



Original Article

Sleep phenotypes in attention deficit hyperactivity disorder

Silvia Miano ^{a,*}, Ninfa Amato ^a, Giuseppe Foderaro ^b, Valdo Pezzoli ^b, Gian Paolo Ramelli ^c, Lorenzo Toffolet ^a, Mauro Manconi ^a

^a Sleep and Epilepsy Center, Neurocenter of Southern Switzerland, Civic Hospital of Lugano (EOC), via Tesserete 46, Lugano, 6903, Switzerland

^b Department of Pediatrics, Civic Hospital of Lugano, Lugano, Switzerland

^c Department of Pediatrics, San Giovanni Hospital, Bellinzona, Switzerland



ARTICLE INFO

Article history:

Received 20 June 2018

Received in revised form

27 July 2018

Accepted 6 August 2018

Available online 20 September 2018

Keywords:

ADHD

Pediatrics – Sleep apnea

Pediatrics – Insomnia

Epilepsy

Narcolepsy

ABSTRACT

Objective: A case-control study was performed to test the hypothesis that children with attention deficit hyperactivity disorder (ADHD) have chronic sleep deprivation and may be classified into specific sleep-related phenotypes.

Methods: Thirty outpatients with ADHD (nine females, mean age 10.1 ± 2.1 years) were recruited consecutively, and given a comprehensive sleep assessment, including blood exams, sleep questionnaires, laboratory video-polysomnographic recordings (v-PSG), multiple sleep latency tests, and one-week actigraphy. The PSG parameters were compared to those of 25 age-matched controls (12 females, mean age 10.34 ± 1.54 years) who underwent only the v-PSG.

Results: ADHD children were classified as follows: a narcolepsy-like phenotype was found in four; delayed sleep onset insomnia in five; obstructive sleep apnea (OSA) in 15; periodic limb movements in eight, and sleep epileptiform discharges in 10 children. All subjects had a total sleep time shorter than 9 h at actigraphy, ferritin levels lower than 60 mcg/L, and a history of sleep problems (mainly OSA and insomnia). Compared to controls, the ADHD group had a higher apnea-hypopnea index at PSG.

Conclusions: A full sleep assessment in children with ADHD confirmed the validity of the sleep phenotypes hypothesis, and revealed a much higher percentage of sleep problems than that found in the literature. Beyond the sleep phenotypes, all children reported a history of sleep problems and slept less than 9 h per night, indicating chronic sleep deprivation that should be evaluated as a possible unifying marker of ADHD.

© 2018 Elsevier B.V. All rights reserved.

1. Introduction

Attention-deficit/hyperactivity disorder is one of the most commonly diagnosed and long-lasting neuropsychiatric conditions, with a prevalence in the general population ranging from 5 to 7% [1,2]. The majority of children with ADHD suffer from comorbid disorders such as oppositional defiant disorder and learning disabilities [3,4]. Considering the early age of onset of ADHD and the potential chronicity of the disorder, several studies have tried to identify endophenotypes and risk factors for ADHD. One of the most extensively investigated areas of research concerns sleep [5]. Sleep complaints are reported in about 25–50% of children with ADHD [6], and persistent behavioral sleep problems are associated with a

severe form of ADHD [7]. Similar to the relationship between insomnia and psychiatric disorders, the link between ADHD and sleep is bidirectional [8,9]; sleep disturbances can lead to behavioral and cognitive consequences that may mimic ADHD, and children with ADHD may have sleep disturbances originating from the same biochemical disturbances underlying their deficits in executive function and attention [10].

Some investigators have hypothesized the existence of a dysfunction in arousal mechanisms in the etiology of ADHD inducing primary hypersomnia (ie, the excessive motor activity might be a strategy used to stay awake and alert) [11,12]. The best electroencephalographic (EEG) marker of this hypoarousability is the reduction of slow oscillatory components of arousals (evaluated using cyclic alternating pattern analysis -CAP), during NREM sleep, reported in narcolepsy [13]. The same dysfunction has been found in a cohort of children with ADHD, affected by a “primary form” of ADHD [13]. Sleep onset insomnia (SOI) is considered the most

* Corresponding author. Fax: +41 0918116915.

E-mail address: silvia.miano@eoc.ch (S. Miano).

List of abbreviations

ADHD	attention deficit hyperactivity disorder
PSG	Polysomnography
EEG	Electroencephalography
OSA	Obstructive Sleep Apnea
PLMs	Periodic Leg Movements
RLS	Restless Legs Syndrome
IEDs	Interictal Epileptiform Discharges
BCTE	Benign Centrottemporal Epilepsy
MSLT	Multiple Sleep Latency Test
CPRS	Conners' Parent Rating Scale
CSHQ	Children's Sleep Habits Questionnaire
SCR	Sleep Clinical Record
PDSS	Pediatric Daytime Sleepiness Scale
IQ	Intelligent Quotient
AHI	Apnea-Hypopnea Index

common sleep disorder reported in children with ADHD (around 30% of cases). SOI can be the expression of a circadian delay in the sleep-wake cycle, which in turn results in a chronic sleep deprivation due to the forced morning awakening required to comply with school schedules [14,15]. Data from the Avon Longitudinal Study of Parents and Children showed that children with ADHD slept for a shorter time and woke up more than their peers. Furthermore, main reason for their shorter sleep duration was later bedtime [16]. Thus, an extensive body of literature demonstrated that children with ADHD have a mild form of OSA. Conversely, children with OSA display diurnal ADHD behavior, reflecting dysfunction of the prefrontal cortex, caused by both intermittent hypoxia and sleep fragmentation [17]. The improvement of ADHD symptoms after adenotonsillectomy has been observed and supports a link of causality between OSA and ADHD [17,18]. Moreover, children with periodic leg movements during sleep (PLMS) and/or restless legs syndrome (RLS) display daytime inattention, hyperactivity, and low school performance. A comorbidity with RLS/PLMS has been reported in about 12% of children with ADHD, with a positive correlation between RLS/PLMS and hyperactivity/opposition scores [19,20]. A solid body of literature supports a relationship between interictal epileptiform discharges (IEDs) during sleep and neuropsychological dysfunctions typical of ADHD [21–25]. When explored by prolonged sleep recordings, the prevalence of IEDs and seizures increases up to 50% in children with ADHD. IEDs are mostly represented by those also observed in benign centrottemporal spike epilepsy (BCTE) [21–25]. Note that a reduced arousability, in terms of CAP analysis, similar to that found in ADHD, has been reported in children with BCTE [26].

