CNS Neuroscience & Therapeutics

ORIGINAL ARTICLE

CNS Neuroscience & Therapeutics

# Sleep-Related Disorders in Children with Attention-Deficit Hyperactivity Disorder: Preliminary Results of a Full Sleep Assessment Study

Silvia Miano,[1] Maria Esposito,[2] Giuseppe Foderaro,[3] Gian Paolo Ramelli,[4] Valdo Pezzoli[3] & Mauro Manconi[1]

1 Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital of Lugano, Lugano, Switzerland
2 Clinic of Child and Adolescent Neuropsychiatry, Department of Mental Health, Physical and Preventive Medicine, Second University of Naples, Naples, Italy
3 Department of Pediatrics, Civic Hospital of Lugano, Lugano, Switzerland
4 Department of Pediatrics, San Giovanni Hospital, Bellinzona, Switzerland

**Keywords**
Attention; Children; Epilepsy; Hyperactivity; Sleep.

**Correspondence**
S. Miano, Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital of Lugano, Lugano 6900, Switzerland.
Tel.: +41-091-811-6416;
Fax: +41-091-811-6915;
E-mail: silvia.miano@gmail.com
Received 22 January 2016; revision 10 April 2016; accepted 5 May 2016

doi: 10.1111/cns.12573

## SUMMARY

**Background and methods:** We present the preliminary results of a prospective case–control sleep study in children with a diagnosis of attention-deficit hyperactivity disorder (ADHD). A deep sleep assessment including sleep questionnaires, sleep habits, a video-polysomnographic recording with full high-density electroencephalography (EEG) and cardiorespiratory polygraphy, multiple sleep latency test, and 1-week actigraphic recording were performed to verify whether children with ADHD may be classified into one of the following five phenotypes: (1) hypoarousal state, resembling narcolepsy, which may be considered a "primary" form of ADHD; (2) delayed sleep onset insomnia; (3) sleep-disordered breathing; (4) restless legs syndrome and/or periodic limb movements; and (5) sleep epilepsy and/or EEG interictal epileptiform discharges. **Results:** Fifteen consecutive outpatients with ADHD were recruited (two female, mean age 10.6 ± 2.2, age range 8–13.7 years) over 6 months. The narcolepsy-like sleep phenotype was observed in three children, the sleep onset insomnia phenotype was observed in one child, mild obstructive sleep apnea was observed in three children, sleep hyperkinesia and/or PLMs were observed in five children, while IEDs and or nocturnal epilepsy were observed in three children. Depending on the sleep phenotype, children received melatonin, iron supplementation, antiepileptic drugs, or stimulants. **Conclusions:** Our study further highlights the need to design an efficient sleep diagnostic algorithm for children with ADHD, thereby more accurately identifying cases in which a full sleep assessment is indicated.

## Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the early childhood neuropsychiatric conditions with the highest prevalence and longest duration, with an onset at around 3/4 years of age, although it is identified at school age, with peak referrals between 6/10 years of age [1–3]. The diagnostic criteria for ADHD are based on clinical observations and include two sets of symptoms: difficulty in maintaining attention and hyperactive-impulsive behavior (Diagnostic and Statistical Manual for Mental Disorders—5th edition; DSM–V; American Psychiatric Association, 2013) [4]. Children with ADHD display a high rate of psychiatric comorbidities, such as mood disorders (depressive disorder and pediatric bipolar disorder), oppositional defiant disorder, conduct disorder, and learning disabilities [5]. Although the pathogenesis of ADHD is still unclear, there is solid evidence supporting a genetic predisposition in ADHD: dopaminergic receptor genes as well as dopamine transporter genes appear to be implicated [2,6]. Brain imaging studies have demonstrated a dysfunction of the dopamine and noradrenergic pathways involved in attention, executive function, motivation, and reward [7]. Hypoactivation has been observed in systems involved in executive function (frontoparietal network) and attention (ventral attentional network), while hyperactivation has been observed in the default, ventral attention (involving the midcingulate cortex), and somatomotor networks [7].

Sleep deprivation is widely known to affect various aspects of diurnal performance, reducing attention, vigilance, decision-making ability, and memory functions [8]. Sleep disturbances are so intrinsically linked to ADHD as to be included in the diagnostic criteria for ADHD in the DSM—third edition [9]. Approximately 25–50% of children and adolescents with ADHD experience sleep problems [10]. Sleep disturbances can lead to behavioral and cognitive consequences that may mimic ADHD and may even

originate from the same biochemical dysfunctions responsible for deficits in executive function and attention [11]. Neuroimaging and EEG studies in children with ADHD have demonstrated a low degree of arousability in frontal, central, and midline regions [10,12]. Cognitive impairment and performance deficits induced by sleep disorders may reflect the occurrence of cortical and subcortical local "islands of sleep" in subjects who are behaviorally fully awake (so-called local sleep). The existence of these "islands of sleep" during wakefulness in ADHD is supported by both EEG and neuroimaging studies. Abnormal electrocortical high slow oscillatory activity (i.e., theta) and reduced fast oscillatory activity (i.e., alpha and beta) during the resting wake state, as well hypoactivation of systems involved in executive function (frontoparietal network) and attention (ventral attentional network), as detected by functional MRI, have been observed in ADHD patients [13].

According to the literature, the overall complexity of the relationship between ADHD and sleep has been summed up in five sleep phenotypes associated with either an increased or decreased level of arousal [13].

The first sleep phenotype is characterized by a hypoarousal state that may be considered a "primary" form of ADHD (i.e., without the interference of other sleep disorders). According to this theory, the motor hyperactivity observed in children with ADHD, who are significantly sleepier than healthy subjects during the day, may be considered an attempt to counteract a primary form of hypersomnolence, as happens in children with narcolepsy [14,15]. An arousal mechanism dysfunction, consisting mainly of a reduction in the arousal slow components, has been demonstrated during non rapid eye movement sleep in adults and children with narcolepsy [16,17]. The same dysfunction was found in a cohort of children with ADHD whose inclusion was based on the absence of other sleep disorders and who were considered to be affected by a "primary form of ADHD" [18].

