REVIEW ARTICLE

Sleep impairment in Attention Deficit Hyperactivity Disorder (ADHD) Is it an additional symptom of ADHD or the result of comorbidities?

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Abstract
Attention Deficit Hyperactivity Disorder (ADHD) is a quite common neuropsychiatric ailment affecting all ages. The diagnosis is based on clinical judgement without a biological diagnostic marker. Thus, both over – and – underdiagnoses are not a rarity. Since it is a developmental disorder the clinical features are altered with age but the classical “triad” of inattention, hyperactivity and impulsivity remain in the majority of the patients throughout their life span. A number of comorbidities are associated with the disorder and in many patients their presence imposes a negative effect on life quality which may be more prominent than that caused directly by the classical "triad". Although cases with the triad have been reported during the last 200 years, the concept of ADHD was solidified in 1987. Sleep impairment as an important comorbidity of ADHD has been slowly unrevealed. Surprisingly, even in DSM-5, any form of sleep impairment was not mentioned in ADHD. This paper is a review of the prevalence, characteristics and possible aetiology of sleep impairment in youngsters and adults with ADHD. Also, the bidirectional association between impaired sleep quality and ADHD is discussed in an attempt to clarify whether impaired sleep is an additional symptom of “pure” ADHD, is the sole result of associated comorbidities or is the result of both.

Key words: ADHD, Sleep, Circadian rhythm, Stimulants , OSA , Anxiety , Depression

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a 24 hours symptomatic condition considered as one of the most common neurodevelopmental disorders of childhood according to the Centres for Disease Control and Prevention (CDC), updated on October 23, 2020. Adolescents and less frequently adults are affected. The main clinical features of the syndrome are inattention, hyperactivity, and impulsivity which winds up during the day to reach a peak severity at the evening, without the ability of winding down towards sleep onset time[1] .The reported worldwide estimated prevalence of ADHD in children is 5%[2,3] . Additional 5% are children with significant pervasive and excessive hyperactivity, inattention and impulsivity which cannot be offered an established definite diagnosed of ADHD[4]. The prevalence of ADHD in school children is 5%-8% [5].In about 50-60% of the affected children, symptoms of ADHD will persist into adulthood[6, 7]. The cross-national estimated prevalence of "true" adult onset ADHD is 2.8%[8] . The population diagnosed with ADHD according to DSM-5 or ICD-10 is quite heterogeneous since 60%–100% of the children suffer from additional childhood onset neurodevelopmental disorders considered as comorbidities [9, 10]. Sleep problems which are very common in children and adolescents without ADHD present as either insufficient or impaired sleep. The affected youngsters suffer from a wide range of additional problems, (some of them are also features of ADHD), such as increased emotional problems[11,] poor school performance[12], inattention, heightened activity and impulsivity[13,] poor concentration, difficult temperament and proneness to accidents[14]. Indeed, during childhood any sleep problem is reported in about 25 % of children [15]. However, prevalence estimates are heterogeneous since those are not uniformly studied. Differences in prevalence rates can be attributed to the source of information based on parental reports in children and self-reports in adolescents. A prevalence rate of sleep problems of 37% was found in community sample of 4-11 years old[16] and 6% among 11 years old in a more recent study by Pagel [17]. Others have reported that 43% of 8-10 years old have sleep problems[18]. The studies which were based on adolescent self-reports highlight the main sleep problem of modern times, i.e. insomnia and sleep deprivation which results in excessive daytime sleepiness. Those features of adolescent and young adults sleep have become prominent with each succeeding generation not only due early school start and academic pressure but also to the steeply increase in the time children and especially adolescents are exposed to nocturnal illumination from electronic screens such as computers, TV and in particular, the quite recent and rapidly increasing addiction to smartphones[19]. Moreover, a new phobia in regard to loosing or being away from the phone was recently coined " nomophobia" [20]. This form of abuse of electronic media is known to negatively influence normal sleep patterns, circadian rhythms and attention[21]. Healthy adolescents tend to extend daytime activities and thus they are at increased risk of evening circadian preference (ECP) [22]. Such a preference is characterized by increased mental and physical activity late in the day with delayed

