Overnight Video-Polysomnographic Studies in Children with Intractable Epileptic Encephalopathies

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Background: The aim of this study was to assess sleep architecture and respiration during sleep in children with intractable epileptic encephalopathies using overnight video-polysomnography (V-PSG).

Material/Methods: Between 2015 to 2017 overnight V-PSG recordings were made for 31 children (22 boys and 9 girls) with intractable epileptic encephalopathy with a mean age of 6.78±3.61 years and a mean body mass index (BMI) of 15.83±3.16 kg/m². Thirty-one healthy children were matched for sex, age, and BMI as the control group. The phases of sleep studied included rapid eye movement (REM) sleep, and non-REM (NREM) phases NREM 1, NREM 2, and NREM 3. Respiratory function during sleep was evaluated.

Results: Children with epileptic encephalopathies receiving antiepileptic treatment had significantly decreased total sleep time (TST) (p=0.038), significantly increased percentage of NREM1 (p=0.033), and a significantly lower percentage of total REM (p<0.0001), compared with the control group. All children 31/31 (100%) with epileptic encephalopathies had interictal epileptiform discharges, and 4/31 (12.9%) had ictal events. The number of respiratory events did not differ significantly between the two groups (p=0.118), but children in the epileptic encephalopathy group had a significantly shorter average duration (p=0.008) and longest duration (p=0.048) of respiratory events. Average (p=0.006) and least (p=0.0004) oxygen saturation (SatO₂) were significantly lower in children with epileptic encephalopathies compared with the control group.

Conclusions: Children with epileptic encephalopathies had altered sleep architecture and marked oxygen desaturation, which supports the need for referral of children with epileptic encephalopathy for overnight sleep evaluation.

MeSH Keywords: Disabled Children • Epilepsy • Polysomnography • Sleep Disorders

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Background

Epileptic encephalopathies are conditions in which epileptic activity directly contributes to cognitive and behavioral impairment that is often greater than that expected from the underlying cerebral pathology alone, which implies that suppression of epileptiform activity might minimize further functional impairment [1]. Global or selective cognitive and behavioral impairment can become worse over time and can present as a spectrum of severity across all forms of epilepsy and at any age [1]. Cognitive dysfunction is more severe when seizures occur in younger age, whereas the later onset of seizures causes more selective neuropsychological dysfunction [2, 3]. Epileptic encephalopathies are rare disorders with an incidence that has been reported to range from between 1/10,000 to 1/1,000,000 live births, representing up to 25% of all forms of pediatric epilepsy [4, 5]. Most patients with epileptic encephalopathy present as isolated cases and are presumed to have an underlying genetic defect, although in some cases metabolic or structural abnormalities can be identified [6].

Previously published studies have shown that 21% of patients with epilepsy have seizures that occur only during sleep, 42% occur only when awake, and 37% of patients have seizures in when both awake and asleep [7]. Patients with epilepsy can experience vicious cycle of seizures in sleep that lead to sleep disruption, resulting in a lower seizure threshold that further increases the frequency of seizures [8]. Non-rapid eye movement (NREM) sleep synchronizes neuronal networks in the reticular activation system of the brainstem, thalamus, and cortex. As NREM deepens, the thalamocortical network progressively hyperpolarizes to facilitate the spread of interictal discharges and seizures. Rapid eye movement (REM) sleep inhibits the thalamocortical spread of epileptiform discharges and promotes skeletal muscle paralysis [9].

Up to 20% of children with epilepsy have medically intractable epilepsy [10], which is defined by at least one seizure per month, despite appropriate anti-epileptic therapy with at least two antiepileptic drugs, in maximally-tolerated doses for 18 months, or adequate seizure control but with unacceptable drug-related side effects [11].

There have been few previously published studies on the interaction between sleep and epilepsy in the pediatric population [12]. Children with partial epilepsy of minor severity and treated with up to two antiepileptic drugs have a higher prevalence of self-reported sleep disturbances compared with healthy children [13]. Children with poorly controlled partial or generalized epilepsy have altered sleep architecture and sleep-disordered breathing [14]. The etiology of sleep disruption in children with epilepsy is multifactorial and is due to the effects of the epileptic seizure and its severity, seizure frequency, sleep-disordered breathing, and the effect of antiepileptic medication [12]. There have been even fewer studies using overnight polysomnography (PSG) to evaluate sleep architecture and sleep-disordered breathing in children with epileptic encephalopathies and, so far, results have been inconsistent.

