European Journal of Pediatrics (2019) 178:1129–1137
https://doi.org/10.1007/s00431-019-03413-9

REVIEW

The role of sleep-related cognitive functions in the spectrum of benign epilepsy with centro-temporal spikes

Silvia Miano[1] · Alexandre N. Datta[2]

Received: 2 March 2019 / Revised: 11 June 2019 / Accepted: 12 June 2019 / Published online: 21 June 2019

Abstract

Heterogeneous cognitive deficits have been described in the spectrum of benign epilepsy with centro-temporal spikes, which strongly correlate with the intensity of interictal epileptiform discharges and its spreading, in particular during sleep, mostly within the perisylvian cognitive network. The aim of this review is to discuss current findings regarding the connection between sleep alterations and cognitive function in the spectrum of benign epilepsy with centro-temporal spikes. A longer sleep onset latency is the only evident sleep macrostructure alteration reported in the spectrum of benign epilepsy with centro-temporal spikes. On a microstructural level, a higher spike count of descending compared to ascending slopes of sleep cycles, an impairment of slow wave downscaling, and amplitude and slope of slow waves were found in the spectrum of benign epilepsy with centro-temporal spikes. Moreover, children with benign epilepsy with centro-temporal spikes had a reduced non-rapid eye movement sleep instability, in terms of cyclic alternating pattern, similar to that found in children with attention-deficit hyperactivity disorders and in children with obstructive sleep apnea and centro-temporal spike during sleep. Children with benign epilepsy with centro-temporal spikes have a known comorbidity with attention-deficit hyperactivity disorders and obstructive sleep apnea.

Conclusion: Considering the common sleep microstructure alterations, the presence of attention deficit and hyperactivity and/or sleep apnea may be a considered warning sign in the case of benign epilepsy with centro-temporal spikes.

What is Known:

• *Sleep related-cognitive deficits have been described in the spectrum of benign epilepsy with centro-temporal spikes. The degree of sleep alterations may predict the neurocognitive outcome, and help clinicians to choose the right treatment.*

What is New:

• *Considering the common sleep microstructure alterations, attention deficit and sleep apnea, may be a considered warning signs.*

Keywords Sleep · Childhood benign epilepsy · Interictal epileptiform discharges · Obstructive sleep apnea

Abbreviations

AED	antiepileptic drug
ADHD	attention-deficit hyperactivity disorder
BECTS	benign focal epilepsy of childhood with centro-temporal spikes
CSWS	Continuous Spike Wave during Slow Sleep (EEG phenomenon)
EECSWS	epileptic encephalopathy with Continuous Spike Wave during Slow Sleep
CAP	cyclic alternating pattern
DMN	default mode network
IED	interictal epileptiform discharges
IFCE	idiopathic focal childhood epilepsies
LKS	Landau–Kleffner syndrome
OSA	obstructive sleep apnea
PN	Perisylvian network
SRE	sleep-related epilepsy
SWA	slow wave activity

Communicated by Mario Bianchetti

✉ Silvia Miano
silvia.miano@eoc.ch

[1] Sleep Center, Neurocenter of Southern Switzerland, Civic Hospital of Lugano (EOC), via Tesserete 46, 6903 Lugano, Switzerland

[2] Department of Pediatric Neurology and Developmental Medicine, University of Basel Children's Hospital, Basel, Switzerland

Introduction

Benign Epilepsy with Centro-Temporal Spikes (BECTS) is part of a spectrum of "idiopathic" focal childhood epilepsies (IFCE) with transient, age-dependent, most probably genetic, non-structural focal epileptic abnormalities. This spectrum consists of a continuum of epilepsies with variable severity and localisation of interictal epileptiform discharges (IED) [27, 29], mostly involving the perisylvian cognitive network. In this review, we concentrate on BECTS, Landau–Kleffner Syndrome (LKS), and epileptic encephalopathy with Continuous Spike Wave during Slow Sleep (EECSWS). BECTS represents the most frequent epilepsy within the spectrum of IFCE, with a prevalence of 15–20% in children younger than 15 years [36]. Nevertheless, centro-temporal spikes (CTS), the electroencephalogram (EEG) hallmark of BECTS, are found in approximately 4% of the childhood population [3].

In the last decades, many papers reported evidence on the role of sleep disruption in epilepsy as a cause of cognitive impairment, mostly related to nocturnal epileptiform activity or to nocturnal subclinical seizures, even in benign epilepsies [49, 71]. It has been hypothesised that epileptiform activity may interfere with neuroplasticity processes, disturbing the occurrence of learning-dependent, slow wave activity (SWA) or spindle activity [49]. Several new aspects have been elaborated, contributing to a deeper understanding of the activation of interictal and ictal epileptic discharges during sleep: the interrelationship between the sleep–wake circuitry and the different epileptic networks along with the sleep microstructure associated with epileptic activation, identified within the system of cyclic alternating pattern (CAP) [26]. Nocturnal frontal lobe epilepsy has been recently renamed as sleep-related hypermotor epilepsy (SHE) [66]. SHE may be accompanied by intellectual disability, behavioural problems and deficits in executive functions in relation to a specific frontal lobe dysfunction, similar to that found in childhood absence epilepsy (a wake-related epilepsy) [9, 74]. On the contrary, the anterior perisylvian network (PN) is involved in BECTS; additionally, the posterior part of PN, mostly bilaterally, is involved in LKS, whereas there is a widespread involvement of large cortical areas including the default-mode network (DMN) in EECSWS [26, 29, 74]. The spectrum of IFCE with localisation in the perisylvian network such as BECTS is accompanied by a broader impact on cognitive ability (from verbal and visuo-constructive, attention, learning disability to autism) and a broader dysfunction of the cerebral network, implicated in left and right hemispheric function development [27]. It represents a sleep-related model which embraces a continuum from simple interictal epileptiform discharges (IED) occurring during sleep (without evident seizures) to the encephalopathic epileptic configuration of EECSWS. The amount, the localisation and the persistence of IED over time correlate with the degree of cognitive deficits, rather than frequent seizures. The slow wave components of the discharges may protect against conventional seizures but on the other hand induce cognitive impairment [27]. The term "cognitive epilepsy" has changed the vision of epilepsy, since not only seizures but also IED may have a harmful impact on the development of the cortical area during vulnerable age [27]. Centro-temporal spikes (CTS) may reflect a local cortical developmental delay and increased local excitability with a potential to regress or progress to epilepsy, including its malignant variant [29]. IED in EECSWS affect e.g. auditory discrimination and may have a long-lasting impact on cognitive function. On the contrary, in typical children with BECTS with a lower degree of IED, plastic brain reorganisation or the preservation of networks may reduce the impact of cognitive deficits [20].