bedtime and sleep setting, shortened total sleep time and difficulty to wake up in the morning early enough to get to school in time. The net result is sleep deprivation. The shift from morning to evening circadian preference carries health risks for increased anxiety, depression, cognitive ability, substance abuse, antisocial behavior and obesity[23]. In a quite recent study of healthy community dwelling adolescents, those with ECP and consequent daytime sleepiness were at the highest risk of impaired daily executive functions[24], one of the main disabilities of subjects with ADHD. Such problems seem to be very common in adolescents. Vignau found that 40% of healthy adolescents report sleep problems[25] and Levy reported that 12% of their cohort of 390 students considered themselves as chronic poor sleepers[26]. Since normally developing (ND) children with sleep disorders are often inattentive and restless, it is logical to assume that such sleep impairment may be exacerbated and even play a leading role in the symptomatology of ADHD.

2. Sleep problems in youngsters with ADHD

It is quite surprising that the diagnostic criteria for ADHD according to DSM-5 lack criteria for the association of ADHD and any sleep problem since there is no doubt that many youngsters with ADHD have sleep problems with recently reported higher prevalence rates in girls[27]. However, up to date, it is not definitely established if impaired sleep is a unique feature of ADHD, is caused or worsened by certain comorbidities or is the result of both. The prevalence of sleep problems in ADHD according to parent questionnaires is very high, reaching 70% in the study by Sung[28]. Such problems seem to be a common feature of all clinical types of ADHD, (predominantly inattentive [ADHDI]; combined [ADHDC]; predominantly hyperactive-impulsive [ADHDHI]). Nevertheless, youngsters suffering from ADHDC had more circadian rhythm problems, sleep-talking, and nightmares (which were also more common in the ADHDHI type) , while hypersomnia was associated with ADHDI type . The parental reports for the HADHDI and HDHDHI types related to sleep habits disclosed the presence of earlier bedtime, later rise time, longer nocturnal sleep, more frequent daytime napping, insomnia, sleep terrors, sleep-talking, snoring and bruxism[29]. Accumulating evidence suggest that there is a bidirectional association between sleep related breathing disorder (SRBD) and ADHD. Due to the fact that the prevalence and severity SRBD is age related, such an association is more prominent in adult onset ADHD, followed by adolescent patients and lastly in school aged children. The most prevalent SRBD in children and adults are Obstructive Sleep Apnea (OSA) and habitual snoring. It was repeatedly shown that SRBD is associated with behavioral, cognitive and scholastic problems in children of school age[30-32], among them are a significant number children and adults with ADHD [33-36]. In a meta-analysis of studies related to this topic, 1113 children (874 with SRBD who had ADHD symptoms; 239 with ADHD and SRBD) were compared to 1405 controls. The authors found that there was a medium relation (Hedges' g effect size) between

ADHD symptoms and SRDB[37]. The most cited explanation for such an association is the effect of SRBD on sleep quality. Periodic Limb Movements Disorder (PLMD), is also more frequent in children with ADHD (23-26%) [38], compared to normally developing (ND) children (7.7-14%) [39, 40] . PMLD affects sleep quality mainly by causing sleep fragmentation, insomnia, nightmares and daytime behavioral problems which may imitate symptoms of ADHD [40, 41].

Polysomnography proved to be a poor predictor of ADHD subtype[42]. Moreover, in a quite recent meta-analysis type study by Scarpelli of 18 reports on PSG in ADHD published 15 years earlier, in about half of those reports, no difference in sleep architecture of children with ADHD, compared to those with typical development, was found [43]. Nevertheless, some interesting differences in PSG macro and microstructure were noted. While non-REM (NREM) sleep did not differ significantly in ADHD compared to normal controls, REM sleep was of longer duration and there was an increase in the number of sleep cycles[42-44.] It was suggested, that increased number of sleep cycles may impose faster transition to REM sleep explaining in part the longer duration of REM sleep in ADHD[44].The main relevant alterations in PSG microstructure in ADHD children are increased theta activity mainly during REM sleep[45]. Similar findings of increased theta – beta ratio in awake surface EEG in ADHD was associated with impaired inhibitory control[46]. The consistently demonstrated altered theta activity both during waking state and sleep led Scarpelli to conclude that increased theta activity may be a biological marker of ADHD in children in spite of the fact that it was based on only 8 studies published between the years 2006-2017[43]. However, this conclusion could not be confirmed in a study by Zhang et al. in 2019[47.]

