Disordered Sleep in Pediatric Patients with Attention Deficit Hyperactivity Disorder: An Overview

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ABSTRACT: There is a well-established correlation between sleep disturbances and attention deficit hyperactivity disorder (ADHD). A large number of pediatric patients diagnosed with ADHD have sleep problems, while patients with sleep disturbances often display behavioral patterns that resemble some features of ADHD. Despite these observations, the relationship between sleep problems and ADHD is not yet fully understood. It is often difficult to pinpoint which of the disorders is the primary and which a byproduct of the other. A complicating factor is that stimulant medication such as methylphenidate, a drug of choice for ADHD, may adversely affect sleep quality in ADHD patients. However, there have also been reports that it may actually improve sleep quality. This review examines the latest trends in the contemporary literature on this clinical dilemma.

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KEY WORDS: attention deficit hyperactivity disorder (ADHD), methylphenidate, stimulants, children, childhood disorders, sleep disorders

Attention deficit hyperactive disorder is a neurodevelopmental disorder that begins in childhood and causes functional impairment in various life settings. It is characterized by persistent symptoms of inattention, hyperactivity and impulsivity. Based on the clinical dominant pattern, it consists of three subtypes: predominantly inattentive type (ADHD-I), predominantly hyperactive-impulsive type (ADHD-HI), and combined type (ADHD-C) [1]. The global prevalence of this disorder has greatly increased and is estimated to be 5.29% [2]. ADHD is no longer considered a disorder that falls solely under the supervision of either a child neurologist or a psychiatrist. Dealing with the diagnosis and treatment of ADHD has become, in recent years, a major part of the pediatrician's daily workload.

THE RELATIONSHIP BETWEEN SLEEP PROBLEMS AND ADHD

Sleep disturbances are reported by 25–50% of parents of children and adolescents with ADHD, emphasizing specifically their child's difficulties in falling asleep and staying asleep [3]. Sleep is not always assessed in ADHD patients but it should be, as research indicates real differences in sleep quality between children with and without ADHD. According to a meta-analysis of both subjective and objective studies, the incidence of sleep disturbances (e.g., sleep latency onset, night awakening) was significantly higher among children with ADHD as compared to a control group [4]. The association between sleep difficulties and ADHD symptoms is not a new observation. Diagnostic criteria and rating scales for the assessment of ADHD incorporate items relating to patterns of sleep and sleep disturbances [5]. The correlation between ADHD symptoms and sleep disorders is also bidirectional. It is known that sleep deprivation on a chronic basis can affect, and may very well lead to, poor daytime performance, which in turn replicates ADHD-like symptoms and overall poor cognitive achievement [6].

The complexity of the connection between sleep disorders and ADHD becomes even more apparent when considering the different subtypes of ADHD. Reports in the literature on the importance of the different ADHD subtypes and the role they play, if any, in sleep disturbances are inconclusive. For example, Corkum and colleagues [7] claim that there are no ADHD subtype differences in dyssomnias and parasomnias, whereas Mayes et al. [8] reported that ADHD-C was associated with more sleep problems than the ADHD-I and control groups, though ADHD-I patients reported an increase in daytime sleepiness. It is not yet known whether sleep disorder is associated with only certain ADHD symptoms or is the leading cause of sleep difficulties. Either way, it is clear that ADHD subtypes and symptoms need to be considered in both clinical practice and research regarding the association of ADHD with sleep problems.

COEXISTENCE PROBLEMS THAT INFLUENCE SLEEP PATTERNS

In addition to ADHD subtypes, there are several comorbid conditions that should be considered with regard to ADHD and sleep disorders. Of all children diagnosed with ADHD, only 30% have isolated ADHD symptoms, with two-thirds reported to have at least one coexisting condition [9]. According to the literature, there are several conditions that are more likely to co-occur with ADHD. For example, psychiatric disorders (such as conduct disorders, mood disorders, anxiety, tic disorders) as well as substance abuse and learning difficulties can all affect sleep by causing insomnia and hypersomnia [10]. Moreover,

ADHD = attention deficit hyperactivity disorder

medications used to treat these disorders can significantly influence patients' sleep quality. For instance, tricyclic antidepressants can decrease sleep latency onset, decrease arousals during sleep stage transitions, and increase daytime somnolence. Selective serotonin reuptake inhibitors cause daytime sedation, increase sleep latency onset and suppress the rapid eye movement stage of sleep [11]. Psychiatric comorbid conditions and hyperactivity may contribute to sleep difficulties, making this combination extremely challenging.