Furthermore, the occurrence of IED during sleep may be associated to ADHD, autism and language disorders [5, 16, 46, 48]. This suggests that CTS is not specific to epilepsy, but may be a common endophenotype of a more widespread neurodevelopmental abnormality, involving the entire perisylvian cognitive network [15, 71]. In agreement with these findings, a high prevalence of IED during sleep has been found in children with ADHD, especially if evaluated via sleep and sleep-deprived recordings with a percentage reaching more than 25% of cases [] and up to 53.1% via full-night polysomnography [65].

The aim of this review is to present current and relevant findings demonstrating the strict connection between sleep and the BECTS spectrum, in terms of interference of ictal and interictal ED with sleep macrostructure, SWA and sleep microstructure. Moreover, the few data available about the comorbidity between paediatric obstructive sleep apnea (OSA) and ADHD/IED during sleep/BECTS will be discussed.

BECTS spectrum

The first paper [27] that tried to unify the benign, transient, age-dependent forms of benign focal epilepsy with the malignant encephalopathic variants (CSWS and others) described them as epileptic spectrum diseases of PN [48]. The atypical evolution of BECTS can result in atypical benign childhood focal epilepsy (ABCFE), status epilepticus of BECTS (SEBECTS), LKS and epileptic encephalopathy with CSWS [36]. A retrospective study on 196 children with BECTS found an atypical evolution in 6.6% of cases [77]. Usually, ABCFE and SEBECTS have a positive outcome when the correct therapeutic measures are taken. On the other hand, prognosis of LKS and EECSWS syndrome is not so good in terms of full cognitive recovery [48]. In addition, it has turned out that CSWS occurs in brain-damaged children with variable aetiologies as well, with the possibility that shared genetic abnormalities may lead to variable cortical developmental changes from silent to permanent dysplastic lesions [29].

The clinical features of BECTS

BECTS is the most frequent non-structural focal epilepsy in childhood, considered as a transitory developmental dysfunction of the brain, appearing between the ages of 5 and 8 years and disappearing during adolescence. The typical form seems to have a complex genetic inheritance, predominantly unknown [48]. It is characterised by infrequent hemi-facial sensorimotor seizures during sleep, occurring in non-rapid eye movement (NREM) sleep, which may secondarily generalise or rarely induce a status epilepticus. Usually, it reflects non-lesional cortical excitability from rolandic regions. The onset of focal seizures is frequently preceded by various developmental deficits, which may cluster in relatives, but without epilepsy [50]. One study showed that among 196 children with BECTS, 31% had ADHD, 21.9% had cognitive deficits and 11.7% had behavioural abnormalities [77]. Another study demonstrated ADHD comorbidity in 65.6% of cases [10]. In the study just mentioned, children who were younger at epilepsy onset demonstrated lower intelligent quotient and higher degree of ADHD symptoms, which correlated strongly with the occurrence of IED during sleep [10]. Heterogeneous cognitive deficits have been described, affecting both non-verbal cognitive functions (visual, executive, fine motor execution, attention, memory and speed processing) and verbal functions (delayed reading, numeracy and spelling; impaired reading performance; delayed language development with mixed phonologic and lexico-syntactic problems, as well as oromotor deficits), during the active phase of the epilepsy [17, 42, 55, 58]. Neuronal networks including PN, designated for such cognitive processes, are also activated by epileptic discharges [13]. Neuroimaging studies have shown subtle cortical abnormalities in the frontal temporal, perisylvian and parietal regions [47]. It seems that neuroimaging abnormalities precede BECTS onset and evolve over time as a marker of a more complex cerebral maturation problem, responsible for both seizures and learning disabilities [50, 82]. The brain tissue responsible for the disorder is localised around the Sylvian fissure and, especially if it involves the left hemisphere, strongly correlates with speech function and cognition [64]. Functional magnetic resonance imaging data supports a functional deficit of DMN. In particular, children with BECTS show reduced activation of the DMN during the rest condition and a deactivation during cognitive effort [45]. Reduced functional connectivity was demonstrated between the sensorimotor network and the left inferior frontal gyrus (Broca's area) [48]. This functional decoupling might be the proof for understanding language impairment, in line with the neuropsychological profile of an anterior language dysfunction [4].

The clinical features of ABCFE and of SEBECTS

Atypical features of BECTS include several clinical and electrophysiological findings: seizures only occur also during daytime, associated to Todd's paralysis or even present as status epilepticus. It may include speech arrest, dysarthria, excessive drooling, oromotor dyspraxia and swallowing difficulties, or generalised tonic–clonic seizures, atypical absences, myoclonic seizures, atonic seizures and negative myoclonus at a later stage (pseudo-Lennox–Gastaut). These atypical seizures tend to be difficult to treat with conventional antiepileptic drugs; however, they disappear before adolescence, along with the neuropsychological deficits. SEBECTS refers to status epilepticus that can be convulsive or non-convulsive and either focal or secondarily generalised, including motor facial seizures and anarthria with persistent drooling. Although some patients remain mentally retarded, ultimate neurocognitive outcome appears good when the disorder is promptly treated [36, 48]. The EEG usually shows a marked increase and a bilateral synchronisation of IED in the rolandic area, or otherwise superimposed ripples (80–250 Hz) which may evolve in CSWS [33].

The clinical features of LKS

LKS, known as acquired epileptic aphasia, is an epileptic encephalopathy characterised by subtle or sudden-onset acquired aphasia with verbal auditory agnosia and various types of seizure. Besides focal motor seizures, children with LKS may have secondarily generalised tonic–clonic seizures, atypical absences, atonic and other types of seizure [36]. Seizures can also completely lack. More than half of these children have problems with receptive language, auditory processing, auditory working memory and verbal memory, as well as learning difficulties and attentional and behavioural problems. In LKS, initially benign EEG patterns evolve into focal CSWS. Despite reorganisational processes, the cause of verbal agnosia may be found in continuous bilateral epileptic activity in the receptive part of the language network [12]. Adequate and early medical intervention may avoid language and cognitive impairments.

