus, the question arises whether complex I deficiency by itself is sufficient to elicit dopaminergic dysfunction in humans. Indeed mitochondrial diseases may affect basal ganglia function such as in Leigh's disease, LHON plus dystonia or in other mitochondrial encephalopathies. Data on the state of the dopamine system in patients with mitochondrial encephalopathies are lacking. We investigated the dopaminergic system in 13 patients with known chronic progressive external ophthalmoplegia (CPEO) and muscular complex I deficiency using 123I-FP-CIT (DatScan) single-photon emission computed tomography (SPECT). 13 patients with CPEO were evaluated (mean age 49, range 32–69 years, 8 w/5m). Biochemical analysis of muscular respiratory chain enzyme activities showed complex I/IV deficiency in all patients. SPECT imaging and evaluation protocol followed the procedure of the [^{123}I]-FP-CIT study group. Semiquantitative evaluation was done using a region of interest (ROI) technique. To evaluate the specific binding of the radiotracer, ROIs were placed over the entire striatum, nucleus caudate and putamen. Specific to non-specific binding ratios were calculated by subtracting mean counts per pixel in the occipital ROI from mean counts per pixel in the basal ganglia regions and divided by mean counts per pixel in the occipital ROI. Specific binding ratios of patients were compared with 15 healthy controls (mean age 61, range 33–79 years, 10w/5m). 123I-FP-CIT-SPECT did not show any significant differences between patients with

CPEO and the control group. However, regression analysis suggested a faster decline of striatal binding ratios over time in the patient vs. the control group. Furthermore, analysis of the right/left asymmetry index revealed a higher asymmetry for the putamen in the patient group but not for putamen or caudate nucleus in controls.

While the present data do not reveal a significant loss of dopaminergic terminals in patients with mitochondrial disorders, they suggest that mitochondrial defects render dopaminergic neurons more susceptible to injuries, thus leading to a faster decline of striatal binding ratios with age.

P625

Dyskinesias and grip control in Parkinson's disease are normalized by chronic stimulation of the subthalamic nucleus. R. Wenzelburger, B.-R. Zhang, M. Poepping, B. Schrader, D. Müller, F. Kopper, U. Fietzek, H.-M. Mehdorn, G. Deuschl, P. Krack, Neurologische Universitätsklinik Kiel, Neurochirurgische Universitätsklinik Kiel, Neurochirurgische Universitätsklinik Eppendorf (Kiel, Hamburg, D)

Deep-brain stimulation of the subthalamic nucleus (STN-DBS) seems to reduce levodopa-induced dyskinesias (LID) but whether this effect is due to the reduction of the total levodopa ingestion or represents a direct effect on the motor system is unknown. Precision grip force of grasping movements and LID was analyzed in 10 parkinsonian patients before and after three months STN-DBS. Peak grip force was abnormally increased before surgery in off and par-ticularly in the on-drug state (sensitization). This grip force upregulation normalized with chronic DBS in both conditions (desensitization). Peak-dose dyskinesias also improved and off-dystonia was completely abolished. Mean dosage of dopaminergic drugs was reduced, but force overflow and dyskinesias were equally improved in two patients without a reduction. De-spite the same single levodopa test dose, force excess and LID were dramatically reduced after 3 months of STN-DBS. This indicates that direct effects of STN-DBS on levodopa-induced dyskinesias are likely to occur.

P626

Unusual presentation of Wilson's disease: report of 13 Iranian cases. A. Soltanzadeh, P. Soltanzadeh, Tehran University of Medical Sciences (Tehran, IR)

Introduction: Wilson's disease is a systemic illness caused by abnormality of copper metabolism. Sometimes the diagnosis is not easily made due to unusual clinical signs and symptoms.

Materials and Methods: Among 36 cases of Wilson's disease, 13 patients who had unusual clinical presentation were studied. All the patients were investigated from the viewpoints of clinical features including Kayser-Fleischer rings, serum copper and ceruloplasmin, hepatic enzymes, urine study, CT scan, and MRI.

Results: Patients were 9 to 30 years old, 7 females and 6 males. Preliminary diagnoses in these patients were encephalitis, depression, schizophrenia, hysterical gait, hysterical tremor, malingering, multiple sclerosis (due to head titubation), subacute sclerosing panencephalitis, and idiopathic thrombocytopenia.

Conclusion: Apart from patients with extrapyramidal or hepatic manifestations, diagnosis of Wilson's disease should be born in mind when encountering cases with psychiatric, hematologic, or some other neurologic presentations.

NB: A video tape of some interesting cases is available for oral presentation.

P627

Oxidative stress affect proteasome activity in neuronal cell culture: implications for the pathogenesis of Parkinson's disease. H. Elkon, E. Melamed, D. Offen, Felsenstein Medical Research Center (Petah-Tikva, IL)

Mutations in familial Parkinson's disease (PD) have been shown to be associated with the failure of the ubiquitin-proteasome system. Impairment of proteasome function has also been suggested to play a role in the pathogenesis of sporadic PD. Damaged proteins seen in the substantia nigra in PD was postulated to be induced by local oxidative metabolism of dopamine. We examined the proteasome activities in cell culture treated with 6-hydroxydopamine (6-OHDA), the dopamine synthetic derivate used in models of PD. We demonstrated that 6-OHDA treatment increased the protein degradation, accumulation of carbonyls groups and caspase–3 activity, while addition of the antioxidant N-acetylcysteine, prevented these phenomena. Moreover, 6-OHDA increased the levels of free ubiquitin and ubiquitin-conjugated proteins, in a dose dependent manner. In addition, there was an increase in proteasome trypsin, chymotrypsin and post-acidic protease-like activities in PC12 cells treated with 10–100 uM of 6-OHDA, whereas higher doses caused a dramatic decline. Similarly, the presence of 0.3 mM 6-OHDA for up to 10 hours increased proteasome activities; 10–24 hrs incubation, however, reduced its activities. In conclusion, our data indicate that mild oxidative stress elevate proteasome activities in response to the increase in protein damage. Severe oxidative insult may lead to failure of the ubiquitin system to clear defective proteins from the cell, causing protein aggregation and cell death. Control of protein clearance will offer a new strategy for therapy in neurodegenerative diseases in general and particularly for PD.

P628

The REAL-PET study: slower progression in early Parkinson's disease (PD) patients taking ropinirole compared with L-dopa. A. Whone, P. Remy, R. Watts, A. J. Stoessl, O. Rascol, W. Poewe, D. Brooks, Imperial College, Commissariat à l'Energie Atomique, Emory University, University of British Columbia, Toulouse University Hospital, University of Innsbruck (London, UK; Orsay, F; Atlanta, USA; Vancouver, CAN; Toulouse, F; Innsbruck, A)

Aim: To compare rates of loss of putamen dopamine terminal function in early PD patients treated with ropinirole or L-dopa.

Background: Preclinical studies show ropinirole has neuroprotective properties and a pilot 18F-dopa positron emission tomography (PET) trial in patients has suggested slower disease progression with ropinirole than L-dopa.

Methods: In this 2-year double-blind multinational study, 186 de novo PD patients were randomized (1:1) to ropinirole or L-dopa. The primary endpoint was change in putamen 18F-dopa uptake (Ki) measured with PET. Data from six PET centres were centrally transformed into standard stereotactic space to normalize brain position and shape and analysed with a standard region of interest (ROI) template. Parametric images were also interrogated with statistical parametric mapping (SPM) to localize regions where significant between-group differences in rates of loss of dopaminergic function were occurring. Secondary endpoints included the incidence of dyskinesias and clinical progression (measured with the UPDRS, and a Clinical Global Impression scale, CGI).

Results: 93 patients were randomized to each group; 73 % of the ropinirole and 74 % of the L-dopa group completed the study. Mean (SD) daily doses of double-blind medication at 2 years were: 12.2 (6.1) mg ropinirole and 558.7 (180.8) mg L-dopa. Only 14 % of the ropinirole and 8 % of the L-dopa group received supplementary L-dopa. Data from PD patients (11 %) found to have normal caudate and putamen 18F-dopa uptake at entry (identified by blinded review) were considered separately. ROI analysis: loss of putamen Ki was significantly slower with ropinirole (–13 %) than with L-dopa (–20 %; $p = 0.022$). The more affected side at baseline showed greater treatment difference in favour of ropinirole. SPM analysis: falls in Ki were significantly slower in putamen and nigra with ropinirole compared with L-dopa (putamen: ropinirole –14 %; –20 % L-dopa; $p = 0.034$; nigra: ropinirole 3 %; L-dopa –8 %; $p = 0.035$). The incidence of dyskinesia was 27 % with L-dopa and 3 % with ropinirole ($p < 0.001$; odds ratio = 0.09). Changes in mean UPDRS motor scores favoured L-dopa by 6 points (95 % CI 3.53, 9.14). CGI scores suggested symptoms were adequately controlled in each group (no significant difference).

Conclusion: 18F-dopa PET shows evidence of significantly slower loss of dopamine terminal function in early PD patients taking ropinirole compared with L-dopa.

P629

Proton magnetic resonance spectosropy in Parkinson's disease, multiple sytem atrophy, and progressive supranuclear palsy. T. Eckert, J. Kaufmann, C. Schrader, T. Peschel, H. J. Heinze, M. Sailer, O.-v.-Guericke-University, Medical School (Magdeburg, Hannover, D)

Introduction: Approximately one-quarter of patients initially diagnosed as having idiopathic Parkinson's disease (IPD) have in the long run another neurodegenerative disorder with a different underlying pathology. The two most common atypical parkinsonian disorders are multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). A correct diagnosis is of great importance since prognosis differs substantially. Proton magnetic resonance spectroscopy (1H-MRS) allows measuring the presence and concentration of brain metabolites in vivo such as N-acetylaspartate (NAA) as a neuronal marker and may discriminate in the pathology involving neuronal damage. Previous studies have shown a reduction of NAA concentration in atypical parkinsonian disorders compared to idiopathic Parkinson's disease although there has been a great overlap between

groups. The aim of this study is to evaluate if proton magnetic spectroscopy is able to detect reliable metabolic differences between patients with distinct clinical parkinsonian syndromes.

Methods: Spectroscopy voxels were localized to both lentiform nucleus, the frontal white matter and the occipital grey matter guided by T2-weighted axial images. Groups consisted of 12 patients with IPD, 12 patients with MSA, 9 patients with progressive PSP and 9 healthy age matched controls. For our calculations resonance intensities of N-acetylaspartate (NAA), creatine (Cr) and choline (Cho) were determined. The results were expressed as ratios of NAA/Cr, NAA/Cho and Cho/Cr, respectively.

Results: NAA/Cho and NAA/Cr ratios of the lentiform nucleus were significantly reduced in the MSA and PSP group compared to the IPD and control group. NAA/Cho and NAA/Cr ratios of the white and the grey matter and Chol/Cr ratios of the lentiform nucleus failed to show differences between the groups.

Discussion: Proton magnetic resonance spectroscopy seems to be a useful non-invasive technique for diagnosing neural loss in the basal ganglia. As no differences between Chol/Cr ratios can be observed reductions in the NAA/Cho and NAA/Cr ratios seem to be due to a reduction in the NAA concentration. The selective reduction in NAA concentration indicates a neural loss of the examined regions of interest. Although the wide range and overlapping of ratio values make it difficult to recognize differences in individual patients.

P630

Deep brain stimulation in nucleus subthalamicus improves a preexisting apraxia of lid opening in a 70-year old parkinsonian patient. G. Fuß, J. Spiegel, T. Magnus, J. R. Moringlane, G. Becker, G. Becker, U. Dillmann, Saarland University (Homburg/Saar, D)

Introduction: Apraxia of lid opening is characterized by difficulties in voluntary lid opening due to non-paralytic levator inhibition. Patients with this syndrome try to compensate this deficit by contraction of M. frontalis. Apraxia of lid opening is definedas a nonparalytic motor abnomality characterized by difficulties in initiating the act of lid elevation. By definition apraxia requires an intact motor system so it has been questioned whether apraxia of lid opening, caused by involuntary supranuclear levator palpebrae muscle inhibition can be classified as a true apraxia syndrome. The pathophysiology of apraxia of lid opening is still unclear. Pathological influences from basal ganglia to brainstem structures that regulate blinking are considered possible causes. Apraxia of lid opening has been described as a side effect of deep brain stimulation in subthalamicus nucleus in up to 5 % of the patients.

Case report: After evaluation of all exclusion and inclusion criteria in July 2001 a deep brain stimulation-operation of both nuclei subthalamici (STN) was performed in a 70-year old Parkinsonian patient with marked motor fluctuations in form of peak-dose hyperkinesias, unpredictable off-periodes and preexisting apraxia of lid opening. We used a kinemetra system (Medtronic®). DBS result in a 70 % reduction of hyperkinesia and a 20 % reduction of the akinesia time. Surprisingly, we also observed a clear improvement of the lid opening apraxia. The improvement was correlated to higher stimulation amplitudes, frequences and pulse widthes especially in the second and third pole. Without stimulation it was nearly impossible for the patient to open her eyes, while with stimulation this was possible for most of the time.

Discussion: Improvement of apraxia of lid opening by chronic deep brain stimulation in nucleus subthalamicus is not described before, but it is still known that this described as a side effect of the stimulation. It may be suggested that the occurrence of lid opening apraxia versus an improvement of a preexisting apraxia of lid opening as described in our patient depend on the part of STN that is inhibited by DBS. Improvement of apraxia of lid opening were described for globus pallidus internus stimulation and for globus pallidus internus pallidotomy in patients with Parkinson. All these findings suggest that the disturbances in the basal ganglia play a crucial role in the generation of apraxia of lid opening.

P631

The impact of having Parkinson's disease in young compared to older-onset Parkinson's disease. A. Schrag, A. Hovris, D. Morley, N. Quinn, M. Jahanshahi, Institute of Neurology (London, UK)

Background: Although Parkinson's disease (PD) characteristically affects patients above the age of 50 years, a substantial minority develop symptoms of PD at a younger age. The effect of this chronic, progressive disease on younger patients' lives is likely to differ from that on older patients.

Methods: 65 patients with onset of PD before the age of 50 and 60 patients with later onset completed a booklet with questionnaires on demographic and clinical variables, quality of life and psychosocial factors.

Results: Apart from a higher rate of medication-induced dyskinesia, the two groups did not differ in self-reported disease severity and disability. A higher percentage of young onset patients was unemployed due to disability. Quality of life as measured on the PDQ–39 was significantly worse in young onset patients than older onset patients. Younger onset patients also had worse scores on the stigma scale and marital satisfaction scales, and had higher depression scores. The two groups also tended to differ in their most commonly employed technique of coping and their satisfaction with emotional and mental support.

Conclusion: The impact of having PD on patients' quality of life is greater if it starts at an early rather than an older age. Young onset patients more frequently experience loss of employment, impairment of family life and greater stigmatization, and are significantly more depressed than older patients with PD. Factors such as lack of emotional and mental social support and unhelpful coping strategies may contribute to greater impairment of quality of life in young patients with PD.

General Neurology

P632

Spinal cord involvement in neuroBehçet's disease. N. Yesilot, O. Gungor, B. Baykan, M. Eraksoy, P. Seradaroglu, G. Akman-Demir, University of Istanbul (Istanbul, TR)

Background: Myelitis which has been reported to be a relatively less common neurological manifestation of Neuro-Behçet's disease (NBD) is an often overlooked pattern of involvement with serious implications in NBD. This study aims to focus on clinical and radiological features of 25 patients with spinal cord involvement with NBD.

Methods: 573 files of the neuro-Behçet clinic were reviewed. Those patients without any evidence of neurological involvement as well as the patients with other possible explanations for the neurological state were excluded. The remaining 225 cases were evaluated as NBD cases and 25 of them (11 %) with predominantly spinal cord involvement were included in this study.

Results: 11 patients had isolated spinal cord involvement, the remaining 14 had spinal (+) type involvement (with additional brainstem and/or cognitive involvement). 44 % of the patients had a course with attack(s) and secondary progression, 24 % had primary progression, 16 % had at least one attack and remission, 12 % had silent neurological involvement of among whom one case had an attack in the follow-up period. All of the patients showed pyramidal signs, 80 % had paraparesis; 50 % of them also had a transverse sensory level. 92 % of the patients had micturitional disturbance and/or impotence. Additionally 32 % of the patients had brainstem involvement and 40 % had cognitive impairment. Fever, pyramidocerebellar signs, quadriparesis and headache were all less common findings. Cranial magnetic resonance imaging (MRI) was performed in 12 (48 %) patients; 4 had white matter lesions, 2 had isolated brainstem lesions, 1 had isolated basal ganglia lesions and 5 were normal. MRI of the spinal cord was performed in 8 patients, 6 were normal and 2 showed pathologic T2 hyperintensities. The remaining cases were evaluated with myelography to exclude the spinal cord compression. Mean follow-up period was 63 months for this group of patients. At the end of this period the ratio of dead/dependent patients were 48 % whereas, it was 28 % in the cases without spinal cord involvement in our previously published series (Akman-Demir et al., Brain 1999).

Conclusions: Although it is a rather less frequent site of involvement in NBD, patients with spinal cord involvement seem to have a poor prognosis.

P633

Acute Korsakoff amnesic state as the sole initial manifestation of primary cerebral lymphoma. C. Mavrogenidou, C. Potagas, P. Papageorgiou, E. Patsouris, N. Matikas, Evangelismos General Hospital Athens, Athens University (Athens, GR)

A 74 years-old woman, smoker and suffering diabetes, presented with an amnesic state of acute installation with typical Korsakoff features, including confabulation. Computed tomography (CT-scan) showed a hypodense lesion in the left temporal lobe. The magnetic resonance imaging (MRI) features strongly suggested a central nervous system lymphoma. No elements of immunosuppression were found. In a very few days the clinical as well as the CT-scan image were dramatically worsened; the patient showed

akinetic mutism. Diagnosis of lymphoma was confirmed by biopsy. Subsequent corticosteroid i. v. treatment permitted an important but transient clinical amelioration (also evident in the CT-scan images). We are interested in the particular initial clinical presentation of this patient and the diagnostic features in neuroimaging (CT-scan and MRI).

P634

Friedriech's ataxia and familial extern left strabism. S. Boukhris, S. Chebel, A. Boughammoura, M. Frih-Ayed, University Hospital Of Monastir (Monastir, TN)

Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder characterized by progressive cerebellar ataxia, areflexia, decreased vibration sense and pyramidal weakness. We report a Tunisian family with four affected and three unaffected children. The father of this family developed a horizontal diplopia, the neurological examination was normal except external left strabism. Their mother was clinically normal. The four affected members had typical FA phenotype. Two of them had external left strabism. The serum vitamin E, cholesterol, triglycerides levels and lipid electrophoresis were normal. Genetic study confirmed the diagnosis of FA.

P635

Friedriech's ataxia: from GAA triplet expansion to phenotypic expressions. P. Arnold, T. Kuntzer, J. Bogousslavsky, Centre Hospitalier Universitaire Vaudois (Lausanne, CH)

Background: Friedreich's ataxia (FA), the most common form of degenerative ataxia, is characterized by progressive gait and limb ataxia, corticospinal signs, sensory neuronopathy and skeletal deformity. Patients may also present cardiomyopathy or diabetes. The disease is caused in the vast majority of cases by a GAA triplet expansion in the FA gene on chromosome 9q13. Age of onset and severity of the disease have been related to the size of expansion of the shortest arm of the abnormal gene, but we wanted to know whether this relation was also true with other potential complications of the disease.

Methods: Nineteen FA patients, 5 men and 14 women (mean age = 33.7 years, range 13 to 68) were prospectively investigated during a 6 month-period. They underwent clinical, electrophysiological, and genetic studies, including quantitative scoring of ataxia (the international cooperative ataxia rating scale or ICARS), motor and sensory nerve conduction studies, measurements of visual and auditory evoked potentials, audiogram, cardiac examination (electrocardiography or ECG, echocardiography or ECHOC) and determination of serum glucose levels. Genetic analysis was performed for the GAA trinucleotide repeat expansion.

Results: ICARS ranges from 21 to 83 (mean 65,5/100). Age of onset and severity of disease were both correlated to the size of the smallest expanded gene that varied from 200 to 1150 triplets. Cardiomyopathy, as demonstrated by ECHOC was present in 10 cases (53 %), and by ECG in 13 cases (68 %), diabetes in 2 cases (10 %) cases. All patient had absent or severely reduced sensory nerve action potentials in upper and lower limbs and normal motor nerve conduction. We additionally found clinical evidence of auditory dysfunction in 9 cases (8/18 cases with abnormal evoked potentials), and 1 patient had clinical visual loss (4/18 with abnormal evoked potentials).

Conclusion: Our study shows that sensory neuronopathy appears early in all FA patients and is independent of number of triplets, severity or duration of disease. This study confirms that severity of disease is proportional to the size of expansion of the shortest arm of FA gene, but also shows that patients with cardiomyopathy, auditory dysfunction and visual loss are those cases with the largest amount of triplet expansion, but not those with diabetes. These findings justify systematic tracking of these complications.

P636

Late-onset cerebellar ataxia in two brothers with hypergonadotropic hypogonadism, polyneuropathy and cognitive impairment. M. Gironi, R. Nemni, C. Marelli, F. Guerini, M. Sgandurra, N. Canal, Don C.Gnocchi Foundation (Milan, I)

Objective: We describe the first family in which two bothers out of seven sibs were affected by the unique combination of progressive late onset (in the fourth decade of life) cerebellar ataxia, hypergonadotropic hypogonadism with azospermia, motor-sensory neuropathy, sensory-neural deafness and cognitive impairment.

Background: The hereditary ataxias represent a clinically and genetically heterogeneous group of disorders. Hypogonadism, mainly of hypogonadotropic type, has been reported as an accompanying feature. The association of ataxia and hypergonadotropic hypogonadism is extremely rare and to date only 4 females of the 17 reported patients had an onset between the first and the third decade. Two males only have been reported so far, both with early onset

Design: Patient 1: a 48-year-old man was admitted to our hospital, has been complaining progressive dysarthria for 9 years and difficulty in walking for 8 years. Azospermia was reported since the age of 30.

Patient 2: a 35-year-old man, a brother of patient 1, has been complaining symptoms similar to patient 1 for 5 years. Both patients underwent laboratory tests including vitamin E blood level and endocrinal assessment, CSF analysis, audiology studies, neurophysiological studies, MRI analysis, neuropsychological evaluation, ophthalmologic evaluation, genetic analysis for SCA and Friedreich's ataxia. Mitochondrial DNA analysis and linkage studies are in progress.

Results: On examination speech was slow and scanning, cerebellar signs were present mainly on lower limbs, pes was cavus. Balance was unsteady and gait was ataxic. Abnormal laboratory and instrumental tests included: decreased testosterone and increased gonadotrophins, mild sensorineural deafness, moderate sensory-motor neuropathy, predominantly of axonal type, cerebellar and pons atrophy, mild cognitive impairment. The parents were non-consanguineous. Clinical history was negative for neurological and gonadic diseases up to third generation.

Conclusions: Pedigree of the family does not suggest any definite pattern of inheritance (autosomal or recessive). However, the involvement of tissues and organs not related either embryologically or functionally let us to evaluate the possibility of the presence of either a primary disorder of mitochondrial DNA or a disorder secondary to mutation or defect of a nuclear gene encoding oxidative phosphorylation (OXPHOS) or non- OXPHOS proteins

P637

Idebenone may improve patients with Friedriech's ataxia in increasing lipid peroxydation. P. Arnold, T. Kuntzer, O. Boulat, M. Markert, J. Bogousslavsky, Centre Hospitalier Universitaire Vaudois (Lausanne, CH)

Background: Friedreich's ataxia (FA), the most common form of degenerative ataxia, is thought to be caused by respiratory deficiency due to mitochondrial iron accumulation and oxidative stress. Idebenone, a free-radical scavenger, protects mitochondrial function in vitro models of FA. A preliminary study has reported improvement of FA-associated cardiomyopathy with idebenone, but its efficacy on neurological dysfunctions is unknown.

Methods: 19 FA patients, 5 men and 14 women (mean age = 33,7 years, range 13 to 68) were proposed to take idebenone and were prospectively followed. The international cooperative ataxia rating scale (ICARS) was used to quantify ataxia. Blood samples were collected to measure malondialdehyde (MDA) levels, a product of lipid peroxydation.

Results: 18/19 FA patients agreed to take idebenone (5 mg/kg in 13 cases, 10 mg/kg in 5 cases). 15 patients (83 %) reported an improvement of dysarthria (12 cases or 67 %), hand skillness (4 cases or 22 %), handwriting (6 cases or 33 %) and fatigue (9 cases or 50 %). Improvement appeared after a few month in most (12 cases), rarely after some weeks (3 cases). In two patients idebenone was stopped and a worsening in ataxia was seen. There were no side effects related to the treatment. MDA levels, measured in whole blood on EDTA, were found to be lower in patients with FA compared with our controls. These values were increased by the treatment with idebenone.

Conclusion: although not controlled this preliminary study suggests a beneficial effect of idebenone in improving cerebellar ataxia in FA patients. The whole blood MDA results obtained in this study suggests that idebenone may be efficient in improving FA patients by a different mechanism than a decrease in oxidative stress.

P638

A cortical blind patient with a fear response to an unseen conditioned visual stimulus. A. Dressel, A. O. Hamm, A. I. Weike, H. T. Schupp, M. Adamaszek, C. Kessler, University of Greifswald (Greifswald, D)

A substantial number of animal and human studies using different experimental procedures and measures of fear have consistently demonstrated that the amygdala is the key structure of the fear circuit. In the animal fear conditioning research it has been demonstrated that this subcortical fear system can be activated without requiring a representation of the conditioned stimuli in the primary sensory cortical areas. Here, we report on a male patient with bilateral cortical blindness in whom an intact fear conditioning to a visual cue was observed.

The patient was admitted to the stroke unit of the University clinic because of a complete loss of vision. Cerebral computed tomography confirmed hypodense lesions in both PCA (posterior cerebral artery) territories, the less hypodense lesion on the left side corresponded to the new PCA infarction, whereas an intense hypodense lesion on the right side corresponded to PCA infarction that happened one year before. Monocular VEP examination was performed with three trials of 100 stimuli each, alternately in the right and left eye. No VEPs could be detected. During fear conditioning a visual cue predicted the occurrence of an aversive electric shock. Acoustic startle probes were presented during and between the conditioned stimuli. Relative to the control condition startle reflexes were substantially potentiated when elicited in the context of the conditioned stimuli. No such potentiation was observed in the pre-conditioning phase. These data suggest that fear learning to visual cues does not require a cortical representation of the conditioned stimulus in the primary sensory cortex.

P639

D-dimer as a diagnostic tool in cerebral sinus thrombosis: a multicenter trial. C. Geyer, R. Nohr, J. Schiefer, J. Schläfer, R. Biniek, B. Koch, M. Schwarz, P. Marx, M. Mull, C. M. Kosinski, Universitätsklinikum Aachen, Freie Universität Berlin, Rheinische Landeskliniken Bonn, Städtische Kliniken Dortmund (Aachen, Berlin, Bonn, Dortmund, D)

Cerebral sinus thrombosis (CVST) is a rare disease. Due to the wide spectrum of clinical symptoms the diagnosis often turns out to be difficult. Considering the possible fatal consequences of not detecting a CVST and the availability of an effective treatment patients have to undergo further diagnostics. Imaging techniques, like MRT, CT venography or even invasive cerebral angiography, are necessary in the search for CVST. These methods are expensive and restricted to certain hospitals. Therefore it would be useful to provide a screening test which helps to exclude a CVST with high probability.

For other thrombotic events, like deep vein thrombosis in the leg or pulmonary embolism measurement of the d-dimer-levels has been extensively validated as a helpful screening test. The goal of this study is to find out whether measurement of d-dimers is useful as a screening test to exclude CVST(negative predictive value).

A multicenter trial was designed including 4 German neurological departments. 250 to 300 patients are expected to enter the study within a period of two years, all with clinical suspect of CVST. The number of positive cases with CVST is assessed to 25–30. This is a progress report after the first year of the study.

All patients underwent appropriate tests to confirm or exclude a CVST, i. e. MRI venography, CT venography, or cerebral angiography. Blood samples were taken after informed consent from the patient was obtained within 24 hours and concentrations of d-dimers were measured in one centre all with the identical technique.

So far 110 patients were included. 8 patients were proven to have a CVST by imaging techniques. All of them had elevated d-dimer levels outside the normal range (< 500 mg/l). 7 patients had elevated d-dimer levels without having a CVST. The remaining 95 had normal levels of d-dimers.

These results suggest that d-dimer testing will probably be a useful screening test with a high sensitivity and a high negative predictive value in the diagnosis of CVST. Further patient inclusion will be necessary to reach higher statistical reliability.

P640

Scrotal pain as the main symptom of lumbar disc herniation. E. J. Wouda, J. A. L. Vanneste, S. Leenstra, Sint Lucas Andreas Hospital, Academic Medical Centre (Amsterdam, NL)

Background: Scrotal pain is usually due to local disease. Scrotal pain due to compression of a sacral nerve root caused by lumbar disc herniation is probably very rare as the literature contains only sporadic single case descriptions. We present two patients with scrotal pain associated with lumbar disc herniation.

Case 1: A 32-year-old man complained of severe left scrotal pain for three months. Urological examination did not reveal testicular or scrotal abnormalities. The left scrotal pain irradiated to his back and the left buttock. He had no sensory symptoms, muscle weakness or bladder dysfunction. Neurological examination was normal. Computed tomography of the lumbar spine showed a left sided sequestered disc at the L5-S1 level, probable compression of the left S1 nerve root, and displacement of the other ipsilateral sacral nerve roots. Surgical removal of the sequestered L5-S1 disc fragment resulted in prompt relief of the scrotal pain. No recurrence occurred.

Case 2: A 47-year-old man complained of intermitted left scrotal pain since two years. No inguinal, scrotal or testicular abnormalities were found. More recently he felt that the scrotal pain irradiated from the testis to the lumbar spine and increased on coughing. Neurological examination was normal apart from a straight leg raise test producing increased left scrotal pain. Magnetic resonance imaging (MRI) of the lumbar spine showed a posterolateral disc hesitation at the L4-L5 level with compression of the passing nerve roots. Removal of the L4-L5 extruded disc led to complete and persistent relief of the scrotal pain.

Comment: Neurogenic scrotal pain can be produced by compression and inflammation of a scrotal somatic sensory nerve along its course or that of its corresponding nerve root. The sensory nerve innervation of the scrotum belongs to the lumbar segments L1 and L2 and the sacral segments S2 and S3. In our patients, absence of local scrotal pathology and complete relief of scrotal pain after lumbar discectomy suggests that the scrotal pain was most probably due to compression of the sacral nerve roots by a herniated lumbar disc. Conclusion: When no local or lower abdominal pathology is found for explaining scrotal pain, a lumbar disc herniation should be considered as the possible cause, even in the absence of other nerve root symptoms or signs.

P641

Spinal cord involvement in Sjögren's syndrome. S. Delalande, J. De Seze, A. Fauchais, E. Hachulla, D. Ferriby, T. Stojkovic, P. Hatron, P. Vermersch, CHU Lille (Lille, F)

Introduction: Sjögren's Syndrome (SS) may be associated with peripheral and central nervous system involvement. Neurological manifestations in SS are heterogeneous but spinal cord involvement has been rarely described.

Aim: To determine the clinical, laboratory, radiological features and clinical outcome of spinal cord involvement occurring in SS.

Methods: 28 patients with myelopathy associated with primary SS as defined by European criteria (Vitali et al., 1996) were studied.

Results: The mean age at onset was 53 years old. There were a female predominance with 20 women. 15 patients presented chronic myelopathy, 9 had acute myelopathy, 2 patients had motor neurone disease and 2 patients primitive lateral sclerosis. Spinal cord MRI was normal in 41 % of patients, showed a lesion in 21 % and multiple lesions in 38 %. 60 % of the patients had oligoclonal bands in the cerebrospinal fluid. The visual evoked potentials were abnormal in 14 patients. 13 patients were treated by cyclophosphamide and the outcome was favourable in 70 % of these cases.

Discussion: Our study underlines the diversity of spinal cord involvement in SS and the potential interest of an early treatment by immunosuppressive drugs. In many cases, differential diagnosis with progressive forms of multiple sclerosis, amyotrophic lateral sclerosis or primitive lateral sclerosis is difficult. These similarities rise the question of the distinction between spinal cord involvement in primary SS and SS associated with neurological diseases defined as secondary SS.

P642

Demyelinating lesions of the central nervous system and another etiologic disease, Hashimoto's encephalopathy: a case report. G. Sahin, K. Uluc, O. Kursun, A. Kurne, B. O. Yildiz, B. Elibol, G. Nurlu, R. Karabudak, Hacettepe University (Ankara, TR)

In the etiology of central nervous system (CNS) demyelinating lesions, not only multiple sclerosis, acute demyelinating encephalomyelopathy and vasculitis; but also other rare diseases should be investigated. Hashimoto encephalopathy is one of them and it is characterized by subacute onset, repetitive and progressive encephalopathy seen in patients with Hashimoto thyroiditis. Disease could present itself in a large spectrum extending from focal neurological signs to global confusion. According to reports in the literature, response to steroid treatment is good.

Case report: A 38-year-old female was admitted with the history of dizziness, light-headedness for one month and confusion and lethargy for one week. In addition, she expereinced numbness and loss of motor power on her right side. Examination showed right hemihypoesthesia, a T4 sensory level, impairment in position sense at right lower extremity and increased deep tendon reflexes on both sides. Examination showed thickening of hairs and coarse facial features. In laboratory analysis routine tests were normal. T3 and T4 hormone levels were within normal limits and thyroid stimulating hormone (TSH) was > 100 IU. Except for the high level of protein in cerebrospinal fluid, the other analyses were normal. IgG index was 0.73. Vasculitic and infection markers were also normal. Cranial magnetic resonance images (MRI) revealed bilateral, multiple, periventricular contrast enhancing lesions. In spinal MRI, there was cervical and thoracic

syringomyelia. Due to the high level of TSH, patient was consulted with the department of endocrinology. On the basis of low free thyroid hormone levels and significantly high antithyroid antibody levels, the diagnosis of Hashimoto thyroiditis was considered. The patient responded well to treatment with thyroid hormone and corticosteroid.

P643
Meningeal granulomatosis as first presentation of Wegener's disease. P. Sola, J. Mandrioli, G. Ficarra, L. Mavilla, E. Merelli, F. Casoni, P. Nichelli, Università di Modena, Istituto di Anatomia Patologica (Modena, I)

Wegener's granulomatosis is a systemic vasculitis, characterized by the involvement of the superior and inferior respiratory tracts and of the kidneys. Ophthalmic and neurological involvement are common(22 % and 54 % of those affected respectively). The most common involvement of the nervous system include peripheral neuropathy, particularly in the form of multiple mononeuritis. Meningeal involvement is exceptional.

We report the case of a 53-year-old man, admitted to the Neurological Clinic of the University of Modena for a five days history of frontal cephalalgia and diplopia. When he was 28 years old, the patient was successfully treated for a Hodgkin's lymphoma. In 1999 he was hospitalized for a spontaneous D1 hematoma, with complete recovery.

Neurological examination at the admission showed a isolated palsy of the left sixth cranial nerve. All metabolic and vascular disease causing mononeuritis were excluded by appropriate tests. Brain and cervical-dorsal MRI revealed diffuse thickening and enhancement of the dura mater, consistent with hypertrophic pachymeningitis, and a nodular lesion near to the left pons. Erythrocyte sedimentation rate and C-reactive protein were moderately elevated, together with other aspecific flogistic markers. Serum angiotensin converting enzyme was normal. The blood research for any bacterial or micotic agent was negative as well as the test for cytoplasmic antineutrophil cytoplasmic antibody (ANCA). Lumbar puncture was performed, and showed mild total protein elevation and mild mononuclear pleocytosis (12 lymphocytes/mm3). No oligoclonal bands were found in the CSF, and all viral, retroviral, bacterial, mycobacteria, and fungi investigation resulted negative. The patient was submitted to dural biopsy, and the pathological examination of the dural specimen showed non-specific arachnoid nests with whirling vorticoid aspect. After two weeks of 50 mg/daily prednisolone p. o. therapy the cephalalgia and the diplopia dramatically improved and erythrocyte sedimentation rate and C-reactive protein values were in the normal range. Brain MRI has been repeated one month later: the nodular lesion near to the pons was disappeared, while the meningeal thickening was unchanged.

P644
Central pontine myelinolysis: role of magnetic resonance imaging in diagnosis. A. Esquivel, F. Diaz Otero, A. García Pastor, L. Muñoz, Hospital General Universitario (Madrid, E)

Background: Although the aetiology of Central Pontine Myelinolysis (CPM) remains elusive, the rapid correction of chronic hyponatraemia has been implicated as a potent causative factor, additional factors may also be significant in the pathogenesis of this condition. We review magnetic resonance imaging (MRI) role in the diagnosis of this singular neurological disorder.

Patients/Methods: Retrospective revision in our institution of all patients with clinical and radiological diagnosis of CPM in the last 15 years.

Results: 9 patients were included, 5 females, 4 males, mean age 45 years. Chronic alcoholism was the most frequent risk factor. Hyponatraemia was found in 5 patients. MRI revealed extensive area of abnormal signal intensity in the pons, consistent with CPM. Extrapontine localization was found in only one patient.

Conclusion: In vivo, diagnosis of CPM may be difficult since clinical presentation is usually masked by severe underlying disorders, changes in mental states as confusion or coma, related with concomitant disease. Some cases are clinically "silent" and are only necropsy findings. With greater availability of MRI this pathological process may increasingly be recognised as a cause of neurological deterioration in the sick patient with metabolic derangement.

Neuro-immunology

P645
Comparison of disc electrophoresis and isoelectric focusing on polyacrylamide gel for detection of oligoclonal IgG bands in cerebrospinal fluid. A. Mitrevski, K. Stojanoski, Clinic of Neurology (Skopje, MK)

Immunoglobulin intrathecal production is an important parameter in inflammatory conditions of the central nervous system, such as multiple sclerosis (MS), in which humoral immune system has been involved. Detection of oligoclonal bands (OCB), limited to cerebrospinal fluid (CSF), has been considered to be the most relevant index for intrathecal production of immunoglobulins. They are detected as distinct bands on the electrophoregram. A great number of methods for separation of CSF proteins and detection of OCB are available. The aim of our study was to compare two methods for detection of OCB on polyacrylamide support medium, disc electrophoresis (DEP) and isoelectric focusing (IEF). In addition, diagnostic effectiveness of these methods for OCB detection in CSF from MS patients were compared. OCB were detected by both methods in 85 % of the patients, in 10 % of the patients with IEF only, and in 2 % of the patients with DEP only. OCB were not found in 3 % of the patients with either method. Sensitivity of two diagnostic tests for detection of OCB were 94.9 % for IEF and 86.4 % for DEP. IEF and silver staining had better capability and resolution than DEP. Additional immunofixation with anti-IgG antiserum made the IEF technique superior for OCB identifiction and helping in MS diagnosis.

P646
Interleukin–18: an emerging role in immune-mediated neuromuscular diseases. S. Jander, H.-P. Hartung, G. Stoll, Heinrich-Heine-University, Julius-Maximilians-University (Düsseldorf, Würzburg, D)

T helper (Th) cells comprise two functionally distinct subpopulations, i. e. Th1 cells promoting cell-mediated and Th2 cells favouring antibody-dependent immune reactions. Interleukin (IL)–18 is a potent Th1-inducing proinflammatory cytokine. In line with a presumed Th1 immunopathogenesis, we found increased expression of IL–18 during acute stages of Guillain-Barré syndrome and its animal model experimental autoimmune neuritis. Surprisingly, however, IL–18 serum levels were also significantly elevated in patients with myasthenia gravis as an autoantibody-mediated disease expected to depend on Th2-mediated immune responses. IL–18 levels were higher in generalized than in ocular myasthenia and decreased upon clinical remission. Thus, IL–18 was overall correlated with clinical disease activity. These findings suggest a role of IL–18 and Th1-dependent pathomechanisms in the development of B cell-mediated autoimmune disease.

P647
Vav1 knockout mice are resistant to experimental autoimmune encephalomyelitis. T. Korn, K.-D. Fischer, G. Köllner, K. Toyka, S. Jung, Neurologische Uniklinik des Saarlandes, Physiologische Chemie, Universität Ulm, Neurologische Uniklinik Würzburg (Homburg/Saar, Ulm, Wurzburg, D)

Background: Vav1 is a guanine nucleotide exchange factor to activate small Rho GTPases signalling downstream of the T cell receptor (TCR) and of costimulatory molecules such as CD28. As a consequence of defective T cell selection, vav1 knockout mice exhibit a peripheral T cell pool which is reduced by 50 percent whereas B cell numbers are unaffected. The remaining T cells have got severe defects in cytoskeleton reorganisation resulting in impaired TCR capping and subsequently, show reduced proliferation and IL–2 production on antigenic stimulation.

Objective: To specify the role of vav1 in autoimmune disease of the CNS and identify it as a possible target for intervention.

Methods: Experimental autoimmune encephalomyelitis (EAE) was induced in wild type (wt) C57BL/6 and vav1 knockout mice by subcutaneous injection of myelin oligodendrocyte glycoprotein (MOG) peptide 35–55 in CFA. The immune response was enhanced by intraperitoneal administration of pertussis toxin on days 1 and 3 after immunization.

Results: On active immunization with MOG 35–55, vav1 knockout mice did not develop overt signs of EAE. In vitro recall of lymph node cells with MOG 35–55 or purified protein derivative (PPD) 12 days after immunization revealed profoundly impaired proliferative and cytokine responses as compared to wt controls. IFN-g and IL–2 secretion were as severely reduced as IL–4 production indicating that vav1 knockout T cells were not able to differentiate into antigen specific cells of Th1 or Th2 lineage. Neither antigen specific proliferation nor production of Th1 cytokines could

be rescued by addition of exogenous IL–2. Vav1 is also expressed in antigen presenting cells (APC). APC of vav1 knockout origin were not capable to stimulate syngeneic wt MOG specific T cells suggesting that APC function is defective in vav1 knockout animals. Histologically, inflammatory infiltrates were significantly reduced in vav1 knockouts although there was no histological pattern to suggest that insufficiency of migration would be limiting for vav1 knockout cells to cause more pronounced EAE.

Conclusion: Resistance to EAE in vav1 knockout mice is mainly due to their inability to mount antigen specific T cell responses. This relies on impaired priming of T cells. Whether defective T cell functions or insufficient antigen presentation during initial priming are more important remains to be determined.

P648

Dexamethasone protects neurones against microglial toxicity. S. Golde, D. A. S. Compston, Cambridge Centre for Brain Repair, University of Cambridge (Cambridge, UK)

Brain inflammation in the lesions of multiple sclerosis is accompanied by marked neuronal degeneration. We explored mechanisms of inflammatory damage to neurons in vitro using co-cultures of rat embryonal cortical neurones with microglia activated by Interferon-gamma (IFN-g) and lipopolysaccharide (LPS). We show that microglia are highly toxic to neurones and that nitric oxide (NO) derived from inducible nitric oxide synthase (iNOS) is essential and sufficient to mediate this toxicity. Immunocytochemical evidence for survival and preservation of metabolic activity (MTT) show that addition of dexamethasone (1 microM) to activated cocultures leads to almost complete neuroprotection. However, dexamethasone does not protect neurones from direct toxicity of the NO-donor DETA-NoNoate, indicating that neuroprotection in co-cultures most likely results from modulation of microglial activation and we show that dexamethasone does downregulate microglial NO-production. Protection is most effective when dexamethasone is administered 24h before induction of iNOS by IFN-g + LPS, but still reduces NO production when given up to 24h later, suggesting that dexamethasone exerts complex effects on microglial NO-production. Quantitative Western blots show that dexamethasone reduces microglial iNOS protein by 68 % and this effect is reversed by the glucocorticoid receptor-blocker, RU 38486. Analysis of iNOS-mRNA and pulse-chase analysis of iNOS protein reveals the relative contribution from inhibition of iNOS expression and promotion of protein degradation in dexamethasone-induced reduction of iNOS activity. Our study explores in vitro mechanisms of glucocorticoid action in primary microglial cells; by reducing NO-toxicity, glucocorticoids may be useful neuroprotectants in the context of inflammatory brain disease.

P649

Behçet's disease: MS-like manifestation. A. Kiyat, G. Akman-Demir, P. Serdaroglu, M. Eraksoy, Istanbul University (Istanbul, TR)

Background and aims: Behcet's disease (BD) is a multisystemic, inflammatory disorder of unknown etiology, and affects mainly the eyes, skin, joints, and the vascular system. Though less frequent, the gastrointestinal system, lungs and the nervous system can also be involved. When the latter is affected, the disease is usually called neuro-Behcet. The presentation of BD is mostly with systemic features such as oral aphtae, genital ulcers or skin lesions, though very rarely pure neurologic signs can be the initial manifestation. The differential diagnosis of neuro-Behcet includes cerebrovascular diseases, brain tumours, infections, myelopathies with different origins, and multiple sclerosis (MS). Differentiation of MS and neuro-Behcet is usually easy, especially when there is the characteristic brainstem-basal ganglia lesion on magnetic resonance imaging (MRI). However, occasionally it might be difficult due to similar clinical presentation or similar lesions on MRI. Our purpose is to present patients with BD, who resemble MS on neuroradiological grounds and to outline their clinical features.

Patients and Methods: 200 patients from our neuro-Behcet clinic were evaluated retrospectively. Patients who had predominantly white matter lesions on cranial MRI were included in the analysis.

Results: Of the 17 patients (7 females, 10 males), the mean age at onset of BD was 30,5 and of neuro-Behcet was 36.7 years. Onset of neuro-Behcet was with an acute attack in 12 patients (71 %). The type of disease progression was secondary progressive in 6, relapsing remitting in 5, primary progressive in 1, and silent in 5 patients. Fifteen (88 %) had pyramidal signs, 8 (47 %) hemiparesis, 1 (6 %) paraparesis, 7 (41 %) sensory deficits, 5 (29 %) cerebellar signs, 6 (35 %) brainstem involvement, 6 (35 %) sphincter dysfunction, while none had optic neuritis. Lumbar punction was carried out in 8 patients. Three (38 %) had protein elevation and pleocytosis in the cerebrospinal fluid (CSF). No oligoclonal bands (OCB)were detected. All patients had cranial MRI examination; all were abnormal and the lesions were all localized in the periventricular white matter.

Conclusion: Clinical presentation, and MRI findings of neuro-Behcet can occasionally mimic MS. A careful search for systemic signs and recording of disease course are helpful to detect BD. The lack of OCB's in the CSF is also a helpful clue.

P650

Complete reversible acute, bilateral and symmetrical CNS lesions coexisting with a CIDP relapse associated with ophthalmoplegia but without anti-GQ1b antibodies. A. Pou-Serradell, A. Rodríguez-Campello, J. Roquer, M-J. Tellez, X. Perich, Hospital del Mar (Barcelona, E)

Background: The Bickerstaff's brainstem encephalitis (BBE) and the Miller Fisher syndrome (MFS) may show overlapping features. CIDP may coexist with areas of increased white matter signal intensity. We report the MRI findings in one patient with overlapping BBE, MFS and CIDP.

Case History: A 69 year-old-man, -with clinical manifestations compatible with sensory polyneuropathy improved after a few weeks at the age of 65- developed loss of vision and hypoacusia, drowsiness, dysarthria, distal limb paresthesiae and unsteady gait. On day 2, he could not stand up (because a severe truncal ataxia), he presented total ophthalmoplegia (but corneal reflexes were intact), oculocephalic reflexes were absent. Vertical nystagmus, cerebellar dysmetria, flaccid tetraparesis, absence of ankle reflexes and a symmetrical distal hypoesthesia were found. The patient had the Fisher's syndrome triad. On day 5, he developed rapid involuntary flinging movements of both arms, they increased with intention and disappeared with sleep and on day 7 they showed a gradual decrease. CT was normal, increased CSF proteins (60 mg/%) without pleocytosis were found. Complete serological studies were negative. Electrophysiologic studies demonstrated a mixed axonal and demyelinating polyneuropathy but conduction velocities were not reduced < 70 % of lower limit of normal. MRI studies detected bilateral and symmetrical lesions in the brain stem just periaqueductal, basal ganglia (thalamus and hypothalamus), cerebellum (vermis and superior cortex) and parietocortical areas; no contrast enhancement of lesions was detected. Serum antiglycolytic antibodies (anti-GQ1b, GM1, GD1a, GD1b, GT1b) measured at the onset of diplopia were not detected. The patient gradually made an almost complete recovery and on day 40 his CNS exam was normal except for a residual nystagmus and he maintains areflexia in lower extremities. From day 70, the MRI became completely normal.

Conclusions: CNS lesions associated with MFS can occur in a more diffuse form than previously described involving not only the brain stem but other symmetrical encephalic areas. The search for anti-GQ1b antibodies being negative, one could consider that this patient developed an immune response directed to another structure than GQ1b. An overlapping syndrome including CIDP, MFS and BBE appears as the most probable diagnostic: The MRI turned the tide entirely in favour of the lumpers.

P651

Is there a restriction in thymocytes and lymphocyte T- cell receptors (TCRs) of patients affected by Myasthenia gravis? M. Clerico, A. Bosio, A. Cucci, G. Isoardo, A. Ricci, S. Deaglio, A. Pipieri, E. Verdun, P. Barbero, F. Malavasi, L. Durelli, B. Bergamasco, University of Turin (Turin, I)

Objective: To evaluate thymocytes and lymphocytes phenotype, specially the expression of Vbeta5.1 and Vbeta8 alleles of the variable regions of the TCR, in patients affected by myasthenia gravis, comparing them with ones of a control group.

Background: Some authors found restriction in the TCR use in myasthenia gravis and this could be important in the disease pathogenesis. The limited number of evaluated cases, due both to the disease and to the complexity of the methodic, needs further studies.

Design and Methods: The phenotype of thymocytes and lymphocytes from thymuses and peripheral blood of 14 myasthenic patients and 9 controls was analysed by immunofluorescence. The expression of MHC I, CD1a, CD3, CD4, CD8, CD19, CD38 and of the Vbeta5.1 and Vbeta8 TCR's regions was evaluated. T-test was used for statistical analysis.

Results: CD1a, immaturity marker of thymic cells, was more expressed in controls than myasthenic patients. Vbeta5.1 was expressed by the 5.53 % of the thymocytes in myasthenic patients and by the 3 % in controls, Vbeta8 by the 5.77 % of the thymocytes in myasthenic patients and by the 2.90 % in controls. The difference was statistically significant for Vbeta8 ($p = 0.047$), not for Vbeta5.1 ($p = 0{,}1639$). There were no differences in the expression of Vbeta5.1 and Vbeta8 in peripheral lymphocytes.

Conclusions: This study demonstrated a restriction in the TCR use in

thymocytes of patients affected by myasthenia gravis. The thymus is strictly involved in the disease pathogenesis. The Vbeta8+ thymocytes could be the pathogenic ones. Further evaluations are needed to confirm this hypothesis.

P652
Profile of autoantibodies in CSF and serum in patients with inflammatory neurological diseases. J. Kraus, O. Fischer, C. Schäfer, W. Meyer, B. Teegen, W. Stöcker, F. Blaes, B.S, Kühne, M. Kaps, P. Oschmann, Justus-Liebig University, Euroimmun (Giessen, Gross-Gronau, D)

Background: Multiple sclerosis (MS) is hypothesized to be a T cell mediated autoimmune disease of the human central nervous system (CNS). Therefore, both autoreactive T and B cells as well as autoantibodies against different cellular proteins have been found in the cerebrospinal fluid (CSF) and the serum of MS patients. Moreover, the prevalence of some of these autoantibodies has been investigated in patients with inflammatory diseases of the CNS as well as the peripheral nervous system.

Objective: To evaluate the distribution of a large profile of autoantibodies in the CSF and the serum of patients with inflammatory neurological diseases by the aid of commercially available immunofluorescence tests (Euroimmun, Groß-Grönau).