SLEEP HYGIENE

Sleep hygiene consists of a range of behavioral and environmental changes that may positively affect sleep initiation and maintenance. When performed appropriately, sleep hygiene can substantially diminish sleep problems. Many children with ADHD tend to have more difficulties acquiring good sleep habits, such as the establishment of a daily routine, a fixed hour for bedtime, and a regular wake-up time [4].

COMORBIDITY OF SLEEP DISORDER

In addition to the adverse effects of poor sleep hygiene, motor activity during sleep can influence sleep patterns. Motor activity during sleep in children with ADHD was found to be higher in both the frequency and duration of movements. Moreover, it is reported that movement disorders such as restless leg syndrome and limb movements are more common among ADHD children when compared to the general population [12]. RLS is characterized by an uncomfortable sensation described as bugs crawling on the skin that is relieved by movement. This syndrome becomes worse in the evenings or during the night and involves an irresistible urge to move. Up to 44% of the ADHD population may experience RLS symptoms compared to 10% in the general population, and up to 26% of those with RLS may have ADHD symptoms [13]. RLS can mimic ADHD symptoms during the day with inattention and restlessness. Furthermore, there is a strong correlation between the number of disruptive movements at night and the degree of hyperactivity severity during the day [13].

Sleep disturbances are common among ADHD patients and should be taken into consideration throughout treatment. Educating the patient about sleep hygiene and behavioral techniques is the first step

Several findings may be responsible for the overlap etiology between these two syndromes. The literature shows a positive correlation between iron deficiency and ADHD symptoms [14] as well as between iron deficiency and RLS [15]. It is well known that iron is a coenzyme of dopamine synthesis and that iron deficiency alters dopamine receptor density and activity in animals [16]. This suggests that both RLS and ADHD are associated with altered dopaminergic central nervous system functioning.

RLS = restless leg syndrome

Other sleep disorders that are affiliated with ADHD include obstructive sleep apnea and sleep breathing disorder. These sleep disturbances are significant in children with ADHD when compared to the general population. Habitual snoring occurs in up to one-third of children with ADHD compared to only 10% of a control group [4,17]. Conversely, sleep difficulties associated with these disorders can also cause ADHD symptoms during the daytime. Moreover, adenotonsillectomy for sleep-disordered breathing has been shown to ameliorate inattention and hyperactivity symptoms [18].

It is still not known whether the presentation of clinical symptoms is more severe in children with ADHD and sleep disorders. It is difficult to determine which disorder is the primary one and which the secondary. Clinical assessment is insufficient when evaluating these disorders due to the similarities in behavioral representations [for review see 19].

METHODOLOGICAL ISSUE: SUBJECTIVE VERSUS OBJECTIVE MEASURES

Up to this point, this article has surveyed the information in the literature concerning the high incidence of varied sleep disorders among children with ADHD. There is objective evidence of sleep problems, but a subjective impression may interfere. For instance, one may think that being a parent of a child with ADHD is a challenge, with poor discipline and atypical behavior to be expected. This may lead to the mistaken impression of sleep problems not supported by objective measures.

Sleep has been extensively studied in children with ADHD but the populations are small and the results are conflicting. In addition, some studies have methodological flaws including selection bias and variability in diagnostic criteria for ADHD, which makes it difficult to compare across studies. For instance, pubertal status is not taken into consideration (the effect of circadian timing on sleep/wake cycles). Methods for assessing sleep can also influence the results. Different sleep assessment tools, including psychometric validated parental child questionnaires, clinical interviews, and sleep diaries do not always correlate with objective measurements [20].

There is a tendency in the literature to emphasize that parents of ADHD children are more likely to report a poor sleep pattern for their children than parents of children who do not have ADHD. O'Brien and co-authors [17] found that 77% of children with significant symptoms of ADHD and 70% of children with mild symptoms of ADHD had sleep disturbances as compared to only 43% of children without ADHD symptoms.

Studies using objective measures of sleep have been suggestive but have not provided clear or specific evidence of differences in sleep quality between children with ADHD

and children without. One objective measure is the actigraph device, an activity-based monitor that was established as a reliable and valid instrument to document sleep-wake patterns for extended periods [21]. This small watch-like computer device measures body movement during sleep as well as sleep/wake periods and total duration of sleep. Studies using an actigraph device have suggested that activity during sleep in children with ADHD is higher and that these children tend to have unstable sleep patterns [22]. Another objective device is an infrared video camera that records movements during sleep and enables researchers to watch sleep behavior. Polysomnography is another reliable tool, although it is less accessible since it is used only in sleep laboratories. Results from several polysomnographic studies in children with ADHD reveal an increase in nocturnal movements, reduced sleep efficiency, and decreased percentage of REM sleep, although the findings are not consistent in all the studies [23]. Whether the correlation between REM reductions in ADHD is statistically significant or not, it is important to note that REM sleep has been associated with learning and performance, particularly executive functions, attention, memory and language. A decrease in REM sleep duration has been correlated with lack in these functions [24].

