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THEME 6 IMAGING, ELECTROPHYSIOLOGY AND MARKERS OF DISEASE PROGRESSION

P114 BRAIN METABOLITES IN ADVANCED ALS: A LONGITUDINAL ^{1}H-MRS STUDY

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Background: Standard MRI in patients suffering from amyotrophic lateral sclerosis (ALS) provides only little information on stage of disease and its progression. Besides the description of hyperintense signal alterations of the corticospinal tract (CST), which have to be considered as non-specific, there are variable findings of disproportionate enlargements of the central sulcus.

Objectives: Several approaches have been made to investigate whether or not proton magnetic resonance spectroscopy (^{1}H MRS) may serve in detecting upper motor neuron degeneration. Nevertheless, decrease of concentrations of N-acetyl-aspartate (NAA) and increase of concentrations of creatine (Cr) and choline (Cho) have been observed in patients with ALS compared to healthy controls, while longitudinal decrease of NAA-, Cr- and Cho-concentrations were detected during the progression of disease. The objective of this study was to investigate the longitudinal development of the concentration of brain metabolites in advanced ALS.

Methods: Ten patients with definite ALS underwent standard single-voxel ^{1}H MRS of the left- and right-hemispheric motor cortex as well as the white matter including the CST in a six month follow-up series of three measurements. MRS data were co-registered with tissue-segmented MRI data to obtain concentrations of the metabolites while fully automated post-processing included spectral fitting of the peak areas of NAA, Cr, and Cho.

Results: In a cross-sectional analysis, the NAA/(Cr + Cho) ratio of the motor cortex was reduced as expected, a reflection of decreased NAA and increased Cr and Cho. All patients showed a marked decline of NAA in the motor cortex areas with nearly stable concentrations of Cr and Cho in the longitudinal follow-up. In contrast, neither the concentration of NAA nor the NAA/(Cr+Cho) ratio in white matter areas showed comparable dynamics.

Conclusions: As reported in the literature, the NAA/(Cr + Cho) ratio of the motor cortex was shown to be in a sustained decline corresponding to a decrease of NAA as a neuron-specific marker. As a result, NAA seems to be the most valuable candidate as a surrogate marker for *in vivo* detection of disease progression and staging.

P115 MR-PATHOLOGICAL COMPARISON OF CERVICAL AND THORACIC SPINAL CORD IN DIFFERENT MOTOR NEURON DISEASES

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Background: Defined types of motor neuron diseases (MND) differ in clinical, electrophysiological, genetic, and histopathological findings, but phenotype differentiation often fails to elude the distinct neuropathological pattern of vulnerability. Furthermore, besides marked changes in lower motor neurons, electrophysiological and neuropathological investigations can show corticospinal tract abnormalities and dorsal column alterations of the spinal cord in MND.

Objectives: This MRI study was performed to evaluate *in vivo* alterations of the spinal cord in defined subgroups of MND, i.e. sporadic amyotrophic lateral sclerosis (ALS), sporadic adult-onset lower motor neuron disease (LMND), and spinobulbar muscular atrophy (Kennedy's disease, KD).

Methods: Standard T1- and T2-weighted MRI examinations of cervical and thoracic spinal cord in 39 ALS, 19 LMND and 19 KD patients were studied with respect to the presence of spinal cord signal changes. The thickness of the spinal cord both at cervical (at C2) and at thoracic level (at T4) was measured, and differences were analysed between MND groups compared with a control collective (n=96).

Results: We found no signal alterations at cervical and thoracic spinal cord in all groups investigated. The diameters of cervical and thoracic spinal cord in ALS and LMND patients showed no differences to controls and to each other. In KD patients, significant atrophy of the upper spinal cord compared to the other groups was detected both at cervical and thoracic level.

Conclusions: In summary, no significant changes in thickness in spinal cord diameter at both levels were observed in ALS and LMND, whereas marked atrophy of the upper spinal cord was seen in KD. This finding seems

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to be a characteristic feature in KD, probably due to the KD-associated central and peripheral distal axonopathy.

P116 MRI-VOLUMETRY OF THE AMYGDALA IN ALS

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Background: The evidence for extra-motor involvement in non-demented patients with ALS has been provided in neuropathological, neurophysiological, electrophysiological and neuroimaging studies. Neuropathological studies have elicited a neuronal loss in the amygdala.

Objectives: The aim of this study was to assess a possible decrease of the amygdala volume by *in vivo* MRI-volumetric measurements.

Methods: Twenty-two patients with a clinical diagnosis of ALS according to the revised El Escorial criteria and 22 age-matched healthy controls were included in the study. None of them showed any relevant cognitive or behavioural deficit. The amygdala volumes and whole brain volumes were measured by 'region-of-interest-based volumetry' (MReg-Software, L. Lemieux, http://www.erg.ion.ucl.ac.uk/). The mean amygdala volume and the ratio of amygdala to whole brain volume were compared between patients and controls.

Results: A decreased volume of the amygdala could be found in the patient group compared to the controls for the mean amygdala volume as well as for the ratio of amygdala to whole brain volume. However, these results did not reveal a statistically significant difference.

Conclusions: By MRI-volumetry, a statistically non-significant trend to decreased amygdala volumes in ALS patients was shown. An investigation into an association between MRI-volumetric alterations of the amygdala and psychopathological changes in ALS is the matter of a current study, in ALS patients with behavioural and cognitive deficits.

P117 STRUCTURAL CHANGES IN THE CORTICAL MOTOR SYSTEM OF ALS PATIENTS? DATA OF AN FMRI STUDY

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Background: Cortical reorganization following lesions in the motor cortex is a well-known mechanism of neuronal plasticity. The aim of the study was to investigate changes of cerebral functions during the course of the progressive degeneration of the motor system of ALS patients.

