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Comprehensive Diagnostics and Correction of Sleep Disorders in Children

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The article is devoted to a relevant problem of modern pediatrics and neurology - comprehensive diagnosis and correction of sleep disorders in children. The features of clinical manifestations of sleep disorders in childhood (insomnia and parasomnias) are considered in detail, great attention is paid to obstructive sleep apnea syndrome as a risk factor for somatic and psychopathological disorders development in children. Modern possibilities of comprehensive instrumental diagnostics of sleep disorders using highly effective methods of polysomnography and pulse oximetry are covered, as well as relevant aspects of both non-drug and drug treatment of sleep disorders in children taking into account the pathogenetic features of their occurrence. High efficiency of herbal medicine methods, based on traditional Chinese recipes, as well as of modern nootropics and magnesium preparations, are demonstrated from the standpoints of evidence-based medicine. It is shown that sleep disorders in children not only lead to a deterioration of emotional mood, cognitive functions, health and school performance, but also are connected with the increasing risk of somatic disorders. That determines the need

for timely diagnosis and comprehensive differentiated medico-psychological pathological states' data correction taking into account the neurophysiological and biochemical mechanisms of their development, as well as polymorphism of clinical manifestations in order to increase the effectiveness of treatment and quality of patients' life.

Keywords: *sleep, children, polysomnography, insomnia, parasomnia, apnea, melatonin, herbal medicine.*

INTRODUCTION

Sleep is a vitally important, periodically occurring special condition of the body, taking about 1/3 of human time per day, characterized by the absence of any activity, almost complete shutdown of sensory effects from the external world, dreams and specific electrophysiological and humoral manifestations [1].

PREVALENCE OF SLEEP DISORDERS IN CHILDREN

Sleep disorders in children is an actual problem of modern pediatrics and neurology: observed in 84% of children under the age of 2.5 years, 25% - at the age of 3-5 years, 13.6% - at the age of 6 years [2-4]. Amongsleep disorders in childhood the most prevalent are: segoviana (84%), nightwalkings (60%), bruxism (45%), night terrors (39%), nocturnal enuresis (25%), difficulty falling asleep (16%), snoring (14 %), rhythmic movements (9%), obstructive sleep apnea (3%) [4-6].

CLASSIFICATION OF SLEEP DISORDERS

In the ICD-10, sleep disorders are presented under the following headings [7].

1. Sleep disorders (G47):
   G47.0 Disorders of initiating and maintaining sleep (insomnias).
   G47.1 Disorders of excessive somnolence (hypersomnias).
   G47.2 Disruptions in circadian rhythm
   G47.3 Sleep apnea (central, obstructive).
   G47.4 Narcolepsy and cataplexy.
   G47.8 Other sleep disorders (Klein-Levin syndrome).
   G47.9 Unspecified sleep disorder

2. Nonorganic sleep disorders (F51):
   F51.0 Nonorganic insomnia.
   F51.1 Nonorganic hypersomnia.
   F51.2 Nonorganic disorder of the sleep-wake schedule.
   F51.3 Sleepwalking (somnambulism).
   F51.4 Sleep terrors (night terrors).
   F51.5 Nightmares.

F51.8 Other nonorganic sleep disorders.

F51.9 Unspecified nonorganic sleep disorder (emotional sleep disorder).

Sleep apnea in the newborn (P28.3) and Pickwick syndrome (E66.2) are also mentioned in the ICD-10.

The International Classification of Sleep Disorders (2005) includes the following sections [8].

1. Insomnias.
2. Disorders of breathing during sleep.
3. Hypersomnia of central origin not associated with circadian rhythm sleep disorder, disorder of breathing during sleep, or disturbed for other reasons night's sleep.
4. Circadian rhythm sleep disorders.
5. Parasomnias.
6. Movement disorders during sleep.
7. Separate symptoms, variants of norm, and unresolved issues.
8. Other sleep disorders.

Phases and stages of sleep

Phases and stages of sleep are as follows [4, 9, 10].

I. The phase of slow wave sleep (nonREM; NREM), which consists of 4 stages:

- The 1st is characterized on the electroencephalogram (EEG) by a reduction in alpha- and beta-rhythms, on electromyography (EMG) – by a reduction in amplitude, and on the electromyography (EMG) – by slow movements of the eyeballs;
- The 2nd ("sleep spindles" stage) is determined by the appearance of "sleep spindles" and of high-amplitude K-complexes, by reduced amplitude on EMG, and by rare slow movements of the eyeballs on EOG;
- The 3rd and 4th ("delta sleep") is characterized by delta-rhythm (20-50% in the analysis' era in the third stage, and more than 50% - in the fourth), by low EMG amplitude, and by preservation of slow movements of the eyeballs.

