



Review article

The relationship between epilepsy, sleep disorders, and attention deficit hyperactivity disorder (ADHD) in children: A review of the literature[☆]



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ABSTRACT

Objective: To analyze the relationship between epilepsy, sleep disorders, and attention deficit hyperactivity disorder (ADHD).

Bibliographic search: A literature search of the PubMed database was performed using the following key words: epilepsy, sleep, and ADHD. In total, 91 articles were located in PubMed, 34 were selected for abstract reading and twelve articles were reviewed, in which the main objectives were examine the relationship between epilepsy, sleep and ADHD from several perspectives, including epidemiology, effect of comorbidities on academic performance and the factors leading to diagnostic difficulties among these three disorders

Results: Among the main findings, there were difficulties to start and maintain sleep in patients with epilepsy and ADHD, reduction in sleep efficiency, decreased seizure threshold, as well as behavioral and cognitive deficits in both groups.

Conclusions: It is important to know which symptom is the predominant one. For this reason, children and adolescents with epilepsy, ADHD and sleep disorders need to be assessed carefully before initiating treatment. Our review concluded that there is an important link in this pathological triad.

1. Introduction

Quality of sleep habits in infants and adolescents has been one of the most studied subjects nowadays. It is known that a great number of pathologies can lead to sleep architecture alterations. Epilepsy and attention deficit hyperactivity disorder (ADHD) are included between the most prevalent diseases [1–3].

Epilepsy syndromes can cause circadian rhythm alterations that act at the hypothalamus, leading to cortical excitability changes, and then, consequently, in seizure expression [4,5]. Before that, seizure patterns can be affected by sleep cycles and vice versa [6].

ADHD is the most prevalent psychiatric comorbidity in epilepsy patients, especially in the refractory cases, when symptoms can achieve 70% of patients [7]. This high prevalence of ADHD symptoms worsens substantially the psychosocial prognosis [7].

Moreover in ADHD, 55–75% of parents report sleep quality changes at their children [8–10]. Diseases mechanisms which explain sleep disorders at ADHD patients remains unclear and seems to be multifactorial [11]. The most frequent complaints are longer sleep

latency and sleep maintenance [8,11,12].

Nevertheless, there are contradictory findings that need a better explanation. For example, Holley et al. [13] objectively measured by actigraphy the sleep of children with epilepsy alongside that of healthy controls. They did not find any differences in sleep measures between both groups. However, significant deficits in cognitive functioning were demonstrated that were not explained by differences in sleep.

Because there are still controversies regarding epilepsy, ADHD and sleep triad it becomes relevant to realize this literature review. The main objective of this article was to perform a review to assess the relationship between epilepsy, sleep disorders and ADHD. We will cover clinical features, diagnosis, comorbidities, and treatments. The approach proposed in the present study might give additional evidence based information to support clinical decision.

1.1. Bibliographic search

Our review was carried out using a protocol based upon the PRISMA statements [14]. A literature search was performed between

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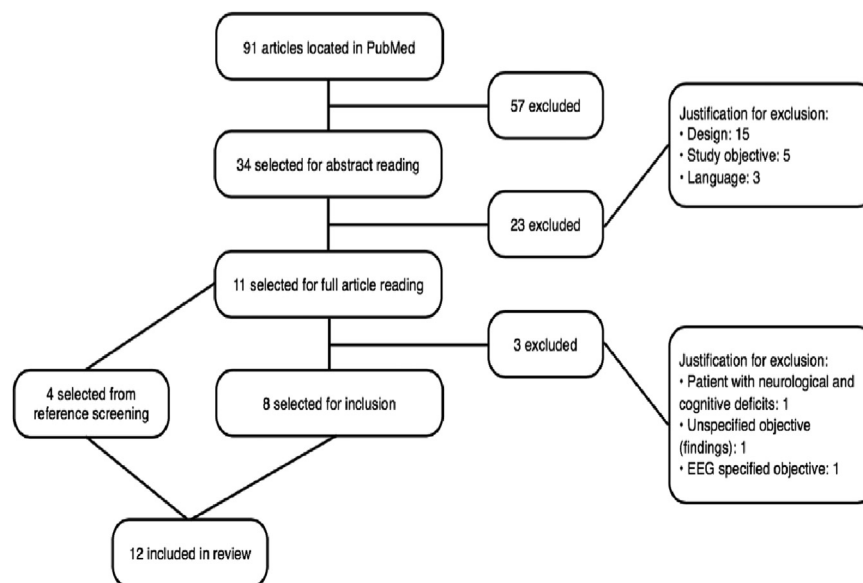


