Original Article

Subjective and objective assessments of sleep problems in children with attention deficit/ hyperactivity disorder and the effects of methylphenidate treatment

Wei-Chih Chin [a,f], Yu-Shu Huang [a,b,f,*], Ya-Hsin Chou [c,f], Chih-Huan Wang [d], Kuang-Tai Chen [c,f], Jen Fu Hsu [e,f], Shih-Chieh Hsu [c,f]

[a] Division of Pediatric Psychiatry, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[b] Craniofacial Research Center and Sleep Center, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[c] Department of Psychiatry, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[d] Department of Psychology, Zhejiang Normal University, Zhejiang, China
[e] Division of Pediatric Neonatology, Department of Pediatrics, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
[f] College of Medicine, Chang Gung University, Taoyuan, Taiwan

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ABSTRACT

Background: to investigate the sleep problems in children with different ADHD presentations and effects of methylphenidate (MPH) on the sleep problems of children with ADHD by both subjective and objective measurements.

Methods: 71 children with ADHD and 30 controls were included. 35 had ADHD with predominantly inattentive presentation (ADHD-I) and 36 with predominantly hyperactive/ impulsive or combined presentation (ADHD-C). We used the pediatric sleep questionnaire (PSQ) and a nocturnal polysomnography (PSG) to assess the sleep problems in children with ADHD before and 6 months after being treated with methylphenidate (0.3–0.7 mg/kg/ dose).

Results: PSG showed significantly higher apnea-hypopnea index and hypopnea counts, and lower slow-wave sleep percentage in children with ADHD. The results of PSQ reported by parents showed significantly higher rates of delay initiation of sleep, sleep onset latency, sleep fragment, daytime sleepiness, enuresis, bruxism, nightmares, periodic limb movement disorder (PLMD), and snoring in children with ADHD compared to normal controls. Comparisons of ADHD presentations revealed no significant difference between ADHD-I and ADHD-C by either PSG or PSQ measurements. After 6-month MPH treatment, the PSG showed significantly increased total sleep time and reduced periodic limb movement index (PLMI). The PSQ indicated significant reduction in bruxism and snoring in ADHD-I, as well as nightmares in ADHD-C, and both subgroups showed significant reduction in PLMD.

* Corresponding author. Department of Child Psychiatry and Sleep Center, Chang Gung Memorial Hospital at Linkou, 5, Fusing St., Gueishan, Taoyuan 333, Taiwan.
   E-mail address: yushuhuang1212@gmail.com (Y.-S. Huang).

Conclusion: subjective and objective approaches produced inconsistent findings regarding the sleep problems in children with ADHD. Besides, MPH didn't worsen the sleep problems in children with ADHD.

At a glance of commentary

Scientific background of the subject

Although children with ADHD have more sleep problems than normally developed children, previous studies of their sleep problems showed inconsistent findings by subjective and objective measure. Stimulant treatment for ADHD such as Methylphenidate may further worsen sleep problems of children with ADHD.

What this study adds to the field

Our results confirmed that there is inconsistency between subjective and objective measurements for sleep problems in children with ADHD. Besides, we also found that MPH didn't worsen their sleep problems. Other sleep disorders, such as obstructive sleep apnea, should be screened and evaluated in children with ADHD.

Attention deficit/hyperactivity disorder (ADHD) is one of the most common behavioral and developmental disorders in childhood, with the prevalence ranging from 5.9 to 7.1% [1]. An increasing number of studies have focused on the sleep structure of children with ADHD and its comorbidity with sleep problems. Children with ADHD or ADHD symptoms were found to have more sleep problems, including insomnia, sleep terrors, nightmares, bruxism, and snoring [2–4]. However, results have always been inconsistent in sleep studies of children with ADHD when comparing both subjective and objective measures [5]. Studies using subjective parent reports of children with ADHD revealed delayed sleep onset [6], shorter [7] or longer sleep duration [8], and more frequent night awakenings [7]. Only some of these findings had been validated by objective measurements, such as polysomnography [9–12].