II. REM sleep (Rapid Eyes Movement) is characterized by rapid eye movements on EOG, very low EMG amplitude, physiological sleep myoclonia, "sawtooth" theta rhythm combined with alpha and beta waves, "vegetative storm" with respiratory and heart arrhythmia, blood pressure fluctuations, episodes of apnea [9, 10].

Phases of slow and REM make one sleep cycle. A healthy person has 4-6 of such cycles per night. The duration of one cycle is 60-100 min (average about 90 min), while in the first half of the night, there are more slow wave sleeps cycles, and in the second half of night there are more REM sleep cycles. The ratio of the various sleep stages remains constant. For an adult, this ratio is:

- 1st stage - less than 5%;
- 2nd stage - 40 - 60%;
- 3rd and 4th stages - 10 - 20%;
- REM sleep - 15- 25% of the total sleep duration [4, 9, 10].

FEATURES OF SLEEP STRUCTURE IN CHILDHOOD

Child sleep is also divided into phases, but they are distributed differently. In the first months of life, REM sleep takes half of all the infant's sleeping time, its representation is reduced to 1/3 by 2 years, and at the age of 10-14 years it takes 1/4 of the sleep duration, as in adult humans [9, 10]. In infants, the sleep begins with REM sleep, while in adults - with slow wave sleep, and REM sleep firstly appears not earlier than after 90 minutes from the time of falling asleep. REM sleep frequently repeats in infants, forming shortened sleep cycles – more often than ~45 min. Up to 6 months, children's sleep cannot be clearly divided into EEG stages corresponding to a mature sleep pattern. Only after 6 months the infant's sleep architecture becomes similar to that of adults [3, 4, 9, 10]. The total sleep time of newborns is distributed evenly between the day- and nighttime. By one year of life, night sleep becomes predominant and combines into one continuous episode. By 4 years, most children do not feel the need for daytime sleep. In adolescence, the need for night sleep is comparable to that in adults [2, 3, 6].

Modern methods of comprehensive diagnostics of child sleep disorders

The most modern and objective method for the diagnosis of sleep disorders is polysomnography [9-12].

Polysomnography is a method of continuous recording of the body's various vital activity parameters during night sleep [9-12]. This research allows to study the length and structure of sleep, to determine which phenomena occur during sleep and may be the cause of its disorders, as well as to eliminate secondary sleep disorders that are more common than primary and are characterized by normal indications of polysomnography data [10, 13].

Polysomnography records such mandatory parameters [6, 9, 11] as EEG, EOG (eye movement), EMG (genial muscles tonus).

Besides this, additional parameters can be recorded: leg movements, snoring, nasal/oral air flow, respiratory movements of the chest and abdominal wall, body position, blood oxygen saturation (SpO_2), and electrocardiogram [6, 9, 11].

EEG, EOG and EMG registration is needed to determine the stages of sleep and sleep structure. Currently, in accordance with the standards of the American Academy of Sleep Medicine, it is recommended to record 6 EEG recordings (frontal, parietal, occipital) for optimal decoding of sleep stages [14].

For a sleep study, various kinds of instrumental diagnostic systems may be used. In accordance with the International Classification of diagnostic somnological systems, there are [10, 14]:

1. stationary systems (18-77 channels): can register 13 and more parameters with sleep stage determination and total sleep time; these systems are intended for in-depth diagnosis of sleep disorders and, in particular, for verifying the genesis of nocturnal paroxysmal conditions, including epilepsy as well as obstructive sleep apnea syndrome. As a rule, these systems are used in hospitals, and in somnological laboratory conditions under personnel control;

   2. mobile polysomnographic system (18-24 channels, 13 and more parameters): study is carried out without continuous staff monitoring (inpatient or outpatient)

3. polygraphic system, registering a limited set of parameters (4-10 channels, 6-12 parameters), without sleep stages determination ;

   4. screening systems (systems of screening using respiratory monitoring and computer pulse oximetry) can be used for the primary screening diagnostics of breathing during sleep disorders followed by diagnosis specification with the help of polysomnography.

