REVIEW ARTICLE

Sleep Science

Polysomnographic Aspects of Sleep Architecture on Self-limited Epilepsy with Centrotemporal Spikes: A Systematic Review and Meta-analysis

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ABSTRACT

Self-limited epilepsy with centrotemporal spikes is the most common paediatric epileptic syndrome, with growing evidence linking it to various degrees and presentations of neuropsychological dysfunction. The objective of this study is to evaluate the possible sleep macro and microstructural alterations in children with this diagnosis. A systematic review of published manuscripts was carried out in Medline, LILACS and Scielo databases, using the MeSH terms *epilepsy*, *sleep* and *polysomnography*. From 753 retrieved references, 5 were selected, and data from macro and, when available, microstructure of sleep were extracted. Meta-analysis was performed with data from 4 studies using standardized mean difference. Findings were heterogeneous between studies, being the most frequent macrostructural findings a smaller proportion and greater latency of REM sleep in two studies and, in meta-analysis, a longer sleep latency was the most significant finding among epileptic patients. Only one study evaluated sleep microstructure, suggesting possible alterations in cyclic alternating pattern in diagnosed children. Studies evaluating macro and microstructure of sleep in children with self-limited epilepsy with centrotemporal spikes are necessary to a better understanding of mechanisms of the neuropsychologic disturbances that are frequently seen in children with this diagnosis.

Keywords: Sleep. Epilepsy. Polysomnography

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INTRODUCTION

Self-limited epilepsy with centrotemporal spikes, previously classified as benign epilepsy with centrotemporal spikes or benign rolandic epilepsy of childhood, is the most common focal epilepsy syndrome in the paediatric age group.[1-3] Seizures occur typically during sleep, and it is considered as being of good prognosis, considering that most cases are idiopathic and resolve before adulthood, irrespective of treatment.[4,5] However, recent data have been linking this type of epilepsy to neuropsychological dysfunctions of variable intensity, such as drop in school performance, as well as speech, behaviour and attentional impairment.[6-9]

Sleep also plays an important role in cognitive function and behaviour, and its› disturbances or deprivation can lead to similar symptoms.[10-12] The association between epilepsy and sleep architecture alterations has been demonstrated especially in the context of refractory or difficult to treat epilepsies.[13,14]

The objective of this study is to systematically review the literature in search of articles evaluating sleep macro and microstructure by means of polysomnography in children diagnosed as having self-limited epilepsy with centrotemporal spikes in order to try to establish a link between sleep organization and the neuropsychological dysfunctions that frequently occur.

Clinical and electroencephalographic findings in self-limited epilepsy with centrotemporal spikes

Self-limited epilepsy with centrotemporal spikes is responsible for around 15% of epilepsies started from 1 and 15 years of age, with an estimated incidence of 10-20/100000 children from 0 to 15 years of age, of which 75% initiate between the ages of 7 and 10 years.[1,15]

Interictal electroencephalogram is characterised by epileptiform activity in the shape of acute centrotemporal sleep-activated waves, over a normal background activity. The epileptogenic activity is activated by sleepiness and NREM sleep, and may be absent during wakefulness.[16] In about one third of patients the epileptogenic activity is bilateral, whether synchronous or asynchronous.[16]

Epileptic seizures are typically focal in 70-80% of cases, affecting laryngeal or facial muscles and, less frequently, the superior limbs.[1,15] Generalized seizures can occur with variable frequency, at times following a focal-onset seizure, and status epilepticus are rare.[17] Most ictal episodes occur during sleep, of which 35% occur in the two hours preceding awakening or upon awakening.[15] Also, about half of the patients experience less than five ictal episodes during the period of active epilepsy, which is usually short (less than 8 years in 97% of patients).[1] Only one publication was found relating epilepsy with centrotemporal spikes to SUDEP (sudden unexpected death in epilepsy), including three clinical cases.[18]

Due to the natural history of seizure remission with or without treatment, pharmacological therapeutic implementation is contradictory and must be individually evaluated, considering seizure frequency and characteristics.[4,19] When pharmacological treatment is preconized, the most indicated drugs are voltage-gated sodium channel blockers carbamazepine or lamotrigine.[20,21]

