Research Article

Periodic Limb Movements of Sleep in Children with Attention-Deficit/ Hyperactivity Disorder: Baseline Frequency and Impact of Psycho-Stimulant Medication

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Abstract

Purpose: This study investigated the rates of periodic limb movements disorder (PLMD) in children with attention-deficit/hyperactivity disorder (ADHD) compared to typically developing (TD) children, the impact of stimulant medication on PLMD, and sleep disparities in children with ADHD with and without PLMD.

Method: 25 medication-naïve children with diagnosed ADHD and 25 TD age- and sex-matched children, 6 -12 years (mean: 8.81 years) were enrolled. Participants completed a 1-week baseline assessment of typical sleep. Participants with ADHD subsequently completed a 4-week blinded randomized controlled trial of stimulant medication (2 weeks each of placebo and medication). Overnight polysomnography was recorded in a sleep laboratory following each condition.

Results: Children with ADHD had significantly higher rates of PLMD (ADHD=26%, TD=4%, p<0.05), longer sleep onset latency (SOL, ADHD=40.92±30.84, TD=24.07±14.01, p<0.05), and increased arousal index (AI, ADHD=11.01±2.47, TD=7.74±2.18, p<0.05). Children with ADHD meeting clinical threshold for PLMD (i.e., periodic limb movement of sleep index of ≥5.0/hour) had increased sleep stages shifts with increased AI compared to children with ADHD without PLMD. Stimulant treatment was not associated with changes in periodic limb movements, however, longer SOL and reduced sleep efficiency (SE) was observed in children with PLMD during treatment compared to placebo.

Conclusion: There are consistent findings across studies (including this one) of increased PLMD in children with ADHD. Children with ADHD and PLMD may have increased sleep difficulties in response to medication. Further study is warranted on the impact of stimulant treatment on sleep in children with ADHD and PLMD.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood neurodevelopmental disorders, affecting up to approximately 5% of children and adolescents worldwide [1]. The Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition (DSM-5) defines ADHD according to two core symptom clusters: developmentally inappropriate levels of inattention and/or hyperactivity/impulsivity [2]. These symptoms significantly impact behavior and performance in both academic and social settings. ADHD is often associated with co-existing (comorbid) mental health disorders, such as conduct disorder, oppositional defiant disorder, and anxiety disorders [3]. In addition to these comorbidities, many children diagnosed with ADHD have been reported to experience significant sleep problems and/or disorders [4].

The relation between ADHD and sleep disturbances has been investigated through numerous studies using both subjective (e.g., parent report, questionnaire) and objective (e.g., actigraphy, Polysomnography [PSG]) measures. The majority of studies using subjective measures have reported that children with ADHD experience more sleep problems compared to Typically Developing (TD) children, particularly difficulties falling asleep, trouble staying asleep, and daytime sleepiness [5-8]. Some studies using Polysomnography (PSG) have found that children with ADHD, compared to their typically developing peers, have a significant decrease in Total Sleep Time (TST) [9,10], increased Sleep Onset Latency (SOL) [9,11], increased slow wave sleep and sleep stage N2 [10], decreased Rapid-Eye Movement sleep (REM) [10,12,13], decreased Sleep Efficiency (SE) [10,14],

and increased movement during sleep [9,12]. Moreover, several other studies using actigraphy have reported decreased TST, SE, and longer SOL [14-16]. In contrast, there are also many studies using objective measures that have not reported any significant difference in sleep variables between ADHD and TD children [17-20].

Corkum and Coulombe [21] conducted a review of existing qualitative (n=5) and quantitative (n=3) systematic reviews to identify consistent findings. The only consistent findings across the quantitative reviews were that: (1) the results of studies employing objective measures did not consistently support the findings of sleep problems often reported based on subjective measures, (2) there were no differences in sleep architecture between ADHD and TD groups, and (3) children with ADHD were more likely to display an increased number of Periodic Limb Movements of Sleep (PLMS).

PLMS is captured by PSG and is characterized by repetitive periodic movement of the lower extremities during sleep, lasting from 0.5 to 10 seconds with an Electromyogram increase of >8µV above the resting baseline and occurring in 5-90 second intervals [22]. The numbers of PLMS are used to calculate the Periodic Limb Movements of Sleep Index (PLMSI), which is based on the number of PLMS per hour of total sleep time. A PLMSI greater than or equal to 5/hour in children is considered abnormal and clinically significant [23,24]. While this criterion is used as a diagnostic criterion for Periodic Limb Movement Disorder (PLMD), the child also has to have other clinical symptoms (e.g., sleep complaint, insomnia, fatigue) to be diagnosed as having PLMD. However, for our study purposes, we will be using the term PLMD if the child was found to have clinically significant PLMS based on PSG.

PLMS has been reported to be associated with repetitive surges in sympathetic nervous system activity, accelerate blood pressure, and increased heart rate [25,26]. Moreover, PLMD often causes sleep disturbances due to frequent arousals and fragmented sleep that can result in excessive daytime sleepiness, fatigue, feeling of non-restorative sleep, and difficulty waking up in the morning [27,28]. In addition, PLMD is frequently associated with Restless Leg Syndrome (RLS), a neurologic sensorimotor disorder characterized by an overwhelming urge to move the legs at rest. In one study, it was found that close to three-quarters of children with RLS exhibit PLMS (74%), but the reverse is not true (i.e., only 28% of children with PLMS exhibit RLS) [29]. While there is a high correlation between the presences of RLS in individuals with PLMD, the present study focuses exclusively on the relation between ADHD and PLMS, as PLMS is captured via PSG whereas RLS is not based on objective measures and the identification of RLS can be challenging in young children [30].