Summarizing the literature and taking into account the whole spectrum of sleep disorders in ADHD, five sleep phenotypes have been hypothesized, as described in clinical reports: (1) hypoarousal state, narcoleptic-like, considered a “primary” form of ADHD; (2) delayed sleep onset insomnia; (3) obstructive sleep apnea-OSA; (4) restless legs syndrome/periodic limb movements during sleep, and (5) sleep EEG epileptiform discharges [8,9]. If assessed by standard polysomnography, comparing children with ADHD to normal controls, the only evidence-based finding is a higher AHI index [17], which seems to contradict the comorbidity between several sleep disorders and ADHD. The contradictory finding might be explained by the different methodologies required to diagnose each specific sleep disorder (such as clinical history, sleep questionnaire, actigraphic recording, a video-polysomnographic recording with extensive EEG channels and multiple sleep latency tests). To our

knowledge, a full sleep assessment involving subjective and objective sleep instruments has never been performed on a sample of drug naïve children with ADHD.

To test this hypothesis, the main objective of this study is to confirm the high comorbidity between ADHD and sleep disorders through a detailed subjective and objective sleep investigation and to verify if a full sleep assessment may help to identify a higher percentage of sleep problems.

The second aim is to compare polysomnographic features between children with ADHD and healthy kids to confirm the literature data [17].

Finally, with the aim of challenging the concept of sleep phenotype in ADHD, a comparison between all the clinical data and sleep parameters of children with ADHD and specific sleep disorders and the polysomnographic parameters of healthy controls, was carried out.

2. Methods

Thirty consecutive drug naïve outpatients who received a diagnosis of ADHD were recruited at the local Pediatric Department (nine females, mean age 10.1 ± 2.1 years) from April 2015 to May 2016. The diagnosis of ADHD was based on DSM-V criteria [3]. To confirm the diagnosis of ADHD, children and parents received a semi-structured psychiatric interview: the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [27]; the Wechsler Intelligence Scale for Children [29]; and a standardized neuropsychological battery for children (NEPSY-II) [30]. Neuropsychological assessment was administered by a neuropsychologist and cognitive psychotherapist (GF), expert in developmental neuropsychology and ADHD assessment. The diagnosis was confirmed by the pediatrician (PV), based on a combination of clinical criteria (parents and teachers information, supported by the neuropsychological tests battery). Medical and family history were collected; a neurological examination and a screening blood exam were also performed. Children with an age range between eight and 12 years were included. Children with a comorbid diagnosis of autistic spectrum disorder, with intelligence quotient <70 , and other neurological conditions, were excluded.

25 normal age-matched control children (12 females mean age 10.34 ± 1.54 years) were recruited from April 2015 to July 2017, through an e-mail addressed to all employees of the Hospital. Parents of the control participants received a phone-interview by the expert in pediatric sleep disorders (SM), to ensure that their children did not have any sleep disorder or neuro-psychiatric comorbidities.

Children with ADHD underwent a complete sleep assessment at our Sleep Lab, which included standardized sleep questionnaires, one week of actigraphic recording, an attended nocturnal video-polysomnographic recording (PSG), which was followed the day after by a multiple sleep latency test (MSLT) only for children with ADHD. Healthy controls underwent only the attended nocturnal video-polysomnographic recording (PSG).

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

For further details, see also Miano et al., [9].

2.1. Sleep questionnaires

Parents of children with ADHD filled out the Children's Sleep Habits Questionnaire (CSHQ) [31]. Children were interviewed by the principal investigator (SM) to screen for SDB by completing the

sleep clinical record (SCR) [32], and to assess daytime sleepiness by completing the pediatric daytime sleepiness scale (PDSS) [33].

2.2. Wrist actigraphic recording

Children with ADHD completed one week of actigraphic recording (Philips Respironics, Actiwatch 2) before or after the PSG study. The device was worn on the non-dominant arm for 24 h/day. The parents filled out a sleep diary during the same week. The Actiwatch 2 is a combined wrist-worn accelerometer and photopic light sensor. This device records acceleration count values for each epoch, which can then be used by the manufacturer's software to estimate whether each epoch is sleeping or awake. The Actiwatch 2 is a validated (against polysomnography) accelerometer which measures both sleep duration and efficiency in children [34,35]. For school-aged children, the medium sensitivity setting (weighted, rolling average ≥ 40 counts/epoch) for the Actiwatch 2 provides an accurate epoch-by-epoch delineation between sleep and wake time as compared to polysomnography (sensitivity = 93%, specificity = 71%, accuracy = 90%) [34].

2.3. Nocturnal video-polysomnography

Participants (ADHD and control subjects) underwent one full-night video-PSG, recorded in a standard sleep laboratory with attenuated sound. Recordings included 18 EEG bipolar channels, an electrooculogram (electrodes placed 1 cm above the right outer canthus and 1 cm below the left outer canthus and referred to A1), a submental electromyogram (EMG), an electrocardiogram (one derivation), and an EMG of the right and left tibialis anterior muscles. Chest and abdomen movements were measured by strain gauges, oro-nasal airflow was recorded using both thermistor and nasal-cannula pressure. Arterial oxygen saturation was monitored with a digital pulse oximeter, and a microphone detected snoring and other sounds. Sleep stages, leg movements, arousals, and cardio-respiratory parameters were scored according to standardized criteria [36], as well as the presence of IEDs, according to the International Federation of Societies for Clinical Neurophysiology standard [37].

The morning after PSG recording, children with ADHD underwent an MSLT consisting of five naps scheduled at 2-h intervals, starting at 09:00 h according to the standard rules [38].

2.4. Criteria for sleep phenotype classification

More than one of the below diagnoses can be found in each patient, and one diagnosis does not exclude the others.

- (1) Narcoleptic-like phenotype: excessive daytime sleepiness was diagnosed by an MSLT <8 min, and/or ≥ 2 sleep-onset REM-sleep periods at MSLT, without reaching the criteria for insufficient sleep syndrome, according to the International classification of sleep disorders [39].
- (2) A major complaint of chronic sleep onset delay insomnia (SOI), based on anamnestic data (sleep latency more than 20 min, for more than three times per week and more than three months) according to the International classification of sleep disorders [39]. Results of the sleep diaries and actigraphic parameters support the diagnosis.
- (3) Central, obstructive and mixed apnea events were counted according to the criteria of the American Academy of Sleep Medicine [36,39]. The apnea/hypopnea index (AHI) was defined as the average number of apneas and/or hypopneas per hour. The diagnosis of OSAS was established based on an AHI > 1 and the presence of one of the following: (A) snoring,

(B) labored child's sleep breathing, (C) sleepiness. Hyperactivity or learning problems, which are part of criterion C, were not considered for diagnosis. Primary snoring was diagnosed in children with a history of habitual snoring and an AHI < 1 .

- (4) Limb movement events were counted according to the criteria of the American Academy of Sleep Medicine [36,39]. PLMS were identified as sequences of four or more LMs, lasting from 0.5 to 10 s in duration and separated by at least 5 s and no more than 90 s. A PLMS index (number of PLM per hour of sleep) higher than ≥ 5 was considered as clinically significant [40]. RLS 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 interictal epileptiform discharges (IEDs), according to the definitions of the International Federation of Societies for Clinical Neurophysiology [37].

