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Features of the Organization of Sleep in Children with Attention Deficit Hyperactivity Disorder

T. P. Kalashnikova[1] and G. V. Anisimov[2]

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This article discusses current concepts of the clinical features of sleep in children with attention deficit hyperactivity disorder (ADHD), along with sleep macrostructure, its cyclical organization, and the possible common pathways in the pathogenesis of sleep disorders and regulatory functions, and levels of social maladaptation of patients with ADHD. Typical features of children with ADHD are difficulty going to sleep and long times to onset of sleep (resistance to sleep time), increased sleep-related movement activity, including the association of ADHD with restless legs syndrome (RLS) and periodic leg movement during sleep syndrome (PLMS), and daytime sleepiness. The occurrence of circadian desynchronization in children with ADHD explains the link between the chronotype, the circadian typology, and the clinical signs of the syndrome. There are opposing data on the level of rapid eye movement (REM) sleep based on nocturnal polysomnography data in children with ADHD depending on age. However, changes in the proportion of REM sleep during the night are regarded as the leading factor in the pathogenesis of signs of ADHD. Common pathogenetic mechanisms are identified for sleep disorders and ADHD: a diversity of impairments to the metabolism of melatonin, dopamine, and serotonin, aggravation of "social jetlag," and changes in blood iron and ferritin concentrations, which may explain the frequency of RLS and PLMS in children with ADHD. This group of patients displays changes in the number of sleep cycles during the night. Possible strategies for correcting sleep disorders in children with ADHD and their influences on the signs of ADHD are discussed.

Keywords: preschool children, sleep impairments, ADHD, polysomnography in children, REM sleep, Homeostres.

The reciprocal influence of the structure of sleep, emotional stress, and cognitive functions is well-known. Each of the main brain states – waking, REM sleep, and slow-wave (non-REM, NREM) sleep – has its own neuroanatomical basis and neurophysiological and neurochemical characteristics and functions [1]. Deeper understanding of the mechanisms involved in impairments to the sleep–waking cycle and abnormal forms of behavior may lead to new diagnostic and therapeutic strategies, including at the early stage of ontogeny [2, 3].

Attention deficit hyperactivity disorder (ADHD) has in recent decades come to be regarded as the most common cause of behavioral impairments and difficulties with school and social adaptation in children with normal intelligence. ADHD is heterogeneous, with several clinical variants, transforming as the child grows up; it has high comorbidity with oppositional behavior, anxiety and depression, tics, and obsessive-compulsive disorder. The heterogeneity of clinical cases may be linked with differently directed changes in sleep in children with ADHD [2, 4–6]. Sleep problems are encountered in 25–50% of children and adolescents with ADHD [7].

In our attempts to define diagnostic criteria for ADHD, sleep impairments are regarded as one of the possible criteria for confirming the syndrome; this is reflected in the Diagnostic and Statistical Manual of Mental Disorders (DSM) 3rd edition. However, these data were excluded from the subsequent and current editions of the DSM and the International Classification of Diseases (DSM), as convincing evidence

[1] Wagner Perm State Medical University, Russian Ministry of Health, Perm, Russia.
[2] The First Medical and Pedagogical Center Lingua Bona, Perm, Russia; e-mail: anis2010@yandex.ru.

that the presence of sleep impairments should be a diagnostic criterion for ADHD have not been obtained [8].

Difficulties in going to sleep and long times to sleep onset (resistance bedtime, sleep resistance, resistance to sleep time) are the most frequent complaints in patients with ADHD [9]. Resistance to sleep in ADHD is often interpreted as the result of taking psychostimulators, and the syndrome itself is not taken as the direct cause of insomnia. However, this view is currently untenable [10, 11].

Resistance to sleep in patients with ADHD evolves during ontogeny. At young school age, 10–15% of children experience difficulty falling asleep. This is twice as common as in healthy peers. By age 12.5 years, 50% of children with ADHD experience difficulty going to sleep and by age 30 years, 7% of patients report taking more than 1 h to go to sleep every night [12].