Despite the good neurologic prognosis associated to epilepsy with centrotemporal spikes, studies have been showing its association to decline in executive and cognitive functions.[6-9] Receptive and expressive language disorders have been identified in patients with this diagnosis in comparison to controls,[22] irrespectively of pharmacological treatment and, in one study, lower performance in reading and spelling tests, as well as in wellbeing, cognitive and behavioural evaluations, with more striking lags in attentional tests, but also showing total and verbal IQ (intelligence quotient) scores an average 11 points lower than in non-affected patients (both with $p=0.000$).[9] Correspondingly, a previous study found lower IQ scores (although still in the normal range) in children with epilepsy with centrotemporal spikes when compared to controls, as well as impairment in short-term memory, visuomotor, attentional and coordination tests, resolved after epilepsy remission.[6] Attentional deficits in children diagnosed with this epileptic syndrome were also described in a systematic review on the subject.[7]

Polysomnography is the gold-standard for sleep evaluation,[23] providing information, after at least one whole night of assessment, of a series of macro and microstructural sleep parameters. Sleep macrostructure encloses parameters such as percentage of each sleep stage, NREM and REM sleep latencies, total awake time after sleep onset and sleep efficiency.[24] Sleep microstructure, on the other hand, comprehends the cyclic alternating pattern (CAP), a distinct periodic activity from the background activity during NREM sleep (bursts of delta waves, K complexes, sleep spindles, intermittent alpha and arousals), representing a physiological marker of sleep instability.[25]

METHODS

A systematic review of published manuscripts was performed, with no limits as to year of publication, in April 2017, in Medline, LILACS and Scielo databases. Search was conducted combining MeSH term *epilepsy* with MeSH terms *sleep* and p*olysomnography*.

To be eligible, studies had to analyse, in children diagnosed with epilepsy with centrotemporal spikes, sleep parameters derived from polysomnographic studies. To be included, manuscripts that studied other types of epilepsies had to have analysed polysomnographic characteristics of patients with epilepsy with centrotemporal spikes separately. Review articles, editorials and book chapters were excluded. Manuscripts that were not published in English, French, Portuguese, or Spanish were also excluded from analyses.

From the selected manuscripts, year of publication, antiepileptic drug prescription, polysomnographic parameters, clinical parameters (as executive functions, daytime sleepiness) and results were extracted. References from the selected articles were searched for other possible articles of interest.

For meta-analysis, differences between groups were estimated using standardized mean differences. This decision was made due to heterogeneous measure of sleep outcomes between studies. To be included, outcome results had to be

available, for the same variable, in more than two studies. Sleep stage 2 reflects S2 alone in two studies,[26,27] and S1 plus S2 in other two studies.[28,29] Results reflect the difference, in standard deviation (SD), between exposed and non-exposed groups for each available sleep outcome. Heterogeneity among studies was assessed using the Q-test and I-square; if either test suggested that the heterogeneity was higher than the expected, random-effects model was used to pool the estimates.

RESULTS

A total of 753 articles were retrieved, of which 15 were duplicates. After reading the 738 titles, 124 full-texts or summaries selected for reading. Of those, 119 were excluded and, in total, 5 articles were selected for this review.[26-30] The flow chart in Figure 1 resumes the article search and selection process. Selected studies› characteristics, as well as their main results, can be found in Table 1.

Barreto *et al.* analysed polysomnographic studies of 23 patients from 4 to 17 years of age (average of 10.8 years), of which 13 were diagnosed as having epilepsy with centrotemporal spikes, and 10 as having idiopathic generalized epilepsy.[27] To be included in the study, participants had to have normal neuro-psychomotor development, as well as normal neurologic examination and neuroimaging, as well as a controlled epileptic syndrome. The control group consisted of 12 healthy children. In the epilepsy with centrotemporal spikes group mean age was 8.9 years, and 7 out of 13 patients were under pharmacological treatment, 5 of which