The second ADHD-related sleep phenotype is linked to the delayed sleep phase syndrome, which is one of the circadian disorders. Indeed, sleep onset insomnia is the most common sleep disorder in children with ADHD (approx. 30% of cases). The difficulty in falling asleep that characterizes this syndrome appears to reflect a delayed sleep–wake cycle as opposed to a simple disorder related to initiating and maintaining sleep [19]. The difficulty in regulating and organizing the sleep–wake rhythms in this phenotype might determine the aforementioned irregularity of the arousal levels [20].

The third phenotype is related to sleep-disordered breathing (SDB), from snoring to obstructive sleep apnea (OSA). Children with ADHD may indeed have a mild form of SDB, disclosed by polysomnography, while children with SDB may have diurnal neurobehavioral problems that resemble those that occur in ADHD [21]. The neurocognitive phenotype of pediatric OSA may reflect a dysfunction in the prefrontal cortex (PFC), whose severity is related to the degree of intermittent hypoxia and sleep fragmentation sustained as a result of the higher number of arousals [22–24]. A recent meta-analysis demonstrated that ADHD symptoms improve after adenotonsillectomy in children with OSA [22].

The fourth phenotype postulates a relationship between restless legs syndrome (RLS) and/or periodic limb movements (PLMs) and ADHD. Children with PLMs and/or RLS, like those with OSA, suffer from daytime inattention, hyperactivity, and a low school performance. A comorbidity with RLS/PLMs has been reported in approximately 12% of children with ADHD, with a positive correlation emerging between RLS/PLMs and hyperactivity/opposition scores [25]. PLMS are associated with a greater sympathetic influence and increased sleep arousability [26,27].

The last phenotype consists of the association between ADHD and sleep epilepsy and/or EEG interictal epileptic discharges. A robust body of evidence in the literature points to a pathogenetic relationship between interictal epileptiform discharges (IEDs) during sleep and neuropsychological dysfunctions in children with ADHD. When explored by means of prolonged sleep and sleep-deprived recordings [25,28], the prevalence of IEDs and seizures rises to 50% in children with ADHD, whose EEG features contain IEDs that resemble those observed in benign centro-temporal spike epilepsy (BCTE). Interestingly, a reduced arousability similar to that found in primary ADHD and in narcolepsy has been reported in children with BCTE [29].

Here, we present the preliminary data of a cross-sectional case–control study conducted on children with ADHD. All the subjects underwent a complete sleep assessment to verify whether it may be possible to classify children with ADHD according to the five aforementioned sleep phenotypes.

## Materials and Methods

Fifteen consecutive outpatients with ADHD were recruited at the local Paediatric Department (two females, mean age 10.6 ± 2.2, age range 8–13.7 years) from April 2015 to October 2015. Children were referred to the Paediatric Department for suspected ADHD by pediatricians and teachers. The diagnosis of ADHD was based on the DSM-V criteria [4]. Both children and parents separately received a semi-structured psychiatric interview, that is, the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) [30]. The K-SADS-PL is a structured interview designed to explore the presence of cardinal symptoms of a number of psychiatric syndromes. The ADHD-Rating Scale (ADHD-RS), adapted for the Italian population [31], was filled out by parents and school teachers. The neurocognitive assessment was performed by means of the Wechsler Intelligence Scale for Children-Revised (WISC-R) [32] (all children with an intelligence quotient (IQ) <70 were excluded); lastly, the standardized neuropsychological battery for children was administered (NEPSY-II) [33]. Medical history and neurological and physical examinations were used to exclude comorbid medical and neurological conditions. The assessment of familial psychiatric disorders was based on careful historical information provided by both parents.

Any children with a comorbid diagnosis of autistic spectrum disorder or who had previously been treated with stimulants or other drugs for ADHD were excluded. The local ethics committee approved the study protocol and all the children's parents gave their informed consent to the procedures.

Children underwent a complete sleep assessment at the Sleep Centre of our Neurological Department, which included

standardized sleep questionnaires and scales, a wrist actigraphic recording for 1 week, an attended nocturnal video-polysomnographic recording (PSG), and a multiple sleep latency test (MSLT) the day after the PSG.

### Sleep Questionnaires and Scales

Parents filled out the Children's Sleep Habits Questionnaire [34] and the sleep clinical record for the screening of SDB [35]; thereafter, each child was interviewed by the principal investigator (SM), who also filled out the pediatric daytime sleepiness scale [36]. The sleep questionnaires and scales were administered on the day of the MSLT recording.

### Wrist Actigraphic Recording for One Week

The sleep–wake cycle was continuously recorded by a wrist accelerometer (actigraph), which was worn on the nondominant hand throughout the week (except during bathing or swimming), to collect information regarding the duration and quality of sleep and the level of physical activity. A sleep diary was kept by the parents throughout the week. The actigraphic recoding was performed either the week before or after the PSG and MSLT.

### Nocturnal Video-Polysomnographic Recording

Each participant underwent one full-night video-PSG performed in a standard sleep laboratory with attenuated sound (noise level to a maximum of 30 dB). Light-out time was calculated according to the sleep log and reflected each child's habitual sleep onset. Children were allowed to sleep until they awoke spontaneously in the morning.

Recordings included high-density scalp EEG (up to 256), electro-oculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to A1), submental electromyogram (EMG), electrocardiogram (one derivation), EMG of the right and left tibialis anterior muscles. Chest and abdomen movements were measured by strain gauges, while oronasal airflow was recorded by means of both thermistor and nasal cannula pressure. Arterial oxygen saturation was monitored using a digital pulse oximeter, while a microphone was used to detect snoring and other sounds. Sleep was subdivided into 30-s epochs, and sleep stages, leg movements, arousals, and respiratory parameters were scored according to standardized guidelines [37].

After the PSG study, all the children underwent a MSLT, which consists of the recordings of five naps scheduled at 2-h intervals starting at 09:00 h. Sleep was recorded and scored according to standard methods [37].