Methods: We included 221 patients with different neurological diseases (different subtypes of MS, bacterial and viral meningitis, Guillain-Barré syndrome [GBS], polyneuropathy [PNP], chronic inflammatory demyelinating PNP [CIDP], systemic lupus erythematosus [SLE] and non-inflammatory neurological diseases [NIND]) in this study. Paired CSF/ serum samples from the patients were investigated for the titers of antinuclear (ANA), ANCA, myelin, MAG, neuroendothelium and gangliosid antibodies by an immunofluorescence test system. In MS patients, we quantified the amount and distribution of cranial lesions as determined by MRI and correlated them to the results of the serological tests.

Results: ANA were detected in the serum of 33.2 % (NIND: 10.3 %) and in CSF of 13 % (NIND: 4 %) of all patients. The distribution of ANA was seen to be significantly ($p < 0.0001$) different for the respective disease groups both in serum and CSF. The highest prevalence rates for ANA were found in patients with SLE and GBS both in CSF and in serum, respectively. In MS patients, ANA titers were positive in 33.9 % of the serum and 14 % of the CSF samples. In addition, we found a trend towards an increased prevalence of MS lesions in the spinal cord and the corpus pallidum of those MS patients who had positive serum titers for ANA.

Conclusions: We found an increased prevalence of ANA in the CSF and in the serum of patients with inflammatory neurological diseases. This finding might indicate a systemic immune dysregulation in these patients.

P653
Expression of CD40 in the human substantia nigra. A. De Iuliis, P. Zambenedetti, V. Gattei, P. Arslan, University of Padua (Padua, I)

Background: CD40,a type 1 membrane glycoprotein, member of TNF-receptor superfamily, is present on B cells, dendritic cells and epithelial cells, and it is also functionally expressed on macrophages, endothelial cells, fibroblasts, smooth muscle cells, during tissue regeneration and inflammatory responses.

CD40 is involved in the regulation of immune processes and, by binding its specific ligand (CD40L), expressed by activated T-lymphocytes, it plays an essential role in proliferation, activation and survival of immune cells. Implications for CD40/CD40L signalling were identified in atherosclerosis, experimental encephalomyelitis and multiple sclerosis.

To investigate functional interaction between nervous and immune cells we have studied the expression of CD40 and its ligand in normal human brain and in two tumour cell lines.

Material & Methods: We have used molecular biology techniques: Northern Blotting and Reverse Transcription-Polymerase Chain Reaction. Total brain and samples from cerebellum, cerebrum cortex, medulla, spinal cord, putamen, occipital, frontal and temporal lobe were examined by Northern Blotting, in commercially filters.

Substantia nigra, commercially obtained, a human neuroblastoma (SKNBE) and a neuroepithelial carcinoma (SKNMC) cell line were analyzed by Reverse Transcription-Polymerase Chain Reaction. RESULTS: We have found no CD40 expression in total human brain, but only in some regions.

CD40 mRNA was present in the spinal cord, in the substantia nigra and only in the neuroepithelial carcinoma cell line. To exclude tissue contamination by circulating B cells (CD40+) we tested all tissues for the presence of CD19 mRNA, which was never detected. CD40L mRNA was not detected in all examined samples.

Conclusions: Our studies point to a broader function of CD40 in the regulation of the some brain tissues. Previous studies indicated the expression of CD40 only in the reactive microglia of inflammatory multiple sclerosis lesions. The detection of the CD40 transcript in the normal substantia nigra is an important asset in the understanding of the signalling pathway that regulates the normal and pathological interactions between nervous and immune cells in this area of the brain. According to previous studies, indicating a possible role of glial cells and inflammation in the pathogenesis of Parkinson's disease, a functional consequence of the CD40 triggering may be related to the neurodegeneration of the substantia nigra.

P654
CSF and serum levels of soluble fractalkine in inflammatory diseases of the nervous system. S. Kastenbauer, U. Koedel, H.-W. Pfister, Klinikum Grosshadern, LMU Munich (Munich, D)

Background: Fractalkine (Fkn, CX3CL1) differs from most chemokines in several aspects: e. g., its membrane-bound form serves as an adhesion molecule for leukocytes expressing the the Fkn receptor CX3CR1 (monocytes, microglial cells, NK cells, and T lymphocytes); following proteolytic cleavage, soluble Fkn (sFkn) has been reported to be a chemoattractant for CX3CR1+ cells but also blocks their adherence to the membrane-bound Fkn; finally, Fkn is most abundant in the brain. However, in neurological diseases, CSF and serum levels of sFkn have not yet been reported.

Methods: sFkn was determined in the CSF and serum of patients with headache (controls, $n = 14$), Bell's palsy (BP, $n = 10$), Guillain-Barré-Syndrome (GBS, $n = 12$), multiple sclerosis (MS, $n = 15$), viral meningitis (VM, $n = 14$), and bacterial meningitis (BM, $n = 14$) by a standard Western Blot protocol. Human recombinant Fkn (hrFkn) served as standard. Specifity was demonstrated by blockade of antibody binding by hrFkn. The bands were quantified by densitometry (results are given as mean ± SD of optical density/nl CSF or OD/pl serum). Due to alpha-correction for multiple comparisons, $p < 0.008$ was considered significant.

Results: In controls, sFkn levels were approximately 1000fold higher in serum than in CSF. We observed a sigificant increase of CSF sFkn in BP (8.3 ± 4.9), GBS (11.5 ± 37.5), MS (6.3 ± 4.3), VM (11.5 ± 6.1), and BM (49.4 ± 68.4) compared with controls (3.1 ± 1.3, $p < 0.001$). In serum, sFkn levels were unchanged in BP (51.6 ± 24.1), GBS (58.0 ± 54.4), or VM (51.1 ± 32.6) compared with controls (45.3 ± 33.0), but tended to be decreased in BM (29.2 ± 24.4, $p = 0.062$) and were significantly increased in MS (237.8 ± 155.5, $p < 0.001$). The sFkn CSF/serum ratios were significantly increased in GBS (5.7 ± 10.2), VM (4.1 ± 4.6), or BM (39.1 ± 167.4) compared with controls (1.9 ± 0.9) and tended to be increased in BP (2.9 ± 2.2, $p = 0.026$) or decreased in MS (0.8 ± 1.4, $p = 0.051$).

Conclusion: We report for the first time alterations of sFkn CSF and serum levels in humans with neurological diseases. Due its putative function as a chemoattractant and modulator of leukocyte adhesion, sFkn may play a role in leukocyte trafficking during inflammatory diseases of the nervous system.

Infection of the Nervous System

P655
Herpes virus encephalopathy presenting as schizofreniform disorder. L. Chiveri, M. Sciacco, G. Scarlato, A. Prelle, Ospedale Maggiore Policlinico University of Milan (Milan, I)

A 21-year old man referred to our hospital for a fluctuating subacute schizophreniform disorder. He had a 10-month history of progressive behavioural changes; symptoms where complicated on two occasions by episodic self-remitting delirium. For these episodes he had been hospitalised in two different neurological departments where EEG, MRI and CSF examinations had been normal.

In our Department, he showed marked emotional lability, infantile behaviour with parental dependence; he spent his time in isolation. Neurological examination, CT scan and MRI were normal. However, EEG showed bilateral temporal epileptiform discharges and antiepileptic therapy was given without improvement. Laboratory tests (thyroid function, autoantibodies, paraneoplastic markers, recreational drug screening, porphyry and metabolic screening) were normal. CSF examination showed 116 mg/dl protein, 4 cells/mm3, normal glucose, no oligoclonal bands and absence of Borrelia Burgdorferi and viral antibodies (herpes simplex 1 and 2, varicella zoster, Epstein-Barr, cytomegalovirus, parvovirus, roseola, measles and parotitis virus). HIV serum antibodies were absent and lym-

phocyte subpopulations were normal. Polymerase chain reaction was positive for HSV–1. This positivity was confirmed by another independent laboratory on a previous sample of CSF. We started i. v. acyclovir treatment with clinical rapid improvement. One week after the end of treatment EEG had improved, CSF proteins were 74 mg/dl with no HSV1 detection at DNA PCR and the patient's conditions returned to normal.

Herpes virus may cause recurrent meningitis but sporadic delirium superimposed on a possible schizophreniform disorder has not been reported as a manifestation of HSV infection. Yet, the reported positivity of PCR for HSV on CSF and the rapid and striking improvement after acyclovir argue strongly in favour of an herpetic encephalopathy. A predominantly frontal localisation could explain the clinical pattern, characterised predominantly by chronic inhibitory behavioural changes resembling psychosis with negative symptoms.

This case underscores two clinical and diagnostic points: first, herpes virus infection may be responsible for otherwise unexplained chronic psychiatric symptoms. Second, it confirms that CSF screening for anti-viral antibodies may not be enough for the diagnosis, which ultimately requires search for specific viral genomic sequences by PCR.

P656

Generalized tetanus in an immunized patient. E. Alexiou, I. E. Markakis, A. Tsakiris, A. Galata, N. Matikas, Ag. Panteleimon General Hospital of Piraeus (Piraeus, Nikea, GR)

Background: Although tetanus remains a major health problem in the developing world, its incidence in Western countries has fallen dramatically due to widespread active immunization.The estimated failure rate of tetanus toxoid vaccination is extremely low (4 per 100 million immunocompetent hosts). We present a case of generalized tetanus in a fully immunized patient.

Case-history: A 62-year old woman was admitted to our department with a 6-day history of difficulties in mastication and deglutition. On examination a low grade fever (37,4 oC) and painful contraction of cervical muscles and tongue were found. A few hours later she presented trismus of the masseters, facial muscle contraction and opisthotonus.

The clinical presentation was considered diagnostic of tetanus. Human tetanus immunoglobulin (3000 iu) was given intramuscularly, as well as 0,5 ml of alum adsorbed tetanus toxoid and metronidazole 500 mg t. i. d. There was no history of recent wounds. Strikingly the patient had another bout of generalized tetanus 2 years before and had received a full immunization with 3 doses of tetanus toxoid.

Serum immunoglobulin levels were normal and there was no other evidence of immunosupression. A tracheostomy was performed and the patient remained under suppression and mechanical ventilation for three weeks.

Conclusions: The diagnosis of tetanus is purely clinical, since there are no specific laboratory tests. In the appropriate clinical setting, it should never be excluded even if a documented immunization history exists.

P657

MV2 (Kuru plaques) variant of sporadic Creutzfeldt-Jakob disease: peripheral neuropathy is part of the clinical spectrum. P. Sola, C. Stucchi, S. Capellari, G. Galassi, F. Roncaroli, J. Mandrioli, P. Cortelli, A. Baruzzi, P. Nichelli, P. Parchi, Università di Modena Clinica Neurologica, Università di Bologna Dipartimento di Scienze Neurologiche, Ospedale Bellaria Servizio di Anatomia Patologica (Modena, Bologna, I)

We describe the case of a 62 year-old male, admitted to the Neurological Clinic of Modena with a one-year history of mild behavioural disturbances and unsteadiness, and a 4 month history of gait instability, sleep-wake abnormalities, and episodes of temporal disorientation. On examination, he had cerebellar tremor, focal myoclonus, cerebellar ataxia, mild cognitive decline with predominant frontal lobe impairment, and distal loss of tactile sensation. EMG revealed a sensorimotor neuropathy with proximal and distal blocks in tibial nerves. Nerve biopsy showed a loss of large myelinated fibres. One month later ataxia significantly worsened and he developed a full-blown dementia and diffuse myoclonus. He died 18 months after onset. EEG examinations did not reveal periodic sharp-waves complexes until the last month of disease course. MRI was unrevealing, even late in the evolution. Level of 14–3–3 protein in the CSF became positive only 3 months before death.

Pathological examination displayed extensive pathology, the most severe lesions being in the thalamus, striatum and fronto-temporal cortices. Numerous kuru-like amyloid plaques were found in the cerebellum. Immunohistochemistry showed a plaque-like pattern of PrP-res deposition. Direct sequencing of PRNP open reading frame revealed no mutations and heterozygosity at codon 129. Western blot analysis showed PrP-res type 2.

The phenotypic heterogeneity of sCJD has been related to two types of PrP-res (type 1 and 2), with distinct physicochemical properties, and the genotype at PRNP codon 129, the site of a methione/valine (MV) polymorphism. Based on these findings and the study of the clinico-pathological phenotype in a large series of cases, sCJD has been recently classified in 6 distinct variants. The third most common combination (9% of sCJD subjects) is linked to PrP-res type 2 and MV at codon 129, and identifies with the so-called kuru-plaque variant of sCJD. To date, this variant has been linked to a disease phenotype characterized by progressive dementia, ataxia, myoclonus, pyramidal and extrapyramidal signs. The patient we studies showed sensory symptoms early in the course of the disease, a feature commonly associated with nvCJD but not consistently reported in sCJD MV2. This case report suggests that peripheral neuropathy is part of the phenotypic spectrum of sCJD MV2 and further underlines the clinical similarities between the MV2 variant of sCJD and nvCJD.

P658

Interaction of Neisseria meningitidis with human dendritic cells. O. Kurzai, G. Dietrich, A. Unkmeir, M. Frosch, A. Kolb-Mäurer, University of Wurzburg (Wurzburg, D)

Neisseria meningitidis is the most common cause of bacterial meningitis. Several factors involved in meningococcal pathogenesis have been characterized, but it remains unclear how N. meningitidis can cross the mucosal barrier. Within the mucosal barrier dendritic cells (DC) play a major role as antigen-presenting cells and represent a first frontier against invading bacteria. The reaction of DC to a contact with N. meningitidis is likely to be crucial for the initiation and efficiency of an immunological response. We have shown, that the expression of meningococcal capsules dramatically reduced DC adherence of N. meningitidis. Unencapsulated mutants of N. meningitidis display significantly increased adherence to DC and are readily phagocytosed whereas encapsulated isogenic strains are hardly internalized at all. DC respond to a contact with N. meningitidis by maturation and a cytokine burst. Except from the capsule, meningococcal lipooligosaccharide (LOS) and bacterial IgA-protease represent important determinants of virulence. The response of DC triggered by deletion mutants of these factors will add to the knowledge about meningococcal pathogenesis. In future experiments different clinical isolates of N. meningitidis will be compared in their interaction with DC. Especially, the reaction pattern of DC to N. meningitidis strains that are frequently isolated from healthy carriers and carry major virulence factors but have never been found as a course of disease, will be addressed.

P659

Experimental pneumococcal meningitis in the rat: the role of blood-labyrinth barrier disruption for meningitis-associated hearing loss. M. Klein, U. Koedel, H.-W. Pfister, S. Kastenbauer, Klinikum Grosshadern, LMU Munich (Munich, D)

Background: Up to 30% of survivors of pneumococcal meningitis suffer from often severe, uni- or bilateral, and usually permanent sensorineural hearing loss. Meningitis-associated hearing loss commonly results from suppurative labyrinthitis, i. e. spread of the inflammation from the subarachnoid space to the inner ear. We have recently demonstrated that meningogenic suppurative labyrinthitis is accompanied by severe disruption of the blood-labyrinth barrier. In this study, we investigated the pathophysiological relevance of blood-labyrinth barrier breaching for meningitis-associated hearing loss.

Methods: Male Wistar rats were infected by transcutaneous intracisternal injection of 150,000, 750,000, or 1,500,000 colony forming units of Streptococcus pneumoniae (low, medium, and high inoculum) or phosphate-buffered saline (PBS, controls). 18 h after infection, animals were treated with 100 mg/kg i. p. ceftriaxone. Hearing was repeatedly assessed by auditory brainstem evoked responses (ABR). 1 h after intraarterial injection of 1% Evans Blue, rats were sacrificed and perfused with PBS. After formalin fixation and paraffin embedding, 7 µm cochlea slices were used for histological quantification of cochlear leukocyte infiltration and fluorescence microscopic determination of Evans Blue extravasation.

Results: Meningitis-associated hearing loss increased with the bacterial inoculum in a dose-dependent fashion (hearing loss after 48 h: controls 0 ± 0 dB; low inoculum 20 ± 23 dB, medium inoculum 59 ± 20 dB, high inoculum 77 ± 15 dB). In animals infected with the high inoculum, hearing loss started approximately after 18 h (11 ± 16 dB) and was rapidly progressive (24 h: 51 ± 18 dB, 48 h: 77 ± 15 dB). The cochlear leukocyte infiltration clearly preceded and also positively correlated with the later devel-

opment of blood-labyrinth barrier disruption and hearing loss. Cochlear Evans Blue extravasation and hearing loss were strongly positively correlated (e. g., in the spiral ligament $r = 0.80$, $p < 0.001$).

Conclusion: Cochlear leukocyte infiltration itself is not sufficient to cause meningitis-associated hearing loss. However, it seems to contribute to the disruption of the blood-labyrinth barrier. The breaching of this barrier, in turn, closely correlates with the extent of hearing loss, suggesting that blood-labyrinth barrier disruption is a pathophysiologically relevant event during meningogenic suppurative labyrinthitis.

P660

Experimental herpes simplex virus encephalitis: sequential diffusion-weighted magnetic resonance imaging. P. Rau, S. Heiland, J. Sellner, K. Sartor, W. Hacke, U. Meyding-Lamadé, University of Heidelberg (Heidelberg, D)

Background & Goals: Herpes simplex virus encephalitis (HSVE) still remains a life-threatening disease with high mortality and morbidity. Chronic progressive magnetic resonance imaging (MRI) abnormalities are found even after early antiviral treatment and elimination of herpes simplex virus (HSV). Secondary autoimmune- and not directly virus-mediated mechanisms may play a key role for HSVE. Treatment with acyclovir and steroids reduced chronic progressive MRI findings and lead to a better long-term outcome. As diffusion-weigthed MRI (DWI) sequences are sensitive for monitoring inflammatory conditions, we aimed to assess DWI as a possible in vivo parameter for the evaluation of effective therapeutic strategies in HSVE.

Methods: Following an experimental model which mimics human HSVE, all mice but a negative control group were intranasally inoculated with HSV–1 strain F. Subsequently animals were randomly assigned to three different therapeutic groups: saline; acyclovir only; acyclovir and methylprednisolone. At different time points post inoculation sequential standard T2- and diffusion-weighted images were obtained. We calculated the appearent diffusion coefficient (ADC) values from temporal lobe T2-hyperintensities.

Results: Negative control animals had an ADC of 621,7*10–6mm2/s ± 87,5*10–6mm2/s in the temporal lobe. After 7 days all three therapeutic groups showed ADCs similar to the above-mentioned value. Imaging 21 days after inoculation revealed significantly reduced ADC values in the acyclovir/methylprednisolone group (480,5*10–6mm2/s ± 80,3*10–6mm2/s; $P < '05$) compared to untreated (655,8*10–6mm2/s ± 127,6*10–6mm2/s) and to acyclovir-treated animals (676,7*10–6mm2/s ± 113,4*10–6mm2/s).

Discussion & Conclusions: Diffusion-weighted MRI is used as a tool for early detection of edema and cell membrane disturbances by measuring the ADC. At day 7 post inoculation no significant ADC changes were seen in the three groups of HSVE mice (untreated, acyclovir-treated, acyclovir/methylprednisolone-treated animals). However, the acyclovir/methylprednisolone-treated group showed a significantly reduced ADC at day 21. This might be due to membrane stabilizing effects and reduced extracellular water contents secondary to corticosteroid treatment. Thus, DWI might be used as an in vivo monitoring tool for the evaluation of the disease course and treatment effectivity of the life-threatening disease.

Multiple Sclerosis

P661

Multiple sclerosis among native qataries: an epidemiological study. A. Hamad, Hamad General Hospital (Doha, QA)

Introduction: The aim of this study is to determine the incidence & prevalence of MS among Qataries. The state of Qatar lies midway along the East Coast of the Arabian Peninsula, east of Saudi Arabia.

Result: 29 Qatari patients were found, M:F ratio: 1.4:1. Mean age: 27.5 years. Symptoms at presentation: optic neuritis 45 %, pain & paraesthesias 24 %, weakness 17 %, ataxia 10 %, diplopia: 4 %. MRI showed demyelinating plaque in brain (93 %), and in cervical cord (81 %). VEP was abnormal in 70 % while SSEP and BSAEP were abnormal in 63 %, CSF oligoclonal bands were positive in 90 %. The course of the disease relapsing-remitting: 48 %. Secondary progressive: 38 % and primary progressive: 14 %. EDSS showed moderate to severe disability in 38 %. Two (7 %) patients died from infection. Between 1980–84 only 3 new cases identified while between 1995–99 ten new cases were identified. This makes M. S. incidence: 1.3/100,000 per year, the prevalence: 15/100,000.

Conclusion: Incidence and prevalence of MS in Qatar lies in the medium risk zone. The increasing incidence is probably real and not due to higher awareness and better methods of diagnosis and could be attributed to influx of immigrants from higher risk zone, frequent travelling abroad and replacement of the traditional seafood by high saturated fat food.

P662

The effect of interferon beta–1b on quantities derived from MT MRI in secondary progressive multiple sclerosis. M. Filippi, M. Inglese, J. H. van Waesberghe, M. Rovaris, F. Barkhof, D. Hahn, L. Kappos, D. H. Miller, A. J. Thompson, T. A. Yousry, G. Comi, Scientific Institute and University HSR, VU Medical Centre, University of Wurzburg, Kantonsspital Basel, Institute of Neurology, Klinikum Grosshadern (Milan, I; Amsterdam, NL; Wurzburg, D; Basel, CH; London, UK; Munich, D)

Magnetization transfer (MT) magnetic resonance imaging (MRI) can provide markers reflecting the severity of irreversible, multiple sclerosis (MS) damage occurring within and outside T2-visible lesions. MT MRI abnormalities are more evident in patients with a more disabling disease and tend to worsen at a greater pace in secondary progressive (SP) MS than in all other MS clinical phenotypes.

We investigated whether interferon beta–1b (IFNbeta–1b) is effective in reducing the accumulation of MT MRI-measured damage of the whole brain in a relatively large cohort of patients with SPMS. Data from a subcohort of patients participating into the European, multi-centre, double-blind, placebo-controlled trial of IFNbeta–1b in SPMS were analyzed. MT MRI scans were post-processed and analyzed to obtain histograms of MT ratio (MTR) values from the whole brain tissue (WBT). A region of interest (ROI) analysis of MTR values from the normal appearing white matter (NAWM) was also performed.

Eighty two SPMS patients from five centres underwent brain T2-weighted and MT MRI at baseline. Evaluable data were available for 75 patients at 12, 54 at 24 and 47 at 36 months. All patients had been randomly allocated to treatment with either placebo or IFNbeta–1b (Betaseron, 8 M. I. U), subcutaneously, on alternate days.

In the overall sample, there was a significant decrease of average brain MTR values from baseline to month 24 (mean change: –4.9 %) and month 36 (mean change: –4.3 %). The average percentage changes of WBT MTR for placebo and IFNbeta–1b patients were –4.8 and –5.0 at month 24, –3.3 and –5.1 at month 36, respectively. These changes were statistically significant for the placebo group at both the timepoints and for the IFNbeta–1b group at month 24 only, with no significant treatment effect. A decrease of NAWM MTR was observed at all the timepoints, with no significant difference between the two treatment arms.

In this cohort of patients with SPMS, IFNbeta–1b as compared to placebo did not show an overall significant effect on the worsening of MT MRI measures. The data show that change in MTR is a robust tool for monitoring disease evolution in SPMS and that the information obtained from MT MRI complements that obtained from MRI measures of lesion load and inflammation.

P663

A genome-wide screen for linkage disequilibrium in multiple sclerosis patients from Turkey. A. E. Hensiek, M. Eraksoy, M. Kurtuncu, G. Akman-Demir, A. Kiyat-Atamer, M. Gedizlioglu, B. Petek-Balci, M. Kilinc, O. Anlar, C. Kutlu, S. Sawcer, A. Compston, H. Ozcan, Addenbrooke's Hospital, Istanbul Medical Faculty for the Turkish Multiple Sclerosis Genetics Study Group (TMGSG)

Previous studies searching for susceptibility genes in multiple sclerosis have confirmed association with alleles of the MHC, but have not succeeded in identifying other genes associated with the disease. Progress in genetic technology has now made it feasible to employ more powerful methods for genetic analysis and the first association based genome screen in multiple sclerosis has recently been completed in probands from the United Kingdom. As part of the GAMES (Genetic Analysis of Multiple Sclerosis in EuropeanS) collaboration, we screened 197 Turkish cases and 199 Turkish controls with the same 6000 microsatellite markers across the genome for evidence of linkage disequilibrium, using pooled DNA. Turkey is an intermediate risk population for Multiple Sclerosis, which offers special opportunities for genetic analysis because the high rate of consanguineous marriages would be expected to increase the power to identify susceptibility factors acting in a recessive manner. Provisional results of our screen indicate that the markers showing greatest evidence of association, are located on chromosomes 1p, 1q, 19q, 2p, 5q and 6p; these overlap with the HLA region and areas implicated in previous linkage genome screens.

P664

Quantification of brain and spinal cord atrophy in multiple sclerosis using high resolution 3-dimensional MRI. X. Lin, C. Constantinescu, L. D. Blumhardt, University of Nottingham (Nottingham, UK)

Atrophy measure provides an important indirect marker of irreversible and destructive pathological processes in multiple sclerosis (MS). We aimed to investigate atrophy in different parts of the central nervous system, and its relationship with clinical measures, in 49 relapsing-remitting (RR) and 48 secondary progressive (SP) MS patients. Conventional dual echo and three-dimensional (3-D) magnetisation prepared rapid acquisition gradient echo imaging was performed on all patients, and on 29 age- and gender-matched healthy controls. The volumes of the supratentorial brain, lateral ventricles, brain stem, cerebellum and upper cervical cord (UCC) were determined on 3-D MRI using modern design stereology associated with point counting.

Significant supratentorial volume reduction ($p < 0.0001$) and lateral ventricular enlargement ($p < 0.0001$) occurred in RR MS patients compared with controls. There was no difference between the control and RR MS groups for cerebellum, brain stem and UCC volumes. Secondary progressive MS patients had significantly smaller normalised supratentorial brain ($p < 0.0001$), cerebellum ($p = 0.007$), brain stem ($p = 0.0004$) and UCC ($p < 0.0001$) volumes, and larger lateral ventricles ($p < 0.0001$), than controls. In the total cohort, mean estimates of volume change (difference from control values) were –7.5 %, –3.2 %, –4.9 %, –9.7 % and 57.5 % for supratentorial brain, cerebellum, brain stem, cervical cord and lateral ventricles, respectively. Supratentorial brain volume was correlated with lateral ventricular ($r = –0.6$, $p < 0.0001$), cerebellar ($r = 0.4$, $p < 0.0001$) and brain stem ($r = 0.5$, $p < 0.0001$) volumes, but not UCC volume ($r = 0.2$, $p = 0.09$). Multiple regression analysis showed that supratentorial brain volume in RR group, and UCC volume in SP group, was the single significant contributor ($p = 0.01$ and 0.04, respectively) to EDSS of all factors entered into the regression model.

In conclusion, supratentorial brain atrophy occurs early in the disease course, whereas generalised atrophy in the brain and cervical cord takes place in SP MS. Quantification of supratentorial brain volume in RR MS, and UCC volume in SP MS, is relevant to functional disability.

P665

Moderately elevated serum S100B levels are associated with treatment response in multple sclerosis. A. Petzold, D. Brassat, P. Mas, G. Keir, G. Giovannoni, M. Clanet, E. Thompson, Institue of Neurology, University of California, Hopital Purpan (London, UK; San Fransisco, USA; Toulouse, F)

Introduction: Characterising treatment responders and non-responders in multiple sclerosis (MS) is important for selecting effective drug therapies and to improve our understanding of the disease pathogenesis.

Increased levels of the brain specific protein S100B, a biomarker of astrocyte activation, are associated with acute disease activity. Nanomolar concentrations of S100B exhibit neurotrophic while micromolar concentrations have cytotoxic properties. This study aimed to investigate whether differences in serum S100B levels are associated with treatment response in MS.

Methods: 47 MS patients treated with interferon 1-beta (IFNb), 14 normal subjects (negative control group) and 11 patients with traumatic brain injury (positive control group, GCS 4–14) were included into this cross-sectional study. MS patients underwent MRI and clinical evaluations using Kurtzke's EDSS in the 12 months prior to sampling. MS patients were stratified into (1) responder to IFNb (less then 2 relapses or no progression of more then 1 point on the EDSS), (2) non-responder to IFNb (at least 2 relapses or new Gd-enhancing lesions on T1 MRI or progression of more then 1 point on the EDSS) and (3) patients treated on mitoxantrone with a mean treatment of 6 intravenous courses of 12 mg/m2 every 5 weeks.

Results: There was a significant trend for increasing proportions of patients with elevated serum S100B levels according to treatment regime and response (Mantel-Haenzel Chi-Square = 25.9, $p < 0.001$). A higher proportion (71.4 %) of responders to IFNb had elevated S100B levels when compared to non-responders (33.3 %, $p = 0.039$, Fisher's exact test) or the control group (7.1 %, $p < 0.001$). A higher proportion of patients treated with mitoxantrone (61.1 %) had high S100b levels when compared to the control group ($p < 0.001$), whereas no significant difference was found between IFNb non-responders and controls. A significantly higher proportion of traumatic brain injury patients had high S100B levels compared to all other groups ($p < 0.001$) but the responders to IFNb treatment.

Discussion: The results of this cross-sectional study suggest that moderately elevated serum S100B levels are associated with a treatment response to IFNb and mitoxantrone in MS patients. Serum S100B may therefore be a predictive marker of a treatment response and needs to be evaluated in a prospective longitudinal study.

P666

Expression of tyrosine hydroxylase in the arcuate nucleus of the rat during acute experimental allergic encephalomyelitis. R. Pego-Reigosa, S. Vidal, L. Moya, P. Pesini, Hospital Xeral-Calde, Universidad de Santiago (Lugo, E)

Prolactin (PRL) plays an important role in the reciprocal communication between the neuroendocrine and the immune systems. In this line of evidence, recent studies have suggested that a moderate hyperprolactinemia is a risk factor to develop autoimmune diseases both in humans and animals. However, data on the regulation of PRL synthesis and release in the course of immune responses is scarce. At present, we are studying the regulation of the PRL secretion in the course of experimental allergic encephalomyelitis (EAE), an experimental model of human multiple sclerosis. We report here that the number of tyrosine hydroxylase (TH)-expressing neurons in the hypothalamic arcuate nucleus varies in the course of acute EAE.

All experiments were carried out in accordance with the ECC Directive of 24 November 1986 (86/609/EEC). Acute EAE was induced in male Lewis rats by the injection of an emulsion containing 50 mg of myelin basic protein. Groups of animals ($n = 4$) were killed: i) at post injection day (PID) 12 when the first symptom (tail flaccidity) appeared, ii) when the animals became paraplegic (PID 13), iii) after recovering (PID 28). A group of Sprague-Dawley rats was injected with the same emulsion and killed at PID 18. In addition, two groups of age-matched intact Lewis and Sprague-Dawley rats were used as controls. After sacrifice, the brains were prepared for standard immunohistochemistry using an anti-TH monoclonal antibody. The sampled sections for each animal were coded and the quantification of the arcuate neurons was carried out blind. Statistical assessment was by the Mann-Whitney test. Significance was considered at $P < 0.05$.

At the PID 12 when rats showed tail flaccidity, the number of arcuate TH-positive cells decreased to a 17 % with regard to control Lewis rats. This number further decreased to a 52 % of the control in the rats severely paraplegic (PID 13). At PID 28 when the symptom had disappeared, the number of TH neurons recover to the level of controls. No significant differences were found either between intact Lewis and Sprague-Dawley rats nor between intact and treated Sprague-Dawley rats. These results were congruent with previous studies reporting hyperprolactinemia in Lewis rats at the onset of EAE. Furthermore, they suggested that a deficient regulation of the arcuate dopaminergic neurons could be related with the susceptibility of Lewis rat to develop EAE.

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P667

Cerebral volume change in secondary progressive multiple sclerosis: effect of intravenous immunoglobulins (IVIG). X. Lin, B. Turner, C. Constantinescu, L. D. Blumhardt, F. Fazekas, M. Filippi, G. Comi, M. Mass Enriquez, O. R. Hommes, University of Nottingham, Karl-Franzens University, Scientific Institute H San Raffaele, Bayer Vital GmbH, European Charcot Foundation the European Study on IVIG in Multiple Sclerosis (ESIMS)

Several studies have demonstrated the importance of measuring brain volume as a surrogate marker of disease progression in multiple sclerosis (MS). The recently completed European Study on IVIG treatment in MS at the dose of 1 g/kg/body weight monthly in patients with secondary progressive MS has provided an opportunity to assess the effect of IVIG treatment on cerebral atrophy using 3-dimensional (3-D) magnetic resonance imaging (MRI). A subgroup of 43 patients from 5 centres underwent and completed T1-weighted magnetisation prepared rapid acquisition gradient echo (MPRAGE) images at 12-month intervals from month 0 to month 24. Expanded Disability Status Scale (EDSS) scores were acquired at 3-month intervals. The volumes of supratentorial and infratentorial structures and the lateral ventricles were estimated using modern design stereology and point counting on 3-D MPRAGE images.

The placebo ($n = 22$) and treated ($n = 21$) groups were well matched for the baseline age (42.9 ± 6.3 vs 44.0 ± 7.0), disease duration (14.6 ± 7.5 vs 12.4 ± 5.8), EDSS (4.8 ± 1.2 vs 4.9 ± 1.0), supratentorial (902 ± 53 vs 911 ± 45 ml), infratentorial (138 ± 13.5 vs 134 ± 14.2 ml) and lateral ventricular (27.1 ± 17.4 vs 23.4 ± 10.8 ml) volumes. There was a significant enlargement of the lateral ventricles at month 24 in both placebo and IVIG treated groups, with a mean increase of 9.8 and 7.4 %, respectively. In parallel, there was a smaller reduction of supratentorial brain volume in IVIG than placebo treated patients (–0.5 vs –2.1 %) over 24 months, but this difference was not significant ($p = 0.25$). However, the placebo group showed a significantly greater infratentorial volume reduction at month 12 (–1.8 vs 2.1 %, $p = 0.022$) and month 24 (–3.3 vs 0.8 %, $p = 0.026$) compared with the IVIG treated group. In the total cohort, the percentage change of lateral

ventricles was correlated with the change in EDSS over 24 months ($r = 0.58$, $p < 0.0001$).

In conclusion, lateral ventricular volume showed significant change that correlated to the functional disability over 24 months. During this period, brain volume reduction was smaller in the IVIG treated group with a statistically significant difference regarding changes in infratentorial brain volume. The mechanism(s) responsible for the impact of IVIG on brain atrophy are yet to be elucidated.

P668

Serotonin-Transporter-Knockout mice display reduced susceptibility for EAE and potentially differential immune regulation compared to wild type C57BL/6 mice. H. Hofstetter, R. Moessner, K. Lesch, R. Gold, Clinical Research Group for MS, Department of Psychiatry (Wuerzburg, D)

Serotonin (5-hydroxytryptamin) is one of the most extensively studied neurotransmitters of the central nervous system and is also present in constituents of the immune system. It has been suggested that serotonin might serve as a mediator of bidirectional interactions between the nervous system and the immune system. Experimental autoimmune encephalomyelitis (EAE) is an autoimmune disease of the central nervous system (CNS) which resembles the human disease multiple sclerosis. It is induced by immunization with myelin autoantigens like myelin basic protein (MBP) or myelin oligodendrocyte glycoprotein (MOG). As it has been demonstrated that serotonergic receptors and the serotonin transporter (5-HTT) are present on cells of the immune system, serotonin might influence the autoimmune reaction in the CNS.

As it has been shown that expression and function of the 5-HTT are modulated by cytokines in inflammation, we have studied EAE induced in 5-HTT knockout mice on the C57BL/6 background, in comparison with wild-type control animals. Both after immunization with MBP and with the immunodominant peptide of MOG, spanning amino acids 35–55, 5-HTT knockout mice display a reduced susceptibility for EAE in relation to the wild-type controls.

To dissect potential immune mechanisms underlying this phenomenon, cytokine measurements were performed to study the nature of the immune response evolving in 5-HTT knockout mice and wild-type controls after immunization with myelin autoantigen. For this purpose, the ELISPOT (enzyme linked immunospot assay) technique for the cytokines interferon-gamma, interleukin–2, interleukin–4, interleukin–5 and interleukin–6 was used. Mononuclear cells were isolated from the spleens of 5-HTT knockout mice and wild-type control animals and tested in cultures without or with antigen for cytokine production. The results show that the genetic inactivation of 5-HTT does not confer impaired priming of an (auto)antigen-specific immune response. Furthermore, also the overall quality of the immune response was identical in both groups. However, differences in the quantity of cytokine production were detected in 5-HTT knockout mice compared with wild type controls, in particular a reduction of antigen-specific production of interferon-gamma. This may suggest differences in the antigen-specific immune regulation in these mice and support a role of serotonin in the fine-tuning of (neuro)antigen-specific immune responses.

P669

A comparison of the incidence and biological effects of neutralizing antibody formation in MS patients treated with two interferon beta–1a products. A. Al-Sabbagh, S. Goelz, W. Jones, S. Eoh, H. Zhang, Biogen, Inc. (Cambridge, USA)

Human interferon (IFN) beta is currently first-line therapy for relapsing-remitting multiple sclerosis (MS). IFN betas exert their clinical effects by binding to receptors on the surface of cells, thereby initiating a cascade of events that culminate in the expression of IFN beta-dependent genes. Similar to other protein therapeutics, both binding (BABs) and neutralizing (NABs) antibodies may develop during treatment with IFN beta. With other protein drugs in other diseases, it has been reported that both BABs and NABs can affect clinical efficacy. However, with IFN beta, little is known about BABs and the importance of NABs is still debated. Although NABs have been shown to reduce the clinical efficacy of IFN betas in MS patients, the definition of clinically relevant titers and the long-term significance of NABs remains controversial. The present study examined the incidence of BABs and NABs to 2 IFN beta–1a preparations (Avonex and Rebif) and the effect of these antibodies on the induction of neopterin by IFN beta–1a. Neopterin was used as a surrogate marker for in vivo receptor activation. This was a multicenter, open-label study involving 76 patients with relapsing MS. NABs were measured in patients who were treated with Avonex (n = 35) 30 mcg IM once weekly or Rebif (n = 41) 22 mcg SC three times weekly for 12 to 18 months. Serum neopterin levels were measured predose and 48 hours postdose. The incidence of NABs (titer 5) was significantly higher in Rebif-treated patients (27 %) compared with Avonex-treated patients (3 %) ($p = 0.011$). When a titer of 20 was used as a cut-off, the incidence of NABs was 22 % for Rebif patients and 3 % for Avonex patients. The incidence of BABs was also higher for Rebif than for Avonex; 76 % vs. 26 % ($p < 0.001$). While BABs had no effect on neopterin induction, it was either diminished or absent in NAB-positive patients compared with NAB-negative patients; this was equally true for low titers (13) and high titers (> 1000). Based on the results of this study, administration of Rebif SC three times weekly is more immunogenic than administration of Avonex IM once weekly. The results of this study indicate that even low levels of NABs can block receptor activation in vivo. Differences in structure, as well as route and frequency of administration, can contribute to the differences in immunogenicity of IFN beta products.

P670

Association of disease severity and clinical disability with geographic localization in MS patients of Lebanese descent. C. Caon, M. Zvartau-Hind, W. Ching, R. Lisak, O. Khan, Wayne State University (Detroit, USA

Objective: To investigate disease severity in a small cohort of MS patients of Lebanese descent and to examine association between clinical disability and geographic localization Background: Many factors may contribute to disease severity in MS. However, it is not known if environmental factors such as region of birth may influence MS disease severity. Lebanon is not considered to be a high prevalence area for MS. A large community of Lebanese descent resides in the Detroit metropolitan area. We investigated the clinical course and disease severity in MS patients born in Lebanon and subsequently immigrated to the U.S after the age of 15 years.

Methods: Records of MS patients born in Lebanon who migrated to the U. S. after the age of 15 were examined.

Results: 21 Lebanese-Americans with CDMS were identified. 12 of 21 were born in the El-Bekaa valley of Lebanon which extends along the Syrian Lebanese border between the 33.3 and 34.3 parallel (group 1). Ten patients were born in the Beirut Metropolitan area which is also between the 33.3 and 34.3 parallel but on the Mediterranean coast of Lebanon (group 2). All except one patient in group 1 had SPMS by Lublin criteria. One patient had PPMS. In group 1, 6 of 12 patients were female. Mean age and disease duration were 38.1 and 8.7 years, respectively. Mean EDSS was 7.57. Brain MRI scans showed significant involvement of brain stem in 8 of 12 patients. All patients in group 2 had RRMS. 7 of 9 were female. Mean age and disease duration were 45.5 and 7.6 years, respectively. Mean EDSS was 2.12. Brain MRI showed brainstem involvement in only one of 9 patients. Additional data on ancestral origins including European influence is being determined. Furthermore, HLA typing and potential determinants of disease severity genetic such as APOE E4 will also be being obtained.

Conclusions: There appears to be a distinct localization of disease severity to geographic localization in a small cohort of MS patients born in Lebanon. Both Beirut and El-Bekaa valley are relatively small geographic areas. Although, there may be several confounding factors affecting the disease course in these two groups, there were significant differences in the clinical course of the disease despite similar disease duration and migration to the US after age 15. We plan to investigate biologic as well as environmental determinants of clinical course in these two groups of patients.

P671

Apolipoprotein E polymorphism as a predictor of progression of multiple sclerosis. A. L. Guerrero, V. Bueno, M. T. Hernández, J. I. Martín-Serradilla, E. Carrasco, I. Cuadrado, Hospital Río Carrión (Palencia, E)

Introduction: Different studies during last years have analyzed, without fully agreement up to now, the association between apolipoprotein E (APOE) polymorphism and clinical course of multiple sclerosis (MS).

Patients and methods: We cross-sectionally studied all 40 patients periodically seen in our unit, diagnosed as relapsing remitting or secondary progressive MS, and with a disease duration of at least 2 years. We analyzed different clinical and radiological parametres in each patient, with special attention to progression index and number of relapses. APOE genotyping was done. In the moment we send this abstract we have received and analyzed genotype distribution of 15 patients.

Results: In our patients 20 % had the e4 allele which was similar to findings of previous European studies. In this point of the analysis, we cannot find significant differences in the clinical variables considered among patients with or without the e4 allele.

Discussion: We pretend to contribute with the view of a non-MS-super-

especialized unit on the problem of the real prognostic value of APOE polymorphism in MS.

P672

Multiple sclerosis associated with idiopathic uveitis. A. Miralles, P. Barreiro, E. Díez-Tejedor, Hospital La Paz (Madrid, E)

Introduction: Purpose: Multiple sclerosis (MS) is usually associated with other autoimmunes diseases. The association with idiopathic uveitis (IU) is uncommon and scarcely known. We propose analyse the presence of IU in patients diagnosed of MS, types of uveitis and severity of uveitis, the weight in disability of MS patients, and the delay between both diseases.

Methods: Patient: We selected patients diagnosed of IU by clinical and funduscopy criteria from database of the MS patients. We analyse the punctuation in the visual functional system (FS) and punctuation in the Kurtzke's Expanded Disability Status Scale (EDSS).

Results: We identified 7 patients with definite MS and UI from a total of 270 patients (2.6 %); Anterior uveitis was observed in 1 patient (14 %), another one was intermediate uveitis (14 %), and 5 patients were posterior uveitis (72 %). It was bilateral in 3 patients (43 %) and unilateral in 4 (57 %). Four patients (57 %) remained with serious decrease of visual acuity, another patient with centrocecal scotoma; in theses cases IU was the main responsible for the total punctuation in EDSS score (most affected FS in 75 % of the patients). Neurologic symptoms occurred before onset of uveitis in 2 patients (29 %) and ophthalmologic manifestations preceded to MS in 4 cases (57 %), the diagnoses were simultaneous in one patient (14 %).

Conclusion: The association of MS and idiopathic uveitis is rare. The most frequent type of uveitis in MS patients is posterior uveitis. There is no clear relationship between the onset of both diseases. Uveitis can be the main responsible of disability in MS and UI patients. It must be considered to identify MS patients with lose of visual acuity, the correct follow-up and specific treatment can prevent irreversible deferred complications.

P673

Multiple sclerosis patients' attitudes towards participation in clinical trials: an Italian survey. E. Cartechini, E. Pucci, C. Taus, G. Giuliani, AUSL 9, Clinica Neurologica (Macerata, Ancona, I)

Objectives: To evaluate multiple sclerosis (MS) patients' attitudes towards participating in randomised clinical trials (RCTs) and the associations between these attitudes and demographic and clinical features.

Participants: 100 consecutive MS patients who had never participated in an RCT, with preserved capacity to consent to treatment.

Methods: We asked patients about attitudes towards their participation in a hypothetical phase III placebo-controlled RCT on a disease-modifying agent. Clear information about the RCT and the available therapy was given. Participants were asked to give a reason for their acceptance or refusal to participate in this hypothetical RCT. "Don't know" responses were accepted. If more than one reason was reported, the examiner urged the participant to choose, if possible. With a view to clearer communication, the examiner was free to comment, paraphrase and reformulate the participant's response. Participants' responses were transcribed and then classified after discussions among the authors.

Demographic and clinical (EDSS, disease duration, use of conventional and unconventional therapies) features were collected.

Main results: Two patients refused to participate in this survey. Out of the 98 patients interviewed, 42 (42.9 %) denied their consent to the hypothetical RCT. The most common reasons were: fear of side-effects (20.4 %); placebo (7.1 %); refusal to play the role of a "laboratory rat" (6.1 %); participation only in case of clinical worsening in the absence of any other available therapy (6.1 %). Patients who gave their consent to the hypothetical RCT were not different from the other participants in demographic and clinical features. At least one unconventional therapy was used at least once by 28.6 % of the patients who denied their hypothetical consent. Among those patients who were being treated with interferon beta (68 out of 98), 41.2 % gave hypothetical consent and only 6, out of the 32 who denied consent, stated the use of placebo as the principal reason for their denial.

Conclusions: A substantial number of MS patients showed fear or prejudice about participation in an RCT. Few patients seemed concerned with the issue of clinical equipoise. Physicians must discuss the value of methodologically correct research with their patients in order to increase confidence in clinical research among consumers, give more information about evidence-based clinical practice and comprehend patients' preferences.

P674

The design of the EVIDENCE trial, the first direct comparison of two interferon beta–1a products for the treatment of relapsing-remitting multiple sclerosis (RR-MS). C. A. Young, Walton Centre for Neurology & Neurosurgery On behalf of Evidence study group

The two interferon beta–1a (IFN-b1a) products available for the treatment of RR-MS differ in their recommended dose and frequency and route of administration. The EVIDENCE trial provides a direct comparison of these two regimens, Rebif&No 61666; (Serono) and Avonex&No 61666; (Biogen), in RR-MS. This was a controlled, assessor-blinded, comparative trial with a rigorous scientific design. The design, endpoints and analysis methods were agreed with the US Food and Drug Administration and it was conducted according to Good Clinical Practice (GCP) guidelines.

677 RR-MS patients with expanded disability status scale scores of 0–5.0 were recruited from 57 centres, in accordance with defined inclusion criteria. All patients gave informed consent and were subject to pre-study screening. Patients were randomised to receive either IFN b–1a 44 mcg subcutaneous three times weekly, or 30 mcg intramuscular once weekly, for an initial period of 24 weeks. Randomisation was carried out centrally using a computer-generated random number list, and was stratified according to centre. Monitoring was as follows:

i) Patients visited their centres every 4 weeks and were contacted by telephone 2 weeks after each visit.
ii) Neurological assessments were at 12-week intervals and as needed for relapse assessment.
iii) Magnetic resonance imaging (MRI) was performed 4 weeks before first dose and at 4-week intervals on treatment.

The assessors of neurological and MRI outcomes were blinded to treatment. Patients and treating physicians were aware of treatment allocation because, given the different injection route, frequency and dose, double-dummy design would be ineffective in blinding. Relapse criteria were defined in advance and all suspected relapses were fully assessed by a blinded evaluator. Follow-up at 24-weeks was completed for 97 % of patients, and the results were analysed according to a predetermined statistical analysis plan, based on an intention-to-treat approach with imputation methods for missing data due to early terminations.

EVIDENCE is a large, comparative, rater-blinded study, conducted according to GCP. Its design and methodology is rigorous, with specific measures being employed to ensure evaluator blinding. In contrast to other comparative studies reported so far, EVIDENCE fulfils the criteria for a class I evidence trial (Neurology 2002;58:169–178). The results of EVIDENCE provide important answers to the current debate over IFN-beta 1a treatment regimens.

P675

International certification of multiple sclerosis nurses. H. Maloni, C. Fraser, J. Halper, M. Heerings, M. Keating, B. Layton, L. McEwan, A. Ross, S. Smeltzer, M. Uccelli, N. Ward, J. Wollin, International Organization of MS Nurses on behalf of the Multiple Sclerosis Nurses International Certification Board

Background: The Multiple Sclerosis Nurses International Certification Board (MSNICB) was formed by special initiative of the International Organization of Multiple Sclerosis Nurses (IOMSN) to establish domains specific to multiple sclerosis (MS) nursing practice. MS nurses with expertise in nursing research, education and practice representing Australia, Canada, the Netherlands, the United Kingdom and the United States gathered to delineate MS nursing roles that cross oceans, borders, cultures and healthcare systems.

Purpose: To achieve the vision of the IOMSN that unites MS nurses through standard practices based on common knowledge, skills and tasks that encourages best outcomes in caring for individuals and families living with multiple sclerosis; To evaluate best practices through examination leading to certification that recognizes and validates international MS nursing knowledge.

Methods: MSNICB developed a certification examination reflecting international domains of multiple sclerosis nursing. Domains encompass the full range of knowledge, skills and tasks of MS nursing responsibility and accountability. Examination questions were submitted from five countries including three continents and are representative of international MS nursing practice. Examination content was reviewed by regional constituents for validity and defensibility.

Results: The domains of clinical practice, advocacy, education and research were delineated by a board of international multiple sclerosis education and practice professionals. The examination conforms to psychometric standards, is relevant to practice and reflects basic preparation for the MS registered nurse. The first examination will be held in June 2002 in

conjunction with the annual meeting of the Consortium of Multiple Sclerosis Centers. The certification examination will be offered in November 2002 and twice yearly thereafter in forty cities throughout North America, Australia, Finland, Italy, the United Kingdom and the Netherlands.

Conclusions: Certification benefits the individual nurse to the full extent of professional expertise with impact on practice outcomes. Certification establishes standards and recognizes those nurses meeting the standards. An International certification is a revolutionary concept in professional nursing care if individuals and families living with multiple sclerosis.

P676

The effects of glatiramer acetate(Copaxone) on cerebrospinal fluid tumor necrosis factor-alpha levels, relapse rate and disease progression in patients with relapsing-remitting multiple sclerosis: results of 12 months of therapy. N. Subutay Oztekin, M. Oztekin, M. Vardar, G. Ozdurdag, SSK Ankara Hospital (Ankara, TR)

Objective: The aim of the study is to investigate the effects of glatiramer acetate on CSF tumor necrosis factor alpha levels, relapse rate, number of relapses and disease progression in patients with relapsing-remitting multiple sclerosis(RR MS) and whether Copaxone has its beneficial effects over the reduction of this proinflamatory cytokine.

Method: 20 patients aged between 18–49 years of age(mean 31.4 y)with clinically definite R-R MS were enrolled to the study. Clinical status was defined according to EDSS and EDSS ranged between 0.5–4(mean EDSS = 2.8)Duration of the disease was 12–204 months(mean = 68 months)The total number of relapses /year before treatment 25(mean 1.15/year).All patients were treated with 20 mg copaxone/day every day 0.20 age matched healthy subjects with no family history of neuropsychiatric disorders were used as controls. CSF samples are obtained before and 3, 6 and 9 months after the start of the treatment with Copaxone. The neurologic examination, EDSS scores and gd-enhanced MRIs of the patients are obtained initially, before the start of treatment and repeated 3 months apart. CSF TNF alfa levels are studied with ELISA method.