Objectives: With the help of functional magnetic resonance imaging (fMRI) we examined cortical activity during actual and imagined hand movements twice in six months in ALS patients and compared the data to those of healthy controls.

Methods: Thirteen patients with sporadic ALS and 14 healthy controls were asked to perform tasks of a grip movement in each hand and both hands together (predefined power of 5N) and to imagine the same action without any actual movement of the hand. The tasks were set in a randomized block design alternating with rest periods. The actual force applied by the participant was recorded simultaneously. Beforehand, the participants had been trained in a scanner dummy to perform the tasks properly. The actual experiment took place in a 1.5 Tesla MRI scanner. Differences in the BOLD signal were analysed with Statistical Parametric Mapping (SPM2, Wellcome Institute of Cognitive Neurology, London, UK).

Results: For ALS patients as well as for healthy controls we found BOLD-signal changes in sensomotory and supplementary (SMA) areas. In contrast, for the imagined hand movements there were signal changes in premotor areas without any signal changes in areas responsible for executive functions. In ALS patients compared to healthy controls there was evidence of differences in functional BOLD-signal changes in cortical and subcortical areas for the imagined movement. Furthermore, changes during the course of the disease over six months were found.

Conclusions: For actual hand movements we found comparable cortical activity for ALS patients and for healthy controls. For the imagined hand movements patients show a different pattern of cortical activation from controls. This might be an indicator of a progressive process of cortical reorganization in the course of the degeneration of the motor system of patients with ALS. The longitudinal data give further insight into the processes of reorganization.

P118 DIFFUSION TENSOR IMAGING (DTI) AND MAGNETIC RESONANCE SPECTROSCOPY (MRS) IN AMYOTROPHIC LATERAL SCLEROSIS (ALS): PREDICTOR INDEX OF INVOLVEMENT OF UPPER MOTOR NEURON (UMN)

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Background: The evidence of UMN dysfunction in ALS is not easily evaluated with either objective markers for discrete clinical UMN signs or for severe simultaneous lesions of the lower LMN. Recently neuroimaging is more often applied with MRS and DTI.

Objectives: The aim of this study was to contribute to the evaluation of the role of MRS and DTI.

Methods: 27 patients (18 male; 58 ± 10 years of age) and 15 healthy controls (HC) (three male; 45 ± 14 years of age) underwent MRI examination. The patients were diagnosed according to El Escorial criteria and re-allocated for statistical purposes into definite/probable (D-ALS) ($n=15$; 8 male) and possible/suspected (S-ALS) ($n=12$; 10 male). MR studies were performed on 1.5 T equipment. DTI indices were calculated (averaged apparent diffusion coefficient, avADC; fractional anisotropy, FA) sampling from grey matter of motor cortex (GM) to brainstem; single voxels MRS were localized in bilateral central regions. Parametric and a non-parametric test were performed for statistical analysis (*t*-test, Mann-Whitney test, ANOVA; Bonferroni's correction; Cuzick's χ^2 test; Pearson and Spearman coefficients).

Results: In patients with D-ALS the mean values of FA were lower and avADC higher than HC, both statistically significant, in bilateral GM and right white matter (WM). Also ANOVA testing considering the three groups (D-ALS, S-ALS and HC), showed statistically significant values for FA and avADC in GM and WM. Bonferroni's correction revealed: for FA, statistically significant differences in D-ALS vs. HC in bilateral GM and right WM; S-ALS vs. HC in left GM. For avADC there were statistically significant differences in D-ALS vs. HC in bilateral GM and right WM; S-ALS vs. HC on the right in GM and WM. In D-ALS vs. S-ALS there was no statistically significant difference. In D-ALS and S-ALS patients the MRS data, compared to normal values, on both sides showed statistically significantly lower values of the ratio of N-acetylaspartate (NAA) /creatine/ phosphocreatine (Cr) and higher values of the ratio of myo-inositol (mI)/(Cr). Also the choline values were higher in ALS than control, but at the limits of statistical significance.

Conclusions: The main difference between the previous studies and the current investigation was the increased avADC and decreased FA in D-ALS compared to HC in GM of motor cortex, associated in MRS testing to reduction of NAA and increased mI. We consider our data directly indicative of GM involvement, not detected in previous studies with volumetric analysis, perhaps due to the poor representation of Betz cell in the motor cortex (about 5% of total cells). In conclusion, despite the lack of 100% specificity, we propose that DTI and MRS are useful diagnostic tools for ALS, supplementing functional MRI, by providing a more strict evaluation of the profound state of water diffusion and metabolite composition of neurons.

P119 THRESHOLD TRACKING TRANSCRANIAL MAGNETIC STIMULATION INDICATES CORTICAL HYPEREXCITABILITY IN MOTOR NEURON DISEASE

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Background: Motor neuron disease (MND) is a progressive neurodegenerative disorder of corticomotoneurons and anterior horn cells (AHC), with median survival of two years. Although first described in 1865, site of disease onset remains unknown. A 'dying forward' hypothesis, which proposes that corticomotoneurons cause excitotoxic AHC death, has been proposed as a possible pathophysiological mechanism in MND. This hypothesis may be assessed by using paired-pulse transcranial magnetic stimulation (TMS) techniques to assess cortical excitability. Conventional paired-pulse techniques use a constant stimulus intensity, which is limited due to marked variability of motor evoked potential (MEP) amplitude. Threshold tracking techniques have the potential to overcome this limitation. Although threshold tracking has been extensively utilized to investigate peripheral nerve function, the feasibility of this technique in the investigation of the central nervous system disorders is lacking.

Objectives: The aim of the present study was; 1) to determine the ability of threshold tracking TMS to assess cortical excitability in healthy controls and 2) to apply this technique in patients with MND so as to determine the site of disease onset.

