

Sleep Abnormalities and Sleep Breathing Disorders in Children with Drug-Resistant Catastrophic Epileptic Encephalopathy

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Abstract

Undiagnosed obstructive sleep apnoea is common in patients with medically refractory epilepsy. The aim of this study is to evaluate sleep alterations and the prevalence of Sleep Breathing Disorders (SBD) in a paediatric population with catastrophic epileptic encephalopathy. To diagnose SBD, polysomnography (PSG) was performed in eleven patients (nine males, two females), with ages ranging between 3 and 11 years old, with epileptic encephalopathy characterized by drug-resistant seizures, occurring both in sleeping and waking, mental retardation and cerebral palsy. All the patients presented alterations of the sleep architecture and were positive for SBD. In particular, seven patients presented a severe form of Obstructive Sleep Apnoea Syndrome (OSAS) with apnoea/hypopnea index (AHI) greater than 10/hr, two patients presented a moderate form with AHI between 5/hr and 10/hr, two patients presented a mild form with AHI lower than 4/hr. In conclusion, SBD and sleep disruption appeared to be in comorbidity with catastrophic epileptic encephalopathy. Their treatment might also have a positive impact in seizures control and quality of life.

Keywords: SBD: Sleep-Related Breathing Disorders; Epilepsy; PSG: Polysomnography; OSAS: Obstructive Sleep Apnoea Syndrome; Drug-Resistant Seizures, AHI: Apnoea/Hypopnea Index.

Introduction

Recurrent unprovoked seizures occur in 1–2% of children. The incidence of epilepsy plateaus in early childhood and decreases after 10 years of age [1, 2, 3]. Approximately 10–40% of children with epilepsy will continue to have seizures despite optimal medical management with antiepileptic drugs (AEDs) [4, 5, 6]. In 2001, the International League Against Epilepsy (ILAE) Task Force on Classification and Terminology recognized epileptic encephalopathies as a distinct category. The epileptic catastrophic encephalopathies are a rare group of conditions characterized by epileptic seizures that are often, but not always, intractable to treatment and associated with significant neurodevelopmental delay [7, 8]. The relation between epilepsy and sleep disorders is well known and their mutual effects are widely documented [9, 10]. Night seizures significantly reduce sleep efficiency [11]. In particular, Sleep Breathing Disorders (SBD) induce a chronic modification of the sleep architecture and a state of intermittent oxygen desaturation, resulting in poor control of seizures and excessive daytime sleepiness [12]. Obstructive apnoea is common in medically refractory epilepsy adult patients [13].

The comorbidity between SBD and epileptic catastrophic encephalopathies in the paediatric population is very poorly investigated in literature and rarely considered in general practice. This study aims to assess the presence of sleep abnormalities and SBD in a cohort of children with catastrophic epileptic encephalopathy, characterized by seizures refractory to standard antiepileptic drugs.

Materials and Methods

Patients were enrolled in the study according to the following criteria: age less than 12 years; clinical and electroencephalographic diagnosis of partial or generalized crypto-symptomatic catastrophic epileptic encephalopathies characterized by drug-resistant seizures, occurring both in sleeping and waking; mental retardation and cerebral palsy; medication regimens optimized; treatment failure with at least three antiepileptic drugs given alone or in combination.

Exclusion criteria were: seizure secondary to infection, cerebral neoplasia and/or haemorrhage, significant history of medical disease (e.g. liver or kidney failure, metabolic illness) or progressive degenerative disease; non epileptic spells, alone or in combinations with epileptic seizures; another primary sleep disorder requiring medication like sedatives or hypnotics, that could affect the results of study; poor compliance to the polysomnography (PSG) by parents-care givers and/or children; previous diagnosis of Obstructive Sleep Apnoea Syndrome (OSAS).

Data including age, sex, body mass index (BMI), Mallampati index were collected. Computed tomography-magnetic resonance brain study, chest X-ray study and Electrocardiography (ECG) were performed through all population.