Results: Basal CSF TNF alfa levels of patients with R-R MS were higher than the levels of patients in the control group($p < 0.05$).There was a prominent reduction in the CSF TNF-alfa levels in the treatment group after the 3rd. 6^{th} and 9^{th} months of treatment, especially after the 3rd month, but the results were not statistically significant($p > 0.05$).CSF TNF alfa levels showed a prominent increase during relapses. There was a 39 % reduction in the relapse rate during the treatment period, but it was not found statistically significant. EDSS scores showed a mild and steady decrease during the treatment period, but the result was not statistically significant; the most prominent decrease was in the 9^{th} month and was found to be statistically significant.

Conclusion: The results of this study showed that subcutaneous Copaxone 20 mg daily significantly reduced the CSF TNF-alfa levels in patients with R-RMS after the 3rd, 6^{th} and 9^{th} months of treatment as well as a reduction in relapse rate and EDSS scores. Given that Copaxone decrease T-cell activation it probably may exert its beneficial effects in relapse rate in patients with R-R MS by reducing proinflamatory cytokine levels in CSF.

P677

The search for a peripheral immunological marker in multiple sclerosis patients (qualitative/quantitative analysis of the TCR Vb chain). D. A. Laplaud, S. Wiertlewski, M. Guillet, P. Brachet, G. Edan, P. Damier, J. P. Soulillou, INSERM U 437, Clinique Neurologique (Nantes, Rennes, F)

Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system associated with T-cells autoreactive for myelin components. The (auto)antigenic peptide is recognized by the T-cell through its hypervariable region on the TCR (Vb chain). The aim of this study was to explore the possible presence of a peripheral marker of an immune component in MS. We analysed the Vb transcriptome at a qualitative and quantitative level in the blood of MS patients using a new method designed in our laboratory. This method allows to detect alterations in the T-cell repertoire and to estimate the T-cells pool size expressing a given altered Vb family. No further cell manipulation is performed during this procedure avoiding selection biases due to cell culture.

Method: Two groups of patients were analyzed. The first group (n = 10) was composed of patients suffering from worsening MS (mitoxantrone treatment). TcLand was performed before and at different time points after treatment. The second group (n = 12) was composed of patients at the onset of the disease. A group of healthy volunteers was also analyzed as a reference.

First, Peripheral blood mononuclear cells were isolated, the RNA was extracted and reverse transcribed to obtain single strand cDNA. Specific primers for 26 Vb family were used to carry out the combined qualitative and quantitative analysis of the TCR. The results were integrated to give colored coded vision of the whole T-cell repertoire referred as T-cell Landscapes (TcLand). After identification of the altered Vb family(ies) for each patient, the cells bearing the altered TCR can be separated with Vb family-specific antibodies. RNA was then extracted and mRNA cytokine production can be analysed in a quantitative manner (TaqMan).

Results: Our data suggest that there are more alterations in the MS groups (12/22) than in the healthy volunteer group (2/10). The alterations may also be more frequent in worsening MS patients (8/10) than at the onset of the disease (4/12)[Chi-square test, p = 0, 02]. In addition, in preliminary experiments, we show that sorting of the cells bearing the altered TCR for transcriptional analysis is possible. The TcLand patterns and transcriptional profiles of the altered T-cells will be detailed. We suggest that this approach may open new opportunities for understanding the magnitude and the type of the immune component in MS.

P678

Bladder dysfunction in multiple sclerosis: relationships with lesion burden and atrophy measurements. F. Caramia, N. Ngo Dinh, E. Giugni, B. Di Pofi, P. Pantano, S. Bastianello, C. Pozzilli, University of Rome (Rome, I)

To determine the relationship of bladder dysfunction (BD) with both lesion burden and atrophy of infratentorial/supratentorial brain structures in multiple sclerosis (MS) patients with different disease course.

Eighty-eight MS patients –33 clinically isolated syndrome (CIS), 31 relapsing remitting (RR), 24 secondary progressive (SP) were recruited from MS Center of our hospital. In each patient we recorded information on bladder dysfunction and we assessed bladder disability by Functional Systems score of the EDSS. Brain MRI was performed with a 1.5 T magnet and the following sequences were acquired: axial proton density- and T2-weighted fast-field echo and T1-weightes conventional spin-echo. Volume estimates for lesions located in the pontine region closely to periacqueductal grey matter (PAG), lateral ventricles and at level of both right and left inferior frontal gyrus (FG) were calculated on both T2-weighted and T1-weighted images as hyperintense and hypointense (black holes) lesion load (LL). All these measurements were calculated from the axial scans using a program that incorporates a semiautomated edge-detection and contouring algorithm. Measurements of atrophy of infratentorial brain compartments (pons, mesencephal, acqueductal), as well as of supratentorial ventricles (3rd ventricles, lateral ventricles) were calculated using a normalized thresholding software. All the structural boundaries were determined according to established anatomical landmarks.

Patients with CIS showed a lower lesion burden at the PAG level and close to lateral ventricles than RR ($p = 0.03$) and SP patients ($p = 0.01$). There was a significant correlation between BD and LL of PAG in CIS patients ($r = 0.48$, $p = 0.006$) and RR patients ($r = 0.36$, $p = 0.01$), but not in SP patients. The latter showed a relationship of BD with T2 and T1 LL located at level of left FG. BD was correlated with the volume of mesencephalic structures in all subtypes (CIS, $r = 0.3$, $p = 0.04$; RR, $r = 0.41$, $p = 0.01$; SP, $r = 0.64$, $p = 0.0001$) whereas in SP patients it was also correlated with the volume of 3rd ventricle ($r = 0.43$, $p = 0.01$) and lateral ventricles ($r = 0.57$, $p = 0.001$). In early phase of MS, BD is related to lesion burden located at the PAG level and to the atrophy of mesencephalic structures. In the advanced phase of disease, neurodegenerative phenomenona (wallerian degeneration) involving frontal lobe and periventricular structures might play an additional role.

P679

Temporal profile of depression and anxiety in patients with clinically isolated syndrome (CIS): a three-year follow-up study. S. Di Legge, C. Pozzilli, V. Di Nepi, P. Pantano, F. Caramia, M. C. Piattella, I. Pestalozza, G. L. Lenzi, University La Sapienza (Rome, I)

Background: Emotional changes are a common and integral part of multiple sclerosis (MS). Whether they are a psychological reaction to the illness or they are related to brain lesion burden is still to be clearly elucidated.

Objective: To investigate the occurrence of depression and anxiety in patients with a Clinically Isolated Syndrome (CIS) suggestive of MS and their changes along time.

Methods: 37 consecutive CIS patients included in a prospective ongoing study and 36 normal controls were studied. All subjects were investigated with the 21-item Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI). Patients inclusion criteria were: i) a first clinical episode suggestive of MS; ii) baseline MRI according to Fazekas criteria (1988) and iii) no corticosteroid treatment in the 2 months pre-

ceeding the study inclusion. Anxiety and depression scales were also administered to MS patients after one period of 33 ± 6 months. We defined as depressed patients showing BDI > 9.

Results: CIS patients were 13 M and 24 F, mean age was 30.3 yrs, mean time since clinical onset was 6.7. months. Patients and controls did not differ in age, gender and education. By ANOVA, CIS patients showed higher scores in STAI 'trait' (46.6 vs 44.2; p = 0.03) and BDI (7 vs 4.3; p = 0.004) than controls. Clinical relapse occurred in 51% (19/37) of patients. Depression at baseline was not correlated with MRI lesion burden or the occurrence of the clinical relapse. On the contrary, patients who developed the clinical relapse had a high occurrence of depression at follow-up (12/19 vs 4/18; c2, p = 0.01). During the follow-up period, 10/19 (42%) of patients who developed a clinical relapse became depressed versus 2/18 (11%) of those who did not develop a clinical relapse (c2, p = 0.007). CIS patients who remained relapse-free showed follow-up BDI scores similar to those observed in the controls.

Conclusions: CIS patients showed higher scores in self-rated scales for depression and anxiety than controls. The occurrence of depression after the first episode suggestive of MS might represent a 'normal' psychological reaction to a chronic and potential invalidating disease, and it was not predictive of the future clinical outcome. A tendency toward a 'normalization' of mood was observed in patients who did not develop a clinical relapse. On the contrary, patients who develop a relapsing-remitting MS within the first years from clinical onset, showed an increased rate of depression.

P680

Association of inducible nitric oxide synthase gene (NOS2A) polymorphisms to multiple sclerosis. Y. Blanco, J. Yagüe, A. Saiz, F. Graus, Hospital Clínic (Barcelona, E)

Introduction: nitric oxide (NO), a nonspecific inflammatory mediator synthesized by NO synthase (iNOS), has been involved in multiple sclerosis (MS) pathogenesis because a intense reactivity for iNOS mRNA and protein is found in postmortem lesions from MS patients, and elevated levels of metabolites of NO in the CSF and serum have been demonstrated in active MS patients.

Objective: to study the influence of the promoter polymorphisms of the iNOS on susceptibility and outcome in multiple sclerosis.

Material and methods: Patients and controls: in a cross-sectional manner, we collected 140 unrelated MS patients (92 relapsing-remitting; 33 secondary progressive; and 15 primary progressive), recruited from the outpatient Service of Neurology. Eighty-three (58%) were women, and 57 (42%) men, with a mean age of 43 * 13 years.

The clinical data collected were EDSS, progression index (PI), the time to reach and EDSS score of 3.0 and 6.0. We classified the course of the disease as benign, moderate or aggressive.

A total of 147 healthy blood donors selected from the same geographical area, matched for sex, age, and ethnicity and of Spanish origin were collected.

Results: the 9-repeat and 13-repeat alleles were more represented in MS patients compared to controls (17.4% cases vs 8.16% controls; OR = 2.37; 95% CI = 1.1 to 4.95; p = 0.022; and 39.8% cases vs 24.5% controls, OR = 1.8; 95% CI = 1.085 to 3; p = 0.023, respectively). MS was negatively associated with the 11/11 genotype (0.7% cases vs 6.1% controls; OR = 0.11; 95% CI = 0.016 to 0.99); p = 0.039).

For the AAAT polymorphism the alleles and genotypes frequencies of the patients were not different from those of the control population. Neither allele or genotype was associated with the demographic and clinical variables studied.

Discussion: we found a significant overrepresentation of 9 and 13 repeat alleles in MS patients compared with healthy control subjects and a negative association with the 11/11 genotype. Because these associations were not observed in a previous work on a Nordic population a population-specific association would be suggested of our study.

P681

Brain atrophy in relapsing multiple sclerosis: A longitudinal study with transcranial ultrasound. B. Kallmann, K. Toyka, P. Rieckmann, M. Mäurer, Neurologische Universitätsklinik (Würzburg, D)

In multiple sclerosis, brain atrophy was shown to correlate with disability and is considered to represent the net effect of tissue destruction. As a parameter for assessment of brain atrophy we could recently show that determination of ventricular width by transcranial ultrasound correlated well with MRI measurements of the ventricular system. Moreover, ultrasound revealed larger ventricular diameters in MS patients in comparison to age and sex matched control patients. It was further shown that brain atrophy determined by ultrasound correlated with EDSS and several neuropsychological tests.

We now conduct a longitudinal follow up of ventricular width with transcranial ultrasound in MS patients. 41 patients (mean age 36 ± 9 years) were included in this 2 year MRI controlled follow up study. A first evaluation with 22 patients who completed the first year was done. The EDSS at baseline was 3.8 ± 1.5 and showed only a minor change to 3.9 ± 2 after one year (not significant). The width of the III. ventricle at baseline was 5.5 ± 2.9 mm. In accordance with the stable clinical situation the diameter of the third ventricle remained nearly unchanged (5.6 ± 3.3 mm, not significant). Ventricular diameter was determined by two independent examiners and revealed highly reproducible results. These preliminary results from a longitudinal study underline the value of transcranial ultrasound as an easily applicable method for evaluation of brain atrophy in MS patients.

P682

The effects of different doses of subcutaneous Interferon beta 1-A (Rebif) on cerebrospinal fluid tumor necrosis factor alpha levels, relapse rate and disease progression in patients with relapsing-remitting multiple sclerosis: results of 12 months of therapy. N. Subutay Oztekin, M. Oztekin, G. Ozdurdag, SSK Ankara Hospital (Ankara, TR)

Objective: The aim of the study is to investigate the two different doses of Rebif on cerebrospinal fluid(CSF) tumor necrosis factor(TNF)-alpha levels, relapse rate, and disease progression in patients with relapsing-remitting (RR)multiple sclerosis(MS).

Method:20 patients with clinically definite RR MS aged between 18–45 years were enrolled in the study and randomized into 2 equal groups, the first 10 patients receiving 22 micrograms of interferon(IFN) beta 1-a and the second group receiving 44 micrograms of IFN beta 1-a three times a week 0.20 age matched healthy subjects were used as the control group for CSF TNF-alpha assessments. The neurologic examination of the treatment groups, EDSS scores and gd-enhanced MRI's are obtained initially and repeated 3 months apart during the 12 months of the study period. The annual exacerbation rate of the patients in both groups were 2.2,.EDSS ranged between 0–5(mean = 3.5).CSF samples are obtained before and during the 3rd, 6^{th}, and 9^{th} months of treatment's TNF-alpha levels are studied with ELISA method.

Results: There was a prominent decrease in CSF TNF-alpha levels in both treatment doses compared to baseline and control group, but the results of the 44 microg treated group was found to be statistically significant. There was also a reduction in the annual exacerbation rate in both arms of the treatment group; 1.5 and 0.7 respectively. The results of the 44 microgram receiving group was found to be statistically significant (p > 0.05).There was no change in the EDSS in the 22 microgram receiving group after one year of treatment, whereas there was a reduction of 20% in the 44 microgm receiving group, but it was also not found statistically significant.

Conclusion: The results of this study revealed that Rebif used subcutaneously both as 22 and 44 microgms have significantly reduced the CSF TNF alpha levels compared to baseline and control group, the reduction being statistically significant in the 44 microgm receiving group. The effects of Rebif 44 microgms have also significant beneficial effects on annual exacerbation rate compared to the 22 microgm receiving group after12 months of treatment.

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Chemokine receptor 5 delta 32 polymorphism: susceptibility to and outcome from multiple sclerosis. J. M. Partridge, A. A. Fryer, R. C. Strange, M. D. Boggild, C. P. Hawkins, Keele Multiple Sclerosis Research Group (Stoke-on-Trent, Liverpool, UK)

Introduction: Multiple sclerosis (MS) is a T cell dependent inflammatory disease of the central nervous system (CNS). Chemokines are important molecules involved in leukocyte recruitment and activation in inflammation in the CNS. Chemokine receptor 5 (CCR5), a chemokine receptor, is expressed in normal CNS tissue as well being overexpressed on infiltrating lymphocytes, predominantly of the proinflammatory Th1 type, important in MS pathogenesis. Interferon-beta significantly reduces T cell surface expression of CCR5 in vitro. CCR5 delta 32 is a truncated allele of the gene that encodes a non-functional receptor. We performed a candidate gene association study to determine whether this allele confers protection from MS onset or severity.

Methods: 346 Caucasian patients (75% female, 25% male) and 204 controls of Northern European origin were recruited. Mean onset age of MS

was 31.3 ± 9.0 years and mean disease duration was 12.4 ± 9.0 years. DNA was extracted from leucocytes and polymerase chain reaction assay was used to identify alleles of CCR5. Outcome was assessed using Kurtzke's Expanded Disability Status Scale (EDSS) and cases were stratified into mild/moderate disability (EDSS 0–5.5) and severe disability (EDSS 6–10) after disease duration of 10 years. Results were analysed using logistic regression to correct for independent covariants of age of onset, gender and disease duration. Significance levels were set at $p < 0.05$.

Results: Borderline significant association was found between mutant homozygotes at CCR5 delta 32 and protection from MS susceptibility (OR = 0.23, 95 % CI 0.05–1.07, p = 0.06) though numbers of mutant homozygote genotypes were small (n = 8). No association was seen between CCR5 delta 32 and severity of MS (OR = 0.88, 95 % CI = 0.41–1.90, p = 0.75).

Conclusion: CCR5 delta 32 may confer protection from MS onset though the number of cases homozygous for the CCR5 delta 32 allele is small. We postulate this protective effect is mediated by inefficient lymphocyte recruitment to sites of inflammation in the CNS. Additional case recruitment or repeat testing in a similarly large second cohort would clarify the association.

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Higher proportion of black holes in MS patients with APOE e4 allele. C. Enzinger, S. Ropele, S. Strasser-Fuchs, P. Kapeller, B. Poltrum, H. Schmidt, R. Schmidt, F. Fazekas, Karl-Franzens University Graz (Graz, A)

Objective: Apolipoprotein E (APOE) plays a major role in lipid transport and neuronal repair. In multiple sclerosis (MS), the e4 allele (e4) has been associated with more rapid clinical deterioration. Hypointense brain lesions on magnetic resonance imaging (MRI) have been shown histopathologically to reflect more severe tissue destruction and, recently, a cross-sectional MRI study has demonstrated a greater proportion of these so-called black holes in MS patients with e4. Therefore we have set out to further explore the effects of APOEe4 on the course of MS using serial MRI of the brain.

Methods: 77 participants of a prospective genetic study (57 women, 20 men; age 36.2 ± 10.9 yrs) with clinically definite MS (67 relapsing-remitting, 7 secondary-, 3 primary-progressive) underwent genotyping, repeated clinical examinations, MRI at baseline and after a mean follow-up of 31 mths (minimum: 24 mths). The mean disease duration was 6.8 ± 7.7 yrs and mefan disability measured by the Expanded Disability Status Scale was 2.1 ± 1.5. Axial T2- and T1-weighted scans were obtained at a 1.5 T unit (CSE; TR/TE 2500/30 and 90; TR/TE 600/15, respectively). Exact repositioning was achieved by using internal landmarks and scouts. Lesions were segmented semi-automatically using DispImage. Only markedly hypointense lesions with a signal intensity between cortical grey matter and cerebrospinal fluid were considered as black holes.

Results: T2- and T1-lesion loads (LL) at baseline were higher in patients with e4 (n = 19; T2-LL: 16.8 ± 23.9 ccm; T1-LL: 1.9 ± 3.8 ccm) than in those without e4 (n = 58; T2-LL: 9.4 ± 11.6 ccm; T1-LL:0.9 ± 2.3 ccm) although disease duration was shorter in the e4-group (e4: 4.5 ± 4.5 yrs vs. non-e4: 7.6 ± 8.4 yrs). None of these differences reached statistical significance due to large standard deviations. At the end of follow-up, non e4-patients showed a moderate increase in T2-LL (11.1 ± 12.5 ccm), whereas T2-LL was relatively unaltered in e4-carriers (16.6 ± 22.1 ccm). In contrast, T1-LL had become larger in the e4-subgroup (2.3 ± 3.3 vs. non-e4: 1.1 ± 1.8; p = 0.05). In parallel, there was a higher proportion of black holes, calculated as (T1LL/T2LL)x100, in patients with e4 (12.2 ± 14.5 % vs. 7.1 ± 9.2 %; p = 0.08).

Conclusions: The serial MR-findings of more pronounced tissue destruction as evidenced by a higher proportion of black holes in patients with e4 add further evidence to the suggested negative impact of the APOE e4-allele on the course of MS.

Myasthenia gravis and muscle disorders

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Quantitative esophageal scintigraphy for the assessment of esophageal function in patients with Myasthenia gravis. R. Linke, K. Tatsch, T. N. Witt, University of Munich (Munich, D)

Background: Myasthenia gravis (MG) is an autoimmune disease in which impairment of neuromuscular transmission results in a pathologic fatigability of striated muscles. Dysphagia is a common symptom in MG. It is caused by a weakness of the striated muscles in pharynx and upper oesophagus. Purpose of our study was to evaluate the role of oesophageal scintigraphy in the assessment of oesophageal function in MG.

Methods: In 15 patients (5 females and 10 males, mean age 58.1 ± 21.3 years, range 20.5–82.8 years) with clinically proven MG (isolated oculopharyngeal manifestation in 6/15 patients, generalised weakness in 9/15 patients) oesophageal transit was investigated scintigraphically with a multiple swallow test protocol using a semisolid test meal. 10/15 patients had a history of dysphagia. 7/15 patients were drug-naive for specific MG-treatment, 8/15 patients were pre-treated with pyridostigmin bromide (mean dosage 160 mg/die, range 60–390 mg/die). Patients were studied twice, at fist under baseline conditions, and immediately after pharmacological stimulation with 10 mg of edrophonium chloride (a short-acting acetylcholinesterase inhibitor). If patients were pre-treated, the medication was withdrawn overnight for at least 10 hours before scintigraphy.

Results: Under baseline conditions all patients showed an impaired oesophageal function (oesophageal emptying (%) = 58 % ± 21; normal range > 85 %). In all patients the dysfunction was located in the oropharynx and/or the portion of the oesophagus predominantly composed of striated muscles. After administration of edrophonium chloride oesophageal transit improved in 14/15 individuals (oesophageal emptying (%) = 75 % ± 18; $p < 0.001$), reaching the normal range in 6 cases. 1/15 patients showed no effect after edrophonium chloride injection.

Conclusions: Oesophageal transit often is compromised in MG. Functional abnormalities may be also present in patients without a history of dysphagia. Residual food in pharynx or oesophagus after swallowing may predispose the patient to develop postdeglutitive aspiration. Inhibition of cholinesterase positively affects striated muscles in the pharynx and upper oesophagus, thus improving oesophageal transit significantly as objectively demonstrated by the scintigraphic data. Oesophageal scintigraphy may be considered as a simple, non invasive method for diagnosing impairment of oesophageal function in patients with MG and to monitor the changes under pharmacological stimulation.

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Only transient increase of serum CoQ10 in patients with mitochondrial chronic progressive external ophthalmoplegia during CoQ10 therapy. F. Hanisch, S. Zierz, Martin-Luther-University (Halle/Saale, D)

Seventeen patients with mitochondrial chronic progressive external ophthalmoplegia (CPEO) were treated with coenzyme Q10 (CoQ10) (dosage: 0,60–1,80 mg/kg body wt) in an open trial. Before treatment CoQ10 concentration in muscle was normal in all patients, but decreased in serum in 4 patients. Serum levels of CoQ10 were monitored before and after 6–9 and 12–15 months of CoQ10 therapy. Eight patients completed the study after 12–15 months. Prior to treatment there was no correlation between CoQ10 in muscle and serum. CoQ10 serum level and body weight related CoQ10 dosage correlated significantly after 6–9 months but not after 12–15 months (p = 0,043 and n. s., respectively). During continued administration of CoQ10 the CoQ10 serum level was increased 2,76 ± 1,00 fold after 6–9 months (range: 1,04–3,80), but returned to 1,70 ± 0,98 fold after 12–15 months (range: 0,91–3,83). Serum lactate did not significantly change during treatment. The only transient increase of CoQ10 has to be considered in any long term treatment with CoQ10-

P688

Clinical and immunological correlations in patients with dysferlin deficiency. M. Sciacco, A. Prelle, L. Tancredi, G. Fagiolari, G. P. Comi, P. Ciscato, M. Serafini, F. Fortunato, C. Zecca, A. Gallanti, L. Chiveri, N. Grimoldi, N. Bresolin, G. Scarlato, M. Moggio, Ospedale Maggiore Policlinico University of Milan, IRCCS Eugenio Medea (Milan, Bosisio Parini, I)

Recently, a novel mammalian gene has been discovered, whose mutations cause two phenotypically different muscle diseases: Limb Girdle Muscular Dystrophy (LGMD) type 2B and distal Miyoshi myopathy (MM). The gene product is the dysferlin protein, normally expressed at skeletal muscle level and absent in affected patients.

We selected a clinically heterogeneous Italian population of myopathic patients with clinical evidence of myopathy and/or hyperCKemia, EMG myopathic pattern, and no alterations of other known skeletal muscle proteins. Dysferlin immunohistochemical and Western Blot analyses allowed us to identify 6 patients with dysferlin deficiency: 1/7 pts with distal myopathy, 4/60 pts with limb girdle myopathy and 1/84 pts with hyperCKemia. There were one patient in a preclinical status, one with early onset and one with late onset. The presymptomatic patient later developed a MM, but, interestingly, the dysferlin deficiency was already complete at both IF and WB analyses in the presymptomatic stage. On the other hand, residual protein amount was found in two LGMD patients, one of them with a late onset form.

Apoptosis was lacking in all six muscle specimens, though the expres-

sion of the pro-apoptotic Fas antigen was mildly increased in two cases. Inflammatory reactions did occur in 2/6 cases, but we found no evidence of immunomediated processes.

P689
Congenital myasthenic syndrome presenting in adulthood. O. O'Toole, D. Costigan, O. Hardiman, Beaumont Hospital (Dublin, IRL)

Congenital myasthenic syndromes are a rare heterogenous group of disorders arising from pre-synaptic, synaptic and post-synaptic defects in the neuromuscular junction. Most are autosomal recessive and present in infancy or childhood. Classic slow channel syndrome is due to an autosomal dominant gene mutation with high penetrance and variable expression. Sporadic cases and late diagnoses have been described on rare occasions.

We report a 43 year old man who presented to an adult neuromuscular clinic with a 1 year history of jaw weakness and difficulty chewing. He also complained of excessive daytime somnolence, fatigue, headache and poor sleeping pattern. He had early developmental milestones. Hr was noticed to have difficulty walking at 3 years of age. A diagnosis of muscular dystrophy was made, type unspecified. His condition remained stable in childhood and improved in adolescence such that he could ride a bicycle for long distances. Neurological examination at age 42 revealed mild restriction in lateral gaze, bilateral ptosis, facial diplegia, and mild wasting of shoulder girdle and upper extremity muscles. Muscle strength was reduced in the upper extremities and normal in the lower extremities. All muscles showed fatigability. There was no family history of muscle disease. Acetyl choline esterase antibodies were negative. Muscle biopsy showed Type I fibre predominance. EMG showed significant decrement response to repetitive stimulation, loss of compound muscle action potential amplitude, distinct after-potentials and a mixture of neuropathic and myopathic recruitment patterns. The pattern was consistent with a slow channel syndrome. Pulmonary function studies revealed a restrictive pattern and severe nocturnal hypoxemia. He was treated with non-invasive positive pressure ventilation with marked improvement in his symptoms of somnolence and fatigue. This patient illustrates that slow channel myasthenic syndrome can occur sporadically and that it can present in adulthood. The limited clinical symptoms that our patient experienced in childhood indicate that the condition can exist in a benign form with relative sparing of the lower extremities, and that progression can occur in midlife with slowly evolving ventilatory failure.

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Noninvasive ventilation with BiPAP in myasthenic crisis: when and for whom? A. Rabinstein, E. Wijdicks, Mayo Clinic (Rochester, USA)

Background: Major exacerbations of myasthenia gravis (MG) result in acute neuromuscular respiratory failure. Non-invasive bilevel positive pressure ventilation (BiPAP) could represent a useful alternative to conventional mechanical ventilation not only to prevent intubation but also to facilitate liberation from the ventilator during the recovery phase.

Objective: Assess the role of BiPAP in the management of patients with respiratory failure due to myasthenic crises.

Methods: Review of the experience with BiPAP in patients with MG admitted to the ICU of a single tertiary center for acute respiratory failure. Comparisons were performed using the Fisher exact test and level was significance was established at $P < 0.01$.

Results: We treated17 episodes of MG exacerbation with BiPAP in 9 patients. When used to avert endotracheal intubation, BiPAP was successful in 7 of 10 instances. As a weaning method, BiPAP succeeded in 5 of 6 cases after failed T-piece trials. Mean BiPAP pressures were 13/6 mm Hg (range 10–18/4–8 mm Hg). Presence of hypercapnia ($pCO2 > 50$ mm Hg) at the time of institution of BiPAP was predictive of BiPAP failure ($P < 0.01$) but bedside respiratory function tests (vital capacity, maximal inspiratory and expiratory pressures) did not predict the outcome of these trials. Most failures occurred within 24 hours of BiPAP use. Ventilation using BiPAP was never precluded by excessive respiratory secretions and it was generally well tolerated. Mean duration of BiPAP use in the hospital was 5 days (range 4 hours to 16 days) and BiPAP was continued after hospital discharge in four episodes.

Conclusions: This is the first reported successful experience with BiPAP as a temporary mode of ventilation in patients with respiratory failure due to MG. It also can facilitate weaning from conventional mechanical ventilation in improving patients. BiPAP should not be attempted in patients in patients with established hypercapnia. BiPAP could be tried first in patients with acute respiratory failure while awaiting the results of intravenous immunoglobulin therapy or plasma exchange.

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Heart in myotonic dystrophy. S. Chebel, K. Ben Hamada, M. Frih-Ayed, M. H. Ben Farhat, University Hospital of Monastir (Monastir, TN)

Objectives: This study aimed to identify cardiac abnormalities in myotonic dystrophy's patients and to find out whether the severity of cardiac involvement is related to the severity of the disease assessed by a previously described scoring system.

Subjects and methods: Subjects included 34 patients belong to 8 families in whom myotonic dystrophy (MD) is diagnosed based on the clinical neurologic examination, family's history, electromyographic, ophthalmologic and endocrine investigations. 18 patients underwent a detailed cardiologic examination, which compromised history, clinical cardiac examination, electrocardiogram (ECG), echocardiography, signle average ECG (SAEG), 24-hr monitoring, intracardiac electrophysical studies and left ventricular ejection isotopic fraction.

The degree of the neuromuscular involvement was assessed according the MRC garding.

Results: The mean onset age was 29 years (ranger 11–47 years), 44 % of patients ($n = 15$) were classified stage II according MRC grading, 18 patients (53 %) have cardiac investigations, only 11 % of them have clinically cardiac symptoms. The most frequent cardiac involvement were auriculoventricular block (39 %), left ventricular systolic function alteration (22 %) and diastolic function alteration (28 %).

Conclusion: The preliminary results shows that cardiac involvement is an integral part in MD and the severity of cardiac involvement seams to be independent of neurologic stage involvement.

P692
Myopathy with cylindrical spirals inclusions. M. Baudrimont, M. Zuber, P. Varlet, X. Pham, C. Daumas-Duport, Sainte-Anne Hospital, Cochin Hospital (Paris, F)

The cylindrical spirals (CS) inclusions were described about 20 years ago. Since then, only 10 adult patients and one child with such CS inclusions have been reported.

We report the observation of a 41-year-old african woman who had a 4-year history of dysphagia. She complained of progressive diffuse myalgia and muscular weakness. When the patient was seen in our institution, she had lost 6 kg over the past 3 years. Myalgia persisted but the patient denied having cramps. The proximal muscle fatigue predominated on hip flexors. The physical examination was otherwise normal. There was no history of previous muscular disorder in the family. Erythrocite sedimental rate was 50, rates of muscular enzymes and electromyography were normal. Blood cultures and serologic tests were all negative, including those for HIV and parasitic infections. The extensive immunological workup was normal, as were all morphological investigations, including throracic and abdominal CT scan and bronchoscopic examination with biopsies. A quadricipital muscular biopsy was performed in order to rule out any inflammatory process. The biopsy showed subsarcolemmal clusters of small granules, preferentially in type II fibers, which stained bright red with the modified trichrome. The clusters were 10–300 microns in length and 5–10 in transverse diameter. With NADH-TR, the abnormal structures appeared brown. All the other histochemical stainings were normal. No inflammatory cells were observed. Electron microscopy revealed that the inclusions were cylinders of 1–2 microns in diameter and 10 in length. They consisted of spiralling membranous lamellae, with 6 to 30 lamellae wrapped around a central cytoplasmic core, which contained glycogen granules and few vesicles. These inclusions appeared as typical CS inclusions. CS inclusions were previously reported associated with a large panel of clinical features, including painful cramps, myalgia, peripheral neuropathy, muscle stiffness, gait disorders and melorheostasis. The origin of the CS remains highly speculative and its specificity is subject of debate. Neurologists involved in neuromuscular diseases should be aware of this rare muscular pathological pattern.

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Selective enrichment of V-beta specific T cells in an involuted thymus and in peripheral blood from a patient with old-onset Myasthenia gravis. B. Tackenberg, A. Ramaswamy, W. H. Oertel, B. Hemmer, N. Sommer, Philipps-University Marburg (Marburg, D)

Myasthenia gravis is a well defined autoimmune disease. Nevertheless the role of the thymus has not been fully elucidated. There is ample evidence that pathogenic CD4+ T-cells are involved early in the pathogenesis of this antibody-mediated disease. Recent studies showed a clear association between thymoma-associated myasthenia gravis and T-cell receptor excision

circles (TREC), a marker for recent thymic emigrant lymphocytes in the peripheral blood. In more than 70 % of MG patients there are changes in thymus pathology – thymic hyperplasia in patients with onset before age 45, and thymoma in patients of all ages. However, the role of the thymus in patients of old age without thymoma is still unclear.

We report a 65-year old woman with recent onset generalised, AChR-antibody positive myasthenia gravis who presented with a large retrosternal mass. The patient underwent thoracotomy due to a suspected thymoma. In fact the retrosternal mass turned out to be a retrosternal struma. During the operation an atrophic thymus was removed as well; histology showed an involuted organ with 97 % fat and 3 % thymic tissue and some sparse Hassal's corpuscles.

By flow cytometry, we analysed the T-cell-receptor (TCR) usage in the involuted thymus and peripheral blood at several time points of this otherwise healthy woman. Staining with monoclonal antibodies against 22 different TCR V-beta chains showed that 91 % of double-positive immature cortical thymocytes (CD4+CD8+CD1a+) belonged to the V-beta–22 (Vb22) family. Peripheral blood showed an increased rate of the Vb22 CD4+ cells (7,9 %; i. e. more than 3 standard deviations above the mean). After surgery there was an increase of this CD4+Vb22+CD1a+ T-cell population in the peripheral blood (maximum at day 15) with a gradual decline until day 45. More than 2 years after surgery the patient still shows a stable overexpression (up to 14 %) of CD4+Vb22+; now CD1a-.

We believe, that these data indicate that the involuted thymus participates in the pathogenesis of this patient with old-onset myasthenia gravis. TREC-analysis for proving the recent thymic origin of this Vb22 T-cell population and spectratyping as well as sequencing of the CDR3 region of the double-positive thymocytes and the peripheral CD4+ T-cells is being performed.

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Effects of repeated doses of intravenous immunoglobulin in myasthenia gravis. D. Lavrnic, V. Rakocevic-Stojanovic, S. Pavlovic, I. Basta, A. Vujic, S. Apostolski, Institute of Neurology (Beograd, YU)

The efficacy of intravenous immunoglobulin therapy (IVIG) in the treatment of myasthenia gravis (MG) has been demonstrated by many authors. Some of them recommended IVIG for exacerbations of MG, while others for chronic forms of the disease.

We report the results of IVIG treatment in 44 patients with severe generalized MG (IIB, III and IV) who were unresponsive to conventional therapy (anticholinesterase drugs, thymectomy and immunosuppressive drugs).

All of the patients received a total dose of 2 g/kg during 5 consecutive days. This treatment was followed by a single IVIG dose every 6 weeks. Each patient received additional immunosuppressive therapy. IVIG therapy allowed us to reduce immunosuppressive drugs in the majority of uor patients. Significant improvement in functional status (expressed by Mean disability score of Besinger) began within a few days of treatment (5–10), and peaked at 2 weeks in 38 % of the patients. However, in most patients (92 %) delayed improvement was noticed, and maintained up to six months. Additional immunosuppressive therapy (corticosteroids and/or azathioprin, or cyclosporine) and repeated doses of IVIG may account for the long duration of IVIG induced improvement. Mean disability score decreased from 12.3 to 5.7 at the end of the follow-up (6months) period. None of the patients expressed serious side effects. Our data indicate that IVIG is a useful and well tolerated treatment, and we recommend it especially for patients with severe, refractory MG.

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Functional evaluation in patients with cervical dystonia: a comparison of results by a three-dimensional electrogoniometer and a standard scale. P. Salvia, O. Champagne, V. Feipel, D. Zegers de Beyl, University of Brussels (Anderlecht, B)

Evaluation of patients with cervical dystonia uses semi-quantitative or subjective approach. Clinical cervical dystonia evaluation focuses on posture more than motion. Quantitative evaluations of the neck with 3D measuring systems are now available to study patient motion. In this paper, we investigated whether quantitative measurements of cervical kinematics are correlated with a clinical rating scale in cervical dystonia.

Nineteen patients with a cervical dystonia (mean age 67) were investigated after at least 3 months following the last BTX injection. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was used for clinical evaluation. Two raters estimated TWSTRS interrater reliability. The results were compared statistically by Spearman rank coefficient. The quantitative investigation was performed by a 6-dof electrogoniometer. This device allowed a continuous tracking of the head relative to the thorax. In output, the system gave values of flexion-extension, lateral bending and axial rotation of the neck. Each patient performed flexion-extension, lateral bending and rotation of the neck. Velocity peak was computed. Statistical significance was tested by non-parametric correlation.

Left and right rotation, left and right laterocollis were equally distributed in our sample. For interrater comparison, correlation coefficients for each item of the TWSTRS ranged from 0.37 to 0.98 for the Torticollis severity scale section. Disability scale and pain scale section showed excellent reproducibility up to 0.88. With goniometry, the percentage of amplitude reduction of neck movements ranges from 9 to 47 % for lateral bending and rotation. The correlation between the TWSTRS score and the amplitude of movement computed by goniometry were significant for left lateral bending ($r = 0.55$) and the left rotation ($r = 0.53$). Correlation between the TWSTRS score and velocity of movement were significant for right and left lateral bending ($r = 0.60$; $r = 0.51$) and left rotation ($r = 0.51$). Relations between qualitative and quantitative measurements for assessment outcome could be identified in our sample. The Torticollis severity scale evaluates only posture and not the pattern of movement. Using a 6 dof measuring system, we are able to quantify the amplitude of movement of the cervical spine and the head. We believe this method to be helpful to quantify the complex three-dimensional posture and motion disorder of head and neck in patients with cervical dystonia.

Neuro-oncology

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Magnetic resonance imaging aspects in three different types of systemic lymphoma. F. A. Antochi, C. Tiu, R. Gherasim, O. Bajenaru, University Hospital (Bucharest, RO)

The involvement of the nevous system in lymphoproliferative disorders may be direct or indirect, and clinical symptoms of the patients may be similar to each other.

The authors present three cases of different systemic lymphomas, with involvement of the spinal cord and spinal roots.

The first case: a 62 years old woman, infected with hepatitis C virus, with tetraparesis and peripheral nerve involvement in C5-C6 territory. Magnetic resonance imaging (MRI)of the cervical spine showed perispinal leptomeningeal infiltration at C5-C7 level with secondary spinal cord compression. Haematological diagnosis: lymphoplasmocytic lymphoma IgA secretor (k lambda).

The second case: 49 years old woman, with paraparesis, abolished patellar and ankle reflexes and bowel and bladder dysfunction. MRI aspect: leptomeningeal infiltration of the lumbosacral plexus. Haematological diagnosis: T cell leukaemic lymphoma of the adult with cutaneous involvement (CD 37, CD4+, CD 45 Ro, CD 25 –, TCR alpha/beta –, lymphoplasmocytosis T4 98 %).

The third case was that of a 39 years old man, with tetraparesis and radicular syndrome C4-C5-C6. MRI aspect: cervical tumoral mass at C1-C3 level, with spinal cord compression and bilateral radicular involvement at this level. Haematological diagnosis: Castleman's disease.

The authors comment upon the MRI aspects of the peripheral and central nervous system involvement, upon the clinical similitude in different types of lymphomas and upon the importance of the haematological investigations in patients with spinal cord and spinal roots compression

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Multifocal neurological symptoms in two cases of paraneoplastic syndrome. K. Uluc, E. M. Arsava, I. A. Yilmaz, G. Nurlu, T. Dalkara, Hacettepe University (Ankara, TR)

Paraneoplastic syndromes are disorders associated with remote effects of cancer without presence of a tumour mass or metastases. Neurologic syndromes appear approximately in 1 % of cancer patients and most cases are associated with small cell lung cancer (SCLC). We report two cases of SCLC patients presenting with ophthalmoparesis, sensory neuropathy, limbic encephalopathy and myelopathy.

Case No 1: A 54-year-old heavy smoker male was admitted with complaints of weight loss, paresthesiae, diplopia and left-sided ptosis. Neurological examination revealed ophthalmoparesis, left-sided ptosis, bilateral symmetric glove and stocking type hypoesthesia, proprioceptive loss predominantly in lower extremities and hypoactive deep tendon reflexes without motor impairment. Sensorimotor axonal neuropathy was detected in the electrophysiological investigations without a neuromuscular junc-

tion abnormality. Due to the emergence of epileptic seizures and depression during the hospitalisation period, the patient was further investigated by electroencephalography (EEG) and magnetic resonance imaging (MRI). EEG demonstrated an active epileptiform focus in the right temporal lobe. MRI detected nonenhancing hyperintense lesions involving brain stem and bilateral mesial temporal regions. As chest computed tomography (CT) showed mediastinal and hilar lymphadenopathies and serum and cerebrospinal fluid (CSF) anti-Hu levels were positive, the patient underwent bronchoscopy and a biopsy confirmed SCLC.

Case No 2: A 55-year-old heavy smoker male was admitted with symptoms of weakness and numbness obvious in lower extremities. Neurologic examination revealed quadriparesis, widespread fasciculations, asymmetric glove and stocking type hypoesthesia, proprioceptive loss, areflexia, extensor plantar responses. Electroneuromyographic studies were consistent with an axonal peripheral neuropathy. Spinal and cortical somatosensory-evoked potentials and compound muscle action potentials in motor evoked potential study were absent. Spinal MRI revealed contrast enhancing intramedullary high signal intensities along cervical and thoracic regions. A mass lesion was detected at chest CT and explorative thoracotomy confirmed diagnosis of SCLC.

This presentation discusses two cases of paraneoplastic syndrome with clinical, laboratory, electrophysiological and radiological findings. The diagnosis of a paraneoplastic syndrome should be considered in patients with multifocal neurological symptoms.

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Posterior leukoencephalopathy in mitomycin C-related hemolytic uremic syndrome. E. Linetsky, T. Siegal, A. Lossos, Hadassah University Hospital (Jerusalem, IL)

Objective: To describe the clinical and neuroimaging findings of posterior reversible leukoencephalopathy (PRL) in mitomycin C – related haemolytic uremic syndrome (HUS).

Background: PRL is a recently described clinical syndrome of headaches, seizures, confusional state and visual disturbances associated with transient, predominantly posterior cerebral lesions on MRI. It has been reported in the setting of hypertension, acute renal failure, immunosuppression with cyclosporin A or tacrolimus, and with cisplatin, interferon alfa, erythropoietin and chemotherapy for ALL.

Case report: A 36-year-old woman with metastatic to liver adenocarcinoma of colon was referred for evaluation of headaches, dyspnea and pedal oedema of subacute onset that developed 11 weeks following last De Gramont- mitomycin C treatment (mitomycin C cumulative dose of 57 mg/m2). Two weeks previously, she had anteroseptal cardiac ischemic changes and pleural effusion. On examination, she was afebrile, pale, tachypneic and tachycardic with 240/120 mm Hg blood pressure, grade II hypertensive retinopathy, hepatomegaly and pitting oedema. Laboratory studies revealed haemolytic anaemia and thrombocytopenia (9 g/dl Hgb, 45000/mL platelets, 1215 u LDH and numerous schisocytes on peripheral blood smear), and oliguric renal failure (272 m mol/l creatinine, 18 m mol/l BUN) consistent with the diagnosis of HUS. She was treated with plasmapheresis, prednisone, antihypertensive agents and aspirin but soon developed acute confusional state, cortical visual deficit and generalized tonic clonic seizures controlled with IV phenytoin. Brain MRI demonstrated extensive hyperintense posterior white matter lesions on T2-weighted images, typical of PRL. Over the next 6 weeks of intensive treatment with additional IVIg, there was a significant clinical improvement and she became neurologically intact. Follow up brain MRI 3 months later showed resolution of the previous changes.

Conclusions: To our knowledge, this is the first report of PRL in the setting of mitomycin C – related HUS. Although considered relatively uncommon, this disorder is associated with serious neurological morbidity. Since RPL is probably in part related to systemic hypertension with regional dysregulation of cerebral vasculature, effective blood pressure control is essential

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Thiamune (vitamin B1) deficiency – a treatable cause of neurological disorders in cancer patients. E. Linetsky, T. Siegal, A. Lossos, Hadassah University Hospital (Jerusalem, IL)

Objective: To report symptomatic thiamine deficiency in two gastrointestinal tract cancer patients.

Background: Thiamine is a water-soluble vitamin involved in carbohydrate metabolism, neurotransmission and neuronal excitability. Thiamine deficiency may cause polyneuropathy with or without heart failure (beriberi) and Wernicke-Korsakoff syndrome with ophthalmoplegia, cognitive changes and gait ataxia. Non-alcoholic thiamine deficiency may occur in cancer patients, mostly in the context of critical illness, hyperalimentation and active systemic chemotherapy.

Methods: Thiamine status was assessed biochemically by a in vitro measuring haemolysed RBC transketolase activity without and with added thiamine pyrophosphate (TPP). Normal thiamine status is reflected by TPP effect of < 15 %, moderate thiamine deficiency by 15 %–25 % and severe thiamine deficiency by > 25 %.

Patients: Patient 1 was a 41-year-old man with advanced gastric cancer treated 1 year previously with partial gastrectomy and followed by 5-fluorouracil and cisplatin chemotherapy until his admission for recurrent vomiting due to a gastric outlet obstruction. While in-patient, he developed diplopia associated with a left abduction deficit, horizontal gaze-evoked nystagmus and areflexia without cognitive impairment or ataxia. Evaluation showed no CNS metastases. RBC TPP effect was 85 % consistent with severe thiamine deficiency, and treatment with IV thiamine 100 mg/d promptly relieved his neurologic deficit. Patient 2 was a 63-year-old woman with advanced cancer of pancreas managed 1 years previously with gastrojejunostomy and later successfully treated with gemcitabine until the development of subacute gait disorder and distal limb paresthesiae. Evaluation showed signs of ataxic predominantly sensory polyneuropathy and ruled out CNS metastases. RBC TPP effect was 60 % consistent with severe thiamine deficiency, and treatment with PO thiamine 100 mg/d significantly improved her neurologic deficit.

Conclusions: Thiamine deficiency is an important and potentially treatable cause of neurological dysfunction in cancer patients. Possible predisposing factors include vomiting, prior gastrointestinal surgery and malabsorption. Thiamine status should be carefully assessed in the appropriate clinical setting, especially in patients with gastrointestinal tract malignancy

P700

Langerhans' cell histiocytosis with primary central nervous system involvement: nine year follow-up in an adult onset case. L. Orsi, A. Boghi, A. Franco, P. Mortara, S. Birolo, D. Caneparo, P. Caroppo, R. Mutani, D. Schiffer, University of Turin (Turin, I)

Langerhans'cell histiocytosis (LCH), previously known as histiocytosis X, is a heterogeneous granulomatous disease of the monocyte/macrophage system. This disease can involve many body system from the skin to the internal organs and the central nervous system (CNS) in every age with different aggressiveness and outcome. Pathognomonic markers of normal and pathological Langerhans'cells are Birbek granules revealed by electron microscopy.

We describe an uncommon adult-onset case of LCH with primary CNS involvement: a 55-year-old woman who developed diabetes insipidus (DI) at the age of 46. MRI scans of the brain disclosed many confluent hyperintense T2-weighted areas in the hypothalamus, hypophysis stalk and cranial brainstem with disomogeneous gadolinium enhancement. Serial systemic screenings for granulomatous disease were negative. The diagnosis was made three years ago by immunoreactive anti-S100 protein antibody staining and from the presence of Birbek granules in biopsy specimens of skin erithemato-papular lesions of the trunk. No other internal organs neither bone marrow involvement have been revealed by radiological, ultrasonographic and bioptical examinations. Our patient has been treated according to the LCH II International Treatment Protocol of the Histiocyte Society in the low-risk arm with vinblastine and oral deltacortene. At the end of the treatment we recorded an improvement of the CNS disease while the systemic screening disclosed an initial pulmonary involvement. She then shifted in the high risk arm of the protocol which adds oral 6-mercaptopurine to the previously used drugs. Actually – after three chemiotherapic cycles – the screening shows a normal lung CT findings and a further improvement of the CNS involvement.

Our case is a chronic disseminated form of LCH which primary affected the CNS. This is a rare form of the disease: in fact even if CNS involvement rises up to 25 % of total cases, the large majority of those occurs late in the natural history of LCH. What's more is very rare an adult onset of primary CNS involvement. The diagnosis of LCH was made six years after the onset of DI. This time is due to the initially diencephalic locations of the disease that limited bioptical approaches. However histological and ultrastructural examinations remain the only diagnostic means. So in our opinion a short term follow up is requested to recognise signs of disease activity above all considering the good response to chemiotherapy.

P701
Expression of TRAIL R1 and TRAIL R2 by human glioma cell lines. E. Ciusani, E. Corsini, M. Gelati, M. De Rossi, S. Frigerio, A. Silvani, A. Boiardi, A. Salmaggi, Istituto Naz.Neurol. (Milan, I)

TNF Related Apoptosis Inducing Ligand (TRAIL) is a member of the TNF/TNF receptor family molecules and is involved in regulation of apoptosis. The expression of both TRAIL and its receptors has been shown in human gliomas (Frank S. Biochem Biophys Res Comm 1999) although with considerable heterogeneity (Nakamura M. Acta Neuropathol 2000). Locoregional TRAIL administration has been shown to effectively eradicate glioma xenografts in nude mice without significant neurotoxicity (Roth W. Biochem Biophys Res Comm 1999). In the present work we evaluated the in vitro expression of TRAIL R1 and TRAIL R2 on human glioma cell lines and their sensitivity to TRAIL-induced apoptosis. Five human glioma cell lines (SW1783, U87, U373, U138, A172) and a human lung tumor cell line (A549), have been grown in complete medium until confluence, harvested, labelled with a biotin-conjugated anti TRAIL-R1 and TRAIL-R2 monoclonal antibodies followed by PE-conjugated streptavidin and analysed by flow cytometry. Sensitivity to TRAIL-mediated apoptosis was also tested using annexin V binding and flow cytometry. Although at different levels, all glioma cell lines displayed expression of TRAIL R2 while TRAIL R1 was expressed at low levels. Conversely, A549 showed higher expression of TRAIL R1 than TRAIL R2. All cell lines were insensitive to TRAIL mediated apoptosis. A dose dependent sensitivity was achieved upon addition of cycloheximide or actinomicin D in all cell lines except in U373. This cell line showed the lowest expression of receptor 1 and 2, suggesting a direct correlation between expression of TRAIL receptors and sensitivity to TRAIL-mediated apoptosis. In vitro treatment with Topotecan (an inhibitor of type I topoisomerase) at IC50, up-regulated TRAIL-R1 and TRAIL-R2 expression in all cell lines. These data suggest that the machinery for TRAIL-dependent apoptosis is potentially functional in the investigated cell lines, but the synthesis of one or more inhibitors can rescue cells from the apoptotic program. Moreover, treatment with inhibitor of type I topoisomerase might increase susceptibility to TRAIL dependent apoptosis.

P702
Intensity of angiogenesis in glioblastoma. E. Izycka-Swieszewska, R. Rzepko, M. Sidorowicz, M. Stempniewicz, H. Draczkowska-Wojcik, Medical University of Gdansk (Gdansk, PL)

The angiogenic potential in glioblastoma (GB) was analyzed by assessment of intensity of microvascular proliferation and vascular density. The paraffin- embedded tissue samples from 38 cases of GB from patients in age 32–78 years were examined. Histologically two types of the microvascular proliferation were distinguished: simple and glomeruloid type. The immunohistochemical staining for vWf was performed to highlight vascular profiles for vessel counting. Microvascular density was assessed with computer analysing system in 10 preselected representative tumor fields under 100x magnification.

Simple type proliferation was found in all patients. The glomeruloid proliferation was found in 28 cases with the mean age of 60,1 yrs, since in group without glomeruloids mean age was 47,4 yrs (the difference statistically significant, $p = 0{,}003$). The mean value of the vascular density was 146,79 vessels/mm2 (median 141,5, SD- 52,7) and the younger age was related to the higher vascular density (correlation coefficient $R = -0{,}35$; $p = 0{,}03$).

Presented results show that in GB microvascular proliferative changes of glomeruloid type are more frequent in the older patients. Higher vascular density is related to the younger age. The correlation of vascular parameters with patients age may suggest the connection of angiogenic potential of GB to the tumor molecular profile.