### Diagnostic Criteria for Sleep Phenotypes

1. Primary hypoarousal state: excessive daytime sleepiness was diagnosed according to the international criteria for central disorders of hypersomnolence [38]. In particular, narcolepsy may be suspected if the MSLT detects a mean sleep latency of $\leq$8 min and two or more sleep onset REM periods (SOREMPs). A SOREMP within 15 min of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs in the MSLT.
2. Sleep onset delay insomnia/advanced sleep phase disorder: delayed sleep phase syndrome was diagnosed according to international criteria on the basis of the anamnestic and actigraphic data [38].
3. Central, obstructive, and mixed apnea and limb movement events were assessed according to the criteria of the American Academy of Sleep Medicine [37,38]. The apnea/hypopnea index (AHI) is defined as the average number of apneas, hypopneas per hour. The diagnosis of OSA is confirmed when the PSG reveals an obstructive AHI >1, or primary snoring is diagnosed in children with a history of habitual snoring, an AHI <1 and microphone-detected snoring.
4. Periodic limb movements were identified as sequences of four or more LMs, lasting from 0.5 to 10 seconds in duration and separated by at least 5 seconds but no more than 90 seconds. A PLM index (number of PLMs per hour of sleep) higher than five was considered as clinically significant [39]. Restless legs syndrome was diagnosed according to international criteria [40].
5. The presence of spikes (transient, clearly distinguishable from background activity, lasting 20–70 ms) and sharp waves (same as spikes, but lasting 70–200 ms), either alone or accompanied by slow waves (the slow wave being of a higher amplitude than the spike or the sharp wave) occurring in isolation or in bursts, was considered representative of IEDs, according to the definitions of the International Federation of Societies for Clinical Neurophysiology [41].

When more than one sleep disorder was diagnosed in a child, the most evident disorder was used to classify each sleep phenotype.

## Results

To date, 15 children have been recruited with a diagnosis of ADHD (10 with combined type, 4 inattentive type, 1 hyperactive type). Table 1 shows the demographic and clinical data, Table 2 shows the sleep questionnaires and actigraphic data, Table 3 shows the sleep polysomnographic and MSLT results, while Table 4 shows the final classification according to each sleep phenotype.

After all the sleep objective and subjective measures and clinical data were considered, children were included in one of the five sleep phenotypes and received melatonin, iron supplementation, antiepileptic drugs, or stimulants accordingly (see Table 4). The narcolepsy-like sleep phenotype was observed in three children, the sleep onset insomnia phenotype was observed in one child, mild OSA was observed in three children, sleep hyperkinesia and/or PLMs were observed in five children, while IEDs and/or nocturnal epilepsy were observed in three children. Table 4 also shows other sleep phenotypes associated with the most clinically relevant signs.

The actigraphic recording revealed a low sleep efficiency (<90%) in all the children, with sleep onset delay being found in eight children (sleep latency longer than 30 min), multiple night awakenings and sleep hyperkinesias in nine, and a reduced time

 

**Table 1** Demographic and clinical data of children with attention-deficit hyperactivity disorder (ADHD)

| Case | Age, years | Sex | Sleep Disorders | Medical history* | Family history | Ferritin μg/L | ADHD type$ | Psychiatric disorder | LD type+ | Neurological examination |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 12.1 | M | Snoring, sleep hyperkinesia | Migraine | No | 41 | 1 | No | 2,3 | Normal |
| 2 | 8.3 | M | Snoring, sleep hyperkinesia | No | Snoring | 12 | 2 | No | 2 | MNS, dyspraxia, OD |
| 3 | 11.5 | F | Snoring, sleep hyperkinesia, apnea, bruxism | Adenotonsillar hypertrophy, liver pathology, hypoferritin | Snoring, bipolar disorder | 28 | 1 | No | 0 | MNS |
| 4 | 8 | M | Arousal disorders, snoring, enuresis, bruxism | Adenotonsillar hypertrophy | No | 33 | 1 | No | 0 | MNS |
| 5 | 8.1 | M | Arousal disorder, enuresis | Encopresis | Obstructive sleep apnea, SIDS, epilepsy | 25 | 3 | ODD | 0 | Normal |
| 6 | 8.9 | M | Sleep onset insomnia | Respiratory allergy, streptococci infections beta type a | Snoring, obsessive compulsive disorder | 33 | 1 | No | 1,3 | MNS |
| 7 | 8.1 | M | No | No | LD | 17 | 1 | No | 0 | MNS |
| 8 | 13.5 | M | Snoring, arousal disorder | Streptococci infections beta type a | Snoring, epilepsy | 37 | 2 | No | 1 | MNS |
| 9 | 9.2 | M | Sleep onset insomnia | Otitis | LD, abuse, alcohol addiction disorder | 54 | 1 | No | 0 | MNS |
| 10 | 10.5 | M | Snoring, sleep hyperkinesia | No | Somnamb. | 43 | 1 | No | 1,2 | Dyspraxia, OD |
| 11 | 8.5 | M | Sleep hyperkinesia, legs paresthesia falling asleep | Broncodysplasia | Sleep central apnea | 22 | 1 | No | 1,3 | MNS, OD |
| 12 | 12.4 | M | Apnea | No | LD |  | 1 | No | 1,2,3 | MNS |
| 13 | 13.8 | M | Sleep onset insomnia | Adenotonsillar hypertrophy, IEDs, milk intolerance | No | 12 | 2 | No | 2 | MNS |
| 14 | 13.7 | F | Sleep onset insomnia | None | Epilepsy, respiratory allergy, psychomotor delay | 11.7 | 2 | No | 2 | Normal |
| 15 | 13.1 | F | Snoring, sleep hyperkinesia | Food and respiratory allergy, laryngospasm | No | 42 | 1 | No | 0 | MNS, OD |

IED, interictal epileptiform discharges; LD, learning disability; SIDS, sudden infant death syndrome, MNS, inimal neurological signs, OD, ocular dyspraxia, *no past history of epilepsy, +LD type 1 = dyslexia, 2 = dyscalculia, 3 = dysgraphia, 0 = no, $ADHD type, 1 = both, 2 = disattentive 3 = hyperactivity.