The prevalence of PLMD is reported to be greater in children with ADHD compared to TD children, although the prevalence range varies widely across studies. A retrospective study by Kirk and Bohn (2004) [27] that examined all PSG studies performed at a tertiary-level pediatric care facility over a 3.5 year period, found that 33 of the 591 (5.6%) participants had PLMs > 5 per hour; whereas 2 of the 28 (7.1%) participants who had a pre-existing diagnosis of ADHD had PLMs > 5 per hour. Two additional studies conducted by Picchetti et al., [31] have reported even higher prevalence rates of PLMD in children with ADHD. In one study, 18 out of 69 (26%) children with ADHD within the age range of 2-15 years showed PLMSI ≥5/h, while only 2 out of 38 (5%) TD children had PLMSI ≥5/h. In another study, 9 out

of 14 (64%) children with ADHD aged 2-15 years were reported to have PLMD, while none of the TD children had PLMD [32]. A recent case-control sleep study reported that 9 out of 15 (36%) children with ADHD were found to have PLMD [9]. In addition to the above-noted studies that were specifically conducted to examine PLMD in children with ADHD, two other studies reported on the prevalence of PLMD in children with ADHD in different research contexts. Huang et al., [33] investigated the association of ADHD with Obstructive Sleep Apnea (OSA) and reported a prevalence of 15.8% for PLMD in children with ADHD (6 out of 38) compared to 0% of 27 controls. Golan et al., [12] investigated the daytime sleepiness in children with ADHD and reported PLMD in 15% of children with ADHD (5 out of 34), while none of 32 controls had PLMD. Across the above-noted studies, the prevalence of PLMD ranged from 0-5% for TD children, compared to 7-64% in children with ADHD.

Three studies have reported the prevalence of ADHD in children with PLMD. In one study, 40 out of 90 (44.4%) children with PLMD were reported to have ADHD [34]. In a second study [35] it was found that 7 out of 58 (12%) of pre-pubertal children with PLMD had ADHD. A further study reported a higher prevalence, with 117 of 129 (91%) participants with PLMD meeting objective criteria for ADHD [32].

The high prevalence rates of PLMD in children with ADHD and of ADHD in children with PLMD provide compelling evidence of the relationship between ADHD and PLMD. Nevertheless, the results of these studies must be interpreted with caution given limitations of the studies, including lack of rigorous diagnostic criteria for ADHD [27,34], comorbidities of the study participants [12,31,35], lack of respiratory monitoring [27,31], and small sample sizes [32]. Moreover, none of the above-mentioned studies samples were comprised of children with ADHD who were medication naïve. In addition to these limitations, the impact of stimulant medication on PLMD has not been extensively explored.

The pathophysiology of ADHD is still unclear; however, an inadequate dopamine and norepinephrine signal in the prefrontal cortex of the brain has been thought to be associated with ADHD [36-38]. These two neurotransmitters play an important role in attention regulation, cognitive function, maintaining alertness and focus, and positive reinforcement [39, 40]. Stimulant medication such as Methylphenidate Hydrochloride (MPH) is the most effective and widespread treatment for ADHD [41]. Half of the children diagnosed with ADHD in North America are treated with these medications [42]. Stimulant medications expedite the release of extra-synaptic dopaminergic and noradrenergic level in the prefrontal cortex by blocking their reuptake and facilitating their release in the prefrontal cortex area [43,44]. By enhancing the amount of dopamine (DA) and Norepinephrine (NE) in the prefrontal cortex and the subcortical striatum, stimulant medication may improve symptoms of inattention, impulsivity, and hyperactivity in ADHD [39,45,46]. While stimulant medication is effective in improving the core symptoms of ADHD (i.e., increasing attention and reducing impulsivity and hyperactivity), it can also impact sleep by reducing total sleep time, increasing sleep onset latency, and decreasing sleep efficiency [47].

Inadequate level of dopamine function has also been reported to be associated with PLMD [48,49]. Pharmacologic studies and some

brain-imaging studies have provided evidence for an underlying dopamine abnormality in PLMD by showing the positive reaction of dopaminergic medication [50-53]. Several dopaminergic agents have been used (e.g., L-DOPA, Valproate (VPA), Selegiline HCI etc.), and research has found significant reduction in PLMS with these medications [54].

There are four studies that have reported the impact of dopaminergic agents on children with ADHD who have PLMD. One study explored the effect of dopamine monotherapy (levodopa and pergolide) in 7 children (4-18 years of age) with ADHD and diagnosed PLMD and RLS to determine whether dopaminergic therapy improves the signs of ADHD and RLS/PLMS. The study found that these agents decreased the number of PLMS per night, decreased the PLMSI (including those associated with arousals and those that were not), and improved core and associated symptoms of ADHD [55]. The study also reported that 5 out of the 7 children no longer met the criteria for a diagnosis of ADHD after being treated for PLMD. Another study investigated the effect of dopaminergic agent (L-DOPA) in the children with ADHD to determine if ADHD symptoms improve differentially in children with and without RLS/PLMS [56].

This study reported that this treatment decreased the PLMSI (in 5 out of 5 participants), however, there were no changes in ADHD symptoms and sleep parameters. The third study by O'Brien and colleagues [57] examined the effect of stimulant medications on sleep characteristics of children with ADHD compared with control children. While there were no statistically significant differences in the percentage of children who had PLMD between the ADHD group who were treated with medication (15%; 8 out of 53), the ADHD group not treated with medication (12%; 4 out of 34), and the control group (11%; 6 out of 53); there was a non-significant trend in that the children who were treated with medication tended to have decreased PLMSI scores compared to the non-medicated children. The final study, which was also conducted by O'Brien et al., [28] examined the sleep characteristics in children with ADHD compared to the control children and found that children with ADHD referred from a sleep clinic had significantly increased PLMS associated arousals compared to children referred from the community. The majority of children referred from a sleep clinic were being treated with stimulant medication (72%; 34 out of 47) compared to the children from the community (51%; 27 out of 53). Given the lack of evidence regarding the impact of stimulant treatment on PLMS, it is imperative to examine the influence of stimulant treatment on sleep of children with ADHD.

