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The cooccurrence of interictal discharges and seizures in pediatric sleep-disordered breathing

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ABSTRACT

Studies in the literature data have shown that the prevalence of obstructive sleep apnea (OSA) in children with epilepsy is high and that treatment for OSA leads to a reduction in the number of seizures; by contrast, few studies have demonstrated an increased prevalence of interictal epileptiform discharges (IEDs) or epilepsy in children with sleep-disordered breathing (SDB). The aim of the present study was to confirm the high prevalence of IEDs or epilepsy in a large sample of children with SDB and to collect follow-up data.

Children were recruited prospectively and underwent their first video-polysomnography (video-PSG) for SDB in a teaching hospital sleep center.

Of the 298 children who fulfilled the diagnostic criteria for sleep-disordered breathing, 48 (16.1%) children were found to have IEDs, three of these 48 children were also found to have nocturnal seizures (two females diagnosed with rolandic epilepsy and a male diagnosed with frontal lobe epilepsy). Only 11 subjects underwent a second video-PSG after 6 months; at the second video-PSG, the IEDs had disappeared in six subjects, who also displayed a reduced AHI and an increased mean overnight saturation. Thirty-eight of the 250 children without IEDs underwent a second video-PSG after 6 months. Of these 250 children, four, who did not display any improvement in the respiratory parameters and were found to experience numerous stereotyped movements during sleep, were diagnosed with nocturnal frontal lobe epilepsy.

Our study confirms the high prevalence of IEDs in children with SDB. Follow-up data indicate that they may recede over time, accompanied by an improvement of sleep respiratory parameters.

1. Introduction

Sleep activates both focal and generalized spikes in about one-third of all individuals with epilepsy. Some types of epilepsy are closely related to sleep, with the clinical onset occurring exclusively or mainly during sleep (e.g., rolandic epilepsy and nocturnal frontal lobe epilepsy) [1]. However, few data are available on the comorbidity of epilepsy and specific sleep disorders, such as obstructive sleep apnea (OSA), restless leg syndrome, and periodic limb movements. Sleep-related breathing disorders may trigger paroxysmal events during sleep, such as parasomnias, and may exacerbate preexisting seizures. Moreover, it has been suggested that sleepiness, a common complaint of patients with epilepsy that is frequently attributed to antiepileptic drugs, may be linked to undiagnosed sleep disorders such as restless leg syndrome or OSA [2–4]. Some authors have reported that melatonin may, by improving sleep efficiency and reducing sleep disruption, help control seizures in children and adolescents with epilepsy [5], while others have reported that the treatment of OSA may improve seizure control and reduce daytime somnolence [6–9]. Numerous studies have explored the relationship between sleep-disordered breathing and epilepsy in adults with epilepsy [8,10]. Interestingly, it has been demonstrated that the use of continuous positive airway pressure in adults with drug-refractory epilepsy and OSA improves seizure control [11]. A high prevalence (approximately 30%) of OSA was recently reported in a relatively large population of children with epilepsy, with a higher incidence being observed in children with refractory epilepsy or on multiple antiepileptic drugs; OSA in that study was, however, investigated solely by means of questionnaires [12]. Another study demonstrated that treatment of OSA in children with epilepsy may reduce seizure frequency, particularly in children with high body mass index scores and younger age at the time of adenotonsillectomy [13]. In addition, a few studies have demonstrated an increased prevalence of interictal epileptiform discharges (IEDs) or of nocturnal seizures in children with sleep-disordered breathing without a previous history of epilepsy [14,15]. We previously reported a high prevalence (14.3%) of IEDs in a population of children with OSA. Children with IEDs were older and had a longer duration of disease, a lower incidence of adenotonsillar hypertrophy, and a higher occurrence

Abbreviations: OSA, obstructive sleep apnea; IEDs, interictal epileptiform discharges; BECTS, benign epilepsy with centrotemporal spikes; PSG, polysomnography; AHI, apnea–hypopnea index; BMI, body mass index; SaO_2, mean overnight oxygen saturation.

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of perinatal injuries than controls. Epileptiform discharges prevalently occurred over the centrotemporal regions, thus being comparable with the IEDs that occur in benign epilepsy with centrotemporal spikes (BECTS). Interictal epileptiform discharges have been hypothesized to disrupt cognitive abilities, such as learning and memory, with a significant improvement in cognitive performances following remission [16]. Many studies have provided data on the relationship between epileptiform discharges during sleep and, in particular, centrotemporal or rolandic spikes and neuropsychological dysfunction in children with language disorders, autism, and ADHD [17–19]. The fact that the EEG patterns changed following treatment and were abnormal only during sleep suggests that they are a physiological phenomenon and not merely a structural deficit [17].

The high prevalence of IEDs in children with OSA possibly reflects a prefrontal cortical dysfunction. Indeed, IEDs may be due to a shift in brain activity during sleep (particularly NREM sleep), with a predominance of thalamocortical activity over prefrontal activity. Some authors have recently postulated that cognitive impairment in subjects with IEDs may be caused by a disruption in sleep architecture [14,20,21]. In this regard, our previous findings may partly explain neurocognitive impairment in children with OSA [14]. The aim of the present study was to replicate our previous study on a larger sample of children with sleep-disordered breathing in order to verify whether there is indeed a high prevalence of IEDs in this pediatric population. We also investigated whether children with IEDs and sleep-disordered breathing are at risk of developing epilepsy, and we collected follow-up data.