Significant increases in the "evening" type of activity have been demonstrated in children with ADHD at age 7–12 years, this showing a positive correlation with resistance to sleep and daytime sleepiness [13]. Results from 13 studies showed that children and adolescents with the late chronotype often suffer from daytime impairments, particularly a tendency to aggression [14].

Impairments to sleep initiation, marked variability in the time of sleep onset, and frequent awakenings in children with ADHD are interpreted as circadian rhythm sleep–wake disorder (CRSWD), which is seen in 70% of cases (compared with 20% in healthy peers). Cortical connections are altered and the perception of environmental signals required for developing the sleep and waking rhythm is impaired. This is apparent as inappropriate thalamic signaling to the hypothalamus, with formation and aggravation of CRSWD [15, 16].

Many researchers have shown that CRSWD is based on changes in the activity of the gene regulating the circadian rhythm (*CLOCK*). There are a few genetic studies reporting a link between polymorphisms in the *CLOCK* gene and ADHD symptoms. Polymorphism can lead to inversion of endogenous melatonin secretion, which peaks in the daytime [17, 18].

The late chronotype in children with ADHD is associated with delayed changes in circadian phase markers, particularly melatonin synthesis, with a resulting delay in sleep onset [10, 19].

Although genetic and/or epigenetic anomalies in the circadian regulation of sleep may predispose children to CRSWD, poor sleep hygiene, negative associations, and "social jetlag" promote persistence of sleep problems [20, 21].

Thus, circadian desynchronization is an important factor mediating the proposed link between chronotype and circadian typology in ADHD [22].

The characteristics of dreams in children with ADHD have been studied. Dream content in children with ADHD is more negatively colored, including more failures, threats, negative consequences, and physical aggression, which may be linked with severe emotional problems [9].

Motor restlessness during sleep is the second relevant aspect of dyssomnic impairments in children with ADHD. Actigraphy studies have demonstrated increased movement activity in patients with ADHD, which are most severe in the combined subtype and the type with predominance of hyperactivity [23, 24].

The ADHD-associated sleep impairments in children include restless legs syndrome (RLS) and periodic leg movement during sleep syndrome (PLMS). There are reports on an interaction between the severity of daytime hyperactivity and the severity of RLS [2]. RLS is seen in 44% of children with ADHD, with a tendency to decline with age [10]. However, the presence of RLS and PLMS cannot ultimately be explained by the neurobiological mechanisms of ADHD. It has been suggested that RLS and PLMS are based on dopamine deficit in the nigrostriatal system. However, this requires further study. It is likely that RLS and PMLS, including when associated with ADHD, are interconnected with impairments to the REM sleep regulatory mechanisms [25].

The significance of iron deficiency in ADHD, PLMS, and RLS is also discussed as a common metabolic component. Children with ADHD have low serum ferritin levels [26]. This is an independent risk factor for sleep-associated motor impairments, including PLMS and RLS. Changes in the ferritin concentration are not specific to children with ADHD; they are also seen in children with autistic spectrum disorders [16].

A number of studies have demonstrated excessive daytime sleepiness (EDS) in children with ADHD [27]. However, the potential influence of daytime sleepiness on success at school in patients requires clarification, some studies have demonstrated that daytime sleepiness correlates more with emotional and behavioral problems at school than with total sleep duration. However, it has no effect in student's mean marks in subjects [28]. Children with predominance of inattention have more severe hypersomnia and extreme daytime sleepiness than patients with other ADHD subtypes [29].

The neurobiological mechanisms underlying ADHD and sleep regulation have much in common. Changes in dopamine levels and noradrenaline deficiency are key neurochemical determinants of ADHD symptoms. Both neurotransmitters play a decisive role in the sequencing of NREM–REM sleep. The serotonin level is also important. Serotonin plays a key role in sleep phase switching and its deficit is regarded as an important neurochemical mechanism of the psychopathology of ADHD [30, 31].