2.5. Statistical analysis of sleep parameters

Normality of data and homogeneity of variance were first assessed using Shapiro-Wilk's test and Levene's test respectively; non-parametric tests were then used for between and within groups comparisons. Polysomnographic parameters obtained in normal controls and children with ADHD were compared using the Kruskal-Wallis test or the χ^2 test when appropriate. Post hoc analysis was performed using the Mann-Whitney U test. Data obtained from patients were compared using the Mann-Whitney U test. We used Holm's correction to deal with multiple testing (Holm, 1979) and differences were considered significant at a level of $p < 0.05$ after correction. All tests were performed using SPSS, version 20 (IBM Inc., New York, USA). We performed a post hoc power analysis using GPower to compute the achieved power. Spearman's rank correlation coefficient or Spearman's rho, a nonparametric measure of rank correlation, was calculated to find the correlation between sleep parameters, laboratory exams, and cognitive assessment.

3. Results

The 30 outpatients received a diagnosis of ADHD combined type in 22 cases, of inattentive type in six, and hyperactive type in two. A comorbid diagnosis of oppositional defiant disorder was established in two subjects, of anxiety disorders in two, and of learning disabilities in 18. One patient received a standard sleep EEG recording at preschool age, showing sleep IEDs over the centrotemporal regions. Prematurity was found in two subjects, and a mild psychomotor delay in two cases. A history of snoring, and/or of OSA was found in 14 children, while 13 had a history of sleep hyperkinesia, nine had behavioral insomnia, and five children had sleep parasomnias. Two subjects reported past hypnagogic hallucinations. The neurological examination showed minimal neurological signs in the majority of children (23 out of 30 children). A left-brain dominance was found in six children and bilateral in three (all of them had a PLMS index ≥ 5).

The blood samples showed a serum ferritin level below 60 $\mu\text{g/L}$ in all children with ADHD, and even below 20 $\mu\text{g/L}$ in eight of the children. The mean body mass index was 18.67 ± 4.43 kg/m^2 and above the normal range only in one subject (34.2 kg/m^2).

3.1. Sleep disorders

According to all sleep measures, questionnaires, history, and laboratory tests, 28 out of 30 ADHD children received a diagnosis of sleep disorders, (see Table 1 and Fig. 1). SOI was found in five males, mean age 12.51 ± 1.37 years (SOI phenotype), OSA was found in 15 children (mean age 10.0 ± 2.17 years, 12 males), PLMS were found in eight (mean age 10.7 ± 1.8 years, six males), without reaching criteria for RLS diagnosis. The narcoleptic-like phenotype was found in four children (one male, mean age 10.84 ± 2.91 years), while EEG interictal or ictal epileptiform discharges were found in 10 subjects (mean age 10.5 ± 2.13 years, seven males): continuous spike and waves or sharp waves during sleep were found in three subjects (see Fig. 2). Three subjects had sleep arousal disorder with mild motor events during SWS, in association with OSA in two cases.

Only two children were not affected by any sleep disorder. Many subjects received more than one diagnosis as shown in Table 1.

3.2. Sleep parameters and comparisons with healthy controls (only for PSG parameters)

- (1) All ADHD children but one (data missing) had a score of CSHQ higher than 41 (which is considered a cut-off for sleep disorders). A PDSS score higher than 20 was found in five ADHD children (indicating severe daytime sleepiness), and an SCR score higher than 6.25 was found in 15 children (indicating higher risk to have OSA) (mean values shown in Table 2).

Table 1

Sleep phenotypes, and sleep comments of polysomnographic recordings.

id	Sleep Phenotype ^a	Sleep comments
1	2,5	Mild OSA, arousal disorder, epileptiform discharges (bilateral frontal sharp waves) and two motor events (probable nocturnal frontal lobe epilepsy)
2	2,5	Moderate OSA, sporadic epileptiform discharges (bilateral frontotemporal sharp waves)
3	2	Mild OSA, with many awakenings during sleep.
4	5	Probable nocturnal frontal lobe epilepsy with mild motor events and ictal theta activity at EEG, epileptiform discharges (bilateral frontotemporal sharp waves, mostly prominent over left regions)
5	2	Mild OSA, with many awakenings during sleep
6	2	Mild OSA with many awakenings during sleep, arousal disorders with delta hypersynchrony over posterior regions, sleep hyperkinesia
7	2,5	Mild OSA, abundant epileptiform discharges during sleep (sharp waves over temporal regions, with alternating predominance)
8	3	Many periodic limb movements during sleep, rapid activity during N1 and wakefulness
9	2	Mild OSA, sleep hyperkinesia
11	2,4	Sporadic epileptiform discharges (bilateral frontal sharp waves)
12	3,5	Abundant epileptiform discharges during sleep (sharp waves over left centrotemporal regions), many periodic limb movements during sleep
13	4	Normal
14	1,2,3	Mild OSA, many periodic limb movements during sleep and foot tremor
15	5	Abundant epileptiform discharges during sleep (sharp waves over left centroparietal regions), without clear motor events
16	4,5	Slow epileptiform discharges (over bilateral frontal regions), without clear motor events, probable nocturnal frontal lobe epilepsy, sleep hyperkinesia
17	3	Sporadic epileptiform discharges (bilateral centrotemporal sharp waves), many periodic limb movements during sleep
18	3,5	Sporadic epileptiform discharges during sleep (diffuse spike and waves, mostly prominent over frontal regions), arousal disorder, oxygen mean saturation below 90% for 22% of sleep time, sleep hyperkinesia
19	3	Many periodic limb movements during sleep, arousal disorders
20	1	Increased sleep latency
21	4,3	Normal
22	1,2	Moderate OSA, many periodic limb movements during sleep
23	2,3,5	Moderate OSA, many periodic limb movements during sleep and alternating legs movements, sporadic epileptiform discharges during sleep (sharp waves over right temporal-parietal regions)
24	2,6	Many periodic limb movements during sleep, mild OSA, arousal disorder
25	1	Sleep latency, REM sleep latency increased and many awakenings
26	none	Normal
27	6	Arousal disorder
28	2,6	Mild OSA, arousal disorder
29	1,2,5	Mild OSA, sporadic epileptiform discharges during sleep (sharp waves over right temporal-parietal regions) bruxism, two upper limb myoclonic event of uncertain meaning
30	2,6	Mild OSA, arousal disorder with many events during sleep with delta hypersynchrony
32	3	Sleep hyperkinesia, oral breathing

^a 1: sleep onset insomnia; 2: obstructive sleep apnea, 3: periodic limb movements, 4: narcolepsy, 5: epilepsy, 6: other.