Therefore, the aim of this study was to assess sleep architecture and respiration during sleep in children with intractable epileptic encephalopathies using overnight video-polysomnography (V-PSG).

Material and Methods

Ethical approval

This study was approved by the Local Ethics Committee. The parents of all the children who participated in the study provided written informed consent for the children to undergo the procedures used in the study. The study was undertaken according to the principles of the Declaration of Helsinki. All children underwent a single night of polysomnographic recording.

Children with epileptic encephalopathies included in the study

Between 2015 and 2017, a prospective, controlled, observational study involved the recording of overnight video-polysomnography (V-PSG) for 31 children with epileptic encephalopathies. The children in the study group included two siblings with early infantile epileptic encephalopathy-25 (EIEE-25) caused by mutation in the SLC13A5 gene; one child with early infantile epileptic encephalopathy-13 (EIEE-13) caused by mutation in the SCN8A gene; six children with West syndrome; four children with Dravet syndrome, previously known as severe myoclonic epilepsy of infancy (SMEI); eight children with Lennox-Gastaut syndrome; four children with Landau-Kleffner syndrome; and six children with epileptic encephalopathy with continuous spikes and waves during sleep (CSWS). Epileptic encephalopathy was diagnosed by experienced pediatric neurologists, and the children were being treated with antiepileptic therapy before the study began.

Inclusion and exclusion criteria for the children in the study group (n=31) and the control group (n=31)

Prior to V-PSG recording, parents were interviewed for the sleep history of the children. All children’s medical records were reviewed. Overnight V-PSG was also recorded for 31 children in the control group, who were referred to our hospital due to the history of past nutritional allergy. The 31 children in the control group were matched with the 31 children in the epileptic encephalopathy study group by gender, age, and body...
mass index (BMI). Children in the control group with the history suggestive of sleep-disordered breathing, paroxysmal nocturnal events, a previous diagnosis of sleep disorder, or those taking any pharmacotherapy were excluded from the study. None of the children from both groups had adenotonsillectomy before V-PSG. Children from both groups also had a similar socio-economic background. Children in both groups were examined before the overnight V-PSG recording, and only children without acute illness underwent the recording. Before overnight V-PSG, children with epileptic encephalopathy were allowed to take their previously prescribed medication.

**Overnight video-polysomnography (V-PSG)**

Overnight V-PSG included the use of infrared video camera, a microphone to record vocalization during sleep, the use of 16-channel electroencephalography (EEG) with the placement of scalp electrodes performed according to the international 10-20 system. Left and right electro-oculography (EOG), chin electromyography (EMG) using surface electrodes, a nasal pressure transducer and a thermistor for detection of respiratory events, thoraco-abdominal plethysmography (strain gauge), 2nd lead electrocardiography (ECG), sensors for pulse rate, and measurement of peripheral blood oxygen saturation (SatO2) were performed. The V-PSG recordings were made using the Nihon Kohden™ recording system (Nihon Kohden, Shinjuku-ku, Tokyo, Japan) and stored on a hard disc for further analysis using Polysmith™ software (Nihon Kohden, Shinjuku-ku, Tokyo, Japan). The scoring systems used for the sleep parameters were performed according to the criteria of the American Academy for Sleep Medicine [15].

**Sleep parameters studied**

All sleep parameters measured and analyzed by the Polysmith™ software (Nihon Kohden, Shinjuku-ku, Tokyo, Japan) used in this study were tabulated for statistical analysis. In all subjects, sleep was subdivided into 30-second epochs for scoring of sleep stages and 2-minute epochs for scoring of respiratory activity. As most of the children with epileptic encephalopathy had an abnormally slow EEG in awake state and interictal discharges during sleep, standard criteria were slightly modified, and sleep stages were scored based on the following [16]. Non-rapid eye movement (NREM) sleep stage 1 (NREM 1) was scored after wakefulness or movement when the EEG tone was diminished, movement artifacts were absent, and the EEG did not show any sleep-specific grapho-elements, for example, sleep spindles and K complexes. NREM sleep stage 2 (NREM 2) was scored in the presence of sleep spindles or K complexes, even between the runs of epileptiform discharges. NREM sleep stage 3 (NREM 3) was characterized by the presence of nearly continuous high-amplitude slow-wave activity. Rapid eye movement (REM) sleep was characterized by decreased EMG tone, rapid eye movement on EOG, shorter duration and lower frequency of epileptiform discharges when compared with NREM sleep.