Methods: MEPs were generated in 15 MND patients, and 25 age-matched healthy controls, using a 90 mm circular coil connected to a BiStim 200 dual pulse magnetic stimulator. Surface electrode recordings were obtained from the abductor pollicis brevis muscle. An MEP amplitude of 0.2 mV was tracked by the conditioned test stimulus.

Results: Threshold tracking TMS was successfully undertaken in controls, with two distinct phases of early intracortical inhibition (ECI) evident, peaking at interstimulus intervals (ISI) of 1 ms (7.8% increase) and 3 ms (11.2% increase). ECI continued up to an ISI of 9 ms. Cortical facilitation then followed from an ISI of 10–30 ms. Late intracortical inhibition occurred at ISI of 50–300 ms, peaking at 150 ms (24.2% increase). In 13 MND patients there was significant reduction of ECI, peaking at an ISI of 3 ms (3.1% increase, $p<0.05$). Cortical facilitation developed at ISI of 4 ms and was significantly increased, peaking at ISI of 10 ms (7.6% decrease, $p<0.05$). In two MND patients with advanced disease the motor cortex was inexcitable. There were no significant differences in late inhibition and cortical silent period duration between groups.

Conclusions: Threshold tracking TMS confirms the presence of cortical hyperexcitability in patients with recent onset MND. Simultaneous threshold tracking studies to assess upper and lower motor neuronal function in MND patients may establish the site of disease onset.

P120 COMPARISON OF THE TRIPLE STIMULATION TECHNIQUE AND CONVENTIONAL TMS STUDY FOR THE DETECTION OF UPPER MOTOR NEURON DYSFUNCTION IN ALS

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Background: Diagnosis of ALS needs clinical evidence of both upper motor neuron (UMN) and lower motor neuron (LMN) signs. Evidence of LMN degeneration by clinical and electrophysiological assessment is usually easy. In contrast, evidence of UMN involvement in ALS patients may be elusive, and obscured by the effects of LMN loss. Transcranial magnetic stimulation (TMS) may contribute to the diagnosis of ALS by reflecting UMN dysfunction that is not clinically detectable. Sensitivity of conventional TMS to detect UMN involvement has been widely discussed. The triple stimulation technique (TST), a new collision technique has been suggested to be more sensitive and useful than conventional TMS techniques to detect sub-clinical UMN involvement.

Objectives: To determine, prospectively, the sensitivity of the two different techniques in the assessment of UMN involvement in two groups, definite/probable and suspected/possible ALS patients.

Methods: We studied 66 patients with definite ($n=25$), probable ($n=26$), or suspected/possible ALS ($n=15$) according to El Escorial criteria. All patients were treated by riluzole at the time of the study. Conventional TMS and TST were recorded on the FDI muscle on one side. The following parameters were studied: amplitude ratio (MEP/ CMAP), central motor conduction time (CMCT), excitability threshold (ET), silent period (SP), and TST amplitude ratio.

Results: In the group 1 definite/probable, mean age of patients was 63 ± 11.2 years (range 37–82 years), 34 were males, mean duration of symptoms was 17.9 ± 18.7 months (range 3–96 months), mean score of ALSFRS was 32.2 ± 3.9 (range 21–38). In the group 2 possible/suspected, mean age was 66.2 ± 11.9 years (range 38–74 years), 11 were males, mean duration of symptoms was 19.1 ± 14.5 months (range 1–51 months), mean score of ALSFRS was 35.9 ± 2.7 (range 31–40). For all patients, CMCT was abnormal in 14 cases (21%) and amplitude ratio in 25 (37.9%). ET was decreased in four cases and increased in 16, so abnormalities were found in 30.3%. SP was abnormal in 30 patients (45.5%). Abnormalities for both CMCT and amplitude ratio, the strongest parameters, were found in 53% of cases. At least one abnormality among the four parameters was found in 70% of cases. Though amplitude ratio by TST is highly reproducible (92% in controls), TST amplitude ratio was abnormal in only 47% of the 66 patients.

Conclusions: Conventional TMS is more sensitive than TST in detecting upper motor neuron dysfunction in ALS. Sensitivity can be improved by increasing the number of muscles studied: studying at least three territories increases the probability of detecting corticospinal pathway abnormalities. TST is highly reproducible, but it can be performed only on the distal segments of the upper limbs in clinical practice. This technical limit leads to its low sensitivity.

P121 CEREBRAL HAEMODYNAMIC CHANGES ACCOMPANYING COGNITIVE IMPAIRMENT IN PRIMARY LATERAL SCLEROSIS

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Background: Primary lateral sclerosis (PLS) is a rare neurodegenerative disorder of the upper motor system. This disease may also present clinically significant cognitive impairment that may be associated with cerebral haemodynamic changes.

Objectives: To assess if PLS patients are subject to cognitive decline, as measured by neuropsychological tests (NT), and determine its relationship with alterations in cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) as measured by computed tomography (CT) Perfusion.

Methods: The PLS patient group consisted of nine males and eight females aged 44 to 72 (mean, 59.11 ± 8.67) years. Data obtained from this group were compared with four male and three female non-PLS controls aged 34 to 63 (mean, 52.86 ± 9.22) years. Patients were then stratified into three groups based on NT scores; those failing 0 test scores ('Normal', $n=4$), 1–3 test scores ('Mild', $n=8$), and 4 or more test scores ('Moderate', $n=6$). On the day of NT, CBF, CBV, and MTT were measured using CT Perfusion. CT images were segmented into the four lobes of the brain and compared across groups and with non-PLS controls. Correlations between CBF, CBV, and MTT and failed NT scores were also analysed.