Besides, in the past, studies that investigate sleep problems across different ADHD presentations also produced inconsistent results. Some concluded that children with ADHD-I had greater daytime sleepiness [13], while others showed that those with ADHD-C had poorer sleep efficiency and more nocturnal movement [13,14]. LeBourgeois et al. [4] concluded that only the ADHD-hyperactive/impulsive subtype was associated with an increased likelihood of chronic snoring and that there were no other significant differences in sleep quality across ADHD subtypes.

CNS stimulant is known as one of the most effective treatments for ADHD [15], but various side effects on sleep have been reported. Methylphenidate (MPH), approved by the Food and Drug Administration (FDA) to treat children with ADHD, is known to cause some sleep problems in school-aged children (e.g., reduced total sleep time, increased sleep-onset latency and sleep disturbances) when prescribed at standard doses

(0.3–0.7 mg/kg/dose) [16–18]. Although administration of MPH to children with ADHD has been proven to have significant effects on their sleep problems, literature reviews of these adverse responses showed a great deal of variability [19–23]. In addition, most therapeutic effects or side effects were based either on parent observations around bedtime or reliable and valid survey of teachers or parents, and not based on objective measurements such as a night polysomnography [24] or actigraphic recording [18]. The correlations between different presentations of measurements continue to be suboptimal.

The present study aimed to evaluate the sleep problems of children with ADHD and variation across different ADHD presentations, by both polysomnography and subjective observations from parents. We explored the impacts of regular use of MPH for 6 months on children with ADHD and compared the impact of MPH across different presentations of ADHD.

Material and methods

Patient population

Children aged 6–12 years old were prospectively recruited from the Child Psychiatry Clinic of a university medical center in Taipei, Taiwan. Inclusion criteria include: (1) ADHD diagnoses based on DSM-5 criteria [25], (2) having a full IQ of more than 70 on the WISC-III [26] or WISC-IV [27], (3) no ADHD medications in the past 6 months before the enrollment, (4) staying on Methylphenidate treatment for at least 6 months after the enrollment. Seventy-one children were enrolled and all participants underwent an initial screening by two experienced psychiatrists who utilized the standard structured interview according to the schedule for Affective Disorder and Schizophrenia for School-Age Children, Adolescent Chinese version (K-SADS-E) [28]. ADHD presentations were determined according to DSM-5 criteria. The results of the screening affirmed the clinical diagnosis and excluded children who had co-morbid pervasive developmental disorder, a history of bipolar disorder, psychosis, severe anxiety disorder, substance abuse history, or mental retardation. We also excluded children with central nervous system disorders, such as seizure, cerebral palsy and brain injury, or other physical diseases after detailed physical and neurological examinations performed by a pediatrician and neurologist. This study was approved by the institutional review board of Chang Gung Memorial Hospital. Parental informed consent and child assent in the presence of a parent were obtained.

30 age-matched healthy children without ADHD or any psychiatric disorder history were recruited from the surrounding schools in the community. These children were assessed at the Child Developmental Evaluation Center at the same medical center by the same psychiatrists and pediatricians as the ADHD group. All the physical, neurological and mental evaluations were completed. The exclusion criteria of

the control group were the same as those in the ADHD group. All the children in the ADHD and the control group completed the same tests, and their parents filled out the same questionnaires.

Assessment instruments

Questionnaires
Questionnaires were completed by parents at the beginning of the study and at 6-month medication follow-up.

1. Child Behavior Checklist (CBCL) [29] in Chinese version (for age 4–16 years old) was used for the evaluation of child's social and behavioral competence.
2. Pediatric Sleep Questionnaire (PSQ) [30] (in Chinese) was used for the evaluation of childhood sleep-related breathing disorder, snoring, excessive daytime sleepiness, periodic limb movement and inattentive/hyperactive behavior.
3. ADHD Rating Scale IV (ADHD-RS IV) [31] is a reliable and easy-to-administer instrument for facilitating the diagnosis of ADHD for children and adolescents aged 5–17 years old because its items correlate to the DSM diagnostic criteria. It also assists us to evaluate the symptom severity by scoring the frequency of inattention and hyperactivity. Thus, we can use it to assess the medication response.

Intelligence tests
WISC-III and IV intelligence scale for children [26,27] were used for the standardized intelligence evaluations of children and adolescents aged 6–16 years old. They were performed by experienced pediatric psychologists in our study.