To our knowledge, this is the first study to report on the effects of methylphenidate (MPH) on PLMS of rigorously diagnosed children with ADHD who were participating in a double-blinded placebo controlled clinical medication trial. The current study has three primary aims: (1) to investigate the rate of PLMD in medication-naïve, rigorously diagnosed children with ADHD compared to TD children; (2) to examine the impact of stimulant medication treatment (i.e., extended release MPH, Biphentin®) on the frequency of PLMS; and (3) to examine the effect of stimulant medication on sleep in children diagnosed with both ADHD and PLMD. An additional, but exploratory aim, was to determine if children with ADHD and PLMD are differentially impacted in terms of sleep side-effects by MPH. This study was part of a larger investigation that examined the effects of stimulant medication on sleep in children with ADHD. The larger project was supported by Canadian Institutes for Health Research (CIHR; grant number FRN 81191).

Materials and Methods

Study Population

Of the 62 children who consented to participate in this study (32 children with ADHD; 30 TD children), 3 were excluded due to discomfort with the overnight PSG procedure [n=2] and abnormal PSG findings [n=1]. After matching for age and sex between the two groups, 25 participants (22 males and 3 females) in each group were retained for further analysis. The children ranged from 6-12 years in age. All participants with ADHD were recruited from an ADHD clinic in a mid-size town in a rural region of Nova Scotia, or from a psychology private practice specializing in children with ADHD in an urban centre in Nova Scotia. The assessment of ADHD followed a rigorous, clinical diagnostic procedure including parent and teacher semi-structured interviews, multiple questionnaires completed by parents and teachers, psycho-educational assessments, and observations conducted during testing and in the classroom (for a description of the diagnostic procedure, please see McGonnell et al., [58]. Only children who met the DSM-IV-TR criteria for ADHD [59] and consented to a clinical trial of MPH by the study pediatrician were included in the ADHD group. The DSM-IV-TR was selected to assess the diagnosis of ADHD as the DSM-V was not published at the time of recruitment.

Additional exclusion criteria included: (1) full scale IQ falling more than one standard deviation below the mean according to the Wechsler Scales of Intelligence - Fourth Edition(WISC-IV) [60]; (2) known neurological or genetic/chromosomal disorder (e.g., Fragile X), metabolic disorder (e.g., PKU), or seizure disorder; (3) previous diagnosis of a primary sleep disorder (e.g., obstructive sleep apnea; OSA); (4) PSG evidence at baseline indicative of a primary sleep disorder (e.g., OSA); (5) treatment (behavioral or pharmacological) for sleep problems; (6) diagnosis of another mental health disorder considered primary (e.g., primary diagnosis of autism with secondary symptoms of ADHD); (7) sexually developed beyond Tanner stage 2 (based on an assessment and questionnaire completed by the pediatrician at the pre-medication consultation); and (8) previous use of psychotropic medication. Children taking prescriptions for medical conditions (e.g., asthma, allergies) were reviewed by the pediatrician on a case-by-case basis to determine the appropriateness of the medication trial. Children were excluded if their current medication had the potential to affect sleep or daytime alertness (e.g., regular use of an anti-histamine). Children with any co-morbid mental health disorders were excluded from the study; however, children diagnosed with a Learning Disability (LD) were not excluded given the high rates of LD in children with ADHD.

Children in the TD group were recruited from the community using online advertisements, newsletters, and other resources (e.g., newsletter distributed to past study participants). TD children were screened using parent-report rating scales and a telephone interview. Children in this group were excluded if they had a chronic medical illness, history of neurological impairments, mental health disorders, or a primary sleep disorder.

Ethical approval for the study was obtained from the Research Ethics Board of a tertiary-care children's hospital. Parental/legal guardian consent and child assent were obtained prior to study participation. Parents received an honorarium and were reimbursed for their costs to attend the overnight PSG recording. The children were provided with movie certificates and dollar store prizes for completing the study procedures.

Outcome Measures

Demographic Questionnaire

Parents completed a demographic questionnaire to collect information regarding the child's age, sex, medical history, ethnicity, family composition, family income, and parental education. Socioeconomic Status (SES) of each family was calculated based on four domains based on the parents' marital status, retired/employment status, educational attainment, and occupational prestige [61]. In this index, parent's education code is rated on a 7-point scale and parent's occupational code is rated on a 9-point scale. A total score is called Hollingshead Four Factor Index of Socioeconomic Index. For two parent households, the index was calculated based on the highest earning parent (range of possible scores: 8-66).

Conners Parent and Teacher Rating Scale - Revised (Long Form) (CP/TRS-R:L)

The CP/TRS-R:L is a standardized rating scale completed by parents and teachers to assess problem behaviors in children 3-17 years of age. The parent version consists of 80 items and the teacher version consists of 59 items. Raw scores are converted into T-scores so that comparisons can be made to the normative sample. A T-score on the ADHD Index was calculated for both the CPRS-R:L and CTRS-R:L. A T-Score of more than or equal to 65 is considered evidence of clinically significant symptoms of ADHD [62,63]. This cut-off was used to exclude children in the TD group and to confirm inclusion of children in the ADHD group.