**Polysomnographic parameters studied**

Polysomnographic parameters analyzed included the total recording time (TRT) (time of lights out to time of lights on in minutes), the total sleep time (TST) in minutes, the percentage of sleep efficiency (SE) (TST/TRT x 100), the sleep latency (SL) in minutes (time from lights out to the first of any sleep epochs), stage R latency (RL) in minutes (sleep onset to the first epochs of stage R), and the total wake time (TWT) in minutes (TRT-TST-SL). Other polysomnographic parameters analyzed included the percentage of TST in each sleep stage (time in each stage/TST*100), the number of arousals, the total number of respiratory events, the number and duration of obstructive and central respiratory events, the apnea-hypopnea index (AHI) (the number of apneas + number of hypopneas x 60/TST), the average and minimum oxygen saturation (SatO2), and the presence of paroxysmal nocturnal events.

**Statistical analysis**

According to the statistical power analysis performed before the study began, the study required the recruitment of at least ten children with epileptic encephalopathy and at least ten healthy children, and the study included 31 children in the study group and 31 children in the control group. Power analysis for the Mann-Whitney U test was performed using G*Power for Windows, version 3.1.5, based on the difference in sleep parameters between the study group of children with epileptic encephalopathy and the control group of healthy children, according to the method of analysis previously reported [17]. The following criteria were used, the power of 0.95, the effect size of 1.8, and two groups (participants and controls) of similar size. Statistical analysis of quantitative data was performed using the mean ± standard deviation (SD). In the case of non-parametric distribution, the median and interquartile range (IQR) were used. Categorical data were expressed as absolute frequencies and percentages (%). Comparisons between the two groups were performed using the Mann-Whitney U test. All p-values <0.05 were considered statistically significant. Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS) version 23 (SPSS, Inc., Chicago, IL, USA).

**Results**

**Demographic and clinical characteristics of the children with epileptic encephalopathy**

The demographic and clinical characteristics of the children with epileptic encephalopathy are shown in Table 1.
Sleep architecture and respiratory sleep parameters

Differences in sleep structure, respiratory parameters, and oxygen saturation (SatO₂) between the group of children with epileptic encephalopathies and the control group are shown in Table 2. The results of this study showed that children with epileptic encephalopathy had significantly decreased total sleep time (TST) (p=0.038), a significantly lower percentage of rapid eye movement (REM) sleep (p<0.0001), and a significantly increased percentage of non-REM (NREM) phase NREM 1 sleep stage (p=0.033). The number of respiratory events did not differ significantly between the two groups (p=0.0118); there were 0.00 (IQR 0.00–1.75) respiratory events in the epileptic encephalopathy group vs. 1.00 (IQR 1.00–1.75) in the control group, but children in the epileptic encephalopathy group had significantly shorter mean duration (p=0.008) and longest duration (p=0.048) of respiratory events. The mean SatO₂ in children with epileptic encephalopathy was significantly lower with a median of 98.00% (IQR, 97.00–98.00; average rank, 25.55) versus a median of 98.00% (IQR, 98.00–99.00; average rank, 37.45) in the control group (p=0.006). The lowest levels of SatO₂ were also significantly lower in children with epileptic encephalopathy, with a median of 91.00% (IQR, 90.00–94.00; average rank, 23.40) versus a median of 93% (IQR, 93.00–94.00; average rank, 39.59) in the control group (p=0.0004). The apnea-hypopnea index (AHI) did not differ significantly between the two study groups (p=0.27).