Polysomnographic measures (PSG)
The following variables were monitored: EEG (4 leads), eye movement chin and leg EMG, ECG (one lead), body-position. The respiration was recorded with nasal pressure transducer, mouth thermo-couple, chest and abdominal inductive plethysmography bands, neck microphone, diaphragmatic-intercostal muscle EMGs, pulse oximetry from which both oxygen saturation (SaO2) and finger-plethysmography were derived, data were collected on a 32 channel recording system,

[Embla N7000 -Covidien, Ontario, Canada], with continuous video monitoring. A family member was present during the nocturnal recording. Sleep and wake were scored using international criteria of American Academy of Sleep Medicine [2014] with identification of stages N 3. EEG arousal was defined according to the American Sleep Disorders Association [32]. Abnormal breathing events during sleep were analyzed using the definitions of apnea and hypopnea as outlined by the American Academy of Sleep Medicine [2014], and the definition of flow limitation with abnormal increase in respiratory effort leading to arousals as outlined by Guille-minault et al. [33]. The AHI and the respiratory disturbance index (RDI: number of apneas, hypopneas, and respiratory effort-related arousals per hour of sleep) were calculated. PSG scoring was performed by a technician blind to the clinical status of the child.

Drug administration

After the baseline assessments, children with ADHD received 0.3–0.7 mg/kg/dose short-acting MPH IR prescribed once or twice (morning and noon) per day over a 6-month period. We didn't have a fixed dosage or dosing schedule for all participants, but followed certain rules. The frequency and dosage of the MPH treatment depended on children with ADHD's clinical condition, including the response to medication, symptom severity, and learning schedule (once per day for children age 6–8 with half day class or twice per day for children age 8–12 with whole day class). This information was obtained by interview with the children and their family members, as well as feedback from school teachers. The dosage began at 5 mg in the morning before children went to school under parents' supervision, and was titrated gradually to at least 0.3 mg/kg/dose in the first month. If the children had whole day class, the noon dose was taken around lunch time at school under their teachers' supervision. Further titration to higher dosage would be performed if the response to medication is inadequate, based on the psychiatrists' interview and clinical judgment, up to 0.7 mg/kg/dose.

At 6-month follow-up, variables obtained at the beginning of this study were collected again, including the CBCL-parent, ADHD-RS IV, PSQ-parent, and nocturnal PSG.

Table 1 Demographic and comorbidity characteristics of prospectively recruited ADHD children (n = 71) and normal controls (n = 30).

Variables	ADHD subgroups			ADHD total (n = 71)	Control group (n = 30)	p value
	ADHD-I (n = 35)	ADHD-C (n = 36)	p value			
Age (years), mean (SD)	9.09 (1.72)	8.58 (1.98)	0.794	8.83 (1.86)	8.48 (2.36)	0.434
Gender, n [male (%)/female (%)]	23 (66)/12 (34)	31 (86)/5 (14)	0.710	54 (76)/17 (24)	15 (50)/15 (50)	0.063
Body mass index (BMI) [mean (SD)]	18.55 (3.54)	19.06 (4.23)	0.892	18.82 (3.89)	18.05 (3.57)	0.673
Full scale IQ [mean (SD)]	96.14 (15.29)	90.78 (11.94)	0.287	93.73 (13.98)	105.00 (14.96)	0.360
Comorbidity						
Learning disorder, n (%)	6 (17.1)	6 (16.7)	0.077	12 (16.9)	0 (0)	0.025
Tic disorder, n (%)	0 (0)	4 (11.1)	0.423	4 (5.6)	0 (0)	0.193
Conduct disorder, n (%)	0 (0)	1 (2.8)		1 (1.4)	0 (0)	0.685
Oppositional defiant disorder, n (%)	0 (0)	8 (22.2)	0.160	8 (11.3)	0 (0)	<0.001

Abbreviations: ADHD-I: ADHD with predominantly inattentive presentation; ADHD-C: ADHD with predominantly hyperactive/impulsive or combined presentation; SD: standard deviation.