3. Is disordered sleep a sole symptom of "pure" ADHD, is cause by comorbidities or is due to both

Neuropsychiatric comorbidities are frequently reported in ADHD. According to parent reports comorbidities were present in 67% of children with ADHD[48.] Those consisted of language impairment (70%)[49], learning disabilities (15-40 %)[50,51] , emotional and mood disorders such as depression (12-50%), conduct and oppositional defiant disorder (30-50%)[52] and impaired motor coordination (30- 50%)[53]. The wide range of prevalence mentioned above can be explained by the heterogeneity of study methods, age range, and cognitive ability, socioeconomic and demographic variables, all known to affect neuropsychiatric morbidity in all ages. About a third of youngsters 6-16 years of age were diagnosed by Takeda as "pure" (without any comorbidity) ADHD [54]. Similar results were reported in two large cohorts of Italian youngsters 12-17 years old [43, 55]. Comparison of the presence of 10 sleep problems (difficulty falling asleep, awakening often during the night, restlessness during sleep, nightmares, sleep talking or walking , enuresis , early awakening, relative short sleep , relative longer sleep , daytime somnolence) between children with "pure" ADHD and ADHD with various

comorbidities using an arbitrary score based on Pediatric Behavior Scale (PBS)[56] , disclosed that the youngsters with ADHDI had slightly less problems than normal controls , and those with ADHDC scored a little higher . Anxiety /depression comorbidity scores were 17% higher in both ADHDI and ADHDC while ADHDC scores were 26% higher than ND children[57]. When sleep was objectively studied by PSG and Multiple Sleep Latency Test (MSLT) in a group of children with and without comorbidity, most of the sleep and MSLT measurements did not differ significantly between the 2 groups, or between the types of ADHD presentation[42] .However, the authors stated that due to the small number of children in each comorbidity, the interpretation of their findings should be taken with caution.

The logical way to assess the bidirectional association between ADHD with comorbidities and sleep impairment is to look for the prevalence of sleep impairment in the most common ADHD comorbidities. In a study of the relation between a variety of sleep disorders and school grades in 2384 Brazilian children 7-10 years old, 733 suffered from symptoms of sleep disorder (SD). Overall, 13.1% failed in language (Portuguese) and 25.5 % in mathematics as compared to 9% and 8.4% respectively in the group without SD. Similar differences were found in children with disorder of initiation and maintenance of sleep regardless of age and gender. The most striking result was the failure in mathematics in all 125 children who suffered from sleep hyperhidrosis[58]. There is also a bidirectional relation between generalized anxiety disorder, as well as subtypes of anxiety, and sleep problems. To overcome the large gap between parent and young anxious patient reports on their sleep quality which hindered several studies of the topic, Masi used a mutual interview with parents and patients in those cases where there was a significant inconsistency between reports of parents and their child. It was found that 51% of youngsters with generalized anxiety disorder experienced sleep problems according to combined child- and parent-reports[59].

Sleep problems are very common in childhood depression. Indeed, 72.7 % of a large cohort of Hungarian children with depression had sleep problems. Out of those 53.5% suffered from insomnia alone, 9 % had hypersomnia alone and 10.1 % suffered from both[60] . It is impossible to determine the true prevalence of sleep problems in conduct disorder, oppositional defiant disorder (ODD) or in both disorders combine. However, there is a bidirectional association between ODD and sleep problems. Possible explanations are the fact that ODD is strongly associated with ADHD, and that in the majority of studies the patient population suffered from combined ODD, depression and generalized anxiety disorder[61]. Although the recognition that youngsters with Developmental Coordination Disorder (DCD) suffer from sleep problems, first reported by Barnett & Wiggs in 2011[62] and recently fortified by subjective and objective sleep evaluation[63,64] , we could not find data stating the prevalence of sleep problems neither in pure DCD nor in ADHD and DCD for comparison.

It is evident from all the above that ADHD and comorbidities have a bidirectional association with heterogeneous sleep disorders, an association which has a negative impact on symptoms of ADHD with and without comorbidity and vice versa. The end result of the variety of sleep disorders in ADHD reviewed above can be summarized as chronic sleep deprivation. Although no clear-cut genetic etiology was documented in ADHD, a recent study of a possible common genetic relation between patients with ADHD and patients with narcolepsy disclosed that polygenic risk scores in ADHD were significantly associated with those of patients with narcolepsy[65].