Using the Multiple Sleep Latency Test (MSLT), Lecendreux et al. [23] showed that children with ADHD seem to have a diurnal variation in daytime alertness. They were sleepier during the day and had a longer reaction time. The differences were not due to alteration in the quality of nocturnal sleep. They had an MSLT profile similar to those of pubertal children and adolescents, suggesting a modified developmental pattern.

It is well accepted that tight control of ADHD symptoms during the day improves sleep quality at night

Overall, these findings indicate that ADHD children present with a deficit in alertness. According to the hypo-arousal theory, it is suggested that children with ADHD may overcompensate for their sleepiness with over-activity in order to maintain alertness [25].

MEDICATION

It is logical to surmise that stimulant therapy causes sleep disturbances since it creates an aerosol state. For example, methylphenidate is considered one of the primary drugs for treating the daytime drowsiness symptoms of narcolepsy and chronic fatigue. MPH raises the level of norepinephrine and dopamine in the brain by partially blocking their uptake and increasing their release in the synapse. Positron emission tomography imaging studies have shown acute increases in extracellular dopamine with MPH administration [26], emphasizing that MPH in particular and stimulants in general correct the underlying deficit related to dopamine regulation and availability. MPH mainly affects the striatum and prefrontal cortex regions of the brain, which are vital for concentration.

There is widespread concern among parents and clinicians that stimulant medication for ADHD can worsen sleep disorders. Parents of children treated with stimulants report a higher prevalence of sleep problems (29% versus 10%) and the most common complaint is of nightly increased sleep latency or insomnia [27]. A more than 30 minute increase in sleep latency onset is frequently reported [12,28]. Ironside et al. [29] conducted a blinded medication trial in 16 stimulant medication-naïve children diagnosed with ADHD between the ages of 6 and 12 years old [29]. Results showed that MPH was associated with a significant increase in motor activity during the sleep latency onset period and significantly reduced relative circadian amplitude and a phase-delay in timing of the daily rhythm [29].

In addition to delaying sleep onset, treatment with MPH can also influence sleep patterns. Using an actigraphic device to estimate sleep activity patterns in adults treated with MPH or placebo, Boonstra and team [30] showed that although MPH reduced total sleep time, it significantly decreased the frequency of night-time awakenings and improved sleep quality by consolidating sleep. These data suggest that the advantage produced by MPH occurs as the result of less interrupted sleep. A study by O'Brien et al. [17] found that children with ADHD had more sleep disturbances than those without ADHD, irrespective of their medication status. This observation may give the impression that sleep quality is influenced by the severity of the disorder rather than by the effect of the medication.

It is unclear to what extent stimulant drugs affect sleep quality. Whether there is a direct effect or whether a rebound affect occurs after the stimulant level decreases during the night is unknown. During the rebound period the child becomes more irritable and agitated [31]. Some studies have reported that adolescents and adults need to take their stimulant medication at night in order to sleep well [11], while other studies in children who take an evening dose report greater delays in sleep onset [32]. Moreover, it is well known that among other side effects, stimulants may cause anorexia as long as the drug is active. As drug levels decrease during night, an increase in hunger can disturb the quality of sleep.

The timing of administration can also influence the effect of stimulant medication on sleep. It is possible that administering the dose immediately before the child gets into bed may avoid the previously described rebound effect. Administration prior to bedtime may also have a positive influence on sleep quality by treating the basic deficit of neurotransmitters such

REM = rapid eye movement
MSLT = Multiple Sleep Latency Test
MPH = methylphenidate

as dopamine, which play an integral role in the pathogenesis of ADHD.

Encouraging evidence regarding the timing of administration was reported by Ashkenasi [33]. This study evaluated the effects of individualizing wear-times of the MPH transdermal system on sleep parameters. In this open-label trial conducted in a single center, 26 children with ADHD and sleep disturbances were randomized (after dose optimization) to one of four groups with different sequence of patch wear-time of 9 to 12 hours per day for 1 week. The parameters measured were sleep latency, total sleep time, sleep quality and ADHD clinical assessment (using ADHD Rating Scale-IV and Connor's Global Impression-Parent). Results indicated a tendency toward improved sleep quality ($P = 0.059$) with longer patch wear-time, although the patch wear-time did not significantly affect sleep latency or total sleep time. Sleep parameters were not adversely affected by longer patch wear-time. Although this study was limited by its small size, it supports the notion that continuous treatment with a stimulant may not always disrupt sleep quality.