Before the study, each patient underwent a detailed interview about personal history, a general clinical examination and a somatometric data collection. Parents or care-givers were asked about patients sleep characteristic, such as total nocturnal sleep time, history of excessive daytime sleepiness, insomnia, nocturnal snoring, and awakenings during sleep.

Parents or care-givers also completed the Brouillette questionnaire on symptoms of OSAS. According the questionnaire, OSAS was not predicted for scores less than -1, inconclusive from -1 to 3,5 and

predicted > 3,5. No change in antiepileptic therapy was performed during the study, or in the four previous months.

Electroencephalographic assessment

Characteristics of epilepsy like frequency of epileptic seizures, circadian rhythm of seizures, previous and current AEDs use were reviewed. The diagnosis of epilepsy was made by an epileptologist based on clinical history of recurrent epileptic seizures and supporting electroencephalographic data. Seizure classification and drug resistant epilepsy definition were based using ILAE criteria [7, 8, 14].

Drug resistant epilepsy was defined as any recurrent complex partial or generalized seizure in the past six months despite adequate use and compliance with at least two tolerated and appropriately chosen AEDs in the past [14].

Polysomnographic recording

The polysomnographic studies were performed in the sleep laboratory of the A.O. Ospedali dei Colli - A.O.R.N. Monaldi in Naples. Overnight sleep studies were carried out in all subjects using a digital PSG equipment (SOMNOLab V 2.01.0001, Weinmann Medical technology, Germany).

The subject was prepared about 1 h before the recording by attaching electrodes using average 12-18 channels. The recording time ranged from 4 to 8 h, started at the patients' usual bedtime, and continued until spontaneous awakening. Patients have not taken sedative or hypnotic medication before the study. All signals were digitally recorded and were reproduced on paper. At all times, patients were under supervision of a qualified technician and raw data were manually scored by 30-second epoch, according to published standards, before final interpretation (9).

The polysomnographic recording included a pressure transducer for nasal air-flow and a thermistor for nasal-oral air-flow, piezoelectric chest and abdominal belts, pulse oximetry monitoring, a snore microphone, two anterior tibial channels, submental electromyogram, electro-oculogram, electroencephalogram (C3/A2-C4/A1 O2/A1, O1A2 of the 10-20 International placement electrode system), electrocardiogram (modified V2 lead), a body position sensor and simultaneous video monitoring.

The following sleep architecture parameters were assessed: total sleep time (TST, time from sleep onset to the end of the final sleep epoch minus time awake), time in bed (TIB), sleep latency (SL), sleep efficiency (TST/time in bed*100), percentage of each stage in total sleep time, snoring percentage.

Sleep stages were visually scored following standard criteria. The respiratory parameters evaluated were: oxygen desaturation index (ODI), average oxygen saturation, nadir oxygen saturation, oxygen saturation less than 90% for more than 30% of the registration period (T 90%) and apnoea-hypopnea index (AHI).

The polysomnographic diagnosis of patients was diagnosed according to American Academy of Sleep Medicine guidelines [15].

An event was defined as obstructive apnoea when the duration was more than two breaths, the amplitude reduction in the thermal sensor was 90% or more, and the respiratory effort was continued or increased throughout the entire period of decrease airflow.

An event was defined as hypopnea when the duration was more than two breaths, the amplitude reduction in the nasal pressure was 50% or more, and the associated oxygen desaturation was 3% or more, or there was presence of arousal or awakening.

Apnoea-hypopnea index was defined as the number of obstructive apnoeas and hypopneas per hour of the total sleep time. Obstructive sleep apnoea was diagnosed if the obstructive index was more than one on PSG.

The severity of obstructive sleep apnoea increase with increasing obstructive index: apnoea/hypopnea index scores were classified as mild (1-5/hour), moderate (5-10/hour), and severe (> 10/hours).