The clinical features of EECSWS

EECSWS syndrome is the extreme end of atypical BECTS; it is a rare childhood epileptic encephalopathy, representing 0.2–2% of the epilepsies. Tassinari et al. introduced these terms in 1977 [69]. The onset of seizures varies, with a peak at about 5 years of age before evolving into epileptic encephalopathy within 1–2 years. Seizure types are not specific; they may be simple focal motor, focal with or without impaired awareness, absence or myoclonic and usually occur at night [36]. Linguistic and neurocognitive decline and neuropsychiatric features, such as autism, are commonly associated with this condition. Typically, the longer the duration of CSWS, the poorer the outcome is [36]. Usually, there are no residual deficits when the period of discharging is less than 13 months,

while it is a rule after 18 months [28]. The EEG pattern shows an almost continuous slow (1.5–3 Hz) spike wave, during NREM sleep, masking the normal feature of NREM sleep. Some authors provide percentages of slow wave sleep that must be occupied by continuous spike and wave e.g. > 50% or > 85% [32]. The abnormal EEG activity interferes with sleep-related physiological functions and neuroplasticity processes, mediating higher cortical functions, such as learning and memory consolidation [67]. Spiking tends to obstruct sleep oscillations and deprives the brain synapsis from pruning and regeneration processes [6]. The majority of the discharges are focal, with spike fields similar to what is observed in BECTS, and their electro-morphology, spatial distribution and functional properties do not follow the classical spike-wave pattern [28]. Functional and volumetric neuroimaging studies supported the idea that the focal epileptic hypermetabolic network over the PN involves secondarily and bilaterally the thalamic structure, propagating through the corpus callosum, and inducing hypoactivation of a large frontal field, probably responsible for the cognitive deterioration [28].

EECSWS can appear on the basis of structure abnormalities, like polymicrogyria over the perisylvian region, shunted hydrocephalus, thalamic lesions, Rett syndrome or the tuberous sclerosis complex [28, 32]. The underlying aetiology to develop EECSWS is unknown although brain malformations, immune disorders and genetic factors have been reported [32]. Therefore, channelopathies may play a role in pathogenesis of EECSWS [32, 35].

Sleep macrostructure

It is well known that epilepsy promotes sleep disruption and significantly affects sleep architecture [34]. Increased sleep fragmentation and a higher percentage of wakefulness and light sleep, along with a decrease in deep sleep and REM sleep, are common findings [44, 76, 81]. Generally, a good outcome and response to treatment is accompanied by a significant amelioration of sleep quality [14]. Compared to the microstructure analysis, few alterations of sleep macrostructure are reported in the spectrum of BECTS. A polysomnographic study reported a reduction in total sleep time, sleep efficiency and REM sleep percentage in children with BECTS [8], while a recent systematic review and meta-analysis of the polysomnographic findings in children with BECTS showed a longer sleep-onset latency as the main finding [25].

SWA in the spectrum of BECTS

Slow waves are characteristic of NREM sleep stage N3 and never as pronounced as during childhood. In the past years, SWA has been recognised as having a crucial role in neuroplasticity [75]. The amount of SWA in the first part of night-sleep and its decline across the night, along with the slow wave slope decline, is considered a marker of synaptic downscaling, when synaptic local recovery through pruning happens [57, 75]. A local pronounced disturbance might interfere with local recovery and plasticity, subsequently leading to neuropsychological deficits. Interestingly, in BECTS, a higher spike count of descending compared to ascending slopes of the sleep cycles was found. CTS declined in line with the dampening course of delta from cycle to cycle [29]. Moreover, slow wave downscaling, measured according to the amount of SWA, amplitude of slow waves, slope of waves and amount of multipeak waves during night sleep are impaired in EECSWS patients [6, 59, 70]. The greatest impairment of the slope decrease has been shown to be located in the highest-amplitude spikes; waves with high density of spikes are directly related to an impaired slow wave slope [7]. As it has been elegantly summarised by Tassinari et al. [71], EECSWS may be considered as the “Penelope syndrome: spinning during the day, spiking during the night”, in which the diurnal activation and creation of a neuronal network is erased by EEG spiking during sleep. After remission of EECSWS, the slope turns back to the physiological decrease overnight.

Taking together all of these findings, the analysis of SWA might serve as a prognostic measure of cognitive outcome in the BECTS spectrum [7].

Sleep microstructure

During NREM sleep, phasic EEG events, such as K-complexes, vertex waves, spindles, delta wave bursts (represented by phase A1 of CAP) and short-lasting arousals show a peculiar time arrangement, indicated as CAP. Functionally, CAP translates a condition of sustained arousal instability, oscillating between a greater arousal level (phase A) and a lesser arousal level (phase B). A1 phases are involved in the build-up and maintenance of deep NREM sleep and can have a protective “antiarousals” role for sleep continuity. On the other hand, A2 and A3 phases are involved in the preparation of REM-on activity, and have the function of maintaining the subject arousability [31]. Several studies showed a direct involvement of CAP in sleep-related learning and memory; in particular, during the A1 phase of CAP, EEG synchronisation shows quasi-optimal network organisation for information processing [18, 19, 49].

CAP has been analysed in several forms of epilepsy. Brief bursts of spikes, polyspikes and spike–wave-like discharges are frequently associated with phase A1, which has an activating effect on IED whereas phase B exerts a prolonged inhibitory action [49, 51, 60, 72, 78]. In genetic generalised epilepsy, a higher CAP rate is reported, along with spikes occurring during phase A1. Similar findings have been reported in lesional temporal lobe epilepsy and in patients with SHE [39, 52, 53, 73].