2. Materials and methods

We consecutively enrolled children undergoing their first diagnostic assessment for OSA in our Paediatric Sleep Centre (Rome, Italy). Diagnosis of OSA was confirmed by a laboratory polysomnography (PSG) showing an obstructive apnea/hypopnea index (AHI) > 1 n/h according to the criteria of the American Academy of Sleep Medicine [22]. A diagnosis of primary snoring in children was based on an AHI < 1 (number/hour) and habitual snoring detected by a microphone. The children were recruited between April 2009 and October 2010. Exclusion criteria were as follows: a history of epilepsy, previous treatment for OSA, acute/chronic cardiorespiratory disorders, acute/chronic neuromuscular diseases, dysmorphism, major craniofacial abnormalities, or associated chromosomal syndromes.

2.1. Subjects

A detailed personal and family history was obtained from all the participants. All the children underwent a general clinical examination as well as a clinical examination of the ear, nose, and throat to grade tonsillar hypertrophy according to a standardized scale ranging from 0 to 4 [23], with grades 3 and 4 being defined as clinically significant tonsillar hypertrophy; adenoid hypertrophy was graded according to Greenfeld et al. [24]. All the children underwent an orthodontic assessment to detect possible jaw deviation from normal occlusion, e.g., deep bite, retrusive bite, and crossbite. The patients underwent PSG in our sleep center after one night of adaptation.

2.2. Interictal epileptiform discharges

Electroencephalogram results were reviewed by one of the authors (SM) at a screen resolution of 10 mm/s. According to the definition of the International Federation of Societies for Clinical Neurophysiology [25], epileptiform discharges were identified by the presence of spikes (transient, clearly distinguishable from background activity, and lasting 20–70 ms) and sharp waves (like spikes but lasting 70–200 ms), either alone or accompanied by slow waves (of higher amplitude than spike or sharp waves), occurring either on their own or in bursts. A subject was considered as having IEDs when a spike and/or sharp wave rate ≥ 1 n/h of recording was present; however, all the subjects in the group had significantly higher numbers of PA/IEDs (range: 10 to 100 n/h).

2.3. Polysomnographic parameters

All the patients underwent a full-night PSG in our sleep center after one night of adaptation. Standard overnight PSG recordings were performed using a Grass Heritage polygraph. The variables recorded included the following: an 8-channel electroencephalogram (bilateral frontal, central, and occipital monopolar montages referred to the contralateral mastoid and bilateral frontotemporal and temporooccipital montages), according to the International "10–20" system to place electrodes in standardized scalp locations; an electrooculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to A1); and a submental electromyogram and an electrocardiogram (1 derivation). Sleep was subdivided into 30-s epochs, and sleep stages were scored according to the standard criteria [26]. Central, obstructive, and mixed apnea events were counted according to standard criteria [26].

Chest and abdominal movements were measured by strain gauges. Oronasal airflow was recorded with a thermocouple (or nasal pressure monitor when children tolerated a nasal cannula). Arterial oxygen saturation was monitored by means of a pulse oximeter.

All recordings started at the patients' usual bedtime and continued until spontaneous awakening.

2.4. Study design

On the basis of the presence of IEDs/seizures, we identified 2 subgroups of subjects. Group 0 (253 subjects) included subjects without IEDs/seizures, while Group 1 (45 subjects) included children with IEDs and/or nocturnal seizures. Group 1 was then subdivided into three groups according to whether the IEDs occurred in the centrotemporal (A), frontal (B), or occipital regions (C) (Group A — 27 subjects, Group B — 10 subjects, and Group C — 11 subjects). The anthropometric and clinical characteristics and sleep respiratory parameters of these groups were then compared. Moreover, we collected follow-up data from each group whenever possible.

The local ethics committee approved the study protocol, and parents gave their informed consent to the procedures.

2.5. Statistical analysis

Data are expressed as mean values ± SD. Analysis of variance followed by post hoc comparisons, parametric testing (t-test and paired sample test) and nonparametric Mann–Whitney U-test, or χ^2 test was used, when appropriate, to compare data; p-values of less than 0.05 were considered as statistically significant. Statistical analysis was performed using the SPSS system (version 12.0; SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Study population

Two hundred and ninety-eight children fulfilled the diagnostic criteria for sleep-disordered breathing (mean age: 5.75 ± 3.17 years; 186 males; body mass index (BMI): 18.04 ± 3.85 kg/m^2, BMI percentile: 69.86 ± 33.74; tonsillar hypertrophy: 42.3%, n = 126 subjects; narrow palate: 42.6%, n = 127 subjects; AHI = 6.04 ± 9.73 n/h; mean overnight oxygen saturation (SaO_2): 97.06 ± 1.52%). Table 1 shows the patients' anthropometric and clinical characteristics, as well as the polysomnographic parameters of children with sleep-disordered breathing without either IEDs or epilepsy (Group 0, 250/298 subjects) compared with those with IEDs and/or nocturnal seizures (Group 1, 48/298 subjects, 16.1% of the total sample). Group 1 included the following: one