Polysomnography (PSG)

Overnight PSG recordings were conducted using the Sandman Elite SD32+TM digital sleep recording system (EMBLA; California, USA) at a sampling rate of 250 Hz with high- and low-pass filters set at 0.3 Hz and 35 Hz, respectively. PSG recording included five electroencephalogram (EEG) channels, two electrooculograms (EOG), three submental electromyogram and four Anterior Tibialis Electromyogram (EMG), two electrocardiogram (ECG), two mastoid reference electrodes (left and right), and one ground electrode. Airflow was measured using a thermistor in those participants that could tolerate this device. Breathing effort and movement were measured using two piezoelectric bands (chest and abdomen). The oxygenation saturation (SpO_2) was recorded using an integrated Sandman Oximeter with a Nellcor probe. A trained Research Assistant (RA) continuously observed participants, and participant's sleep was recorded using an infrared camera. To detect snoring, a room microphone was used. The study room was soundproof, darkened, with an ambient temperature of approximately 24°C. The participant's bedtime for the overnight PSG recording night was based on the typical weekday bedtime measured by actigraphy data collected during the baseline week, and sleep was terminated when the child spontaneously woke up or was woken by a research assistant

30 minutes after typical weekday wake time. While PSG studies occurred on the weekend, the children were kept on their weekday sleep routine and schedule.

All sleep studies were manually scored using standard AASM [22] criteria by a registered PSG technologist (supervised by a board-certified sleep physician, MR) who was blinded to each participant's medication status. Periodic limb movements were scored if they were 0.5 to 10 seconds in length and had an EMG amplitude of >8 microvolt above the resting EMG. PLMS were scored if limb movements occurred as part of a series of 4 or more, with 5-90 seconds between each movement. PLMSI was calculated as the number of PLMS per hour of total sleep time (number of PLMs/hour total sleep time, PLMSI/hr). PLM arousal index (number of PLMs associated with arousals/hour total sleep time, PLMAI/hr) were calculated collapsed across all sleep stages, as well as during Rapid Eye Movement (REM) and Non-Rapid Eye Movement (NREM) sleep stage, separately. NREM sleep and REM sleep stages are denoted as N and R, respectively. The following sleep parameters were calculated: a) total time in bed (TIB), time from 'lights off' to 'lights on'; min b) Total Sleep Time ((TST), total minutes of sleep stages N1-N3 and R sleep stages); c) Sleep Onset Latency ((SOL), time from 'lights off' to the first epoch of any sleep stage; min); d) sleep efficiency ((SE), the ratio of TST to TIB ('lights off' to 'lights on')*100; %); e) the relative percentages of sleep stages (N1-N3 and R sleep stages): the total time (minutes) in each sleep stage divided by the TST (e.g., (N1/TST)*100); f) Sleep Stage Transition (SST, total number of transition between sleep stages), and g) total arousal index per hour of TST (AI/hr of TST): total number of arousals divided by TST*60. Additionally, OSA and any other sleep related disorders were assessed using PSG.

Procedures

All participants from the ADHD group and TD group completed an in-home baseline assessment period during which their sleep and sleep routines were recorded via actigraphy and sleep diary. Following the baseline assessment, children in the ADHD group participated in a blinded acute medication trial: placebo and MPH treatment, with each condition of the trial lasting two weeks. In order to reduce potential order effects, 50% of participants first received the active medication treatment followed by the placebo, while the other 50% had the reversed schedule. The child, family, teachers and study staff were all blinded to the order of the conditions; only the study pediatricians and pharmacists were aware of the order of the conditions.

The medication trial was a clinical trial provided by one of three pediatricians. A standard clinical blind protocol was followed for extended-release MPH (Biphentin®). Dosing was based on a weight-adjusted dose of 0.7mg/kg, which reflects a moderate dose of MPH according to current practice guidelines regarding pharmacological treatment for ADHD [23]. Children weighing less than 20 kg received a 20 mg dose daily at breakfast, while children weighing 20-30 kg were given 30 mg, and children weighing over 30 kg were given 40 mg. Participants received one dose of MPH (Biphentin®) daily within one hour of waking in the morning. This medication dose is consistent with a previous double-blind, cross-over, placebo-controlled study that investigated the impact of a multilayer release (MLR) formulation methylphenidate (MPH; Biphentin®) with Immediate-Release (IR) MPH (Ritalin®) in patients with ADHD [64]. One of two

pharmacies prepared the medication and placebo, which were placed in identical gelatin capsules so that children and parents could not identify whether capsules contained the medication or the placebo. The medication trial always began on a weekend day and concluded on the following Friday or Saturday, at which time an overnight PSG recording was conducted in the sleep laboratory located at the university-affiliated hospital. On the PSG night (which happened at the end of the first week of baseline, placebo, and medication weeks), the parent brought their child to the sleep laboratory approximately two to three hours before typical bedtime. The parent either stayed in the same room with their child and slept on a separate cot or slept in a neighboring bedroom.

Statistical Analyses

A power analysis was performed using the statistical analysis software G Power [65]. The sample size of 25 in each group was needed to detect the power with an alpha level of 0.05. The post-hoc analysis revealed that the statistical power for this study was 0.68 with an effect size of 0.70, which represents adequate power.