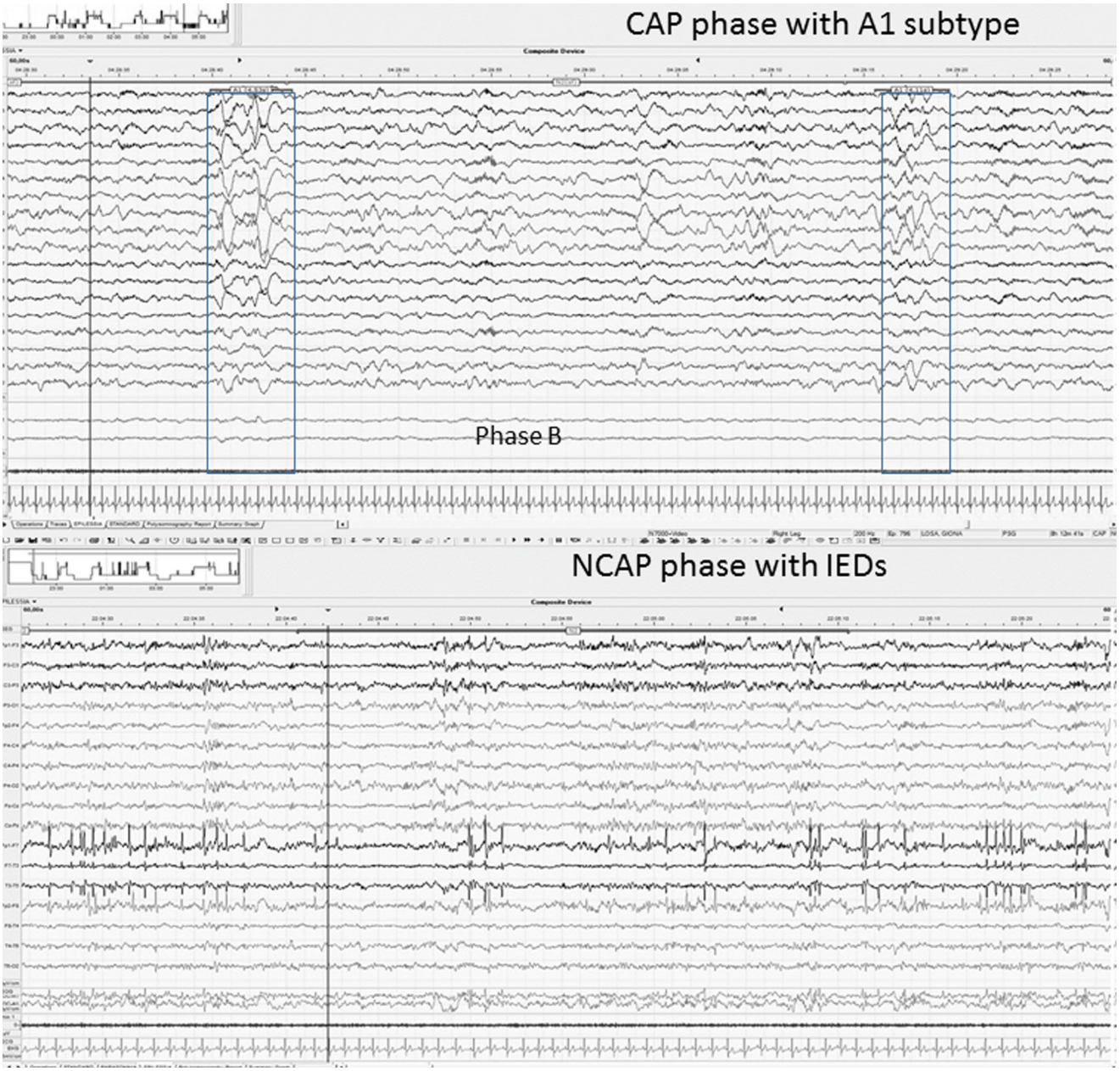

Fig. 1 Examples of a normal cyclic alternating pattern (CAP) phase, with occurrence of A1 subtype, compared to a non-CAP (NCAP) phase with interictal epileptiform discharges (IEDs). Page of 60 s, 100 μV

On the contrary, in other idiopathic epilepsies, such as BECTS, discharges are mainly modulated by sigma and spindling activity [29, 43, 49]. In a relatively small sample of children with BECTS, a significant high correlation between IED and sigma and spindling activity with respect to SWA has been demonstrated [39]. Taking into account that increases in spindle activity, number and density of spindles are prominent after the learning of verbal memory tasks [21, 23, 49, 62], the preponderance of the sigma band in the IED-promoting mechanism may play a significant role in cognitive deterioration. In accordance with this finding [39], children with BECTS show a reduced total CAP rate, mainly in stage N2, reduced phase A1 and arousals during stages N1 and N2 [8]. The reduction in the physiological NREM instability modulated by CAP might be linked with the inhibitory action of spindling activity and spikes on arousals [8]. Figure 1 shows examples of a normal CAP phase and a non CAP (NCAP) phase with IED.

Beside epilepsy, numerous studies have been performed on CAP in many developmental conditions such as paediatric sleep disordered breathing, sleep disorders of arousal, paediatric narcolepsy and learning disabilities (dyslexia, ADHD). CAP rate is almost always decreased in these conditions with the exception of the disorders of arousal and some cases of sleep apnea. Another constant result is the reduction of A1 subtypes,

probably in relationship with the degree of cognitive impairment [21]. In particular, similar to BECTS, children with ADHD presented lower total CAP rates as well as lower CAP rates in general, during stage N2, lower number of CAP sequences and a reduced total A1 index, than normal controls [37].

The relationship between, BECTS, OSA and ADHD

Literature data supports a close relationship between the occurrence of IEDs during sleep, OSA and diurnal ADHD symptoms [37]. OSA has been reported in as many as 20 to 30% of children with ADHD [30, 83]. Recently, throughout an extensive sleep assessment, a comorbid condition with OSA was found in 15 subjects with ADHD, 10 subjects had IED during sleep (from classical CTS to CSWS) and an overlap between OSA and IEDs was found in 5 cases [37]. Besides a differential diagnosis between OSA and nocturnal epilepsy with ictal apnea [80], few reports showed activation of CTSs induced by OSA in children without a previous history of epilepsy. A preliminary study showed the appearance of CTS during sleep in 18/127 (14.2%) of children with OSA. Children with CTS and OSA were older and had a longer OSA duration of disease [38]. Considering that PSG recordings revealed an epileptiform activity during sleep in 1.4% of healthy children [61], OSA may represent an additional risk factor to develop CTS or BECTS. Subjects with IEDs had a high occurrence of perinatal injuries, suggesting the possibility that a primary brain insult may predispose to both OSA and the occurrence of IED [38]. Furthermore, CAP analysis showed findings similar to those of BECTS: a lower CAP rate and A1 index during slow wave sleep and a lower A2 index [38]. The same results were confirmed in a population of 298 children with OSA or snorers; 48 children were found to have CTS. After 6 months, the IED had disappeared in those subjects who reported improvement of OSA, while it appeared or persisted in those without changes in OSA parameters [40]. Another study found a higher apnea hypopnea index in children with BECTS compared to the normal control, as well as a trend towards lower oxygen saturation and longer duration of apnoea [24]. Literature data demonstrated that hypoxemia and sleep fragmentation induce persistent systemic inflammation and oxidative stress. Both of them lead to disruption of the blood–brain barrier and neuronal injuries in children with OSA [63]. Recent magnetic resonance imaging studies have found reduced grey matter volume in areas of the superior frontal, prefrontal and superior and lateral parietal cortices in children with OSA [54]. A huge amount of data has demonstrated that a prompt and appropriate treatment of OSA may induce a complete remission of ADHD symptomatology [63], whereas no data are available regarding the remission of ictal or IED during sleep and its role on neurobehavioural amelioration.