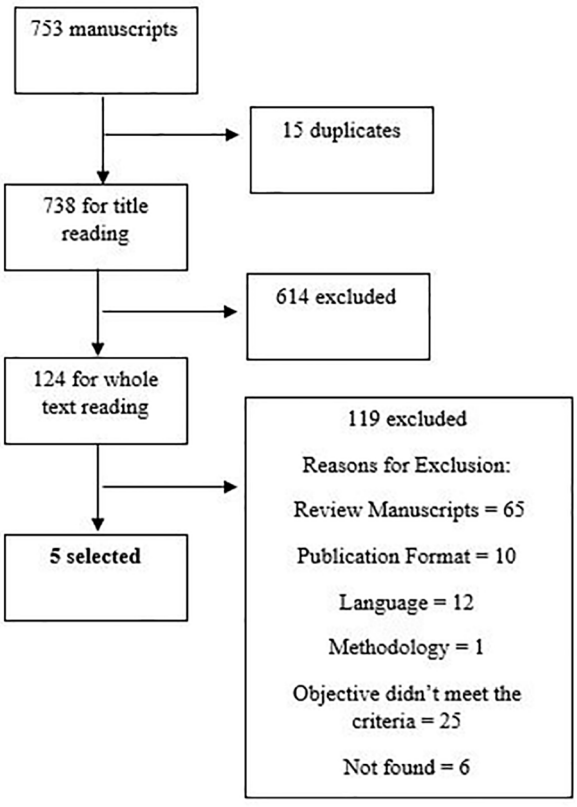

Figure 1. Flow chart of article search and selection process.

in monotherapy with carbamazepine (other treatments included flunarizine and phenobarbital). This group of children also had longer Total Sleep Time (TST) when compared to children with generalized idiopathic epilepsy (441.62 min *versus* 368.75 min; p=0.01), as well as longer NREM sleep duration (333.89 *versus* 272.05; p=0.001). REM sleep duration was similar between patients with epilepsy with centrotemporal spikes and the control group (107.73 min in epileptic patients and 90.17 min in the control group); however, REM sleep latency was greater among epileptic patients, despite being under the normal range and without significant statistical difference (115.46 min *versus* 101.04; p=0.71). No differences in sleep parameters were found among patients with epilepsy with centrotemporal spikes when considering current pharmacological treatment.

The study conducted by Bruni *et al* included only children free of medication and with no daytime symptoms of sleep disturbances.[26] The average age among the 10 participants was 8.1 years (6-10 years). A group of 10 healthy children was used as the control group. Children spent one adaptation night in the sleep laboratory, and the study data were obtained in a second night of recording, aiming to avoid first night effect. Compared to controls, children with epilepsy with centrotemporal spikes showed shorter TST (444.4 min *versus* 507.2 min; p=0.046), longer REM sleep latency (170.3 min *versus* 109.8 min; p=0.008), lower sleep efficiency (87.7% *versus* 93.2%; p=0.035), and lower percentage of REM sleep (15.5% *versus* 21.2%; p=0.0052).

Epileptic children showed, in microstructure analysis, smaller CAP proportion (18.7 *versus* 33.5; p<0.012), especially in Stage 2 sleep (8.3 *versus* 27.7; p<0.00025), reduced A1 index (intermittent alpha rhythm in Stage 1, K complex sequences or delta waves in other stages associated with mild polygraphic alterations) mainly in Stages 1 and 2 (1.91 versus 16.28; p<0.0033; 15.01 *versus* 41.91; p<0.0033; stages S1 and S2, respectively), and reduced A2 index (k complexes with alpha and beta activity and arousals with slow-wave synchronization, associated with a moderate increase in muscle tone and/or cardio-respiratory rate), especially during Stage 1 (1.14 *versus* 4.91; p<0.033), increased A3 index (desynchronized EEG patterns alone or exceeding one third of phase A duration, associated to a significant increase in muscle tone and/or cardio-respiratory rate) in Stage 3 (17.0% *versus* 8.1%; p<0.024), a reduction in the average duration of A3 (10.3 *versus* 17.2s; p<0.005) and in the number of CAP sequences (20.5 *versus* 35.8; p<0.0009).