Results: No significant difference was found between the cognitively 'normal' PLS patients and non-PLS controls for any measured parameter in any region ($p > 0.05$). MTT was significantly increased in the 'moderate' cognitively impaired PLS patients in all regions compared to non-PLS control subjects and cognitively 'normal' patients, with the exception of the temporal lobe in the 'normal' group ($p < 0.05$). CBF was significantly decreased in the 'moderate' group compared to controls for the temporal and occipital region ($p < 0.05$). CBF was negatively correlated with failed NT scores in all regions of the brain ranging from $-0.43 \leqslant r \leqslant -0.68$ ($p < 0.05$). MTT was positively correlated ($0.49 \leqslant r \leqslant 0.65$) with failed NT scores across all regions ($p < 0.05$). CBV was not significantly correlated with failed tests scores and was not significantly different between groups.

Conclusions: The most sensitive haemodynamic marker for changes in cognition was found to be mean transit time. MTT was significantly elevated across all regions in the 'moderate' group when compared to the non-PLS controls. Cognitive decline in PLS patients is associated with the activation of the cerebrovascular reserve, manifested as trends of increasing CBV and decreasing CBF. From these data we can conclude that a subgroup of PLS patients is subject to cognitive decline that is reflected by changes in cerebral haemodynamics as measured by CT Perfusion.

Acknowledgement: This research was funded by ALSA.

P122 DEFICITS OBSERVED IN PATIENTS WITH PRIMARY LATERAL SCLEROSIS ARE ASSOCIATED WITH CHANGES IN CEREBRAL HAEMODYNAMICS

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Background: Primary lateral sclerosis (PLS) is a neurodegenerative disorder involving the upper motor system. Computed tomography (CT) Perfusion can be used to evaluate alterations in cerebral haemodynamic parameters.

Objectives: Our aim was to evaluate whether specific symptoms of this disease could be associated with alterations in CT Perfusion parameters.

Methods: Eighteen patients with PLS, nine males and nine females aged 44 to 72 (mean, 59.11 ± 8.67) years, underwent CT Perfusion scans to determine their cerebral blood flow (CBF) and volume (CBV). Mean transit time (MTT) is a calculated measure: CBV/CBF. CT images were segmented into four lobes and each lobe was further subdivided into grey and white matter (GM and WM, respectively). The Mann-Whitney test was used to determine if haemodynamic parameters differed between groups based on the presence of each symptom at onset and follow-up. SPSS was used to perform statistical analyses.

Results: The presence of bulbar symptoms ($n=12$) was associated with a significantly lower CBV in the GM of the parietal lobe ($p < 0.05$). The presence of cardiovascular disease ($n=7$) was associated with significantly higher CBV in the WM of the temporal and parietal lobe ($p < 0.02$). There was a trend towards significance for onset of stiffness as a presenting symptom ($n=7$) with higher CBV in the grey matter of the basal ganglia, $p=0.085$.

Conclusions: From these data we conclude that certain deficits in PLS patients may be associated with changes in cerebral haemodynamics, which are readily measured using CT Perfusion. Additionally, certain associated diseases such as cardiovascular disease may have an impact or be concomitant with other disease states that affect cerebral haemodynamics.

Acknowledgement: This work is funded by the ALSA.

P123 MOTOR UNIT INVOLVEMENT IN PLS, ALS AND KENNEDY'S DISEASE

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Background: Primary lateral sclerosis (PLS), Kennedy's disease and amyotrophic lateral sclerosis (ALS) are diseases characterized by progressive loss of upper motor neurons (UMN), lower motor neurons (LMN) or both. Clinically, PLS is usually considered as a pure UMN disorder. The rate of motor unit (MU) loss in Kennedy's disease is poorly documented.

Objectives: Aims of this study were to compare the MU involvement in these three diseases, to document possible sub-clinical LMN involvement in PLS and to measure respective rate of MU loss.

Methods: Data were collected from 26 patients with ALS ($n=16$), PLS ($n=5$) and Kennedy's disease ($n=5$). Patients underwent CMAP measurements (tibialis anterior and thenar muscles bilaterally). The CMAP score was calculated by: Σ CMAP area/4. On the less affected side, we assessed MUNE, F-responses and decremental responses (after repetitive nerve stimulation at 3 Hz) from thenar muscles. Thenar MUNE was estimated by using the adapted multiple point stimulation (AMPS) method. The rate of MU loss was calculated by comparing two successive MUNE values. F-index was calculated by: occurrence X maximal peak-to-peak amplitude (32 supramaximal stimuli were applied).

Results:

	PLS	ALS	Kennedy
Age (years)	57 ± 8	57 ± 12	54 ± 7
Disease duration (months)	140 ± 38	35 ± 19	67 ± 56
CMAP score (mV.ms)	34 ± 8 (0/5)	21 ± 13 (8/16)	37 ± 8 (1/5)
Thenar MUNE	68 ± 38 (4/5)	58 ± 65 (12/16)	53 ± 69 (4/5)
Rate of MU loss (%/month)	3.0 ± 2.1	7.2 ± 7.7	0.5 ± 0.1
Decrement (%)	4.8 ± 0.8 (0/5)	12.2 ± 7.6 (8/16)	6.0 ± 2.1 (0/5)
F-index	245 ± 104	70 ± 93	52 ± 22

(number of values beyond limits of normal)

Conclusions: Thenar MUNE was reduced in the three groups without significant difference between them. Rate of MU loss was high in ALS (7.2% per month), low in Kennedy's disease (0.5% per month) and intermediate in PLS (3.0% per month). Thenar MUNE was more sensitive than CMAP to detect MU involvement, particularly in chronic diseases. In fact, in PLS and Kennedy's disease, CMAP scores remained within normal limits in 9/10 patients, whereas thenar MUNE was decreased in 8/10 patients. In ALS patients, disease duration at baseline was shorter than in other patients and there were more cases with decremental responses (greater than 10% in 8/16 patients). These findings were consistent with a subacute course. In PLS, we found a subclinical MU involvement in 4/5 patients and an increase in the F-index probably related to the predominant UMN involvement. In Kennedy's disease, decreased thenar MUNE with a very slow MUNE decline suggested a MU loss starting early in life and with long-lasting subclinical course.

