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Sleep alterations in children with refractory epileptic encephalopathies: A polysomnographic study

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ABSTRACT

Data on the relationship between sleep disturbances and refractory epileptic encephalopathies (EEs) are scarce. Our aim was to assess, by means of nocturnal polysomnography, if children with EEs present with objective alterations in sleep organization. Twenty-three children with EEs (12 males; mean age: 8.7 ± 1.4 years) and 40 healthy controls (22 males; mean age: 8.8 ± 1.1 years) underwent an overnight full polysomnography (PSG). Relative to controls, children with EEs showed a significant reduction in all PSG parameters related to sleep duration time in bed (TIB-min $p < 0.001$), total sleep time (TST-min $p < 0.001$), and sleep percentage (SPT-min $p < 0.001$), as well as significantly higher REM latency (FRL-min $p < 0.001$), rate in stage shifting ($p = 0.005$), and number of awakenings/hour ($p = 0.002$).
Relative to controls, children with EEs also showed significant differences in respiratory parameters (AHI/h $p < 0.001$, ODI/h $p < 0.001$, SpO2% $p < 0.001$, SpO2 nadir% $p < 0.001$) and a higher rate of periodic limb movements (PLMs% $p < 0.001$). Our findings suggest that sleep evaluation could be considered mandatory in children with refractory epileptic encephalopathy in order to improve the clinical management and the therapeutic strategies.

1. Introduction

In clinical literature, there has been a growing interest in the mutual relations between sleep and epilepsy, kindled by the realization of several potentially relevant two-way interactions [1]. Seizures are frequent during sleep, and the epileptogenic discharges can alter and/or disrupt the sleep architecture, leading to an increase in seizure frequency [1–5].

The nonrapid eye movement (NREM) sleep phases can activate interictal epileptiform discharges (IEDs), but the facilitating influences on IED production may be exerted separately by either spindle activity or delta synchronization mechanisms, and the activating properties of sleep are not due to the stage per se but depend largely on the level of activity of synchronizing mechanisms [6]. Indeed, the REM sleep stage tends to suppress IEDs and may restrict their field of distribution to the epileptogenic region [7,8]. On the other hand, with regard to the causes of sleep fragmentation, sleep-related breathing disorders (SRBDs) could be considered a potential trigger for paroxysmal activity and IEDs. This suggests that children with obstructive sleep apnea syndrome (OSAS) may have a dysfunction of the arousal system control, which is probably due to the putative effect of a primary brain insult as a predisposing factor for both OSAS and paroxysmal EEG activity [9].

The effect of the epilepsy etiology on sleep architecture during childhood has not been studied in detail, and, to our knowledge, there are no specific sleep studies related to epileptic encephalopathies (EEs).

Epileptic encephalopathies are described as epilepsy with ictal and interictal epileptiform anomalies (clinical and EEG) and progressive cerebral dysfunction [10]. According to the classification and terminology criteria of International League against Epilepsy (ILAE), the following syndromes meet the EE criteria: Dravet syndrome, Doose syndrome, CSWSS (continuous spike–wave during slow-wave sleep), Landau–Kleffner syndrome, Lennox–Gastaut syndrome, Ohtahara syndrome, and West syndrome. Severe epilepsy with multiple independent spike foci is recently included in this group [11].

The importance of the relationship between EEs and sleep is also supported by the role of the ketogenic diet in improving sleep quality with increased REM sleep [12].

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The aim of this study was to compare, by means of polysomnography, sleep objective parameters in a group of children with EEs and in healthy controls. We hypothesized we would find a significantly higher prevalence of objective sleep alterations in children with EEs.

2. Materials and methods

Twenty-three children with EEs (12 males) (mean age: 8.7 years; SD ± 1.4) and 40 healthy children (22 males) (mean age: 8.9 years; SD ± 1.1) underwent an overnight polysomnography (PSG) recording in the Sleep Laboratory of the Clinic of Child and Adolescent Neuropsychiatry of Naples and in the Unit of Clinical and Instrumental Neurology and Neurophysiopathology of the Oasi Institute of Troina after one adaptation night in order to avoid the first-night effect.

Children were considered eligible for the full PSG if affected by one of EEs diagnosed according to the ILAE classification.

The subjects in both groups were recruited from the same urban area; participants were all Caucasian and were of middle-class socioeconomic status (between class 2 and class 3, corresponding to 28,000–55,000 euros/year to 55,000–75,000 euros/year, respectively, according to the current Italian economic legislation parameters).

Neuroimaging pathological findings were an exclusionary criterion.

All subjects with EEs enrolled in this study were on polypharmacological treatment and were taking at least three or more antiepileptic drugs.

All parents gave written informed consent during the first screening visit.

The reported investigation was carried out in accordance with the principles of the Declaration of Helsinki [13].