Clemens *et al* evaluated 11 children diagnosed with epilepsy with centrotemporal spikes, aged between 6 and 15 years, free of medication, or in use of a single drug in low therapeutic doses (not specified), and none having presented seizures in the month preceding evaluation.[28] The control group consisted of 8 healthy children in the same age group. Epileptic children showed sleep duration in average 34 minutes shorter when compared to controls (458 min *versus* 492 min), although this difference, however, was not statistically significant, (p value not specified), and longer WASO (wake after sleep onset) (24 *versus* 6 min; p<0.3). Sleep efficiency, percentage of sleep stages and sleep latency of each sleep stage was similar between groups.

Table 1. Selected manuscripts after full text reading (n=5)

Author, year	Number and characteristics of participants	Number of nights of exam	Polysomnographic parameters	Main Results	Other Results
Barreto,[27] 2002	10 generalized idiopathic epilepsy 13 epilepsy with centrotemporal spikes 12 controls	1 night	TPS TST WASO Sleep latency REM sleep latency Duration of stages S1, S2, S3, S4, NREM (total), and REM	Children with epilepsy with centrotemporal spikes: 1. Longer TPS e TST in comparison to other groups 2. Shorter WASO in comparison to other groups 3. Longer REM sleep latency in relation to the control group, but shorter when compared to the generalized idiopathic epilepsy group	1.Absence of difference in sleep characteristics in individuals receiving antiepileptic treatment in comparison to medication-free patients
Bruni,[26] 2010	10 epilepsy with centrotemporal spikes, free of treatment, with normal development and with no daytime symptoms of sleep disturbances 10 controls	1, after 1 adaptation night	Time in bed TPS TST Sleep latency REM sleep latency Number of stage shifts/hour Number of arousals per hour Sleep efficiency WASO Duration of stages S1, S2, S3, and REM Proportion of CAP throughout the night and at each sleep stage Number of A1, A2 and A3 phases in every sleep stage	Sleep macrostructure among epileptic children: 1. Shorter TST and lower sleep efficiency 2. Smaller percentage of REM sleep and increased REM sleep latency Sleep microstructure among epileptic patients: 1. Shorter CAP rate, especially in S2 2. Reduced A1 index, especially in S1 and S2 3. Reduced A2 index, especially in S1 4. Increased A3 index in S3 5. Shorter A3 average duration 6. Reduced number of CAP sequences	
Clemens,[28] 1987	11 children with epilepsy with centrotemporal spikes, either free of medication or receiving 1 drug, seizure free for at least 1 month 11 controls	1, after 1 adaptation night	Time in bed TST WASO Sleep efficiency S1-S2, S3, and REM sleep latencies Duration of sleep stages S1-2, S3, and REM Arousals lasting over 320s Percentages of short (3 min), medium (3-30 min) or long (30 min) sleep stages	1. Sleep organization and architecture similar between both groups 2. Epileptic children showed longer WASO, although without not significant statistical difference	
Gogou,[29] 2016	15 children with epilepsy with centrotemporal spikes 27 controls	1 night	TST Sleep latency Sleep efficiency Duration of stages S1-S2, S3, and REM AI PLMI	Children with epilepsy with centrotemporal spikes: 1. Smaller proportion of REM sleep ($p<0.01$)	1. Higher PLMI among epileptic children 2. Obstructive apnoea and apnoea/hypopnoea indexes higher among epileptic children ($p<0.001$)
Rose,[30] 1984	6 children with epilepsy with centrotemporal spikes	1 night, patients free of treatment Same individuals, for 1 night, 1 to 2 years after treatment implementation	Duration of every sleep stage to total registered time Duration of REM sleep in TST Number of arousals	From pre to post treatment phase: 1. Reduction in REM sleep percentage 2. Increase in S2 duration 3. Reduction in night time wakings	