P124 EMG SURFACE INTERFERENCE PATTERN-INDEX MEASUREMENT IN ALS

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Background: EMG surface interference pattern (SIP) contains information on motor unit (MU) number and size that can be useful in assessing neurogenic disorders such as ALS.

Objectives: We have developed a new measurement of the SIP called SIP-Index that is derived from the compound muscle action potential (CMAP) measurement.

Methods: After obtaining the CMAP, the same surface electrodes were used to record the SIP at various force levels ranging from slight to maximal effort. A plot of SIP-Index versus SIP area was then constructed. An area within this plot, called the 'normal cloud', contained all expected data points for a normal muscle. We recorded SIP (10 epochs per study) and the CMAP from the hypothenar muscle of 28 healthy subjects to develop the normal cloud. Ten patients with definite ALS were tested.

Results: In ALS patients, data points fell on the lower side and outside of the normal cloud reflecting MU loss. This pattern was seen even when the CMAPs had normal amplitudes. This reflected increased MU size. With significant MU loss, data points were further away from the normal cloud and closer to the abscissa of the plot. During visual assessment of the SIP, high amplitude, fast-firing MUs were easy to recognize. SIP can be recorded fairly quickly in less than 5 min.

Conclusions: This method can be used as a 'quick' screen to assess MU number and size abnormalities in patients during the routine motor conduction studies.

P125 CORRELATION BETWEEN DISTAL MOTOR LATENCY AND COMPOUND MUSCLE ACTION POTENTIAL IN AMYOTROPHIC LATERAL SCLEROSIS

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Background: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder, characterized by a selective progressive degeneration of the motor system. Electromyography is essential for the diagnosis of ALS.

Objectives: The measurement of motor conduction of peripheral nerves is of major importance to recognize other possible causes of progressive muscle wasting. However, there are also pathological changes in nerve conduction studies in ALS patients.

Methods: In this prospective study we analysed the values of distal motor latency (DML), compound muscle action potential (CMAP) and motor nerve conduction velocity (MNCV) in 95 patients with definite ALS.

Results: We found slight slowing of MNCV and moderate to strong reduction of CMAP and a prolongation of DML. We found no significant correlation between MNCV and CMAP.

Conclusions: The main finding of the present work was the negative correlation between DML and CMAP. It is interpreted as a very distal axonal damage as the main reason for prolongation of DML in ALS patients.

P126 PROGNOSTIC VALUE OF AMPS METHOD IN ALS PATIENTS

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Background: The adapted multiple point stimulation (AMPS) method is a manual motor unit number estimate (MUNE) technique which is reliable, non-invasive, comfortable and easily performed in patients and on any EMG device. Previous studies have demonstrated the high sensitivity of MUNE techniques to detect and quantify motor unit (MU) loss in amyotrophic lateral sclerosis (ALS) patients and changes over time.

Objectives: The goal of this study was to determine the AMPS efficiency to distinguish ALS patients according to a slow or rapid progression and in predicting prognosis.

Methods: Data were collected from 16 patients with ALS, age ranging from 36 to 74 (mean 60 ± 10) years. Patients died after a mean total disease duration (TDD) of 38 ± 20 months (range 8–72; nine patients died before three years TDD and seven patients later). AMPS was applied at least twice in each patient at 3–4 month intervals. Incremental stimulation (50 μs stimulation duration, weak intensity gradually increased by increments of 0.1–0.5 mA) was used to allow sequential activation of individual motor axons. Incremental stimulation was administered at distinct points along the median nerve. At each stimulation point, two or three motor unit potentials (SMUP), free of alternation, were successively evoked. By dividing the maximum CMAP size by the average SMUP size, a MUNE was obtained. Survival probability was calculated by Kaplan-Meier method.

Results: MUNE at baseline (cross-sectional study) was correlated with the time to death in patients with TDD longer than three years only ($r=0.80$). The rate of MU loss (longitudinal study), calculated by comparing the last and initial thenar MUNE measurements, was negatively correlated with TDD ($r=-0.83$). Thenar MUNE decline was less ($n=8$) or more ($n=8$) than 30% over four months and less ($n=6$) or more ($n=6$) than 40% over eight months. The best survival probability was observed in patients with the lower MUNE decline. In these patients, after the first four months, survival probability was 50% at month 18 (versus 0% in patients with MUNE decline more than 30%) and after the first eight months, survival probability was 83% at month 9 (versus 0% in patients with MUNE decline more than 40%).

Conclusions: This cross-sectional study suggested that thenar MUNE might be a survival indicator. In fact, in patients with a slow rate of progression (TDD > 3 years) the higher the thenar MUNE at baseline, the longer time to death. This was confirmed by the longitudinal study. There was a significant negative correlation between the rate of MU loss, estimated by AMPS, and TDD. Survival curves indicated that the prognostic value of AMPS was better after a MUNE evaluation over eight months than over four months.

P127 DIFFERENTIAL MARKERS OF CHRONIC PARTIAL DENERVATION IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS AND BENIGN MOTOR NEURON DISORDERS

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Background: Previous needle electromyography (EMG) studies suggest that duration of motor unit potentials (MUPs) are increased in affected muscles in amyotrophic lateral sclerosis (ALS) and benign motor neuron diseases (BMNDs) and increase with the course of the disease over six months follow-up.