Statistical analysis

The demographic distribution of participants and comorbidity with other disorders were presented as number and frequency across different presentations and groups. The PSG and questionnaire data were presented as mean and standard deviation (SD). We used analysis of variance (ANOVA), chi-square and t-test for group comparisons. The Fisher's exact test was used when small groups were compared. Paired t-test was used for pre-post treatment within-group data comparisons. A p-value of less than 0.05 was considered significant. All statistics were performed using the commercially available software SPSS 13.0 for Windows (SPSS®, Chicago, IL).

Results

Demographic data

Demographic data is showed in Table 1. A total of 101 children, including 71 subjects with ADHD and 30 normal controls, were prospectively recruited. All evaluations, questionnaires and neuropsychometric assessments were completed. In the ADHD group, 35 children were ADHD with predominantly inattentive presentation (ADHD-I) and 36 children were ADHD with predominantly hyperactive/impulsive or combined presentation (ADHD-C). Except for the relatively higher ratio of boys-to-girls in the ADHD group than the control group (3:1 vs. 1:1, $p = .063$),

there were no significant differences between these two groups in terms of age, body mass index (BMI) and IQ. However, 25 (35.2%) of the ADHD group were found to have psychiatric traits or disorders. While there was no statistically significant difference between the ADHD-I and ADHD-C groups in terms of comorbidity, only the ADHD-C group had children with comorbid mental disorders including tic disorder, conduct disorder and oppositional defiant disorder. Both groups have an equal number of children with learning disorder.

Comparison of PSG data before and after the MPH treatment

Using the Rechtschaffen and Kales scoring criteria [34], comparison between ADHD and control group showed no significant differences in total sleep time (TST), sleep efficiency, sleep latency, percentages of stage 1, 2 and REM sleep at the beginning of the study. Significant higher AHI ($p = .002$), hypopnea counts ($p = .003$), and a significantly lower percentage of slow wave sleep (SWS) ($p = .006$) were found in the ADHD group. For the ADHD-C group and the ADHD-I group, there were no significant differences in all these parameters at the beginning of the study.

In the total ADHD group, the PSG data showed significantly increased TST ($p = .005$) and decreased periodic limb movement index (PLMI) ($p = .031$) after 6-month MPH treatment. Significant increases in AHI ($p = .012$) and hypopnea counts ($p = .008$) were also noted. There were no significant differences in the other parameters of the PSG (Table 2).

Table 2 The polysomnographic (PSG) variables before and after 6-months treatment of MPH in ADHD children.