In addition to the timing of administration, it is important to consider the duration of the treatment. The impact of MPH is likely to be greater in children who just started receiving stimulants compared to those on medication for an extended period and hence accustomed to it [34]. Moreover, studies of flexible dosing (individually tailored according to clinical improvement) are less likely to detect a dose effect or acute disruptions in sleep where the dose is not increased after the response is obtained [35].

Sleep should be carefully assessed individually at baseline before medication is initiated, as well as during the treatment

STIMULANT VERSUS NON-STIMULANT

An interesting question regarding ADHD medication is whether there are differences in sleep quality between stimulants and non-stimulants, and if there is any correlation between the drug's effectiveness in treating ADHD symptoms and sleep disorders. Sangal and collaborators [36] addressed this issue by comparing the effects of atomoxetine twice daily and MPH thrice daily on sleep patterns in children with ADHD. In this double-blind crossover trial conducted at two sites in 85 children aged 6 to 14 years diagnosed with ADHD, each randomized group was treated with each of the drugs for 6 to 7 weeks followed by a wash-out period prior to crossover to the alternative agent. Thirty-nine children underwent polysomnography studies evaluating parameters such as onset of sleep, time in each sleep stage, REM latency, total sleep time, and number of awakenings. The parameter of time-to-sleep onset was measured by three methods: actigraph, parental and child reports, and polysomnography. Actigraph data showed that MPH was associated with delayed sleep onset significantly more than atomoxetine (39.2 vs. 12.1 minutes, $P < 0.001$) with a similar decrease in total sleep interval. Polysomnography child diaries supported the notion that atomoxetine is associated with better sleep quality than MPH. In addition, the children reported that it was easier to fall asleep and easier to get up in the morning using atomoxetine as compared to MPH. In contrast, MPH was associated with significantly fewer sleep interruptions or awakenings [36].

GENETIC BACKGROUND AND MEDICATION RESPONSE

Since the pathogenesis of ADHD is related to a dysfunction of the dopamine system [37], several dopamine-related genes have been suggested as candidate genes for ADHD. Among them is the catechol-O-methyltransferase (*COMT*) gene, encoding an enzyme that participates in the degradation of catecholamine transmitters [38]. It was found that single nucleotide polymorphism in G to A transition at codon 158 causes substitution of valine to methionine resulting in a three- to fourfold decrease in enzyme activity [39].

A recent study by Gruber et al. [40] examined whether genetic background contributes to sleep disorders and ADHD medication response. It was shown that ADHD children with Val form (high activity allele) genotypes of the *COMT* gene may be more prone to sleep problems when treated with MPH or placebo compared to the Met form of the *COMT* gene [40]. The authors concluded that sleep disturbances in children with ADHD are related to the underlying pathophysiology of the disorder.

SUMMARY

The mutual connection between ADHD and sleep disorders is undeniable, although at times it is difficult to distinguish the cause from the result. It is assumed that there is a common etiologic pathway, most likely related to a hypofunctioning dopaminergic system. The relationship between ADHD, sleep disturbances and medical therapy has been investigated extensively, but there is still no consensus regarding the differences of sleep architecture in children with or without ADHD. An interesting fact is that stimulants do not always worsen sleep, and at times may even improve it.

There are several obstacles to the achievement of reproducible research results. The first is the lack of homogeneity of the ADHD population that participated in the studies on the different subtypes of ADHD syndrome and the genetic polymorphism in the specific genes that may contribute to the natural history or to the different reaction to drugs. Second is the existence of psychiatric comorbidities (and their medical treatments) and the presence of primary sleep disorders that mimic ADHD symptoms. A third factor is the effect of medical management, since the type of medicine (i.e., stimulant versus non-stimulant), dosage, timing of administration

during the day, and duration of treatment may influence the sleep parameters. At this point we still cannot predict who among ADHD patients will have improved or worsened sleeping difficulties as a result of stimulant medication.

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"To give pleasure to a single heart by a single kind act is better than a thousand head-bowings in prayer"

Saadi (c. 1200 AD), Persian poet, widely quoted in western sources, recognized for the quality of his writings and for the depth of his social and moral thoughts