Statistical analysis was carried out using PASW Statistics Base 22.0 (SPSS, Inc., Chicago, IL, USA). Independent-samples t-test or chi-square tests were performed between the TD and ADHD groups to determine whether there were any significant differences in the demographic background variables including age, sex, ethnicity, and SES. A baseline assessment of sleep in children with ADHD and TD was compared using independent-sample t-test. To determine if the presence of PLMS differed significantly in the children with ADHD compared to TD children during baseline and between treatment conditions in the children with ADHD (i.e., baseline vs. MPH/Placebo, MPH vs. Placebo), a non-parametric chi-square test or Fisher Exact-test was performed as appropriate (i.e., Fisher's Exact-test was used if any expected frequencies were less than five). In addition, independent samples t-test were performed to determine whether the PLMSI scores during stage N and stage R sleep differed significantly between ADHD and TD groups in which PLMS scores is a dependent continuous variable. To evaluate the effect of extended release MPH on sleep in children with ADHD and PLMD (ADHD+PLMD) compared to children with ADHD but without PLMD (ADHD-PLMD) exploratory analyses were performed. Paired

sample t-test where used to determine if there were any differences in sleep variables between the MPH and placebo conditions for both ADHD+PLMD and ADHD-PLMD, and these differences were examined for consistency between the two groups.

Results

Sample Description

The sample characteristics are shown in Table 1. The ADHD and TD groups did not differ in terms of their age, sex, ethnicity, family composition, family income, or SES. The ADHD group had more symptoms of ADHD as reported by the ratings of parents and teachers (CPRS-R: Land CTRS-R: L is both in clinical range, while TD scores were in the average range).

Regarding the baseline assessment, sleep measures were compared between the ADHD and TD groups using independent t-test (Table 2). Compared to the TD children, children in the ADHD group had significantly longer sleep latency (ADHD: M = 40.92, SD = 30.84min; TD: M = 24.07, SD = 14.01; t(48)=2.49, p<0.05). The AI scores were significantly higher in the ADHD group compared to the children in the TD group (ADHD: M=11.00, SD=2.47; TD: 7.74, SD = 2.18, t(48)=5.08, p<0.001). However, other sleep measures (i.e., TIB, TST, SE, WASO, Sleep stage N1-N3, Stage R, and SST) did not differ between groups. Apnea-Hyponea Index (AHI) between ADHD and TD groups was not statistically significant and no participant in either group met clinical threshold (AHI>5.0 /hour of TST).

Rate of PLMD in Children with ADHD and TD

A Chi-square test was performed to investigate the rate of PLMD in children with ADHD and TD children. For this, PLMSI scores were divided into two groups: PLMSI<5.0 and PLMSI≥5.0. The rate of PLMD in children with ADHD was significantly higher than in TD children at baseline. Six out of 25 (24%) children with ADHD had a PLSMI≥5.0/hr, while only 1 out of 25 (4%) children in the TD group met this criterion (χ2(1) = 4.15, p<0.05). The PLMSI scores were analyzed separately during stage N (N1-N3) and stage R sleep. The average PLMSI score was higher in children with ADHD than in TD children during stage N sleep (ADHD: M = 3.36, SD = 6.88; TD: M = 0.59, SD = 2.47; t(48)=1.89, p=0.07). During stage R, the average PLMSI score for the ADHD group was 1.82 (SD: 4.16); no participant

Table 1: Demographic information (Average ± SD).

	ADHD (*n*=25)	TD (*n*=25)	t	p
Age in months (Average ± SD)	105.72 ± 22.57	103.92 ± 21.07	0.29	0.77
Sex (Male, n (%))	22(88%)	22 (88%)	0.00 [a]	1
Caucasian Ethnicity (n (%))	23 (92)	21 (84)	6.09 [a]	0.31
Family Composition (Average (range))[b]	4.60(2-7)	4.28(3-7)	-0.97	0.34
Family Income (Average ± SD)[c]	6.92 ± 2.63	5.60 ± 3.18	-1.6	0.12
Socio-economic Status (SES ± SD)[d]	62.46 ± 21.84	63.94 ± 15.41	-0.28	0.78
CPRS-R:L ADHD Index (T-Score ± SD)	70.36 ± 9.69	46.47 ± 6.58	9.90	0
CTRS-R:L ADHD Index (T-Score ± SD)	68.44 ± 9.56	47.93 ± 7.94	7.44	0

[a]Indicates χ2 values; all others are t-values; [b]Indicates a total number of family member who live at home with child (including child); [c]Family Income was reported by parents according to nominal scale where a value of 1 = <$20,000, 2 = 21,000-$30,000, 3 = $31,000-$40,000, 4 = $41,000- $50,000, 5 = $51,000-$60,000, 6 = $61,000-$70,000, 7 = $71,000-$80,000, 8 = $81,000-$90,000, 9 = $91,000-$100,000, 10 = $100,000+; [d] Indicates average parental SES score calculated based on the Hollings head Four-Factor Index of Socioeconomic Status: marital status, retired/employed status, educational attainment, and occupational prestige.

A total SES score is between 8-66 and a higher score indicates upper social class; ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; CPRS, Conner's Parent Rating Scale-Revised: (Long Form); CTRS, Conner's Teacher Rating Scale-Revised: (Long Form).

Table 2: Sleep characteristics based on PSG at baseline.