Peripheral neuropathy

P703
Elevation in anti-GQ1b, anti-GD1a, GD1b and GT1b IgG antibodies in two patients with GBS exclusively presenting with sensory disturbances and promptly recovery without oropharyngeal palsy or ophthalmoplegia. A. Pou-Serradell, J. Pascual, M-J. Téllez, R. Rojas, I. Illa-Sendra, Hospital del Mar, Hospital de Sant Pau (Barcelona, E)

Background: Elevation of anti-GQ1b IgG antibodies in sera from patients without ophthalmoplegia is rare. Only 3 cases in UK (with oropharyngeal palsy and ataxia) and 1 in Japan (with oropharyngeal palsy and weakness of the 4 limbs) have been reported.

We report two patients with elevated anti-GQ1b IgG antibodies without ophthalmoplegia or oropharyngeal palsy.

Patient 1: A 83 year-old-woman, without previously febrile illness or diarrhoea, manifested distal paresthesias that predominated in the upper limbs and severe lumbar pain. Cranial nerves were normal; mild limb weakness (4/5), absent ankle reflexes, mild distal hypoesthesia and a positive Lasègue's manoeuvre were noted. Electrophysiological studies showed: undetectable SNAPs of right Median and Ulnar nerves. EMG showed simple patterns of proximal muscles and F-waves were present.

Patient 2: A 54 year-old-woman, with a mild respiratory infection two weeks before, developed mild general weakness and paresthesias in her four limbs; a mild distal hypoesthesia in the four limbs, ankle arreflexia and a positive Lasègue's manoeuvre. Electrophysiological studies: 24 h. from onset, mild alteration of sensory nerve potentials was detected with normal conduction velocity. One week later, a reduction of the SNAPs amplitudes (right median nerve SNAP: 2.6 microV) and slowing of the SNC (r. med. n. SNC: 30 m/sec) were detected. F-waves at the lower limbs were abolished.

In both patients, CSF proteins were slightly increased. High titers of anti-GQ1b (1/1100 and 1/25 000 respectively), anti-GD1a, GD1b and GT1b IgG antibodies were detected in both patients. *C. jejuni* and *M. Pneumoniae* serologies were negative. The neurological manifestations disappeared within two weeks.

Conclusions: High titers of serum anti-GQ1b IgG antibodies may be associated clinically just with sensory disturbances. According to the similarity of the clinical symptomatology in two patients, we consider that the combination of the antibodies detected in their sera could be involved in this neuropathic pattern.

P704
Clinical and neurophysiological differences in painful and painless diabetic polyneuropathy. A. Barada, M. Reljanovic, S. Vuckovic-Rebrina, Z. Metelko, University Clinic (Zagreb, HR)

Diabetic polyneuropathy as the most frequent complication of diabetes mellitus can be manifested clinically as painful and painless. However, the above categories merely represent two extremes in the spectrum of various subjective difficulties and clinical signs. The aim of the study was to determine the differences in the clinical and neurophysiological parameters in painful (Group 1, $N = 26$) and painless diabetic polyneuropathy (Group 2, $N = 29$). Painful symptoms in the Group 1 (burning, cramps, shooting pains etc) had been presented in lower legs and feet for 6 months or longer. Polyneuropathy was evaluated according to the clinical signs (Neuropathic Clinical Score), electroneurographic analysis of median, peroneal and sural nerves, and quantitative sensory testing of the sensations of temperature and vibration of distal segments of the right extremities. The sympathetic skin response was also measured on the right palm and foot. The studied groups of patients were matched according to age, sex and the type and duration of diabetes. Between the groups there were significant differences in neuropathic score ($p = 0.046$), sural nerve conduction velocity ($p = 0.0006$) and amplitude ($p = 0.0007$), vibration sensation at toe ($p = 0.01$) and heat sensation ($p = 0.013$) and sympathetic skin response ($p = 0.001$) at feet. There was no statistical difference between two groups in neurophysiological parameters of median and peroneal nerves. The results indicate the specific damage of all kinds of sensory neurons in the lower limbs in patients with painful diabetic neuropathy.

P705
Antibodies to heparan sulfate: clinical correlations with neurological diseases. C. Briani, S. Ruggero, A. Alaedini, G. Zara, E. Nardelli, S. Ferrari, I. Wirguin, L. Battistin, N. Latov, University of Padua, Cornell University, University of Verona, Ben-Gurion University (Padua, I; New York, USA; Verona, I; Beer-Sheva, IL)

Background: Anti-heparan sulfate (HS) antibodies have been reported in patients with peripheral neuropathies, but also in patients without neuropathy. A related glycosaminoglycan, chondroitin sulfate C (ChS C), was also initially reported to be a target for antibodies in sensory axonal neuropathy, but anti-ChS C antibodies were later also found in other neurological diseases.

Objective: To determine the clinical correlations of anti-heparan sulfate (HS) antibodies in neurological diseases.

Patients and Methods: Sera from more than 300 neurological patients were tested for antibodies to HS using a newly developed avidin-biotin ELISA system. The specificity of antibodies to HS and/or ChS C was assessed with absorption studies.

Results: Sera from normal subjects had IgM anti-HS antibody titers of up to 25,600, and IgG anti-HS antibodies of up to 6,400. Border-line titers of 51,200 for IgM and 12,800 for IgG anti-HS antibodies were seen in a variety of diseases. Titers higher than 51,200, all IgM, were observed in 10 patients: 7 with peripheral neuropathy, and 3 with other neurological diseases (1 multiple sclerosis, 1 Alzheimer's disease, and 1 cerebral vasculitis). Of the 7 patients with neuropathy, 1 had a severe inflammatory neuropathy with anti-sulfatides and anti ChS C antibodies, 1 had a vasculitic neuropathy, 3 a demyelinating sensory-motor neuropathy (in one case with anti-MAG antibodies), 1 a multifocal motor neuropathy with anti-GM1 antibodies, and 1 a chronic inflammatory demyelinating polyneuropathy. In 5 of 10 cases antibody titers were high for both HS and ChS C. In 3 cases absorption studies confirmed the cross-reactivity between HS and ChS C, whereas in 2 cases absorption with ChS C abolished the reactivity towards ChS C but not to HS, indicating distinct antibody populations. No cross-reactivity was found between antibodies to HS and GM1, sulfatides or MAG.

Conclusions: Antibodies to HS occur in several inflammatory diseases, including inflammatory neuropathies or cerebral vasculitis. HS proteoglycans are richly represented in the capillaries, and they might contribute to the associated vasculopathy or breakdown of the blood-brain or blood-nerve barrier. Whether the antibodies contribute to the vascular damage, or arise secondarily to vessel alterations needs to be addressed in further studies.

P706

Sequencing of MPZ and PMP22 genes in Czech Charcot-Marie-Tooth type 1, type 2 and Dejerine-Sottas neuropathy patients without the CMT1A duplication. High frequency of T118M mutation in PMP22 gene. P. Seeman, V. Benes, P. Suslikova, R. Mazanec, K. Huehne, B. Rautenstrauss, Charles University Prague, University Erlangen-Nuernberg (Prague, CZ; Nuernberg, D)

Objective: Charcot-Marie-Tooth (CMT) are a group of the most common neuromuscular disorders. CMT is genetically heterogeneous, but most (50–70 %) CMT patients carry a 1,5 Mb duplication on chromosome 17p including the PMP22 gene – the CMT1A duplication. The CMT phenotype, characterised by distal muscle weakness and atrophies, foot deformities, tendon areflexia, sensory disturbances and changes in nerve electrophysiology can also be caused by mutations in at least 17 known genes. Mutations in myelin protein zero (MPZ) and connexin 32 (Cx32) are after the CMT1A duplication still common causes of CMT. Point mutations in peripheral myelin protein 22 (PMP22) are reported rarely.

In more than half of the patients tested in our laboratory for CMT, the CMT1A duplication is excluded. Search for mutations in other genes is followed in typical CMT cases.

Results: Complete coding region of MPZ or PMP22 genes or both was sequenced in 38 unrelated Czech CMT patients of various clinical CMT subtypes without CMT1A duplication.

MPZ gene was sequenced in 25 and PMP22 gene in 27 unrelated patients and both of these genes were sequenced in 15 patients.

4 different mutations (Thr124Met, Arg98Cys, Glu97Val and Gly213Arg) in 5 families (20 %) and 2 different polymorphisms (Gly200Gly and Ser228Ser) in three families were found in MPZ gene. Two of the mutations were previously reported by others and two were novel.

Only one missense mutation (Ser72Leu – previously reported) was detected in PMP22 gene in one patient with congenital hypomyelination out of 27 unrelated cases (3,7 %). The Thr118Met mutation in PMP22 gene, which is speculated to be a polymorphism or a recessive mutation, was found in heterozygous state in 3 patients, in one of them it was found over the CMT1A duplication.

Conclusions: Mutations in MPZ gene can cause up to 20 % of CMT cases without CMT1A duplication. Mutations in MPZ gene can be found in different subtypes of CMT patients – demyelinating as well as axonal, in very early onset cases as well as in late adult onset cases. Cases with severe phenotype are often sporadic and are often caused by a de-novo dominant mutations.

Point mutations in PMP22 gene are very rare and were found in less then 5 % of CMT cases without CMT1A duplication. T118M mutation in PMP22 seems to be very frequent in Czech CMT patients.

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P707

Campylobacter jejuni-derived LPS abrogates oral tolerance to experimental autoimmune neuritis. S. Jung, E. Lueneberg, M. Frosch, H. Karch, K. Toyka, S. Schäfer, University of the Saarland (Homburg/Saar, Würzburg, D)

The inflammatory form of the Guillain-Barré syndrome (AIDP; GBS) is an acute polyradiculoneuritis mediated by T lymphocytes, macrophages, and antibodies directed against the PNS. In about 30 % of the patients with AIDP evidence for a recent infection by Campylobacter jejuni is found.

We evaluated the functional relevance of cellular and humoral immune responses to C. jejuni in the pathogenesis of neuritis using experimental autoimmune neuritis (EAN) of Lewis rats as an animal model of AIDP. EAN can be induced by immunization with PNS myelin or by adoptive transfer of activated T lymphocytes specific for the PNS myelin protein P2 (AT-EAN).

Active immunization of naive rats with antigen preparations of various C. jejuni strains derived from GBS patients did not induce clinical or histopathological signs of neuritis. Nevertheless, animals generated high titers of C. jejuni-specific antibodies. Subsequent injection of P2-specific T cells caused typical neuritis and opened the blood-nerve-barrier, but clinical disease course or nerve histopathology were not aggravated in C. jejuni-immunized rats compared to CFA-sensitized animals.

Signs of active EAN induced by immunization with PNS-myelin could be mitigated by precedent feeding of myelin (oral tolerance). However, if pronase digested LPS prepared from C. jejuni had been added to the enterally applied myelin, tolerance induction was completely prevented and rats developed an accelerated neuritis. Feeding of LPS alone did not modulate the course of EAN.

The findings demonstrate that C. jejuni-derived LPS can disturb natural immunoregulation by the gut-associated lymphoid tissue.

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P708

Local macrophage response in heterozygously P0-deficient mice: evidence for activation and proliferation of resident endoneurial macrophages with progressive neuropathy. M. Müller, M. Mäurer, I. Kobsar, C. Leonhard, R. Kiefer, R. Martini, University of Münster, University of Würzburg (Münster, Würzburg, D)

Inherited demyelinating peripheral neuropathies are chronic diseases of the peripheral nervous system caused by genetic defects in several culprit genes. However, the pathogenetic mechanisms leading from a genetic defect to myelin loss are still unknown. Using a mouse model of one distinct hereditary demyelinating neuropathy (heterozygous P0-deficiency, P0±) the pathogenetic importance of the immune system was recently demonstrated. Especially macrophages play an important role since they were increased in number and were shown to actively strip myelin from axons. To clarify whether these activated endoneurial macrophages in P0-deficient animals are derived from local endoneurial macrophages or have invaded from the blood, we transplanted bone marrow from green fluorescent protein (gfp) transgenic mice into mice heterozygously deficient for P0. In such animals, haematogenous cells are green fluorescent and can be discriminated from non-fluorescent resident cells. Using this model in wildtype recipients, we recently revealed an early activation and proliferation of resident endoneurial macrophages after nerve injury that occurred prior to the influx of haematogenous macrophages, pointing towards an important role of local macrophages in Wallerian degeneration. Here we found an increased number of endoneurial macrophages in 6-months-old chimeric P0± mice compared with chimeric wild type littermate controls four months after bone marrow transplantation. The ratio of gfp+ and gfp- macrophages was only slightly different from chimeric wildtype controls with a trend towards an increase of the gfp+, haematogenous cell population. Proliferation, myelin phagocytosis and MHC class II expression were observed in both gfp+ and gfp- macrophages. Since gfp+ resident endoneurial macrophages enter the nerve under physiological conditions as part of a slow turnover, the proportional increase of both macrophage populations in P0± mice points towards a predominantly local generation of the macrophage response rather than an influx of macrophages induced by the disease. Thus, activated macrophages involved in the pathogenesis of inherited demyelinating neuropathies are predominantly derived from local endoneurial macrophages.

P709

Clustering of perivascular macrophages in chronic inflammatory demyelinating neuropathy (CIDP). C. Sommer, S. Koch, M. Marziniak, K. Toyka, University of Wuerzburg (Wuerzburg, D)

Background: Inflammatory neuropathies are characterized by the presence of epi- and endoneurial T-cells and macrophages (Schmidt et al., Muscle Nerve 1996). A secondary immune reaction may also occur in hereditary neuropathies (HNP, Mäurer et al. J. Anat. 2002). The aim of this study was to identify markers that might help to differentiate between CIDP and demyelinating hereditary neuropathies on sural nerve biopsies.

Methods: Out of 323 patients who underwent sural nerve biopsies for diagnostic purposes between January 1998 and December 2001, 14 patients fulfilled the criteria of the Ad Hoc Subcommittee for CIDP, 13 patients had a HNP proven by genetic testing and/or positive family history. Five biopsies served as disease controls with no pathology. The following markers were evaluated: Number and distribution of macrophages (CD 68) and T-cells (CD3), tumor necrosis factor-alpha (TNF), interleukin–1ß (IL–1ß), interleukin–6 (IL–6), matrix-metalloprotease (MMP) 2 and 9. Quantification was aided by a computer based morphometry system (Image Pro Plus 4.0).

Results: Numbers of endoneurial T-cells per nerve were slightly higher in CIDP (7.2 ± 14.5) than in HNP (4.8 ± 3.8, n. s) and in both compared to controls (1.0 ± 1.7, $p < 0.05$). The absolute number of macrophages per nerve was higher in CIDP (110.4 ± 47.1) than in the hereditary neuropathies (53.8 ± 17.1, $p < 0.05$) and in the controls (37.7 ± 12.3, $p < 0.05$). The percentage of perivascular macrophages was not significantly different between CIDP (28.2 ± 14.2 %), hereditary neuropathies (39.4 ± 9.3 %), and controls (33.9 ± 20.6 %). Perivascular macrophage clusters defined as three or more discernible macrophages grouped close together were found in 9.6 ± 9.3 % of microvessels in CIDP, in 1.2 ± 2.1 % ($p < 0.05$) in hereditary neuropathies and in 0.8 ± 1.3 % ($p < 0.05$) in normal controls. Cytokine immunoreactivity did not differentiate between the groups. Endoneurial MMP–9 immunoreactive vessels were more frequent in CIDP and in the hereditary neuropathies than in normal controls. Three of the CIDP patients and none of the other patients had 30 % or more MMP–9 immunoreactive vessels.

Discussion: Perivascular macrophage clusters seem to be of diagnostic value in CIDP. Absolute numbers of T-cells and macrophages were not helpful to distinguish CIDP from HNP. These findings underscore the role of a secondary immune reaction in HNP. High values of MMP–9 positive vessels seem to occur in CIDP, but not in HNP.

P710

CANOMAD: good response to treatment with intravenous immunoglobulin. D. Pareyson, M. Morbin, I. Allegri, C. Ciano, F. Andreetta, R. Mantegazza, G. Lauria, A. Sghirlanzoni, Istituto Nazionale Neurologico (Milan, I)

Background: CANOMAD is the acronym indicating a very rare form of dysimmune neuropathy, characterized by Chronic Ataxic Neuropathy, Ophthalmoplegia, IgM paraproteinemia, cold Agglutinin, and Disialosyl antibodies.

Goals: We describe clinical course and response to treatment of CANOMAD in a 73-year-old male patient.

Case Report: He presented with an 8-year-long history of diplopia, loss of balance, and distal limb paresthesiae. The disease had a fluctuating course with alternating periods of spontaneous worsening and improvement, which however had worsened over the years. When first seen at our Center, he showed diplopia and strabismus in all gaze directions, stance and gait ataxia, positive Romberg sign, generalized deep tendon areflexia, distal sensory loss to all modalities, particularly severe for position and vibration sense. Haematological work-up revealed the presence of an IgM-k monoclonal gammopathy. Nerve conduction studies showed decreased conduction velocities in motor and sensory nerves; amplitudes of sensory action potentials were markedly reduced, while compound muscle action potential amplitudes were decreased to a lesser extent. Serum immunologic investigations demonstrated high titers of anti-disialosyl IgM antibodies. Therefore, all the features of CANOMAD but cold agglutinin (reported in 50 % of patients) were present. Myelinated fiber density was still within normal limits at light microscopy examination of sural nerve biopsy. Some fibers had thin myelin sheaths and occasionally were surrounded by small onion bulbs. Signs of wallerian-like degeneration were sporadically observed; however, there were a lot of regenerative clusters. Electron microscopy study disclosed the presence of collagen pockets and denervated Schwann cell processes. Intriguingly, a good deal of fibers had unusual myelin sheath structure, appearing either as widening of lamellae or as myelin loop formation. Literature data on course of CANOMAD and response to treatment are very scanty. The patient received three courses of high dose intravenous immunoglobulin (IVIg) and each time he showed dramatic improvement of diplopia, ataxia and paresthesias which started during the infusion period and lasted for about 1 month. Treatment with low dose steroids after the first IVIg course did not prevent a relapse, which was reverted by two further IVIg courses.

Conclusions: CANOMAD is a rare dysimmune neuropathy which may be successfully treated with IVIg.

P711

FADD-like IL–1beta-converting enzyme-inhibitory protein (FLIP) – an antiapoptotic pathway in vasculitic neuropathy. T. Leuschner, B. Neundörfer, D. Heuss, University of Erlangen (Erlangen, D)

Objective: The mechanisms regulating the inflammation in vasculitic neuropathy are incompletely understood. For apoptosis of inflammatory mononuclear cells a nonsecretory ligand-mediated mechanism has been proposed by interaction of Fas and Fas-ligand followed by recruitment of a death-inducing signalling-complex DISC (Fas-associated death domain FADD and caspase–8). Limited spontaneous recovery in vasculitis implies antagonistic mechanisms to apoptosis. In tumorigenesis it has been suspected that overexpression of FLIP blocks the DISC and therefore could be responsible for treatment resistance. The aim of this study was to characteríze antiapoptotic mechanisms in vasculitic neuropathy.

Methods: Nerve biopsies of patients with vasculitic neuropathy and controls were studied by means of immunohistochemistry using antibodies against Fas/FasLigand, FADD, caspase–8 and FLIP.

Results: In vasculitic neuropathy infiltrating mononuclear cells expressed molecules of the DISC and FLIP. In controls only sporadic positive mononuclear cells could be detected.

Conclusion: These data suggest that FLIP is a factor to maintain the inflammatory activity in vasculitic neuropathy. Therefore, down-regulation of FLIP by metabolic inhibitors like cycloheximide and actinomycin D or chemotherapeutic agents like cisplatin could provide therapeutic options by supporting the apoptotic process.

Poster Session 5

Cerebrovascular Disorders

P712

Donepezil improves cognition and global function in patients with vascular dementia: Results from Study 307, a 24-week, randomized, double-blind, placebo-controlled trial. R. D. Pratt, C. A. Perdomo, Eisai Inc. on behalf of the 307 Study Group

Background: Evidence to suggest that patients with vascular dementia (VaD) may benefit from treatment with cholinesterase inhibitors is accumulating.

Objective: Evaluation of the efficacy and tolerability of donepezil in patients with probable or possible VaD.

Design: A randomized, double-blind, placebo-controlled, 24-week, parallel-group study (Study 307).

Methods: A diagnosis of probable or possible VaD according to NINDS-AIREN criteria was required for enrollment (i. e. evidence of dementia and a probable or possible relationship between dementia and cerebrovascular disease [CVD]). Patients with a prior diagnosis of Alzheimer's disease (AD) and subsequent cognitive impairment due to stroke or CVD were excluded. Patients were randomized to receive placebo, donepezil 5 mg/day or donepezil 10 mg/day (5 mg/day for first 28 days). Efficacy assessments included the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), the Mini-mental state examination (MMSE), and the Clinician's interview-based impression of change-plus version (CIBIC-plus). Results are reported for intent-to-treat observed cases.

Results: 603 patients were enrolled (199 placebo, 198 donepezil 5 mg/day, 206 donepezil 10 mg/day); 425 (70 %) had probable VaD and 30 % had possible VaD. At Week 24, both donepezil-treated groups showed significant improvements in cognitive function compared with placebo: mean change from baseline score effect size favored donepezil for the ADAS-cog (donepezil 5 mg/day, –1.86, $P = 0.002$; donepezil 10 mg/day, –2.37, $P < 0.001$) and the MMSE (donepezil 5 mg/day, 0.46, $P = 0.16$; donepezil 10 mg/day, 0.86, $P = 0.009$). The donepezil 5 mg/day group

showed significant improvements in global function compared with placebo (% of patients rated as showing improvement on the CIBIC-plus at Week 24: placebo, 32 %; donepezil 5 mg/day, 38 %, P = 0.01; donepezil 10 mg/day, 31 %, P = 0.27). Donepezil was well tolerated in this population (of whom 89 % had cardiovascular disease), with low withdrawal rates due to adverse events (AEs) (placebo, 11.1 %; donepezil 5 mg/day, 11.1 %; donepezil 10 mg/day, 21.8 %) and a similar incidence of cardiovascular AEs across all treatment groups (placebo, 18.1 %; donepezil 5 mg/day, 20.7 %; donepezil 10 mg/day, 20.4 %).

Conclusions: Donepezil-treated patients with possible or probable VaD demonstrate cognitive and global improvements. Donepezil is well tolerated in this population, which has a high incidence of cardiovascular disease.

P713

Donepezil-treated patients with vascular dementia demonstrate cognitive and global benefits: Results from Study 308, a 24-week, randomized, double-blind, placebo-controlled trial. R. D. Pratt, C. A. Perdomo, Eisai Inc. on behalf of the 308 Study Group

Background: Pathological evidence suggests that vascular dementia (VaD) is associated with a cholinergic deficit. Patients with VaD may therefore benefit from therapy with cholinesterase inhibitors such as donepezil.

Objective: Evaluation of the efficacy and tolerability of donepezil in patients with probable or possible VaD.

Design: A randomized, double-blind, placebo-controlled, parallel-group, 24-week clinical trial (Study 308).

Methods: A diagnosis of probable or possible VaD according to NINDS-AIREN criteria was required for enrollment: evidence of dementia (impaired memory and two other domains); evidence of cerebrovascular disease (CVD) from neuroimaging, history, and physical examination; and a probable or possible relationship between dementia and CVD. Patients with a prior diagnosis of Alzheimer's disease (AD) and subsequent cognitive impairment due to stroke or other cerebrovascular disease were excluded. Patients were randomized to receive placebo, donepezil 5 mg/day or donepezil 10 mg/day (5 mg/day for first 28 days). Efficacy assessments included the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), the Clinician's interview-based impression of change scale (CIBIC-plus), and the Mini-mental state examination (MMSE). Results are reported for intent-to-treat observed cases.

Results: 616 patients were enrolled (193 placebo, 208 donepezil 5 mg/day, 215 donepezil 10 mg/day); 468 (76 %) had probable VaD and 24 % had possible VaD. Both donepezil-treated groups showed significant improvements in cognitive function compared with placebo (ADAS-cog mean change from baseline score effect size at Week 24: donepezil 5 mg/day, –1.60, P = 0.006; donepezil 10 mg/day, –2.12, P < 0.001; MMSE mean change from baseline score effect size at Week 24: donepezil 5 mg/day, 1.04, P = 0.002; donepezil 10 mg/day, 1.20, P < 0.001). Greater improvements on the CIBIC-plus were observed with both donepezil groups than with the placebo group (% patients showing improvement at Week 24: placebo, 26 %; donepezil 5 mg/day, 44 %, P = 0.006; donepezil 10 mg/day, 35 %, P = 0.08). Donepezil was well tolerated in this population (of whom 90 % had comorbid cardiovascular disease), with low withdrawal rates due to adverse events (placebo, 8.8 %; donepezil 5 mg, 10.1 %; donepezil 10 mg, 16.3 %).

Conclusions: Donepezil is an efficacious and well-tolerated treatment for patients with possible or probable VaD, and may have an important role in the management of patients with VaD.

P714

Migraine and tension-type headache in Croatia. A population-based survey of precipitating factors. R. Zivadinov, K. Willheim, D. Sepic-Grahovac, A. Jurjevic, M. Bucuk, O. Brnabic-Razmilic, G. Relja, M. Zorzon, Neurological Clinic (Trieste, I; Rijeka, HR)

Background: The careful monitoring of the trigger factors of headache could be an important step in treatment, because their avoidance may lessen the frequency and severity of attacks.

Objectives: The aim of the present study was to establish the frequency of precipitant-dependent attacks in subjects with migraine and TTH in the adult population of Bakar, County of the Coast and Gorski Kotar, Croatia, and to examine the relationship of the precipitating factors with migraine and TTH, and with migraine subtypes

Methods: We performed a population based survey using a "face to face-door to door" method. The participants (73.3 % of whole surveyed sample) were screened for headache history according to the International Headache Society (IHS) criteria. Headache screen-positive responders, 2475 (65.7 %), were interviewed by trained medical students with a structured detailed interview focused on the precipitating factors. The following precipitating factors in lifetime migraine and tension-type headachers have been assessed by using univariate and multivariate regression analyses: stress, sleep disturbances, frequent travelling, eating habits, menstrual cycle, oral contraceptives, food items, afferent stimulation, changes in weather conditions and temperature, and physical activity.

Results: A total of 720 lifetime migraineurs and 1319 tension-type headachers have been identified. The most common precipitants for both migraine and TTH were mental tension risk factors. Comparing migraine and TTH, stress ($p < 0.00001$), afferent stimulation ($p = 0.0005$), changes in weather conditions and temperature ($p = 0.0006$) and sleep disturbances ($p = 0.0006$) were significantly and independently associated with migraine, whereas physical activity ($p < 0.00001$) was related to TTH. Comparing MWA and MWOA, frequent travelling ($p < 0.00001$), food items ($p < 0.00001$) and changes in weather conditions and temperature (0.0006) exhibited a significant positive association with MWA, whereas afferent stimulation ($p = 0.04$) was associated with MWOA.

Conclusions: The present study demonstrated that lifetime migraineurs experienced more frequently headache attacks preceded by triggering factors than tension-type headachers. MWA was more frequently associated with precipitating factors than MWOA. We suggest that some triggering factors in particular the mental tension risk factors may contribute to the higher occurrence of precipitant-dependent headache attacks in susceptible individuals.

P715

Clinically analysis of occurrence of high level of homocysteine in stroke patients. W. Palasik, W. Tadeusiak, E. Dlawichowska, W. Lechowicz, U. Fiszer, Center for Postgraduate Education, Instute of Psychiatry and Neurology (Warsaw, PL)

A high level of total homocysteine is an strong, well known and independent risk factor for cardiovascular and cerebrovascular diseases. The role of hyperhomocysteinemia in atherosclerotic and thromboembolic process and is very complicated and depended on many factors such as level of foliate, vitamins B6 and B12. The level of increased serum homocysteine, which correlate with state of vascular damage. We examined sera of 136 patients in early stage of stroke, successively admitted to the Department of Neurology and Epileptology. Total plasma homocysteine concentrations were measured by fluorescence polarisation immunoassay (FPIA-ABBOTT). Patients were classified into one of four stroke types according to the Oxfordshire Community Stroke Project (OCSP) classification: TACI (Total anterior circulation infarction), PACI (Partial anterior circulation infarction), LACI (Lacunar infarction), POCI (Posterior circulation infarction). References values of normal level of homocysteine were 5–15 umol/l. We found increase, pathological level of homocysteine in 35,3 % (50 cases – 22 female and 28 male). The presence of highest levels was most frequently observed among patients with LACI. In this group the level of homocysteine above 15 umol/l was observed in 51,2 % of patients. In the group of patients with PACI increased level of homocysteine was found in 28,4 % subjects, and respectively in TACI – 33,3 %, and POCI – 14,3 %. Therefore is important measure the level of increased serum homocysteine, which correlate with state of vascular damage. A widely used examination of this factor may have a benefit role in prevention of stroke.

P716

Multiple petechial haemorrhages and cerebral amyloid angiopathy. M. Gomis, J. Roquer, A. Rodríguez Campello, J. Izquierdo, V. Puente, A. Pou Serradell, Hospital del Mar Cerebrovascular

Introduction: The Boston Group (CAABG) has established the diagnostic criteria of Cerebral Amyloid Angiopathy (CAA) in four categories: definite CAA, probable CAA with supporting pathology, probable CAA and possible CAA. The diagnostic criteria of probable CAA are and neuroradiological findings consist of: over 60 years old patients, multiple haemorrhage limited at certain areas (cortical-subcortical region) and lack of other intracerebral haemorrhage cause.

Objective: To evaluate the impact of MRI with T2* sequence in the diagnosis of probable CAA in patients with a single lobar haemorrhage in CT scan.

Methods: We studied using MRI 31 cases of spontaneous lobar haemorrhage in patients over 60 years admitted to our hospital. All of them were evaluated using FSE T2, SE T1 and Echo-gradient (T2*) sequences.

Results: 1.Sixteen patients (51.6 %) showed multiple haemorrhage lesions, either on the form of petechial haemorrhages (81.2 %) or as haemorrhages (50 %). 2. Seven patients (22.5 %) fulfilled the radiological crite-

ria of probable CAA. 3. T2* sequence had a higher sensibility for detecting haemorrhages and specially petechial haemorrhages. 4. The number of lobar petechial haemorrhages was significantly higher in the patients with suspected probable CAA ($p < 0.004$). 5. All the patients fulfilling the CAABG criteria had cognitive symptoms.

Conclusions: 1. In patients with single lobar haemorrhages, MRI is very useful for diagnosing probable CAA. 2. The sequence T2* increases the sensibility in detecting haemorrhages therefore it should be the first line sequence for detecting cerebral petechial haemorrhages.

P717

Mutations in the Abcc6-gene were not found in patients with spontaneous cervical artery dissections. M. Morcher, I. Hausser, T. Brandt, C. Grond-Ginsbach, Universität Heidelberg (Heidelberg, D)

Background and purpose: Most patients (60 %) with spontaneous cervical artery dissections (sCAD) show connective tissue abnormalities as diagnosed in skin biopsies. Some of the electron microscopic findings (accumulation of morphologically abnormal and mineralised elastic fibres) are similar to those found in biopsie from heterozygous carriers of pseudoxanthoma elasticum (PXE). The majority of PXE patients carries mutations in the ABCC6 (ATP- binding cassette)-gene. In this study we searched for mutations in the ABCC6-gene in patients with sCAD. Mutation search appeared to be complicated, since two additional non-functional copies of the 5'-region of the ABCC6-gene (pseudogenes) have accumulated multiple mutations.

Methods: We analyzed genomic DNA from 13 sCAD patients with pronounced electron microscopic alterations and from 2 patients with PXE. All 31 exons of the ABCC6 gene were amplified by polymerase chain reaction (PCR), analysed on 2 % agarose gels and subsequently processed for SSCP or DNA sequence analysis. Exons 1–9 of the ABCC6 gene were amplified with allele specific oligonucleotides in order to avoid the amplification of homologous pseudogene sequences

Results: One unknown conservative missense mutation (A580G) was found in only one patient with sCAD. It could not be found amongst 25 healthy control subjects. One patient with PXE we found to be compound heterozygous for two missense point mutations, the second patient with PXE is currently being studied. No disease-causing mutation was found in the other 12 patients with sCAD. We observed several sequence variations resulting in amino acid substitutions in patients H623Q, R3190W and R1268Q that were also observed in a series 25 healthy control subjects.

Conclusions: The finding of several missense mutations in sCAD pateints and of disease mutations in PXE patients suggest that our strategy of mutation search is reliable. We nevertheless did not find ABCC6 mutations in the majority of patients with sCAD. We therefore suggest that ABCC6 is not a candidate gene for this cerebrovascular disease.

P718

A novel test battery for neuropsychological evaluation of patients undergoing carotid surgery. A. Faulstich, P. Marx, B. Mann, A. Hartmann, University Hospital Benjamin Franklin (Berlin, D)

Background and Purpose: Information on changes of cognitive functions and emotional status of patients undergoing surgical treatment of high-grade internal carotid artery stenosis is scarce. Conventional test batteries are often too time-consuming for clinical routine. Our goal was to construct and apply a practicable psychological test battery for the measurement of cognitive and emotional changes following carotid endarteriectomy.

Methods: The test battery included established tests: Mini-Mental, 9-Hole-Peg-Test, Erlangen Depression Scale (EDS), Multiple choice vocabulary test (MVT), and the Digit memory test (from HAWIE-R). A shortened version of the Standard Progressive Matrices test (SPM) balanced for item difficulty was used. Additionally we developed a test consisting of 13 visual analog scales (VAS) for the self-assessment of the patients' emotional status and cognitive skills. A face recognition test (FRT) of 18 faces after 1, 15 and 45 minutes was constructed. The tests were applied before carotid surgery and 4 months following the procedure. To minimize retest effects, parallelized tests of the MVT, SPM, and FRT were used. Standard neurologic examinations and complete cerebrovascular ultrasound investigations were also performed.

Results: Until January 2001, 19 patients were examined before surgery and 8 patients after the operation in our ongoing study. The test battery required 70 minutes, and all patients were able to complete the tasks. Floor and ceiling effects were not observed except for the Mini-Mental (mean score 28.8, sd 1.4). Preliminary analysis revealed no significant changes of test results for any of the test components after carotid surgery.

Conclusion: Our new test battery is a practical tool for the assessment of changes in cognitive and emotional status after carotid endarteriectomy. More patients need to be evaluated to confidently prove surgery-related changes.

P719

Patients with vascular dementia differ from patients with Alzheimer's disease with respect to population characteristics and pattern of cognitive decline. R. D. Pratt, C. A. Perdomo, Eisai Inc. The 307 and 308 Study Groups

Background: The link between cerebrovascular disease and dementia is well established. For example, 25 % of patients experiencing a stroke develop dementia. However, there are difficulties in accurately defining patients with pure vascular dementia (VaD) and, therefore, little is known about the rate of cognitive decline and the characteristics of this population.

Objective: To examine the population characteristics and pattern of cognitive decline in patients with VaD enrolled in two randomized, double-blind, placebo-controlled, 24-week clinical trials of the efficacy and tolerability of donepezil (Studies 307 and 308).

Methods: Enrolled patients had probable or possible VaD, classified according to NINDS-AIREN criteria. Patients were excluded if they had a diagnosis of Alzheimer's disease (AD) or dementia caused by other conditions not associated with the cardiovascular system.

Results: 1219 patients were enrolled; 73 % had probable VaD and 27 % had possible VaD. At screening, patients had a mean Hachinski score of 9.7 and memory impairment was the most prominent feature of their dementia. 73 % of patients had experienced an abrupt onset of cognitive symptoms. 68 % of patients had a history of at least one stroke, 28 % of patients had a history of transient ischemic attack. Vascular risk factors were prominent and included hypertension (70 %), smoking (62 %), and hypercholesterolemia (39 %). Almost all patients had abnormal CT or MRI scans. 99 % of patients were taking concomitant medication (63 % were taking aspirin). Placebo-treated patients with VaD demonstrated no decline in cognition (ADAS-cog LS mean change from baseline score at Week 24 [observed cases], –0.10; n = 310). This contrasts with the cognitive decline observed in placebo-treated patients with AD in donepezil trials (ADAS-cog LS mean change from baseline score at Week 24, 0.94; n = 491).

Conclusions: The patients enrolled in these trials had probable or possible VaD and a broad range of cardiovascular disease, and therefore differ from those enrolled in AD trials. Placebo-treated patients with VaD, in contrast to placebo-treated patients with AD, demonstrated stable cognitive function over 24 weeks.

P720

Cerebral infarction associated with first use of MDMA (Ecstasy). A. Ecke, C. Zimmer, H.-C. Koennecke, Ev. Krankenhaus Königin Elisabeth, Charité Campus Mitte (Berlin, D)

Background: Abuse of amphetamines and related agents (like Ecstasy) is an increasingly common cause of cerebrovascular accidents in young adults. In the vast majority of such cases, intracerebral and subarachnoid hemorrhages have been associated with episodes of raised blood pressure, intracerebral vascular malformations, and/or amphetamine-induced cerebral vasculitis, whereas cerebral ischaemia has rarely been linked to amphetamine abuse.

Case description: We report on a 18-year old right-handed man who had been found helpless in his apartment. On admission he was alert but inadequately euphoric. In addition, he was slightly aphasic, had a right homonymous hemianopia in combination with right visual neglect, mydriatic but reactive pupils, and a right hemiparesis predominantely affecting the arm. Immediate cranial CT demonstrated an acute left fronto-parietal infarct, but no other unequivocal ischaemic lesions. Further questioning revealed that he had taken Ecstasy (MDMA, 3,4-methylenedioxymethamphetamine) for the first time 36 hours prior to admission. According to his medical and family history he had no cardiovascular risk factors. Laboratory results including lumbar puncture and several tests for hypercoagulability were unremarkable. In addition, neurosonography, cerebral angiography (day 10), ECG, and echocardiography revealed normal results. MRI (day 4) demonstrated several predominantly cortical lesions mainly in the left hemisphere and a single lesion in the right frontal cortex, of which one lesion in the left central region showed contrast enhancement. The patient made a partial recovery.

Discussion: Lack of other definite stroke risk factors in this patient, together with the temporal coincidence of drug intake and stroke, suggest a causal association of MDMA and acute cerebral infarction. MDMA is known to alter brain serotonin (5-HT) concentrations. Furthermore, cere-

bral postsynaptic 5-HT receptors play a role in the regulation of brain microvasculature. Thus, even a single administration of MDMA might induce transitory vasospasm by increasing the 5-HT concentration in the intersynaptic space.

Cerebral angiitis following amphetamine abuse needs to be discussed as another possible cause. However, the normal results of cerebral angiography together with normal CSF findings argue against this assumption.

In conclusion, transient vasospasm triggered by MDMA is the most likely etiologic mechanism in this unusual case of ischaemic stroke.

P721

Spontaneous carotid-cavernous sinus fistula in a patient with Ehlers-Danlos syndrome type IV. R. Weber, I. Hausser, C. Koerner, F. Wigger, T. Brandt, C. Grond-Ginsbach, University of Heidelberg (Heidelberg, D)

Background: Ehlers-Danlos syndrome (EDS) type IV is an autosomal dominant disorder that results from mutations in the COL3A1 gene, which encodes chains of type III procollagen. Individuals with this disorder are predisposed to rupture of arteries, the bowel, and the uterus. Affected patients are prone to develop carotid-cavernous fistulas, aneurysms or dissections.

Case report: A 35 yr old patient presented with left-sided headache and a pulssynchronous tinnitus. On clinical examination she showed paralysis of the VI. cranial nerve and phenotypic signs of an underlying connective tissue disorder. Family history revealed a'connective tissue weakness'in the patient's sister. Angiography showed a carotid-cavernous fistula on the left side. The fistula was treated by interventional occlusion of the left internal carotid artery. Additionally digital subtraction angiography showed an aneurysm of the left renal artery and a stenosis of the right renal artery. A skin biopsy was taken and the electron microscopic picture revealed clear correspondence to the diagnosis of EDS IV. Molecular analysis of the coding region of COL3A1 revealed a heterocygous Gly-Arg substitution at position 721. Similar glycin substiutions in the triple-helical region of COL3A1 in Ehlers-Danlos patients have already been described. Therefore the heterocygous Gly-Arg substitution must be considered as a causal factor in our patient. Molecular analysis of the patient's sister revealed the same mutation in the coding region of COL3A1. A few days later after discharge the patient was readmitted to the department of surgery with acute abdominal pain. She died in hemorrhagic shock due to rupture of the aneurysm of the left renal artery.

Conclusion: Presence of spontaneous carotid-cavernous sinus fistula must enclose the differential diagnosis of a potential underlying connective tissue disorder. Early clinical recognition and diagnosis are very important because of its implications for acute and long-term managment and potentially for other family members and family planning. Occurence of neurological complications in Ehlers-Danlos patients should lead to noninvasive diagnostic procedures such as Doppler sonography and magnetic resonance angiography. Family history should be taken carefully in every patient with suspicion of an underlying connective tissue disorder.

P722

Symptomatic peripheral vascular and brain ischemia. J. Gracia, S. Monteagudo, S. Escalante, V. Mejías, B. Fuentes, E. Díez Tejedor, University Hospital La Paz (Madrid, E)

Background: Symptomatic peripheral vascular disease (SPVD) and cerebral ischemia are considered manifestations of a same process, Atherothrombosis. Our purpose was to analyse the presence of SPVD in patients with cerebral ischemia, as well as in the etiological subtypes (TIA, cardioembolic stroke and no cardioembolic stroke).

Methods: Observational study from our stroke data bank, since 1998 to 1999. We identified patients with cerebral ischemia and SPVD, and analysed vascular risk factors, age and sex. Statistical analysis: t- student and &No 61539;2 test.

Results: 973 stroke patients were admitted during the study period, 842 with brain ischemia: 170 TIA and 672 brain infarct (158 cardioembolic, 191 atherothrombotic, 236 lacunar, and 87 undetermined). SPVD was present in 6.89 % of the patients with cerebral ischemia and it was distributed as: 5.29 % TIA, 6.32 % cardioembolic stroke, 10.99 % atherothrombotic stroke, 5.93 % lacunar stroke, and 4.59 % undetermined stroke, without statistically significant difference ($p > 0.05$). Significant association between TIA and SPVD with hypertension ($p = 0.017$); cardioembolic stroke and SPVD with smoking ($p = 0.012$); no cardioembolic stroke and SPVD with diabetes mellitus, hypercholesterolemia, smoking and males ($p < 0.05$) were found.

Conclusion: Symptomatic peripheral vascular disease was present in a small percentage of patients with cerebral ischemia, without any differences between etiological subtypes (TIA, cardioembolic stroke, atherothrombotic stroke, lacunar stroke and undetermined stroke), and not only in aterothrombotic ones. The most frequently risk factor associated was smoking.

P723

Mathematical analysis of the effects of hyperventilation on the middle cerebral artery velocities. S. Jeangette, R. Sa, N. Azar, M. Pandolfo, M. Manto, Neurologie Erasme, Physique Biomédicale ULB, FNRS Neurologie (Brussels, B)

Hyperventilation is known to modify the characteristics of ocular movements in patients with cerebellar disorders. A period of 70 sec of hyperventilation is applied to modify the slow-phase of the downbeat nystagmus (Neurology 1999;53:1576–1579). It has been shown recently that hyperventilation impairs also the control of limb movements. It has been hypothesized that the effect is mediated through metabolic changes on cerebellar calcium channels. It is well known that hyperventilation induces a strong depression on the cerebral blood flow (CBF). However, no mathematical model focusing on the consequences of a hyperventilation of 70 sec on CBF is available. This model might help us understand the pathogenesis of the changes in ocular and limb movements associated with hyperventilation.

We used bilateral transcranial doppler (TCD) ultrasonography (Nicolet EME's pioneer TCD device, 2MHz probes, fixed using a head probeholder, depth set to 56mm) to determine the effects of hyperventilation on the middle cerebral artery (MCA) velocities in 6 healthy subjects (11 sides recorded). Mean age was 30.2 ± 7.1 years (6 men). Mean velocity was calculated over a running window of 3s, applied to each velocity profile. A basal recording of 120 sec was followed by 70 sec of hyperventilation, followed by 110 sec of normal ventilation. We fitted the decrease in the mean velocities over an interval of 80 sec using an exponential decay curve. The following equation was applied: $y = a + b.(\exp(-ct))$, with a Quasi-Newton estimation method (convergence criterion: 0.0001; Statistica Software). The minimum value of mean velocities from the very beginning of the hyperventilation to the minimum observed in the following 80 sec dropped to 47.1 ± 18.1 % of the initial values. This change is highly significant with $p < 0.0005$. One subject could not maintain the hyperventilation during the procedure. The R values of the exponential curve fit varied from 0.67 to 0.90 for the 5 remaining subjects. The value c (time constant of the decay = 1/c) ranged from 0.09 s^(–1) to 0.64 s^(–1). We thus show that a hyperventilation of 70 sec has dramatic effects upon the velocities in middle cerebral arteries. These effects should be taken into account in the interpretation of the changes in ocular and arm movements occurring in ataxic patients, especially because the cerebral areas involved in the compensation of cerebellar deficits are vascularized by the middle cerebral arteries.

P724

Early hyperbaric oxygen treatment decreases infarct volume in permanent focal cerebral ischemia. A. Günther, M. Schneider, I. Kunert, S. Schmidt, S. Roßner, D. Schneider, A. Wagner, J. Berrouschot, University of Leipzig (Leipzig, D)

Objective: Hyperbaric oxygen (HBO) is known to increase oxygen supply to ischemic areas and to effect infarct size in focal cerebral ischemia. We investigated the role of single and repeated HBO-treatment in a permanent ischemia model.

Methods: In three experimental series we treated 122 spontaneously hypertensive rats (SHR) after permanent middle cerebral artery occlusion (MCAO) either with hyperbaric oxygen (2.5 atm abs, 100 % oxygen, 90 min) or room air (control group, n = 18) in a small animal HBO-chamber. After initiation of ischemia 4 groups (n = 10 each) were treated once (15, 90, 180 or 360 min after MCAO), 4 groups (n = 10 each) were repeatedly treated (8 times: first treatment as above, then 3, 12, 24, 48, 72, 96 and 120 h after first treatment). In a third series of experiments we examined animals receiving HBO-treatment once starting at 90 min after MCAO (n = 8), twice (3h after first treatment, n = 8) or 4 times (3, 6 and 24h after first treatment, n = 8). All rats were sacrificed at 7 days after MCAO and infarct volume was measured.

Results: The infarct volume of the single HBO-treatment groups was significantly decreased at 15 min after MCAO ($76\,mm^3 \pm 17$, $p < 0.05$), but not significantly (n. s) at 90 min ($84\,mm^3 \pm 18$), at 180 min ($87\,mm^3 \pm 12$), at 360 min ($91\,mm^3 \pm 18$) after MCAO compared to the control group ($98\,mm^3 \pm 15$), similar results were determined for the 8 times treated animals (at 15 min after MCAO $71\,mm^3 \pm 19$, $p < 0.05$; at 90 min $74\,mm^3 \pm 17$, $p < 0.05$; at 180 min $89\,mm^3 \pm 22$, n. s.; at 360 min $92\,mm^3 \pm 17$, n. s). Results of the third experimental series showed a tendency towards better effects

of a single treatment compared to repeated HBO-exposure (1HBO-treatment: 65 mm3 ± 14, n. s.; 2 HBO-treatments 70 mm3 ± 10, n. s.; 4 HBO-treatment 82 mm3 ± 15 n. s. compared to the control group 77 mm3 ± 16).

Conclusions: In permanent focal cerebral ischemia HBO-treatment at 2.5 atm abs significantly reduced infarct volume when administered early (15 and 90 min after onset of ischemia). Repeated HBO-treatments did not show a further effect.

P725

Correlation between Canadian Stroke Scale and functional scales (modified rankin scale and barthel index) in an acute stroke prospective study. F. Diaz, A. Garcia-Pastor, B. Castaño, L. Vigil, M. L. Martíne-Ginés, A. Gil-Nuñez, J. Villanueva, Hospital Gregorio Marañon (Madrid, E)

Introduction: Neurological scales are a useful tool in the evaluation of acute stroke patients. They are widely used in clinical trials for measuring neurological deficits and functional outcome. Previous studies evaluate the correlation between neurological deficit scales and functional scales with different results and conclusions. The aim of this study was to obtain a correlation index between neurological deficit and functional status with Canadian, Barthel and Rankin scales.

Methods: 157 acute stroke patients were admitted in our Neurology Department from March to June 2000 with the following criteria: modified Rankin Scale (mRS) score previous to stroke < = 2; mRS at admission < = 4. Canadian Stroke Scale (CSS) and mRS score were registered at admission and CSS, mRS, and Barthel Index (BI) at discharge. We used Spearman's rho (r) as a correlation measure between CSS and functional scales.

Results: We observed a good correlation between CSS and functional scales as represented in the following table:

CSS and mRS at admission $r = -0.78$ $p < 0.01$

CSS and mRS at discharge $r = -0.84$ $p < 0.01$

CSS and BI at discharge $r = 0.74$ $p < 0.01$

Conclusions: Neurological deficit measured by CSS correlates well with functional outcome as reflected in mRS and BI. In case of striking discordance between neurological deficit scales and functional scales, other conditions different than stroke (e. g. systemic disease) may be involved.

P726

Usefulness of combination of CT and SPECT in early diagnostics of acute stroke. M. Arkuszewski, S. Ochudlo, G. Opala, B. Jasiñska-Myga, M. Piêta, M. Oewiat, J. Siuda, A. Gorzkowska, E. Krzystanek, Silesian Medical University (Katowice, PL)

Introduction: Computed Tomography (CT) allows showing cerebral haemorrhage, acute stroke and other changes of vascular origin. Single Photon Emission Computed Tomography (SPECT) is sensitive examination (close to 90 %) of cerebral flow disturbances and allows showing acute stroke in early stage, when changes are not observed in routine CT, also shows good correlation with clinical status.

Aim: Evaluation of usefulness of two combined techniques in central nervous system blood flow disturbances imaging.

Material and methods: In year 2001 to our department 250 cases of recent stroke were admitted. Within 12 hours from admitting in all cases CT brain examination was conducted to confirm diagnosis of early stroke. In this group 21 patients were examined using SPECT method within 48 hours.

Results: Brain CT: In 14 cases recent hypodense regions of vascular origin were shown, correlating to localizational diagnosis (sensitivity 67 %). Ischemical brain disturbances not correlating to clinical status were not shown. In 12 cases (57 %)"older" vascular brain damages were shown and in 18 cases (86 %) we observed changes diagnosed as cortical and/or subcortical atrophy. SPECT: In all cases (100 %) focal ischemical deficit was observed in different brain regions. With SPECT we confirmed ischemical changes correlated with clinical symptoms observed in CT in 12 from 14 cases (sensitivity in comparison to CT is 86 %). In 19 cases (90 %) we observed different regions of weak radionuclide binding than corresponding to those shown in CT examination. In this group, in 14 cases (74 %) focal perfusion deficit was in correlation with clinical symptoms, in 4 cases we observed narrowing of the ischemical region in comparison with CT, in 10 cases (53 %) new ischemical regions correlating to clinical signs were shown. Comprising to CT examination, confirmation of clinical localisation of cerebral stroke was established in 6 cases (86 %), among those 7 with normal CT result. In another way, in whole group we diagnosed localisation of recent stroke using both those methods in 20 cases (sensitivity 95 %).

Conclusions: Both described brain imaging techniques are useful in diagnostic process of neurological vascular associated disorders, and the value of them can not be overestimated. Although, those techniques combined in the acute stroke patient evaluation bring much more information about character and size of ischemical process and this method can be recommended in difficult clinical cases.

P727

Psychotic symptoms after stroke: a 3-year follow-up study. A. Verdelho, H. Hénon, F. Lebert, F. Pasquier, D. Leys, University of Lille (Lille, F)

Background: Psychotic symptoms (PS) have been described after stroke, but little is known about their predictors, time-course and relationship with dementia, because they are not frequent. The aim of this study was to determine the prevalence, determinants and time-course of PS occurring after stroke, and their relationship with pre- and post-stroke dementia.