Objectives: We verified feasibility of short interval follow-up needle EMG in ALS and BMND for differential diagnosis.

Methods: We studied 25 patients with definite ALS, 10 patients with BMNDs (spinal amyotrophies) and 10 healthy volunteers. Needle EMG was performed in trapezius, adductor pollicis brevis and gastrocnemius lateralis muscles three times with two-month intervals.

Results: Test-retest correlation in healthy volunteers was $\kappa=0.85$–0.9, $p<0.05$; in muscles with MUPs duration lower than -20%, duration and amplitude correlated negatively ($r=-0.7$; $p=0.02$) and where it was over -20% correlation was positive ($r=0.4$; $p=0.03$). This suggested reliability of data. All studied muscles in BMNDs had no paresis and higher MUPs duration (mean 27.9, range 24.4–32.5; and mean -6.4%, range -19.7 to -4.4; $p<0.0001$), than 75 muscles in the ALS group (4–5 degrees of paresis by MRC scale). MUPs duration increased in follow-up study in muscles close (+6.9%) and far from site of onset (+18.3%), but

decreased within site of onset (−6.5%). This was not observed in BMNDs.

Conclusions: MUPs duration over +20% in muscles with no paresis is a differential BMNDs marker, but not for ALS. In ALS high MUPs duration accompanies severe paresis. In follow-up study in ALS, but not BMNDs, MUPs duration may decrease in muscles at the site of onset.

P128 COMPARISON OF A COMPOUND MUSCLE ACTION POTENTIAL MEGASCORE (CMAPM) AND FORCED VITAL CAPACITY (FVC) TO FOLLOW DISEASE PROGRESSION IN ALS

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Background: Objective markers for disease progression are urgently needed. CMAP measures of various muscles have been used and found to be sensitive to change. This also applies for the forced vital capacity (FVC) which is a recommended and established measure in ALS clinical trials. However, it is not clear if any of these measures is superior when applied in a multi-centre randomized controlled clinical trial.

Objectives: To evaluate whether FVC or a CMAPM is a better marker of disease progression.

Methods: Thirty-one ALS patients with a mean age of 59 (32–75) years were enrolled in a randomized study (Novartis TCH 346A) at two sites. Patients underwent ALSFRS-R scoring, CMAP (ABP, ADM, EDB, AH bilaterally) and FVC measurements over a 1-year period at regular 8–12 weekly intervals. The CMAP megascore (CMAPM) was calculated by: CMAP amplitudes (ABP, ADM, EDB, AH bilaterally)/8. Measures at the beginning and during follow- up were compared using the paired *t*-test.

Results: At study entry mean FVC was 99.8 ± 15.0. Mean CMAPM was 5.23 ± 2.7 and mean ALSFRSR 41.4 ± 4.0. After 12 months FVC had dropped to 57.6 ± 15.8, CMAPM to 2.3 ± 2.7 and ALS-FRSR to 32.9 ± 7.8. Changes became significant for FVC and CMAPM at week 24 ($p < 0.003$, paired *t*-test) and ALS-FRSR at week 16 ($p < 0.006$, paired *t*-test). Slope of decline was similar for FVC, CMAPM and ALSFRS. The correlation between ALS-FRSR and FVC ($r = 0.48$; $p < 1.5 \times 10^{-7}$) was slightly greater than between ALS-FRSR and CMAPM ($r = 0.41$; $p < 1.0 \times 10^{-6}$). In six patients FVC could not be reliably obtained through the entire observation period due to leakage of the mouthpiece, but CMAPM measurements could be performed at all times.

Conclusion: FVC, CMAPM and ALSFRSR show a stable decline over a 1-year period and are sensitive markers of disease progression. Both FVC and CMAPM exhibit a significant correlation with the ALSFRS-R. However, complete measurements during the entire observation period could be only obtained for CMAPM measures. This suggests that in addition to FVC, neurophysiological markers should be used in multi-centre randomized clinical trials.

P129 USE OF PERCENT OF PREDICTED NORMAL STRENGTH VERSUS MEGASCORE SLOPES TO MEASURE DISEASE PROGRESSION IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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Background: Over the past two decades, use of maximal voluntary isometric contraction (MVIC) has become a standard outcome measure in ALS clinical trials. Megascores are calculated by converting raw MVIC values to z-scores for each muscle group based on a population mean and standard deviation derived from a natural history ALS databank. The arm megascore is the mean of 10 individual arm z-scores. Disease progression is then expressed as the slope of the megascore over time. An alternative method for summarizing MVIC data involves converting raw MVIC values to percent of predicted normal (PPN) using regression equations derived from a databank of 493 healthy adults. The regression equations use each individual's age, gender, height and weight to produce a predicted MVIC value for each muscle group. The ratio of the raw score and the predicted score multiplied by 100 yields the PPN score. The average PPN arm score is the mean of the 10 individual arm PPN scores. Disease progression is then expressed as the change in PPN over time.

Objectives: To compare two methods that use MVIC data to describe disease progression: 1) megascore slopes, and 2) change of percent of predicted normal (PPN) over time.

Methods: Data from 10 males and 10 females in an ALS natural history databank containing monthly MVIC tests over a 1-year period were randomly selected for analysis. The disease progression was calculated using two methods: 1) the slope of the arm megascore, and 2) the change of PPN arm score per year.

Results: Although the correlation between megaslope and PPN slope was high (0.84) for the combined group of 20, the two methods revealed significant differences in subgroup analysis comparing males and females. The average change in the arm PPN over the year was lower in males than females (28% vs. 35%), yet the arm megascore slope was greater in the subgroup of males versus the subgroup of females (mean arm megascore slope was 1.4 for males vs. 0.9 for females).