Variables	ADHD (*n* = 25)	TD (*n* = 25)	*t* value	*p* value
TIB (min)	554.82 ± 61.34	565.78 ± 40.39	-0.75	0.46
SOL (min)	40.92 ± 30.84	24.07 ± 14.01	2.49	0.02
TST (min)	466.09 ± 69.08	477.76 ± 48.98	-0.69	0.49
SE (%)	84.07 ± 9.13	84.46 ± 6.37	-0.18	0.86
WASO (min)	18.96 ± 8.43	21.92 ± 7.98	-1.27	0.21
N 1 (%)	5.79 ± 2.65	4.99 ± 2.15	1.18	0.25
N 2 (%)	43.69 ± 9.21	45.45 ± 8.84	-0.69	0.49
N 3 (%)	27.79 ± 9.17	28.45 ± 8.59	-0.26	0.79
Stage R (%)	22.71 ± 5.21	21.09 ± 3.93	1.24	0.22
SST (n)	135.00 ± 26.78	133.04 ± 33.76	0.23	0.82
Arousal Index	11.00± 2.47	7.74 ± 2.18	5.08	0
AHI (/hr TST)	0.06 ±0.16	0.004 ± 0.02	1.83	0.08
PLMSI≥5.0 (n (%)	6 (24%)	1 (4%)	4.15[a]	0.04
PLMSI score at N stage	3.36 ± 6.88	0.59± 2.47	1.89	0.07
PLMSI score at stage R	1.82 ± 4.16	00±00	-	-

[a]χ2 test between ADHD/TD and PLMSI<5.0 /PLMSI>=5.0/hr of TST with significance level of p<0.01; ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; TIB, Time in Bed; SOL, sleep onset latency; TST, total sleep time; SE, sleep efficiency; WASO, wake after sleep onset; N, non-rapid eye movement sleep stage; R, rapid eye movement sleep; SST, sleep stage transition; AHI, Apnea-Hypopnea Index; PLMSI, periodic limb movements of sleep index. Data displayed as Mean ±SD.

had a score of PLMSI ≥5/hr in TD group during stage R sleep (and as such no analyses could be conducted).

Sleep in Children with ADHD and PLMD

Sleep in children with ADHD who had PLMSI≥5.0/hr (ADHD+PLMD group, n = 6) was compared to sleep in children with ADHD without PLMD (PLMSI<5.0, ADHD-PLMD group, n = 19) (Table 3). Compared to children in the ADHD-PLMD group, children in the ADHD+PLMD group had significantly more frequent SST (ADHD+PLMD: M = 165.50, SD = 10.78; ADHD-PLMD: M = 125.37, SD = 22.72, t(23) = 5.88, p < 0.001) and elevated arousal index(ADHD+PLMD: M = 14.05, SD = 2.87; ADHD-PLMD: M

= 10.27, SD = 1.73, t(23) = 3.97, p <0.01). None of the other sleep measures (i.e., TIB, SOL, TST, SE, WASO, N1-N3, R) significantly differed between the two groups.

Impact of MPH Treatment on the Rate of PLMD in Children with ADHD

The distribution of PLMD in children with ADHD at baseline, MPH, and placebo conditions is shown in Table 4. The rate of PLMD in children with ADHD at baseline was compared to the rates in the MPH treatment and placebo conditions using Fisher's Exact test. Compared to the rate of PLMD in children with ADHD at baseline, a significant lower rate was observed during the MPH condition (Baseline: 24% vs. MPH: 16%, p<0.001), as well as placebo condition

Table 3: Sleep characteristics of children with ADHD+PLMD and ADHD-PLMD at Baseline.

	ADHD+PLMD	ADHD-PLMD		
			t-values	p-values
Sleep variables	(n=6)	(n=19)		
TIB (min)	569.48 ± 54.11	550.19± 64.10	0.66	0.51
SOL (min)	29.53 ± 15.71	44.52±33.80	-1.04	0.31
TST (min)	506.27 ± 58.58	453.40±68.57	1.7	0.1
SE (%)	88.83 ±4.24	82.56±9.80	1.5	0.15
WASO (min)	19.67 ±9.75	18.74±8.26	0.23	0.82
N1 (%)	5.20 ±3.14	5.98±2.54	-0.62	0.54
N2 (%)	41.17 ±9.78	44.48±9.15	-0.76	0.45
N3 (%)	29.52 ±9.82	27.23±9.16	0.5	0.61
Stage R(%)	24.13 ±5.26	22.26±5.26	0.76	0.45
SST (n)	165.50 ±10.78	125.37±22.72	**5.88**	**0**
Arousal Index (n)	14.05 ±2.87	10.27±1.73	**3.97**	**0.001**

TIB, time in bed; SOL, sleep-onset latency; TST, total sleep time; SE, sleep efficiency; SST, Sleep stage transition; WASO, wake after sleep onset; N, non-rapid eye movement sleep stage; R stage, rapid eye movement sleep. Data displayed as Mean (SD). Independent sample t-test with a significant level of p<0.05.

Table 4: Periodic Limb Movements of Sleep Index and the rate of PLMD (PLMSI≥5.0) in children with ADHD at baseline, MPH and Placebo treatment period.

Variables	Baseline	MPH	Placebo	BL x MPH	BL x PL	MPH x PL
name	(*n*=25)	(*n*=25)	(*n*=25)	*p*	*p*	*p*
PLMD$_a$	6 (24%)	4(16%)	4(16%)	0.01	0	0.11
PLMSI score						
During Stage N	3.36 ± 6.88	3.22 ± 8.26	2.20 ± 3.78	0.86	0.25	0.4
During Stage R	1.82 ± 4.16	0.86 ± 2.01	1.62 ± 2.89	0.28	0.79	0.29

$_a$χ2 test or Fisher's Exact test, all others are t values; ADHD, attention-deficit/hyperactivity disorder; MPH, methylphenidate hydrochloride; N, non-rapid eye movement sleep stage; R, rapid eye movement sleep stage; BL, Baseline; PL, Placebo. Data displayed as total number (%) or Mean ± standard deviation (SD).

Table 5: Distribution of Periodic Limb Movements of Sleep Index at baseline, MPH and Placebo treatment period for the children with ADHD who met the criteria of PLMD (Bold number indicates PLMSI≥5.0).