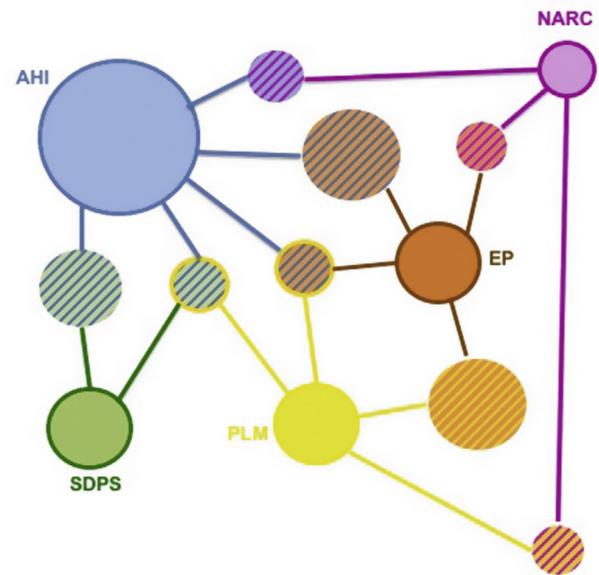


Fig. 1. The sleep phenotype distribution in all the sample of children with ADHD (30 subjects). AHI: apnea-hypopnea index, NARC: narcolepsy-like, PLM: periodic limb movements, EP: epilepsy, SPDS: sleep delayed phase syndrome (sleep onset insomnia).

- (2) The actigraphic analysis showed a low sleep efficiency (<90%) in all ADHD children, a sleep latency longer than 30 min in nine children, and multiple night awakenings and/



Fig. 2. Thirty-second epoch of PSG-EEG standard recording showing the occurrence of frontotemporal bilateral and asynchronous sharp waves and spike activity, more prominent over the left side, during slow wave sleep.

or severe sleep hyperkinesias in seven. Eleven subjects showed a reduced time in bed (the mean was lower than 9 h). All children slept less than 9 h in mean.

- (3) MSL at MSLT was lower than eight minutes in one child, and one or more sleep onset REM sleep periods were found in 11 children (three sleep onset REM in four subjects, mean values are shown in Table 2).

Table 3 shows the statistical comparisons of clinical data and PSG parameters between ADHD and controls: children with ADHD had a higher AHI compared to controls. The comparisons reached a power higher than 0.8, indicating that the tests were powered to detect significance.

3.3. Correlations between sleep measurements, cognitive assessments, and laboratory tests

ADHD scores on Conner's scale correlated negatively with total sleep time at actigraphic recording ($r = -0.422, p = 0.028$). At PSG Conner's hyperactivity and ADHD total scores correlated negatively with total sleep time ($r = -0.404, p = 0.036$; $r = -0.423, p = 0.28$ respectively), with sleep efficiency ($r = -0.473, p = 0.013$; $r = -0.473, p = 0.013$, respectively), and positively with sleep latency ($r = 0.481, p = 0.011$; $r = 0.387, p = 0.046$, respectively).

The scores of NEPSY auditory sustained attention inhibition errors correlated negatively with sleep efficiency at actigraphic recording ($r = -0.381, p = 0.042$). A negative correlation was found

Table 2
Neuropsychological scores, blood exams and sleep parameters of children with attention deficit hyperactive disorder.

mean ± standard deviation							
Wechsler Intelligence Scale for Children (WISC-IV) scores							
Intelligence Quotient		Verbal index		Visuo-Spatial index		Working memory index	
100.19 ± 10.74		103.00 ± 3.54		108.55 ± 16.65		92.57 ± 5.35	
Processing Speed Index							
91.38 ± 4.51							
Neuropsychological battery for children (NEPSY-II) scores							
Nepsy Visual attention	Nepsy auditory sustained attention total	Nepsy auditory sustained attention omissions	Nepsy auditory sustained attention inhibition errors	Nepsy response set total	Nepsy response set omissions	Nepsy response set inhibition errors	Nepsy inhibition A time
9.50 ± 0.35	7.10 ± 1.49	8.76 ± 0.88	9.38 ± 0.44	7.10 ± 0.78	7.31 ± 1.90	8.97 ± 0.73	8.00 ± 0.71
Nepsy inhibition A errors	Nepsy inhibition B time	Nepsy inhibition B errors	Nepsy semantic verbal fluency	Nepsy comprehension	Nepsy visuo-motor ability time	Nepsy visuomotor ability errors	
8.03 ± 0.02	8.21 ± 2.27	7.14 ± 1.51	9.00 ± 0.71	8.79 ± 1.56	10.04 ± 0.73	6.96 ± 2.10	
Blood exams				Multiple sleep latency test parameters			
Ferritin, µg/L	ASO, U/mL	TSH, mU/L	FT4, pmol/L	Mean sleep latency (minutes)		SOREMPs at MSLT (number)	
28.49 ± 13.47	365.87 ± 281.99	2.51 ± 1.51	10.23 ± 1.27	15.78 ± 3.77		0.67 ± 1.06	
Conners-Rating Scale for parents scores				KSADS scores			
Attention		hyperactivity		Total		ADHD	
76.81 ± 10.03		70.81 ± 12.44		76.11 ± 10.78		2.93 ± 0.26	
						conduct	
						1.07 ± 0.26	
						oppositional defiant	
						1.38 ± 0.73	
Actigraphic Parameters				Sleep questionnaires and Scales			
Time in bed mean (hours)	Sleep latency mean (min)	Sleep efficiency mean (%)	Total sleep time mean (hours)	Children's Sleep Habits score	Pediatric daytime sleepiness score	Sleep Clinical Record score	
9.31 ± 0.76	22.36 ± 16.02	82.35 ± 5.74	7.66 ± 0.64	53.55 ± 8.61	14.30 ± 6.17	6.53 ± 2.65	

Thyroid stimulant hormone: TSH; antistreptolysin-O: ASO; Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version: KSADS; Sleep Onset REM period: SOREMP.

Table 3
Statistical comparisons of clinical data and polysomnographic parameters between children with attention deficit hyperactivity disorders and normal controls, values expressed by mean \pm standard deviation or total number.

	ADHD (n = 30)	Controls (n = 25)	Uncorrected (Mann Whitney test or χ^2) p values	Corrected (Holm's correction) p values
Age years	10.52 \pm 2.07	10.34 \pm 1.54	0.958	1
Body Mass Index Kg/m ²	18.67 \pm 4.43	17.42 \pm 2.84	0.351	1
Male/Female	21/9	13/12	0.171	1
Right handed	18	22	0.075	1
TST min	421.49 \pm 58.93	462.8 \pm 69.57	<0.022	0.44
SPT min	463.72 \pm 35.21	472.75 \pm 44.46	0.31	1
SE %	83.06 \pm 12.51	88.48 \pm 8.78	0.055	1
SL min	45.52 \pm 33.53	29.81 \pm 25.54	0.083	1
RL min	118.28 \pm 51.93	106.94 \pm 50.78	0.302	1
N1%	5.9 \pm 3.7	6.26 \pm 3.22	0.78	1
N2%	47.41 \pm 8.26	46.31 \pm 6.76	0.306	1
N3%	28.53 \pm 7.13	27.9 \pm 6.22	0.866	1
REM%	18.16 \pm 5.61	19.5 \pm 4.96	0.393	1
WASO %	9.04 \pm 11.76	6.69 \pm 8.1	0.589	1
AI (n/h)	7.82 \pm 4.02	5.95 \pm 3.01	0.086	1
AHI (n/h)	1.98 \pm 1.7	0.64 \pm 0.75	<0.001	<0.002
AHI REM	3.28 \pm 4.32	0.7 \pm 1.52	<0.001	<0.002
MOS (%)	97.12 \pm 0.92	97.18 \pm 0.57	0.89	1
OSN (%)	87.54 \pm 17.73	91.96 \pm 4.06	0.134	1
ODI (n/h)	0.43 \pm 0.46	0.34 \pm 0.77	0.167	1
LMI (n/h)	10.57 \pm 5.17	11.01 \pm 6.35	0.852	1
PLMI (n/h)	2.9 \pm 2.8	3 \pm 3.8	0.852	1