Variables	ADHD-I (n = 35)			ADHD-C (n = 36)			Total (n = 71)		
	Before treatment	After treatment	p value	Before treatment	After treatment	p value	Before treatment	After treatment	p value
AHI (apnea-hypopnea index) (/h)	1.14 (1.37)	2.09 (2.81)	0.098	1.27 (1.22)	1.94 (2.91)	0.224	1.20 (1.29)	1.98 (2.78)	0.012[a]
DI (desaturation index) (/h)	0.17 (0.26)	0.30 (0.60)	0.150	0.39 (0.85)	0.30 (0.45)	0.503	0.28 (0.64)	0.36 (0.90)	0.112
Apnea index (/h), [mean (SD)]	0.54 (1.05)	0.37 (0.69)	0.516	0.34 (0.67)	0.21 (0.41)	0.187	0.43 (0.87)	0.28 (0.55)	0.140
Awake [%, mean (SD)]	6.90 (7.82)	7.77 (9.54)	0.102	10.32 (10.24)	8.97 (12.89)	0.351	8.63 (9.23)	8.11 (11.01)	0.058
Rapid eye movement [%, mean (SD)]	12.01 (4.87)	12.56 (5.54)	0.109	12.16 (4.22)	13.60 (5.14)	0.618	11.91 (4.72)	13.34 (5.03)	0.138
Stage 1 [%, mean (SD)]	8.76 (4.76)	6.87 (5.40)	0.100	10.58 (9.34)	9.14 (5.68)	0.727	9.56 (7.51)	7.98 (5.48)	0.366
Stage 2 [%, mean (SD)]	40.41 (12.76)	40.89 (9.92)	0.401	37.68 (11.53)	39.43 (13.08)	0.438	39.03 (12.15)	40.48 (11.44)	0.485
SWS (slow wave sleep) [%, mean (SD)]	29.45 (11.23)	31.80 (12.63)	0.928	28.19 (7.13)	30.36 (9.54)	0.306	27.50 (8.68)	30.78 (10.85)	0.480
TST (total sleep time) [min, mean (SD)]	380.15 (32.42)	386.93 (42.59)	0.158	363.01 (42.44)	389.38 (24.30)	0.027[a]	371.46 (38.54)	388.80 (33.63)	0.005[a]
Sleep Efficiency (SE) [%, mean (SD)]	88.65 (8.57)	89.92 (10.67)	0.617	84.74 (10.91)	89.39 (7.12)	0.240	86.67 (9.95)	89.93 (8.75)	0.220
Sleep latency [min, mean (SD)]	17.91 (11.97)	13.93 (12.93)	0.402	21.15 (15.67)	16.91 (14.63)	0.479	19.24 (14.16)	15.26 (13.62)	0.300
Mean SaO$_2$	96.89 (1.09)	97.19 (1.40)	0.253	96.72 (1.41)	96.89 (1.25)	0.433	96.80 (1.26)	96.96 (1.42)	0.252
Periodic limb movement index [mean (SD)]	0.65 (1.34)	0.63 (1.31)	0.731	1.00 (2.66)	0.56 (1.23)	0.896	0.83 (2.10)	0.59 (1.27)	0.031[a]
Hypopnea count	3.37 (3.02)	7.53 (11.97)	0.130	5.15 (5.34)	7.03 (7.48)	0.443	4.32 (4.42)	7.30 (9.70)	0.008[a]

Abbreviations: DI (desaturation index): number of desaturation of 4% or more/hour of sleep; PSG: polysomnography; MPH: methylphenidate; ADHD-I: ADHD with predominantly inattentive presentation; ADHD-C: ADHD with predominantly hyperactive/impulsive or combined presentation.
[a] Indicate significant difference when compared with base-line pre-treatment data, with a p value of less than .05.

We also noted significantly increased total sleep time ($p = .027$) in the ADHD-C group after MPH treatment.

Comparison of PSQ data before and after the MPH treatment

Children with ADHD were found to have significantly higher rate of delay initiation of sleep ($p = .013$), sleep onset latency ($p = .021$), sleep fragment ($p = .001$), daytime sleepiness ($p = .038$), enuresis ($p = .047$), bruxism ($p = .001$), nightmare ($p = .003$), periodic limb movement disorder (PLMD) ($p = .029$), and snoring ($p = .004$) than normal controls at the beginning of the study. When ADHD-C was compared with ADHD-I, there were no significant differences at the beginning of the study.

In children with ADHD, comparisons of subjective parent report (i.e., results from the PSQ) before and after the 6-month MPH treatment are presented in Table 3. We found significantly decreased rates of PLMD ($p = .029$) and sleep onset latency ($p = .021$), although the percentage of participants with delay initiation of sleep was not significantly different. However, when we analyzed the treatment effects across different ADHD subgroups, there were significantly lower rates of bruxism ($p = .022$) and snoring ($p = .046$) in the ADHD-I group, and significantly lower rates of nightmares ($p = .021$) in the ADHD-C group. Both the ADHD-I and ADHD-C had significant reduction in PLMD ($p = .007$ and $p = .020$ respectively) after the treatment.

Comparison of CBCL and ADHD-RS score before and after the MPH treatment

A comparison of behavior measured by CBCL indicated a significant difference between the control and ADHD groups in most subscales ($p = .043$ in somatic complaint and $p < .001$ in others subscales) except the obsession/compulsion subscale ($p = .082$) and the anxiety subscale ($p = .100$), at the beginning of the study. Comparing different presentations of ADHD at the beginning of the study, there were significant elevations in the depression subscale ($p < .001$), aggressive behavior ($p < .001$), and conduct problems ($p = .015$) in the ADHD-C group, compared to the ADHD-I group. At the beginning of the study, there were significant difference between the ADHD group and the control group in the ADHD-RS scores ($p < .001$), but no significant differences between the ADHD-I group and the ADHD-C group in the ADHD-RS scores.