Conclusions: Megascores control for differences between large and small muscles. However, megascores do not account for personal factors that determine normal strength. For example, MVIC of a young male should be more than twice as high as an elderly female, assuming they both have normal strength. By controlling for differences in age, height, weight, and gender, PPN allows a fair comparison between subjects who have large differences in their expected strength due to these factors. Therefore, use of PPN to summarize MVIC data may offer a more accurate comparison between subjects, by neutralizing the effects of gender, age and size.

P130 CAN WE PREDICT DISEASE PROGRESSION IN ALS?

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Background: Survival has been a major study endpoint in ALS clinical trials, and the prognostic factors influencing survival have been well defined. As an outcome measure in clinical trials, survival mandates prolonged trials with large numbers of patients. Using disease progression as an endpoint would reduce the need for large patient cohorts and reduce the length of the study. However, to reduce the heterogeneity of the population enrolled, and to improve baseline stratification, a greater understanding of the relevant predictors of disease progression would be required; and at present such data are lacking.

Objectives: In order to determine the predictors of disease progression we performed a historical cohort study of ALS patients referred to our ALS Clinic over the last 20 years.

Methods: In a group of 832 patients with the diagnosis of definite or probable ALS the effects of individual prognostic factors on disease progression were assessed with the Kaplan-Meier life-table method. Disease progression was defined as a time to 20-point change in Appel score (AALSS), which reflects a change in patient's lifestyle and clinical status. In addition, the prognostic value of each factor was estimated using both univariate and multivariate Cox proportional hazard analyses.

Results: The median time to a 20-AALSS-point change in our patient population was nine months. Age, site of symptom onset, diagnostic delay, total AALSS at first exam and AALSS preslope (rate of disease progression between first symptom and first examination) have been revealed as significant and independent covariates of disease progression in our population. Forced vital capacity (FVC) has been shown to be a significant covariate of disease progression in both univariate and multivariate Cox model after adjustment for age, sex and site of onset but was eliminated as an independent predictor in the final statistical model.

Conclusions: Our results support the use of a 20-point change in Appel score as a reliable study endpoint, which can be achieved within a 1-year clinical trial. Moreover, the identification of predictors of disease progression may facilitate better design of therapeutic trials, permitting the use of disease progression as a primary endpoint and improving baseline stratification of patient populations. In addition, defining the prognostic factors that influence disease progression may help improve patient management and care.

P131 ALS-FRS AND APPEL ALS SCORES: DISCORDANCE IN ADVANCED STAGES OF DISEASE

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Background: The ALS functional rating scale (ALS-FRS) score is a validated questionnaire used to measure ALS progression. It includes no objective measurement of strength or breathing capacity. The Appel ALS (AALS) score is also a validated measure of ALS progression, consisting of 5 subscores measuring swallowing, respiratory function, muscle strength, and upper & lower extremity function.

Objectives: To determine if the ALS-FRS & AALS scores correlate at different stages of the ALS disease.

Methods: We examined the ALS-FRS and AALS scores for 32 ALS patients at their visits over 10 months, a total of 68 AALS and ALS-FRS score pairings, with an average of two visits per patient. A Spearman's rho correlation analysis and a multiple regression analysis were conducted on the AALS total score to determine their relationship to the ALS-FRS total score.

Results: ALS-FRS and AALS scores significantly correlated when the complete range of scores for each was considered ($p < 0.01$). However, when analyzed for Appel score-defined life-altering changes as measured by a 20-point change in the AALS scale score (40–60, 60–80, 80–100, 100–120, >120), there was significant correlation ($p = 0.008$) only in the 40–60 range, the initial stage of the disease. In all other ranges, the AALS score and ALS-FRS correlation did not reach significance.

Conclusions: Our findings suggest that objective measurements from AALS and questionnaire based ALS-FRS scores may not correlate as the disease progresses, especially in the advanced stages. Our results suggest that further studies of validating questionnaire-based measurements against multiple system measurements at different stages of the disease are needed before functional questionnaires are accepted as sufficient measurement tools for therapeutic trials in ALS.

P132 NON-LINEAR BEHAVIOUR OF THE ALS-FRS IN ALS PATIENTS TOWARD THE END OF LIFE

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Background: The ALS-FRS disability scale is usually regarded as behaving linearly throughout the disease. This is important in the evaluation of new drug treatments and in the planning of clinical trials. Existing data on linearity of ALS-FRS were obtained mainly from patients with mild to moderate disease participating in clinical trials. There are no available data about the sequential changes in ALS-FRS over time in the last part of patients' lives.

Objectives: To compare the slope of deterioration of ALS-FRS in ALS patients during mild to moderate stages of disease and toward end of life in order to determine if the slope changes over time and if this change is predictive regarding survival.

Methods: Among 295 patients with ALS followed up in our clinic during recent years, 60 had at least four visits with documented ALS-FRS and time of death. For each of these patients we calculated the maximal FRS slope, the critical time (time elapsed between the point of maximal slope and death) and the critical FRS (FRS value at which the maximal slope occurred).

Results: Included patients had 4–16 FRS determinations (mean 5.6) over a period of 16–137 months (mean 30). Their critical time occurred 2–74 months before death (mean 16). The critical FRS had a broad range of values of 5–38, with a mean of 25. The critical time was negatively correlated to the maximal slope ($p=0.027$). Stratification of maximal slope values by critical time showed that patients with steeper maximal slopes had a shorter critical time (less than one year) compared to those with lower slopes, compatible with more aggressive disease.

Conclusions: The ALS-FRS behaves linearly for the greater part of follow-up in patients with ALS, but changes its curve late in the disease. Changes in the slope of deterioration of FRS could serve as an additional prognostic factor for survival.