Methods: We prospectively evaluated the presence of PS (defined as hallucinations and delusions), in 202 consecutive stroke patients, followed-up over a 3-year period.

Results: Psychotic symptoms were present in 13 %, 10 %, 7 % and 4 % of the survivors after 6, 12, 24 and 36 months, respectively. Bivariate analysis found PS at month–6 to be more frequent in patients with pre-stroke dementia, severe cerebral atrophy and leukoaraiosis on CT performed at admission, acute confusional syndrome during hospitalization, worse functional status at month–6 and in patients demented at month–6. Logistic regression analysis found leukoaraiosis, right superficial lesions and acute confusional syndrome during hospitalization to be independent predictors of PS at month–6. Bivariate analysis found PS at year–3 to be more frequent in patients with previous history of stroke, higher IQCODE score, severe leukoaraiosis on CT performed at admission, acute confusional syndrome during hospitalization, worse functional status at discharge and at year–3, and in patients demented at year–3. Logistic regression analysis found acute confusional syndrome during hospitalization to be the only predictor of PS at year–3.

Conclusion: PS are not frequent after stroke and are related with dementia at short and long-term follow-up. The occurrence of an acute confusional syndrome during hospitalization predicts PS at long-term follow-up.

P728

Blepharospasm associated with a left thalamic haematoma. A. Verdelho, P. Caldeira, J. Costa, Hospital Santa Maria (Lisbon, P)

Background and purpose: Blepharospasm is a form of focal dystonia characterised by intermittent or persistent, involuntary, usually bilateral eye closure produced by contractions of the orbicularis oculi muscle. Its association with focal brain lesions is rare, and just a few cases of post-stroke blepharospasm were published.

We report a patient with bilateral blepharospasm associated with a left thalamo-mesencephalic haematoma and performed a systematic review of the literature.

Case report: A 50-year-old hypertensive woman without other relevant past history was admitted to our hospital with drowsiness, right hemiparesis and hypoesthesia, and paralysis of vertical and horizontal eye movements with horizontal nystagmus; A computed tomography scan showed a left thalamo-mesencephalic haematoma with slight hydrocephalus. Ten days after admission, while is clinical condition improved, she developed a new-onset bilateral blepharospasm, that was exacerbated by exposure to bright light and watching television. The CT scan performed that day showed improvement of both haematoma and hydrocephalus.

Literature review: We retrieved 12 cases of post-stroke blepharospasm. Lesions were more often located in the thalamus, diencephalon and mesencephalon, but 4 patients had cortical strokes. Blepharospasm was mainly of late onset, between few months and 3 years after stroke.

Conclusion: Blepharospasm has been rarely reported after stroke and neuro-anatomic mechanisms remain unclear. The late development after stroke can make this condition underestimated as a complication after a vascular insult.

P729

Pitfall Raeder syndrome: unexpected cause of multiple cerebral nerve paresis in a patient with acute myelid leukemia. C. Muhl, W. Nacimiento, Wedau Kliniken Duisburg (Duisburg, D)

Introduction: acute paresis of multiple cerebral nerves can be caused by different mechanisms such as cerebral or peripheral ischemia, inflammation or neoplasia. We report a 47-years old man in whom history of acute

myeloid leukemia (AML) masked diagnosis of internal carotid artery (ICA) dissection and led to invasive steps in diagnostics.

Case-report: admission to hospital was due to acute paresis of lower cranial nerves (IX, X, XI,XII)right, combined with a Horner-syndrome of the same side. He reported a central artery occlusion of the right eye two weeks ago with a persisting vision disorder. Further history taking revealed an AML known since 7 years and treated with chemotherapy and radiation. Ultrasound sonography (US)showed occlusion of the right ICA and magnetic resonance tomography (MRT)revealed a space-occupying structure in the soft tissues of the right neck side. These findings hint to the suspicion of a AML relapse and we supposed secondary compression of ICA and the lower cranial nerves IX-XII by the surrounding tissues. Extirpation of cervical lymph nodes showed no abnormal histologic detections and micro-invasive exploration of the right neck side showed no significant tumor in contrast to the initial MRT findings. A further MRI- now with transversal images of the skull base-revealed a vascular wall haematoma of the ICA, typical for dissection, although a passed trauma could not be explored. We diagnosed a Raeder-Syndrome, started an intravenous therapy with heparin and saw a decimalisation of ICA in control US after one week.

Conclusion: a severe pre-existing illness in a patient's history can mislead diagnosis so that another-even also rare – differential diagnosis is not thought of right from the beginning.

P730

Recurrent stroke rates and risk profile in 277 patients. C. Bolcu Emir, M. Gur, Y. Güzey, S. Ozyedek, J. Agaoglu, P. Samurkas, O. Tanik, E. Demiralp, SSK Okmeydani Teaching Hospital (Istanbul, TR)

Background: Recurrent stroke occurs in about 30 % of patients within 5 years and occurs more frequently in stroke patients with higher blood pressures and in the presence of cardiac morbidity. The aim of this study was to identify the recurrence rates, risk factor profile and outcome of the stroke patients.

Method: We retrospectively investigated 277 patients with recurrent stroke (aged 32–86 years of age)who referred to our neurology unit between January 1999 and January 2002. We analyzed the relationship between the patient age, sex, risk factors and recurrence rate in the first year and lesion subtype (large artery and small vessel disease) in all patients.

Results:45.8 % of patients were female and 54.2 % was male. Large artery atherosclerosis was the most common cause of recurrence in middle aged patients (45–70 years) and they showed the highest male predominance. The highest prevalence of hypertension, diabetes mellitus and hyperlipidemia was found in small vessel disease. Cardioembolism was particularly common in patients with a high rate of early recurrence. Another important finding was the high frequency of self withdrawal of the antiplatelet and antihypertensive drug therapy in patients with recurrent stroke.

Conclusion: Prevention of a new stroke after previous strokes requires identification and treatment of people at particularly high risk of recurrent stroke; in other words those with hypertension and atrial fibrillation.

P731

Indomethacine has a toxic effect on the dopaminergic nigrostriatal system. M. Babiuch, I. Kurkowska-Jastrzebska, I. Joniec, A. Przybylkowski, A. Czlonkowski, A. Czlonkowska, Institute of Psychiatry and Neurology, Medical Academy (Warsaw, PL)

Non-steroid anti-inflammatory agents (NSAIDs) are considered to use in brain pathologies including neurodegenerative diseases. They have anti-inflammatory and neuroprotective properties that could be beneficial for neuronal survival in many pathologic conditions. However NSAIDs may exert toxic effect in the brain.

The aim of this study was to investigate the influence of two doses of indomethacin (Ind) on dopaminergic nigrostriatal system.

Mice C57BL received Ind in the doses of 1 mg/kg and 2,5 mg/kg introperitoneally every day during 3 and 7 days. The dopamine content in striatum was measured using HPLC, and the number of dopaminergic neurons, microglia and lymphocytes was counted in the substantia nigra.

Ind diminished dopamine content in striatum and the number of TH positive neurons in the substantia nigra. The injury depended on the dose of Ind and on the duration of administration. On the 3rd day following Ind administration the dopamine depletion was observed but was not statistically significant. There was observed a dopamine content depletion by 19 % for 1 mg/kg and 32 % for 2,5 mg/kg on the 7th day. The decrease of the TH cells number was by 8 % for 1 mg/kg and 14 % for 2,5 mg/kg. The inflammatory reaction consisting of microglial activation and lymphocytic infiltration indicated also dopaminergic neurons injury.

Our observations suggest that NSAIDs may be toxic to some neurons population in the brain. It has to be consider planning clinical trials with NSAIDs in neurodegenerative diseases.

Parkinson's disease and extrapyramidal disorders

P732

Transcranial sonography of the substantia nigra in patients with Parkinson's disease: conventional B-mode versus tissue harmonic imaging. R. Hertel, N. Savyer, A. Kühn, C. Nolte, L. Niehaus, Charité Campus Virchow-Hospital (Berlin, D)

Recently it has been shown that patients with idiopathic Parkinson's disease (IPD) exhibit an increased echogenicity of the substantia nigra (SN) on transcranial sonography (TCS) (Berg et al. 2001, J Neurol 248: 684–9). TCS using conventional B-mode imaging (CI) is limited by low contrast resolution. Tissue harmonic imaging (THI), as a new diagnostic tool, promises a more detailed visualization of parenchymal brain structures on TCS. The purpose of the study was to investigate whether THI is also useful to delineate the SN within the mesencephalic brainstem and to demonstrate abnormal echo pattern in IPD.

Methods: Mesencephalic brainstem was investigated by TCS (Sonoline Elegra, Siemens) in 36 healthy volunteers and 36 patients with IPD. TCS examination was performed with a 2.5 MHz phased-array probe through the temporal bone window using conventional B-mode and tissue harmonic imaging. The SN was visually identified by two investigators separately and the area-size of elevated echogenicity was measured.

Results: The contours of the mesencephalon and the SN were visualized more clearly by THI than by CI. Due to insufficient temporal bone window CI did not demonstrate SN in 19 % of healthy subjects and 8 % of patients with IPD, while THI more frequently failed to show SN in both groups (22 % and 14 %). The mean area-size of SN in healthy volunteers measured by CI was 13.5 ± 3.3 mm§, compared to 11.8 ± 4.0 mm2 when applying THI (not significant). In IPD patients the SN area was significantly larger when using both CI and THI: CI displayed 19.5 ± 4.9 mm2 and THI gave 19.2 ± 6.7 mm2 (CI: $p < 0.05$; THI: $p < 0.05$).

Conclusion: Transcranial ultrasonography may be applied to differentiate IPD patients from healthy subjects by assessing the area size of the SN. Using both conventional and transient harmonic imaging the present study demonstrates that the SN area is greater in IPD patients than in healthy subjects. The main advantage of THI is the improvement of visualization of the mesencephalon and SN. However, its usefulness is slightly more restricted by a higher frequency of insufficient bone windows in comparison to conventional TCS.

P733

A study of the early diagnosis of Parkinson's disease using SPECT imaging with radio-labelled ioflupane. D. Kolokouris, G. Limouris, A. Frantzis, C. Zournas, Aeginition University Hospital, Areteion University Hospital (Athens, GR)

Objectives: Parkinson Disease (PD) is neuropathologically associated with degeneration of the dopamine (DA) cells in pars compacta of the substantia nigra. Loss of DA transporters (DAT) is the first and most serious pathological sign of PD. A SPECT imaging using iodine labelled ioflupane (I-FP-CIT) has the ability to link to DAT and gives us the opportunity to diagnose early PD. Furthermore, it helps to differential diagnosis from essential tremor (ET). It is common knowledge that ET can imitate early PD. The applicability of this ligand is tested in PD patients (less than two years of disease) and healthy volunteers (two of them had ET).

Methods:123I-FP-CIT SPECT was performed in 8 patients with PD and 4 healthy volunteers (2 of them had ET). All PD patients had an asymmetrical onset of the disease and were classified according to UKPDS motor scale and Hoehn and Yahr scale. SPECT imaging was performed 1 and 4 hours after injection of radiolabelled ioflupane.

Results: 1)I-FP-CIT uptake in PD patients was significantly lower comparing to healthy volunteers. More precisely, the index of radioligand binding was 0.6 (SD = 0.23) for left striatum (LS) and 0.51 (SD = 0.13) for right striatum (RS) in PD patients and 0.82 (SD = 0.18) for LS and 0.85 (SD = 0.19) for RS in healthy volunteers. It is important to underline that ET patients had normal indexes. 2) The contralateral striatum of PD patients with asymmetrical onset seemed to present a lower index of binding but this was not statistically significant especially in PD patients with Hoehn and Yahr stage > = 2 in time of imaging. 3) I-FP-CIT SPECT imaging was more accurate 4 hours(hrs) after injection of the radioligand than

1 hr after injection. 4) Total body scan showed that radiolabelled ioflupane had a significant predilection and high binding in lungs.

Conclusion: SPECT imaging can provide a safe early diagnosis of PD and can allow the administration of proper therapy as early as possible. Correlation of the imaging and clinical status of patients according to Hoehn and Yahr scale needs a greater sample. This study is in progress as in Greece I-FP-CIT SPECT imaging is legally used from June 2001.

P734

Lisuride protects and rescues dopaminergic neurons from glutamate toxicity and shows antioxidative properties. G. Gille, A. Uhlig, G. Xu, W. D. Rausch, B. Janetzky, A. Engfer, H. Reichmann, Technical University of Dresden, Veterinary Medical University, Schering Deutschland GmbH (Dresden, D; Vienna, A; Berlin, D)

The dopamine agonist lisuride is an ergoline derivative which binds to D1, D2, D3 and D4 receptors with highest affinity to the D2 receptor. We investigated the potential of lisuride to counteract glutamate toxicity on dopaminergic neurons in primary culture from embryonic mouse mesencephalon. Furthermore, we explored lisuride's potential to inhibit L-DOPA from autoxidation. Differentiated dopaminergic (8 days in vitro (DIV)) neurons were pre-treated with lisuride (0.001–10 microM) for 24 h and 0.5 mM glutamate was added on the 9th DIV for 10 min without lisuride being present. Afterwards, cultures were exposed to 2 days of recovery without any further treatment. Glutamate reduced the number of dopaminergic neurons to 31 %, while lisuride reduced cell loss by 51 % at 0.1 microM. Even when lisuride was added only after glutamate treatment (0.5 mM on the 9th DIV for 10 min) during 2 days of recovery, it rescued dopaminergic neurons from death by reducing cell loss by 54 % at 0.1 microM.

In an in vitro approach we found that lisuride was able to inhibit dose-dependently the autoxidation of 200 microM L-DOPA exposed to light and air. Lisuride suppressed autoxidation by 80 % at 1 mM being even more potent than vitamin C which achieved only 53 % reduction of autoxidation at 1 mM.

These data imply that lisuride exerts neuroprotective effects in primary dopaminergic cultures when added 24 h prior to or even after glutamate treatment. The inhibitory effect of lisuride on L-DOPA autoxidation indicates direct antioxidative properties of the agonist.

P735

Recovery functions in parkinsonian patients studied with paired auditory stimulation. I. Karaban, E. Lukhanina, M. Kapustina, N. Melnik, J. Burenok, Institute of Gerontology, Institute of Physiology NASU (Kiev, UKR)

A large body of evidence has been accumulated showing that the symptoms of Parkinson's disease (PD) are due to imbalance of inhibitory and facilitatory processes in motor cortical circuits. It is shown also that movement disorders of PD patients are connected with sensory disturbances which affect sensorimotor integration. The aim of this study was to analyze postexcitatory cortical inhibition in the auditory system in patients with PD upon paired auditory stimulation. The central (Cz) auditory evoked potentials (AEP) were examined in 10 patients with PD, mean age 60.1 ± 3.0 years, 2.0–3.0 Hoeh-Yahr scale, 4–10 years duration of the disease. As a control 7 healthy age-matched (mean age 57.9 ± 2.6 years) and 9 young (mean age 24.9 ± 0.9 years) subjects were studied. Paired stimuli were delivered at 500, 700, 900, 1100 and 2000 ms intervals. At each interval 20 responses were averaged. Amplitudes of N1-P2 complex in the first (A1) and the second (A2) responses were analyzed and the coefficients A2:A1 were calculated. The Mann-Whitney criterion was used to compare data in the different groups of subjects. In the young and age-matched subjects A2:A1 coefficients had no significant differences. In the young subjects they were equal to 0.47 ± 0.04, 0.56 ± 0.04, 0.61 ± 0.06, 0.74 ± 0.05, 0.92 ± 0.08 and in the age-matched subjects they were equal to 0.56 ± 0.05, 0.56 ± 0.05, 0.63 ± 0.02, 0.78 ± 0.07, 1.00 ± 0.06 for 500, 700, 900, 1100 and 2000 ms intervals respectively. In PD patients these coefficients were significantly increased to 0.71 ± 0.06 ($p < 0.05$), 0.82 ± 0.05 ($p < 0.05$), 0.90 ± 0.05 ($p < 0.01$) for intervals 500, 700 and 900 ms respectively as compared with their age-matched subjects. The latencies and amplitudes of cortical AEPs produced by the single auditory stimuli in patients with PD were normal.

Our data revealed reduction of cortical inhibition in the auditory system in patients with PD. One possible reason is the loss of dopaminergic transmission in the basal ganglia and a dysfunction of the caudal pallidum that sends its direct projections to the medial geniculate nucleus, inferior colliculus and temporal cerebral cortex (Shammah-Lagnado, al. 1996).

P736

Clinicopathological studies of olfactory dysfunction in sporadic and familial 4 repeat tauopathies. Y. Tsuboi, Z. K. Wszolek, R. J. Uitti, D. W. Dickson, Mayo Clinic (Jacksonville, Florida, USA))

Objective: To determine pathologic findings in sporadic [progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD)] and familial 4 repeat tauopathy [pallido-ponto-nigral degeneration (PPND)], correlating these findings with olfactory dysfunction documented during life.

Background: The PPND family has a frontotemporal dementia and parkinsonism linked to chromosome 17 due to N279K mutation in the tau gene. Olfactory function in PPND is profoundly impaired, but normal in PSP and CBD (Wszolek ZK, et al. 1998). Olfactory dysfunction is significantly worse in clinically affected compared with genealogically at-risk individuals in the PPND kindred based upon University Pennsylvania Smell Identification Test (UPSIT) scores (mean UPSIT score of 10.4 in 8 affected versus 28.4 in 8 at risk). While pathological studies of PPND, PSP and CBD have shown numerous tau-positive neuronal and glial lesions in cortical and subcortical regions, histopathological studies of olfactory bulb have not been described in any of these disorders.

Methods: We studied pathology in the olfactory bulb of 27 cases of PSP (mean age 73 years, mean Braak stage 2.0), 3 cases of CBD (mean age 78 years, mean Braak stage 2.3) and 1 patient with PPND (who also had olfactory testing with UPSIT). Tau immunohistochemical staining was used to evaluate olfactory bulb pathology. Neurofibrillary tangles (NFT) and neuropil threads were assessed in the anterior olfactory nucleus (AON) with a semi-quantitative method: 0 = negative;1 = mild; 2 = moderate; and 3 = severe. Correlations were made between AON tau pathology score and Braak stage.

Results: The UPSIT score in the PPND family member was 11 out of 40 (normal > 37). Tau pathology was not detected in the AON of PPND or CBD, but was found in 10 of 27 cases of PSP (37 %). The mean tau score in PSP was 0.5, and all 10 PSP cases with tau pathology in the AON had Braak stages of 2 or 3. The tau pathology score correlated with Braak stage. (Spearman rank order correlation: $r = 0.415$, $p < 0.05$).

Conclusions: No tau inclusions were detected in the AON in PPND, CBD and the majority of PSP cases. Tau deposits in AON in PSP brains correlated with the Braak stage, suggesting that olfactory bulb pathology in 4 repeat tauopathies is a function of concurrent Alzheimer's type neurofibrillary changes. Moreover, olfactory dysfunction in PPND, which may present even in otherwise presymptomatic stages, is most likely due to central, rather that AON, pathology.

P737

L-dopa treatment changes the intracellular dopamine content of peripheral blood lymphocytes in Parkinson's disease patients – are the lymphocytes the Trojan horse in the treatment of Parkinson's disease? C. Rajda, Gy. Dibó, L. Vécsei, J. Bergquist, University of Szeged, Uppsala University (Szeged, HUN; Uppsala, S)

Background and aims: We measured the intracellular content of dopamine and their metabolites in the peripheral blood lymphocyte (PBL) of Parkinson's disease (PD) patients and healthy controls. Assuming that the dopaminergic pathway in the lymphocytes is affected in PD patients, the catecholaminergic content of the lymphocytes might reflect pathological changes early at disease onset, and may tell about the effect of L-dihydroxylphenylalanine (L-DOPA) treatment.

Patients and method: The PD patients were divided into 3 subgroups: 1) without L-DOPA substitution (n = 3); 2) who received a low dose L-DOPA substitution (300–700 mg/day, n = 8,); and 3) who received higher doses of L-DOPA (between 800 and 1050 mg/day, n = 6). The intracellular catecholamine levels of the PBL were measured using capillary electrophoresis with electrochemical detection.

Results: A significant elevation ($p = 0.004$) of intracellular dopamine content of PD patients' lymphocytes receiving high-dose L-DOPA compared to the healthy controls were found, and a significant increase of the dopamine content proved to be in the high L-DOPA dose PD patients versus low L-DOPA dose PD patients ($p = 0.014$).

Conclusion: Our findings suggest that the dopamine metabolism in the peripheral lymphocytes is influenced by L-DOPA substitution by PD patients, and that the metabolism of dopamine differs from the controls, resulting in increased DOPAC levels in PD patients.

P738

Neuropsychological effects of continuous infusion of apomorphine in Parkinson's disease. M. Alegret, M. Pilleri, M. J. Marti, F. Valldeoriola, E. Tolosa, Hospital Clinic (Barcelona, E)

Continuous infusion of apomorphine has been reported to improve motor fluctuations and dyskinesias in advanced Parkinson's disease. However, there is no report about its effects on cognition. So, the aim of the present study was to assess the neuropsychological effects of continuous infusion of apomorphine in Parkinson's disease (PD). A group of 5 consecutive patients candidates for apomorphine treatment were included in the study. We selected a neuropsychological battery sensitive to the cognitive functions usually impaired in PD. The following tests were administered before (3 days) and after (6 months) treatment: Rey's Auditory-Verbal Learning Test, Benton's Visual Retention Test, Stroop Test, Luria's motor alternances, Judgment of Line Orientation, Trail Making, phonetic verbal fluency and Beck's Depression Questionnaire. Comparison between pre-treatment and post-treatment performances were carried out by Wilcoxon's non parametric tests. Results did only show a tendence to improve on Trail Making B ($z = -1.82$, $p = 0.068$). At 6 months follow-up, all patients performed more quickly this task than before treatment. Our results suggest that continuous infusion of apomorphine could increase the speed in solving some prefrontal tasks and it could facilitate the shifting abilities. However, further follow-up is needed to ascertain the effects of continuous infusion of apomorphine on prefrontal function.

P739

The usefulness of double axis accelerometer in assessment of parkinsonian tremor. A. Machowska-Majchrzak, K. Pierzchala, S. Pietraszek, Silesian Medical Academy, Silesian University of Technology (Zabrze, Gliwice, PL)

The aim of the work was development the method supporting the diagnosis of patients with Parkinson Disease (PD) by application spectral analysis of tremor recorded from palm, using accelerometer sensor.

Material: 17 subjects (11 men and 6 women, age 42–81 years, mean 61,1) with clinically confirmed PD and 10 control subjects participated

Method: recordings were performed with the use of double axis accelerometer and computer interface. The sampling frequency was 50 Hz per channel. Sensor was mounted at the dorsal of palm or fingers. Spectral analysis was done in Matlab of line. Signals were bandpass filtered from 1 to 15 Hz using 4 order Butterforth filter. The spectral analysis was done in 10.2 seconds wide epochs, using 512 point FFT and Hanning window. Analysis focused on determination shape of spectrum, the frequency of peak, central frequency, and harmonic index (HI).

Results: In all subjects with clinically confirmed PD the characteristic sharp peak in spectrum was present at frequencies 5,1 to 7,8 Hz. In subsequent epochs the shape of spectrum significantly differs and HI varies from 0,8 to 0,95. In control group the spectrum was wide and consists of many peaks at frequencies from 3 to 8 Hz. The HI was 0,6 to 0,8. In PD patients we observe some difficulties in averaging of spectrum from the epochs, probably due to changes of energy of signal. However, by visual inspection we can select windows with similar spectrum and all the parameters. Now we are working towards evaluation the automatic routines for segmentation of signal.

Conclusion: At the present state of our investigation the spectral analysis of acceleration signal recorded from palm seemed to be promising tool for supporting the diagnosis of Parkinsonian tremor.

P740

A genome-wide linkage disequilibrium screen for Parkinson's disease. T. Foltynie, S. Sawcer, S. Lewis, A. Jonasdottir, A. Hicks, C. Brayne, D. A. S. Compston, R. Barker, Cambridge Centre for Brain Repair, DeCODE, Institute of Public Health (Cambridge, UK; Reykjavik, IS)

Background/Goals: There are a growing number of genes and genetic loci that have been linked or associated with the development of Parkinson's disease (PD). To date, the majority of attention has focused on young onset patients with clear mendelian patterns of inheritance. More recently, genetic risks have been identified for the more common late onset forms of the disease. Employing the methodology and resources derived from the GAMES (Genetic Analysis of Multiple sclerosis in EuropeanS) collaborative we have performed a genome wide linkage dysequilibrium screen to search for further loci associated with all forms of PD. A total of 5511 polymorphic microsatellite repeat markers were typed in 195 UK PD patients and 219 UK blood donor controls, using the pooled DNA method.

Methods: The DNA from 195 UK PD patients meeting Brain Bank criteria was compared to DNA from a population of UK disease free blood donor controls. The polymerase chain reaction was used to amplify pooled DNA from our cases and controls at each of 5511 primers sites. The frequencies of alleles were estimated from the allele image profiles generated after capillary array electrophoresis using Applied Biosystems 3700 machines.

Results and conclusions: Four hundred and ninety two loci revealed a statistically significant difference between cases and controls ($p < 0.05$). Considerable additional analysis will be required in order to determine which of the 492 potential associations are genuine and which result from technical errors in the method, but initial analysis shows that four of the most strongly associated markers are D1S2684, D7S2485, D21S1920, and D12S375. Further populations of PD patients will be required to examine the true importance of these loci.

P741

Effect of chronic bilateral subthalamic stimulation in multisystem atrophy (MSA): a case report. E. Caputo, F. Tamma, M. Egidi, V. Chiesa, M. Locatelli, A. Pesenti, P. Rampini, A. Priori, Ospedale San Paolo, IRCCS Ospedale Maggiore Policlinico (Milan, I)

While Deep Brain Stimulation of the Subthalamic Nucleus (STN DBS)has proved to be effective for the treatment of advanced Parkinson's disease (PD), only a few reports on its effects in parkinsonisms are found in the literature.

We describe the case of a 56-year-old man with a seven year history of MSA, who underwent STN DBS in May 2001. At the time of surgery he had a full blown MSA picture with severe dysautonomic features associated with marked parkinsonism partially responsive to levodopa.

The STN electrical activity detected by intraoperative microrecording didn't differ from the pattern generally found in PD patient. Macrostimulation induced a reduction of rigidity on both sides.

During the present 9 months follow-up, a bipolar stimulation has been choosen and at each follow up visit the effect of different stimulation parameters examined. Clinical evaluation (timed tapping test, repetitive finger movements, rigidity, and blood pressure measurement in recumbent and standing positions) were repeated by the same neurologist. At the end of each visit one single parameter was changed (i. e. frequency, voltage or pulse width) in order to assess its effect after a chronic challenge. For the time being, the best clinical improvement has been obtained at the higher frequencies and voltages. No significant influence of the different parameters on blood pressure was found. Walking hasn't been systematically assessed because the patient was mainly wheelchair bound before surgery. At present, even though still dependent on his wheelchair, he is able to take a slow walk around the block every day, helped by his caregiver.

The overall clinical picture constantly and rapidly worsening just before surgery, appears now to have stabilised after an initial mild improvement.

P742

Continuous subcutaneous infusion of apomorphine in the treatment of advanced Parkinson's disease. M. Pilleri, M. J. Martí, M. Alegret, F. Valldeoriola, E. Tolosa, Hospital Clínic (Barcelona, E)

Continuous subcutaneous infusion of apomorphine (CSIA) has been reported to improve levodopa-induced motor fluctuations and dyskinesias in advanced Parkinson's disease. We present our experience in a series of five Parkinsonian patients.

Patients and Methods: Patients were treated with CSIA using an Apogo driver pump during 16 hours per day. Treatment was optimised progressively increasing the dose of apomorphine and reducing oral antiparkinsonian medication. Levodopa intake was limited to an early morning or nocturnal dose of levodopa. Motor fluctuations and dyskinesias were assessed by through self-reported home diaries and objective evaluations performed by the same clinician every 60 minutes during eight hours using UPDRS III and AIMS scales. Patients were evaluated before treatment application and at six months.

Results: Mean daily dose of apomorphine was 85 mg (ranged 80–120 mg/day). Mean levodopa dose was reduced by a mean 77 % (from 1572 ± 491 to 365 ± 86 mg.day). Mean daily "on" period time increased from 59 ± 17 % to 87 ± 14 % with a parallel increment in the duration of time with dyskinesias. No significant changes were observed the severity and disability of dyskinesias. An improvement of UPDRS-III score was observed in both "on" and "off" condition. Side effect were mild and did not limit the treatment.

Conclusions: This preliminary report confirms the favourable effect of CSIA on motor fluctuations. However, the expected improvement of dyskinesias was not observed in our patients.

P743
Cholinesterase inhibitors can improve cognitive impairment in subjects with parkin gene mutations. R. Marconi, A. Tenerini, S. Carapelli, M. Mancuso, C. Paradiso, Ospedale della Misericordia (Grosseto, I)

Autosomal recessive juvenile parkinsonism (AR-JP) is a disease entity that has been shown to result from the loss of function of the parkin gene. Subjects with mutations of this gene display the typical features of parkinsonism with onset usually as before the age of 40. However, we have observed onset as late as age 58 years in a subject carrying a homozygous exon 4 deletion of the parkin gene. Now, this patient, a 77 years-old man, developed attention deficits, cognitive impairment and visual hallucinations. Global cognitive functions did not improve after levodopa dosage reduction or pergolide withdrawal. Cognitive assessment was performed at baseline by Mini Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale (ADAS-cog). Scales of autonomy in Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) were used to evaluate global deterioration. Motor evaluation was assessed by the UPDRS (part III). Other conditions promoting dementia were excluded. At baseline, the MMSE adjusted-score was = 16, ADL = 1, IADL = 2. The Hachinski Ischemic Score was = 2. A cholinesterase inhibitor, donepezil (5 mg) and subsequently galantamine (8 mg) produced a moderate, prolonged improvement of cognitive functions (31 %) at MMSE, without significant deterioration of the motor signs.

These results suggest that a cholinergic deficit can occur in patients carrying parkin gene mutations and concomitant cognitive impairment.

The observation support the notion that a dysfunction of cholinergic neurons in nucleus basalis of Meynert in the brain of these subjects can be hypothesized. Cholinesterase inhibitors can improve the cognitive state of patients with parkin gene mutations without producing significant motor worsening.

P744
Transdermal slow release apomorphine treatement: a new add-on therapy for motor fluctuations in Parkinson's disease. L. Priano, G. Albani, A. Brioschi, S. Calderoni, L. Pradotto, L. Lopiano, M. Rizzone, B. Bergamasco, A. Mauro, IRCCS Istituto Auxologico Italiano, University of Turin (Piancavallo, Turin, I)

Apomorphine is a potent dopamine agonist used as diagnostic tool and therapeutic drug in Parkinson's Disease, particularly to treat daytime off-periods and severe rise and falls in motor functions. Nevertheless its use is limited by its short time of action and the local side effects.

Objective: Aim of the study was to verify the efficacy on parkinsonian off periods of a new formulation of Apomorphine, administered by an epicutaneous-transdermal route, able to give a constant release of the drug for 12 hours.

Materials and methods: 12 patients with idiopathic Parkinson's Disease, severe motor fluctuations (III-IV Hohen-Yahr stage) and positive Apomorphine test were treated with 30 mg of Apomorphine dissolved in a water-soluble cream, applied to a 100 cm2 area over the anterior part of the chest at 8 a. m. and left for 12 hours. Blood samples were collected at regular intervals from 8 a.m for 14 hours and Apomorphine concentration analyzed by high performance liquid chromatography with electrochemical detection. Motor performances were evaluated at regular intervals during the treatment, on the previous and the following days, using UPDRS scale.

Results: pharmacokinetic analysis confirmed a constant release of Apomorphine (mean rate of absorbtion 160 mcg/h/cm^2; mean Cmax: 35 ± 19 ng/ml, mean Tmax: 290 ± 125 min; duration of effect: 12–14 hours). Clinical improvement showed a mean latency of 45 minute after the application of Apomorphine, reached a maximum 3 hours after the application (mean UPDRS-III score reduction compared to baseline: 8 points) and lasted 12–14 hours (mean UPDRS-III score reduction compared to baseline: 6 points); Mean off periods duration reduced from 4.2 hours to 2.3 hours.

No patient presented severe side-effects; a transient mild erythematous rash in the application area appeared in 75 % of cases, but did not cause the interruption of treatment. One patient had worsening of dyskinesias.

Conclusion: our study suggests that this new route of administration (epicutaneous-transdermal), giving a constant absorption of the drug for at least 12 hours, could be a useful add-on treatment in parkinsonian patients with prolonged, repetitive and not completely controlled off periods.

P744a
Candidate gene research in Tourette syndrome – are there shared genetic susceptibility factors with attention-deficit hyperactivity disorder? S. Schönian, I. König, W. Oertel, H. Remschmidt, A. Ziegler, J. Hebebrand, O. Bandmann, Philipps-University Marburg (Marburg, D)

There is strong evidence for a contributory genetic component in the pathogenesis of Tourette's syndrome (TS). However, all previously undertaken molecular genetic studies have failed to identify a distinct genetic risk factor for this disorder. In contrast, several polymorphisms have been reported to be associated with attention deficit hyperactivity disorder (ADHD): The 480 bp allele of the dopamine transporter gene (DAT1), a Taq-polymorphism (allele 2) in the dopamine-beta-hydroxylase gene (DBH), a 120 bp-tandem duplication (long allele 549 bp) of the dopamine D4 receptor gene (DR4) and the 148 bp allele of the dopamine D5 receptor gene (DR5).

There is clinical overlap between TS and ADHD and the existence of shared genetic susceptibility factors has been suggested. However, this has never been evaluated systematically on a molecular genetic level. We investigated whether any of the above polymorphisms might be associated with TS.

Methods: The polymorphisms in the DAT1, DBH, DR4 and DR5 genes were investigated in 100 triplets (100 triplets with the affected child (index case) and the parents (controls)). Subsequent to PCR amplification, standard methods such as gel electrophoresis, restriction enzyme digest and GENESCAN were used to identify the different alleles. The extended transmission-disequilibrium test (ETDT) was applied to analyze transmission disequilibrium in all triplets.

Results: In all cases the ETDT failed to detect transmission disequilibrium for any of the alleles of DAT1, DBH, DR4 and DR5 in our 100 TS triplets.

Conclusion: Our study failed to identify a shared genetic susceptibility factor for ADHD and TS. Additional polymorphisms are currently being investigated.

General Neurology

P745
Simultaneous spinal chronic hematoma and intracranial hemosiderosis. H. Niederhofer, T. Moroder, General Hospital of Salzburg (Salzburg, A)

Introduction: Spontaneous spinal chronic haematomas are extremely rare (Abla et al., 2000; Chaves et al., 1993; Roricht et al., 1994) and likely combined with chronic intracranial hematomas (Leber et al., 1997).

They may cause paraplegia (Abla et al., 2000; Black et al., 1978). Symptomatology can be reduced by surgical intervention (Khosla et al., 1985; Langmayr et al., 1995).

Extremely rare, chronic spinal subdural hematomes can bleed into the cerebrospinal fluid and cause hemosiderosis. Hemosiderosis typically involves slowly progressive ataxia, hypoacousis and dementia, possibly with pyramidal signs and sphincter disturbances (Stillhard et al., 1993; River et al., 1994; Maggioni et al., 1994; Stevens et al., 1991; Roricht et al., 1994; Lemmerling et al., 1998). It is mainly caused by hereditary ceruloplasmin deficiency (Servan et al., 1998).

Epidural and subdural spinal haematomas can be diagnosed by magnetic resonance tomography (Felber et al., 1994).

Case Report: This case report describes a 60 year old male patient with a chronic subdural haematoma and hemosiderosis, showing cognitive deficits. The effects on psychopathology of a chronic subdural haematoma via hemosiderosis are documented. First symptoms of his course of illness were described as ataxia and disorientation. After having done quite a lot of examinations and analyses, finally cMRI showed arachnoidal hemosiderosis. As a consequence, liquor analysis was performed – and showed siderophages. Additionally, we did – almost at the same time as the liquor analysis – a spinal MRI and found a chronic subdural haematoma.

Conclusions: Spinal chronic subdural haematoma and hemosiderosis might also be the reason for unclear psychopathology, especially disorientation treating patients with unclear disorientation, additionally spinal MRI should be done to exclude chronic spinal haematomas as a possible cause for psychopathology.

P746

Neuropsychological aspects of neurofibromatosis type 1. C.I Badiu, University GR T Popa (Iasi, RO)

Neuropsychological deficits are so common in neurofibromatosis type 1 (NF1) that they are often considered hallmarks of this disease. While the number of reports published on the cognitive phenotype of NF1 is bigger every year, their spectrum and aetiology has not been clarified. The correlation between MRI lesions (unidentified bright objects), migrational abnormalities and neuropsychological findings is still controversial. New evidences suggest that neurofibromin (the NF1 gene protein) has many different actions in regulating the growth and differentiation of various cell types and so, it plays a role in the orderly differentiation of central nervous system neurons.

52 patients (aged 6 to 72 years) with NF1 according to the diagnostic criteria formulated by The NIH CDC Statement Neurofibromatosis (1988) have been evaluated to determine the frequency, severity and spectrum of cognitive deficits due to NF1.

NF1 patients were selected by review of their medical record, physician referral or self referral. Their evaluation included review of family history, physical exam (dermatologic, neurological etc) and in some cases electrophysiological exam (EEG, EP) and imaging investigation (CT, MRI, SPECT). A psychometrical evaluation was performed in all cases.

Intellectual assessments using the Wechsler Scales demonstrated a mild intellectual impairment in the majority of the NF1 patients included in this series (mean full scale IQ = 83.4). However, 7 patients were mentally retarded. There was no discrepancy between verbal and performance IQ. Most frequent these NF1 patients presented attention deficits (33 cases). A significant number of cases had an impairment of the visual-spatial functions (31 cases). The different language disorders (expressive and/or receptive)seen in 20 cases were less frequent and better preserved than visual-spatial skills. Planning skills deficiencies and memory deficits have been identified. Clinical aspects like age, sex, family history or severity of dermatological, neurological etc manifestations were weakly correlated with cognitive deficits.

Executive function difficulties including planning, attention, flexibility etc, which are often hidden cause of school failure, have been seen frequently in this series, confirming the importance of a full neuropsychological assessment in NF1 children. The results obtained emphasize the heterogeneity of cognitive dysfunctions in NF1 and the need for a psychoeducational intervention.

P747

Transient rotational vertigo revealing a middle cerebral artery territory infarct. S. Debette, E. Michelin, H. Henon, D. Leys, University of Lille (Lille, F)

Background: Acute rotational vertigos secondary to stroke lesions involving the vestibular cortex are less well known than those due to a brainstem lesions or temporal epilepsy. A single case with an acute rotational vertigo in a middle cerebral artery infarct has been reported in a patient with a cardiac source of stroke. We report here a second case in a patient with cervical artery dissection.

Case report: A 51-year old man developed cervical pain and right ptosis after having carried heavy loads. Two weeks later he suddenly experienced a severe transient rotational vertigo with nausea followed by a left hemiplegia. A cerebral magnetic resonance imaging scan revealed an infarct in the territory of the middle cerebral and anterior choroidal arteries. Duplex ultrasonography of the cervical arteries revealed an occlusion of the right internal carotid artery. A magnetic resonance angiographic scan demonstrated a mural haematoma, suggesting a right internal carotid artery dissection. The patient was treated with anticoagulation. Two months later the only residual deficit was a slight body tilt to the left.

Conclusion: Rotational vertigos can be the consequence of a lesion located anywhere on the vestibular pathways, between the inner ear and the vestibular cortex, including the auditory nerve, brainstem structures and thalamic sub nuclei. In Humans, the vestibular cortex is not well known. However there is increasing evidence that the parietoinsular cortex receives vestibular afferents. Vestibular syndromes of supratentorial origin remain scarce. This case shows that the occurrence of an acute rotational vertigo in a patient with a middle cerebral artery infarct is not necessarily due to an associated brainstem infarct nor vestibular epilepsy.

P748

Paraplegia after ligation of esophageal varices. S. Debette, J-Y. Gauvrit, H. Henon, D. Leys, University of Lille (Lille, F)

Background: a case of spinal infarct has already been described in a patient who underwent endoscopic sclerotherapy of oesophageal varices: the suggested mechanism was a regurgitation of the prothrombogenic sclerosant into the spinal veins and hemodynamic changes. Nowadays, variceal ligation is the first line therapy in oesophageal variceal hemorrhages, and is usually well tolerated. We report the first case of paraplegia occurring after an endoscopic variceal ligation without sclerotherapy.

Case report: A 65-year old man with alcoholic cirrhosis, developed a motor deficit in the left leg three days after endoscopic variceal ligation for active bleeding from oesophageal varices. Three days later, he described an acute back pain rapidly followed by a flaccid paraplegia. A magnetic resonance imaging scan revealed 2 hemorrhagic lesions appearing as areas of higher intensity on T1- and T2-weighted images, in the central part of the spinal cord, without any abnormality of the vertebral body. Arguments sustaining the hypothesis of a venous infarction with hemorrhagic changes are the clinical features, the location of the lesion in the central part of the spinal cord, presence of hemorrhagic changes, the extension of the lesion along the spinal cord, and the lack of associated infarct in the vertebral body.

Conclusion: The possible occurrence of a spinal venous infarct after endoscopic ligation of oesophageal varices suggests that hemodynamical changes alone may also induce spinal strokes, in the absence of sclerosant drugs.

P749

Central pontine myelinolysis and potassium level. S. Diez, U. Beck, M. Jurgeleit, Neurologische Praxis, Zentrum für Psychiatrie (Calw, Bad Wildbad, D)

Central pontine myelinolysis (CPM) has often been described as a consequence of rapid changes in serum sodium levels. Some publications demonstrate that CPM appears also in patients with normal sodium levels. Only a few case reports show that disturbance in serum potassium can also be linked to CPM.

We present a patient who was admitted with paranoid psychosis which was due to heavy drinking. During psychiatric treatment potassium level rose from 2.2 mmol/l to 6.2 mmol/l. The reason for this increase remained unexplained. No i. v. fluids were given. A small dose of potassium was administered orally for two days. After discharge paranoid symptoms had improved. The patient remained anxious and depressed. One week after discharge she developed spasticity and hypokinesia and was therefore seen by the neurologist. CT scan and MRI scan showed central pontine myelinolysis. Spasticity as well as depression improved steadily without specific treatment. On a follow up MRI after five months the pontine lesion was partly improved. Spasticity and psychiatric symptoms were completely normalized.

The literature is reviewed in view of CPM in patients with potassium disturbances and in view of CPM in patients with normal sodium. The roles of rapid potassium changes and other pathogenetic factors are discussed.

P750

Recurrent headache and sixth nerve palsy associated with lumbar ependymoma. K. M. Gormley, N. J. Gutowski, Royal Devon and Exeter Hospital (Exeter, UK)

A 39 year old man presented with neurological symptoms three times over two years. Each episode started with mild low back ache for two days followed by a gradual onset of generalised throbbing headache with vomiting lasting up to 9 days. There was no previous history of migraine or back pain. The only neurological sign was a transient left sixth nerve palsy during the last two more severe episodes. The first episode resolved quickly without investigation. Cerebrospinal fluid (CSF) examination on the subsequent two episodes showed blood stained fluid and the CSF glucose was less than half the serum value. Cerebral angiography and brain Magnetic Resonance Imaging (MRI) were normal. Endocrine screening, including pituitary function and catecholamine levels were normal. An elective lumbar puncture after resolution of the last episode revealed bloodstained fluid but a CSF glucose greater than half the serum value. As each episode started with backache a spinal MRI was undertaken. This showed an enhancing heterogeneous intra-dural mass at L3/4, which at surgery proved to be an ependymoma. The temporal relationship of back ache followed by headache and sixth nerve palsy suggest that the trigger to each episode was bleeding from the previously unrecognised lumbar ependymoma.

P751

Progressive multifocal leukoencephalopathy (PML) presenting as Epilepsia partialis continua (EPC). J. Berciano, C. Leno, J. Figols, A. García, J. M. Polo, A. Ariza, University Hospital Marqués de Valdecilla, Hospital German Trias i Pujol (Santander, Badalona, E)

The aim of this work is to describe the clinical features of a non-immunocompromised PML patient presenting with EPC. This right-handed 45-year-old woman presented, in March 2000, with clumsiness and myoclonic jerks in her right hand. Serial examination from May to October showed continuous myoclonus mainly involving flexo-extensor finger muscles and progressive right hemiparesis. Routine laboratory investigations, HIV serology, antineuronal antibodies and serum tumour markers were normal or negative. Two cerebrospinal fluid studies revealed normal results; neither oligoclonal bands nor JC virus DNA were detected. EEG recordings showed an initially normal background activity and left fronto-rolandic discharges of sharp theta waves occasionally correlated with thenar myoclonic jerks. Simultaneous electromyographic recording from extensor and flexor right forearm muscles showed synchronous and almost continuous bursts at 6 to 13 Hz, which were present at rest and during movement. Central motor conduction after magnetic stimulation was normal to the left abductor pollicis brevis muscle and unobtainable to the right. Six serial MR imaging studies (June 2000 to March 2001) showed a non-expansive and non-enhancing lesion, which initially involved the left subcortical white matter of motor region and afterwards the opposite motor region. In November brain biopsy showed an inflammatory process characterized by extensive macrophage infiltrates often with perivascular distribution, here accompanied by T lymphocytes, demyelination and astrocytosis; no oligodendroglial inclusions were observed. A diagnosis of adult-onset Rasmussen encephalitis was entertained. Sequential treatment with pulses of methylprednisolone and cyclophosphamide and IVIG was administered with no response. As of October 2000 identical semeiology occurred on her left extremities culminating in quadriplegia and complete bulbar palsy. In spite of this she remained lucid until her death in June 2001. Autopsy revealed the characteristic findings of PML mainly involving both parietal regions There was severe demyelination and gliosis more marked in the cortico-subcortical edge. The cerebral cortex showed mild inflammation but was otherwise normal. Numerous oligodendroglial intranuclear inclusions positive for JC virus were observed. We conclude that, although exceptional, PML should be considered as a possible cause of new-onset EPC even in non-immunocompromised patients.

P752

An unusual case of lumbar radiculopathy. S. Peters, M. Schöllhammer, R. Grabs, W. Pennekamp, St. Josef Hospital (Bochum, D)

A 34 year-old male presented to our emergency room with an acute left-sided L4 radiculopathy with pain in the L4-dermatome, weakness of knee extension and leg adduction and absent knee jerk.

One month prior, the patient had received a gunshot wound to the left lower abdomen, necessitating diagnostic laparotomy with partial resection of the perforated colon descendens. The bullet, lodged at the left anterior surface of the fourth lumbar vertebra, had been surgically removed via a dorsal approach. The patient had been inconspicuous postoperatively.

Emergency MRI of the abdomen revealed a pseudoaneurysm of a left-sided lumbar artery at the fourth lumbar vertebra. The finding was confirmed on an ensuing abdominal aortogram, and endovascular embolization with coils was performed. MRI controls disclosed successful embolization of the aneurysm. The patient immediately recovered.

The etiology of lumbar radiculopathy in this case was compression of the fourth left lumbar root by a traumatic pseudoaneurysm of an adjacent lumbar artery.

Pseudoaneurysms of lumbar arteries usually present secondary to vessel injury, and are an entity seldom on reported to date. To our knowledge, this is the first reported case following civilian gunshot injury. These lesions can entail potentially life-threatening complications and are often difficult to access and manage operatively.

Computed tomography and magnetic resonance imaging readily visualize the extent of accompanying hemorrhage and contrast-enhanced magnetic resonance angiography is effective in delineating the lesion. Endovascular coil embolization is a safe and proven therapy for artery aneurysms, and has been applied to the treatment of lumbar artery pseudoaneurysm in the past. The great advantage of coil embolization is the avoidance of the necessity of general anesthesia and difficult operative dissection. In treating lumbar aneurysms, the origin of the arteria radicularis magna (Adamkiewicz) and the lumbar artery collateral network must first be assessed to avoid severe neurological injury secondary to spinal ischemia.

This case demonstrates an unusual cause of posttraumatic lumbar radiculopathy. Since, however, spontaneous and life-threatening lumbar artery pseudoaneurysm formation has also been reported in the past, particularly in the elderly, one should consider this entity, albeit rare, in the differential diagnosis of etiologically obscure lumbar radiculopathy.

P753

Marchiafava-Bignami's disease complicated by difficult-to-treat status epilepticus but favorable outcome. D. Ulbricht, R. J. Metz, F. Macian, G. Dooms, Centre Hospitalier de Luxembourg (Luxembourg, LUX)

We describe a case of MBD presenting with Status epilepticus (SE) and an anterior callosal lesion. Marchiafava-Bignami's disease (MBD) is a rare disease complicating long-lasting chronic alcoholism. The clinical picture in the acute stage is non-specific in comprising impressive fluctuations of agitated and apathetic behaviour as well as seizures. Historically, the diagnosis could only be made at autopsy; nowadays it is made by means of MRI, which demonstrates centrocallosal necrosis.

A 42 year-old Italian consumed 1 bottle of red wine at home and lots of Whisky in his pizzeria for several years. Due to a divorce, he stopped drinking wine. Soon, he became unusually quiet and was admitted on psychiatry for therapy of alcoholism. After 2 days, he developed generalized tonic-clonic SE and was transferred on the ICU. Control of SE was achieved only after 2 weeks. He carried over severe dysathrophonia being merely able to communicate, ataxic gait, left-handed diagnostic dyspraxia and profound apathia. MRI disclosed an anterior callosal lesion highly suggestive of MBD. EEG showed slight right temporal focal irritability without any clinically apparent seizures. In SPECT, there was general hypometabolism and a small hot spot in the right temporal lobe. Therapy included Phenobarbital, Phenytoine, and vitamin substitution, especially high dosed Vitamin B1 und B12. At one-year follow-up, the patient regained nearly complete autonomy but was not able to return to work yet.

Long-lasting SE in our patient complicated MBD. Both carry an elevated lethality. For SE, there is strong epidemiological evidence, whereas the notion of elevated lethality of MBD might be the result of the diagnostic before the advent of MRI. Whether more alcoholics carry MBD is unknown, as is the pathophysiology, which seems to be alcoholic pseudopellagra or direct toxicity in susceptible individuals as shown in animals. The frequent seizures or even the SE in MBD might result of an acute necrosis of the CC with acute loss of inhibitory fibres disinhibiting an instable cortex provoked by alcohol cessation. The presence of an only anterior callosal lesion is atypical but did not show up with an anterior disconnection syndrome. At the other hand, the lesion is not compatible with that seen in chronic epileptics where a non-specific splenial hyperintensity has recently been described. Despite severe SE there was a satisfying outcome, which is in favour of the pseudopellagra as causal factor of MBD.

P754

Posterior reversible encephalopathy syndrome with moderate hypertension. I. Bonnaud, J. P. Cottier, D. Saudeau, B. De Toffol, A. Autret, Hopital Bretonneau (Tours, F)

Background: Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiological entity, recognized in several medical conditions. It has been reported in patients with mild but abrupt elevations in blood pressure.

Case report: A 33-year-old woman had a medical background of smoking, obesity, and moderate untreated hypertension. She experienced headaches of increasing intensity and nausea during two days, followed by a generalized seizure. At admission, she was drowsy, and complained of severe headaches, nausea and blurred vision. Blood pressure was 180/80 mm Hg, and then increased at 220/120 mm Hg after two hours. A CT scan examination was performed and considered as normal, CSF examination was normal. Diagnosis of cerebral venous thrombosis was suspected and an anticoagulant treatment was initiated. The day following her admission, an angio-MRI examination was performed and disclosed, in T2 weighted images, bilateral thalamic and parieto-occipital hyperintense lesions, evoking an ischemic process. Intracranial vessels seemed to be normal. Anticoagulant therapy was stopped. Blood pressure hovered in the 180–220/80–100 mm Hg range. Calcium channel antagonists and diuretic drugs were introduced. Blood pressure normalized and all symptoms resolved completely within two days after initiation of antihypertensive therapy. A second MRI examination, performed six days after the first one, showed only a small parieto-ocipital hyperintense signal remaining in T2 weighted sequences. Two months after discharge, MRI examination with diffusion weighted sequences, was normal, confirming the diagnosis of PRES.