When we compared the pre- and post-treatment CBCL scores by paired sample t-test (Table 4), there were significant decreases in externalizing problems ($p = .022$), anxiety ($p = .033$), obsession ($p = .016$) and aggressive behavior ($p = .027$). Significant reductions in ADHD-RS total score ($p < .001$), as well as inattention and hyperactivity subscale scores ($p = .014$ and $.005$ respectively) were found after 6 months of treatment with MPH.

Discussion

Subjective evaluations (e.g., sleep questionnaires) and objective standardized assessments (e.g., PSG or actigraphy) of sleep problems in children with ADHD have yielded inconsistent results in the past [9,12,35]. In this study, subjective parent reports showed significantly greater sleep disturbances in children with ADHD compared to healthy controls.

Table 3 The pediatric sleep questionnaire (PSQ) variables before and after 6-months treatment of MPH in ADHD children.

Variables	ADHD-I (n = 35)			ADHD-C (n = 36)			Total (n = 71)		
	Before treatment	After treatment	p value	Before treatment	After treatment	p value	Before treatment	After treatment	p value
Delay initiation of sleep, n (%)	14 (40)	14 (40)	0.985	11 (30.6)	8 (22.2)	0.542	25 (35.2)	22 (31.0)	0.592
Sleep onset latency, min [mean (SD)]	20.76 (19.89)	15.82 (13.29)	0.304	28.33 (20.88)	19.18 (15.69)	0.059	24.22 (20.48)	17.5 (13.8)	0.021[a]
Sleep fragment, n (%)	1 (2.9)	0 (0)	0.055	4 (11.1)	3 (8.3)	0.661	5 (7.0)	3 (4.2)	0.050
Total sleep time in weekday, h [mean (SD)]	8.55 (0.80)	8.59 (0.98)	0.668	8.80 (0.82)	8.64 (0.77)	0.396	8.68 (0.81)	8.61 (0.84)	0.516
Total sleep time in weekend, h [mean (SD)]	9.74 (1.27)	9.70 (1.01)	0.898	9.62 (1.04)	9.78 (1.32)	0.570	9.68 (1.15)	9.75 (1.19)	0.722
Daytime sleepiness, n (%)	6 (17.1)	4 (11.43)	0.413	6 (16.7)	4 (11.11)	0.552	12 (16.9)	8 (11.3)	0.152
Enuresis, n (%)	7 (20)	4 (11.43)	0.198	9 (25)	9 (25.0)	0.821	16 (22.5)	13 (18.3)	0.325
Bruxism, n (%)	17 (48.6)	10 (28.57)	0.022[a]	13 (36.1)	15 (41.67)	0.621	30 (42.3)	25 (35.2)	0.454
Sleep walking, n (%)	4 (11.4)	3 (8.57)	0.468	2 (5.6)	3 (8.3)	0.576	6 (8.4)	6 (8.5)	0.912
Nightmare, n (%)	7 (20)	7 (20)	0.914	10 (27.8)	5 (13.89)	0.021[a]	17 (23.9)	12 (16.9)	0.134
Obstructive sleep apnea, n (%)	2 (5.7)	1 (2.86)	0.357	1 (2.8)	2 (5.56)	0.236	3 (4.2)	3 (4.2)	0.998
Periodic limb movement disorder, n (%)	10 (28.6)	1 (2.86)	0.007[a]	8 (22.2)	1 (2.78)	0.020[a]	18 (25.4)	2 (2.8)	0.029[a]
Snoring, n (%)	12 (34.3)	9 (25.71)	0.046[a]	14 (38.9)	16 (44.4)	0.640	26 (36.6)	25 (35.2)	0.745

Delay initiation of sleep is sleep onset latency more than 30 mins.
Abbreviations: PSG: polysomnography; ADHD-I: ADHD with predominantly inattentive presentation; ADHD-C: ADHD with predominantly hyperactive/impulsive or combined presentation; MPH: methylphenidate; SD: standard deviation.
[a] Indicate significant difference when compared with base-line pre-treatment data, with a p value of less than .05.