Fig. 1. Article selection and exclusion process.

the months of October and December 2015 from PubMed database. The key words used were: sleep AND epilepsy AND ADHD. Review articles were excluded, as well as editorials and case reports. We also excluded studies which the relation between sleep, ADHD and epilepsy were not adequately specified. The search totaled 91 articles in the PubMed database. Of these, 57 were excluded for not meeting the inclusion criteria, and 34 were considered relevant for this paper. 23 articles were excluded due to differences in study design (15), objective (5) and language (3). Of these, eleven were selected to be read as full texts. After, 3 articles were excluded secondary to unspecified findings (1), EEG specified objective (1) and inclusion of patients with neurological and cognitive deficits (1). Eight articles were considered relevant for this study [15–22].

The full reading and analysis of the studies also offered the possibility of access of other publications, which made it possible to include four new references in this review [23–26].

The process of search, selection and exclusion of articles in the literature is shown in Fig. 1.

1.2. Sleep×ADHD×Epilepsy: review of studies, interactions and cause-effect relationships

Epileptic patients often presents changes in sleep macrostructure, and this fact is reflected in the reduction of sleep efficiency, increase in number and duration of nocturnal awakenings, as well as increased sleep onset latency and the fragmentation of REM sleep [27]. As a major example, BECTS, a very well known benign epilepsy, in which attacks occur predominantly during sleep, after the child sleep or awakening [28–30].

Due to a number of descriptions of sleep related epileptic syndromes (ex.: autosomal dominant nocturnal frontal lobe epilepsy), the American Academy of Sleep Medicine created the term sleep related epilepsy (SRE), in order to designate those epilepsies in which more than 70% of seizures occur during sleep [31,32].

It is known that the quality of sleep expressed by bad habits during sleep is directly related to the control of seizures; however, other factors such as development delay, nocturnal crisis, polytherapy or generalized seizures are also associated to poor quality of sleep [33]. Patients with generalized and refractory epilepsy are more likely to have sleep abnormalities [34,35]. Although sleep problems are one of the main responsible for behavioral changes in patients with epilepsy, this fact is often ignored [36].

Wiebe et al. assessed the association between habitual sleep patterns and one night sleep polysomnography PSG with daytime sleepiness in ADHD patients and normal developing children. The authors analyzed eighty-two children (26 ADHD, 56 typically developing children) between 7 and 11 years. The patients had nighttime sleep recorded using actigraphy (habitual sleep patterns) over five nights and polysomnography (immediate sleep patterns) over one night. Daytime sleepiness was examined using the multiple sleep latency test (MSLT). Longer sleep latency (using both PSG and actigraphy) was related to longer mean sleep latencies in the MSLT in typically developing children. Time awake and night activity were positively related to MSLT in ADHD patients. The results showed that typically developing children and ADHD patients show a different relationship for habitual and immediate sleep patterns with daytime sleepiness. Moreover, their findings suggested that difficulties to initiate and to maintain sleep can be present in both nighttime and daytime sleep [23].

Hvolby and colleagues observed the quality of sleep in patients with ADHD through actigraphic and parental reports. A case-control study was designed, in which two hundred six children aged 5–11 years were analyzed. Fortyfive children with ADHD, 64 with other psychiatric diagnoses (psychiatric control group) and 97 healthy control subjects were selected. As a result, there was a longer sleep onset latency of patients with ADHD (26.3 min) and more irregular sleep pattern compared to the other two groups (psychiatric group had 18.3 min, while controls showed a shorter time of 13.5 min) [24]. The authors concluded that some children with ADHD have disturbed sleep that cannot be justified by comorbid oppositional defiant disorder. In the same study, a discrepancy was held between objective sleep analysis and subjective reporting of parents who overestimated the time of sleep latency [24].

On the other hand, Gruber et al., in a study using actigraphic monitoring over five consecutive nights and sleep diaries. The number of participants selected for the study was thirty-eight school-age boys with ADHD diagnosis and 64 control school-age boys. They observed an increased instability in sleep onset and duration in the ADHD group compared to controls. These findings support the idea that children with ADHD have a sleep-wake system instability [25].

In a retrospective study, Crabtree et al. examined the sleep of 97 children aged 3–18 years diagnosed with ADHD [26]. In 36% of patients who undergo polysomnography periodic limb movement disorders (PLMD) has been demonstrated, whereas in 16 patients who were evaluated by actigraphy was observed a large variability every

night on the total sleep time and sleep latency time. Between the major findings of this paper is a high prevalence of subjective sleep complaints among the parents of ADHD children, including difficulties to initiate and to maintain sleep, restless sleep and daytime sleepiness. Moreover, objective sleep analysis showed delayed sleep onset, increased nocturnal variability in sleep structure and pattern, and a high proportion of children with PLMD [26].