Discussion: PRES associates symptoms such as headache, vomiting, visual disturbances, altered mental status, seizures and rare focal neurological signs. Other diagnostic hypothesis, such as cerebral venous thrombosis, or ischemic" top of the basilar " syndrome, may be considered in this clinical picture. Imaging findings show diffuse hyperintensity in the parieto-occipital white matter, basal ganglia, brainstem and cerebellum, representing extra-cellular oedema. PRES can occur during immunosuppressive therapies, in hypertensive encephalopathy, and also with moderate hypertension, and its pathophysiological mechanism remains debated.

Conclusion: PRES should be considered even with mild elevation in blood pressure, because prompt initiation of antihypertensive treatment can lead to complete clinical recovery with reversal of MRI lesions.

P755

Atypical presentation of aortic aneurism: ischemic rhabdomyolisis, vertebral body infarction and lumbar radiculopathy. M. Braga, M. Ferrarini, M. Pederzoli, G. Casati, M. Repaci, P. Bazzi, S. Beretta, V. Crespi, Ospedale Civile di Vimercate (Vimercate, Milan, I)

Embolisms of aortic aneurysms with intraluminar clots are frequent; they induce ischemic damage predominantly in lower limbs. Ischemic damage of lumbar root and muscles, a frequent complication after surgery, is a rare form of clinical presentation.

Case description: A 51 years old man was admitted in the neurological ward because of the acute onset of low back pain associated with gait impairment. Neurological examination showed asymmetric proximal limb paraparesis. Deep tendon reflex were reduced in left limb. In the lumbar region hemorrhagic skin changes were also observed. Routine blood examination showed increase of creatine kinase (CK) levels (1000 U/L). Electrophysiological examination revealed mild signs of denervation in lower limbs predominantly in the left side. Spinal MRI, using 1 T superconductive scanner, 3 hrs after the beginning of symptoms was unremarkable, CT abdominal scan demonstrated abdominal aneurysm (diameter 4.5 cm) with intraluminal clots and enlargement of the left psoas muscle. At the third day, CK raised the level of 27 000 U/L and then slowly decreased. Increase of CSF protein was also observed. Two months later, spinal MRI showed abnormal bone marrow signal in L2, L3 and L4 vertebral bodies, predominantly on the T2 weighted images. CK were normal, and electrophysiological evaluation detected denervation in lumbar root L2-L4. After two months follow-up the neurological examination showed proximal asymmetric weakness predominantly in the left lower limb. A follow-up abdominal CT scan demonstrated a evident hypotrophy of both psoas muscles with focal signal alteration suggestive for ischemic damage.

Conclusions: In our best knowledge there are only few reports about lumbar muscle ischemic rhabdomyolysis as presentation of aortic aneurism. Lumbosacral radiculopathy was also infrequent. Vertebral body infarction were previously reported in association with spinal infarcts and only rarely with lumbar root damage.

P756

Report of a Tunisian family with autosomal recessive form of neurodenerative disorder. F. Bahri- Ben mrad, R. Gouider, M. Fredj, A. Mrabet, Charles Nicolle Hospital (Tunis, TN)

The authors report clinical and paraclinical findings of a Tunisian family suffering from an autosomal recessive form of neurodegenerative disorder. Two brothers, 32 and 34 year-old, developed in childhood intentional tremor, bilateral cerebellar syndrome followed by progressive intellectual impairment. Pendular nystagmus with altered deep tendon reflexes are observed in one patient. This family was characterised by intrafamilial variability of age at onset, clinical presentation and course of the disease.

Sensory evoked potentials (SEP) and visual evoked potentials (VEP) were altered. Electromyography (EMG) showed a mild neurogenic pattern. T2 cerebral MRI revealed bilateral low signal intensities of palladium, substantia nigra, red nuclei associated to a high signal intensities of white matter, cerebrum and cerebellum atrophy.

Clinical features combined to the above MRI abnormalities seems to be related to a olivopontocerebellar atrophy with autosomal recessive inheritance. Wilson disease is ruled out by normal plasma levels of copper and coeruloplasmin. The mode of inheritance and cerebellar MRI findings (low signal intensities of palladium and substantia nigra) oriented to Hallervorden-Spatz syndrome but clinical features are not common in this disease.

P757

Autosomal dominant spastic paraplegia, deafness, peripheral neuropathy and optic atrophy: new entity? S. Chebel, S. Boukhris, A. Boughammoura, M. Frih-Ayed, University Hospital of Monastir (Monastir, TN)

We report clinical and electrophysiological features of a large Tunisian family including 11 affected patients suffering from a particular form of spastic paraplegia with deafness, peripheral neuropathy and optic atrophy. The inheritence was autosomal dominant. The clinical phenotype was heterogenous it is caracterized by an onset during first or second decade, a progressive course and variable association between patients of spastic paraplegia, peripheral neuropathy, visual and hearing loss. The reported syndrome can be a new entity and genetic analyses will classify this family.

P758

Clinical and neuroimaging features in myelopathy induced by vitamin B12 deficiency. R. Gentile, L. Capone, G. Tabiadon, R. Pentore, Regional Hospital (Bolzano, Carpi, I)

Three patients affected by cervical myelopathy caused by vitamin B12 deficiency are reported. The first patient (male, 73 years old) had partial gastrectomy because of peptic ulcer 20 years ago. The second (female, 55 years old) and the third patient (male, 47 years old) had positive antibodies against the gastric wall cells. All the patients complained paresthesiae with glove and sock distribution, ascending from feet to thoracic level in two of them, and to cervical in the last one. At the neurological evaluation the first patient showed impaired distal touch and pin-prick sensation, with glove and sock distribution, without deficit of warm and cold perception. The second and the third patients had no superficial sensitivity impairment. Deep sensitivity (joint position and vibration sense) was affected in the first two patients. The first patient showed ataxia of gait and limbs, particularly in the upper extremities, that worsened closing the eyes. The second one had only oscillations in Romberg position. The third patient complained a subjective difficulty in controlling the left arm movement. No sign of neuropsychological impairment was found in all patients. A T2-hyperintense and T1-hypointense lesion was found at magnetic resonance (MR) study in the posterior part of the cervical spinal cord, involving in the second and third patient also the upper dorsal segment. Cerebral MR and cerebrospinal fluid were normal. Laboratory showed macrocytosis without severe anaemia and reduced Vitamin B12 levels in serum. Parenteral therapy with high dosage Vitamin B12 was performed in all patients. The clinical feature gradually improved with the treatment. At a follow up after 1 and 6 months MRI study showed an evident reduction of spinal cord T1- and T2- lesion and the patients reported a subjective and objective improvement of their neurological symptoms.

Comment: Undernutrition, particularly vitamins deficiency, causes a wide spectrum of neurological disorders. Vitamin B12 deficiency is a treatable cause of isolated spinal cord lesion. In these cases macrocytosis was the laboratory marker of gastric malabsorption of Vitamin B12.

Neuro-immunology

P759

Nigrostriatal degeneration caused by MPTP intoxication is reduced by autoimmune response followed by MOG 35–55 administration in the C57BL/6 mice model. E. Balkowiec-Iskra, I. Kurkowska-Jastrzebska, I. Joniec, A. Muszynska, A. Przybylkowski, A. Czlonkowska, A. Czlonkowski, Medical University of Warsaw, Inst. of Psychiatry and Neurology (Warsaw, PL)

Neuroinflamation has recently been shown to be a condition that makes a contribution to tissue injury in neurodegenerative diseases.

Inflammation is an important feature of experimental autoimmune encephalomyelitis (EAE), which is exemplified by the infiltration of immune cells and expression of inflammatory mediators in the brain and in the spinal cord.

MPTP (1-methyl–4-phenyl–1,2,3,6-tetrahydropiridine) produces a dopamine content depletion in the striatum and the degeneration of dopaminergic cells in the substantia nigra (SN). The injury is followed by inflammatory reaction, characterised by glial activation, lymphocytic infiltration and the increase in proinflamatory cytokines level.

The aim of the present study was to determine, whether autoimmune reaction (achieved by immunization with 150 micrograms of MOG 35–55 peptide in complete Freund's adjuvant (CFA) supplemented with 500 mi-

crograms/ml of Mycobacterium Tuberculosis in concert with immediate and 2 days after administration of 300 nanograms of Bordetella pertussis toxin) can promote survival or deterioration of dopaminergic neurons injured by MPTP intoxication. 6 days after immunization with MOG 35–55 peptide, mice received MPTP-HCl in a dose of 40 mg/kg, as control mice, which had not been immunised. Mice were sacrificed on the 3rd and 7th day after MPTP administration. Using HPLC method we examined dopamine levels in the striatum isolated from mice treated both with MOG 35–55 peptide and MPTP (MOG+MPTP) and compared with dopamine levels in the striatum isolated from mice treated only with MPTP. Mice MOG+MPTP had higher dopamine level by 32 % than mice from MPTP group and the difference appeared to be statistically significant ($p < 0.001$). Verification with TH (tyrosine hydroxylase) staining confirmed HPLC results.

This study indicates that active immunization with myelin-associated peptides prior to intoxication with MPTP leads to dopaminergic neurons' protection.

The protective effect of CNS inflammation shows a new approach to neurodegenerative diseases treatment.

P760

Influence of nigrostriatal degeneration caused by MPTP on clinical symptoms of experimental autoimmune encephalomyelitis (EAE) in the C57BL/6 mice model. I. Kurkowska-Jastrzebska, E. Balkowiec-Iskra, I. Joniec, A. Muszynska, A. Przybylkowski, A. Czlonkowski, A. Czlonkowska, Inst. of Psychiatry and Neurology, Medical University of Warsaw (Warsaw, PL)

It has been shown, that central dopaminergic system alters the immunological response.

In the present study we investigated an effect of nigrostriatal degeneration caused by 1-methyl–4-phenyl–1,2,3,6-tetrahydropiridine (MPTP) on clinical course of EAE.

Mice C57BL/6 received 4 i. p. injections of MPTP to the total dose of 40 mg/kg. 7 days after intoxication when the dopamine level was about 40 % less in this group comparing to control, they had EAE induced (MPTP/EAE group). Animals were injected subcutaneously in the flank with MOG 35–55 peptide (150 micrograms) in complete Freund's adjuvant (CFA) supplemented with 500 micrograms of Mycobacterium Tuberculosis. Bordatella Pertussis toxin was administered iv, in a dose of 300 ng immediately after immunization and 2 days later. The control group was injected with 0,9 % NaCl and than it had EAE induced in the same manner. Each group consisted of 8–10 animals.

Mice were observed daily for 50 days and clinical manifestations of the EAE were scored on a scale of 0–5 (0, no clinical signs; 1, flaccid tail; 2, hind-leg paralysis; 3, hind-leg paralysis with lower body paresis; 4, hind-leg and foreleg paralysis; 5, death).

The control group started the first symptoms on the 9th day after immunization. Animals had 2 relapses each of about 1.5 mean score. Mice, from EAE/MPTP group started the first symptoms earlier than the control group (on the 6th day), animals had 3 relapses, each clinically more severe than the control.

Our results showed, that the nigrostriatal dopaminergic system has strong influence on autoimmune response induction and course.

P761

Behçet's disease presenting as transverse myelitis with novel demonstration of immune complex vasculitis. J. Lynch, O. Hardiman, P. Brennan, M. Farrell, C. Quigley, M. Keogan, Beaumont Hospital, Wexford (Dublin, IRL)

Neurological involvement in Behçet's disease occurs in 5–30 % of cases. The pathogenesis of the condition is unclear.

We describe a 47 year old female who presented with features of a transverse myelitis. There was no significant past medical history. General examination was otherwise normal.

Lumbar puncture revealed 400 leukocytes (90 % lymphocytes, 10 % neutrophils), an elevated protein (174 mg%) and low CSF glucose. CSF analysis for Lyme disease, HIV, HSV, VERL, Entero and ECHO viruses was negative. Serum autoantibodies including dsDNA, ANA, anti Ro, anti La and anti cardiolipin were negative. An MRI of spine showed a signal change from T8-T10. Brain MRI showed gadolinium-enhancing lesions in the left medulla, pons, right midbrain and left temporal lobe. There was no improvement with steroid therapy.

A stereotactic brain biopsy was performed of a discrete gadolinium enhancing lesion. Histology demonstrated a marked perivascular and transmural lymphocytic infiltrate. Direct immunofluorescence demonstrated C3, IGF, kappa and lambda granular positivity in medium sized cerebral vessels extending into the perivascular areas. These findings strongly suggested an active lymphocytic vasculitis with immune complex deposition.

Two months following presentation the patient developed oro-genital ulceration, bilateral swollen knees and pathergy reaction at intravenous injection sites, thus fulfilling the diagnostic criteria for Behçet's disease.

This patient illustrates that Behçet's disease can present with exclusively neurological signs, and that this diagnosis should be considered in the differential of an otherwise unexplained inflammatory process in the CNS. Furthermore, the definitive evidence of vasculitis and immune complex deposition in the CNS arterioles indicates that the pathogenic process in neuro-Behcet is B-cell mediated vasculitis. This observation argues strongly for the use of drugs with specific anti-B cell activity as the first line treatment of neuro-Behcet disease.

P762

Experimental autoimmune encephalomyelitis in beta–2 microglobulin knockout mice: insights into the role of CD8 positive T-cells in chronic inflammatory disease of the central nervous system. R. A. Linker, E. Rott, H. Hofstetter, T. Hanke, K. V. Toyka, R. Gold, Klinische Forschungsgruppe für Neuroimmunologie, Institut für Immunbiologie (Würzburg, D)

Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system (CNS) which was traditionally thought to be mainly mediated by CD4 positive T-cells. Recently there is accumulating evidence that also CD8 positive T-cells may play a role in disease pathogenesis. To further assess the role of CD8 positive T-cells we investigated experimental autoimmune encephalomyelitis (EAE) in beta–2 microglobulin knock-out mice (ß2m -/- mice). These mice are deficient in functional major histocompatibility complex I (MHC I) molecules and also lack MHC I restricted CD8 positive T-cells. ß2m -/- mice do not exhibit a spontaneous phenotype. EAE was induced in ß2m -/- mice or C57BL/6 control mice either with myelin oligodendrocyte glycoprotein (MOG) peptide 35–55 or whole rat myelin basic protein (rMBP). Mice were followed clinically and further studied by T cell proliferation assays, ELISPOT, and immunocytochemical analysis of inflamed spinal cord.

For both antigens, disease course in ß2m -/- mice was more severe with an increased mortality of the knockout mice as compared to littermates. There was no difference in disease incidence or onset of disease between both groups. Lymph node lymphocyte proliferation assays did not show a differential priming of immune cells after immunization either with MOG peptide or rMBP. Blinded analysis of hematoxylin/eosin staining did not reveal any significant difference in the extent of inflammatory infiltrates in ß2m -/- mice. Also, infiltration of CD3 positive T-lymphocytes was similar in ß2m -/- mice as compared to control mice after induction of EAE with MOG 35–55 or rMBP. However, the infiltrate in ß2m -/- mice was characterized by a statistically significant increase in Mac–3 positive cells. These data may explain the more severe disease course, speaking for a predominant macrophage and microglia infiltration in ß2m -/- mice. The functional consequence on cytokine production in situ is demonstrated by ELISPOT analysis. Thus disturbed immune regulation as a consequence of lack of functional MHC I molecules and CD8 positive T-cells aggravates autoimmunity in the CNS.

P763

Changes in cytokine serum levels and white blood cell counts during high-dose glucocorticoid therapy in patients with inflammatory diseases of the nervous system. T. Kümpfel, M. Gottschalk, T. Pollmächer, C. Trenkwalder, F. Weber, Max-Planck-Institute of Psychiatry, Universitätsklinik Göttingen (Munich, Göttingen, D)

Corticosteroids are widely used for the treatment of inflammatory diseases of the nervous system (NS), mainly of suggested autoimmune origin, but their actions and interplay within the immune system are still not well understood. In this study we investigated the time course of white blood cell counts and cytokine serum levels during high dose methylprednisolone (MP) pulse therapy in patients with inflammatory diseases of the NS.

Fifteen patients, 10 patients with multiple sclerosis (MS) in acute relapse, 5 patients with other acute inflammatory diseases of the NS (OND), were treated with 500 mg MP i. v. each day for 5 days. Blood samples were collected every morning at baseline, on day 1, 2, 3, 5 and on day 7 after therapy. Differential white blood cell counts were determined on each day and cytokine serum levels of tumor necrosis factor-alpha (TNF-alpha), soluble TNF-receptors p55 (sTNF-RI) and p75 (sTNF-RII), interleukin–6 (IL–6), interleukin–10 (IL–10), interleukin–1 receptor antagonist (IL–1ra) and soluble interleukin–2 receptor (sIL–2r) were quantified using commercial enzyme linked immunosorbent assays.

MP-therapy induced an increase in granulocyte counts which was par-

alleled by decreased lymphocyte counts. While granulocyte count remained high during the whole observation period, lymphocyte count increased above baseline levels at the end of therapy. Serum levels of TNF-alpha and sTNF-RII decreased significantly during MP-therapy, but returned to baseline levels on day 7 ($p < 0.05$). IL–6 levels were reduced only after the first administration of MP, while sIL–2r concentrations increased significantly after the first therapy before gradually returning to baseline levels. Serum levels of sTNF-RI and IL–1ra were not significantly affected by glucocorticoid therapy at all. IL–10 serum levels were below the detection limit in several blood samples and could therefore not be used for statistical analysis. Besides higher baseline cytokine concentrations in OND patients there were no detectable differences between MS patients and patients with OND.

In summary our results demonstrate that high dose glucocorticoid therapy exerts heterogenous effects on white blood cells, cytokines and soluble cytokine receptors, which may contribute to its efficacy in the treatment of inflammatory diseases of the NS. All values, however, returned to baseline after treatment, which indicates, that the corticoid induced changes of the investigated parameters are short.

P764

Anti-Tr like reactivity in a woman with cerebellar ataxia without tumor. R. Fazio, D. Ginocchio, M. Maianti, A. Quattrini, S. Previtali, E. Brambilla, G. Martino, G. Comi, S. Raffaele Hospital (Milan, I)

We describe a 38 year old woman suffering from a worsening cerebellar ataxia since may 2000.

In September 2000 the patient was admitted to our Hospital and her neurological examination disclosed a rotatory and vertical nystagmus, slurred speech, hypotonia, dysmetria and dysdiadococinesis in all four limbs, difficult standing and walking without supports. No sensitive abnormalities were present. Serum laboratory findings were negative except for the presence of high titer of anticerebellar antibodies with a course granular cytoplasmatic staining of Purkinje cells and molecular layer cells. and the same autoantibodies were also present in the CSF were oligoclonal bands were found. Western Blot analysis on cerebellar proteins failed to reveal any positivity. By laser confocal microscopy the immunoreactivity of patient serum was found localized in the cytosol of molecular layer neurons and in the Purkinje cell bodies and dendrites as anti-Tr antibodies. Brain MRI was negative. During the nine months follow-up, total body CT scan and Bone Marrow biopsy failed to reveal any lymphoproliferative disease.Our patient (a woman) was the first having an anti-Tr like reactivity without evidence of a tumor since 9 months from the appearance of the serum and CSF cerebellar autoantibodies.

P765

Suppression of EAMG by IL–10-modified dendritic cells. H. Link, Y. Huang, B. Xiao, Karolinska Institute (Stockholm, S)

Dendritic cells (DC) are usually regarded as antigen-presenting cells involved in T cell activation. Directly or indirectly, DC also affect B cell differentiation, antibody production and isotype switch. Under certain conditions, DC even silence T cell immune responses. The search for ideal tolerogenic DC for the treatment of autoimmune diseases has just begun. In this study, we used DC derived from Lewis rats during incipient experimental autoimmune myasthenia gravis (EAMG), exposed these EAMG-DC in vitro to IL–10, and used thus IL–10-modified EAMG-DC to treat ongoing EAMG in Lewis rats. IL–10-modified EAMG-DC effectively suppressed clinical signs of EAMG, accompanied with decrease of body weight loss. Rats injected with IL–10-modified EAMG-DC, compared to rats injected with medium only, showed reduced expression of the co-stimulatory molecules CD80 and CD86, decreased T cell proliferation, lowered IL–10 and IFN-gamma secretion, as well as reduced numbers of anti-AChR IgG antibody secreting cells and decreased affinity of serum anti-AChR antibodies. These results indicate that DC modified in vitro by exposure to IL–10 and, thereby, made tolerogenic, could be important for future therapy of antibody-mediated autoimmune diseases like myasthenia gravis.

P766

Erdheim-Chester disease: a new treatment trial for a rare chronic progressive systemic lipogranulomatous disease? V. I. Leussink, K. Schmidt, D. Brechtelsbauer, K. V. Toyka, B. Allolio, University of Würzburg (Würzburg, D)

Introduction: Erdheim-Chester disease is a rare progressive disease of unknown etiology characterized by lipoid granulomatosis and histiocytic proliferation. Multiple organ systems including the musculoskeletal, cardiac, pulmonary, endocrine and nervous system can be affected. The most frequent CNS symptoms reported include diabetes insipidus, cerebellar ataxia and dysarthria.

Case report: We present a 49-year-old male patient who developed knee and shoulder pain over years, followed by gynecomastia. Erdheim-Chester disease was diagnosed by characteristic radiological and histological findings. Endocrinological testing revealed primary hypogonadism and hyperprolactinemia. A year after diagnosis, the patient noted progressive fatigue, impairment of memory and unsteadiness of gait. Neurological examination showed neuropsychological and cognitive deficits, cerebellar dysarthria and ataxia. Brain magnetic resonance imaging (MRI) showed multiple enhancing masses in the brainstem with meningeal involvement, in the cerebellum, supratentorial hemispheres and neurohypophysis. Since treatment with glucocorticosteroids, cyclophosphamide and mycophenolatmofetil had not been effective in halting the progression of clinical and paraclinical disease course with worse neuropsychological deficits and new orbital lesions on MRI, we started therapy with pioglitazone, a thiazolidinedione derivate, which activates peroxisome proliferator-activated receptor-g (PPAR-g). Under this treatment regimen supplemented by testosterone substitution and symptomatic therapy of the cerebellar symptoms, clinical and paraclinical examinations remained stable over a follow-up time of one year.

Conclusions: We here describe neuropsychological and affective deficits in a patient with Erdheim-Chester disease accompanied by cerebellar and endocrine dysfunctions and musculoskeletal symptoms showing the clinical variability of this rare systemic lipogranulomatosis. Immunosuppressive treatment with glucocorticosteroids, cyclophosphamide, or mycophenolatmofetil appears to be of limited value in halting the disease progression. Pioglitazone, a novel antidiabetic thiazolidinedione derivate with agonistic effects on PPAR-g, is a promising new tool by modulating macrophage lipid metabolism. Further longitudinal studies are necessary to evaluate the long-term effects of pioglitazone in Erdheim-Chester disease.

P767

Anti-GAD cerebellar ataxia: good response to high-dose steroids and IVIG. G. Lauria, G. Capri, P. Pitzolu, D. Pareyson, National Neurological Institute, National Cancer Institute (Milan, I)

Autoantibodies to glutamic acid decarboxylase (GAD) have been recently recognized as a rare cause of autoimmune cerebellar ataxia. Treatment response of patients with autoimmune disease is still anecdotal. We describe a patient with cerebellar ataxia related to anti-GAD antibodies who showed a dramatic response to high-dose intravenous steroids and a further improvement with intravenous immunoglobulin (IVIG). A 66-year-old woman, with autoimmune hypothyroidism for 6 years, complained of blurred vision and progressive gait unbalance since March 2001. She reported a mild progression of symptoms during the next 6 months, followed by a more severe worsening over 4 weeks that led to inability to walk and stance without assistance, oscillopsia, and left arm clumsiness. She complained also of episodic painful muscular spasms in the thigh during the night. On admission, neurological examination showed gaze-evoked down-beat nystagmus, marked gait ataxia and dysmetria on left-side finger-to-nose test. International cooperative ataxia rating scale (ICARS) score was 30. Cerebral magnetic resonance showed mild atrophy of cerebellar vermis. High-titer anti-GAD antibodies were detected in the serum. Gastric parietal cell and low-titer IgA anti-gliadin antibodies were also found. Cerebrospinal fluid (CSF) examination showed 9 cell/mmc and 68 mg/dl protein, without intrathecal IgG production. Celiac ataxia was ruled out by digiunal biopsies and HLA typing. Screening for malignancies, including total-body positron emitted tomography was negative. Two weeks later, the patient had a subacute worsening of the neurological symptoms: she became wheelchair-bound with severe trunk ataxia and developed all limb dysmetria, persistent nystagmus, dysarthria, increased tendon reflexes and muscle tone in lower limbs, and bilateral Babinski sign. ICARS score was 60. Methyprednisolone (1000 mg/day i. v) was administered for 5 days and tapered off in 3 weeks. Soon after steroid therapy was started, the patient showed a dramatic improvement of the clinical picture. ICARS score was 36 at one-month follow-up visit. Later, she complained of mild worsening of ataxia, oscillopsia, and nocturnal muscular spasms. Repeat CSF examination showed 1.6 cells/mmc and 51 mg/dl protein. A trial of IVIG (0.4 g/kg/day for 5 days) caused a further improvement.

P768
Effect of WIN 55,212–2, a synthetic cannabinoid agonist, on apoptosis of lymphoid cells in experimental allergic encephalomyelitis. A. Sánchez, C. Puerta, P. Ortiz, P. Baranda, A. García-Merino, Hospital Puerta de Hierro (Madrid, E)

Background: Experimental allergic encephalomyelitis (EAE) is a neuroinflammatory disease used as a model of multiple sclerosis (MS). In EAE, apoptosis is a mechanism involved in the balance of activated immune cells. Cannabinoids may play a role in the regulation of several aspects of EAE. Type 1 receptor (CB1) is found predominantly in the CNS; type 2 receptor (CB2) is expressed in the immune system. We have previously reported that the distribution of CB1 receptors is modulated in cortical and striatal neurons during the course of EAE. In contrast with results reported elsewhere with tetrahidrocannabinol(THC), we found in previous experiments that WIN 55,212–2, a synthetic agonist of CB1 and CB2, not only did not suppress active EAE in rats, but made the outcome worse. In an attemp to correlate these observations with the survival of lymphoid cells, we studied the effect of this drug on the apoptotic rate of lymp node cells (LNCs).

Materials and Methods: Male Lewis rats were immunized with guinea pig myelin basic protein and treated daily with a single intraperitoneal dose of WIN 55,212–2 (2 mg/kg body weight), starting on day 0 post inoculation (PI). Rats were examined daily for the presence of neurological signs. Animals from each group were sacrificed on day 10 PI and LNCs were obtained after removal of the popliteal and inguinal lymph nodes. Apoptosis was detected by annexin-V staining and FACS analysis.

Results: On day 10 PI, no neurological signs were observed in any of the two groups. Compared to untreated EAE rats, apoptosis of T (CD3+) and B (CD45+) cells was significantly decreased in WIN 55,212–2 treated rats.

Conclusions: The extended survival of lymphoid cells from the draining lymph nodes might explain the protracted clinical course and the worse outcome of the animals treated with this cannabinoid agonist.

Infection of the nervous system

P769
'Neurological manifestations of tuberculosis: clinical and radiological heterogeneity. J. de Seze, L. Deligne, L. Defebvre, D. Ferriby, P. Charpentier, T. Stojkovic, A. Destée, P. Vermersch, Hopital R. Salengro (Lille, F)

Neurological manifestations of tuberculosis are rare, especially in immunocompetent subjects. The heterogeneity of clinical and radiological features induces frequently a delay for diagnosis.

Aim of the study: To study clinical and radiological presentation of 12 cases of neuro-tuberculosis and to evaluate clinical outcome.

Methods: We performed clinical, CSF, MRI and outcome evaluation in all patients. We also performed a mycobacterium analysis by polymerase chain reaction (PCR).

Results: Patients were 7 women and 5 men with a mean age of 45.4 years. Clinical presentations were meningeal symptoms in 10 cases and focal manifestations in 5 cases. CSF was abnormal in 83 % of cases (protein increase in 75 %, pleocytosis in 67 %, decrease CSF glucose level in 50 % and chlorure levels in 42 %). The best diagnostic test was PCR (positive in 50 % of cases). CSF cultures were positive in only 2 cases (17 %). Only 2 patients had chest involvement. MRI was abnormal in 67 % of cases (pseudotumour, arachnoiditis, vascular lesions or medullar involvement). Outcome was good in all cases but two (one patient died and one patient had paraplegia due to delay of diagnosis).

Conclusion: Neurological manifestations of tuberculosis are extremely various in term of clinical and radiological presentation. Outcome is frequently favourable if any diagnostic delay is avoided.

P770
Meningitis by Gemella morbillorum with associated pituitary apoplexy. E. Villegas, J. De Otero, L. Ferrer, B. Oms, F. Ferrer-Ruscalleda, M. Sandiumenge, Hospital Creu Roja (Barcelona, E)

Gemella morbillorum is a commensal microorganism of the human gastrointestinal, respiratory, and genitourinary tracts. The spectrum of disease is very similar to that caused by S. viridans, although the microorganism seems to be rarely associated with infections other than infective endocarditis and bacteremia. We report a case of meningitis due to G. morbillorum followed by hypophyseal hematoma with pituitary apoplexy, and secondary panhypopituitarism.

A 56-year old man was admitted to our hospital with a five-days history of severe headache and vomiting. Two days before admission he developed fever (39–40˚C) and malaise. The initial exploration showed very bad status, slight confusion and nucheal rigidity. A cranial CT scan was normal. Cerebrospinal fluid (CSF) analysis showed pleocytosis, hyperproteinorraquia and normal level of glucose. The gram stain was negative. Intravenous therapy with cefotaxime was started. A week after admission the patient acutely developed an impairment of headache and clinical status, with left hemianopsia. The MRI showed acute hypophyseal hematoma, with optic chiasm compression and lateralization, compression of cavernous sinus, and maxillary, sphenoid, ethmoid and frontal sinus ocupation, suggesting the diagnosis of pansinusitis. Laboratory tests confirmed a panhypopituitarism and therapy with dexametasone was started. CSF culture revealed growth of G. morbillorum and antimicrobial treatment was changed to benzilpenicillin, ceftazidime and clindamycin. After two days the general condition and neurological status improved greatly. Antibiotics were administered for 15 days and the patient was discharged in good condition. No relapse was observed.

Human infections caused by G. morbillorum are extremely rare. In fact, only two previous cases of meningitis by this microorganism are reported in the literature. Furthermore, our patient suffered a pituitary apoplexy, a very unusual complication of sepsis and meningoencephalitis. Despite its rarity, our case suggests that the pathogenecity of G. morbillorum should not be underestimated.

P771
The duplicity of cerebral gumma: neurosyphilis in an older married couple. M. von Ekesparre, A. Thie, Krankenhaus Itzehoe (Itzehoe, D)

Despite the increase of neurosyphilis in recent years, few cases of magnetic resonance imaging (MRI) in neurosyphilis have been reported. Among these, frontal and temporal atrophy, ischemic lesions or non – specific white matter lesions are the most common features. Case reports on cerebral gumma are much more rare.

We report on two immunocompetent patients with neurosyphilis. A 62 – year – old woman presented with mild personality change and cognitive deficits one year after neurosurgical extirpation of a presumed astrocytoma grade II. MRI showed widely extending oedema of the same hemisphere with cortical enhancement. Spinal fluid analysis suggested neuroborreliosis to prompt intravenous (i. v) treatment with ceftriaxone. Further studies revealed false – positive results because of cross – reactivity to active neurosyphilis. Treatment with ceftriaxone was continued for three weeks. Three months later, spinal fluid and MRI were almost normal correlating to clinical improvement. We postulate that the extirpated "tumour" was a cerebral gumma.

Two months later, the husband of our patient, aged 62, was admitted to hospital because of psychopathological decline. MRI revealed a polycystic tumour located in the right frontotemporal hemisphere with perifocal oedema. Again, spinal fluid analysis revealed neurosyphilis with cross – reactivity to neuroborreliosis. Treatment with penicillin G i. v. every 4 hours was administered for three weeks. First follow – up results of MRI and spinal fluid showed an improvement.

The two patients emphasize the need to consider neurosyphilis in cerebral mass lesions and in inflammatory disease mimicking neuroborreliosis. Serological cross – reactivity must be accounted for. Differential diagnosis of "cerebral tumour" on MRI should include cerebral gumma.

P772
Optic neuritis and Guillain-Barré syndrome after Mycoplasma pneumoniae infection. R. C. Ginestal, J. F. Plaza, J. M. Callejo, N. Rodriguez-Espinosa, J. Masjuán, L. C. Fernández-Ruiz, Hospital Ramón y Cajal (Madrid, E)

Introduction: Infections may be complicated by acute inflammatory demyelination in the peripheral nervous system (PNS), central nervous system (CNS) or both of them. Association between Mycoplasma infection and acute optic neuritis has been rarely described, and a condition in which that syndrome is followed by an acute polyradiculoneuropathy has not been reported yet. We report a case of Guillain-Barré syndrome (GBS) after bilateral optic neuritis, following an acute Mycoplasma pneumoniae infection.

Case report: A 69 years old man was admitted to our hospital. Two weeks before low grade fever and sore throat developed. No antibiotics were given. The patient improved in a week. Two days before admission he had noticed progressive bilateral loss of vision. Examination only revealed a severe loss of visual acuity (he could only see fingers at 30 cm distance)and low reactive pupils. Both optic discs were swollen. Blood sedi-

mentation rate was 88; all others haematological and biochemical parameters were normal. Brain MRI was normal. At this time he was treated with methyl-prednisolone, 60 mg daily. With an important improvement of visual acuity (right eye 5/10, left eye 3/10), on the 8th hospital day, the patient complained of progressive weakness and paresthesias at the four limbs. An areflexic quadriparesis followed. Lumbar puncture showed 4 leucocytes and 0,85 g/l of proteins. A five days course of intravenous immunoglobuline was started on day 10. Later on, an electromiography showed an axonal motor polyradiculoneuropathy. Biochemical, immunological, infectious, endocrinological and toxic parameters were normal or negative, except for serum Mycoplasma pneumoniae Ig M and cryoglobulines. 44 days after admission the patient was discharged walking on his own with mild paraparesis and moderate visual loss.

Discussion: There have been a few reports of relationship between optic neuritis and GBS. Mycoplasma pneumoniae infection is known to be associated with PNS and CNS complications. Coexistence of optic neuritis with GBS due to Mycoplasma pneumoniae infection has been described only twice. Both of them began with areflexic quadriparesis and a few days later complained of visual loss. In our patient, optic neuritis had become clear in advance (10 days) before GBS developed. This chronological order has not been reported previously.

P773

Neuroborreliosis presenting with myelopathy. M. Schuepbach, M. Steinlin, M. Sturzenegger, Inselspital (Bern, CH)

Introduction: Common manifestations of neuroborreliosis are polyradiculitis and lymphocytic meningitis. The spectrum of symptoms and signs which may be attributed to chronic neuroborreliosis is disputed.

Patients and methods: We present six patients (3 women, 3 men) who were admitted to our clinic (University Dept. of Neurology with a catchment area of 1.4 million people) with a spastic ataxic gait disorder between 1992 and 2001, and who turned out to have neuroborreliosis. Requirements for the diagnosis of neuroborreliosis were: positive serology in serum and cerebrospinal fluid (CSF), inflammatory CSF changes and favourable response to antibiotic therapy.

Results: Mean time from onset of symptoms to correct diagnosis was 6.5 years (range 4 months to 17 years). The mean age was 43 years (range 16 to 76 years). CSF pleocytosis (30 to 191 mononuclear cells) and increased protein were found in all patients, hypoglycorrhachia in 3/6. IgG against Borrelia Burgdorferi was positive in all CSF specimens, IgM only in one case. CSF/serum index of specific IgG was diagnostic in 4/6. All patients had accompanying symptoms of encephalopathy (fatigue, headache, dizziness, neuropsychological abnormalities). Myelitic signs consisted in paraspastic ataxic gait, paraparesis, sensory loss (mainly vibration sense), and voiding disturbances of bladder and bowel. The longer the interval from onset to diagnosis, the more severe was the clinical picture. The longer the course of the illness, the less pronounced was the response to i. v. therapy with ceftriaxone. Improvement of clinical and CSF findings began clearly noticeably during the first weeks of treatment and continued gradually over years, yet none of the patients completely recovered.

Conclusion: A predominantly paraspastic picture due to neuroborreliosis is rare, and the aetiology may not be considered for years, resulting in irreversible neural damage. The upper limbs were much less affected in our patients. The diagnosis is established by CSF analysis with signs of inflammation and a CSF/serum index of specific antibodies > 0.3. Because early treatment with i. v. ceftriaxone has a favourable outcome, neuroborreliosis must be considered in all patients with acute or chronic myelopathy and CSF analysis should be performed.

P774

Neurocysticercosis: old disease and new problem in Spain. R. Merino, S. Escalante, S. Monteagudo, J. Gracia, P. Barreiro, E. Díez Tejedor, University Hospital La Paz (Madrid, E)

Objectives: Neurocysticercosis (NCC) is the most common parasitic infection of the central nervous system. We studied if the increase of immigration of people from endemic areas has caused an increase in the incidence of this parasitic disease in our country.

Methods: Patients diagnosed of NCC from January 1995 to November 2001 based on proposed diagnostic criteria for neurocysticercosis Committee (Absolute criteria) was included. Neuroimaging studies and inmunologic tests for the detection of anticysticercal antibodies were used. We analyzed frequency, risk food, place of birth, residence or travel history and clinical manifestations.

Results: 11 cases, 7 women and 4 men, has been reported with ages among 18–45 years. There is a variation of frequency from < 1 case/year to 7 cases/11 months (annual increase > 10). 45'5 % of the patients consumed risk food. 81'8 % came from endemic areas. 90'9 % were diagnosed of parenchymal brain cysticercosis and only 9'1 % extraparenchymal neurocysticercosis.

Conclusions: Immigration of people from endemic areas (Latin America) has caused a recent increase in the incidence of neurocysticercosis in our country. On the other hand, we have to suspect NCC in young people with epidemiological risk and seizures.

P775

Intrathecal administration of fluconazole in the treatment of cryptococcal meningitis. W. Chenghan, Y. Bosheng, W. Huayian, Nr. 2 People's Hospital (Fujian, CHN)

Abstract: Objective: To evaluate the efficacy and safety of intrathecal administration of fluconazole FCZ) in the treatment of cryptococcal meningitis.

Methods: Of the 45 patients with cryptococcal meningitis, 15 received intravenous FCZ (group A) and 30 received intrathecal FCZ therapy combined with intravenous FCZ (group B), seven of them with especially high intracranial pressure received spinal administration blockade at L4–5 was placed epidural catheter with subarachnoid drainage, other two patients added to ventricular drainage.

Results: In group A, 7 patients were cured, 1 improved, 7 fail to respond, and the total effective rate was 53.3 %. In group B, 24 cured,2 improved, 4 fail to respond, and the total effective rate was 86.7 %, the group B were more effective than group A($P < 0.05$).Of the 7 patients treated with subarachnoid drainage, 6 were cured, 1 improved. Other 2 patients added to ventricular drainage were cured.

Conclusion: the efficacy and safety of intrathecal administration of fluconazole (FCZ) were obvious and causes less side effacts. Subarachnoid drainage and ventricular drainage were effective methods in the treatment of severe cryptococcal meningitis and reducing high intracranial pressure.

Motor neuron disease

P776

Reversible ALS-like disorder in Hashimoto disease. D. Kountouris, Center For Neurological Diagnosis (Athens, GR)

We describe the clinical features, treatment and outcome of one case which shows the symptomatology of ALS simultaneously with Hashimoto.

Case report: Over a period of 4 years one patient who suffers from Hashimoto, has been reviewed for symptomatology of ALS. El-Escorial criteria were used for the identification of the patient and the seriousness of his disease, as well as with the clinical features of electromyography (EMG), CSF, blood test and virological studies.

Results: An immunosuppressive treatment (CD4 cell = 84,2 mm3) showed a significant clinical improvement of symptoms according the El-Escorial criteria. The direction of ECGs that was monitored particularly with the density of a muscle fibre, a clear improvement was observed with a corresponding improvement in Hashimoto condition.

Conclusion: This case shows that there is a link between ALS and Hashimoto. This may suggest that both diseases have an immune mechanism which is responded in immunosuppressive treatment and cortisone

P777

Coupling of grip force and load force during dynamic object manipulation in amyotrophic lateral sclerosis. D. A. Nowak, J. Hermsdörfer, H. Topka, Akademisches Lehrkrankenhaus München-Bogenhausen (Munich, D)

Background: Moving a grasped object involves predictive grip force adjustments for fluctuations in inertial loads. The anticipatory grip force adjustments to movement-induced load fluctuations suggest that motion planning is based on an internal model of both the limb dynamics and the physical object properties.

Methods: In the present study we analysed grip force control in a patient with Amyotrophic Lateral Sclerosis (ALS) and in three healthy sex- and age-matched control subjects. ALS is a progressive degenerative disorder of motor neurons in the spinal cord, brainstem and motor cortex. All participants performed vertical arm movements with an instrumented hand-held object. During the discrete up and down movements the object was held stationary.

Results: The patient produced significantly greater grip forces than the control subjects to hold the object in between single arm movements. In addition, the patient produced greater maximum grip forces and a greater force ratio between maximum grip and load forces during movements in both vertical directions. When performing the arm movements, the patient showed an earlier rise in grip force when making downward movements compared to the controls.

Conclusion: From these observations we conclude that in ALS the ability to scale the grip force magnitude in an economical way according to the actual loading requirements is impaired. In addition, there may be a particular problem in predicting movement-induced inertial load profiles and to adjust the grip force profile accordingly.

P778

Progressive autonomic dysfunction in amyotrophic lateral sclerosis and effects of intrathecal BDNF. M. Beck, P. Flachenecker, T. Magnus, W. Wuerffel, R. Giess, K. Reiners, M. Naumann, K. Toyka, University of Wuerzburg (Wuerzburg, D)

Objective: Amyotrophy lateral sclerosis (ALS) is a multisystem degenerative disorder predominantly affecting motoneurons. Dysfunction of the autonomic nervous system has been described early in the course of the disease. However, it is unclear whether and to what extent there is progression of autonomic function in these patients, and whether therapy by intrathecally administered brain derived neurotrophic factor (BDNF) has an effect on autonomic function.

Patients and Methods: Sudomotor (sweat rate by vapour pressure gradient), parasympathetic (heart rate responses to Valsalva manoeuvre, deep breathing and active change of posture), and sympathetic vasomotor function (blood pressure responses to active change of posture and sustained handgrip[BP-grip])as well as supine serum levels of epinephrine (EPI) and norepinephrine (NE) were studied in 13 ALS patients participating in a placebo-controlled study of intrathecally administered BDNF (5 women, 8 men, aged 53.0 ± 12.4 years, mean ALS function rating scale [ALSFRS] score 34 ± 4, mean vital capacity [VC%]94.0 ± 7.6). The battery of autonomic tests was performed before and after 9 months on treatment. After unblinding, results of patients treated with BDNF (25 or 150mcg/day, n = 8) were compared to those treated with placebo (n = 5).

Results: In all patients sudomotor function significantly worsened within the follow-up period (55.4 vs. 38.9 g/m2h, $p < 0.03$), as did median BP-grip (19 vs. 15mmHg, $p < 0.02$). Similarly, results of cardiovagal tests were lower at follow-up although statistical significance was missed. Median EPI levels tended to be lower after 9 months (41 vs. 32ng/l, $p < 0.08$). However, median NE levels significantly increased within that period (255 vs. 691ng/l, $p < 0.005$) indicating higher exertion due to progressive disability. When comparing data of BDNF treated patients with placebo-patients as controls no statistically significant differences in change of any autonomic parameter were found between both groups.

Conclusions: In all ALS-patients sympathetic and parasympathetic nervous system function deteriorate during the follow-up period. This occurs independently from treatment with BDNF.

P779

Reversible diffuse motor neuron syndrome related to bacille Calmette-Guerin (BCG) treatment for local bladder cancer. P. Sánchez-Juan, C. García-Penco, J. Calleja, J. Berciano, J. Pascual, University Hospital Marqués de Valde (Santander, E)

Background and objectives: There are some data suggesting an involvement of the immune system in motor neuron disorders (MND). We report on a patient who developed a diffuse, reversible MND after BCG immunotherapy.

Case report: In 1990 this 64-year-old man was diagnosed as having local bladder neoplasm. In June 1999, he had a second local relapse, BCG therapy then being started. Two months later he developed malaise, dysphagia, progressive diffuse weakness, muscle twitching and 12-kg weight loss. He denied sensory loss or bladder dysfunction. Examination disclosed diffuse amyotrophy, spontaneous fasciculations in all four limbs and mild generalized weakness. Tendon reflexes were somewhat brisk. Sensory exam was unremarkable. Electromyography showed 3 or more fasciculation potentials in 4 out of 5 examined muscles. Conduction velocities and F-waves were normal. Extensive laboratory determinations, thoracic and abdominal CT and cranial and spinal MRI showed no abnormalities. He continued to worsen, becoming wheelchair bound. He received no treatment. In June 2000, he spontaneously began to improve and in March 2001 both physical and neurophysiological exams were normal.

Conclusions: We hypothesize that this patient, in the course of a hypersensitivity process against BCG antigens, developed an autoimmune reaction directed to motor neurons, which induced a reversible amyotrophic lateral sclerosis-like clinical syndrome. These clinical features support a role for autoimmunity in the pathophysiology of MND in some patients.

P780

Selective vulnerability in amyotrophic lateral sclerosis – impact of calcium-binding proteins. S. Probst-Cousin, M. Bergmann, B. Neundörfer, D. Heuß, Centre of Neuromuscular Disorders, Institute of Clinical Neuropathology (Erlangen, Bremen, D)

Clinically, amyotrophic lateral sclerosis (ALS) usually presents as a pure motor system disorder, whereas oculomotor control as well as control of sphincter muscles of the anus and the bladder appear to be spared. The molecular factors contributing to the exemption of the motor neurons of the cranial nerves III (NO), IV and VI as well as the Onufrowicz nucleus (ON) remain to be defined. Previous investigations demonstrated lacking expression of calbindin and parvalbumin in vulnerable motor neurons compared to the above mentioned nuclei, suggesting a role of calcium-binding proteins (CBP's) in their selective vulnerability in ALS.

The annexins comprise a family of CBP's, which are believed to exert functions in calcium-homoeostasis, membrane trafficking, transmembrane channel activity, and intracellular modification of calcium-regulated pathways. Studies on rat spinal cord tissue showed a differential expression of annexins 1–6, however, data on human material is only very limited so far. We compared the expression patterns of annexins in different neuronal populations in ALS-cases to investigate whether these CBP's might also contribute to the selective vulnerability in this disorder.

Post mortem tissues (especially midbrain and S2-level spinal cord) from 24 ALS patients and 5 age-matched controls without neurological disease were investigated by immunohistochemistry for expression of annexins 1, 2, 4, 5, 6 and 7. 16 patients were male, 8 patients were female. Age of death varied between 26 and 82 years (62,6 years) and the duration of disease ranged from 4 to 64 months (24,1 months). Clinically, 6 cases represented primary lateral sclerosis, 6 cases were progressive spinal muscular atrophy, one case showed progressive bulbar palsy, and 11 cases combined the above. Neuropathologically, neuronal losses in ON or NO were not observed.

Annexin 1 was expressed in ependymal cells and motor neurons. Annexin 2 could be detected in ependymal cells, endothelial cells and motor neurons. Annexins 4 and 5 were found in both ependymal and glial cells. Annexin 6 was strongly expressed in motor neurons as well as in ON and NO. Annexin 7 appeared to be totally absent from central nervous system tissue. These expression patterns did not vary between ALS cases and controls.

The expression patterns of annexins suggest individual functions of these CBP's. A role of annexins in the selective vulnerability in ALS, however, could not be derived from these observations.

P781

The involvement of dopamine peroxidation in the pathogenesis of Parkinson's disease. A. De Iuliis, A. P. Burlina, R. Boschetto, P. Zambenedetti, N. Pennelli, L. Galzigna, University of Padua (Padua, I)

Background: A characteristic autoptic finding of Parkinson's disease (PD) is a depigmented substantia nigra with loss of melanized neurons. Neuromelanin, for long considered as a waste product of catecholamines, has been recently investigated for its possible protective role due to its power of chelating toxic metals and iron in particular. A required precursor of neuromelanin is dopaminochrome, a toxic quinone produced by oxidative cyclization of dopamine catalyzed by peroxidizing enzymes. Recently, we have demonstrated the presence of an enzyme specifically responsible for such a reaction in nigral dopaminergic neurons of the rat. Furthermore, the presence of a crude dopamine peroxidizing activity was demonstrated in the autopsied substantia nigra of normal human brain.

In the present study, to evaluate the possible involvement of this enzyme in PD, we have analysed the dopamine peroxidizing activity and dopamine concentration in post-mortem samples of midbrain and basal ganglia from subjects with PD.

Materials & Methods: The crude activity was determined spectrophotometrically in extracts of paraffin-embedded obtained from autopsied brain (5 control brains, mean age 65 years; and 5 PD brains, mean age 76 years). No addition of substrate was necessary since endogenous substrates such as dopamine and hydrogen peroxide were present in the samples. Dopamine concentration was determined by High Performance Liquid Chromatography with electrochemical detection.

Results: In PD midbrains the dopamine peroxidizing activity (dpa) was substantially increased compared to normal midbrain (PD dpa mean value = 789 µmol/min/mg protein; control dpa mean value = 249). Dopamine concentration was 31 and 62 nmol/L (mean value) in the midbrain of PD and control samples respectively. Moreover, the dopamine peroxidizing activity, which was absent in basal ganglia of control subjects, was always detectable in those of Parkinson's patients (PD dpa mean value = 529 µmol/min/mg protein; dpa control mean value = 0). Dopamine concentration was 43 and 54 nmol/L(mean value)in the basal ganglia of PD and control samples respectively.

Conclusion: These observations confirm that a selective peroxidizing pathway of dopamine is present in human brain. Furthermore, our results suggest that an increased peroxidase activity in the autoptic brain of PD patients, resulting in the production of the toxic compound dopaminochrome, may play a role in the pathogenesis of this disease.

P782

Oropharyngeal dysphagia in motor neuron disease: investigation of pathophysiology, progression and critical analysis of diagnostic procedures. D. Kidney, M. Alexander, M. Harney, O. Hardiman, Beaumont Hospital (Dublin, IRL)

Oropharyngeal dysphagia is well-recognised as a clinical feature of motor neurone disease (MND). However, the pathophysiology and progression of this clinical finding has not been studied in detail, nor has there been a definitive validation of the diagnostic procedures currently utilised to characterise and stage progression.

Objectives: 1. To investigate the presentation and progression of oropharyngeal dysphagia by defining patterns of specific motoric activity in both voluntary and involuntary muscles,

2. To identify the strengths, limitations and usefulness of currently used diagnostic procedures for dysphagia analysis in MND.

Methods: Patients with bulbar MND were recruited to the study from a specialist MND clinic. All patients were subjected to videofluoroscopic (VFE) and fibreoptic evaluation (FEES) of swallowing. Analysis of presenting dysphagia was undertaken using the Multidimensional Depth Airway Invasion and Residue Single Scoring System; Aspiratin-Penetration Scale, and the Dysphagia Outcome Severity Scale (DOSS). Results were analysed using qualitative and quantitative statistical methods. Patients were categorised in accordance with the DOSS rating and musculature dysfunction scale. This revealed the relative contribution of percentage analysis of the various well0defined muscle groups as the disease progressed.

Results: 16 patients were enrolled in the study, and were evaluated at 3 month intervals. A variety of different swallowing patterns were identified in patients with MND. Patients whose initial presentation was bulbar exhibited more severely impaired swallow function. The rate of progression of deterioration of oropharyngeal dysphagia was not significantly different from non-bulbar onset patients.