Discussion

The aim of our study was to evaluate sleep architecture and respiration in children with intractable epileptic encephalopathies, using overnight video-polysomnography (V-PSG). The main findings of this study showed that, compared with a normal population of children matched for age, sex, and body mass index (BMI), children with epileptic encephalopathies had a significantly decreased total sleep time (TST) (p=0.038), a significantly lower percentage of time in the rapid eye movement (REM) sleep (p<0.0001), and a significantly increased percentage of time in non-REM stage 1 (NREM 1) sleep (p=0.033).

Nunes et al. [18] have also reported reduced total sleep time in 17 children with refractory focal epilepsy, which these authors explained as being due either to the epileptic syndrome or to the chronic use of antiepileptic drugs. Data from previously published studies using polysomnography in children with epilepsy are highly variable in terms of methodology, demographic, and clinical features of the children studied, which could be the reason for conflicting results of the duration of sleep phases. However, the findings of the present study are supported by those of Maganti et al. Who showed an increase in NREM 1 sleep stage in 11 school-aged children with primary generalized epilepsy [19]. Other polysomnographic studies have reported reduced REM sleep [18,20] and delayed REM latency in children with epilepsy [19,20]. However, Kaleyias et al. [14] showed a higher percentage of REM sleep in children with poorly controlled partial and generalized epilepsy.

An Italian study of 23 children with epileptic encephalopathy, which included 14 children with Lennox-Gastaut syndrome, five children with Dravet syndrome and four children with epilepsy with myoclonic-ataxic seizures, reported reduced total

| Table 1. Demographic and clinical characteristics of children with epileptic encephalopathies. |
|----------------------------------|-----------------|
| Age (years) (±SD)                | 6.78±3.61       |
| Male/Female                      | 22/9            |
| Body Mass Index (kg/m²) (±SD)    | 15.83±3.16      |
| Cause of epileptic encephalopathies |
| Structural                       | 13/31 (41.93%)  |
| Genetic                          | 9/31 (29.03%)   |
| Unknown                          | 9/31 (29.03%)   |
| Antiepileptic therapy            |
| Monotherapy                      | 7/31 (22.58%)   |
| Polytherapy                      | 10/31 (32.25%)  |
| 2 antiepileptic drugs            | 8/31 (25.80%)   |
| 3 antiepileptic drugs            | 5/31 (16.13%)   |
| 4 antiepileptic drugs            | 1/31 (3.22%)    |
| Ketogenic diet                   | 1/31 (3.22%)    |
| Antiepileptic drugs              |
| Valproates                       | 17/30 (56.66%)  |
| Clobazam                         | 14/30 (46.67%)  |
| Levetiracetam                    | 7/30 (23.33%)   |
| Oxcarbazepin                     | 6/30 (20.00%)   |
| Topiramat                        | 5/30 (16.67%)   |
| Ethosuximide                     | 5/30 (16.67%)   |
| Vigabatrin                       | 4/30 (13.33%)   |
| Lamotrigin                       | 3/30 (10.00%)   |
| Zonisamide                       | 1/30 (3.33%)    |
| Encephalographic epileptiform activity |
| Interictal                       | 31/31 (100%)    |
| Ictal events                     | 4/31 (12.9%)    |

Values are expressed as absolute numbers and percentage, unless otherwise specified. Children in the epileptic encephalopathy and control group were matched for sex, age (p=0.98) and BMI (p=0.26).
Table 2. Differences in sleep structure, respiratory parameters and sat\textsubscript{0} 2 between the group of children with epileptic encephalopathies and the control group.