Furthermore, by analyzing the ADHD etiology in epilepsy, the greatest evidence that symptoms of attention deficit are not secondary to factors related to epilepsy, is the presence of symptoms of deficits in attention that precede the onset of epileptic disease in patients with newly diagnosed epilepsy (cryptogenic or idiopathic) [37,38]. These epilepsy prevalence of ADHD is at least 2.5 times higher [39,40].

The precedence of the symptoms of ADHD in relation to the onset of seizures suggests the possibility of matching conditions [41] that have different pathophysiological mechanisms, unrelated to the epilepsy variables such as seizures, epileptiform discharges and use of antiepileptic drugs (AED).

Wannag et al. [15] studied children with ADHD and nocturnal epileptiform activity admitted to a epilepsy Center. It was a prospective study of children aged 6–14 years. Among the 362 patients with epilepsy and normal intellectual functioning, 46 were referred with a probable diagnosis of ADHD. Of these, 43 were using AED and 30 had the diagnosis ADHD. Seven out of 30 ADHD patients presented focal nocturnal epileptiform activity (FNEA) on EEG. The proportion of children with ADHD in this study was higher than the rate reported in children with newly diagnosed seizures, but lower compared with rates from another tertiary centers. One of the main findings of this study demonstrated the occurrence of subclinical epileptiform activity during 24-h full EEG recording in children with ADHD and epilepsy.

In 2015 a retrospective study was conducted by Uliel-Sibony [16], seventeen patients with BECTS (3.5–10 years) were identified, and the spike-wave index (SWI) and learning disabilities were observed. All children had ADHD diagnosis and all patients were using AED. The follow-up range time was 1–10.5 years. Of these, 6 children were diagnosed with learning disabilities in addition to ADHD. One boy had only ADHD and behavioral difficulties. One patient had aggression and other patients had behavioral problems, which required psychiatric medications. Curiously, six patients had ADHD or speech difficulty diagnosis during preschool years, long before the diagnosis of epilepsy had been established. A behavioral deterioration was not detected in any of them. This study suggested that when treating a child with BECTS, high SWI (> 60%) and learning difficulties, the most important parameter for deciding whether to use a new AED is a formal psychological evaluation that proves cognitive decline. Other way, these medications must be avoided.

Continuing on the same subject, 196 patients (118 male and 78 female) with BECTS were evaluated and followed-up for a mean time of 4.4 years (range 2–11) [17]. All patients had their epilepsy diagnosis between 3 and 14 years of age. Seventy-eight patients experienced a generalized tonic-clonic seizure during the follow-up period. Levels of regression were evidenced by IQ decline in four children, ADHD in five, aggressive behavior in three and language deterioration in four children. Nine patients developed electrical status epilepticus in slow waves sleep (ESES). Sixty-one patients (31%) had ADHD, 43 (21.9%) had cognitive deficits and 23 (11.7%) had behavioral abnormalities. This study strengthened the high prevalence of ADHD between BECTS patients.

Cohen and colleagues [18] analyzed 186 children (109 males and 77 females) aged 2–18 years. Their parents were asked to apply the Sleep Disturbance Scale for Children (SDSC). The questionnaire were divided into three groups according to their major neurological diagnosis: epilepsy (58 patients), ADHD (62 patients), or others (66). Fifty children had an abnormal total sleep score. The most predominant sleep disorders reported were excessive somnolence (25.3%), initiating and maintaining sleep (24.7%) and arousal nightmares

(23.1%). There was no significant group difference in prevalence of a pathological total sleep score or of any sleep abnormality. The only significant findings were that sleep-wake transition disorders (SWTD) was more frequent in children with epilepsy.

Comorbidities of attention deficit-hyperactivity disorder were evaluated by Ishii et al. [19]. The subjects consisted of 68 children and adolescents (nine preschool children aged 4–6 years, 50 elementary school children aged 7–12 years, nine adolescents aged 13–19 years; mean age: 9.7 years). Patients with mental age below age 4, and those with IQ under 50 were excluded, as well as those meeting criteria for pervasive developmental disorder. In 36 cases no comorbidity were recognized, although multiple comorbid disorders were noted in several cases. Among these, two cases had sleep disorders (parasomnias such as night terrors or sleepwalking) and five had the diagnosis of epilepsy (two non-febrile convulsion, one frontal lobe epilepsy and two not specified).