**Table 2** Sleep questionnaire and scale, and actigraphic parameters

| Case | Age, years | Sex | CSHQ | PDSS | SCR | Time in bed | Time light out | Sleep latency, min | Time light on | Total sleep time | Sleep efficiency, % | Actigraphic diagnosis* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 12.1 | M | 42 | 8 | 3 | 9 h 43 min | 22 h 15 min | 11.31 | 7 h 57 min | 7 h 25 min | 75.68 | 2 |
| 2 | 8.3 | M | 50 | 14 | 10 | 10 h 16 min | 21 h 06 min | 48.43 | 7 h 23 min | 6 h 10 min | 60.13 | 1,2 |
| 3 | 11.5 | F | 55 | 17 | 8 | 9 h 27 min | 23 h 09 min | 7.86 | 8 h 36 min | 8 h 27 min | 89.4 | 0 |
| 4 | 8 | M | 49 | 5 | 7 | 10 h 21 min | 21 h 10 min | 36.79 | 7 h 31 min | 8 h 17 min | 80.1 | 0 |
| 5 | 8.1 | M | 61 | 15 | 13 | 9 h 43 min | 22 h 01 min | 4.75 | 7 h 43 min | 7 h 54 min | 81.45 | 2 |
| 6 | 8.9 | M | 53 | 6 | 5 | 10 h 41 min | 20 h 25 min | 46.07 | 7 h 07 min | 8 h 04 min | 75.65 | 1 |
| 7 | 8.1 | M | 53 | 25 | 6 | 9 h 51 min | 21 h 15 min | 22.31 | 7 h 06 min | 7 h 50 min | 79.71 | 1,2 |
| 8 | 13.5 | M | 46 | 16 | 7 | 8 h 44 min | 22 h 25 min | 30.44 | 7 h 10 min | 7 h 05 min | 81.12 | 1,5 |
| 9 | 9.2 | M | 65 | 22 | 5 | 10 h 21 min | 21 h 36 min | 11.93 | 7 h 57 min | 8 h 38 min | 83.15 | 0 |
| 10 | 10.5 | M | 56 | 2 | 9 | 8 h 05 min | 21 h 55 min | 38.57 | 5 h 59 min | 6 h 44 min | 83.67 | 1,2,5 |
| 11 | 8.5 | M | 48 | 16 | 4 | 10 h 26 min | 22 h 03 min | 15 | 8 h 28 min | 7 h 43 min | 74.32 | 2,5 |
| 12 | 12.4 | M | 47 | 9 | 6 | 8 h 55 min | 21 h 50 min | 30.88 | 6 h 46 min | 7 h 36 min | 85.26 | 1,3,5 |
| 13 | 13.8 | M | 60 | 22 | 7 | 8 h 26 min | 23 h 30 min | 11.9 | 7 h 57 min | 7 h 06 min | 84.82 | 1,2,3,5 |
| 14 | 13.7 | F | 43 | 8 | 4 | 9 h 04 min | 22 h 07 min | 32.06 | 7 h 12 min | 7 h 23 min | 81.66 | 2 |
| 15 | 12.1 | F | 48 | 9 | 9 | 9 h 05 min | 22 h 12 min | 20.86 | 7 h 17 min | 7 h 43 min | 84.93 | 1,2 |

CSHQ, Children's Sleep Habits Questionnaire, PDSS, pediatric daytime sleepiness scale, SCR, sleep clinical record, SOD, sleep onset insomnia, MNA, multiple night awakenings, D, diurnal, ETIB, excessive time in bed, RTIB, reduced time in bed, *actigraphic diagnosis SOD = 1, MNA = 2, DNAPS = 3, ETIB = 4, RTIB = 5, normal = 0.

in bed (less than 9 h) in five. The polysomnographic recording revealed SDB (from mild-to-moderate OSA) in five children, primary insomnia in one child (who displayed sleep hyperkinesia at the actigraphic recording), and a mild form of PLMs in two children. Sleep IEDs without nocturnal seizures were found in four children, subcontinuous centro-temporal IEDs or continuous spike and waves during sleep in two children, and nocturnal epilepsy with temporal or fronto-temporal IEDs in two children (in one of whom the diagnosis was "probable"). More than three SOREMPs were found in three children (with a mean MSLT of 13.2 min, 10.6 min, 8.1 min, respectively), although only one met the criteria for a strong suspicion of narcolepsy (three SOREMPS and a mean sleep latency of 8.1 min).

A comorbid diagnosis of oppositional defiant disorder (ODD) was established in one child and of learning disabilities in eight children. One patient had displayed sleep IEDs over the centro-temporal regions in a standard sleep electroencephalographic recording at preschool age, while none had previously received a past diagnosis of epilepsy or had had seizures. After a complete neuropsychological evaluation, a further two children received a comorbid diagnosis of ODD, while learning disability (LD) was confirmed in three children. Seven children were found to have a past history of snoring, one child had sleep apnea, three children had a history of sleep onset insomnia, while six children had sleep hyperkinesias (see Table 1).

The neurological examination revealed minimal neurological signs and dyspraxia or oculomotor dyspraxia in the majority of children. A familial history of learning disabilities, sleep disorders, psychiatric disorder, and epilepsy was also found. A blood sample showed a low serum ferritin level in most of the children, with ferritin levels below 20 $\mu$g/L in four children. All the children scored higher than 41 (which is considered a cutoff for sleep disorders) at the CSHQ, while a pediatric daytime sleepiness scale (PDSS) score over 20 (indicating severe daytime sleepiness) was observed in three children, and a SCR score over 6.25 was found in eight children (Table 2).

## Discussion

The study presents the preliminary results of a thorough investigation of sleep and sleep disorders in a sample of consecutively recruited drug-free children with ADHD. Notwithstanding, the limited number of children recruited so far, this preliminary study confirms the validity of a sleep phenotype classification of ADHD [13]. According to the sleep phenotypes of ADHD, treatment for each underlying sleep disorder (primary form, sleep onset insomnia, RLS, and/or PLMs during sleep, OSA, continuous spikes and waves during slow-wave sleep, or nocturnal epilepsy) should be tailored so as to improve alertness during daytime and reduce the interference of sleep disorders on the severity of ADHD.