Table 4 CBCL andADHD-RS variables before and after 6-months treatment of MPH in ADHD children.

Variables	ADHD (n = 71)		
	Before treatment	After treatment	p value
Internalizing problems	60.40 (10.61)	58.71 (11.88)	0.114
Externalizing problems	63.66 (9.95)	61.44 (10.62)	0.022[a]
Anxiety	57.79 (10.52)	54.89 (10.97)	0.033[a]
Depression	60.80 (11.10)	59.51 (13.14)	0.315
Obsession/compulsion	60.46 (10.58)	57.80 (11.19)	0.016[a]
Somatic complaints	55.69 (10.77)	54.65 (13.20)	0.325
Social withdrawal	59.18 (12.32)	58.80 (13.40)	0.526
Inattention/hyperactivity	64.69 (11.73)	63.13 (10.93)	0.183
Aggressive behavior	62.41 (11.35)	60.11 (11.43)	0.027[a]
Conduct problem	61.78 (10.49)	59.67 (12.36)	0.113
ADHD-RS total score [mean (SD)]	32.46 (6.09)	26.19 (7.50)	<0.001[a]
ADHD-RS inatt. subscore [mean (SD)]	18.27 (3.41)	16.27 (6.34)	0.014[a]
ADHD-RS hyper. subscore [mean (SD)]	14.18 (4.14)	12.03 (6.76)	0.005[a]

Abbreviations: PSG: polysomnography; ADHD-I: ADHD with predominantly inattentive presentation; ADHD-C: ADHD with predominantly hyperactive/impulsive or combined presentation; MPH: methylphenidate; ADHD RS: ADHD rating scales; SD: standard deviation.
The ADHD-RS score: higher scores indicate greater severity in ADHD, (score > 25 is suggestive of ADHD in boys and >22 in girls).
[a] Indicate significant difference when compared with base-line pre-treatment data, with a p value of less than .05.

However, objective PSG measurements in our study found only a fraction of these sleep problems, which is consistent with previous studies [2,9,35].

However, a meta-analysis showed that children with ADHD were significantly more impaired than controls in most of the subjective sleep parameters [9] and our study found less sleep disturbances via subjective measurements than these previous studies. Our PSG results also did not support previous findings that showed significantly different sleep—architecture parameters between children with ADHD and controls.

These differences can be partially explained by the confounding factors that we have attempted to control. Although psychiatric comorbidities were common in children with ADHD, we controlled it as possible and excluded children with severe psychiatric disorders and neurological diseases. We also enrolled only drug naïve patients to avoid the impact of previous medication status. Some studies did not exclude children with ADHD who had severe comorbid psychiatric disorders, which might account for some of the sleep disturbances [4,12]. Other studies did not exclude or control for the medication status of the children [9], and pre-existing pharmacologic treatments might affect children's sleep and alertness. Further investigation of the impact of various confounding factors may be necessary.

Besides, our PSG results showed decreased mean PLMI after 6 months of MPH treatment in children with ADHD. Our PSQ results of children with ADHD also showed increased PLMD symptom at baseline comparing with the control group, and it decreased after 6 months of MPH treatment. Because

MPH increases the levels of <u>dopamine</u> and <u>norepinephrine</u> in the brain, our findings could support the hypothesis of dopaminergic dysfunction being a common factor for both ADHD and PLMD [36]. However, no randomized double-blind trials assessing the potential effectiveness of the dopaminergic agents for children with both ADHD and PLMD have been published yet.

In contrast to previous studies [12—14], our study demonstrated no significant differences between the ADHD-I and ADHD-C groups across all of the sleep parameters at baseline. However, we later noted significant differences in their responses to the MPH treatment (Tables 2 and 3). After 6-month MPH treatment, PSG showed significant increased total sleep time in the ADHD-C group, but no significant change in the ADHD-I group. PSQ showed significantly less bruxism and snoring in the ADHD-I group, and significantly less nightmares in the ADHD-C group. Further meta-analysis of subjective and objective studies is required before a consensus can be reached about this issue.