The Departmental Ethics Committee of the Second University of Naples approved the study.

2.1. Polysomnographic evaluation

The EEG recordings and electrode placement were performed according to the 10–20 system [14], and the PSG montage included at least 19 EEG channels (Fp1, Fp2, F7, F8, F3, F4, C3, C4, T3, T4, T5, T6, P3, P4, O1, O2, Fz, Cz, and Pz) referenced to the contralateral mastoid, left and right electrooculogram (EOG), chin electromyogram (EMG), left and right tibialis EMG, electrocardiogram (ECG) (1 derivation), nasal cannula, measures of thorax and abdominal effort, peripheral oxygen saturation, and pulse and position sensors [15].

Recordings were carried out using a Brain Quick Micromed System 98 recording machine, and signals were sampled at 256 Hz and stored on a hard disk for further analysis. Electroencephalography signals were digitally band-pass filtered at 0.1–120 Hz, 12-bit A/D precision.

Moreover, the presence of high-amplitude sharp waves or spikes and slow waves together with the reduced occurrence of K complexes, sleep spindles, and rapid eye movements made it difficult to score sleep using usual criteria. Therefore, as per Miano et al. [16] and a previous report [17], we scored sleep stages based on the following criteria:

1. N1 was detected when, after wakefulness or movement, the EMG tone was clearly diminished, movement artifacts were absent, and the EEG did not show sleep-specific patterns (such as spindles or K complexes).
2. N2 was recognized because of the presence of sleep spindles and K complexes even during the pauses between the different runs of epileptiform discharges.
3. N3 was also defined when composed mostly of subcontinuous sharp wave or spike–slow-wave complexes.
4. Rapid eye movement sleep was characterized by decreased EMG tone with shorter epileptiform discharge duration and lower frequency compared with NREM sleep.

Accordingly, the following conventional sleep parameters were evaluated:

- Time in bed (TIB);
- Sleep period time (SPT): the time from sleep onset to sleep end;
- Total sleep time (TST): the time from sleep onset to the end of the final sleep epoch minus time awake;
- Sleep latency (SL): the time from lights out to sleep onset, defined as the first of two consecutive epochs of sleep stage 1 or one epoch of any other stage, in minutes;
- REM latency (RL): the time from sleep onset to the first REM sleep epoch;
- Number of stage shifts/hour (SS/h);
- Number of awakenings/hour (AWN/h);
- Sleep efficiency (SE%): the percentage ratio between total sleep time and time in bed (TST/TIB * 100);
- Percentage of SPT spent in wakefulness after sleep onset (WASO%), i.e., the time spent awake between sleep onset and end of sleep;
- Percentage of SPT spent in sleep stages 1 (N1%), 2 (N2%), slow-wave sleep (N3%), and REM sleep (REM%).

All recordings started at the subject's usual bedtime and continued until spontaneous morning awakening.

Sleep was subdivided into 30-s epochs, and sleep stages were scored according to the standard criteria [18] and analyzed by means of Hypnolab 1.2 sleep software analysis (SWS Soft, Italy). All the recordings were visually scored, and the sleep parameters derived were tabulated for statistical analysis.

With regard to respiratory parameters, central, obstructive, and mixed apnea and hypopnea events were counted according to the standard criteria [19]. In particular, the apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of total sleep time; an obstructive apnea index > 1 was selected as the cutoff for normality [20,21].

The episodes of periodic limb movements (PLMs) were identified according to the standard criteria [22], and a PLMI ≥ 5 was considered abnormal.

3. Statistical analysis

The study design was based upon data collected from an independent pilot study (5 subjects with EEs versus 5 control children) that showed a strong difference between the mean duration of the TST between the groups (412 ± 49.9 in the group of children with EEs versus 520 ± 32.7 in normal subjects; $p = 0.004$).

The sample size was calculated with the online software http://www.dssresearch.com/toolkit/sscalc/size_a2.asp.

Group differences in demographic and clinical characteristics (full-scale intelligent quotient (FIQ), PSG parameters, respiratory (AHI, ODI, and mean oxygen saturation%) patterns, and PLMs%) were assessed by means of the Mann–Whitney *U* test or the chi-squared test where appropriate. Full scale intelligent quotient (FIQ), PSG parameters, respiratory (AHI, ODI and mean oxygen saturation%) patterns and PLMs% between EE subjects and control group children using the Mann-Whitney *U* test and the chi-squared test where appropriate.

The statistical power was calculated with the online software http://www.dssresearch.com/toolkit/spcalc/power_a2.asp. The alpha error level of confidence interval was 5%.

p values <0.05 were considered statistically significant. The STATISTICA software version 6.0 (StatSoft, Inc.; 2001) was used for all statistical tests.

4. Results

The study population and the control group were matched for age ($p = 0.596$), sex (chi-squared = 0.002; $p = 0.963$), and BMI