One of the most surprising findings that emerges from this study is the association between ADHD and IEDs, either with or without nocturnal seizures, which confirms that epilepsy and IEDs are frequent in ADHD and may have an impact on sleep structure, potentially interfering with the attention network [42]. Our study confirms previous reports of a frequent association between the occurrence of IEDs during sleep (prevalently frontal, centro-temporal, and rolandic spikes) and neuropsychological dysfunctions

**Table 3** Sleep parameters and diagnosis

| Case | Total sleep time, min | Sleep period time, min | Sleep efficiency | Sleep latency, min | REM latency, min | N1, % | N2, % | N3, % | REM, % | WASO, % | WASO, min | Awake index, n/h | Arousal index, n/h |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 224 | 436.6 | 44 | 72 | 250 | 18.3 | 15.6 | 52.7 | 13.4 | 48.7 | 212.6 | 19 | 8.8 |
| 2 | 464.7 | 471.7 | 85.9 | 69 | 74 | 3.7 | 42.6 | 24.6 | 29.1 | 1.5 | 7 | 6 | 7.8 |
| 3 | 458.5 | 466.8 | 96.2 | 9.7 | 67 | 4.6 | 45 | 40.7 | 9.7 | 1.8 | 8.3 | 9 | 4.7 |
| 4 | 339 | 476.6 | 67.7 | 23.9 | 88.5 | 11.8 | 33.9 | 38.3 | 15.9 | 28.9 | 137.6 | 7 | 19 |
| 5 | 392.3 | 408.3 | 73.5 | 125.5 | 110.5 | 3.6 | 54.5 | 23.4 | 18.5 | 3.9 | 16 | 8 | 3.8 |
| 6 | 458.6 | 481.1 | 90.5 | 25.5 | 82 | 9.2 | 47.7 | 28.1 | 15 | 4.7 | 22.5 | 5 | 10.6 |
| 7 | 495.5 | 498.2 | 89.7 | 54 | 23.1 | 4 | 42.6 | 30.3 | 23.1 | 0.5 | 2.7 | 2 | 7.5 |
| 8 | 450.5 | 458.3 | 91.9 | 32.1 | 96.5 | 6.9 | 50.7 | 27.5 | 14.9 | 1.7 | 7.8 | 8 | 6.4 |
| 9 | 470 | 480.2 | 91.4 | 34.2 | 124.5 | 4.6 | 46.7 | 25.9 | 22.9 | 2.1 | 10.2 | 3 | 8.6 |
| 10 | 417.9 | 480.4 | 79.5 | 45.2 | 148.5 | 12.7 | 38.6 | 30 | 18.6 | 13 | 62.5 | 12 | 4.5 |
| 11 | 435.5 | 458.7 | 79.2 | 91.5 | 89 | 10.6 | 42.3 | 31.2 | 16 | 5.1 | 23.2 | 6 | 6.8 |
| 12 | 387.5 | 508.3 | 71 | 37.6 | 163 | 3.7 | 50.7 | 29.5 | 16 | 23.8 | 120.8 | 12 | 4.6 |
| 13 | 469.5 | 474.2 | 97.7 | 6.5 | 68.5 | 4.7 | 55.3 | 30.9 | 9.2 | 1 | 4.7 | 2 | 2.8 |
| 14 | 451.5 | 477.4 | 91.6 | 15.2 | 168 | 6.8 | 37.7 | 28.7 | 26.9 | 5.4 | 25.9 | 9 | 13.2 |
| 15 | 454.3 | 458.8 | 82.9 | 89 | 88 | 3.4 | 50.6 | 19.4 | 26.6 | 1 | 4.5 | 4 | 5 |

| Case | Apnea hypopnea index (AHI n/h) | AHI supine, n/h | AHI REM n/h | Mean SaO2 | Minimal SaO2 | ODI | ODI supine | LMs index n/h | PLMs index n/h | Supine % | MSLT mean latency | SOREMp, n | PSG diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 3.5 | 3.5 | 6 | 96.3 | 90 | 1.3 | 3.8 | 12.9 | 0.8 | 100 | 11 | 0 | 3 |
| 2 | 3.2 | 4.2 | 6.7 | 96.3 | 82 | 1.2 | 0.6 | 12.3 | 3.1 |  | 12.9 | 1 | 1,5,6 |
| 3 | 2.8 | 1.4 | 1.3 | 98.1 | 95 | 0.1 | 0.4 | 1.4 | 0 | 67 | 16.2 | 1 | 1,4 |
| 4 | 6.9 | 2.1 | 5.6 | 96.6 | 93 | 0.4 | 0 | 12.1 | 2.8 | 16.8 | 20 | 0 | 1, 2 |
| 5 | 1.2 | 2.4 | 0.8 | 97.8 | 94 | 0.6 | 0 | 4.1 | 0 | 19.3 | 15.8 | 0 | 1 |
| 6 | 4.7 | 7.6 | 1.1 | 97.5 | 90 | 0.7 | 0.8 | 11.5 | 3 | 32.7 | 20 | 0 | 1 |
| 7 | 1.2 | 0 | 0.5 | 97.1 | 90 | 0.4 | 4.5 | 12.8 | 2.9 | 16.2 | 13.2 | 3 | 2 |
| 8 | 3.7 | 2.6 | 2.7 | 98.4 | 91 | 0.7 | 1.4 | 13.5 | 5.2 | 57.1 | 12.5 | 1 | 7 |
| 9 | 0.3 | 1 | 1 |  |  |  |  | 10.1 | 0 | 0 | 20 | 0 | 5 |
| 10 | 2.3 | 1.5 | 5.4 | 96.9 | 94 | 0 | 0.5 | 14.5 | 6.2 | 28 | 12.5 | 0 | 7 |
| 11 | 3.1 | 3.1 | 13.3 | 97.3 | 92 | 0.7 | 1.8 | 7.3 | 0 | 53.8 | 16.1 | 0 | 1 |
| 12 | 1.1 | 0.8 | 1 | 96.3 | 90 | 1.4 | 0.8 | 15.5 | 6.7 | 19 | 19.9 | 0 | 2,7 |
| 13 | 1.3 | 0 | 2.8 | 98.4 | 0 | 0 | 0 | 7.7 | 1.8 | 0 | 12.2 | 1 | 4 |
| 14 | 2.8 | 3.1 | 5.5 | 97.8 | 94 | 0 | 0.4 | 4.9 | 0 | 34.4 | 10.6 | 3 | 0 |
| 15 | 0.3 | 1 | 1 | 98 | 89 | 0.1 | 1 | 0.5 | 9.9 | 0.9 | 8.1 | 3 | 2,8 |