TPS: total period of sleep; TST: total sleep time; WASO: Wake after sleep onset until lights on; REM: rapid-eye-movements; NREM: non-REM; S1: sleep stage 1; S2: sleep stage 2; S3: sleep stage 3; S4: sleep stage 4; CAP: cyclic alternating pattern; A1: intermittent alpha rhythm in Stage 1, k complex sequences or delta waves in other stages associated with mild polygraphic alterations); A2: k complexes with alpha and beta activity and arousals with slow-wave synchronization, associated with a moderate increase in muscle tone and/or cardio-respiratory rate; A3: desynchronized EEG patterns alone or exceeding one third of phase A duration, associated to a significant increase in muscle tone and/or cardio-respiratory rate; AI: Awakenings index (number of arousals per hour of sleep); PLMI: periodic leg movements index per hour of sleep

In the study by Gogou 15 children with a diagnosis of epilepsy with centrotemporal spikes were included, paired with 27 controls.(29) Among epileptic children, 11 were receiving pharmacological monotherapy, 2 received two medications, and 2 were treatment-free. Percentage of REM sleep was significantly lower among children with epilepsy in relation to controls (17.32% ± 4.61 *versus* 21.24% ± 4.65; p<0.01). The remainder of sleep parameters were similar between groups. Differences in respiratory parameters were also sought by the authors, who found significantly higher obstructive apnoea/hypopnoea indexes among children with epilepsy with centrotemporal spikes (2.38±1.7 versus 1.21 ±0.83; p<0.01 e 1.49±0.85 versus 0.64±0.5; p<0.01), as well as a trend towards lower oxygen saturation and longer duration of apnoeas.

Rose and Duron, in the decade of 1980, obtained polysomnographic exams of 6 children with epilepsy with