Furthermore, there is commonality in the biochemical transformation of serotonin and melatonin. Melatonin is synthesized from the amino acid tryptophan, which is involved in serotonin synthesis, and this in turn is converted to melatonin by the enzyme serotonin-N-acetyltransferase. Melatonin is an indole derivative of serotonin. Thus, impairments to serotonin metabolism can influence melatonin synthesis and, thus, sleep quality [16].

Impairments to melatonin metabolism are linked with impairments to expression of the gene influencing the enzyme N-acetylserotonin O-methyltransferase (ASMT), which catalyzes the final reaction in melatonin biosynthesis. At the same time, wider use of media in combination with the bright screens of multimedia devices may promote changes in melatonin secretion [32].

Many polymorphisms of the CYP1A2 gene altering dopamine degradation are associated with developmental disorders, including ADHD. This explains the lack of efficacy using melatonin to correct circadian rhythms in patients in some situations [33].

Finally, orexin deficiency can also promote both the formation of the clinical signs of ADHD and sleep impairments. Orexinergic neurons are "multitasking" neurons. Data have been reported providing evidence that the orexin/hypocretinergic system helps maintain attention by increasing cortical acetylcholine release and modulating cortical neuron activity [34, 35]. Orexin neurons have connections with brain areas involved in the processes of recognizing and regulating mood, including the hippocampus. Orexins increase hippocampal neurogenesis and improve the spatial learning ability and measures of memory. Conversely, orexin deficiency leads to learning deficit and reductions in memory, as well as depression [34, 36].

Existing polysomnography (PSG) data on the structure of sleep in patients with ADHD are contradictory, which may be linked with a variety of methodological factors (selection of study group, clinical identification of ADHD, effects of medication, presence of comorbid conditions, adaptation to laboratory conditions, etc.).

Changes in REM sleep are among the most frequent PSG changes in ADHD. Nine of 14 polysomnography reports (64%) demonstrated changes in REM sleep in children with ADHD [37]. In view of the fundamental properties of REM sleep, this is worthy of focused attention. Powerful endogenous activation of the brain during REM sleep plays a unique role supporting stimulation-dependent development of the child's CNS, with expression of genes associated with changes in plasticity in the cortical zones [1].

Changes (increases or decreases) in REM sleep have been found in different directions and levels of severity in different investigations [26, 37].

The lower proportion of REM sleep in children with ADHD was linked with higher indicators of inattention, hyperactivity, and impulsivity, as well as impaired cognitive functions, including language skills and working memory [29, 38, 39].

Studies including children aged from 8 to 15–16 years with the comorbid type of ADHD showed increased REM sleep, which was associated with high-severity inattention, hyperactivity, and impulsivity. In addition, sleep in ADHD patients can be characterized by impairment to the sequencing of the NREM and REM sleep phases [2, 37].

It should be emphasized that the proportion of REM sleep in children with ADHD depends on age. Patients younger than 9–10 years showed decreases in the proportion of REM sleep from the level in healthy peers. Conversely, children older than age 9–10 years showed increases in the proportion of REM sleep during the night [5]. Overall, the results indicated that REM sleep can have opposite actions on neurobehavioral functioning [28].

Our own investigations using nocturnal PSG data identified the following features of sleep in ADHD children aged 5–9 years: decreased total sleep duration, increaseds in the latency and duration of the drowsiness stage, increases in the latency of REM sleep and decreases in its duration, increases in waking during sleep and the number of awakenings, including those lasting >3 min, and decreases in the index of sleep effectiveness. Anxiety levels had no effect on sleep structure [40].

Given that the pathogenesis of ADHD is believed to include inherited factors, it was important to extract PSG patterns for genetic screening. However, there have been no such multifaceted studies. There is one investigation including comparison of actigraphy indicators during nocturnal sleep and the finding of single-nucleotide polymorphisms (SNP) in relation to catecholamine-O-methyltransferase (COMT). The authors demonstrated that among ADHD children, those with the gene with the Val-Val SNP had more stable sleep measures [41].

Data have been reported on changes in the cyclic organization of sleep in a group of children with ADHD as compared with controls, these consisting of a significant reduction in the total number of sleep cycles during the night in children with ADHD (up to 2.7 ± 0.6 cycles, as compared with six cycles in healthy peers), with increases in the duration of the first sleep cycle. Distortion of ultradian rhythms is more marked in boys and patients with the combined subtype ADHD [42].