PSG diagnosis: 1 = obstructive sleep apnea, 2 = interictal epileptiform discharges (IEDs), 3 = primary insomnia, 4 = continuous spike and waves during sleep or focal subcontinuous IEDs, 5 = nocturnal epilepsy, 6 = arousal disorder, 7 = periodic limb movements (PLMs), 8 = bruxism 0 = normal, ODI, oxygen desaturation index, SaO2, overnight oxygen saturation, SOREMp, sleep onset REM sleep period.

**Table 4** Final diagnosis of sleep phenotypes (bold indicate the most relevant values) and comorbidity

| Case | Age, years | Sex | Comorbidity | Therapy | Sleep phenotype: 1 = narcoleptic type, 2 = SOI, 3 = OSA, 4 = PLMs and or sleep hyperkinesia, 5: sleep IEDs, epilepsy |
|---|---|---|---|---|---|
| 1 | 12.1 | M | None | Atomoxetine, iron supplementation | **4** |
| 2 | 8.3 | M | None | Lamotrigine | 3, **5** |
| 3 | 11.5 | F | None | Lamotrigine | 3, **5** |
| 4 | 8 | M | Oppositional defiant disorder (ODD) | No | **3** |
| 5 | 8.1 | M | ODD, arousal disorder | Iron supplementation | 3,**4** |
| 6 | 8.9 | M | Learning disability (LD), tics | No | **3** |
| 7 | 8.1 | M | None | Methylphenidate | **1**,2 |
| 8 | 13.5 | M | ODD | Iron supplementation | **4** |
| 9 | 9.2 | M | None | Melatonin | **2**, 4, 5 |
| 10 | 10.5 | M | LD | Iron supplementation | **4** |
| 11 | 8.5 | M | None | None | **3** |
| 12 | 12.4 | M | LD | Lamotrigine | **5** |
| 13 | 13.8 | M | None | Iron supplementation | **4** |
| 14 | 13.7 | F | ODD | Methylphenidate, iron supplementation | **1**,4 |
| 15 | 12.4 | F | None | Atomoxetine, melatonin | **1**,2,5 |

in children with ADHD [25]. The prevalence of interictal or ictal IEDs is known to be higher in children with ADHD if evaluated via sleep and sleep-deprived recordings [27], with values rising to as much as 53% when children are evaluated by means of a full-night video-PSG [24]. Furthermore, video-PSG allows nocturnal seizures, which may escape detection, to be diagnosed [25]. Although the prevalence of ADHD in childhood epilepsy is between 12 and 17% [43], the literature available on the relationship between these two disorders is limited, with few uncontrolled studies, conducted on small samples of children with ADHD and IEDs, reporting a positive effect of antiepileptic drugs on sleep quality [44,45]. Almost 40% of children with epilepsy also present behavioral deficits, including ADHD, autism, anxiety, as well as general learning and memory impairment. However, the precise role of IEDs in cognition remains unclear [46]. The association between frequently generalized early life seizures and hippocampal-dependent cognition has been thoroughly investigated in studies on rodent models, which support the theory that epileptic discharges disrupt the normal development of hippocampal networks [47]. In addition, many children with epilepsy might rarely experience seizures despite the occurrence of frequent focal neocortical interictal spikes associated with serious cognitive and behavioral impairments, for example, children with continuous spike-waves during sleep [46]. A recent study analyzed the effects of microinjections of bicuculline, a competitive GABA-A antagonist, in the PFC to induce an inhibitory/excitatory network imbalance leading to focal IEDs in adolescent rats. The results of that study showed that prefrontal IEDs during development are associated with both long-lasting alterations in short-term synaptic plasticity and deficits in attention and sociability in rodents [46]. The body of literature investigating whether PFC damage induced by IEDs is reversible, or is irreversible and consequently causes high cognitive dysfunction (such as attention, learning, and working memory process impairments), in this sleep phenotype of ADHD is still small but is growing. With the exception of cognitive disabilities, children in our sample did not display any risk factors suggesting sleep IEDs or epilepsy. Moreover, the data that emerged from the anamnestic clinical reports and questionnaires revealed unspecific sleep disorders related to initiating and maintaining sleep, or snoring and witnessed apnea, although no other signs that might raise suspicions. Although the majority of the children were placed on antiepileptic therapy after the study ended, the efficacy of this treatment still needs to be followed up. For all these reasons, prospective studies based on larger sample sizes as well as neuroimaging are warranted to ascertain the clinical benefits of antiepileptic drugs in this category of patients [45].

As shown in Table 4, three cases belonged to the first sleep phenotype, which is considered "a primary form of ADHD" that resembles narcolepsy. Three SOREMPs were detected at the MSLT in these children; moreover, their results at the mean sleep latency test were borderline, with only one satisfying the criteria for strong suspicion of narcolepsy (three SOREMPS and a mean sleep latency of 8.1 min). These children received treatment with methylphenidate or atomoxetine. We are not yet able to determine whether they suffer from narcolepsy or a primary form of hypersomnia, although a more thorough diagnostic characterization is expected in the future follow-up examinations. A recent retrospective study found that a positive history of childhood ADHD symptomatology was common in adult narcoleptic patients, particularly among those with a lower MSLT score. Future research is warranted on adult narcoleptics to verify this relationship [48]. To investigate ADHD symptoms in pediatric narcolepsy, one study gathered cross-sectional data from a large cohort of children and adolescents with type 1 and 2 narcolepsy, nearly all whom were receiving modafinil; additional treatments included methylphenidate in approximately 50% of the subjects [49]. The authors found that pediatric patients with narcolepsy display approximately twice as many ADHD symptoms as controls and that ADHD symptoms, unlike narcolepsy symptoms, are largely unresponsive to psychostimulant therapy [49].