Sleep hypoventilation syndrome (SHVS) was diagnosed in presence of sustained hypoxemia with arterial oxygen saturation <90% for more than 30% of the registration period, during sleep, not related to apnoea or hypopnea episodes.

Primary snoring was diagnosed if there is not polysomnographic evidence of sleep apnoea or hypoventilation in a patient with history of snoring.

Results

Demographic data

The cohort of the patients was composed by eleven Caucasian subjects. Nine of them were males and two were females. There were no obese children (Table 1).

Clinical results

Nine patients presented hypersomnia, morning headaches, nocturia and impaired concentration, (Brouillette questionnaire > 3,5).

Of these, five patients complained awakenings and two patients presented choking during sleep.

Two patients showed only daytime sleepiness. Nine subjects were referred for snoring or sleep-related breathing problems.

The clinical profile of the patients included diagnosis of epileptic syndrome associated neurological symptoms.

All patients had both diurnal and nocturnal complex seizures and were in therapy with a various combination of Lamotrigine, Carbamazepine, Phenobarbital, Phenytoin, Valproate and Levetiracetam.

Electroencephalographic results

The epileptic syndromes included generalized encephalopathy (five), Lennox Gastaut syndrome (LGS) (one), partial secondary generalized epilepsy (PSGE) (three), tuberous sclerosis complex (TSC) (one), Malignant migrating partial seizures (one). (Table 1).

The seizure type, often combined in a given patient, included spasms and tonic seizure (three), polymorphous seizures (four), tonic-clonic seizures (seven), and partial with or without secondary generalization (five).

All patients presented seizures during the recording night. Seizures occurred more frequently during the stage 3 of non-REM sleep.

Patient	Sex	Age (yo)	Mallampati Index	Epileptic syndrome
1	M	7	3	Generalized encephalopathy
2	F	6	3	LGS
3	F	6	4	TSC
4	M	8	2	Generalized encephalopathy
5	M	8	2	Generalized encephalopathy
6	M	3	4	Generalized encephalopathy
7	M	6	4	PSGE
8	M	11	3	Malignant migrating partial seizures
9	M	11	3	PSGE
10	M	7	3	PSGE
11	M	5	4	Generalized encephalopathy

Table 1: Clinical characteristics of the 11 study patients. (M: male; F: Female, LSG: Lennox-Gastaud syndrome; PSGE: partial secondary generalised epilepsy; TSC: tuberous sclerosis complex).

Polysomnographic results

The eleven patients resulted positive for OSAS. In particular, seven patients presented severe OSAS, two presented moderate OSAS and two patients were found to have mild OSAS. SHVS was diagnosed in five patients. Mallampati score has a strong linear correlation with AHI and hence OSAS (Table 2).

Patient	ODI/h	AHI/h	Average SpO2 (%)	Nadir SpO2 (%)	T90 (%)
1	4.1	1.2	95.1	82.3	22.1
2	17.2	28.7	95.2	52.7	16.8
3	4.4	3.9	96.7	82.4	55.3
4	5.0	5.5	93.6	86.1	0.4
5	13.9	14.3	94.8	87.2	8.8
6	14.4	16.3	96.4	75.3	13.3
7	13.9	11.8	95.0	81.2	42.6
8	6.6	26.4	95.7	83.5	40.2
9	31.1	7.7	89.3	80.8	57.4
10	27.5	18.3	92.1	82.1	25.3
11	32.1	26.2	86.4	63.4	60.5

Table 2: The respiratory polysomnographic parameters of the 11 study patients. (AHI: Apnoea-Hypopnea Index; Average SpO2: Average Oxygen Saturation; Nadir SpO2%: Nadir Oxygen Saturation ODI: Oxygen Desaturation Index; Nadir SpO2%: Nadir Oxygen Saturation; T90%: oxygen saturation less than 90% for more than 30% of the registration period).