Another relevant question, is the relation between ADHD and electroencephalogram (EEG). Altunel [20] conducted a retrospective chart study of 134 patients who met the diagnostic criteria for combined ADHD. The main objective of this study was to elucidate the EEG abnormalities in ADHD. None of the patients had any other disease or behavioral manifestation other than ADHD. A total of 134 EEG were analyzed, and all patients presented spike and wave paroxysms that changes with age. 38 patients had a finding of benign focal epilepsy of childhood. Only half of the patients presented seizures and 46 patients had neither seizures nor foci. The authors concluded that spike and wave activity changes in time and that EEG discharges, even when a diagnosable epileptic disorder is absent, can be related to neuropsychiatric symptoms.

On a similar subject matter, an Italian group [21] explored the prevalence of ictal and interictal epileptic discharges (IED) and sleep disorders in ADHD children. Forty-two ADHD patients (mean age 8.9 years) were included in this study. They were referred by psychiatry and pediatric neurologists to a sleep clinic. None of the ADHD patients showed intellectual deficit. 6% presented co-morbid Tic disorder, 12.8% dyspraxia, 33.3% learning disorders, 7.6% eating disorder and 12.8% language. A high prevalence (86%) of sleep disorders was reported. Among these, 26% has restless leg syndrome (RLS), 53.1% had IEDs, and three patients had nocturnal seizures. The general findings of this paper reinforce the fact that seizures/IEDs play an important role on cognitive and behavioral abilities, as well as ADHD is a condition frequently associated to EEG epileptiform abnormalities.

Another frequent syndrome in children is myoclonic epilepsy in infancy (MEI). Caraballo et al. [22] realized a follow-up of 38 patients with MEI. After a mean follow-up of 13.5 years, 32 patients had normal neurologic and neuropsychological evaluations. Four patients had significant learning difficulties (two of them with ADHD) and another two patients had important cognitive impairment, despite adequate seizure control (Table 1).

2. Discussion

The number of studies available in the literature specifying the relationship between sleep/ADHD/epilepsy still scarce. The combination of these three pathologies is a source of continuous clinical debate, as our review demonstrate. The necessity for a correct treatment raises the question about cause-consequence.

Attention deficit hyperactivity disorder (ADHD) is a common neuropsychiatric syndrome. It is characterized by a persistent lack of attention and hyperactivity pattern, more severe and frequently than observed in the same age group [42]. It's prevalence varies from 3.5% to 18% according to the diagnostic criteria utilized [43].

ADHD diagnosis is eminently based upon clinical symptoms and data scales (Ex: SNAP IV) that analyze individual characteristics which cause significant losses in the child's behavior in different environments. There is consensus that is not necessary the use of any complementary method for the diagnosis of ADHD [44].

Table 1
Studies reviewed, authors, age range, number of participants, main objective, findings, and outcomes.

Author/year of publication	Age range	n	Main objective	Findings	Conclusions
Wannag et al. [14], 2010	6–14 years	46	– Determine relationship between ADHD and quantity of focal nocturnal epileptiform activity (FNEA) – Avoid aggressive therapies in BECTS, ESES and academic difficulties	– FNEA present in 7/30 ADHD patients – High SWI and ADHD prevalence	– No possible causal effect of FNEA on ADHD – Formal psychological evaluation is the most important parameter to use a new AED – Prevalence of atypical forms of BECTS is low, but ADHD is high
Uziel-Sibony et al. [15], 2015	3–10 years	17	– Delineate the frequency of atypical features of BECTS	– 61 had ADHD – 9 had ESES – 50 children had abnormal sleep score	– Sleep disorders mechanisms may not be related to primary disease – Multiple comorbid disorders in several cases
Tovia et al. [16], 2011	3–14 years	196	– Detect sleep disturbances applying SDSC	– 5 had epilepsy – 2 sleep disorders – 38 BECTS – All presented spike/ wave at some time	– EEG discharges are related to neuropsychiatric symptoms
Cohen et al. [17], 2013	2–18 years	186	– Comorbidity in ADHD	– 86% sleep disorders	– Seizures/IED have important role on cognitive abilities and ADHD
Ishii et al. [18], 2003	4–19 years	68	– EEG abnormalities	– 53.1% had IEDs – 4 learning disabilities (two ADHD)	– Good outcome in terms of seizure control and neuropsychological profile
Altunel et al. [19], 2013	–	134	– Prevalence of IED and seizures in ADHD children	– ADHD had longer sleep onset latency – Increased sleep onset and duration in ADHD – 36% PLMD	– Discrepancy between objective sleep analysis and subjective reporting of parents – Instability of sleep-wake system in children with ADHD
Silvestri et al. [20], 2007	8,9 (mean Age)	42	– Analyze features, treatment and outcome of MEI	– Variability in total sleep time and latency	– High prevalence of subjective sleep complaints among parents of children with ADHD
Caraballo et al. [21], 2013	5–11 years	206	– Actigraphic and parental reports of sleep difficulties in ADHD	– Compare ADHD sleep/sleepiness to control	– Both groups can have difficulties to start and maintain sleep, by different mechanisms
Hvolby et al. [23], 2008	5–11 years	206	– Compare sleep-wake system of ADHD with controls	– Sleep in ADHD with PSG	
Gruber et al. [24], 2000	–	102	– Sleep in ADHD with PSG		
Crabbree et al. [25], 2003	3–18 years	97	– Compare ADHD sleep/sleepiness to control		
Wiebe et al. [22], 2013	7–11 years	82	– Compare ADHD sleep/sleepiness to control		