Discussion

The degree of sleep alterations (in terms of SWA, sleep homeostatic process, decrease in NREM instability) may help clinicians to predict the neurocognitive outcome and to choose the right treatment and timing. Whereas the onset of antiepileptic drugs (AEDs) or corticosteroids is not under debate for the most severe form of the BECTS spectrum, a clear recommendation is still lacking for the transitions between the self-limited "benign forms" of BECTS and CSWS without epileptic encephalopathy. In this case, a comorbidity with ADHD and/or with OSA may help clinicians to be aware of a more

Table 1 CAP features compared to normal controls and neuropsychological deficits in childhood with centro-temporal spikes (BECTS), obstructive sleep apnea (OSA) and sleep interictal epileptiform discharges (IEDs), and children with attention-deficit hyperactivity disorder (ADHD)

	CAP features	Neuropsychological deficits, besides ADHD
BECTS	Reduced CAP rate, mainly in sleep stage N2, and reduced total A1 index during stages N1 and N2	Disorders in visuospatial short-term memory Attention span Cognitive flexibility Verbal fluency Phonological awareness Visuoperceptual skills Academic performance
OSA	Reduced CAP rate during sleep stage N3, reduced A1 index during sleep stage N3, reduced A2 index during total NREM sleep *(children with OSA plus IEDs compared to children with OSA without IEDs)*	General intelligence, verbal intelligence, executive function, learning, memory, visuospatial skills, language, phonological awareness, concept formation, analytical thinking and mathematical abilities
ADHD	Reduced total CAP rates, mainly in sleep stage N2, reduced the number of CAP sequences and a reduced total A1 index, mainly in sleep stages N1 and N2.	Learning disabilities

intrusive impact of epilepsy. It has been suggested that the most important parameter for deciding whether to start antiepileptic treatment in BECTS and its spectrum is a formal psychological evaluation that proves cognitive decline [79]. In many cases, AED treatment is still only currently started if seizures are frequent or occurring in the daytime [68]. A recent Cochrane systematic review on AEDs in BECTS [68] found only one placebo-controlled trial demonstrated the efficacy of sulthiame on seizure remission (moderate quality evidence). There is still insufficient evidence about whether or not treatment with AED may have an effect on being seizure-free in the long term, or on a child's cognition [56, 68].

An early recognition and therapeutic intervention devoted to the stabilisation of sleep structure, seizures and IED reduction should represent the main goals to prevent cognitive deterioration. Unfortunately, IED continue to be unaffected by most currently used AEDs [11, 29]. Few uncontrolled studies, conducted on small samples of children with ADHD and IED, reported a positive effect of AEDs on sleep quality [2, 22].

In a multicentre-prospective study, 167 children with both epilepsy and inattentive ADHD were treated with methylphenidate, showing a mild decrease of ADHD symptoms in 75% of patients, without effect on seizure relapse. Interestingly, the authors observed that ADHD preceded the occurrence of the first seizure in 32% of patients, mostly in idiopathic focal epilepsy. Whether or not severity and/or evolution of ADHD symptoms during the follow-up are associated to the abundance of IED remains an important open question [1].

We can argue that paediatric OSA should be considered an additional triggering factor to develop neurodevelopmental abnormalities, involving the PN, with the occurrence of CTSs during sleep as a marker of the endophenotype. Considering the overlap between BECTS/ADHD/OSA and the common CAP alterations, the presence of both ADHD symptoms or other neuropsychological impairment and OSA may be a considered warning sign in the case of BECTS (see Table 1). Multicentre and prospective studies including the assessment of sleep disorders and of neuropsychological deficits are warranted, in order to better establish the timing of a personalised therapy in the spectrum of BECTS.

Authors' contributions Dr Miano conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr Datta conceptualized the study, and reviewed and revised the manuscript.