TST: total sleep time, SPT: sleep period time; SE: sleep efficiency; SL: sleep latency, RL: REM latency; WASO: wakefulness after sleep onset; AI: arousal index; AHI: apnea-hypopnea index; MOS: mean oxygen saturation, OSN: oxygen saturation nadir; ODI: oxygen desaturation index; PLMI: periodic limbs movements index; min: minutes; n/h: number/hour; N.S: not significant.

between scores of NEPSY inhibition A errors and sleep latency at PSG ($r = -0.404$, $p = 0.027$), while the scores of NEPSY inhibition B errors correlated negatively with REM percentage ($r = -0.403$, $p = 0.030$). The scores of NEPSY inhibition A time correlated positively with N2% and negatively with N3% ($r = 0.474$, $p = 0.008$; $r = -0.371$, $p = 0.044$, respectively). REM latency at PSG correlated negatively with the scores of NEPSY auditory sustained attention ($r = -0.468$, $p = 0.010$). The scores of NEPSY visuomotor ability time correlated negatively with arousal index and AHI during REM sleep ($r = -0.422$, $p = 0.025$; $r = -0.408$, $p = 0.031$).

Finally, the mean ferritin levels correlated positively with mean oxygen saturation during sleep ($r = 0.511$, $p = 0.011$).

3.4. Comparisons of all the clinical data and sleep parameters of children with ADHD and specific sleep disorders, with healthy controls (only for PSG parameters)

Table 4 shows the mean values and statistically significant results.

Children belonging to the group with SOI were older than the other children with ADHD ($p = 0.019$) and controls ($p = 0.005$). They had a later fall-asleep time than the other children with ADHD (10:30 pm vs. 9:17 pm, $p = 0.02$, after Holm's correction). Children with SOI had a shorter time in bed, as measured by actigraphic recording. Moreover, they showed a lower REM sleep latency at the first nap of the MSLT. Furthermore, they had a better score at the NEPSY inhibition B time. Not all these results were confirmed after Holm's correction.

Children with PLMS had a bilateral brain dominance in three cases and none were left-handed, with a statistically significant difference compared to controls ($n = 0$, $p = 0.004$) and to the other children with ADHD ($n = 0$, $p = 0.006$).

According to the definition criteria, children with AHI showed higher AHI compared to the other two groups. Also, they showed a higher arousal index and a higher respiratory movement's index compared to the other two groups (not confirmed after Holm's correction). They also had a better score on the NEPSY inhibition A

time compared to the other children with ADHD (not confirmed after Holm's correction). According to the definition criteria, children with PLMs have higher LMI and PLMI compared to the other two groups. They also had a higher number of awakenings during sleep compared to the other two groups, and a higher AHI compared to controls (not confirmed after Holm's correction).

According to the definition, children with narcolepsy-like phenotype had a lower MSL and a higher number of SOREMPs compared to the other ADHD children. Moreover, they had a higher total sleep time and REM sleep percentage compared to the other two groups (not confirmed after Holm's correction). Compared to the other ADHD children, they showed a lower Processing Speed Index and a lower score at NEPSY inhibition A and B times (not confirmed after Holm's correction).

Finally, children with epilepsy showed a higher AHI compared to controls.

Most of the comparisons that showed a significant difference after correction reached a power higher than 0.8, indicating that the tests were powered to detect significances. Comparisons not reaching this level of power are indicated in Table 4.

4. Discussion

This study reports the results of a full sleep assessment in a sample of consecutively recruited, drug-free children with ADHD. According to the sleep phenotype hypothesis [8], 28 out of 30 children had a sleep disorder comorbidity, a percentage much higher than that found in the literature, which is around 25–50% [6]. This is a surprising finding, which needs to be replicated and confirmed in a larger sample of children with ADHD. A full and detailed sleep assessment, including subjective and objective measurements, performed by a pediatric sleep expert (SM), may have influenced this result. Moreover, we recruited children with ADHD consecutively diagnosed in our Pediatric Department the staff of which were asked to perform a full sleep investigation, requiring a dedicated collaboration of children and parents; one may suppose that those with sleep problems and their parents

Table 4

Statistical significant results of comparison between clinical data, blood exams, cognitive and sleep parameters in groups: ADHD with the sleep disorder compared to ADHD without, and also to controls for polysomnographic parameters, values expressed by mean \pm standard deviation or total number.