 

A low level of serum ferritin was found in most of our sample, in whom it was associated with sleep hyperkinesias and/or PLMs during sleep. These patients received oral iron supplementation. Sleep hyperkinesias remained an unspecific symptom and sign, not associated with clear criteria for a diagnosis of pediatric RLS. The role of iron deficiency in ADHD remains unclear. A systematic review [50] reported that one MRI study detected significantly lower thalamic iron indices in ADHD than in control subjects; two trials, one of which was open-label and the other a pilot randomized placebo-controlled study, found that ADHD symptoms improved following iron supplementation; three studies showed that children with ADHD plus sleep disorders, and in particular RLS, are at risk of iron deficiency; lastly, two studies suggested that iron deficiency might decrease the effectiveness of psychostimulant treatment.

Actigraphic recordings help to discriminate children with pure sleep onset insomnia, with restricted time in bed and consequent sleep deprivation, from children with sleep fragmentation and sleep maintenance insomnia, which are more likely to be related to a major sleep disorder. The actigraphic recording could not obviously help to discriminate children with IEDs or nocturnal epilepsy from children with other sleep disorders. These children received melatonin at an appropriate hour on the basis of the actigraphic recording [51].

Our preliminary results confirm the high prevalence of SDB in children with ADHD. Interestingly, the children in our sample had a mild form of OSA, a past history of snoring, sleep apnea, and adenotonsillar hypertrophy, and displayed craniofacial risk factors, as demonstrated by the sleep clinical record. In keeping with data in the literature, according to which children with ADHD usually have a mild form of OSA [22], our results might be influenced by the age at which the children are investigated: bearing in mind that that the onset of pediatric OSA peaks at the preschool age, school-aged children with ADHD may come to the pediatrician's attention many years after the onset of OSA, which might by then have been treated or have spontaneously improved [22,52].

Our study highlights the need to establish a structured sleep diagnostic algorithm in children with ADHD, particularly in view of the considerable cost of a complete instrumental sleep assessment. We suggest that sleep disorders in ADHD children be screened by means of sleep questionnaire scales and actigraphic recordings. The aim of the preliminary screening is to identify those children that are likely to benefit from a full V-PSG recording with large EEG montage, and in particular in children with suspected OSA. In the remaining children, we strongly recommend a standard sleep EEG as a screening tool to detect IEDs or seizures in "asymptomatic" children with ADHD. A diagnosis of nocturnal epilepsy or of sleep IEDs is important not only to prescribe the most appropriate treatment, but also to make an accurate prognosis. We should bear in mind that active sleep IEDs might reflect an epileptic encephalopathy due to focal cortical dysplasia in frontal and extra-frontal nocturnal epilepsy [53].

## References


1. Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: A systematic review and metaregression analysis. *Am J Psychiatry* 2007;**164**:942–948.
2. Volkow N.D, Swanson JM. Clinical practice: Adult attention deficit-hyperactivity disorder. *N Engl J Med* 2013;**369**:1935–1944.
3. American Academy of Pediatrics. Clinical practice guideline: Diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. *Pediatrics* 2000;**105**:1158–1170.
4. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 5th*. Washington, DC.: American Psychiatric Publishing, 2013.
5. Donfrancesco R, Miano S, Mrtines F, et al. Bipolar disorder co-morbidity in children with attention deficit hyperactivity disorder. *Psychiatry Res* 2011;**186**:333–337.
6. Schmidt S, Petermann F. Developmental psychopathology: Attention Deficit Hyperactivity Disorder (ADHD). *BMC Psychiatry* 2009;**9**:58.
7. Cortese S, Kelly C, Chabernaud C, et al. Toward systems neuroscience of ADHD: A meta-analysis of 55 fMRI studies. *Am J Psychiatry* 2012;**169**:1038–1055.
8. Nobili L, De Gennaro L, Proserpio P, et al. Local aspects of sleep: Observations from intracerebral recordings in humans. *Prog Brain Res* 2012;**199**:219–232.
9. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders, 3th*. Washington, DC.: American Psychiatric Publishing, 1980.
10. Cortese S, Faraone SV, Konofal E, et al. Sleep in children with attention-deficit/hyperactivity disorder: Meta-analysis of subjective and objective studies. *J Am Acad Child Adolesc Psychiatry* 2009;**48**:894–908.
11. Cohen-Zion M, Ancoli-Israel S. Sleep in children with attention-deficit hyperactivity disorder (ADHD): A review of naturalistic and stimulant intervention studies. *Sleep Med Rev* 2004;**8**:379–402.
12. Borbély AA, Achermann P. Sleep homeostasis and models of sleep regulation. *J Biol Rhythms* 1999;**14**:557–568.
13. Miano S, Parisi P, Villa MP. The sleep phenotypes of attention deficit hyperactivity disorder: The role of arousal during sleep and implications for treatment. *Med Hypotheses* 2012;**79**:147–153.
14. Lecendreux M, Konofal E, Bouvard M, et al. Sleep and alertness in children with ADHD. *J Child Psychol Psychiatry* 2000;**41**:803–812.
15. Weinberg WA, Brumback RA. Primary disorder of vigilance: A novel explanation of inattentiveness, daydreaming, boredom, restlessness, and sleepiness. *J Pediatr* 1990;**116**:720–725.
16. Ferri R, Miano S, Bruni O, et al. NREM sleep alterations in narcolepsy/cataplexy. *Clinical Neurophysiol* 2005;**116**:2675–2684.
17. Ferri R, Franceschini C, Zucconi M, et al. Sleep polygraphic study of children and adolescents with narcolepsy/cataplexy. *Developmental Neuropsychol* 2009;**34**:523–538.
18. Ferri R, Bruni O, Miano S, et al. Topographic mapping of the spectral components of the cyclic alternating pattern (CAP). *Sleep Med* 2005;**6**:29–36.
19. Van der Heijden KB, Smits MG, Van Someren EJ, et al. Idiopathic chronic sleep onset insomnia in attention-deficit/hyperactivity disorder: A circadian rhythm sleep disorder. *Chronobiol Int* 2005;**22**:559–570.
20. Gruber R, Sadeh A, Raviv A. Instability of sleep patterns in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2000;**39**:495–501.
21. Owens JA. The ADHD and sleep conundrum: A review. *J Dev Behav Pediatr* 2005;**26**:312–322.
22. Sedky K, Bennett DS, Carvalho KS. Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: A meta-analysis. *Sleep Med Rev* 2014;**18**:349–356.
23. Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex: Towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *J Sleep Res* 2002;**11**:1–16.
24. Montesano M, Miano S, Paolino MC, et al. Autonomic cardiovascular tests in children with obstructive sleep apnea syndrome. *Sleep* 2010;**33**:1349–1355.
25. Silvestri R, Gagliano A, Calarese T, et al. Ictal and interictal EEG abnormalities in ADHD children recorded over night by video-polysomnography. *Epilepsy Res* 2007;**75**:130–137.
26. Walter LM, Foster AM, Patterson RR, et al. Cardiovascular variability during periodic leg movements in sleep in children. *Sleep* 2009;**32**:1093–1099.
27. Wing YK, Zhang J, Ho CK, Au CT, Li AM. Periodic limb movement during sleep is associated with nocturnal hypertension in children. *Sleep* 2010;**33**:759–765.
28. Millichap JG, Millichap JJ, Stack CV. Utility of the electroencephalogram in attention deficit hyperactivity disorder. *Clin EEG Neurosci* 2011;**42**:180–184.
29. Bruni O, Novelli L, Luchetti A, et al. Reduced NREM sleep instability in benign childhood epilepsy with centro-temporal spikes. *Clin Neurophysiol* 2010;**121**:665–671.
30. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997;**36**:980–988.
31. Marzocchi GM, Cornoldi C. Una scala di facile uso per la rilevazione dei comportamenti problematici dei bambini con deficit di attenzione e iperattività. *Psicologia Clinica dello Sviluppo* 2000;**4**:43–64.
32. Wechsler D. *Wechsler intelligence scale for children-revised*. New York: The Psychological Corporation, 1973.