References

1. Altunel A, Altunel EÖ, Sever A (2017) Response to adrenocorticotropic in attention deficit hyperactivity disorder-like symptoms in electrical status epilepticus in sleep syndrome is related to electroencephalographic improvement: a retrospective study. Epilepsy Behav 74:161–166
2. Bakke KA, Larsson PG, Eriksson AS, Eeg-Olofsson O (2011) Levetiracetam reduces the frequency of interictal epileptiform discharges during NREM sleep in children with ADHD. Eur J Paediatr Neurol 15:532–538
3. Bali B, Kull LL, Strug LJ, Clarke T, Murphy PL, Akman CI, Greenberg DA, Pal DK (2007) Autosomical dominant inheritance of centrotemporal sharp waves in rolandic epilepsy families. Epilepsia 48:2266–2272
4. Besseling RM, Jansen JF, Overvliet GM et al (2013) Reduced functional integration of the sensorimotor and language network in Rolandic epilepsy. Neuroimage Clin 2:239–246
5. Billard C, Hassairi I, Delteil F (2010) Specific language impairment and electroencephalogram: which recommendations in clinical practice? A cohort of 24 children. Arch Pediatr 17:350–358
6. Bölsterli Heinzle BK, Schmitt B, Bast T, Critelli H, Heinzle J, Jenni OG, Huber R (2011) Impaired slow wave sleep downscaling in encephalography with status epilepticus during sleep (ESES). Clin Neurophysiol 122:1779–1787
7. Bölsterli Heinzle BK, Fattinger S, Kurth S, Lebourgeois MK, Ringli M, Bast T, Critelli H, Schmitt B, Huber R (2014) Spike wave location and density disturb sleep slow waves in patients with CSWS (continuous spike waves during sleep). Epilepsia 55:584–591
8. Bruni O, Novelli L, Luchetti A, Zarowski M, Meloni M, Cecili M, Villa M, Ferri R (2010) Reduced NREM sleep instability in benign childhood epilepsy with centro-temporal spikes. Clin Neurophysiol 121:665–671
9. Cheng D, Yan X, Gao Z, Xu K, Zhou X, Chen Q (2017) Neurocognitive profiles in childhood absence epilepsy. J Child Neurol 32:46–52
10. Danhofer P, Pejčochová J, Dušek L, Rektor I, Ošlejšková H (2018) The influence of EEG-detected nocturnal centrotemporal discharges on the expression of core symptoms of ADHD in children with benign childhood epilepsy with centrotemporal spikes (BCECTS): a prospective study in a tertiary referral center. Epilepsy Behav Feb 79:75–81
11. D'Antuono M, Köhling R, Ricalzone S, Gotman J, Biagini G, Avoli M (2010) Antiepileptic drugs abolish ictal but not interictal epileptiform discharges in vitro. Epilepsia 51:423–431
12. Datta AN, Oser N, Ramelli GP, Gobbin NZ, Lantz G, Penner IK, Weber P (2013) BECTS evolving to Landau-Kleffner Syndrome and back by subsequent recovery: a longitudinal language reorganization case study using fMRI, source EEG, and neuropsychological testing. Epilepsy Behav 27:107–114
13. Deonna TW, Roulet E, Fontan D, Marcoz JP (1993) Speech and oromotor deficits of epileptic origin in benign partial epilepsy of childhood with rolandic spikes (BPERS). Relationship to the acquired aphasia-epilepsy syndrome. Neuropediatrics. 24:83–87
14. Dinopoulos A, Tsirouda MA, Bonakis A, Pons R, Pavlopoulou ID, Tsoumakas K (2018) Sleep architecture and epileptic characteristics of drug naïve patients in childhood absence epilepsy spectrum. A prospective study. Seizure 59:99–107
15. Doose H, Neubauer B, Carlsson G (1996) Children with benign focal sharp waves in the EEG-developmental disorders and epilepsy. Neuropediatrics 27:227–241
16. Duvelleroy-Hommet C, Billard C, Lucas B, Gillet P, Barthez MA, Santini JJ, Degiovanni E, Henry F, de Toffol B, Autret A (1995) Sleep EEG and developmental dysphasia: lack of a consistent relationship with paroxysmal EEG activity during sleep. Neuropediatrics 26:14–18
17. Ebus SC, Overvliet GM, Arends JB, Aldenkamp AP (2011) Reading performance in children with rolandic epilepsy correlates with nocturnal epileptiform activity, but not with epileptiform activity while awake. Epilepsy Behav 22:518–227
18. Ferri R, Rundo F, Bruni O, Terzano MG, Stam CJ (2008) The functional connectivity of different EEG bands moves towards