	ADHD with AHI	ADHD without AHI	Controls	p values			
				1vs2, or 1vs2,3	1vs2	1vs3	in2vs3
Nepsy inhibition A time	9 \pm 2.4	7 \pm 2.6		0.026^a			
Arousal index n/h	9.39 \pm 4.2	6.24 \pm 3.2	5.95 \pm 3.01	0.016^a	<i>0.017</i>	<i>0.008</i>	0.856
AHI n/h	3.1 \pm 1.6	0.87 \pm 0.8	0.64 \pm 0.75	0.000	0.000	0.000	0.274
AHI supine n/h	3.3 \pm 2.0	0.74 \pm 0.82	0.74 \pm 0.98	0.000	0.000	0.000	0.843
AHI REM n/h	5.0 \pm 5.4	1.56 \pm 1.73	0.7 \pm 1.52	0.000	0.007^a	0.000	0.012^a
RLMI n/h	0.343 \pm 0.56	0.067 \pm 0.16	0.056 \pm 0.14	0.019^a	<i>0.053</i>	<i>0.008</i>	0.659
	ADHD with SOI	ADHD without SOI	Controls	p values			
Nepsy inhibition B time	10 \pm 1.2	7.83 \pm 2.5	N.A	0.03^a			
Time in bed mean (h)	8.5 \pm 0.3	9.52 \pm 0.7	N.A	0.010^a			
Time in bed max (h)	9.6 \pm 0.7	10.3 \pm 0.9	N.A	0.045^a			
Time in bed min (h)	6.8 \pm 1.2	8.3 \pm 0.9	N.A	0.008^a			
Latency to REM at first MSLT (min)	10.3 \pm 9	15.8 \pm 7	N.A	0.042^a			
	ADHD with PLMs	ADHD without PLMs	Controls	p values			
Number of awakenings	10.6 \pm 3.5	6.82 \pm 3.96	23.3 \pm 26.7	0.03^a	<i>0.016</i>	0.833	0.03
AHI n/h	1.9 \pm 1.7	2.02 \pm 1.7	0.64 \pm 0.75	0.002^a (0.09)	1	0.013^a (0.507)	0.001
AHI supine n/h	1.6 \pm 1.7	2.17 \pm 2.16	0.74 \pm 0.98	0.04^a	0.629	<i>0.07</i>	0.02
AHI REM n/h	3.8 \pm 6.9	3.03 \pm 3.08	0.7 \pm 1.52	0.000	0.504	0.03^a	0.000
LMI n/h	16.6 \pm 2.6	8.4 \pm 3.96	11.01 \pm 6.35	0.001	0.000	<i>0.008</i>	0.263
PLMI n/h	6.7 \pm 1.7	1.5 \pm 1.5	3 \pm 3.8	0.000	0.000	0.004^a	0.214
	ADHD with narcolepsy	ADHD without narcolepsy	Controls	p values			
Processing Speed Index	77.3 \pm 4.1	91 \pm 13.1	N.A	0.02^a			
Nepsy inhibition A time	5 \pm 3.1	7 \pm 2.6	N.A	0.03^a			
Nepsy inhibition B time	4.7 \pm 2.6	7.93 \pm 1.7	N.A	0.009^a			
MSL (min)	9.7 \pm 2.7	14.95 \pm 4.2	N.A	0.004^a (0.06)			
Number of SOREMP	3 \pm 0	0.87 \pm 1.2	N.A	0.000			
Total sleep time (min)	462.5 \pm 22.2	415.2 \pm 60.5	462.8 \pm 69.57	0.037^a	0.2	0.8	0.14
REM %	24.5 \pm 2.7	17.18 \pm 5.3	19.5 \pm 4.96	0.022^a	0.019	0.37	<i>0.000</i>
AHI n/h	1.3 \pm 1.1	2.1 \pm 1.8	0.64 \pm 0.75	0.002^a (0.076)	0.376	0.144	0.000
AHI supine n/h	1.2 \pm 1.3	2.15 \pm 2.1	0.74 \pm 0.98	0.027^a	0.374	0.442	0.008
AHI REM n/h	1.7 \pm 2.5	3.52 \pm 4.5	0.7 \pm 1.52	0.000	0.178	0.31	0.000
	ADHD with epilepsy	ADHD without epilepsy	Controls	p values			
AHI n/h	2.2 \pm 2.2	1.89 \pm 1.38	0.64 \pm 0.75	0.000	0.877	0.03^a	0.001
AHI supine n/h	1.7 \pm 1.7	2.18 \pm 2.17	0.74 \pm 0.98	0.03^a	0.681	0.083	0.02
AHI REM n/h	4.1 \pm 6.2	2.87 \pm 3.12	0.7 \pm 1.52	0.000	0.914	0.003^a	0.000

TST: total sleep time, AHI: apnea-hypopnea index; RLMI: respiratory related limbs movements; PLMI: periodic limbs movements index; min: minutes; SOREMP: Sleep Onset REM period, Nepsy: Neuropsychological battery for children; n/h: number/hour; N.S: not significant, N.A: not available. Kruskal Wallis test was used for comparisons between three groups, and Mann–Whitney test for comparisons between two groups.

^a Not significant after Holm's correction (p-value if close to 0.05 are specified). In italic the value not reaching a power level ≥ 8 at Gpower analysis.

were more prone to participate. Our findings might be also influenced by the different methodologies required to diagnose each specific sleep disorder (such as clinical history, sleep questionnaires, actigraphic recording, video-polysomnographic recording with extensive EEG channels, and a multiple sleep latency test), whereas previous studies have been focused on the analysis of a single specific sleep disorder, employing few sleep measurements.

Apart from the specific sleep phenotype recognized, and in accord with the actigraphic and PSG results, all children with ADHD slept less than the normal amount expected for their age (<9 h) and less than control children. The historical clinical investigation confirmed the long-lasting duration and chronicity of sleep disorders, which can affect vigilance, decision-making ability and memory functions [41]. The majority of children with ADHD in our sample had a history of sleep disorders, primarily represented by sleep hyperkinesia and OSA. Recent papers confirmed an association between early sleep problems, mostly regarding increased motor nocturnal activity, and irregular sleep patterns assessed by actigraphy, temperament and ADHD symptoms, in pre-school children [42,43].

We believe that our finding consolidates the idea of a key role of sleep and in particular of chronic sleep deprivation as a

predisposing background for ADHD. In all probability, the size and the reversibility of the executive dysfunctions induced by untreated chronic sleep perturbation depend on the children's developmental period in which the sleep impairment occurs as well as its duration. The significant association between sleep debt and ADHD was also confirmed by the negative correlation between the Conner's rating scale scores and total sleep time in both actigraphic recording and PSG. As expected, if the total sample of children with ADHD were to be compared to healthy children, a higher AHI was found, confirming literature data [17]. Comparing the subgroup of children with ADHD according to a specific sleep phenotype was confirmed for the subgroups of children with OSA and with epilepsy. To increase the compliance of the study, we gave healthy controls only a PSG recording. All children underwent only one attended PSG recording, not avoiding the first night effect. These are important limits of the study one should take into account.

Despite the relevant role of OSA, diagnosed in 15 children with ADHD (50% of the sample), this study reinforces the hypothesis that ADHD is likely to be strongly heterogeneous regarding pathophysiology, thus representing a syndrome and showing that different sleep disorders may affect children with ADHD [8]. Considering all sleep measures, questionnaires, history and

laboratory tests, in order of frequency children with ADHD were classified as follows: 15 children had a mild form of OSA; 10 children showed IEDs and/or nocturnal epilepsy; eight fulfilled the criteria of the PLMs phenotype, five children had a sleep onset insomnia; and finally, four children had a narcoleptic-like phenotype. The majority of them had more than one sleep disorder in comorbidity (Fig. 1, Table 1). Two subjects out of 30 could not be classified according to the aforementioned five sleep phenotypes and did not have any sleep disorders. Our data confirmed the association between ADHD and IEDs with or without nocturnal seizures. The literature on the role of IEDs in inducing reversible or irreversible damage of prefrontal cortex, and consequently high cognitive dysfunction (such as attention, learning, and working memory process), is still scarce, and guidelines about antiepileptic treatment are needed. A recent study reported a prevalence of epileptiform discharges in 32% of ADHD children, suggesting that a conventional EEG should be considered before prescribing stimulant medications [44]. A narcoleptic-like phenotype was found in four subjects. Two subjects showed a mean MSLT of 7.1 and 8.1 min; all had three SOREMPs. Since the occurrence of three SOREMPs is quite unusual – normal healthy controls at the same age had a mean sleep latency at MSLT ranging from 16.3 to 18.5 min [45] – the other two ADHD subjects with a mean latency of 10.6 and 13.2 min respectively, were also classified as a narcoleptic-like phenotype. Considering that a higher percentage of ADHD and inattentive symptoms have been found in children and adults with narcolepsy [46,47], follow-up data will clarify if they have a definitive diagnosis of central hypersomnia. At the time of the investigation, they did not report other symptoms or signs of narcolepsy type 1 or 2. Regarding prognosis, the narcoleptic phenotypes seem to have a more impaired neurocognitive profile.