Participant	Group	Baseline (n=25)	MPH (n=25)	Placebo (n=25)
1	ADHD	25.6	29.4	9.4
2	ADHD	6	9.4	11.1
3	ADHD	10.7	6.7	0.9
4	ADHD	10	1.5	7.1
5	ADHD	8.6	4.6	7.5
6	ADHD	5.3	0	0
7	ADHD	1.1	5.4	3

Table 6: Effect of MPH treatment on sleep in children with ADHD who met the criteria of PLMD at baseline.

Variables	ADHD+PLMD (n=6)				ADHD-PLMD (n=19)		
	MPH	Placebo	*p*		MPH	Placebo	*p*
SOL (min)	38.03 ±8.47	17.17± 17.38	**0.02**		40.57 ±36.43	35.38 ± 26.56	0.61
TST (min)	497.82± 43.69	532.92± 35.30	0.09		479.66 ± 73.83	492.23± 63.21	0.44
SE (%)	81.98 ± 10.00	91.63± 4.25	**0.01**		86.67 ± 8.23	86.77 ± 7.04	0.97
WASO (min)	21.17 ± 6.14	20.83 ± 5.84	0.94		18.26 ± 6.51	20.10 ± 9.24	0.28
N1 (%)	5.48 ± 1.51	4.38 ± 1.13	0.21		4.61 ± 2.05	5.22 ±2.74	0.23
N2 (%)	41.25 ± 9.28	41.17 ± 9.51	0.98		43.28 ± 8.30	45.36 ±8.03	0.18
N3 (%)	26.07± 10.37	26.23 ± 9.88	0.94		28.80 ± 8.86	26.43 ±7.33	0.11
Stage R (%)	27.25± 5.50	28.20± 2.91	0.78		23.26 ±5.97	22.97 ± 4.23	0.85
SST (n)	129.66± 64.88	152.67 ± 43.29	0.47		125.84 ±39.25	129.05 ± 33.72	0.7
Arousal Index	12.82±2.44	11.57 ±2.22	0.32		9.78 ± 2.31	10.54 ± 2.87	0.19

ADHD, attention-deficit/hyperactivity disorder; TD, typically developing; MPH, methylphenidate hydrochloride; PLMD, periodic limb movements disorder; SOL, sleep-onset latency; TST, total sleep time; SE, sleep efficiency; WASO, wake after sleep onset; N, non-rapid eye movement sleep stage; R, rapid eye movement sleep stage; SST, sleep stage transition. Data displayed as Mean (SD). Paired-samples t-test on MPH vs. Placebo within ADHD+PLMD group and ADHD-PLMD with a significance level of p<0.05.

(Baseline: 24% vs. Placebo: 16%, p<0.001). No significant difference was found in the rate of PLMD between MPH and placebo conditions (MPH: 4(16%) vs. Placebo: 4(16%), p=0.11). The PLMSI scores in the N stage and R stage sleep were compared between baseline and MPH / placebo conditions using paired sample t-test. No significant differences were found in the average score of PLMSI between baseline and MPH, between baseline and placebo, or between MPH and placebo conditions.

The seven children with ADHD who met the criteria for PLMD in any of the conditions (e.g., baseline, MPH, and Placebo) are listed in

Table 5. Of the 6 children who had PLMD at baseline, only 2 of these children reached criteria during both MPH and placebo conditions, 3 reached at either MPH or placebo conditions, or one did not meet at either the placebo or MPH conditions. One participant did not meet criteria of PLMD at either baseline or placebo but did meet the criteria at MPH treatment period.

Impact of MPH on Sleep in Children with ADHD + PLMD

The focus of these exploratory analyses was to determine whether the MPH-placebo differences were greater for the children with ADHD+PLMD (n=6) or for the children with ADHD-PLMD

(n=19) (Table 6). Children with ADHD+PLMD had a significantly longer sleep onset latency and reduced sleep efficiency during MPH treatment period compared to placebo treatment condition (SOL, MPH: M = 38.03, SD = 8.47; Placebo: 17.17, SD =17.38, t(5) = 3.21, p< 0.05; SE, MPH: M = 81.98, SD = 10.00; Placebo: 91.63, SD=4.25, t(5) = -3.66, p<0.01). In addition, a trend was found with reduced total sleep time in children with ADHD+PLMD during MPH treatment condition compared to placebo treatment condition (MPH: M = 497.82, SD = 43.69; Placebo: 532.92, SD=35.30, t(5) = -2.12, p = 0.09). No significance differences were observed between MPH and placebo in children with ADHD-PLMD.

Discussion

The present study sought to determine: 1) the baseline rates of PLMD in medication-naïve, rigorously diagnosed children with ADHD compared to TD children, 2) whether stimulant medication treatment (i.e., extended release MPH, Biphentin®) changes these rates of PLMD, and 3) whether children with ADHD who have PLMD, compared to children with ADHD without PLMD, are differentially affected by stimulant medication. A fourth, exploratory aim was to determine if children with ADHD and PLMD are differentially impacted in terms of sleep side-effects by MPH.

Twenty-five medication-naïve children rigorously diagnosed with ADHD were compared to 25 age- and sex-matched TD children. The two groups were also comparable in terms of ethnicity, family composition, family income and SES. The mean T-scores of ADHD Index on Conner's Parent Rating Scale and Conner's Teacher Rating Scale in children with ADHD were significantly higher compared to the TD children. In term of sleep at baseline, the two groups did not differ on most sleep variables, except that the ADHD group had longer SOL and higher Arousal Index. After baseline, children with ADHD received a placebo-controlled medication trial of extended-release MPH. The treatment period took place over four weeks: two weeks of MPH and two weeks of placebo treatment. At the end of each period, participants visited the sleep lab for a full overnight PSG session. The main findings of this study were: 1) that there is a higher rate of PLMD in children with ADHD compared to TD, 2) treatment with MPH did not change the rates of PLMS, and 3) children with ADHD+PLMD were differentially impacted by MPH.