It has been suggested that stimulant treatments of ADHD would lead to sleep disturbances, but mixed or conflicting results were found [16—23,37,38]. To our knowledge, our study is the first to have used a longitudinal, prospective follow-up design, and to have assessed for medication effects by objective PSG measurements. Our findings of post-treatment PSG data were different from other studies, showing MPH didn't aggravate in most sleep problems in children with ADHD. We found significantly increased total sleep time and significantly decreased PLMI after MPH treatment. In our study, the second MPH dose was given around the lunch time. This dose schedule could avoid the direct "stimulant effect" on night time sleep. Besides, it is important to note that some studies have previously demonstrated no change in sleep quantity [38] and even increased sleep efficiency after MPH use [39].

Subjective parents also reported shortened sleep latency after MPH treatment by PSQ, compared to baseline (i.e., without medication). Our result of reduced PLMD, snoring, nightmares, and bruxism after 6 months of MPH treatment was in line with the findings from Kooij et al. [39], which concluded that stimulant medications could improve subjective sleep quality in adults with ADHD. Sleep quality was previously found to correspond to the severity of ADHD symptoms during the day [19,39]. Thus, we may expect parallel improvements in both daytime ADHD symptoms and night time sleep problems after MPH treatment.

Significant increased AHI and hypopnea counts were noted after MPH treatment. We found that children with ADHD who have high AHI of more than 5 events per hour before MPH treatment continued to have high AHI after treatment. In fact, their AHI severity increased, which might explain our finding of increased AHI and hypopnea counts. These children did not receive treatments for their high AHI during the 6-month period, which could account for the later increased AHI and hypopnea counts after the MPH treatment. These children were diagnosed with Obstructive Sleep Apnea after further follow-up and specific interventions were indicated. While MPH treatment may improve certain aspects of sleep in children with ADHD, evaluation of other sleep disorders should be performed before the stimulant treatment [40].

There are some limitations in this study. First, we performed PSG for only one night at baseline and once again after 6 months of MPH treatment, instead of two consecutive nights at each time point. There might have been variability in measurements from night to night. Second, although we tried to control comorbidities and excluded severe psychiatric disorders and neurological diseases, we still included ADHD children with other psychiatric disorders such as Tourette's disorder, oppositional defiant disorder and conduct disorder. Patients with these psychiatric comorbidities also can have sleep disturbances.

Third, we didn't track the compliance of children with ADHD. It was difficult to determine their compliance because we could not check the MPH blood level. However, we did find significantly decreased ADHD-RS and improvement in some CBCL subscales after 6 months of treatment, which might relate to MPH use. Besides, we asked parents and teachers of children with ADHD to supervise the MPH use during the 6-month period. Fourth, the dosage and frequency of the MPH use in our study were not fixed, and MPH was prescribed according to the response of children with ADHD and clinical judgment. The guideline of Wolraich et al. [41] suggested MPH prescription should be prescribed the low dosage in naïve patients, and base on the need of different individuals. Thus, optimizing the dosage and dosing schedule for individual difference is necessary and our study can reveal the actual clinical condition of the MPH use.

Fifth, Restless leg syndrome (RLS) is not evaluated in our study. We only evaluated PLM by PSG because PSG is more objective and reliable and RLS is highly correlated with PLM in children. We checked CBC/DC, Fe and ferritin if the patient had the diagnosis of PLMD (PLMI>5/hr). Two patients were noted to have anemia and lower Fe level, and treated with Fe supplement. We could not find correlation between ferritin level and ADHD because of the small sample size.

Though with limitations, this study is the first prospective study investigating the medication effect on drug naïve children with ADHD after 6-month follow-up, assessed by both PSG and PSQ. More future prospective studies are needed to further clarify the long-term medication effect on children with ADHD and their sleep problems.

Conclusion

Our results showed that MPH didn't worsen the sleep problems of children with ADHD. Besides, after MPH treatment, PSG showed significantly increased TST and decreased PLMI, while PSQ showed decreased rates of PLMD and time of sleep onset latency. Significant increases in AHI and hypopnea counts were also revealed by PSG. Thus, other sleep disorders, such as obstructive sleep apnea, should be screened and evaluated in children with ADHD.

Conflicts of interest

The authors declare that they have no competing interests.

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