Recently, it has been suggested that pragmatic trials should be performed to characterize better and treat specific ADHD sleep phenotypes. In agreement with the results of this study, a focused and tailored treatment for every patient should be prescribed, based on the underlying sleep disorder [48]. The long-term consequences of sleep problems in individuals with ADHD include obesity, poor academic performance, and disrupted parent-child interactions. Early intervention and recognition of sleep problems may be proposed as an approach to prevent these debilitating outcomes, with novel treatment approaches ranging from melatonin and light therapy to myofunctional therapy [5] to antiepileptic drugs or corticosteroids (indicated in those types characterized by sub-continuous sleep epileptiform discharges or nocturnal epilepsy). However, the long-term benefits of a specific treatment for sleep disorders in ADHD need to be proved by prospective, randomized clinical trials that are still unavailable. Serum ferritin level was below 60 µg/L in all cases, and below 20 µg/L in eight children. The role of iron deficiency in ADHD remains unclear. One MRI study reported significantly low indices of thalamic iron in ADHD versus control subjects [49]. Two trials, an open-label, and a randomized placebo-controlled study showed an improvement in ADHD symptoms with iron supplementation, in children with serum ferritin below 30 µg/L [50,51]. A recent meta-analysis demonstrated that serum ferritin levels were significantly lower in patients with ADHD compared with healthy controls [52]. The evidence-based and consensus of clinical practice guidelines for the oral iron treatment of RLS in children recommend starting treatment when the iron level is below 50 µg/L, while in adults the cut-off is higher (below 75 µg/L). However, the cut-off is still debated [53]. We suggest treating children with ADHD and low ferritin level if they had PLMS and/or RLS.

The significance of the results of the within-groups comparisons of children with ADHD and specific sleep disorders discussed below are limited by the loss of statistical significance after Holm's

correction for many of them. This is an important limit to take into account; it may be due to the low effect size and the overlap of sleep disorders in each of the subjects with ADHD. Further studies should be performed to confirm this preliminary analysis. Children with SOI were older and showed lower impulsivity. The occurrence of SOREMP at the first nap of the MSLT, together with the later bedtime habitual hours, and a shorter time in bed, may confirm that these children had a delayed sleep onset, rather than real insomnia with difficulty falling asleep. In children with the PLMs phenotype, sleep hyperkinesia remained an unspecific symptom, not associated with clear criteria for a diagnosis of pediatric restless legs syndrome, although an increased number of night awakenings may be considered a red flag. The OSA subjects showed an increase in sleep microstructure instability and a higher number of limb movements related to respiratory events. Notably, they showed better executive abilities compared to the other ADHD subjects. Except for AHI, children with IEDs did not show any red flags to suspect sleep IEDs or epilepsy. At this time, we are not able to demonstrate if a higher AHI is a predictive factor for IEDs or epilepsy, although this association between OSA and IEDs or nocturnal epilepsy has been already reported [54]. Children with the narcoleptic-like phenotype showed peculiar neuropsychological features: a lower Processing Speed Index, and a lower score at NEPSY inhibition A and B times, suggesting a sluggish cognitive speed of processing profile, together with a higher tendency to impulsivity. These neuropsychological features have never been reported in narcoleptic children [46]. Moreover, they had a higher total sleep time and REM sleep percentage compared to the other two groups, as a red flag for a narcoleptic-like phenotype.

Our study adds to evidence supporting a clear role of sleep disorders and chronic sleep deprivation in the pathogenesis of ADHD, which seems to be a syndrome with relevant cognitive differences according to sleep phenotype.

Future studies need to address some crucial questions emerging from present and past studies that confirm the model of sleep phenotypes: (1) if a particular sleep phenotype is associated with a particular daytime clinical phenotype of ADHD and is able to predict it; (2) if this sleep phenotype predicts the prognosis of the disease; (3) which period of life is more vulnerable to sleep disorder for the development of ADHD; (4) if there is a unifying and causal sleep-related marker, like chronic sleep deprivation, that, regardless of the specific sleep phenotype, is associated with ADHD, and (5) overall if the prompt treatment of sleep disorders may influence the natural course of ADHD positively.

Funding

This work was supported by a grant of the Ente Ospedaliero Cantonale (ABREOC).

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: <https://doi.org/10.1016/j.sleep.2018.08.026>.

References

- [1] Polanczyk G, de Lima MS, Horta BL, et al. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *Am J Psychiatry* 2007;164(6):942–8.
- [2] Volkow ND, Swanson JM. Clinical practice: adult attention deficit-hyperactivity disorder. *N Engl J Med* 2013;369(20):1935–44.
- [3] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.