| V-PSG parameter | Children with EE (N=31) | Control group (N=31) | Mann Whitney U test |
|-----------------|-------------------------|----------------------|---------------------|
|                 | Median (IQR)            | Median (IQR)         | U       | p-Value |
| TRT (min)       | 462.00 (432.50–499.25)  | 486.00 (460.25–506.25) | 364.00   | 0.101   |
| TST (min)       | 395.00 (326.25–429.25)  | 414.00 (395.25–432.75) | 333.50   | 0.038   |
| SE (%)          | 82.99 (70.81–88.90)     | 87.30 (81.70–90.74)   | 369.00   | 0.116   |
| SL (min)        | 27.00 (11.25–45.12)     | 23.00 (11.25–43.00)   | 459.00   | 0.761   |
| RL (min)        | 124.00 (69.00–177.00)   | 109.50 (74.00–147.00) | 392.00   | 0.391   |
| TWT (min)       | 45.00 (17.25–74.50)     | 24.00 (18.00–48.00)   | 407.50   | 0.304   |
| Sleep efficiency (%) | 88.16 (77.65–96.46)     | 93.08 (87.57–96.40)   | 368.00   | 0.113   |
| N1%             | 2.10 (1.10–3.08)        | 1.40 (1.03–1.88)      | 329.00   | 0.033   |
| N2%             | 46.60 (31.53–53.98)     | 43.10 (37.10–48.43)   | 448.00   | 0.647   |
| N3%             | 27.90 (17.55–44.70)     | 31.60 (26.17–33.85)   | 408.00   | 0.307   |
| REM%            | 13.80 (8.40–16.78)      | 19.80 (17.60–22.20)   | 146.50   | P<0.0001 |
| Number of arousals (N) | 7.5 (3.00–10.00)       | 8.00 (6.00–10.00)     | 286.00   | 0.340   |
| Number of respiratory events (N) | 0.00 (0.00–1.75)     | 1.00 (1.00–1.75)      | 374.50   | 0.118   |
| Average duration of respiratory events (s) | 0.00 (0.00–10.00)    | 10.00 (8.25–12.00)    | 297.00   | 0.008   |
| Longest duration of respiratory events (s) | 0.00 (0.00–11.75)    | 10.00 (8.25–12.00)    | 343.50   | 0.048   |
| Apnea-Hypopnea Index (AHI) | 0.00 (0.00–0.26)     | 0.15 (0.12–0.24)     | 404.50   | 0.27    |
| Average sat\textsubscript{0} 2 (%) | 98.00 (97.00–98.00) 25.55* | (98.00–99.00) 37.45* | 296.00   | 0.0061  |
| Minimum sat\textsubscript{0} 2 (%) | 91.00 (90.00–94.00) 23.40* | (93.00–94.00) 39.59* | 229.50   | 0.0004  |

* Average rank.

Sleep time (TST), longer REM latency, and increased NREM 3, compared with a group of healthy children [17]. However, a contradictory finding was shown in polysomnographic studies on five children with Dravet syndrome, which did not demonstrate disturbance in sleep architecture [21]. Hrackovy et al. found reduced total sleep time (TST) and a significantly reduced percentage of REM sleep in 32 patients with infantile spasms, compared with normal values for the age of the study population [22]. Subgroup analysis of patients with a higher percentage of REM sleep in the same study showed that this was associated with clinical and encephalographic
improvement [22]. Therefore, it might be possible that the proportion of REM sleep could serve as a marker of intractable epileptic encephalopathy [23]. Beside the dysfunction of acetylcholine neurons in the pedunculopontine nucleus, which is the origin of REM sleep, REM duration could also be affected by sleep fragmentation due to interictal discharges and antiepileptic drug treatment [24]. The findings of the present study, showing disturbed sleep architecture in children with epileptic encephalopathy, are in some agreement with the findings of previously published studies. However, the variable results among the studies could be due to different types of epilepsy studied, the different clinical stages of epilepsy involved, the extent of interictal discharges, and the effects of different anticonvulsant treatment [25,26].

Antiepileptic drugs can alter sleep in both positive and negative ways, independent of their anticonvulsive actions [27]. Antiepileptic drugs inhibit neuronal excitability but also stabilize sleep, reduce sleep transitions, and reduce seizure rates [12]. The number of antiepileptic drugs used for each child is also an important factor in the analysis of their effects on sleep, as it has been previously shown the more antiepileptic drugs that are used, the more sleep efficiency and REM sleep is likely to be reduced [28]. Most of the children in the present study were treated with valproates 17/31 (56.6%), and data on the effect of valproates on sleep are variable; some studies have shown no alteration in sleep architecture [29], other studies have shown that valproates reduce REM sleep and increase NREM1 sleep [30]. In the present study, 14/31 children (46.6%) were treated with clobazam, which has been shown by a previously published randomized, double-blind, placebo-controlled study to reduce sleep latency, NREM 1, and NREM 3, and to increase NREM 2 [31]. Data from previously published studies on the effects of carbamazepine are more variable, but it seems that it reduces sleep latency and arousal, and increases sleep efficiency and NREM 3 [32]. A placebo-controlled study on healthy volunteers found no effect of levetiracetam on sleep structure [33], while another randomized placebo-controlled double-blind study reported an increase in total sleep time (TST), sleep efficiency, NREM 2, and a reduction in REM sleep [34]. Also, the impact of antiepileptic drugs on sleep is dose-dependant and could be modulated by co-administration of other antiepileptic drugs [35].

