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Efficacy and tolerability of levetiracetam during one-year follow-up as add-on therapy in patients with treatment-resistant generalised epilepsy

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Objective: We investigated the efficacy and tolerability of Levetiracetam (LEV) as add-on therapy in Cypriot patients with treatment- resistant generalized epilepsy.

Methods: We retrospectively identified twelve patients ranging in age from 14 to 41 years old. Eight patients had symptomatic generalized epilepsy (SGE) and four patients had primary generalized epilepsy (PGE). The patients were studied for a 12-month period. Patients received LEV as add-on therapy to 2–6 (mean 2.4) anticonvulsants. We compared mean seizure frequency for a 3-month period prior to and 12 months after introduction of LEV. Maximum doses ranged from 1000 to 3000 mg daily. All subjects had physical and neurological examinations, routine baseline hematological, biochemical, and urinary investigations at entry.

Results: Two patients (16.71 %) became seizure free. Four patients (33.3 %) had seizure reduction of by 75 % or greater. Two patients (16.7 %) had seizure reduction by 50 % or greater. Three patients (25 %) became worse and two of them discontinued the study. More than 50 % reduction in the number of their seizures was seen in 62.5 % of the patients suffering from SGE and in 75 % of the patients suffering from PGE. Efficacy was clinically apparent from the first trimester of treatment. Both seizure free patients required 1000 mg of LEV as daily adjunctive therapy. There was a decreased chance of the patients becoming seizure-free as the number of previously used AED's increased. Reasons for discontinuation of LEV were either lack of efficacy (1 patient), adverse events (1 patient) or both (1 patient). The withdrawal range was 25 %. Side effects reported were: Sedation (2 patients), headaches (1 patient), dizziness (1 patient), weakness (1 patient), weight increase (1 patient) and behavioral discontrol (1 patient). No patient showed significant changes from baseline hematological, biochemical and urinary parameters.

Conclusion: Our results show that LEV has efficacy in both symptomatic as well as in primary generalized epilepsy as seen by a significant reduction of seizures. 66.7 % of our patients with refractory epilepsy experienced a reduction of 50 % or more on their seizure frequency with the addition of LEV in their antiepileptic drug regimen during the twelve months of their evaluation. Levetiracetam was also well tolerated by the majority of our patients.

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A hypothesis how non-REM sleep might promote seizures in partial epilepsies: a transcranial magnetic stimulation study

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Objective: To investigate alterations of inhibitory and excitatory cortical circuits during NREM sleep in drug-naïve patients with partial epilepsies and sleep-bound seizures only.

Methods: Paired-pulse TMS-paradigm was performed to test intracortical inhibition (ICI) and facilitation (ICF) in the hemisphere of the epileptic focus in three untreated patients with non-lesional, non-genetic frontal lobe epilepsy in NREM2 (n = 3 patients), NREM3/4 (n = 1), and wakefulness (n = 3).

Results: All three patients exhibited major decrease of ICI in NREM sleep as opposed to the physiological enhancement of ICI with the progression of NREM sleep.

Conclusion: Decreased ICI might reflect a substrate for the association of epileptic processes with thalamo-cortical networks that propagate sleep. Thus, our findings contribute to a hypothesis how NREM sleep could promote seizures.

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Active brain processes during human quiescent sleep: an EEG / fMRI study of non-REM slow oscillations

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Introduction and Objectives: Functional neuroimaging studies in humans have characterized non-REM sleep (NREM) as a stage of brain deactivation (1). However, NREM is dominated by slow oscillations, with alternating hyperpolarization and depolarization phases at the cellular level in animals. The depolarization ("up") phases correspond to periods of intense neuronal firing. This implies that, at the macroscopic level in humans, NREM may not be a pure quiescent state but might show increased brain activations in the up state of slow oscillations. Using simultaneous electroencephalography (EEG) / functional magnetic resonance imaging (fMRI), we aimed at characterizing the regional cerebral activities during NREM and specific to slow oscillations.

Methods: 26 non-sleep deprived, healthy, young subjects were scanned during the first half of the night in a 3Tesla fMRI scanner (echo-planar imaging sequence, 32 slices, repetition time = 2.46 s, echo time = 40 ms, voxel size = 3.4 x 3.4 x 3 mm^3), with a continuous 64-channels EEG recording.

After scanner and pulse artifact removal, NREM (stages 2–4) epochs and corresponding fMRI time series were selected. Slow waves were automatically detected on EEG epochs as in (2). The maximum negativity, chosen as the up state onset, was taken as event of interest for each detected slow oscillation. The analysis (conducted with the software Statistical Parametric Mapping 5 [SPM5]) looked for the brain areas in which responses were significantly correlated with the occurrence of slow oscillations (up states) across subjects.

Results: 14 subjects slept and were used for analyses. Positive brain responses correlated to slow oscillations were found in the thalamus, medial prefrontal cortex, auditory cortex, hippocampus, brainstem and cerebellum. We found no significant negative brain responses.

Conclusion: In keeping with our hypothesis, we show that the brain remains active during NREM, in phase with the slow oscillations, in a set of brain areas potentially involved in sleep oscillations mechanisms. Activations were also located in brain areas involved in the processing of declarative memories during wakefulness, further supporting the hypothesis that slow waves participate in the consolidation of memory traces during NREM.

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Daytime REM sleep under high and low sleep pressure in narcolepsy patients and healthy controls

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Objective: The interaction between a circadian and a homeostatic sleep-wake dependant process determines the occurrence of sleep and wakefulness as well as the sleep structure. REM propensity is high in the early morning hours. In the present study duration of REM sleep, REM latency and number of interventions to prevent REM sleep are used to explore REM regulation in narcolepsy patients and healthy controls under varying sleep pressure (SP).

Methods: Ten HLA DQB1*0602 positive and hypocretin deficient patients (7/7) with narcolepsy-cataplexy (NC) and ten age, gender and body mass index matched controls (C) underwent a four session crossover sleep-study protocol. There were two sessions with a night of sleep deprivation to increase the SP and 2 sessions with a 4 h night time sleep episode (23:00–3:00 h) to reduce SP, followed by daytime sleep (DS, 7:00–15:00). In two sessions (one with high and one with low sleep pressure) the subjects were repeatedly awakened during the first four hours of the DS episode to prevent REM. DS was undisturbed in the other 2 sessions. Group comparisons were based on t-tests.

Results: The number of interventions (NOI) to prevent REM was higher in NC compared to C in both conditions (high SP, 26.5±12.8, resp. 10±4.4, $p = 0.003$; low SP, 26.2±10.1, resp. 12.9±5.5, $p = 0.003$). Different SP did not change significantly the NOI in NC, whereas in C a trend towards higher NOI under low SP was observed. The amount of REM in C (within the first four hours of undisturbed DS) was significantly higher under the condition of low SP compared to high SP ($p < 0.001$). In NC no significant differences were observed. Low SP shortened significantly REM latency in controls ($p = 0.013$). Nine NC and four C showed sleep onset REM (SOREM) under low SP. Under high SP again nine NC showed SOREM (the patients entering sleep in NREM being different for the two conditions) but only one C (same patient had also SOREM under low SP).

Conclusion: We suggest that markers of REM sleep behave differently in NC and C, obeying the interaction between the circadian and the homeostatic regulating processes in C but not in NC.

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