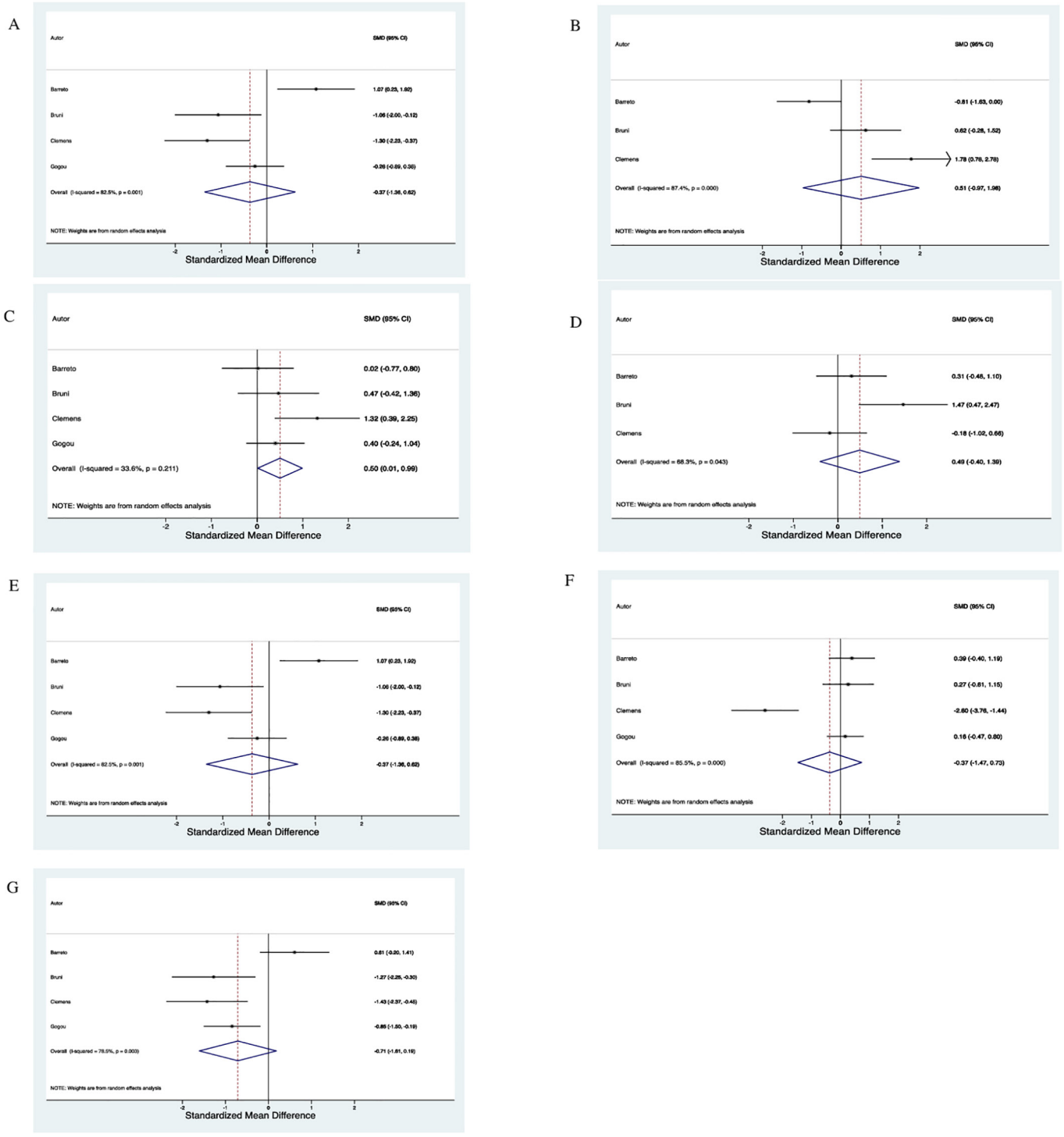

Figure 2. Standardized mean differences for sleep outcomes. Forest plots indicate standardized mean differences (SMD) and 95% confidence intervals for total sleep time (A), wake after sleep onset (B), sleep latency (C), REM sleep latency (D), duration of S2 (E), duration of S3 (F) and duration of REM sleep (G)

centrotemporal spikes, initially free of pharmacological treatment, and 1 or 2 years after medication treatment implementation.[30] Although results were presented only as comparisons, without statistical analysis, their data showed a reduction in the percentage of REM sleep from before to after treatment, from the lower limit of normality (21.2%) to limits below normal ranges (16.7%). On the other hand, Stage 2 sleep duration increased from 32.8 to 45.8% after therapy onset, concurrently to a reduction in the percentage of awake time during the recording (from 10.5 to 7.2%).

Four studies were eligible for meta-analysis (Figure 2).[26-29] Standardized mean differences (SMD) were obtained for TST, WASO, sleep latency, REM sleep latency, and duration of Stages S2, S3 and REM according to availability. Pooled SMD showed that epileptic patients had TST 0.37 SD shorter than controls (CI95% -1.356 - 0.620; p=0.465), S2 0.37 SD shorter than controls (CI95% -1.356 - 0.620; p=0.465) as well as shorter S3 (SD = -0.37; CI95% -1.468 - 0.732; p=0.512) and REM sleep (SD = -0.712; CI95% -1.610 - 0.186; p=0.120) duration, and a 0.51 SD longer WASO (CI95% -0.966 - 1.980; p=0.500) as well as sleep (SD=0.50; CI95% 0.013 - 0.992; p=0.044) and REM sleep latencies (SD=0.494; CI95% -0.400 - 1.388; p=0.279). As noted, statistically significant differences between groups were found for sleep latency, with data deriving from 4 studies. Because the heterogeneity was statistically significant, pooled effects were estimated using random-effects model.

DISCUSSION

To our knowledge, this is the first manuscript to systematically review the polysomnographic characteristics of self-limited epilepsy with centrotemporal spikes. In current literature, the number of studies addressing sleep structure disturbances in patients with this epileptic syndrome is scarce, which may be due to the good prognosis associated with the diagnosis. Likewise, in the existing studies, the number of participants is small, although counting with control groups.