Consistent with our hypothesis, we found higher rates of PLMD in the children with ADHD relative to TD children (24% versus 4%, respectively), and the average total score of PLMSI was also significantly higher in children with ADHD during stage N sleep (3.36 versus 0.59) and stage R sleep (1.82 versus 0.00). The prevalence rate of PLMD in our study is similar to the prevalence of 23% reported by Martinez and Guilleminault [35] and 26% reported by Picchietti et al., [31], but much higher than the 7% reported by Kirk and Bohn [27] and the 8% reported by Crabtree VML et al., [34]. Differences in rates of PLMD may be due to different referral sources (e.g., clinic, community), diagnostic procedures for ADHD, and exclusion of children with OSA.

When comparing children with ADHD with and without clinically significant PLMD, we found that the ADHD+PLMD group had a significantly increased number of sleep stage transitions and elevated arousal index compared to the ADHD-PLMD group, but all other sleep measures were similar between the two groups. To our knowledge, the current study is the only one that has objectively examined sleep in children with ADHD who have PLMD versus those that do not have PLMD. However, one other study examined sleep in children with ADHD who had PLMD and compared this to children with PLMD only or healthy children without PLMD or ADHD [34]. Crabtree et al. reported a reduced R stage sleep in children with ADHD+PLMD compared to the PLMD only or control. This potentially could be explained by the fact that children with both ADHD and PLMD group were on prescribed psychotropic medications (68%) compared with the other two groups and the psychotropic medications may contribute to the reduced R sleep stage [66].Our findings are more in line with the findings reported by Marcus et al., [67] investigating sleep in healthy children with or without PLMS. Marcus et al., [67] reported increased arousal index in children with PLMSI>5.0 compared to the children with PLMSI >5.0 and did not find any significant difference in any other sleep measures. These findings suggest, similar to our findings, that an elevated PLMSI may increase the arousal index, which may contribute to the frequent sleep stage transition.

There were no differences in the rates of PLMD during the medication compared to the placebo condition; however, both were lower than during the baseline condition. Of the 6 children who had PLMD at baseline, only 2 of these children reached criteria for PLMD during both MPH and placebo conditions, 3 reached criteria at either MPH or placebo conditions, and one did not meet at either the placebo or MPH conditions. One participant did not meet criteria of PLMD at either baseline or placebo but did meet the criteria at MPH treatment period. The inconsistency in the rate of PLMD across assessment periods was also reported in a previous study by Picchietti et al., [29] and revealed high level of night-to-night variability in PLMS index in children. What is clear from these results is that PLMD rates did not change from the placebo and MPH condition in this current study. By using a dopaminergic therapy, L-DOPA, Walters et al., [55] and England et al., [56] reported an improvement of PLMS in children with ADHD comorbid with PLMD and RLS. Although L-dopa increases DA levels in the synapse and has no direct effect on NA, the mechanism of action (DA agonism) is different from that of MPH. L-dopa is an indirect agonist that increases the amount of pre-synaptic DA, whereas MPH increases the level of both DA and NE by acting as re-uptake inhibitor. The discrepancies in the findings between our study and the above studies regarding the improvement of PLMS may be explained by the differences in mechanism of drug or the different dosages used in these studies. Further studies are needed to clarify whether MPH exerts a marked effect on PLMS.

In an exploratory analysis we compared sleep variables across medication conditions separately for children with ADHD+PLMD and children with ADHD-PLMD. The goal was to determine if children with ADHD+PLMD were differentially impacted by medication. In the ADHD+PLMD group, significant longer sleep latency and a decreased sleep efficiency was found during MPH treatment, but not during the placebo condition. This was not found in the ADHD-PLMD group. There are currently no published studies evaluating the differential impact of MPH in sleep as a result of comorbid ADHD and PLMD, therefore it is difficult to compare the current findings. Further study with a larger sample size is warranted to investigate the potential differential impact of the MPH treatment in children with ADHD comorbid with PLMD compared to children with ADHD without PLMD.

There are a number of strengths and limitations that must be considered when interpreting the results of this study. The strengths of this study are that ADHD and PLMD were rigorously assessed, all participants were medication naïve, no participants had comorbid mental health disorders (with the exception of LD), and none of the children had respiratory-related sleep problems. The limitation of this study is that we had a relatively small sample size of children with ADHD who had PLMD. As such, caution should be exercised in interpreting our results of a differential impact of treatment. Despite this sample size, the current study followed a strict experimental protocol of a double-blind placebo-controlled trial.

In conclusion, we believe that this study further strengthens the findings on the relation between ADHD and PLMD by demonstrating a high rate of PLMD in children with ADHD. This study also presented evidence for the negative impact of MPH treatment in sleep of the children with ADHD diagnosed PLMD by revealing a longer latency and decreased sleep efficiency in children with both disorders. An adequate amount of sleep and poor sleep quality at night are related to daytime performance and behavioral regulation [68,69]. Therefore, medication-related impact on sleep may have the potential to accelerate the severity of daytime ADHD symptoms in this group of children who have both ADHD and PLMD. Further study with a large sample size should be conducted in order to confirm the findings from the current study.

Acknowledgments

Authors' Contribution

Penny Corkum is the Principal Investigator of the larger study. For the current study, she participated in all aspects, from data collection to being involved with the preparation of the manuscript. Esmot A Begum performed the statistical analysis and took a lead in writing the paper. Amy Goodday, Rajda Malgorzata and Kathy Spurr were instrumental in the implementation of this study and all contributed to the writing of the paper.

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