In terms of sleep disturbance, in the present study, the parents of the children with epileptic encephalopathy reported that 23/31 (74.1%) usually slept calmly, and 25/31 (80.64%) of children with epileptic encephalopathy were drowsy during the day, which could be explained by the effects of the antiepileptic drugs. Due to the small sample and cohort heterogeneity, it was not possible to evaluate the impact of individual and combined antiepileptic therapy on sleep parameters in this study. Furthermore, sleep architecture can be abnormal due to the epileptic syndrome itself, independent of antiepileptic drug effects, which is in keeping with the finding in this study of ictal events and interictal epileptiform discharges (less pronounced in REM phase) contributing to sleep disruption. This finding is supported by the findings of a study published by Becker et al., who reported that children with epilepsy had disrupted sleep even during the seizure-free nights when compared with healthy controls, due to interictal discharges that prevent normal progression through the stages of sleep [36]. Interictal discharges can alter normal sleep graphoelements, for example, lower amplitude of sleep spindles and intrude into NREM and REM sleep [37], and sleep can also activate and change the morphology of interictal discharges [26].

In the present study, the number of respiratory events did not differ significantly between the study group and the control group (p=0.118), but in the epileptic encephalopathy group, duration of respiratory events was significantly shorter for both average duration (p=0.008) and longest duration (p=0.048). The average and lowest oxygen saturation (SatO₂) was also significantly lower in children with epileptic encephalopathy (p=0.006) and (p=0.0004), respectively. The apnea-hypopnea index (AHI) did not differ significantly between the two study groups (p=0.27).

In this study, the body mass index (BMI) of all the children in both groups were in the normal range, according to the WHO Child Growth Standards [38]. In a study by Kaleyias et al. [14], which reported that 42% of children with epilepsy had sleep-disordered breathing, one of the reasons for this opposing results could be the high BMI of children in their study, with a median BMI of 29 kg/m² (IQR, 27–37) compared with the normal BMI of children in the present study of 16.98 kg/m² (IQR, 14–18). Also, it is important to highlight that the present study showed a significant sleep-associated oxygen desaturation in children with epileptic encephalopathy, which could have been due to several factors including, differences in autonomic control of ventilation [39], the nature of the epileptic syndrome, the type and number of antiepileptic drugs, and the anatomy of the upper respiratory tract [14].

This study had several limitations. Children were recruited to the study who had different types of epileptic encephalopathy in different clinical stages, and who were already receiving anticonvulsant treatment. Only one night of polysomnography recording was performed per child. However, a previous study has reported that there is little variability between the first and second night of polysomnography recording in the data on sleep structure and respiratory parameters and therefore two consecutive polysomnographic recordings may not be necessary [40]. To the best of our knowledge, this is the largest cohort overnight V-PSG study in children with intractable epileptic encephalopathies, and the findings might provide further insight into sleep disorders in this group of children and form the basis for further research.
Conclusions

The findings of a video-polysomnographic (V-PSG) study in 31 children with epileptic encephalopathy receiving antiepileptic treatment, showed altered sleep architecture, and although the number of respiratory events was not significantly different from a normal controlled population of children, there was a significant reduction in oxygen saturation (SatO₂). All children in the study group had interictal epileptiform discharges, and four of them had icctal events. The findings of this study support referral of children with epileptic encephalopathy for the evaluation of sleep architecture and respiratory patterns. Further multicenter investigations are needed to determine sleep phenotypes in children with specific forms of epileptic encephalopathies that could lead to prescription of adequate antiepileptic drug combinations.

Conflict of interest

None.

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