Analysis of VFE and FEES indicate a 92 % concordance with respect to the identification of sub-glottal aspiration. Greater in-depth qualitative information was obtained from VFE, including lingual, labial, buccal, upper pharyngeal, velopharyngeal and crico-pharyngeal musculature, which were highly associated with the presenting dysphagia.

Conclusion: A variety of different patterns of swallowing abnormalities have been identified in patients with MND. Patients with bulbar onset disease do not progress at a more rapid pace than those with non-bulbar onset. A combination of VFE and FEES is preferable for detailed analysis of pharyngeal dysfunction in patients with dysphagia.

P783

The clinical pattern and temporal trend of the incidence and prevalence of amyotrophic lateral sclerosis in Ireland over a seven-year study period, 1995–2001. B. J. Traynor, M. Alexander, B. Corr, E. Frost, L. Mahon, O. O'-Toole, O. Hardiman, Beaumont Hospital, Irish MND Association (Dublin, IRL)

Objective: (a)To study the evolving patterns of clinical presentation and demographics among the Irish Amyotrophic Lateral Sclerosis (ALS) population, 1995–2001. (b)To examine the temporal trend of the ALS incidence and prevalence in the Republic of Ireland over a seven-year period.

Design: Population-based Register of all ALS patients in Ireland using multiple sources of information to ensure complete case ascertainment.

Patients: Four hundred and fifty two residents of Ireland with ALS initially diagnosed between 1st January 1995 and 31st December 2001. For the purposes of this study, ALS patients are divided into two cohorts: an "early cohort" consisting of patients diagnosed in the first three years of the study (1st January 1995–31st December1997) and a "late" cohort comprised of individuals diagnosed in the subsequent four years (1st January 1998–31st December 2001).

Results: The demographic features of the early and late cohorts are very similar: the median age at diagnosis in the early cohort was 64.2 years for men and 67.8 for women, compared to 64.5 years and 67.1 years in the late cohort. There was a preponderance of males among the incident cases in both cohorts: 133 males and 102 females in the first three years, compared to 143 males and 74 females in the last three years. Sixteen (6.8 %) and six (2.9 %) patients were familial ALS in the early and late cohorts respectively. At presentation 115 (49 %) patients had bulbar dysfunction as their first symptoms, whereas 104 (48 %) individuals presented with bulbar symptoms in the late cohort.

The annual incidence of ALS was essentially unchanged over the six years of the study and for both the early and late cohorts. In contrast, the prevalence of ALS on the 31st December of each year has consistently increased: 5.3 per 100,000 of the population over the age of 15 years on the 31st December 1995 versus 7.7 on the 31st December 2001.

Conclusions: The Irish ALS Register is among the first to prospectively examine the clinical features and epidemiology of every ALS patient for an entire country over a prolonged period of time. Our study shows that the incidence rate of ALS in Ireland has remained constant over a seven-year period, but that the prevalence rate has steadily increased over the same interval. This temporal trend may reflect improving survival among ALS patients, the advent of Riluzole and the adoption of a more aggressive approach to symptomatic management among Irish neurologists.

P784

The effects of riluzole on serum amino acids in patients with ALS. I. Niebroj-Dobosz, P. Janik, H. Kwiecinski, Medical University (Warsaw, PL)

Objective: To assess the effects of riluzole on serum levels of glutamate, aspartate, GABA, glycine and total amino acids, in patients with amyotrophic lateral sclerosis (ALS).

Background: The efficacy of riluzole in prolonging the survival of patients with ALS has been demonstrated in two large controlled trials. Riluzole is believed to be a glutamate antagonist but the exact mode of its action is not known. There is evidence that an imbalance between glutamatergic neurotransmission and inhibitory neurotransmission may contribute to selective neurodegeneration in ALS.

Design/Methods: We prospectively studied 17 patients with ALS (diagnosed according to the El Escorial criteria) who received long-term treatment with riluzole (100 mg per day). The subjects were evaluated at baseline (before treatment) and 6, 12 and 18 months on drug. Assessments included the functional status of the patients and serum levels of amino acids. Analysis of the serum amino acids was performed by using high performance liquid chromatography (HPLC) techniques.

Results: At baseline, the patients with severe ALS (n = 9) showed significantly increased levels of glutamate (216.5 ± 94.8 microM/L), aspartate (36.3 ± 30.2 microM/L), GABA (8.8 ± 5.3 microM/L) and total amino acids (2027.1 ± 377.1 microM/L), as compared with healthy control group. In patients with mild ALS (n = 8) the baseline concentrations of glutamate and aspartate were decreased. After the first 6 months of riluzole treatment, a significant decrease in glutamate concentration (125.8 ± 43.0 microM/L; $p < 0.002$) was found in patients with severe ALS. This was a transient decrease and after 12 months of treatment the glutamate level returned to its high initial values. We did not observe a similar effects of riluzole on glutamate and other amino acids in patients with less advanced ALS.

Conclusions: These data suggest that riluzole may decrease the serum glutamate concentrations in patients with advanced ALS, but only during first months of treatment.

P785

Depression in amyotrophic lateral sclerosis patients. J. Ilzecka, T. Kazalska, Z. Stelmasiak, Medical University (Lublin, PL)

Introduction: Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by progression of muscle wasting until death due to respiratory failure. Previous studies state that depression occurred rarely in ALS patients, and that these patients have a low rate of suicide.

Objectives: The aim of the study was to determine the frequency of depression occurrence in ALS patients, and to examine the relation with age, sex, clinical state of patients, type of ALS onset, and duration of the disease.

Methods: The study concerned 26 ALS patients (17 males/ 9 females) with average age of 58 (40–77 years). Mean ALS duration was 18 months. The ALS patients were diagnosed according to the El Escorial criteria. They were divided into the groups depending on sex, age (young – up to 55 years, old – over 55 years), duration of ALS (short – up to 12 months/ long – over

12 months), clinical state (mild/ severe), and type of ALS onset (bulbar/ limb). Zung Depression scale was used to assess this symptom. For statistical analysis the Fisher test was used.

Results: In our study depression was found in 10 ALS patients (38.5 % of the whole group); in 5 males/ 5 females, 3 young persons/ 7 old persons, 5 patients with short/ 5 patients with long duration of ALS, 5 patients with mild/ 5 patients with severe symptoms, 6 patients with limb onset/ 4 patients with bulbar onset of the disease. Depression was not depend on sex ($p = 0.18$), age ($p = 0.39$), neurological state of patients ($p = 0.65$), duration of the disease ($p = 0.41$), and type of ALS onset ($p = 0.08$).

Conclusions: The study confirms occurrence of depression in less than half group of ALS patients. Depression was not depend on age, sex, and clinical parameters of the disease.

P786

Atypical familial spinal amyotrophy: muscular hypertrophy with cramps and myalgias. M. Galeotti, A. Gallanti, E. Pegoraro, R. Rinaldi, P. De Carolis, Hospital of Lugo, Neurological Clinic (Lugo di Romagna, Milan, Padua, I)

A 65 year old man has been complaining of cramps and myalgias of the lower limbs for the last 20 years; sometimes he suffers from remarkable pain and stiffness of the legs, especially after long effort. He has experienced a persistently high serum creatine phosphokinase (CPK) activity, ranging from 237 to 473 U/l (normal values: 24–195), even after stopping the use of pravastatine. The patient declared that his father, daughter, some of his 3 brothers and 3 sisters, all have had "enlarged" leg muscles with myalgias. The dead uncle had the same signs and symptoms, and one of his two sons as well; our patient's first cousin has complained of painful cramps and has been forced to stop playing football. Neurological examination showed gross hypertrophy of all muscles of the lower limbs with sporadic fasciculations and idiomuscular responses, mild bilateral weakness of the foot extensors, normal tendon reflexes and plantar responses. Neither sensory signs nor skeletal deformity were noted. Serum CK, measured on two separate occasions, was still high: 237 and 209 U/l; the other biochemical exams showed normal values, needle electromyography detected mixed abnormalities which were mainly neurogenic with complex repetitive discharges; myotonic discharges were not found, not even after cooling. Nerve conduction studies and a decrement test were normal. An open muscle biopsy of the right quadriceps was consistent with a neuropathic process. A 30 year old woman, the sole daughter of our patient showed large hypertrophy of the calves with rare cramps and myalgias; serum CK was 254 U/l and needle EMG revealed neurogenic abnormalities with normal nerve conduction studies. Her muscle biopsy showed a mild neuropathic process. Neurophysiological, histopathological and biochemical studies of the other members of the family are in progress. Our cases could be a rare variant of spinal muscular atrophy with an autosomal dominant inheritance and a slow but not disabling course. Muscle hypertrophy is uncommon in genetically determined motor neuron disorders, but it can occur bilaterally and symmetrically, unassociated with spontaneous activity. It has been suggested that mechanical and genetic factor may play a role in the myofiber hypertrophy of partially denervated muscle. In our first patient both increased muscle bulk and myalgias could be enhanced with chronic muscle stimulation by the complex repetitive discharges, never described in inherited disorders.

P787

Kennedy's disease – the study of a Polish family. B. Tomik, J. Majka, T. Rog, M. Tutaj, A. Pichor, M. Bala-Slodowska, E. Gryz, M. Banach, A. Szczudlik (Cracow, PL)

Background: Spinal and bulbar muscular atrophy (SBMA, Kennedy's disease) is a rare, adult form of X-linked motor neurone disease caused by the expansion of a polymorphic trinucleotide CAG -repeat sequence in the first exon of the androgen receptor (AR) gene. The CAG repeat within the AR gene is polymorphic in normal individuals, ranging in size from 5–33 repeats. In SBMA patients, however, the CAG repeat ranges in size from 40–62 repeats.

The current study presents clinical, neurophysiological and molecular features of SBMA in three cases within one Polish family.

Cases description: We examined three brothers out of six male of a three-generation family with clinical phenotype of SBMA. Patients presented history of slowly progressing limb and facial muscular weakness with fasciculation, amyotrophy, nasal voice and hands tremor as well as gynecomastia of adult onset.

Methods: Clinical data regarding pedigree, age of onset and a type of symptoms were collected. The patients underwent the standard neurological examination and neurophysiological studies. Serum levels of creatine kinase (CK) and hormones (testosterone, LH, FSH) were measured. DNAs were extracted from peripheral blood according to standard procedures for banking. The detection of a pathologically expanded CAG sequence in the AR gene was performed by polymerase chain reaction (PCR) techniques.

Results: DNA analysis showed expanded size of CAG repeats in Xq11–12 in the AR gene in two out of three examined brothers. In the remaining affected case the CAG repeat within the AR was normal. Neurophysiological studies showed signs of chronic denervation in all cases studied.

Conclusion: For the first time we present three cases within one Polish family affected by SBMA with classic funding of the disease including X-linked inheritance, classical phenotype with slowly bulbospinal progression of motor neurone signs and gynecomastia. Genetic data from the other relatives are in progress.

P788

Chromosomal translocation t(18;21)(q23;q22) in a patient with amyotrophic lateral sclerosis and frontotemporal dementia. J. Prudlo, T. Martin, V. M. Kalscheuer, A. C. Ludolph, B. Alber, T. Meyer, University of the Saarland, MPI for Molecular Genetics, University of Ulm, Humboldt University, Charité (Homburg/Saar, Berlin, Ulm, D)

We describe a variant of ALS with frontotemporal dementia in a man aged 64 years who carried a reciprocal chromosomal translocation t(18;21)(q23;q22). Fluorescence in situ hybridization localized the breakpoint to the region 21q22.1 that harbours the locus of the superoxide dismutase (SOD1) gene to which part of the familial ALS cases have been linked. The physical involvement of the SOD1 gene was analysed by Southern blot analysis of the genomic DNA. The patient carried neither a disruption nor a deletion of the SOD1 gene. An expression study of the complete SOD1 mRNA using reverse transcription and competitive PCR failed to reveal an altered gene-dosage effect of SOD1.

Besides the index patient, his 37 years old clinically unaffected son was found to carry the same balanced translocation. The mother and two sisters of the patient were karyotypically normal. The father of the patient was deceased. There was no family history of neurological illness. The absence of chromosomal abnormalities in the progenies suggested a de novo translocation. This conclusion is limited by lacking knowledge on the chromosomal status of the father of the patient. However, the probability that the present disease and a balanced translocation would coexist as unrelated conditions is very low since the prevalence of chromosomal aberrations among asymptomatic individuals has been found in only 0.5 to 1 per 1000. These odds led to the assumption that the relation between the neurodegenerative phenotype and the chromosomal translocation t(18;21) in our patient is not random. The characterization of the breakpoints of disease-associated chromosomal aberration may contribute to the elucidation of the molecular pathogenesis of ALS. Furthermore, our observation underlines the importance of systematic cytogenetic analysis in ALS, dementia and other late-onset neurodegenerative disorders.

P789

Prognostic factors of survival in amyotrophic lateral sclerosis. P. Sola, P. Faglioni, E. Merelli, J. Mandrioli, Clinica Neurologica (Modena, I)

Amyotrophic lateral sclerosis (ALS) is a progressive neurological disease with fatal outcome in about 3 years. Nevertheless, survival is known to vary considerably and it is difficult to predict the duration of disease in individual cases. Identification of factors predicting survival is remarkable both for clinical practice and for counselling patients and their families. The aim of the present study is to investigate the presence of possible prognostic factors in ALS survival.

In a previous retrospective epidemiological survey on ALS in the province of Modena (Emilia-Romagna region of northern Italy) from 1990 through 1999, we found 143 cases, with mean annual incidence, prevalence, and mortality rates of 2,16, 4,02 and 1,69 per 100 000 persons, respectively.

For the survival study, we included 123 patients of our casuistic, with a disease onset from 31/12/1989 to 31/12/1998, and with a follow up of at least one year. The survival curves were calculated by means of the actuarial method and comparisons were made with the Cox's and Koch, Johnson and Tolley's methods. Our results indicate that the 50 % of patients died in 2,5 years and the 89 % in 7 years. In our patients, sex and Riluzole therapy did not significantly influenced the survival time. The only relevant prognostic factors resulted age and clinical forms at onset. In particular, survival time was longer in younger patients: the 50 % of cases died in 1,8 years if older than 75 years, and in 2,8 years if younger than 60 years. Re-

garding to the clinical form of ALS, the 50 % of patients with onset at lower limbs died after 3,5 years, while patients with bulbar forms after 2,2 years.

In conclusion, in agreement with previous literature data, our study shows that the clinical form as well as the age at onset affect the survival time in ALS. Although it is possible to individuate prognostic factors, there is still an unexplained heterogenous progression in the disease, indicating other yet unknown prognostic factors. A search for these factors remains an important task in ALS, to allow reliable estimation of survival in the individual patient.

P790

Individual quality of life is not correlated with general health status in patients with amyotrophic lateral sclerosis. C. Neudert, M. Wasner, G. D. Borasio, Ludwig-Maximilians-University (Munich, D)

Objectives: To compare the change over time of individual quality of life (QoL) vs. functional and generic health status in patients with amyotrophic lateral sclerosis (ALS).

Methods: 42 ALS patients performed three health status measures: the ALS functional rating scale (ALSFRS), the Sickness Impact Profile (SIP), and the Short Form 36 (SF–36), as well as the Schedule for the Evaluation of Individual QoL – Direct Weighting (SEIQoL-DW), which assesses individual quality of life. Patients were examined at least three times at two-month intervals. The SIP and ALSFRS were filled out by all patients, the SF–36 and the SEIQoL-DW were assigned at random.

Results: There was a significant decrease from visit 1 to 3 in the SIP (76.3 to 71.9, $p < 0.001$), the SF–36 (94.4 to 87.4, $p = 0.018$), and the ALSFRS (68.8 to 55, $p < 0.001$). Despite this progressive decline of physical function and general health status, there was no significant difference for the same period in the SEIQoL-DW, which actually increased slightly from 75.4 to 75.6. Correspondingly, there was no correlation between the SEIQoL-DW and the functional scales.

Conclusions: Individual QoL in patients with ALS does not correlate with measures of function and general health, and is likely to be largely based on other factors such as psychosocial and spiritual well-being.

P791

Investigation of maximum voluntary isometric muscle strength in polio and comparison with a normal Irish population. D. Meldrum, E. Cahalane, O. Hardiman, Beaumont Hospital (Dublin, IRL)

The cause of new symptoms 20–30 years following poliomyelitis is unclear. Differentiation must be made between ongoing neuronal loss as a result of polio, and the normal effects of aging. An objective measure of muscle strength is crucial when analysing progression. Many studies have chosen small numbers of muscle for analysis of strength, however, few have examined the overall body profile. Analysis of a large group of muscles is more accurate in post-polio syndrome, as the distribution of affected muscles varies greatlyamong patients. Maximum voluntary isometric contraction (MVIC) is a computerised system that uses a strain gauge attached to orthopedic bars at one end, and to the patient at the other, on a standard plinth. MVIC produces reliable and valid data that are more sensitive to change and more objective than manual muscle testing.

The purpose of this study was to analyse MVIC values in a sample of patients with a history of poliomyelitis, who describe new symptoms suggestive of a post polio syndrome. Changes in muscle strength were measured over time, and results were compared with those of a normal population.

23 patients (16 female, 7 male, mean age 52.4, range 42–72) with varying degrees of residual weakness were tested. All had subjectively reported declining muscle strength. MVIC values were obtained bilaterally for upper and lower limbs. 17 patients had 2 tests performed, with an average of 8 months beteen tests. Values were compared to age and sex matched normals.

Patients with a prior histor of polio were significantly weaker in all tests when compared to normals ($p < 0.5$). Average MVIC values decreased slightly over time (average 5.5 %) but only reached statistical significance in 4 tests (knee extension, hip flexion, shoulder adduction and elbow flexion ($p < 0.05$). There was a large variation in decline of strength among the group, with some patients showing no change over time.

In conclusion, MVIC is a sensitive and objective measure of muscle strength, which can be used to evaluate declining muscle strength over time. In this study, patients who had reported new weakness showed a trend towards decreased MVIC values when evaluated prospectively. This progresion is likely to be slow, and the cohort will require further follow before the magnitude of decline can be accurately measured.

P792

Mills syndrome: a clinical variant of amyotrophic lateral sclerosis. M.H Soriani, C. Desnuelle, Hopital Archet (Nice, F)

Objective: To discuss a clinical variant of Amyotrophic Lateral Sclerosis (ALS)

Background: Mills syndrome has been described as a progressive, unilateral ascending or descending variant of ALS.

Method/results: We studied four cases of the clinical Mills syndrome. Case n°1 was a 57 year old man who consulted for a slowly progressive weakness of the right inferior limb secondary extended in the right upper limb. On examination, combined motor and cortico-spinal sign were noted in the right upper and lower limbs without bulbar manifestation. Cerebral and spinal cevical MRI imaging were normal. EMG examination showed in detection denervation-reinervation signs in different muscles of right limbs. The follow up is now of 8 years. Case n°2 was a 33 year-old man presenting with a right distal weakness in the lower limb progresivelly extended in the right upper limb. Right spastic hemiparesis and bilateral cortico-spinal syndrome was evidenced on examination. On EMG examination denervation-reinervation signs were noted in muscles of the right limbs. Brain and cervical spinal cord MRI imaging were normal on initial examination but T2-weighted medullar cervical hypersignal was noted on repeated examination 5 years later. The follow-up is of 6 years. Case n°3 was a 65 years of age man. He consulted for a right progressive hemiparesis, without facial or bulbar involvement, associated with a bilateral cortico-spinal syndrome. On cerebral MRI, periventricular hypersignal were noted along with a T2-weighted cervical medullar hypersignal. EMG showed peripheral denervation in four limbs. The follow up is presently of 12 years. Case n°4 was a 62 year-old woman presenting with distal motor deficit of lower right limb combined with brisk reflexes and Babinski's sign. Denervation signs were present in the right plantar extensor and flexor, cerebral MRI was normal and cervical medullar MRI showed a T2-weighted hypersignal. The follow up is of 4 years. In all cases CSF examination was no contributive. No abnormal pattern was described on evisual and auditive evoked potential.

Conclusion: In agreement with few previous reports, Mills syndrome may be considered as a long course clinical variant presentation of ALS. However, the differential diagnosis with a progressive hemiplegic form of multiple sclerosis remains difficult and justify to repeat examinations and especially cervical medullar MRI.

P793

An evaluation of the patterns of respiratory failure in amyotrophic lateral sclerosis (ALS). M. D. Alexander, R. K. Morgan, S. McNally, B. Corr, E. Frost, R. Costello, O. Hardiman, Beaumont Hospital, MND Association (Dublin, IRL)

Introduction: Respiratory muscle involvement in ALS leads to increasing dyspnoea and is the commonest cause of death in ALS, but patterns of decline vary between patients. Diaphragmatic paralysis is presumed responsible for the decline in respiratory function but the extent of its involvement is unclear. Forced vital capacity measurements have been shown to be inefficient in assessing early signs of respiratory decline in ALS, especially in patients with bulbar dysfunction. The role of static mouth pressures (MIP/MEPs) and sniff nasal pressures (SNPs) have been advocated in ALS, and oesophageal manometry (OM), although an invasive technique, has proven efficient in estimating trans-diaphragmatic pressures.

Aims: To prospectively evaluate patterns of respiratory decline in ALS patients and to identify the optimal prognostic indicator of impending respiratory failure.

Methods: Patients were recruited from our MND clinic. Spirometry was performed according to standard protocols and OM was performed using a Mui Scientific compressor, infuser and manometer. A hand held mouth pressure meter has been adapted to perform SNPs. This has been validated by a comparison with MIP/MEPs in 100 age and sex matched controls.

Results: No statistical difference was observed between MIP/MEPs and SNPs in the validation of the hand held meter. To date 30 ALS patients have undergone serial spirometry and a comprison has been made with MIP/MEPs and SNPs. A seperate cohort of 18 patients has undergone a 3–4 monthly evaluation of respiratory status, involving standard ALS rating scales, physical examination, spirometry, MIP/MEPs, SNPs, OM, and where appropriate, nocturnal oximetry. Sevent five percent of patients recruited have limb onset disease and 70 % of these have developed some bulbar involvement. In patients with minimal or no bulbar involvement MIP, SNIP and OM show a good concordance and are most likely to indicate evidence of nocturnal dasaturation. MIP/MEPs and FVC correlate poorly with SNIP and OM when there is evidence of significant bulbar involvement.

Conclusions: Repeated assessments have identified SNPs and OM as re-

liable markers of significant respiratory compromise. Portable oximetry units can be used in a hospital or domestic setting to confirm nocturnal oxygen desaturation in patients identified to be most at risk, and hence those who will benefit most from non-invasive positive pressure ventilation.

P794
Bulbar-onset ALS among elderly Irish women: findings of the Irish ALS Register over a seven-year period, 1995–2001. B.J Traynor, M. D. Alexander, B. Corr, E. Frost, L. Mahon, O. O'Toole, O. Hardiman, Beaumont Hospital, MND Association (Dublin, IRL)

Objective: To identify the existence of a distinct cohort of Amyotrophic Lateral Sclerosis (ALS) among the Irish ALS population, 1995–2001 using data from the Irish ALS Register.

Background: We have previously reported a higher incidence of bulbar-onset disease among the Irish ALS population. This study is now extended to determine factors that may account for this observation.

Design: Population-based Register of all ALS patients in Ireland using multiple sources of information to ensure complete case ascertainment.

Patients: Four hundred and fifty two residents of Ireland with ALS initially diagnosed between 1st January 1995 and 31st December 2001.

Results: The median age at diagnosis was 64.8 years for males and 67.5 years for females. Over the seven-year study period, 176 women and 276 men (M:F ratio = 1.6) were diagnosed with ALS in Ireland. With increasing age at time of diagnosis of ALS, the ratio of male to female age-specific incidence decreases to unity at age 75 years. Bulbar-onset disease was far more common among women than among men: Over two thirds of Irish female ALS patients presented with bulbar- or generalised-onset disease, compared to 46 % of their male counterparts. The occurrence of bulbar-onset disease increased among females with rising age, but no such increase was observed among elderly males: Of the 61 female patients diagnosed with ALS in their eight decade of life, 46 (75 %) presented with bulbar or generalised onset disease. In contrast, bulbar-onset disease only accounted for 54 % of the 93 Irish males diagnosed with ALS after 70 years of age.

Conclusions: Although there is an overall male predominance in the Irish ALS population, the incidence of ALS rapidly increases among women after the age of 55 (i. e. post-menopausal). In the eight-decade, male- and female-specific incidence rates of ALS are almost identical. This observation may be related to an increased incidence of bulbar-onset disease among this age group. This observation suggests that menopause may be a risk factor for bulbar-onset disease among women, possibly because of loss of a protective role of Estrogen. Bulbar-onset ALS among elderly female patients may represent a distinct cohort of ALS, with a distinct risk factor and even pathogenic mechanism.

Multiple sclerosis

P795
Is Devic's neuromyelitis optica a separate disease? A comparative study with multiple sclerosis. J. de Seze, C. Lebrun, T. Stojkovic, D. Ferriby, M. Chatel, P. Vermersch, Hopital R. Salengro, CHRU of Nice (Lille, Nice, F)

Background: Devic's neuromyelitis optica (NMO) associates optic neuritis and myelitis without other neurological signs. Many patients with NMO may be diagnosed as having multiple sclerosis (MS), optic neuritis and myelitis being the inaugural symptom in 20 % and 5 % of MS cases, respectively. However, there have been no previous studies comparing these two pathologies and it is still unclear if NMO is a separate entity or a syndrome including MS, systemic or infectious diseases.

Aim of the study: To compare NMO patients with MS patients revealing by optic neuritis or myelitis, in order to determine the place of NMO in the spectrum of MS.

Methods: We retrospectively studied 30 patients diagnosed with NMO according to Wingerchuk et al.'s criteria. We compared these patients with 50 consecutive MS cases revealed by optic neuritis (n = 26) or acute myelitis (n = 24). Patients were diagnosed as MS only if a second relapse occurred demonstrating time and space dissemination. We compared the groups in terms of clinical presentation, initial laboratory findings (MRI, visual evoked potentials and CSF) and clinical outcome (evaluated by the expanded disability status scale (EDSS) and the index of progression (IP) = EDSS/duration of the disease).

Results: NMO patients were older and more frequently female than MS patients but the differences were not significant. CSF and MRI data were different: oligoclonal bands were found in 23 % of NMO cases and 88 % of MS ($p < 0.001$), abnormal brain MRI data following Barkhof et al.'s criteria were observed in 10 % of NMO cases and 66 % of MS cases ($p < 0.001$). Clinical outcome was evaluated as more severe in the NMO group ($p < 0.001$ for both EDSS and IP). If we include MRI data only two of the NMO patients met criteria for MS and one of the MS patients met the criteria for NMO.

Conclusion: Our study demonstrates that NMO and MS should be considered as two different entities. This finding could have implications for future therapeutic trials.

P796
Severe injection site reaction with necrosis after glatiramer acetate application in multiple sclerosis. M. Starck, H. Albrecht, W. Pöllmann, N. König, Marianne-Strauss-Klinik (Berg, D)

Background: Injection site reactions with erythema are well known after glatiramer acetate (GLAT) injections for immunomodulatory therapy in multiple sclerosis (MS). These reactions usually are less severe than those after subcutaneous beta interferon application, where necrosis at injection site is reported up to 4 %. We saw two patients with clinically definite relapsing remitting MS with severe skin reactions after GLAT injection.

Case reports: patient 1, a 45 years old female, suffered from MS for 21 years. Since April 1996 she has been successfully treated with GLAT without any serious adverse events. Occasionally there had occurred a mild erythema at injection site and small subcutaneous indurations. Between August and November 2001 she developed injection site inflammation after each injection with a necrosis on the left side of abdomen.

Patient 2, a 31 year old female has been treated with GLAT since October 1997 without any MS relapses or serious side effects, respectively. At her last visit in our outpatient department she presented with a residuum of a small necrosis at the umbilical region, which had developed since 7 weeks ago.

In both patients all injections had been made correctly without any changes in injection technique.

As far as we know these are the first reports of necrosis after subcutaneous injection of GLAT. Up to now the mechanism of these skin reactions is not quite clear.

P797
Effects of IVIg treatment in different models of myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE). T. Seifert, A. Stefferl, M. Held, F. Fazekas, H.-P. Hartung, C. Linington, M. K. Storch, University Graz, MPI, University Düsseldorf (Graz, A; Martinsried; Düsseldorf, D)

Objective: Recent studies showed the effectiveness of IVIg in the treatment of multiple sclerosis (MS) and of myelin basic protein (MBP)-induced EAE. MBP-induced EAE is a purely T cell mediated monophasic inflammatory disease with little or no demyelination and thus not reflecting MS. In a subgroup of MS patients demyelinating antibodies, acting on the background of a T cell mediated inflammatory response, lead to the demyelinating lesions. MOG-EAE is a T cell- and antibody mediated disease that replicates the inflammatory demyelinating pathology of MS. We investigated the effects of IVIg treatment in a model of actively induced MOG-EAE with a predominant T cell response and another model with a predominant antibody response as well as in adoptive transfer EAE with MOG-specific T cells.

Methods: DA and BN rats were immunized with 75 mg rMOG in IFA or 50 mg rMOG in CFA, respectively. Animals were treated prophylactically (day of immunization till outbreak of disease) or therapeutically (after onset of disease) with 0,4 g/kg IVIg. Controls were treated with placebo.

Similarly IVIg was administered in adoptive transfer EAE. Animals have been perfused at various time points of disease and CNS underwent a detailed histopathological analysis.

Results: No significant difference was observed between treated and untreated animals with respect to inflammation. At early stages of disease (11–14 d. p. i) treated DA rats showed demyelination to a lower extent compared to controls ($p = 0{,}021$), at later time points of disease (20 d. p. i) there was no significant difference in the extent of demyelination to detect. Therapeutically treated BN rats showed from day 20 p. i. milder clinical disease and prophylactically treated BN rats did not show symptoms from day 23 p. i. In contrast, control BN rats suffered from severe clinical disease. In both treated BN groups the extent of demyelination was lower (both groups versus control, $p = 0{,}0145$) compared to the controls and in some treated BN rats signs of remyelination were to detect.

Conclusions: Patients with demyelinating antibodies as demyelinating amplification factor might benefit from administration of IVIg. On the

contrary, no effectiveness is to expect in MS patients with predominant T cell mediated disease.

P798

sCD14 in multiple sclerosis: plasma and cerebrospinal fluid levels during acute relapse and effect of corticosteroid therapy. D. Ecker, M. Maier, C. Zinser, A. Claus, S. Süssmuth, E. Elitok, I. Uttner, H. Tumani, University of Ulm (Ulm, D)

Background: CD14 is an important cell surface molecule located mainly on monocytes/macrophages. Its soluble form sCD14, a 55 kDa protein, is known to be increased in plasma of patients with bacterial infection and with autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematous. It is also known that sCD14 is increased in cerebrospinal fluid (CSF) during bacterial infection of the central nervous system and viral meningitis.

Aim: To determine sCD14 levels in plasma and CSF in patients with multiple sclerosis during relapse and to analyse the effect of corticosteroid therapy on plasma levels.

Material and Methods: In a prospective study design CSF and plasma levels from 9 patients admitted to hospital during a relapse were analysed for sCD14. Patients had EDSS values between 1,0 and 3,0. At the end of intravenous treatment with high-dose methylprednisolone (MP) for 5 days and 2 months thereafter plasma levels o sCD14 were determined. sCD14 levels were measured by an ELISA. Statistical analysis was done by Friedman-Test.

Results: We found slightly increased sCD14 levels in plasma during acute relapse (median and SD, 4,12 ± 1,29 mg/l; mean and SD from non-inflammatory controls 2,94 ± 0,79 mg/l). 5 days following MP therapy plasma sCD14 levels decreased to a median concentration of 1,70 ± 0,25 mg/l. At 2 months sCD14 plasma levels re-increased to a median concentration of 3,09 ± 0,64 mg/l. The pattern of changes of plasma sCD14 levels over time was significantly different ($p < 0,01$).

The CSF/serum ratio (median 9,4 x 10–3 ± 3,92 x 10–3) indicate an increased local synthesis of sCD14 in CSF during acute relapse as compared to non-inflammatory controls.

Conclusion: In clinically active multiple sclerosis sCD14 levels are slightly increased in plasma and in CSF. Plasma levels of sCD14 are temporarily suppressed by corticosteroid therapy. There is also an increase of intrathecal synthesis of sCD14 during the relapse. sCD14 might be a suitable marker for monitoring monocyte/macrophage activity in multiple sclerosis.

P799

IFN-beta and glatiramer acetate as combination therapy for multiple sclerosis reduce CD1a and enhance Th2 response more than IFN-beta alone. Y. Huang, Y. Hussien, A. Sanna, M. Soderstrom, H. Link, Karolinska Institute, Sassari Medical University (Stockholm, S; Sassari, I)

Objective: To evaluate influence of MS treatment with IFN-beta1a vs. IFN-b1a + glatiramer acetate (GA) on surface molecules of HLA-DR+ blood mononuclear cells (MNC) and cytokine production by MNC.

Background: Cell surface molecules and cytokines are believed to play an important role in a proposed immunopathogenesis of MS. Clinical studies demonstrate beneficial effects of IFN-b and GA in MS. But each agent shows only modest clinical efficacy. Further, not all patients respond to monotherapy. IFN-b and GA act in MS in different ways. Based on our in vitro study, combination therapy with IFN-b + GA could be more efficient in patients progressing clinically despite treatment with IFN-b or GA alone.

Design: Blood MNC were isolated from 18 untreated MS patients, 22 treated with IFN-b1a alone, 14 treated with IFN-b1a + GA, and 23 healthy controls (HC). Flow cytometry was used to analyse surface molecule expression and ELISA to measure cytokine production in MNC culture supernatants. Results: MS patients compared to HC had higher CD11c+ and CD80+, and lower CD86+HLA-DR+ MNC. Upon subgrouping, only untreated MS patients had higher CD1a+ cells and CD80+ cells, and lower CD86+ and CD123+HLA-DR+ MNC. Patients treated with IFN-b1a alone had lower CD1a+HLA-DR+ and CD11c+HLA-DR+ MNC, and higher CD123+ (IL–3Ra) HLA-DR+ MNC, compared to untreated MS patients. Patients treated with IFN-b1a + GA had lower CD1a+HLA-DR+ MNC compared to untreated MS patients. Untreated MS patients compared to HC had lower IL–10 and IFN-g, and higher IL–12p70 production in MNC culture supernatants. Patients treated with IFN-b1a alone had higher IL–10 compared to untreated MS patients. Patients treated with IFN-b1a + GA had higher IL–10, but lower IL–12p70 and IFN-g production compared to untreated MS patients.

Conclusions: Treatment with IFN-b1a + GA resulted in more profound effects on reducing CD1a+HLA-DR+ MNC and augmenting IL–10 production in MNC supernatants than treatment with IFN-b1a alone. Furthermore, treatment with IFN-b1a + GA resulted in reduced IL–12p70 and IFN-g production. Follow-up studies on combined therapy with IFN-b1a plus GA in relation to clinical outcome in MS are ongoing.

P800

Affect perception in individuals with multiple sclerosis. S. Mitrousi, A. Kouyoumtzi, P. Roussi, M. Pashalidou, M. Gelagoti, M. Kosmidis, Aristotle University of Thessaloniki, AHEPA Hospital (Thessaloniki, GR)

There is evidence of co-morbid emotional disorders in individuals with multiple sclerosis (MS) at a rate higher than in the population at large. Some investigators have suggested that this co-morbidity reflects a common pathophysiology of MS and emotional disorders, to the extent that they both involve white matter changes. Other researchers studying affect perception have proposed that the ability to perceive emotions in others is related to the ability to recreate them in one's self. Given the wide range of cognitive deficits often observed in MS, we sought to investigate potential impairment in the ability to perceive affect in this group.

Fifteen individuals with a diagnosis of MS and 15 healthy controls (HC), matched for age, education, and sex, participated in this study. Our patient group had the diagnosis for a mean of 8.9 years (73 % recurring-remitting, 27 % chronic-progressive; mean EDSS = 2.3). MRI scans revealed lesions predominantly in the corpus callosum and brainstem, with some cortical atrophy, as well. HC participants reported no history of a psychiatric or neurological disorder, substance abuse/dependence, or a closed head injury.

We administered a visual and an auditory test measuring affect perception. These tests were administered as part of a broader neuropsychological battery, used to assess attention, memory, language, visuospatial skills, executive functioning and information processing speed.

We found that the patient group did not differ from the healthy group on either identity [$F(1, 28) = 1.56$, ns, MS mean = 24.3 (3.4), HC mean = 25.9 (3.6)] and affect matching [$F(1, 28) = 2.26$, ns, MS mean = 24.4 (4.5), HC mean = 26.5 (2.8)], or on prosody [$F(1, 28) = 3.79$, ns, MS mean = 24.1 (3.8), HC mean = 26.5 (2.9)]. This is in contrast to their deficits in a wide range of other cognitive functions (i. e., verbal memory, focus/execute visual attention, executive functioning, and speed of information processing on a complex, but not a simple, task).

Our results suggest that patients with MS do not present deficits in affect perception, at least when their symptoms are in the mild to moderate range of severity. This is in spite of deficits in other cognitive functions. Further research with larger groups, a broader range of severity levels and tests measuring additional aspects of affect perception may be helpful in understanding the mechanisms for preserving this cognitive skill over others.

P801

Long-term cost-effectiveness of Interferon-beta–1a (Rebif 44 mcg tiw) in the treatment of relapsing-remitting multiple sclerosis: an Econometroc model. P. K. Coyle, T. Vollmer, C. Lepen, L. Blumhardt, H. Lilliu, A. Beresniak, SUNY, Yale University, University Paris-Dauphine, Queen's Medical Centre, CLP Santé, Serono International SA (New York, New Haven, USA; Paris, F; Nottingham, UK; Geneva, CH)

Background: In the absence of long-term clinical trial data in relapsing-remitting multiple sclerosis (RRMS), pharmacoeconomic modelling can aide policy decisions regarding the cost-effectiveness of new therapies. Existing Markov-type models may not be appropriate for disease-modifying therapies, because Markov models do not take into account the history of the disease. We have evaluated the cost-effectiveness of subcutaneous interferon beta–1a (IFNb–1a; Rebif 44 mcg tiw) using an econometric model.

Methods: Data on patients treated with IFNb–1a or placebo for up to 4 years were obtained from the PRISMS study. Effectiveness was defined as the ability to slow progression of RRMS as measured by Expanded Disability Status Scale (EDSS) score. Area under the EDSS score-time curve was used as an integrated measure of disability, and the effectiveness of therapy was expressed as EDSS months of disability prevented. Results were projected to 10 and 20 years using an econometric time series regression model. Cost data were obtained for the health systems of the UK and France, and discounted at a rate of 6 % per year.

Results: Statistical analysis confirmed the robustness of the model and the long run superiority of Rebif 44 mcg tiw versus Rebif 22 mcg tiw and versus placebo ("no treatment"). Over 10 years, treatment with IFNb–1a (Rebif 44mcg tiw) prevented 121 EDSS months of additional disability, at a

cost of Euro732 per EDSS month. Over 20 years, 321 EDSS months were saved at a cost of Euro359 each.

Conclusions: This robust time-series regression model suggests treatment with Rebif 44mcg tiw is increasingly cost-effective over time, results in significant savings, and is a cost-effective therapy for RR MS.

P802

Interferon beta bioavailability evaluation by MxA mRNA quantification during a 96-hours-time course in multiple sclerosis patients. A. di Sapio, F. Gilli, A. Sala, S. Malucchi, M. Capobianco, E. Milano, F. Melis, R. Bottero, M. Iudicello, F. Marnetto, F. Boccalatte, M. Giordana, A. Bertolotto, Centro Sclerosi Multipla (Orbassano Turin, I)

Objective: to evaluate Interferon beta (IFN-b) bioavailability in multiple sclerosis (MS)patients during 96 hours (h) of treatment, considering neutralising antibodies (NAbs) presence and type of IFN.

Background: bioavailability, representing cells activation after drug-receptor interaction, is necessary for IFN-b clinical effect and MxA mRNA quantification in peripheral blood mononuclear cells (PBMCs) is a reliable method for its evaluation.

Design/method: we quantified, by a new quantitative-competitive PCR method, MxA mRNA in PBMCs of 42 treated and 73 drug free patients.

42 IFN-b treated patients (12 Avonex, 11 Betaferon, 19 Rebif22) underwent MxA mRNA dosage every day, from Monday to Friday. Avonex was administered on Monday evening, whereas Betaferon and Rebif22 on Monday and Wednesday evening. No patients switched the type of IFN-b before MxA mRNA dosage. NAbs to IFN-b were evaluated every trimester by a cytopathic effect assay. Patients with no positive sample were considered NAbs negative (NAbs-); subjects with at least two consecutive positive samples were considered NAbs positive (NAbs+).

Results: MxA mRNA levels were detectable in all untreated patients (mean = 34 ± 33 fgMxA/pgGAPDH) and the upper threshold was 133 fgMxA/pgGAPDH. In 35 NAbs- patients (9 Avonex, 9 Betaferon and 16 Rebif22) similar bioavailability among the three drugs was observed on Tuesday (+12h) and Wednesday (+36h). On the contrary, bioavailability was statistically different Monday ($p < 0.05$), Thursday ($p < 0.001$) and Friday ($p < 0.05$). Indeed MxA mRNA amount was greater in Betaferon and Rebif22 than in Avonex treated patients. Considering the whole area under the MxA mRNA amount-time, bioavailability was 40 % and 39 % greater in Betaferon and Rebif respectively.

96h time course in 7 NAbs+ patients (2 Avonex, 2 Betaferon and 3 Rebif22) showed that IFN-b injections always failed in increasing MxA mRNA levels. Comparing NAbs- and NAbs+ time course, areas under MxA mRNA levels curve demonstrated statistically significant difference between the two groups of patients (NAbs+vs Avonex $p = 0.003$; NAbs+vs Betaferon $p = 0.0079$; NAbs+vs Rebif $p = 0.008$).

Conclusions: the more frequent administration of Betaferon and Rebif provided a significant greater weekly bioavailability in NAbs- patients compared to patients treated once a week with Avonex. Otherwise, no differences were observed in NAbs+ patients in whom, although a more frequent administration, NAbs presence abolish IFN-b biological effects.

P803

The effect of a combined administration of mitoxantrone and methylprednisolone on the course of primary and secondary chronic-progressive multiple sclerosis. O. Schüler, M. Strupp, S. von Stuckrad-Barrè, R. Hohlfeld, T. Brandt, Ludwig-Maximilians University, Johann Wolfgang Goethe-University (Munich, Frankfurt am Main, D)

After controlled studies have proven the efficacy of mitoxantrone (MIX) for treatment of severe and progressive forms of multiple sclerosis (MS), we report on our experience with a combination therapy of MIX and methylprednisolone (MP) and its effect on the clinical course of patients with primary and secondary chronic-progressive MS.

70 patients with primary or secondary progressive MS were included in the study if their EDSS had decreased by at least 1 point during the previous 12 months. The patients were given a short infusion of 500 mg i. v. MP per day for 5 days and MIX at a dosage of 10 mg/m2 body surface at day 3. During the first year the patients received further cycles of therapy every 3 months, then every 6 months. Before each administration of MP and MIX the EDSS was determined.

44 patients (n = 28 females, age 47 ± 12 years) with secondary chronic-progressive MS were observed over a period of 14 ± 11 months. 3 patients (6.8 %) showed an improvement of the EDSS by >/ = 1 point and 7 patients (16 %) an improvement of the EDSS by 0.5 points, while the EDSS of 26 patients (61.4 %) remained stable. The EDSS of 1 patient worsened by 0.5 points, and the EDSS of another 6 patients (13.6 %) rose by >/ = 1. All in all, the EDSS improved in 10 of the 44 patients (22.7 %) with secondary chronic-progressive MS, stabilized in 26 patients (61.4 %), and worsened in 7 (15.9 %).

We also observed 26 patients (n = 8 females, age 51 ± 11 years) with primary chronic-progressive MS over a period of 14 ± 9 months. During this therapy the EDSS improved in 1 patient by >/ = 1, in another patient by 0.5 points, and remained stable in 20 patients (76.9 %). The EDSS of 1 patient worsened by 0.5 points, and in another 3 (11.5 %) by >/ = 1 points. All in all, of the 26 patients with primary chronic-progressive MS the EDSS of 2 patients (7.7 %) improved, that of 20 patients (76.9 %) stabilized, and it worsened in 4 patients (15.4 %).

Our findings show that the combination treatment with MIX and MP has positive effects on the development of the disability in patients with both primary and secondary chronic-progressive MS. These results are supported by findings of other groups using MIX monotherapy. The design and the short follow-up in the current study do not permit a general recommendation of combined therapy to patients. However, the stabilization or improvement in more than 80 % of the patients strongly supports the initiation of a prospective, placebo-controlled multicenter study.

P804

Multiple sclerosis: the question of unresponsiveness to interferon beta therapy. F. Casoni, L. Manneschi, I. Pesci, E. Montanari, E. Merelli, University of Modena, Fidenza Hospital (Modena, Parma, I)

Background: Interferon beta (INFb) is an immunomodulatory worldwide, first choice therapy for relapsing remitting multiple sclerosis (RRMS): Taking into account that a proportion of patients did not show to benefit from the INFb, withdrawal criteria were used to stop the therapy (The INFB Multiple Sclerosis Study Group, Neurology 1993).

Objectives: In a retrospective study we analysed a group of RRMS belonging to 2 Northern Italy MS Centres treated with INFb and dropped out for inefficacy of the therapy. The aim of the survey was to evaluate the follow-up of the patients who suspended the INFb and to identify the characteristics of unresponder subjects.

Patients and Methods: 21 out of 186 RRMS patients (11.3 %) dropped out from the three approved forms of INFb after a mean period of 24 months and were followed for a mean period of 2 years. Withdrawal criteria were: 1) steady progression of disability with 1 or more EDSS points for 1 year; 2) treatment with 3 or more courses of steroids during a 1 year period. Moreover MRI investigations were considered as additional data. EDSS was evaluated at the beginning, after 24 months of therapy and during the follow-up. The number of relapses was recorded in the 2 years before and after 24 months of therapy and in the course of the follow-up. MRI investigations were performed at the same steps.

Results: Mean EDSS of the 21 patients at the beginning of therapy was 3.02+ 7–0.64, significantly lower than at the suspension of the therapy: 3.92+ 7–1.23 ($p = 0.001$). The mean number of relapses during the 2 years before therapy was 3.0 ± 0.86, significantly higher than during the therapy: 1.22+ 7–1.20 ($p = 0.0001$). All the patients shifted to immunosuppressive therapies, notwithstanding the EDSS progressed to 4.61 ± 0.92 ($p = 0.009$). The mean number of relapses remained stable in the 24 months of follow-up compared with the two years of INFb therapy ($p = 0.46$). MRI investigation worsened or remained stable in all patients during treatment and follow-up.

Conclusion: Our preliminary data seem indicate that a subgroup of MS patients unresponsive to INFb progress without variation even if shifted to immunosuppressive therapy. This may signify that those subjects are different in the pharmacological response from other MS population or represent a progressive relapsing group of patients. A larger prospective study involving the two MS Centres has been projected to answer these questions.

P805

Low-dose oral methotrexate (LDOM) in chronic progressive multiple sclerosis (CPMS): an extension study. D. Farina, C. M. Caporale, M. E. Nives, D. Gambi, A. Lugaresi, Clinica Neurologica (Chieti, I)

Background: LDOM (7.5 mg/week) has been proposed as a possible therapy for CPMS. We have reported encouraging data on safety at 2 years.

Objective: To further assess safety and efficacy of LDOM.

Patients and methods: We have studied 34 patients (including the previously reported 20) aged 32–67 (10 Females, 24 secondary progressive). All patients had been progressing in the year before starting treatment. Baseline EDSS was 3.0–8.0 (between 6.0 and 6.5 in 17).

Results: Treatment duration at present is: 3 years or more in 8 (6 stable), 2 years in 9 (6 stable). Three pts have discontinued treatment in the

first year because of toxicity in 2, of perceived inefficacy in 1. Four pts have interrupted treatment at yr 1 for inefficacy, 1 at mo 0.14 for perceived inefficacy. Three pts have interrupted and 2 have associated interferon beta treatment for inefficacy at yr 2; 1 pt interrupted treatment for mild but persistent side effects (nausea and increased liver enzymes) at yr 2. Three pts are lost to follow-up since yr 1. Gadolinium-enhanced MRI scans have been performed at baseline (active in 11/34) and yearly thereafter. MRI scans are stable in all but 4: 3 at yr 1 (increased lesion load, no enhancement in 1, enhancement in 2), 1 with enhancing lesions at yr 2. All pts showing enhancement during treatment showed enhancement also at baseline. Tolerability has been good in most: liver echography (performed yearly) shows mild steatosis or is normal in all; blood chemistry has shown transient increases in liver enzymes (grade 1) in < 50 %. Two pts had localized, uncomplicated herpes zoster. The most common clinical side effect is nausea, well controlled with domperidone pre-medication and dose fractionation. Other reported side effects are headache and fever. In the 2 cases where interferon beta has been associated to LDOM no additional toxicity has been observed. In 2 pts the dosage has been doubled for insufficient efficacy after 18 mo.in 1 and 3 mo. in 1 without additional efficacy.

Conclusions: LDOM appears to be safe up to 3 years. Efficacy can't be judged in a small open study, although our results seem to indicate a good response both on clinical and MRI parameters. We believe that a prospective randomised trial against interferon beta should be performed both to assess relative efficacy and tolerability.

P806

A longitudinal study of the serum levels of MCP1, TNF-alpha and TGF-beta and their relationship with clinical relapses in patients with multiple sclerosis treated with interferon beta–1b. T. Arbizu, M. Alvarez-Mon, O. Sanchez-Solino, A. Prieto, Hospital de Bellvitge, Universidad Alcala de Henares, Schering Espana, S. A. on behalf of the GENIO-I Group

The aim of this study was to determine changes in the serum levels of monocyte chemoattractant protein–1 (MCP1), tumor necrotizing factor alpha (TNF-alpha) and transforming growth factor beta (TGF-beta) and their relationship with clinical relapses in patients with relapsing-remitting multiple sclerosis (RR-MS) starting therapy with interferon beta–1b (IFNB–1b).

Methods: Interferon-naive RR-MS patients with EDSS 5.5 or below and at least two relapses in the past two years were included after providing informed consent. Serum MCP1, TNF-alpha and TGF-beta were measured at baseline, after 3, 6 and 12 months, and during relapse. Frozen serum samples (–20° C) were analyzed with ELISA in a central laboratory. Valid cases were completers with samples and clinical data available at all time points. Descriptive analyses were performed for demographics, adverse reactions, number of relapses on study, and MCP1, TNF-alpha and TGF-beta values (pg), and were compared to baseline, and between patients with (W) and without (WO) relapses at baseline and 3, 6 and 12 months.

Results: 54 patients (37 females) aged 18–56 years (mean 36.5 ± 8.74 SD) from 19 centers in Spain were analysed. Of the 29 valid cases, 19 were free of relapse after 12 months. 10 patients had 10 relapses in the first 6 months and, of these, 5 patients had 8 more relapses until month 12. The W group showed a higher level of MCP1 at all timepoints (334.7, 416.1, 332.2, 476.9) than the WO group (256.7, 336.1, 329.4, and 317.2). Mean serum levels of TNF-alpha in both groups at the same timepoints showed a slight, steady increase in the WO group (3.9, 4.1, 4.9, 5.9) and a very high increase until month 6 with a sharp reduction at month 12 in the W group (3.7, 7.6, 7.9, 4.2). Mean serum levels of TGF-beta increased after 3 months and had steady levels until month 12 in the WO group (3729.2, 4153.5, 4151.2, 4239.1), whereas a sharp decrease at month 3, a high increase at month 6 and further decrease at month 12 were observed in the W group (3892.2, 3103.5, 4727.0, 4195.5).

Six adverse reactions were reported, all mild or moderate except one severe depression and one urticaria.

Conclusion: This longitudinal study showed that IFNB–1b exerts an immunomodulatory action over time associated with stable, higher levels of chemokine MCP1 and cytokines TNF-alpha and TGF-beta in patients without relapses, whereas an erratic pattern was found in patients with relapses.