Very often the episodes of apnoea and hypopnea occurred during the epileptic crisis. Seven patients showed a significant reduction of the total time in bed and of the total sleep time. All patients presented a reduction of REM sleep percentage. Apnoea/hypopnea index and average oxygen saturation are negatively correlated with REM sleep percentage ($p < 0.05$). Nadir oxygen saturation negatively correlates with the efficiency of sleep ($p < 0.05$). No other significant correlation with polysomnographic data were detected.

Discussion

This pilot study shows that paediatric patients with drug-resistant epilepsy, cerebral palsy and mental retardation often present sleep disruption and are frequently affected by obstructive sleep apnoea. Abnormalities in sleep architecture included reduction of the total time in bed, of the total sleep time and of REM sleep percentage. In our study apnoea/hypopnea index and average oxygen saturation are negatively correlated with REM sleep percentage. Nadir oxygen saturation negatively correlates with the efficiency of sleep. We have also demonstrated that the severity of OSAS strongly influence the quality of sleep.

The limit of the study is that we can't generalize our findings because of the small number of patients analysed. This conclusion of our pilot study should be supported by a larger sample size.

Several studies have reported that epilepsy and OSAS, when coexist, profoundly exacerbate each other's [16]. On the one hand, OSAS has been hypnotized to exacerbate seizure frequency by disrupting REM sleep [17], on the other hand, children with epilepsy report sleep deprivation as a significant seizures-precipitating factor and drug poor control.

In our population, we believe that the epilepsy encephalopathy itself caused the observed abnormalities in sleep architecture. We also argue that the respiratory abnormalities, may have contributed to the results.

In fact, OSAS and sleep deprivation very often coexist with drug-resistant epilepsy in childhood and adult patients [18]. In addition, sleep deprivation in children might be associated with cognitive and behavioural dysfunction, and consequent downgrading of the quality of life [19].

Nevertheless, is very difficult to recognize symptoms associated with sleep breathing disorders in these patients, despite the significant abnormalities of the sleep architecture and the serious impairment of respiratory parameters, characterized by frequent episodes of apnoeas and severe nocturnal oxygen desaturation [20].

Consequently, sleep breathing disorders are underdiagnosed in patients with epilepsy, especially in children with catastrophic epileptic encephalopathy [21]. One possibility is that antiepileptic drugs increases daytime sleepiness with the influence of the sleep architecture, acting as a confounding factor. AEDs can also induce insomnia [22]. Antiepileptic medications may also contribute to sleep disorders. For example, in a patient predisposed to obstructive sleep apnoea (OSAS), barbiturates and benzodiazepines may worsen the frequency of apnoeas and hypopneas by decreasing upper airway resistance or arousal mechanisms [23, 24]. In our population of patients it is possible that AEDs may have contributed to the changes seen in the sleep architecture. As demonstrated in this pilot study, it can be extremely useful to look at the Mallampati index since Mallampati score has been found to have a strong linear correlation with AHI. In fact, in children, a high Mallampati score is more

predictive of the presence of OSAS than in adults because the main cause of the obstruction is pharyngeal [25].

Previous studies have also demonstrated that an improvement in seizure frequency in refractory epileptic patients is achieved with the treatment of OSAS [26, 27]. The screening for SBD to recognize an altered nocturnal respiratory function in the medically refractory epilepsy population is particularly outstanding to set up early intervention strategies [28, 29].

This may lead to overall improved night oxygen saturation, seizure control, sleep quality, daytime functioning and quality of life.

Conclusion

Sleep architecture and nocturnal respiratory parameters are abnormal in children with catastrophic refractory epileptic encephalopathy. In this population SBD very often occur. Although the abnormalities could be determined by respiratory events, they could be ascribed to the encephalopathy itself.

The findings of this pilot study offer preliminary data regarding nocturnal respiratory parameters and sleep abnormalities in children with drug resistant epileptic encephalopathy and support the perspective of a prospective study with a larger sample size, with the objective to better design the polysomnographic profile in this paediatric population.

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