33. Korkman M, Kirk U, Kemp S. *A developmental neuropsychological assessment*. Psychological Corporation: San Antonio, TX, 1998, (Edizione italiana: Urgesi C, Campanella F, Fabbro F, Giunti OS, 2011).
34. Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. *Sleep* 2000;**15**:1043–1051.
35. Villa MP, Paolino MC, Castaldo R, et al. Sleep clinical record: An aid to rapid and accurate diagnosis of paediatric sleep disordered breathing. *Eur Respir J* 2013;**41**:1355–1361.
36. Drake C, Nickel C, Burduvali E, et al. The pediatric daytime sleepiness scale (PDSS): Sleep habits and school outcomes in middle-school children. *Sleep* 2003;**26**:455–458.
37. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. *The AASM manual for the scoring of sleep and associated events: Rules, terminology, and technical specifications*. Westchester, IL: American Academy of Sleep Medicine, 2007.
38. American Academy of Sleep Medicine. *International classification of sleep disorders—ICSD*. 3nd ed. Westchester, IL: American Academy of Sleep Medicine, 2014.
39. Crabtree VM, Ivanenko A, O'Brien LM, , et al. . Periodic limb movement disorder of sleep in children. *J Sleep Res* 2003;**12**:73–81.
40. Walters AS. Toward a better definition of the restless legs syndrome. The International Restless Legs Syndrome Study Group. *Mov Disord* 1995;**10**:634–642.
41. International Federation of Societies for Clinical Neurophysiology. A glossary of terms most commonly used by clinical electroencephalographers. *Electroencephalogr Clin Neurophysiol* 1974;**37**:538–544.
42. Parisi P, Bruni O, Pia Villa M, et al. The relationship between sleep and epilepsy: The effect on cognitive functioning in children. *Dev Med Child Neurol* 2010;**52**:805–810.
43. Reilly CJ. Attention deficit hyperactivity disorder (ADHD) in childhood epilepsy. *Res Dev Disabil* 2011;**32**:883–893.
44. Gagliano A, Aricò I, Calarese T, et al. Restless Leg Syndrome in ADHD children: Levetiracetam as a reasonable therapeutic option. *Brain Dev* 2011;**33**:480–486.
45. Bakke KA, Larsson PG, Eriksson AS, et al. Levetiracetam reduces the frequency of interictal epileptiform discharges during NREM sleep in children with ADHD. *Eur J Paediatr Neurol* 2011;**15**:532–538.
46. Hernan AE, Alexander A, Jenks KR, et al. Focal epileptiform activity in the prefrontal cortex is associated with long-term attention and sociability deficits. *Neurobiol Dis* 2014;**63**:25–34.
47. Chang Y-C, Kuo Y-M, Huang A-M, Huang C-C. Repetitive febrile seizures in rat pups cause long-lasting deficits in synaptic plasticity and NR2A tyrosine phosphorylation. *Neurobiol Dis* 2005;**18**:466–475.
48. Modestino EJ, Winchester J. A retrospective survey of childhood ADHD symptomatology among adult narcoleptics. *J Atten Disord* 2013;**17**:574–582.
49. Lecendreux M, Lavault S, Lopez R, et al. Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms in Pediatric Narcolepsy: A Cross-Sectional Study. *Sleep* 2015;**38**:1285–1295.
50. Cortese S, Angriman M, Lecendreux M, et al. Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. *Expert Rev Neurother* 2012;**12**:1227–1240.
51. Bruni O, Alonso-Alconada D, Besag F, et al. Current role of melatonin in pediatric neurology: Clinical recommendations. *Eur J Paediatr Neurol* 2015;**19**:122–133.
52. Chervin RD, Ellenberg SS, Hou X, et al. Childhood. Adenotonsillectomy Trial. Prognosis for Spontaneous Resolution of OSA in Children. *Chest* 2015;**148**:1204–1213.
53. Ferri L, Bisulli F, Nobili L, et al. Auditory aura in nocturnal frontal lobe epilepsy: A red flag to suspect an extra-frontal epileptogenic zone. *Sleep Med* 2014;**15**:1417–1423.