small-world network organization during sleep. Clin Neurophysiol 119:2026–2036
19. Ferri R, Huber R, Aricò D, Drago V, Rundo F, Ghilardi MF, Massimini M, Tononi G (2008) The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes. Neurosci Lett 432:228–231
20. Filippini M, Boni A, Giannotta M, Pini A, Russo A, Musti MA, Guerra A, Lassonde M, Gobbi G (2015) Comparing cortical auditory processing in children with typical and atypical benign epilepsy with centrotemporal spikes: electrophysiologic evidence of the role of non–rapid eye movement sleep abnormalities. Epilepsia 56: 726–734
21. Fogel SM, Smith CT (2006) Learning-dependent changes in sleep spindles and stage 2 sleep. J Sleep Res 15:250–255
22. Gagliano A, Arico I, Calarese T et al (2011) Restless Leg Syndrome in ADHD children: Levetiracetam as a reasonable therapeutic option. Brain Dev 33:480–486
23. Gais S, Molle M, Helms K, Born J (2002) Learning-dependent increases in sleep spindle density. J Neurosci 22:6830–6834
24. Gogou M, Haidopoulou K, Eboriadou M, Pavlou E (2017) Sleep disturbances in children with rolandic epilepsy. Neuropediatrics 48: 30–35
25. Halal CDS, Horta BL, Nunes ML (2017) Polysomnographic aspects of sleep architecture on self-limited epilepsy with centrotemporal spikes: a systematic review and meta-analysis. Sleep Sci 10:161–167
26. Halász P (2013) How sleep activates epileptic networks? Epilepsy Res Treat 2013:425697. https://doi.org/10.1155/2013/425697
27. Halász P, Kelemen A, Clemens B, Saracz J, Rosdy B, Rásonyi G, Szücs A (2005) The perisylvian epileptic network. A unifying concept. Ideggyogy Sz 58:21–31
28. Halász P, Hegyi M, Ziegler ZS, Fogarasi A (2014) Encephalopathy with electrical status epilepticus in slow wave sleep - a review with an emphasis on the regional (perisylvian) aspects. J Epileptol 22: 71–87
29. Halász P, Kelemen A, Rosdy B, Rásonyi G, Clemens B, Szűcs A (2019) Perisylvian epileptic network revisited. Seizure 5:31–41
30. Henriques Filho PS (2016) Sleep disorder investigation might be considered to be mandatory in attention deficit/hyperactivity disorder guideline. Arq Neuropsiquiatr 74:701–707
31. Hirshkowitz M (2002) Arousals and anti-arousals. Sleep Med 3: 203–204
32. Kessi M, Peng J, Yang L, Xiong J, Duan H, Pang N, Yin F (2018) Genetic etiologies of the electrical status epilepticus during slow wave sleep: systematic review. BMC Genet 19:40
33. van Klink NE, van't Klooster MA, Leijten FS, Jacobs J, Braun KP, Zijlmans M (2016) Ripples on rolandic spikes: a marker of epilepsy severity. Epilepsia 57:1179–1189
34. Kothare SV, Kaleyias J (2010) Sleep and epilepsy in children and adolescents. Sleep Med 11:674–685
35. de Kovel CGF, Syrbe S, Brilstra EH, Verbeek N, Kerr B, Dubbs H, Bayat A, Desai S, Naidu S, Srivastava S, Cagaylan H, Yis U, Saunders C, Rook M, Plugge S, Muhle H, Afawi Z, Klein KM, Jayaraman V, Rajagopalan R, Goldberg E, Marsh E, Kessler S, Bergqvist C, Conlin LK, Krok BL, Thiffault I, Pendziwiat M, Helbig I, Polster T, Borggraefe I, Lemke JR, van den Boogaardt MJ, Møller RS, Koeleman BPC (2017) Neurodevelopmental disorders caused by De novo variants in KCNB1 genotypes and phenotypes. JAMA Neurol 74:1228–1236
36. Lee YJ, Hwang SK, Kwon S (2017) The clinical spectrum of benign epilepsy with centro-temporal spikes: a challenge in categorization and predictability. J Epilepsy Res 30(7):1–6
37. Miano S, Donfrancesco R, Bruni O, Ferri R, Galiffa S, Pagani J, Montemitro E, Kheirandish L, Gozal D, Pia Villa M (2006) NREM sleep instability is reduced in children with attention-deficit/hyperactivity disorder. Sleep 29:797–803
38. Miano S, Paolino MC, Peraita-Adrados R, Montesano M, Barberi S, Villa MP (2009) Prevalence of EEG paroxysmal activity in a population of children with obstructive sleep apnea syndrome. Sleep 32:522–529
39. Miano S, Bachiller C, Gutiérrez M, Salcedo A, Villa MP, Peraita-Adrados R (2010) Paroxysmal activity and seizures associated with sleep breathing disorder in children: a possible overlap between diurnal and nocturnal symptoms. Seizure 19:547–552
40. Miano S, Tabarrini A, Vitelli O, Mazzotta A, Del Pozzo M, Rabasco J, Barreto M, Parisi P, Ferretti A, Villa MP (2013) The cooccurrence of interictal discharges and seizures in pediatric sleep-disordered breathing. Epilepsy Behav 29:508–512
41. Miano S, Amato N, Foderaro G, Pezzoli V, Ramelli GP, Toffolet L, Manconi M (2018). Sleep phenotypes in attention deficit hyperactivity disorder. Sleep Med. doi: https://doi.org/10.1016/j.sleep.2018.08.026
42. Monjauze C, Tuller L, Hommet C, Barthez MA, Khomsi A (2005) Language in benign childhood epilepsy with centro-temporal spikes abbreviated form: rolandic epilepsy and language. Brain Lang 92:300–308
43. Nobili L, Ferrillo F, Baglietto MG, Beelke M, De Carli F, De Negri E et al (1999) Relationship of sleep interictal epileptiform discharges to sigma activity (12– 16 Hz) in benign epilepsy of childhood with rolandic spikes. Clin Neurophysiol 110:39–46
44. Nunes ML, Ferri R, Arzimanoglou A, Curzi L, Appel CC, Costa da Costa J (2003) Sleep organization in children with partial refractory epilepsy. J Child Neurol 18:763–766
45. Oser N, Hubacher M, Specht K, Datta AN, Weber P, Penner IK (2014) Default mode network alterations during language task performance in children with benign epilepsy with centrotemporal spikes (BECTS). Epilepsy Behav 33:12–17
46. Overvliet GM, Besseling RM, Vles JS, Hofman PA, Backes WH, van Hall MH et al (2010) Nocturnal epileptiform EEG discharges, nocturnal epileptic seizures, and language impairments in children: review of the literature. Epilepsy Behav 19:550–558
47. Overvliet GM, Besseling RM, Jansen JF, van der Kruijs SJ, Vles JS, Hofman PA et al (2013) Early onset of cortical thinning in children with rolandic epilepsy. Neuroimage clin 2:434–439
48. Pal DK, Ferrie C, Addis L, Akiyama T, Capovilla G, Caraballo R, de Saint-Martin A, Fejerman N, Guerrini R, Hamandi K, Helbig I, Ioannides AA, Kobayashi K, Lal D, Lesca G, Muhle H, Neubauer BA, Pisano T, Rudolf G, Seegmuller C, Shibata T, Smith A, Striano P, Strug LJ, Szepetowski P, Valeta T, Yoshinaga H, Koutroumanidis M (2016) Idiopathic focal epilepsies: the "lost tribe". Epileptic Disord 18:252–288
49. Parisi P, Bruni O, Pia Villa M, Verrotti A, Miano S, Luchetti A, Curatolo P (2010) The relationship between sleep and epilepsy: the effect on cognitive functioning in children. Dev Med Child Neurol 52:805–810
50. Parisi P, Paolino MC, Raucci U, Ferretti A, Villa MP, Trenite DK (2017) "Atypical forms" of benign epilepsy with centrotemporal spikes (BECTS): how to diagnose and guide these children. A practical/scientific approach. Epilepsy Behav 75:165–169
51. Parrino L, Halasz P, Tassinari CA, Terzano MG (2006) CAP, epilepsy and motor events during sleep: the unifying role of arousal. Sleep Med Rev 10:267–285
52. Parrino L, De Paolis F, Milioli G, Gioi G, Grassi A, Riccardi S, Colizzi E, Terzano MG (2012) Distinctive polysomnographic traits in nocturnal frontal lobe epilepsy. Epilepsia 53:1178–1184
53. Pereira AM, Bruni O, Ferri R, Palmini A, Nunes ML (2012) The impact of epilepsy on sleep architecture during childhood. Epilepsia 53:1519–1525
54. Philby MF, Macey PM, Ma RA, Kumar R, Gozal D, Kheirandish-Gozal L (2017) Reduced regional grey matter volumes in pediatric obstructive sleep apnea. Sci Rep 7:44566