About 25–50% of children and adolescents with ADHD show sleep disturbances [12]. Among these include nocturnal awakenings, delay of the sleep phases, increased nocturnal activity [11,25] and insomnia [45,46]. Children show significant commitment of sleep in both subjective (questionnaires) and objective (polysomnography or actigraphy) measures [1,3]. 55–74% of parents of ADHD patients refer sleep complaints in their child [3]. Therefore, an adequate evaluation and treatment can bring improvement in quality of life of these patients.

The highest incidence of epilepsy occurs in infancy [47], and it affects 0.5–1% of children [48]. It is known that children with epilepsy shows commitment in quality of life, cognitive function and sleep [49,50].

ADHD is the most prevalent psychiatric comorbidity in epileptic patients, mainly in the refractory cases, where symptoms can be presented in up to 60–70% of patients [7]. In patients with epilepsy, the high prevalence of symptoms of ADHD worsens substantially the psychosocial prognosis, mostly when taking into account the caregiver burden [7].

About a third of epileptic patients present seizures during sleep [51]. Sleep can activate the occurrence of seizures and electroencephalogram (EEG) abnormalities [52]. Van Golde refers that during NREM (non-rapid eye movement) sleep discharges are facilitated (most likely for the synchronized pattern of EEG), while a suppression occurs at REM (rapid eye movement) sleep, making it difficult the propagation of the discharges secondary to a desynchronized pattern [53,54].

The effect of sleep in some epileptic syndromes is well known, as in benign epilepsy with centro-temporal spikes (BECTS). It is also recognized that sleep deprivation can be responsible for epileptiform activity; however, it still exists the discussion if it occurs secondary to sleep induction or neuronal excitability [53,54].

Increase of awakenings, daytime sleepiness, reduced total sleep and the greatest need for the presence of parents at bedtime are important characteristics of children with epilepsy, from the behavioral point of view [55,56]. Moreover, it is also known that sleep patterns and behavior changes may come to affect both children and parents [57].

Anxiety and fear that the child have a night crisis is a plausible hypothesis to explain the worsening of sleep quality [58]. According to Parisi et al. this is reflected in the fact that children with epilepsy present better cognitive and behavioral prognosis when they have an adequate quality of sleep and seizure control [59].

Another important issue is to evaluate possible differences between the sleep of patients with “primary” ADHD and patients with ADHD as epilepsy comorbidity. The second key issue is the influence of methylphenidate on sleep quality of patients with epilepsy and ADHD. In a recent study [60], it was demonstrated by means of actigraph, differences among ADHD patients using methylphenidate and those using placebo. The methylphenidate users showed a significant decrease in the analysis of average activity and a significant reduction in total sleep time compared to placebo.

This fact leads us to another question: despite the effectiveness of methylphenidate, with improvement in approximately 70% of patients [61], and few side effects, a major impasse in daily clinical practice is the decision to treat epileptic patients or those with epileptiform EEG abnormalities [62]. Thus, the uncertainty of decreased threshold for seizures can interfere with medical management, depriving the patient receiving the drug which has the greatest efficacy on the symptoms it presents.

Our study exposes and reinforces the importance to know which symptom is the predominant one. Is it seizures? Is it inattention/hyperactivity? Sleep problems are a primary disorder or consequence of another pathology? For this reason, children and adolescents with epilepsy, ADHD and sleep disorders need to be assessed carefully before initiating treatment.

Conflicts of interest

The authors declare no conflict of interest.

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