Results from the studies were conflicting, ranging from alterations in TST and specific sleep stages to very similar sleep characteristics between participants with or without the diagnosis. In meta-analysis, a longer sleep latency was the strongest outcome associated to the epilepsy. A smaller proportion[26,29,30] and greater REM sleep latency[26,27] were described in two studies each, and the study by Rose found a reduction in REM sleep proportion after treatment initiation,[30] in patients receiving valproate, phenobarbital or diazepam, drugs that are known to increase NREM and reduce REM sleep proportions, and that nowadays are not first line treatment for epilepsy with centrotemporal spikes.[31,32] The only study to evaluate the differences in sleep between treated and untreated patients didn't find significant disparities between groups.[27] Studies in children with other epilepsy types and difficult to treat epilepsies also found a reduction in total sleep time, in the proportion of REM sleep, as well as an increase in REM sleep latency.[14,33]

One study described an increase in obstructive respiratory events among epileptic children.[29] However, most patients were receiving pharmacologic treatment, and the described alterations may be due to the myorelaxing effect of antiepileptic drugs, and not to epilepsy itself.[33] Further studies with specific delineations are needed to clarify this possible association.

Three studies found a reduction in REM sleep percentage.[26,29,30] An increase in number of awakenings, with higher WASO and, consequently, lower sleep efficiency could explain this reduction.[13] There wasn›t, however, a consistency between other sleep parameters and this specific finding. The study by Gogou, for example, didn›t find a significant difference between groups in regards to total sleep time, sleep efficiency, or the proportion of other sleep stages that could justify a reduction in the percentage of REM sleep.[29] In contrast, the study by Bruni showed smaller TST and sleep efficiency in this group.[26] Barreto, on the other hand, found a longer sleep duration and smaller percentage of REM sleep among his patients.[27] Further studies with larger number of participants, and designed to compare treated against non-treated patients could be useful in clarifying this association.

Sleep microstructure was analysed in one study only.[26] The main differences observed between children with epilepsy with centrotemporal spikes and healthy subjects were in microstructural aspects of sleep, especially during Stage 2, and not in its macrostructure. In their study in the 1990s, Terzano *et al* evaluated the influence of CAP on the distribution of centrotemporal spikes, without finding a significant association between both, suggesting epileptogenic discharges in children with epilepsy with centrotemporal spikes are not modulated by CAP mechanisms.[34] Bruni suggests that a reduction in NREM instability may be associated to an inhibitory action of spindle activity and epileptogenic spikes over arousals and, consequently, over CAP.

Sleep-induced paroxysmal activity is present in other epileptic syndromes, such as Landau-Kleffner and continuous spike-and-wave during sleep, in which daytime behaviour, attention and language skills are often severely compromised. (35) Benign epilepsy with centro-temporal spikes may share a common pathophysiological background and may be considered the more benign endpoint of the same epileptic spectrum, and affected children may transition from one syndrome to another over time.(36) Therefore, repeated electroencephalographic evaluation, as well as neuropsychologic testing, may be important to determine diagnosis and define whether behavioural and or cognitive changes were due to self-limited epilepsy with centrotemporal spikes or to another syndrome of the spectrum.

None of the manuscripts evaluated possible neuropsychological disturbances among participating children. Efforts to clarify this question are of important relevance, considering that studies included mainly children with good seizure control and that may, in spite of that, be affected in terms of cognition and behaviour. The level of NREM disturbance associated to frequency and intensity of epileptiform discharges and its consequent effect over sleep spindle activity and intensity could also have an effect over the behavioural aspects of children diagnosed with epilepsy with centrotemporal spikes, under pharmacological treatment or not.[37]

CONCLUSION

Published data describing objective sleep parameters in children diagnosed with self-limited epilepsy with centrotemporal spikes is scarce and contradictory. However, in contrast to the idea of the little morbidity associated with this type of epileptic syndrome, there is growing evidence linking epilepsy with centrotemporal spikes to behavioural, attentional, and cognitive disturbances, which may also be observed among children with sleep disturbances. The effect of pharmacological treatment over sleep stages and its possible long-term behavioural/cognitive effect in children with epilepsy with centrotemporal spikes must also be better clarified. Studies aiming to evaluate the possible mediating effect of macro and microstructure of sleep over clinical manifestations found in this type of epilepsy are paramount to determine this possible association, leading to environmental or therapeutic measures aiming at improving global cognitive functioning in these individuals.

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