55. Pinton F, Ducot B, Motte J, Arbuès AS, Barondiot C, Barthez MA, Chaix Y, Cheminal R, Livet MO, Penniello MJ, Peudenier S, de Saint-Martin A, Billard C (2006) Cognitive functions in children with benign childhood epilepsy with centrotemporal spikes (BECTS). Epileptic Disord 8:1123
56. Rating D, Wolf C, Bast T (2000) Sulthiame as monotherapy in children with benign childhood epilepsy with centrotemporal spikes: a 6-month randomized, doubleblind, placebo-controlled study. Epilepsia 41:1284–1288
57. Riedner BA, Vyazovskiy VV, Huber R, Massimini M, Esser S, Murphy M, Tononi G (2007) Sleep homeostasis and cortical synchronaization: III: a high density EEG study of sleep slow waves. Sleep 30:475–480
58. Riva D, Vago C, Franceschetti S, Pantaleoni C, D'Arrigo S, Granata T, Bulgheroni S (2007) Intellectual and language findings and their relationship to EEG characteristics in benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav 10:278–285
59. Roulet Perez E, Davidoff V, Despland PA, Deonna T (1993) Mental and behavioural deterioration of children with epilepsy and CSWS: acquired epileptic frontal syndrome. Dev Med Child Neurol 118: 1497–1520
60. Salih F, Khatami R, Steinheimer S, Kretz R, Schmitz B, Grosse P (2007) A hypothesis for how non-REM sleep might promote seizures in partial epilepsies: a transcranial magnetic stimulation study. Epilepsia 48:1538–1542
61. Sans Capdevila O, Dayyat E, Kheirandish-Gozal L, Gozal D (2008) Prevalence of epileptiform activity in healthy children during sleep. Sleep Med 9:303–309
62. Schabus M, Hoedlmoser K, Pecherstorfer T, Anderer P, Gruber G, Parapatics S, Sauter C, Kloesch G, Klimesch W, Saletu B, Zeitlhofer J (2008) Interindividual sleep spindle differences and their relation to learningrelated enhancements. Brain Res 1191: 127–135
63. Sedky K, Bennett DS, Carvalho KS (2014) Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: a meta-analysis. Sleep Med Rev 18:349–356
64. Shakeri M, Datta AN, Oser N, Létourneau-Guillon L, Lapointe LV, Martin F, Malfait D, Tucholka A, Kadoury S, Lippé S (2017). Brain morphometry and its relationship with cognition in rolandic epilepsy, resubmitted at Epilepsy Research, 138:39–45
65. Silvestri R, Gagliano A, Calarese T, Aricò I, Cedro C, Condurso R, Germanò E, Vita G, Tortorella G (2007) Ictal and interictal EEG abnormalities in ADHD children recorded over night by videopolysomnography. Epilepsy Res 75:130–137
66. Smith ML (2016) Rethinking cognition and behavior in the new classification for childhood epilepsy: examples from frontal lobe and temporal lobe epilepsies. Epilepsy Behav 64:313–317
67. Striano P, Capovilla G (2013) Epileptic encephalopathy with continuous spikes and waves during sleep. Curr Neurol Neurosci Rep 13:360
68. Tan HJ, Singh J, Gupta R, de Goede C (2014) Comparison of antiepileptic drugs, no treatment, or placebo for children with benign epilepsy with centro temporal spikes. Cochrane Database Syst Rev 9:CD006779
69. Tassinari CA, Dravet CR (1977) Encephalopathy related to electrical status epilepticus during slow sleep. Electroencephalogr Clin Neurophysiol 43:529e30
70. Tassinari CA, Rubboli G, Volpi L, Meletti S, d'Orsi G, Franca M, Sabetta AR, Riguzzi P, Gardella E, Zaniboni A, Michelucci R (2000) Encephalopathy with electrical status epilepticus during slow sleep or ESES syndrome including the acquired aphasia. Clin Neurophysiol 111(S2):S94–S102
71. Tassinari CA, Cantalupo G, Rios-Pohl L, Giustina ED, Rubboli G (2009) Encephalopathy with status epilepticus during slow sleep: 'the Penelope syndrome. Epilepsia 50:4–8
72. Terzaghi M, Sartori I, Mai R, Tassi L, Francione S, Cardinale F, Castana L, Cossu M, LoRusso G, Manni R, Nobili L (2008) Coupling of minor motor events and epileptiform discharges with arousal fluctuations in NFLE. Epilepsia 49:670–676
73. Terzano MG, Monge-Straws MF, Mikol F, Spaggiari MC, Parrino L (1997) Cyclic alternating pattern as a provocative factor in nocturnal paroxysmal dystonia. Epilepsia 38:1015–1025
74. Tinuper P, Bisulli F, Cross JH, Hesdorffer D, Kahane P, Nobili L, Provini F, Scheffer IE, Tassi L, Vignatelli L, Bassetti C, Cirignotta F, Derry C, Gambardella A, Guerrini R, Halasz P, Licchetta L, Mahowald M, Manni R, Marini C, Mostacci B, Naldi I, Parrino L, Picard F, Pugliatti M, Ryvlin P, Vigevano F, Zucconi M, Berkovic S, Ottman R (2016) Definition and diagnostic criteria of sleep-related hypermotor epilepsy. Neurology 86:1834–1842
75. Tononi G, Cirelli C (2006) Sleep function and synaptic homeostasis. Sleep Med Rev 10:49–62
76. Touchon J, Baldy-Moulinier M, Billiard M, Besset A, Cadilhac J (1991) Sleep organization and epilepsy. Epilepsy Res Suppl 2:73–81
77. Tovia E, Goldberg-Stern H, Ben Zeev B, Heyman E, Watemberg N, Fattal-Valevski A, Kramer U (2011) The prevalence of atypical presentations and comorbidities of benign childhood epilepsy with centrotemporal spikes. Epilepsia 52:1483–1488
78. Ulbert I, Heit G, Madsen J, Karmos G, Halgren E (2004) Laminar analysis of human neocortical interictal spike generation and propagation: current source density and multiunit analysis in vivo. Epilepsia 45:48–56
79. Uliel-Sibony S, Kramer U (2015) Benign childhood epilepsy with centro-temporal spikes (BCECTSs), electrical status epilepticus in sleep (ESES), and academic decline–how aggressive should we be? Epilepsy Behav 44:117–120
80. Vitelli O, Miano S, Tabarrini A, Mazzotta AR, Supino MC, Forlani M, Villa MP (2014) Epilepsy and sleep-disordered breathing as false friends: a case report. J Child Neurol 29:NP114–NP117
81. Wang YQ, Zhang MQ, Li R, Qu WM, Huang ZL (2018) The mutual interaction between sleep and epilepsy on the neurobiological basis and therapy. Curr Neuropharmacol 16:5–16
82. Xiao F, Lei D, An D, Li L, Chen S, Chen F, Yang T, Ren J, Huang X, Gong Q, Zhou D (2015) Functional brain connectome and sensorimotor networks in rolandic epilepsy. Epilepsy Res 113:113–125
83. Youssef NA, Ege M, Angly SS, Strauss JL, Marx CE (2011) Is obstructive sleep apnea associated with ADHD? Ann Clin Psychiatry 23:213–224