4. Is there a neuroanatomical explanation for a link between ADHD and impaired sleep

Sleep impairment is associated with widespread regional changes in brain activity shown by numerous objective methods to be involved in sustained attention, distraction, impulsivity and memory. In a recent meta-analysis of publications dealing with structural and functional neuroimaging in ADHD ,at rest and during neuropsychological tasks, revealed wide range differences between ADHD subjects compared to normal controls. Those findings may indicated that ADHD is caused by malfunction of certain neuronal network, in particular the default mode network which consists of medial prefrontal cortex, posterior cingulate cortex/precuneus and angular gyrus[66, 67]. In a large cohort of children with ADHD and sleep impairment symptoms, brain MRI (3 Tesla) disclosed an anatomical overlap between ADHD and sleep impairment symptoms in the middle and inferior frontal gyrus, amygdala, insula and corpus striatum where the grey mater volume was decreased. Moreover, 40% of this overlap was considered as the impact of ADHD on sleep[68]. In a quite recent meta-analysis of functional MRI (fMRI) it was found that in both normal sleep deprived and ADHD subjects there was an overlap of hypoactivation in attention regulating executive functioning networks (dorsal anterior cingulate cortex, precentral gyrus, inferior frontal gyrus and posterior parietal cortex), while accompanying hyperactivation of the thalamus was found ***only*** in the sleep deprived group. Those results suggest that a compensatory arousal mechanism, the thalamic normal wake – promoting systems, can compensate for sleep loss in normal sleep deprived individuals. However, this compensatory "recuse" system is not present or is inactive in ADHD[69].

5. Sleep and drug treatment of ADHD

Stimulant drugs are the treatment recommended for symptoms of moderate to severe ADHD. Of the various stimulants , methylphenidate (Ritalin^{R}) is the most frequently used worldwide[70] and was shown to be effective and well tolerated in most treated children and adolescents[71].The notion that stimulants and in particular Ritalin , may either cause sleep problems or aggravate existing sleep problems in ADHD is supported by parent and patient experience . Moreover, a significant number of clinicians also share this view and are hesitant in prescribing stimulants for ADHD. The

negative impact of stimulants on sleep quality is also supported by several publications[71,72], while in other studies it was found that untreated children with ADHD compared to untreated, did not differed significantly in regard to objective and subjective sleep problems[73]. Indeed, in a double-blind cross over questionnaire study of drug naïve children with ADHD which were given long- acting Ritalin (Concerta[R)] in a dose schedule defined as low , medium and high adjusted to body weight for 4 weeks ,new sleep problems were recorded in 23% of the children who did not suffer from previous sleep problems only when the high dose was given. In contrast, no sleep problems were recorded in 62.5% of the children with previous sleep problems when given the high dose. It is of interest that the children with lower weight and BMI were at the highest risk of having sleep problems when given the high dose of Ritalin[74].In an open labeled study design, 83 children with ADHD were given Ritalin for 8 weeks in the form of gradually increasing doses until sufficient therapeutic effect was reached. Only 10 of the patients had sleep problems during the first 2-weeks of the study when the initial dose of Ritalin (mean dose 20.9 mg. daily) was given[75].

There are only few studies involving small cohorts of adults with ADHD in which Ritalin was found to improve sleep quality[76, 77]. With regard to newer stimulants, a double blind-placebo controlled study of 2 comparable large groups of adults with ADHD, sleep quality was scored before and after a treatment periods of about 7 months with either lisdexamfetamine (Vyvanse[R]) or mixed amphetamine salts (Adderal[R], Attent[R)]. A third of the participants (treated and placebo) showed significant and meaningful improvement is sleep scores. The authors concluded that their findings indicate that the improvement found was not related to stimulant therapy groups [78]. In an updated review of the literature on the effect of stimulants on subjects with ADHD compared to primary insomnia the authors concluded that insomnia is associated with adult ADHD in 30-80% of the patients regardless of drug treatment for ADHD. Nevertheless, they postulated that the studies which showed better sleep quality with drug treatment for ADHD, the improvement could be the result of improved daytime function as a result of the treatment[79.]

6. **Conclusion**

Sleep impairment in ADHD is the combined result of ADHD and comorbidities with a bidirectional negative impact on sleep quality and ADHD symptoms.

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