P133 THE PERFORMANCE OF AN INSTRUMENT TO MEASURE CHANGE IN DYSPNEA IN PATIENTS WITH ALS

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Background: Respiratory complications are the most common cause of mortality in patients with ALS. Limitations in activity from limb muscle weakness can make assessing dyspnea difficult. It is important to be able to accurately measure dyspnea over time for assessment and treatment of patients and as an outcome in clinical studies.

Objectives: This study evaluated the Baseline Dyspnea Index (BDI) and Transitional Dyspnea Index (TDI), a measure of change from baseline, in subjects with ALS.

Methods: Subjects were enrolled in a randomized, controlled trial of high frequency chest wall oscillation (HFCWO) and had El Escorial probable or definite ALS, an ALS Functional Rating Scale respiratory subscale (ALSFRS-RS) $\leqslant 11$ and >5, and FVC $\geq 40\%$ predicted. Pulmonary function tests, ALSFRS, and dyspnea scales were measured at baseline, four weeks, and 12 weeks after enrolment. The BDI and TDI consist of three categories: functional impairment, magnitude of task, and magnitude of effort. Each category of BDI is graded from 0 (severe) to 4 (unimpaired). In the TDI, changes in dyspnea are graded from -3 (major deterioration) to +3 (major improvement). Intraclass correlation coefficients (ICC) were calculated to determine reproducibility of the BDI and TDI within patients. ICCs were calculated for 11 subjects in the BDI and 10 in the TDI. Differences in BDI-TDI scores were compared by χ^2. TDI scores were compared with changes in FVC, ALSFRS-RS, and a visual analog scale (VAS) of breathlessness using Spearman rank coefficients and *t*-tests.

Results: Forty-six subjects were enrolled and 35 returned for the 12-week follow-up. Twenty-two subjects were assigned to HFCWO. Although there was a trend for more deterioration in dyspnea in the control group compared to HFCWO, this was not significant and data are presented for the two groups combined. Forty-six percent were male, 74% were Caucasian, and 50% had college degrees. The mean FVC was $66.3 \pm 14\%$, 50% used BiPAP, and the mean ALSFRS-RS was 9.1 ± 1.9. The ICC for each category of the BDI and TDI was ≥ 0.98 indicating near perfect reproducibility. By BDI score at entry, 15 subjects (32.6%) had moderate to severe functional impairment due to dyspnea, 25 (54.3%) reported moderate tasks or less resulted in

dyspnea, and 25 subjects reported that moderate effort or less resulted in dyspnea. At four weeks, 15 (38.5%) patients reported deterioration in at least one TDI measure and at 12 weeks, 19 (54.3%) had deterioration in at least one TDI measure. Only 5/17 (29.4%) of patients had any decline in the respiratory subscale of the ALSFRS. On a 10-point VAS (0=no breathlessness and 10=maximal breathlessness), the mean rating at baseline was 2.8 and actually decreased at week 12 to 2.4. Deterioration in TDI was significantly associated with decline in FVC and was significantly correlated with worsening breathlessness and ALSFRS-RS.

Conclusions: The BDI-TDI is highly reproducible in patients with ALS, is sensitive to changes in dyspnea in as little as one month and correlates with other measures of dyspnea. The BDI-TDI has potential importance for clinical management of patients and as an outcome in clinical trials.

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P134 INTRODUCTION OF ELECTRONIC DATA CAPTURE AND DATA MANAGEMENT TECHNOLOGY TO INVESTIGATOR-INITIATED CLINICAL TRIALS AND BIOMARKER STUDIES IN AN ACADEMIC ENVIRONMENT

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Background: Out of thousands of active clinical trials at academic institutions approximately one-third are investigator-initiated studies. The efficiency and regulatory compliance of conducting such trials are as important as the quality of the results. Running in-house coordination centre and data management operation for more than one multi-centre trial is an extremely aggressive target and difficult to maintain using paper-based processes for managing clinical trials. PharmaENGINE℠ Electronic Data Capture (EDC) and Data Management (DM) platform deployed by Neurology Clinical Trials Unit (NCTU) enables investigators and coordinators to directly record trial data over the internet, using electronic Case Report Forms (eCRFs) instead of the traditional paper CRFs. The system validates the data at the point of entry, raises alert queries and utilizes a central server. Data validation at the input stage ensures accrual of fewer invalid subjects. The availability of real time information also gives trial sponsors, PIs and project managers an early warning of issues in the trials (e.g. subject recruitment, adverse events). Information is loaded into the clinical trials database in real time, making subject data instantly available to data managers, coordinators and management, thereby overcoming the traditional delay period. Data validation at the point of entry and rapid query response improves data quality. The intuitiveness and efficiency of user interface and data clarification workflow plays a significant role in speeding up clinical trial processes and reducing overall costs. EDC and DM systems also improve time to database lock and data analysis, as availability of accurate information allows biostatisticians to undertake statistical analysis of the trial within days, not months, after the last patient completes the study. The system also readily provides interim analysis of data during the trial.

Objectives: A comparison of data management models between two clinical studies conducted by the NCTU was performed.

Methods: The first study, a 25-center 300-subjcect clinical trial of celebrex in ALS was conducted over a 3-year period using a paper-based model. In another study, Clinical Trial of Coenzyme Q10 in Subjects with ALS (MDA), a 4-center, 30-subject trial utilized the EDC system.

Results: More than 2200 Data Clarification Forms were written and faxed to the sites in the first study, taking more than four months to receive site responses and entering and cleaning the data to lock the database. In contrast, within three weeks of the second study's last subject's visit, the database was locked and data analyzed.

Conclusions: The significant reduction in queries, the corresponding cost reduction in dealing with the remaining queries resulting in faster database lock, and data analysis makes the EDC and DM model the only viable alternative for academic Coordination and DM centers. To ensure a successful EDC deployment four key components (technology, logistics, process change and organizational change) need to be addressed.