- [4] Donfrancesco R, Miano S, Martines F, et al. Bipolar disorder co-morbidity in children with attention deficit hyperactivity disorder. *Psychiatry Res* 2011;186(2–3):333–7.
- [5] Um YH, Hong SC, Jeong JH. Sleep problems as predictors in attention-deficit hyperactivity disorder: causal mechanisms, consequences and treatment. *Clin Psychopharmacol Neurosci* 2017;15(1):9–18.
- [6] 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(9):894–908.
- [7] Lycett K, Mensah FK, Hiscock H, et al. A prospective study of sleep problems in children with ADHD. *Sleep Med* 2014;15(11):1354–61.
- [8] 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(2):147–53.
- [9] Miano S, Esposito M, Foderaro G, et al. Sleep-related disorders in children with attention-deficit hyperactivity disorder: preliminary results of a full sleep assessment study. *CNS Neurosci Ther* 2016;22(11):906–14.
- [10] Miano S, Donfrancesco R, Bruni O, et al. NREM sleep instability is reduced in children with attention-deficit/hyperactivity disorder. *Sleep* 2006;29(6):797–803.
- [11] Lecendreux M, Konofal E, Bouvard M, et al. Sleep and alertness in children with ADHD. *J Child Psychol Psychiatry* 2000;41(6):803–12.
- [12] Modestino EJ, Winchester J. A retrospective survey of childhood ADHD symptomatology among adult narcoleptics. *J Atten Disord* 2013;17(7):574–82.
- [13] Ferri R, Miano S, Bruni O, et al. NREM sleep alterations in narcolepsy/cataplexy. *Clin Neurophysiol* 2005;116(11):2675–84.
- [14] 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(3):559–70.
- [15] Coogan AN, McGowan NM. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. *Atten Defic Hyperact Disord* 2017;9(3):129–47.
- [16] Scott N, Blair PS, Emond AM, et al. Sleep patterns in children with ADHD: a population-based cohort study from birth to 11 years. *J Sleep Res* 2013 Apr;22(2):121–8.
- [17] Sedky K, Bennett DS, Carvalho KS. Attention deficit hyperactivity disorder and sleep disordered breathing in pediatric populations: a meta-analysis. *Sleep Res* 2014;18(4):349–56.
- [18] 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):1–16.
- [19] Gagliano A, Aricò I, Calarese T, et al. Restless Leg Syndrome in ADHD children: levitracetam as a reasonable therapeutic option. *Brain Dev* 2011;33(6):480–6.
- [20] Angriman M, Cortese S, Bruni O. Somatic and neuropsychiatric comorbidities in pediatric restless legs syndrome: a systematic review of the literature. *Sleep Med Rev* 2017;34:34–45.
- [21] 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(9):805–10.
- [22] Silvestri R, Gagliano A, Calarese T, et al. Ictal and interictal EEG abnormalities in ADHD children recorded overnight by video-polysomnography. *Epilepsy Res* 2007;75(2–3):130–7.
- [23] Reilly CJ. Attention deficit hyperactivity disorder (ADHD) in childhood epilepsy. *Res Dev Disabil* 2011;32(3):883–93.
- [24] Millichap JG, Millichap JJ, Stack CV. Utility of the electroencephalogram in attention deficit hyperactivity disorder. *Clin EEG Neurosci* 2011;42(3):180–4.
- [25] Rheims S, Herbillon V, Villeneuve N, et al. Investigators of the Paediatric Epilepsy REsearch NETwork (PERENE). ADHD in childhood epilepsy: clinical determinants of severity and of the response to methylphenidate. *Epilepsia* 2016;57(7):1069–77.
- [26] Bruni O, Novelli L, Luchetti A, et al. Reduced NREM sleep instability in benign childhood epilepsy with centro-temporal spikes. *Clin Neurophysiol* 2010;121(5):665–71.
- [27] 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(7):980–8.
- [28] Conners CK, Sitarenios G, Parker JD, et al. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998;26(4):257–68.
- [29] Wechsler D. Wechsler intelligence scale for children-IV. A cura di Arturo Orsini, Lina Pezzuti, Laura Picone. Firenze: Giunti OS; 2012.
- [30] Korkman M, Kirk U, Kemp S. A developmental neuropsychological assessment. San Antonio, TX; 1998, (Edizione italiana: Urgesi C, Campanella F, Fabbro F. Giunti OS; 2011.
- [31] 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;23(15):1043–51.
- [32] 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(6):1355–561.
- [33] 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(4):455–8.
- [34] Meltzer LJ, Walsh CM, Traylor J, et al. Direct comparison of two new actigraphs and polysomnography in children and adolescents. *Sleep* 2012;35(1):159–66.
- [35] Weiss AR, Johnson NL, Berger NA, et al. Validity of activity-based devices to estimate sleep. *J Clin Sleep Med* 2010;6(4):336–42.
- [36] Iber C, Ancoli-Israel S, Chesson AL, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
- [37] International Federation of Societies for Clinical Neurophysiology. A glossary of terms most commonly used by clinical electroencephalographers. *Electroencephalogr Clin Neurophysiol* 1974;37:538–44.
- [38] Aurora RN, Lamm CI, Zak RS, et al. Practice parameters for the non-respiratory indications for polysomnography and multiple sleep latency testing for children. *Sleep* 2012;35(11):1467–73.
- [39] American Academy of Sleep Medicine. International classification of sleep disorders—ICSD. 3rd ed. 2015. Westchester, IL.
- [40] Picchietti DL, Bruni O, de Weerd A, et al. International restless legs syndrome study group (IRLSSG). Pediatric restless legs syndrome diagnostic criteria: an update by the international restless legs syndrome study group. *Sleep Med* 2013;14(12):1253–9.
- [41] Nobili L, De Gennaro L, Proserpio P, et al. Local aspects of sleep: observations from intracerebral recordings in humans. *Prog Brain Res* 2012;199:219–32.
- [42] Melegari MG, Vittori E, Mallia L, et al. Actigraphic sleep pattern of pre-schoolers with ADHD. *J Atten Disord* 2016;4. doi: 1087054716672336.
- [43] Bundgaard AF, Asmussen J, Pedersen NS, et al. Disturbed sleep and activity in toddlers with early signs of attention deficit hyperactivity disorder (ADHD). *J Sleep Res* 2018;12. <https://doi.org/10.1111/jsr.12686>.
- [44] Miano S, Tabarrini A, Vitelli O, et al. The cooccurrence of interictal discharges and seizures in pediatric sleep-disordered breathing. *Epilepsy Behav* 2013;29(3):508–12.
- [45] Carskadon MA. The second decade. In: Guilleminault C, editor. *Sleeping and waking disorders: indications and techniques*. Menlo Park: Addison Wesley; 1982. p. 99–125.
- [46] Posar A, Pizzi F, Parmeggiani A, et al. Neuropsychological findings in childhood narcolepsy. *J Child Neurol* 2014;29(10):1370–6.
- [47] Lecendreux M, Lavault S, Lopez R, et al. Attention-deficit/hyperactivity disorder (ADHD) symptoms in pediatric narcolepsy: a cross-sectional study. *Sleep* 2015;38(8):1285–95.
- [48] Cortese S, Angriman M. Treatment of sleep disorders in youth with ADHD: what is the evidence from randomised controlled trials and how should the field move forward? *Expert Rev Neurother* 2017;17(6):525–7.
- [49] Cortese S, Azoulay R, Castellanos FX, et al. Brain iron levels in attention-deficit/hyperactivity disorder: a pilot MRI study. *World J Biol Psychiatry* 2012;13(3):223–31.
- [50] Konofal E, Lecendreux M, Deron J, et al. Effects of iron supplementation on attention deficit hyperactivity disorder in children. *Pediatr Neurol* 2008;38(1):20–6.
- [51] Sever Y, Ashkenazi A, Tyano S, et al. Iron treatment in children with attention deficit hyperactivity disorder. A preliminary report. *Neuropsychobiology* 1997;35(4):178–80.
- [52] Wang Y, Huang L, Zhang L, et al. Iron status in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *PLoS One* 2017;12(1):e0169145.
- [53] Allen RP, Picchietti DL, Auerbach M, et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. *Sleep Med* 2018;41:27–44.
- [54] Swatzyna RJ, Tarnow JD, Roark A, et al. The utility of EEG in attention deficit hyperactivity disorder: a replication study. *Clin EEG Neurosci* 2017;48(4):243–5.