P807

Differential expressed genes in brain from multiple sclerosis patients. U. Graumann, B. Erne, A. J. Steck, R. Reynolds, N. Schaeren-Wiemers, University Hospital, Charing Cross Hospital (Basel, CH; London, UK)

Multiple Sclerosis (MS) is a chronic disease that leads to selective and focal destruction of myelin sheaths in the central nervous system. The mechanisms behind the myelin destruction are not well understood but investigations of the oligodendrocyte pathology in various kinds of lesion lead to the suggestion that there is a heterogeneous pathogenesis among MS patients. We are interested in determining whether abnormalities occur in normal appearing white matter (NAWM) in MS brain tissue. We have investigated the gene-expression profiles in autopsy MS brain tissues, obtained from the UK MS tissue bank in London. 37 tissue blocks from 25 MS patients and 21 blocks from 13 controls were screened for their RNA integrity and their cellular pathology. We characterized the expression pattern of the post-mortem brain tissues by differential screening of the AtlasTM Human 3.6 membranes (Clontech) representing 3'528 known human cDNA sequences. Data analysis revealed that in NAWM of 11 MS tissues and white matter of 7 controls about 5–10 % of the sequences are differentially regulated. Statistical analysis of our data showed high interindividual variations within the control as well as in MS patients. However, reproducibility of array hybridization was verified in triplicate. Interestingly, very few alterations in the expression pattern of inflammation related genes (e. g. TNF, IFN, interleukins) were detected with a small number of exceptions, namely Rantes and its receptor. These data are in line with our observation that T-lymphocytes were scant or absent and microglia were activated but not macrophage-like. Additionally, differential expression of many genes related to different cell types was identified. Quantitative RT-PCR is currently being performed for verification of these data. Furthermore, in situ hybridization and immunohistochemistry is being performed to define the cellular identity of the particular differentially expressed gene. Taken together, our study demonstrates that molecular alterations are already evident in NAWM of MS patients and indicate that oligodendrocyte specific genes are differentially expressed in NAWM brain tissues from MS patients. In conclusion, the availability of sufficient amount of post-mortem tissues with intact RNAs and the high sensitivity of the microarray system used allows us to perform a comprehensive study of oligodendrocyte pathology at the transcriptional and protein expression level.

P808

Intellectual decline in relapsing-remitting multiple sclerosis (RRMS): neuropsychological evaluation in a series of patients treated with interferon-beta (INF). C. Zuliani, P. Boni, N. Favaro, F. Canato, C. Fattorello Salimbeni, Civil Hospital (Mirano, I)

Cognitive dysfunction is a common clinical problem in MS, even early in the disease, when overall physical disability is mild to moderate. The aim of this study was to investigate the cognitive impairment by comparing Intellective Quotient (IQ) estimated according to the Wechsler Adult Intelligence Scale (WAIS) with the IQ estimate using the Short Intelligence Test (SIT), based upon the ability in pronouncing irregular words, which is not affected in dementia.

This test documents therefore the IQ before the onset of the disease: the difference between the SIT and WAIS IQ represent the real intellectual decline. We studied 16 subjects with RRMS treated with INFbeta–1a and 1b, 13 females and 3 males, at a mean age of 42 ± 8.4 years, with a MS duration from 3 to 22 years (mean 11.56 ± 6.45) and an Expanded Disability Status Scale (EDSS) score from 1 to 4.5 (mean 2.37). The same tests were submitted to a control group comparable in age, sex, years of education. In all patients Magnetic Resonance Imaging (MRI) indicated multiple areas of abnormal signal intensity in a periventricular and grey-white matter junction distribution, without cerebral atrophy.

Was also submitted the Beck Depression Inventory Scale, which showed absence of depression in 2, minimum in 9, mild in 1 and moderate in 4. Statistical analysis was performed with Student's t-Test.

By comparing predicted IQ (with S. I. T) with WAIS IQ, all cases except 3 showed an intellectual decline, while in the control group the IQ values at SIT and WAIS were the same.

Mean value of decline was strongly statistically significant in Total (T) and Verbal (V) IQ (both $p > 0.005$), not in Performance (P) IQ. With regard to EDSS score, there was a statistically significant impairment in T and VIQ ($p < 0.025$ in the group with 1–2.5 score, $p < 0.05$ in the group = / > 3.5). Patients with less than 10 years MS duration showed a statistically significant impairment in T and V IQ $p < 0.05$), while a MS duration of more than 10 years was strongly associated with intellectual decline (TIQ = $p < 0.001$; VIQ = $p < 0.025$).

It was impossible to compare cognitive impairment with brain MRI findings, rather homogeneous in our MS population. In conclusion our data, through a test which allows to assess premorbid IQ, document a significant decline in intellectual performances in MS patients, mainly correlated with the disease duration rather than the clinical severity of disease and MRI lesion load.

P809

Results of the long-term (8-year) prospective, open label-trial of glatiramer acetate for relapsing multiple sclerosis. K. P. Johnson, B. B. Brooks, C. C. Ford, A. D. Goodman, J. B. Guarnaccia, R. P. Lisak, L. W. Myers, H. S. Panitch, N. Kachuck, J. S. Wolinsky, University of Maryland Baltimore, Middleton Memorial VA Hospital, University of New Mexico, University of Rochester, Yale University, Wayne State University, University of California Los Angeles, University of Vermont, University of Southern California, University of Texas (Baltimore, Madison, Albuquerque, Rochester, New Haven, Detroit, Los Angeles, Burlington, Houston, USA)

To present results of an 8-year prospective open label trial of glatiramer acetate (GA) treatment of relapsing remitting multiple sclerosis. In 1991–92, 251 relapsing-remitting multiple sclerosis (RRMS) patients were randomized in a placebo-controlled, double blind (DB) trial of approximately 30 months duration. This trial led to FDA approval of glatiramer acetate (GA) or Copaxone in 1996. At the end of the DB trial, placebo patients were crossed over to GA and a prospective, organized open label study was begun. Now beyond its 8th year, the study is the longest ever, prospective MS investigation. Patients are evaluated for disability status by EDSS every 6 months. They are seen within 7 days of suspected relapse. The same neurologist and nurse coordinator complete the assessment of each patient. The 142 patients continuing in the study have a yearly relapse rate of < 0.2 or a relapse every 5 years whereas, prior to randomization, the yearly rate was 1.49. The majority, 65.3 % of those always on GA, are improved or unchanged from their initial neurologic status while for those who received placebo for the first ± 30 months, 50.4 % are improved or unchanged. The mean EDSS level for the entire cohort is 3.1, an increase of 0.5 step from randomization. When comparing those always on GA (72) with those crossed over after ± 30 months on placebo (70), there are still discernible differences (i. e. disability and brain atrophy) arguing for the need for early therapy. The daily subcutaneous injections of GA are well tolerated and no safety issues have emerged. Dropouts, which occurred for many reasons, such as relocation, pregnancy and disease worsening, will be discussed. The average MS duration was 7.0 years prior to randomization for the entire cohort, so this carefully studied population has had MS for approximately 15 years. Based on the neurologic disability experience documented in several MS natural history studies, one would expect progression in disability to an mean EDSS level of > 4 with > 50 % reaching a level of EDSS 6 (need for full-time walking aids) in 15 years after diagnosis.

Conclusions: In this long GA trial, the yearly MS relapse rate has fallen to a low level (approximately 1 in 5 years) while the percent of patients worsening has been low especially for patients always on GA. Discernible reduced clinical effects are seen for those who received placebo for ± 30 months. Natural history studies would have predicted a poorer outcome.

P810

Axonal protection mediated by flecainide therapy in experimental inflammatory demyelinating disease. D. A. Bechtold, R. Kapoor, K. J. Smith, King's College London, Guy's King's & St. Thomas Med. School Dpt. Neuroimmunology Hodgkin Building (London, UK)

Axonal degeneration is a major cause of permanent neurological deficit in multiple sclerosis (MS). While the events that lead to axon loss in MS remain unclear, it is likely that inflammatory mediators, such as nitric oxide (NO) may play a role. We have recently shown that axons can degenerate if they are exposed to exogenous NO while electrically active at physiological frequencies. Furthermore, we have also shown that flecainide, a class Ic Na±channel blocking agent, can protect axons from such degeneration. Here we assess the ability of flecainide treatment to reduce axonal degeneration in an animal model of MS, chronic relapsing experimental autoimmune encephalomyelitis (CR-EAE). CR-EAE was induced in male DA rats by inoculation with syngenic spinal cord homogenate in complete Freund's adjuvent. CR-EAE rats received either flecainide (15 mg/kg flecainide twice per day, s/c) or vehicle from 7 days post-inoculation (p. i). Morphometric examination of neurofilament-labeled axons in the spinal cord of severely affected animals, taken 29 days p. i., revealed that the fasciculus gracilis contained significantly more axons in flecainide-treated animals (4922 ± 1259 axons) than their vehicle treated counterparts (3132 ± 682, $P = 0.001$). These findings may indicate a novel avenue for axonal protection in MS and other inflammatory disorders of the CNS.

P811

Decrypting the specificity of the intrathecal IgG response in patients with multiple sclerosis by protein array technology. S. Cepok, S. Stei, S. Nessler, K. Büssow, N. Sommer, B. Hemmer, Philipps-University Marburg, Max Planck Institute of Molecular Ge (Marburg, Berlin, D)

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system (CNS) with an as yet unknown aetiology. Studies on immune cells in the cerebrospinal fluid (CSF) and CNS lesions of MS patients have demonstrated oligoclonal expansions of B cells and somatic hypermutations of the B-cell receptor genes compatible with extensive antigen maturation. Similarly, oligoclonal intrathecal immunogloblin G (IgG) synthesis is observed in most MS patients. Both findings are consistent with an ongoing humoral immune response in the CNS of MS patients. Based on findings in infectious diseases it is likely that the immune response targets disease relevant antigens expressed in CNS tissue. To investigate antigen specificity of the local humoral antibody response in MS patients we applied a novel protein array technology. Arrays, comprising 35,000 cDNA inserts from a human foetal brain library, were probed with CSF and serum of 15 MS patients and 5 controls. Immune responses to 25 proteins were identified in MS patients, which were not observed in controls. These candidate antigens were selected to analyze a larger cohort of MS patients and controls for immunreactivity. Elevated titers were more frequently observed in MS patients than controls for some of the possible target antigens. Interestingly, different patterns of immune reactivity were found among individual MS patients, suggesting heterogeneity in the intrathecal immune response. Further studies will address the encephalitogenicity of possible target antigens in experimental animal models to support the role of these antigens in the pathogenesis of MS.

P812

The intake of defined processed meat products in multiple sclerosis (MS): a case-control study. M. Geilenkeuser, K. Griesenbeck, W. Firnhaber, K. Lauer, Klinikum Darmstadt (Darmstadt, D)

Objectives: To test the association between the consumption of different smoked meat products (Mult Scl 1997;3:282) and MS in the same patient group, but a different control group.

Methods: In 177 MS patients and 88 hospital controls with minor surgery, both born after 1944, the consumption during childhood of (a) hot-smoked sausages, (b) cold-smoked meat and (c) cold-smoked sausages was assessed by means of a questionnaire. The intake of oat flakes, total fat, animal fat and butter, nursing, the onset of measles and of any childhood disease, the socio-economic status of the parent family, and the size of residence (rural, semirural or urban) at age 8 were also interrogated. Bivariate analysis was made using the Odds Ratio (OR) and 95 % confidence intervals (CI), and significant findings ($p < 0{,}05$), year of birth and gender were entered into a stepwise logistic regression model using Statistica for Windows.

Results: In bivariate analysis all 3 smoked foot items, animal fat and low oat-flake consumption were significantly associated with MS. In logistic regression, only hot-smoked sausages (OR = 3.0; 95 % CI: 1.7–5.3; $p = 0.0001$) and animal fat intake (OR = 2.0; 95 % CI: 1.1–3.7; $p = 0.028$) made an independent contribution to the MS risk. Analysis by subgroups revealed hot-smoked sausages and cold-smoked meat only in females and in rural/semirural patients, and hot-smoked sausages only in patients having a father with a manual occupation. Conclusions: In agreement with numerous ecological studies and two case-control studies (Neuroepidemiology 1993;12:234; Mult Scl 1997;3:282) smoked meat products were shown as a risk factor in MS. A hypothesis on a possible role of nitro-phenolic compounds from smoking and nitrite-curing, occurring in processed meat (J Sci Food Agricult 1975;26:267), has been published (Mol Immunol 1990;27:697; Med Hypotheses 1993;40:368).

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P813

Correlation of disability and chemokine receptors expression on blood CD4+ T cells in multiple sclerosis patients following methylprednizolone treatment. N. Grigoriadis, A. Kalpatsinidis, D. Litsa, R. Lagoudaki, M. Karadrakonti, M. Bouchtsi, A. Lourbopoulos, I. Milonas, AHEPA University Hospital (Thessaloniki, GR)

Chemokines appear to play crucial role in recruiting selective subsets of leukocytes in the inflammatory process in multiple sclerosis (MS). However, there are limited reports regarding any relation between the level of disability and chemokine receptor (CR) expression. In the present study,

the CR expression was analyzed in relapsing remitting MS patients with a clinically definite relapse and under no immunosuppressive treatment within the previous three months. Patients were clinically examined at relapse, 5 days and 1 month after the initiation of a 5-day course with a daily dose of 1000 mg methylprednizolone (MP), intravenously. Peripheral blood mononuclear cells were isolated from patients at the same time as well as from healthy controls. Lymphocytes were gated and analysed by flow cytometry for the following markers: T-helper 1 type cytokines (IFN-gamma, IL2, TNF-alpha) and chemokines (CXCR3, CCR5) as well as T-helper 2 cytokine (IL4) and chemokine (CCR3). The reduction in the EDSS following MP treatment was significant only at 1 month follow-up (–1,21 ± 0,859, mean ± SD, $P < 0,05$). All three chemokine receptors expression tested at relapse was significantly higher compared to that of controls ($p < 0,05$). Neither the cytokine nor the chemokine receptor expression changed significantly during follow up after treatment with MP and remained constantly above the correspondent control levels. However, among the markers studied, only CCR3 expression could be reversibly correlated with EDSS changes ($p < 0,05$). Our results indicate that high dose of MP treatment may reduce the EDSS score in MS patients within a month after a relapse. The reduction noticed in disability may not be attributed to any change in the expression of blood chemokine receptors. However, blood CD4+ CCR3 expression, which is a T- helper 2 linked chemokine, may well be correlated with a better outcome after MP treatment of a relapse.

P814

Tolerability of interferon beta–1b (Betaferon(R)/Betaseron(R)) can be significantly improved using both interferon-free needle and automated injection techniques. C. Tornatore, D. Bartlett (Washington DC, USA)

Betaferon/Betaseron is highly effective in treating relapsing/remitting (RR) and secondary progressive multiple sclerosis (MS). Although injection-site reactions (ISRs) are reported with beta interferon, improved injection technique is believed to reduce their occurrence. An automated injection device (Autoject) using an interferon-free needle can help achieve this. Also, replacing the needle used to prepare Betaferon/Betaseron with an interferon-free needle prior to injection may reduce ISRs most likely by minimizing contact between Betaferon/Betaseron and skin or subcutaneous tissue.

We performed a 12-week, randomized, Latin-square crossover study in 26 people with MS to determine whether alternative administration methods reduce ISRs. All patients had RRMS, consistently experienced ISRs and had used Betaferon/Betaseron for a mean of 15 months (7–29 months).

Patients self-administered Betaferon/Betaseron using standard subcutaneous injection during study days 1–9, then were randomized to receive Betaferon/Betaseron in one of three pre-defined sequences. Each included approximately 21 days of standard subcutaneous injection, interferon-free needle administration and using Autoject. During the study 252 doses of Betaferon/Betaseron were administered using the standard injection technique, 251 using interferon-free needles, and 255 using Autoject. The primary outcome measure was the number of ISRs. Secondary outcomes were also measured.

Using Autoject resulted in fewer ISRs (21, 8.2 % of all injections) than the interferon-free needle (34, 15.3 %) and standard techniques (54, 28.1 %). Both Autoject and the interferon-free needle technique significantly reduced the number of injections associated with ISRs relative to the standard technique –61.6 % ($p = 0.0001$) for Autoject and 27.5 % ($p = 0.001$) for the interferon-free needle technique. Four patients (15.4 %) experienced no ISRs with the standard technique versus 7 (27 %; $p = 0.01$) using the interferon-free needle technique and 12 (46.2 %; $p = 0.001$) using Autoject. Autoject also appeared to reduce the risk of severe erythematous reactions and injection site pain, although statistical analysis was not possible due to the small sample size.

Using Autoject significantly reduced ISRs associated with Betaferon/Betaseron administration by over 60 % and is likely to offer greater convenience to people with MS. An interferon-free needle technique offers advantages over standard administration where Autoject is not appropriate.

P815

Personality traits predispose to fatigue experience in multiple sclerosis (MS) patients. S. Merkelbach, J. Koenig, H. Sittinger, University Hospital (Homburg/Saar, D)

Objectives: There is substantial debate about whether organic or non-organic sources have to be favored regarding the pathogenesis of tatigue experience in MS. The high relevance of personality characteristics found in patients with chronic fatigue syndrome (CFS) might be questioned for MS, because MS patients do not uniquely suffer from fatigue, and in MS various competing fatigue sources have to be considered.

Patients and methods: To determine the impact of personality characteristics and to compare the results with the impact of bodily impairment, a total of 80 patients with definite MS (mean age 38.5 ± 9.0 years, 62 females) were surveyed using questionnaires assessing both fatigue experience and personality traits (German Freiburg Personality Inventory-Revised; FPI-R). The relationship between fatigue scores, FPI-R scores, and clinical severity of MS was calculated by using correlation analysis. To identify independent FPI-R items, stepwise regression analysis was used. Partial regression analysis was performed to evaluate the relevance of personality traits towards fatigue as compared to bodily impairment.

Results: Only less substantiated relationships could be demonstrated between personality traits and the severity or the duration of MS ($r < 0.28$). The correlation between fatigue scores and FPI-R scores was much closer ($r < 0.47$). Out of 11 personality items, increased levels of neuroticism and sensitivity, and decreased levels of extraversion were found to relate independently to fatigue ($0.21 < \text{beta} < 0.52$; $0.0001 < p < 0.05$). The impact of these personality traits towards fatigue (partial R square ranging up to 0.32; $0.0001 < p < 0.02$) was much higher than the impact of physical impairment (partial R square ranging from 0.02 to 0.04; not significant).

Conclusion: A psychological model of fatigue im MS was supported by the fact that personality items, especially emotional lability, were significantly associated with the presence and severitiy of fatigue in MS. Because all patients in our study were chronically ill (similar to CFS studies), but not all patients did complain about fatigue experience, personality style and especially increased neuroticism may specifically relate to fatigue experience and not only to the chronicity of any chronic disease. Since FPI-R items highly over-weighted somatic sources of the complex fatigue syndrome in our study, therapeutical strategies considering not only bodily aspects of MS have to be discusssed.

P816

Hormonal dysfunction in multiple sclerosis: an open question. M. Paschalidou, E. Vafiadou, M. Bouchtsi, M. Karadrakonti, M. Karamouzis, I. Giovos, A. Dimitriadou, I. Milonas, AHEPA University Hospital Aristotle University of Thessaloniki (Thessaloniki, GR)

Investigation of a possible relation of hormonal dysfunction with the immunopathogenetic defect in Multiple Sclerosis (MS).

27 women with MS were studied, 20 with relapsing-remitting and 7 with secondary progressive type, aged 19–48 years with a normal menstrual cycle and in a remission of the disease. Thirty women were the control group. In 10 women, in early follicular phase, a stimulation of the hypothalamus-hypophysis-ovaries (HHG) axis occurred using an intravenous infusion of GnRH. The hormones FSH, LH, estradiol (E2), progesterone (PG), cortisole, prolactin (PRL), testosterone, androstendione (AD) and DHEAS were measured in time zero. Gonadotropins were evaluated every 30 minutes, for 2 hours after the infusion of GnRH. In the remaining 17 women cortisole, PRL, testosterone, AD and DHEAS were estimated. In the GnRH-stimulated group, FSH and LH were normal as well as the reaction after the stimulation. E2 and PG were low in all women ranging 37–196.9 pmol/l and 0.04–1.3 nmol/l respectively. Also the levels of cortisole were low in all 10 patients (106–233 mol/l). PRL was found to be high in 6 women, (318.6–395.4 mU/l), and normal in 4. Testosterone was low in 6 women. DHEAS was low in 7 women (23–234 ng/ml). AD levels were normal in all 10 women. In the second group, we observed low cortisole in 10 women (11.4–239 nmol/l), high PRL in 12 women (306–450 mU/l) and low testosterone and DHEAS in 10 (0–0.5 nmol/l) and 13 (1.8–228.5 ng/ml) patients respectively. The normal reaction of hypophysis to GnRH declares the integrity of function of the hypophysis and rule out the primary defect of the ovaries. The dysfunction of the HHG axis is connected to the hypothalamic area. The low levels of estrogens, are likely involved indirectly, through the ranging of interleukines in the immunopathogenetic processing of MS. Furthermore, the low levels of cortisole are also related either as a primary factor or as a consequence of treatment with corticosteroids. The significant increase of PRL in 18 women is a likely factor involved in the activation of the disease, either as a cause, or as a result. The low values of testosterone (59 %) and DHEAS (74 %) are classified within the frames of the dysfunction of the HHG axis.

The results of this study supports the hypothesis that there is a hormonal dysfunction in women suffering from MS which is probably related with the immunogenetic character of the disease, either as a primary or as a secondary cause.

P817

Acute psychosis in multiple sclerosis. B. Castaño-Garcia, M.-L Martinez-Gines, A. Esquivel, M. Rodriguez-Yañez, C. de Andres, L. Muñoz-Almazan, H. G. U. Gregorio Marañón (Madrid, E)

Background: Psychiatric disorders are common in patients suffering from multiple sclerosis (MS), being predominantly affective disorders. Psychosis is a rare complication in this disease. We present three patients with MS and Psychosis.

Patients and Methods: Case 1: A 50-year-old woman was admitted to hospital because an acute paranoid psychosis. The diagnosis of clinical definitive MS was made 2 years before. Cranial magnetic resonance imaging (MRI) showed bilaterally demyelinating lesions in the areas surrounding the temporal horns of the lateral ventricles. Single positron emission computerized tomography (SPECT) showed hipoperfusion in the right frontal and temporal lobes. She was treated with a 5-day course of high-dose corticosteroid and neuroleptic. The patient's status gradually improved within a few weeks.

Case 2: A 26-year-old woman with MS was hospitalized in a Psychiatric Department for acute paranoid psychosis. She had presented two remissions and relapses of MS since the age of 15, and was neurologically stable at the time of the psychosis. MRI showed left hippocampus lesion. She was treated with neuroleptic, improving in the following weeks.

Case 3: A 35-year-old woman had one-year MS history, and presented an acute psychosis with predominant paranoid symptoms, after a 3-week adrenocorticotropin (ACTH) treatment. She also required neuroleptic therapy.

Discussion: Psychosis is not a prominent feature of MS. When it happens, usually is not a chance occurrence, but rather a consequence of the disease process, caused by lesions in the temporal horns of lateral ventricles, as occurs in case 1 and 2. Case 3 was secondary to corticosteroid therapy. Physiopathology is not clear. It has been hypothesized the paper of temporal-limbic circuits, which could be interrupted by acute demyelination. Some clinical features orientated psychosis is not primary: a later age of onset, the absence of psychiatric disorders previous to the MS development, the auto-limited duration of symptoms, low tases of recurrence, and the absence of psychiatric family's histories. Corticoids could theoretically improve psychosis related to acute demyelination, against the general opinion of them exacerbating psychiatric symptoms, and should be consider when psychosis is attributed to MS lesions.

P818

Effect of multiple sclerosis treatment with interferon beta 1b and interferon beta 1a (Rebif) on the depressive symptomatology. M. P. Sánchez, T. Olivares, A. Nieto, T. Wollmann, M. A. Hernández, J. Barroso, Universidad de La Laguna, Hospital Universitario Nuestra Señora de la Cander (Tenerife, E)

Background: Depression is a suspected side effect of inmonumodulatory therapy in patients with multiple sclerosis (MS). There are conflicting data that depression may occur with interferon beta–1b (IFNB–1b) and interferon beta–1a (IFNB–1a) treatments. Methodologic factors could contribute to these discrepancies.

Objective: a) to examine and to compare the changes in emotional state in relapsing-remitting MS patients after the first year of treatment with IFNB–1b and IFNB–1a (rebif) b) to assess the relationship between mood state and some clinical variables: physical disability and number of exacerbations.

Methods: Data are reported for 37 patients with relapsing-remitting (RR) multiple sclerosis and a neurological disability score (Kurtzke Expanded Disability Status Scale, EDSS) less than 3.5. Fourteen patients were treated with IFNB–1b, fifteen with IFNB–1a (rebif) and eight without interferon treatment. Mood disturbance was assessed by the Beck Depression Inventory (BDI) and physical disability was examined with de EDSS. The first testing was done before the start of treatment and the second testing was done one year later.

Results and conclusions: Our findings show a significant improvement of emotional state after 1 year only in the two groups of treatment: IFNB–1b and IFNB–1a [$F(1, 43) = 6, 204$, $p = 0, 017$]. No evidence of significant correlations between the EDSS scores and the number of exacerbations with the BDI scores was obtained. These results suggest that the inmonumodulatory therapy had a beneficial effect on emotional state and this effect is not related with the clinical variables examined.

P819

Proton magnetic resonance spectroscopy for metabolic characterization of plaques and normal appearing white matter in multiple sclerosis. N. Isik, F. Candan, A. Dincer, T. Seleker, D. Dama, SSK Goztepe Educational Hospital, Bakirkoy Radyotom – Radyomar Imaging (Istanbul, TR)

Regional in vivo proton MR-Spectroscopy provides quantitative data on metabolic characterization of plaques in patients with multiple sclerosis (MS). Recent MRI and pathological studies have indicated that axonal loss is a major contributor to progression. Also some previous studies clearly showed that some biochemical abnormalities present in the normal appearing white matter (NAWM)of patients and this may will be a mechanism for progression and increased disability.

In this study we performed proton magnetic resonance spectroscopic (P-MRS) examinations in 22 clinically definite MS patients and 7 healthy controls. Then we assessed the levels of N-acetyl aspartate/creatine (NAA/Cr) ratio and some other metabolites in chronic plaques and NAWM of patients. Spectra localized to chronic plaques showed a decreased NAA/Cr ratio comparing to NAWM and minimally increased Myoinositol/Cr ratio. Spectra localized to NAWM showed a significantly lower NAA/Cr ratio in patients than controls ($p < 0.05$).

Since it's believed that NAA is a reliable neuronal marker our results suggest that axonal loss occurs in NAWM of MS patients.

P820

Clinical and RMI impact of mitoxantrone in 111 secondary progressive multiple sclerosis patients. G. Taurin, E. Leray, E. Lepage, E. Sartori, M. Coustans, G. Edan, CHU Pontchaillou (Rennes, F)

Introduction: The clinical benefit of MITOXANTRONE (Mito) for worsening RR and SPMS has been supported by 2 controlled trials. This study sought to assess clinical and MRI follow up of 111 consecutive secondary progressive multiple sclerosis patients treated with Mito over a median duration of 3years.

Methods, patients: In our MS center, 111 SPMS had received Mito according to 2 different protocols: 53 SPMS, were treated monthly with Mito IV, 20 mg, and methylprednisolone 1 g IV for 6 months (cumulative dose: 77.2 mg/m2), followed 3 months later by a maintenance therapy (13 patients by Mito every 3 months, 8 patients by Interferon Beta, 14 patients by Methotrexate, 8 patients by Azathioprine). 58 other patients were treated with Mito, 20 mg, every 3 months (cumulative dose: 60.1 mg/m2), followed by other maintenance therapies (9 patients by Interferon Beta, 3 patients by Methotrexate, 1 patient by Azathioprine). The median duration of MS and the median duration of progressive course, before initiating Mito, were respectively 14 years and 8 years.The mean worsening of EDSS within the 24 months before Mito was 1.5. 67 patients (60 %) had superimposed relapses within 2 years prior Mito. 36 % had gadolinium enhanced lesions on MRI. Clinical and MRI data were collected yearly in EDMUS.

Results: The mean EDSS didn't change significantly from baseline: from 6.0 to 6.1 at 1 year (108 patients), from 6.0 to 6.2 at 2 years (74 patients) and from 5.9 to 6.2 at 3 years (39 patients). 1 point EDSS worsening at time point from baseline was 23 % of patients at 1 year, 18 % of patients at 2 years, and 20 % of patients at 3 years of follow up. The mean annual relapse rate decrease from baseline: from 0.7 to 0.1 at 1 year from 0.9 to 0.2 at 2 years and from 1.0 to 0.3 at 3 years of follow up. 10 % of MRI after discontinuing Mito, has gadolinium enhanced lesions. Data according to the 2 different protocols will be also presented.

Conclusion: This open trial supported the conclusion of the previous controlled trials, that MITOXATRONE has a clinical and MRI impact on the inflammatory markers of the disease.

P821

The presence of auto antibodies against class III ß-tubulin in patients with focal brain lesions. K. Kranda, M. Bojar, L. Glosova, R. Liscak, J. Baurle, V. Vladyka, FU-Berlin, CUNI, Hospital Na Homolce (Berlin, D; Prague, CZ)

Neurodegeneration constitute a neuronal loss resulting from a brain disease or a trauma. In chronic neurodegenerative diseases, this loss is gradual whereas acute and episodic phenomena such as brain hemorrhage, stroke, or a radio-surgical treatment of malignant tumours with a linear accelerator (LINEAC) or Leksel gamma knife (LGN) should lead to a more pronounced as well as rapid loss of neurones which is chronologically restricted. We searched for a biological marker of neurodegeneration by targeting auto-antibodies against amino-acid sequences of the degraded cytoskeleton, in particular class III ß-tubulin, which is found only in the brain. The initial screening of several disease groups, included demyeli-

nating conditions such as multiple sclerosis (MS), chronic neuroboreliosis and two patient groups with either encephalitis or brain tumours, some of whom had already undergone radiation therapy with LINEAC or LGN. Auto-antibodies generated against the end sequence of class III ß-tubulin were measured in the serum with an ELISA-test developed for this purpose. We found auto-antibodies in 21 cases out of 199 sera tested of patients with suspected inflammatory indication, including MS chronic borelliosis. and encephalitis. None of the patients with brain tumours tested positive, not even after an extensive radiation surgery. Whether patients who have undergone radio-surgery will generate auto-antibodies against this tubulin epitope at a later date, remains to be seen in the course of a long term monitoring of this patient group. The momentary positive rate ("10 %) of patients suffering from inflammatory and demyelinating diseases is relatively low (the positive rate in the normal population of comparable age is below 1 %) but this rate may increase if such patients are monitored over a longer period of time.

P822

Prospective surveillance of different INF beta preparations in early relapsing-remitting MS. J. Haas, Jewish Hospital Berlin (Berlin, D)

Introduction: In the last six years three INF beta preperations were licensed in Germany for relapsing remitting MS –1996 Betaferon (INF beta 1b) '1997 Avonex(INF beta 1a im) and 1998 Rebif (22ug INF beta 1a sc). According to the consensus of the German speaking MS experts MS patients get the recommendation for an early treatment. Based on the product informations they could made the choice between the three INF beta products.There is in ongoing discussion concerning the efficacy of the different INF beta preparations.

Methods: To compare the three INF beta products in the daily practice we evaluated prospectively the course of the disease in 228 MS patients (EDSSS 0 –3,5) treated with INFb 1b n = 86 'INFb 1a i. m. n = 88, INFb 1a s. c. n = 54. The baseline data and the follow up data (EDSS, number of exacerbations, side effects) were documented (data base MUSIS) and evaluated with statistical methods. The dat were compared with the active arms of the double blind studies in exacerbating remitting MS.If available the MRI findings before and after one and two years of treatment were evaluated concerning Gadolinium enhancing lesions.

Results: The base line data revealed no statistical significant differences concerning mean age (36.2–36.7 y), mean duration of disease (6,7 –9,6 y), relapse rates (2,2 –2,1), EDSS (2–2.2). Scheduled visits were every 3 months in the first year and every 6 months in the following years (24 months – 60 months) Until now we evaluated at least 24 months of observation. All INF beta preparations reduced significantly the relapse rates compared to prestudy data. The reduction was minus 67 % for Avonex and minus 50 % for Betaferon and Rebif respectively. Freedom of relapses was 41 % for Avonex '43 % for Rebif and 48 % for Betaferon. Freedom of progression was 74 % (Avonex) 72 % (Betaferon) 78 % (Rebif).The data were comparable to the study data.There were no significant differences concerning the discontinuation rate (38 % for Avonex, 38 % for Betaferon and 33 % for Rebif).The MRI data will be presented.

Conclusions: The 24 months analysis revealed a benefit concerning relapse rates, freedom of relapses and progression for all applied INF beta preparations.The data confirm the daily life relevance of the study data concerning the chance for freedom of relapses and freedom of progression.

P823

Hepatic abnormalities reported during interferon beta–1a therapy. G. S. Francis, Y. Grumser, F. O'Brien, P. Chang, Serono, Inc. on behalf of the Rebif Safety Study Group (Rockland, USA)

Objective: Analyze the hepatic safety profile of interferon beta–1a (IFN) therapy and devise management recommendations.

Background: IFN is associated with hepatotoxicity but the precise incidence and dose effect issues have not been fully explored.

Methods: Safety data for 1,995 IFN-treated and 824 placebo patients from 6 controlled studies at various doses were analyzed at 6 months (n = 2,819) and 24 months (n = 1,178) for adverse events (AE) and laboratory abnormalities. WHO grades were used for ALT elevation (Grade 1 < 2.5 times normal; Grade 2 = 2.5 to < 5 times normal; Grade 3 = 5–20 times normal; Grade 4 = > 20 times normal)

Results: Hepatic AE were reported in 3 % placebo, 4 % 22mcg qw, 7 % 30mcg qw, 4 % 44mcg qw, 15 % 22mcg tiw and 20 % 44mcg tiw patients between 0 and 6 months. Between 0 and 24 months, hepatic AE were reported in 9 % placebo, 27 % 22mcg tiw and 34 % 44mcg tiw patients. The vast majority of hepatic events (90 %) were elevated transaminases, particularly ALT. ALT was elevated on at least one occasion, regardless of reporting as an AE, in 16 % placebo, 28 % 22mcg qw, 28 % 30mcg qw, 28 % 44mcg qw, 44 % 22mcg tiw and 59 % 44mcg tiw patients between baseline and 6 months and 26 %, 53 % and 68 % for placebo, 22mcg tiw and 44mcg tiw from 0 to 24 months. For high-dose IFN, 67 % of elevations were Grade 1 with 7 % Grade 3 (cf. 2 % placebo). No Grade 4 elevations were seen. Half of all patients who develop elevated ALT do so in the first 3 months and 75 % by 6 months on therapy. ALT decreases spontaneously or with dose alteration. IFN can be re-introduced later often without recurrence of toxicity. The percentage of patients with ALT elevation at 2 years was 6 % in placebo, 8 % in 22mcg tiw patients and 10 % of 44mcg tiw patients. Approximately 8 % of patients on 44mcg tiw will have persistent elevation, at any grade, for over 12 consecutive months. Less than 1 % of high dose patients stop therapy for elevated ALT.

Discussion: Hepatic dysfunction is common with IFN therapy. ALT elevation is dose-related but is infrequently severe (Grade 3), results in a small proportion (1 %) of patients stopping therapy and is reversible spontaneously or with dose modification. Less than 10 % have abnormal values (all grades) after 2 years on therapy. Blood tests at baseline, 1, 3 and 6 months will permit early detection of patients destined to have liver dysfunction and will allow appropriate dose modification.

P824

Neopterin serum level and interferon beta 1a (Avonex) therapy in multiple sclerosis: a two-year prospective study. F. Casoni, R. Bedin, P. Sola, A. Bertolotto, E. Merelli, University of Modena (Modena, Turin, I)

Background: Interferon Beta (INF-b) may induce the expression of several proteins, including neopterin, which is considered a biological marker of INF-b*f*n activity.

Objectives: we aimed to determine possible variation of the neopterin serum level profile at the beginning and during the therapy with IFN-b–1a (AvonexTM) in relapsing-remitting multiple sclerosis (r-r MS) patients, and to individuate possible relationships between the protein synthesis and the clinical course of patients. Methods: thirteen patients were treated with i. m. 6 MIU/weekly INF-b–1a for two years. Blood samples for neopterin determinations were collected before each injection and after 12, 48, 72, 96, 120 and 144 hours at time zero, and at 6^{th}, 12^{th}, 24^{th} month of therapy. Moreover neutralizing antibodies (NABs) determinations were performed Results: neopterin level after 24 hours from the injection was significantly higher than the baseline, maintained elevated for 72–96 hours, and returned at the baseline level after 120 hours. Nine of the 13 patients had clinical benefit from therapy, while 4 patients dropped out for the progression of the disease. After 1 year of therapy the two groups of patients significantly differed for the synthesis of the neopterin while only one patient was positive for NABs. Conclusion: the protein may be considered a suitable biological marker of IFN-b1a activity, and as preliminary result, neopterin could be considered also a marker of the clinical response to IFN-b therapy.

P825

Characterization of molecular alterations in normal appearing white matter from multiple sclerosis patients. N. Schaeren-Wiemers, U. Graumann, R. Reynolds, A. J. Steck, University Hospital Basel, Charing Cross Hospital (Basel, CH; London, UK)

Multiple Sclerosis is a chronic disease that leads to selective and focal destruction of myelin sheaths in the central nervous system. Although macroscopic changes in MS brain are detectable in the lesion sites, it is more difficult to determine whether abnormalities occur in normal appearing white matter (NAWM). Magnetic Transfer Imaging studies of NAWM have shown that alterations were already evident before the blood brain barrier was affected. Therefore, our major interest is to understand how oligodendrocytes react to the demyelinating insult in MS and if their molecular expression pattern is already altered in NAWM, which may give an indication of a possible predisposition to damage. We have investigated the gene-expression profiles in autopsy MS brain tissues, obtained from the UK MS tissue bank in London. We characterized the expression pattern of the postmortem brain tissues by differential screening of 3'528 known human cDNA sequences by the microarray technology. Data analysis revealed that in NAWM of MS patients and white matter controls about 5–10 % of the sequences are differentially regulated. Many of the differentially expressed genes show an upregulation in MS while some of them were down regulated. Interestingly, particular genes playing a role in myelination such as phospholipase A2, MAL, MAG and MOG show a tendency to be upregulated in NAWM in some MS cases. Furthermore, we have identified that several genes, which play a role in oligodendrocyte de-

velopment, are upregulated indicating that already in NAWM molecular processes take place affecting the oligodendrocyte lineage. Overall analysis of the microarray study showed up- and down regulation of a number of unexpected genes such as for example 14–3–3, which is strongly upregulated and veli–1, which is downregulated. Both genes are known to be expressed in neurons, and therefore we are currently investigating their expression pattern in NAWM. In conclusion, we have shown that in NAWM in MS brains many genes are already specifically differentially regulated, although from the cellular and morphological point of view alterations were not yet visible. Our results support the observations by MRI that NAWM is abnormal in MS. The identification of differentially expressed genes in NAWM will bring new insight into the pathophysiology of MS and will enable us to better understand the molecular and cellular alterations in oligodendrocytes leading to demyelination and failure of remyelination.

P826

Development of an international patient-centered quality of life scale for multiple sclerosis. A. Beresniak, M. C. Simeoni, O. Fernandez, P. Flachenecker, J. Pelletier, S. Stecchi, L. Blumhardt, P. Auquier, Serono International SA, Observatoire Regional Epidemiologie, Hospital Carlos Haya, Neurologische Klinik, Hopital de la Timone, Villa Mazzacorati, Queen's Medical Centre and the MUSIQOL Study Group

The Multiple Sclerosis International Quality of Life (MuSIQoL) Questionnaire is a multi-dimensional self-administered specific health-related quality of life (QOL) scale for multiple sclerosis (MS). The questionnaire focuses on concerns identified by patients with MS and has been developed simultaneously in several western languages. None of the five health-related QOL scales commonly used in MS fulfills both of these criteria. The MuSIQoL Questionnaire will be used to assess different therapeutic strategies and to evaluate patients' use of health care services. It is designed to be useful for patients with differing levels of impairment.

We interviewed 94 patients in France, Germany, Italy, Spain and the UK who had a diagnosis of MS according to the Poser criteria. Both in and outpatients with varying levels of disease severity were involved, including patients with relapsing-remitting, primary progressive and secondary progressive MS and with isolated clinical syndromes. After analyzing the content of the audio-taped interviews, we selected 73 items describing social relationships, mental and physical health and activities, for which we established trans-cultural equivalence using forward-backward translation. The acceptability and comprehensibility of this preliminary questionnaire were tested among 80 additional patients in the five countries.

Since the initial interviews, eleven more countries have joined this project: the USA, Canada, Turkey, Brazil, Norway, Sweden, Lebanon, Argentina, Israel, Mexico and Russia. The next steps will be to integrate these countries by conducting cross-cultural validation and testing acceptability of the preliminary questionnaire; to produce a shorter questionnaire by selecting the most informative items from a study including at least 300 patients from all 16 countries; and to evaluate the psychometric properties of this questionnaire in at least 1000 patients.

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P827

Gluten sensitivity in MS-like neurological syndromes. A. Ghezzi, M. Zaffaroni, A. Falini, M. Filippi, Centro Studi SM, Hospital San Raffaele (Gallarate, Milan, I)

Background. Celiac disease can present a wide spectrum of neurological complications such as dementia, myelopathy, peripheral neuropathy, ataxia, epilepsy, brainstem involvement. Cerebellar involvement ("gluten ataxia", Hadjivassilliou et al. Lancet 1996) is a well recognized clinical entity Cases with a relapsing course are described, with characteristics similar to MS. (Ghezzi et al. Neurology 1997). Rarely, neurological manifestations may occur in subjects free from gastrointestinal symptoms. We present here 4 new cases recently observed, with MRI and CSF findings (in 3 cases) suggestive of MS. Gastrointestinal symptoms were scanty (case 1) or absent (case 2, 3, 4). In all patients vasculitis was ruled out, anti-gliadin antibodies were increased in repeated samples, and jejunal biopsy was normal.

Case 1, female subject 22 years old. She presented 3 attacks with loss of consciousness and diffuse tonic clonic movements. Brain MRI showed multiple periventricular lesions within the white matter. CSF showed IgG oligoclonal bands.

Case 2, male subject 35 years old. He developed acute right hemiparesis. Brain MRI showed a large periventricular lesion in the left temporal lobe and two small periventricular lesions. CSF examination revealed IgG oligoclonal bands.

Case 3, female subject 42 years old. She developed progressive cerebellar ataxia. Multiple white matter lesions were found on brain MRI, CSF was normal.

Case 4, female subject 40 years old. She presented clinical manifestations of progressive myelopathy. Brain MRI showed small periventrivular lesions, oligoclonal bands were found in the CSF.

In all cases MRI, CSF and anti-gliadin antibodies findings were confirmed in the follow up. Brain MRI with MT technique and spectroscopy were also performed to better evaluate the characteristics of lesions, compared to MS.

Conclusions a) clinical/CSF/MRI findings suggested the diagnosis of MS in these cases, in spite of atypical aspects(Epilepsy in case1, the large temporal lesion in case 2, the normal CSF in case 3, the discrepancy between disability and MRI lesion load in case 4, b) An inflammatory autoimmune mechanism is supposed in these cases. Anti-gliadin antibodies could play a role in the pathogenesis of CNS involvement as suggested for subjects with "gluten ataxia" (1). c) CSF and MRI findings were abnormal, as observed in demyelinating inflammatory diseases: "gluten-encephalopathy" should be considered in differential diagnosis of MS.

P828

Campath–1H in the treatment of patients with multiple sclerosis: a pilot study. E. Le Page, A. J. Coles, A. Cox, V. Denys, D. Miller, D. A. S. Compston, Addenbrooke's Hospital, Queen Square (Cambridge, London, UK)

Campath–1H, a humanised anti-leukocyte (CD52) monoclonal antibody was previously assessed in the treatment of patients with secondary progressive multiple sclerosis (SPMS). These results indicated the need to assess efficacy in patients with active multiple sclerosis treated before the onset of disease progression.

This is a retrospective study of all 47 patients treated with Campath–1H in Cambridge, since 1991 (36 from the previous study: cohort 1 and 11 subsequently treated on a compassionate basis: cohort 2). All patients were evaluated clinically every 3–6 months to record disability (EDSS) and new relapses; lymphocyte sub-populations (CD4, CD8, CD19, CD52, CD45 RO and CD16) were used to follow the depletion induced by Campath–1H; and serial MRI was performed in 25 patients from cohort 1.

In cohort I, Campath–1H was started at a mean of 11 and 4 years after disease onset and progression, respectively. The mean duration of follow-up was 6 years. At most recent assessment, the majority of patients showed progressive disability, starting 2–3 years after treatment in those who were initially stabilised; seven were re-treated but without any further benefit. In cohort 2, Campath–1H was given at a mean of 21 months after disease onset; although cases were selected for active relapsing-remitting disease, 3 were subsequently shown to have developed disease progression, 4–8 months before treatment. Mean number of relapses was 3/patient in the year before treatment (with 56 episodes collectively since disease onset) during which EDSS changed by 2.5 points. At present, mean duration of follow-up in the 8 patients with relapsing disease is 10 (range 1–25) months. Two had a single relapse 12 and 15 months after Campath–1H but without a change in EDSS; six had no evidence of active disease during the period of follow-up (range 1–25 months). This represents a change in annualised relapse rate from 2.9 to 0.3. Of the 3 with SPMS, one continued to worsen despite having no new disease activity; one had a single relapse 18 months after Campath–1H with change in disability; and the third remains unchanged after 3 months.

This study strengthens the evidence for improved efficacy of Campath–1H given during the period of disease activity attributable to inflammation. These principles are now being adopted in a randomised trial comparing Campath–1H with interferon beta.

P829

Cytokine from cytometry in patients with multiple sclerosis relapsing-remitting. P. de Castro, D. Lazaro, A. Sanchez Ibarrola, University Clinic, (Pamplona, E))

Background: In previous studies we have examined intracellular cytokines in peripheral blood mononuclear cells (PBMC) of MS patients, by flow cytometry (cytokine flow cytometry) in MS secondary progressive patients showed an increased number of cells producing interferon gamma (Inf-Y). These cells belonged to the CD4 and CD8 subsets in similar proportions.

Objective: To know the production of interferon gamma in MS (RR) patients.

Patients and method: 20 clinically definite MS RR patients. Main age 36 years (rank 20–51). Mean EDSS 2 (rank 0–3.5). Determination of cells producing Inf-Y after activation compared with 20 healthy subjects, ages and sex-matched.

Results: MS patients have a negative correlation between age and time of evolution and percentage of CD4 cells producing Inf-Y ($p < 0,04$ y $p < 0,01$).

Conclusion: Also in MSRR patients, the percentage of cells CD4 producing gamma interferon decrease with age and time of evolution. The production of CD8 gamma interferon remains unchanged.

P831

Cytomegalovirus antibodies positivity predicts a better clinical and radiological outcome in multiple sclerosis patients. R. Zivadinov, M. Zorzon, D. Nasuelli, M. A. Tommasi, M. Serafin, A. Bratina, M. Ukmar, R. S. Pozzi-Mucelli, E. Millefiorini, L. Monti-Bragadin, A. Grop, R. M. Antonello, G. Cazzato, Neurological Clinic, Cattinara Research Laboratory, Biomedical European Foundation (Trieste, Rome, I)

Background. Viruses have long been suggested to be involved in the etiology of multiple sclerosis (MS).

Objectives. In this cross-sectional study, our purpose was to look for an association between some clinical and conventional and non-conventional MRI long-term measures of disease activity and the presence and titer of IgG antibodies against seven different common serum specific viruses (measles, rubella, Herpes Simplex virus type 1 and 2, Varicella zoster virus, Cytomegalovirus and Epstein-Barr virus).

Methods. 140 (90F/50M) patients with definite MS (mean age 42.1 [SD 10.9] years, mean disease duration 10.9 [SD 7.5] years) and 131 age- and sex-matched controls participated in the study. The antibody positivity and titer was ascertained by ELISA technique. The clinical assessment was performed by evaluating the EDSS score and the lifetime relapse rate (LRR). All patients underwent a 1.5 tesla MR examination of the brain. The T1- and T2-lesion loads (LL) and the brain parenchymal fraction (BPF) have been calculated using reproducible semiautomated and automated techniques. Partial correlation, multiple regression and cluster analyses showed that there was an association between the antibody positivity against CMV and better clinical and MRI outcomes.

Results. The analyses indicated that the patients with presence and higher titer against CMV antibodies presented significantly lower rates of brain atrophy ($p = 0.004$), slower accumulation of T2- ($p = 0.028$) and T1-LL ($p = 0.046$), rarer number of relapses ($p = 0.003$), older age ($p = 0.0008$) and lower EDSS rates ($p = 0.04$). There was no significant differences between the patients and controls as regards the presence of specific virus antibodies.

Conclusions. The main finding of our investigation was unexpected. Surprisingly, our results focused the attention on the "protective" role of a particular virus. We showed that MS patients with CMV antibodies and higher CMV antibodies titers are somehow protected against more severe clinical progression and disease activity. CMV is probably capable to trigger some immune deviation mechanisms and to decrease immune reactivity in MS patients. These mechanisms may be implicated in the explanation of our findings. Further studies are needed to confirm and elucidate our study results on a larger sample of MS patients and in animal model studies.

P832

Whole brain N-acetylaspartate concentrations are reduced in patients presenting with clinically isolated syndromes suggestive of MS. M. Filippi, M. Bozzali, A. Gambini, M. Rovaris, A. Falini, A. Ghezzi, V. Martinelli, G. Scotti, G. Comi, Scientific Institute and University HSR, Ospedale di Gallarate (Milan, Gallarate, I)

Permanent tissue damage can occur early in the course of multiple sclerosis (MS) and might have a predictive value for the subsequent disease evolution. Whole brain N-acetylaspartate (WBNAA), a global measure of axonal loss/dysfunction, was found to be lower in relapsing-remitting MS patients than in normal controls.

We quantified the extent of axonal damage in patients at presentation with clinically isolated syndromes (CIS) at risk for subsequent conversion to definite MS, by measuring WBNAA concentration.

Twenty-three patients with CIS and 11 matched healthy controls were studied. All patients had had a CIS within the three months preceding MR acquisition. During a single session, the following brain MR sequences were acquired: a) 1H-MRS pulse sequence based on a four-step cycle of non-selective 180°inversion pulses to obtain WBNAA measurement; b) dual-echo turbo spin echo (SE); c) T1-weighted conventional SE, before and after gadolinium (Gd) administration. Image analysis was performed by two observers, unaware to whom the scans belonged. The number and location of T2-hyperintense, T1-hypointense and Gd-enhancing lesions were evaluated and the fulfilment of Barkhof's criteria was assessed. Whole brain volume was calculated using a semi-automated segmentation technique. Absolute WBNAA amounts (in mmoles – mM) were calculated using a phantom replacement method and were then corrected for individual subjects' brain volumes.

Thirteen CIS patients fulfilled Barkhof's criteria, while brain MRI was normal in all controls. The median number of brain T2 lesions per patient was 13.5 (range: 3–57). Brain volume was lower in patients than in controls (mean values were 1155 and 1276 ml, respectively; $p = 0.08$). The average WBNAA concentration (corrected for brain volume) was significantly reduced in patients compared to controls (mean values: 11.3 and 14.3 mM, respectively; $p = 0.002$). Patients who fulfilled Barkhof's criteria had, on average, lower brain volume than those who did not (mean values: 1112 and 1220 ml, respectively; $p = 0.02$), whereas the average WBNAA concentration was not significantly different between these two subgroups (mean values: 10 and 11 mM, respectively; $p = 0.73$).

These findings suggest that axonal loss/dysfunction occurs at a very early stage in patients at presentation with CIS suggestive of MS and might be independent of the extent of T2-visible MRI lesions.