However, studies reported by Kirov et al. [10, 25] identified an increase in the number of sleep cycles in children with ADHD. It was suggested that the decrease in REM sleep might also promote increase in the duration of absolute REM sleep and lead to a higher frequency of sleep cycles. Deformation of ultradian cycles may be associated with changes in brain monoamines and lead to inhibition of cerebral cortex development and increases in the psychopathology of ADHD.

These results from somnological research in ADHD have provided evidence that these patients need the appropriate treatment tactics. Before pharmacological treatment, children with ADHD need to undergo assessment of the state of sleep, as sleep problems can play a causal role or exacerbate the clinical signs of the syndrome [11, 32]. In addition, sleep impairments themselves can induce symptoms similar to those of ADHD, forming clinical phenocopies; an example is provided by obstructive sleep apnea [30, 40].

The first step in correcting sleep problems in children with ADHD is good sleep hygiene and cognitive behavioral psychotherapy [14]. The second direction in therapy is the question of selecting and modifying drug doses.

Studies reported by France et al. [43] included assessment of rational combinations of behavioral interventions and medication with gradual withdrawal of the latter. Data have been obtained showing the high efficacy of the multicomponent homeopathic formulation Homeostres (Buaron, France) in sleep impairments and anxiety disorders from the third day of use [44, 45]. Clinical homeopathy in the Russian Federation has a legislative basis, in particular Russian Federation Ministry of Health Order No. 335 of November 29, 1995, "The use of homeopathy in healthcare practice." The formulation contains plant-derived substances (aconitum, celandine, licorice, viburnum, belladonna and calendula) at the sixth Hahnemann dilution (CH6). The user instructions indicate that Homeostres is available without prescription, produces no lethargy or habituation and is used in children from three years old at a dose of two tablets three times daily for two weeks.

Outside Russia, methylphenidate is the profile drug for the treatment of ADHD. Use of CNS-stimulating drugs can exacerbate sleeplessness in children with ADHD and increase motor restlessness during sleep, which has been confirmed by actigraphic studies [46].

One study showed that continuous treatment with methylphenidate for six weeks had no further negative influence on sleep architecture in children with ADHD [47]. Studies have been reported demonstrating that methylphenidate facilitates sleep onset and reduces its duration and decreases the proportion of REM sleep in children with ADHD [10]. Along with suppressing ADHD symptoms, methylphenidate and other stimulators have been shown to improve regulatory functions and emotional status by mechanisms including optimization of the processing of emotionally significant information during sleep [31].

An important conclusion is that there is a need for a differential approach to evaluating the effects of methylphenidate on sleep. The efficacy of methylphenidate in ADHD depends on the characteristics of sleep. In children with sleep impairments and ADHD, prescription of methylphenidate is followed by improvements in sleep, while sleep worsens in patients with ADHD and no initial somnological complaints [22].

Results in different directions were also obtained in relation to the efficacy of melatonin in the treatment of ADHD. Data have been reported showing that use of melatonin in the treatment of insomnia in children with ADHD is effective at doses of 3–6 mg [32]. Studies conducted by Holvoet et al. [48] demonstrated improvements in behavior and mood on prolonged use of melatonin, i.e., for 2–3 years. However, drug withdrawal led to recurrence of sleeplessness. Melatonin therapy in children with ADHD produces better results in persistent sleeplessness, especially where there is an obvious phase shift in the endogenous circadian rhythm.

A number of studies have evaluated the efficacy of non-medication methods of treating ADHD – positive effects were obtained using biological feedback and phototherapy [49].

Conclusions. Thus, sleep impairments and behavioral dysfunction have mutual influences. Sleep changes described in ADHD are generally not specific and are mostly linked with maturation of the sleep mechanism. This reflects deep impairments in the formation of the integrative functions of the brain, including the integrative mechanisms of sleep and chronobiological processes in ontogeny.

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