Analyzed sleep parameters, obtained as a result of polysomnographic observation [4, 6]:

1. Quantitative indicators of the night sleep structure:

   - the total sleep duration (TSD) - time from the onset of objective polygraphic sleep image till full morning awakening minus the wakefulness time within sleep;
   - latent periods of stages - time elapsed from beginning of the first stage until the beginning of 2nd, 3rd or 4th stages of slow wave sleep and REM sleep;
   - latent period of falling asleep - time from the start of polygraphic recording until the appearance of the first "sleep spindle";
   - percentage representation of stages towards the locomotor system and the time of day;
   - the total duration of the periods of wakefulness within sleep;
   - the number of spontaneous awakenings from sleep;

2. indicators of motor activity during sleep: quantity of movements calculated for 1 sleep hour (in general) or for 1 hour of each stage;

3. activation indicators:

   - movements associated with the movement activation, after which the transition to more superficial sleep stage is marked;
   - movements activation index - percentage representation of movements associated with activation to a common number of movements during sleep (in around sleep at whole) or to the number of movements at sleep stages (in stages);

4. vegetative indices in night sleep: heart rate for each third of appropriate sleep stages and then averaged for each of the stages of the slow wave sleep and REM sleep;

5. Qualitative indices of slow wave sleep [4, 6]:

- "Sleepy spindles" index: is determined by counting EEG-waves in the range of "sleepy spindles" in all the stages of the 2nd slow wave sleep phase with following calculation of their number per step minute;
- K-complexes index: counting K-complexes quantity in all stages of the 2nd phase of slow wave sleep with a following recalculation of their number per 2nd phase minute;
- delta index: figure of delta waves percentage (with an amplitude of not less than 50 microvolts and with frequency of up to 3v s) relative to the duration of the epoch. Were counted in each third epoch and then averaged for the whole sleep and each cycle of sleep (I - IV cycles); delta-index for the 3 and 4 stages was calculated separately (stage 3 + 4);

6. Qualitative indicators of REM sleep - REM index: counting the number of REM in all stages of REM sleep followed by calculationg their amount in 1 minute of REM sleep [4, 10].

There is a common sleep index (SI) formula:

SI = TSD / time spent in bed [4, 10].

Additionally, the integrative quality of sleep index can be calculated. This index is obtained by mathematical analysis based on the calculation of the confidence interval of 37 polysomnograms parameters, herewith, the lower are the values of this parameter, the more physiologically optimal sleep is [4, 10].

Polysomnographic study helps to clarify the clinical diagnosis of sleep disorders, which are quite diverse in children.

CLINICAL FORMS OF SLEEP DISORDERS IN CHILDREN

Insomnia

Recurring troubles with initiation, duration, consolidation or quality of sleep, that occur despite the presence of sufficient time and opportunity for sleep, and characterized by a variety of day activity disorders that may occur in the form of fatigue, poor attention, concentration and memory, social dysfunction, mood disorders, irritability, daytime sleepiness, reduced motivation and initiative, propensity to errors behind the wheel and in the workplace, muscle tension, headaches, gastrointestinal disturbances, and persistent concern about the state of one’s sleep [4, 6]. Mental disorders in patients with insomnia are detected 2.5 times more likely than in healthy people. It is shown that the lifetime risk of developing depression with insomnia increases by 4 times [13, 15].

A special form of insomnia is child behavioral insomnia [6, 13]. There are two forms of the disorder: in the insomnia type connected with incorrect associations about falling asleep, children form false stereotypes associated with sleep (for example, the need to sleep only during rocking, feeding), and when you try to remove or adjust these stereotypes, the resistance of the child arises, resulting in the reduction of sleep time [6]. These children do not go to sleep at night without the active participation of their parents, wake up many times during the night and require the usual associations from adults. Insomnia type connected with an incorrect sleep setting means that a child refuses to go to sleep at a specified time or in a certain place, protesting with lengthy and frequent requests to feed, to go to the toilet, to comfort ("the call from outside the door" symptom), or comes to the parents' bed to sleep at night [6].

Hypersomnia is defined as a state of excessive sleepiness and sleep attacks during the day or as a protracted transition to a state of full wakefulness during awakening. One of the manifestations of hypersomnia is narcolepsy - a disease the main symptom which is bouts of irresistible sleepiness [8, 12].

Parasomnias

Quite prevalent are phenomena of parasomnias (up to 37%), occurring during sleep or when falling asleep and waking up and not directly related to disorders of the circadian rhythm of sleep-wake cycle. Parasomnias include sleep-talking, bruxism, nocturnal enuresis, sleepwalking, night terrors, nightmares, rhythmic movement disorder [8, 12, 16].

Sleep-talking is uttering words or sounds during sleep, in the absence of the subjective awareness of the episode [8, 12]. It is a benign phenomenon that occurs much more frequently in children than in adults. Thus, in the category of "often or every night" sleep-talking occurs in 5-20% of children and 1-5% of the adult general population [8, 12].

Sleepwalking is a form of altered consciousness in which states of sleep and wakefulness are combined. During an episode of somnambulism, a person gets out of bed, usually during the first third of nocturnal sleep, and walks, showing low levels of awareness, reactivity, and motor skills, and upon awakening, he usually does not remember what happened. Sleepwalking occurs usually during the 3rd and 4th stages of slow wave sleep. About 5% of sleepwalking has an epileptic nature [8, 12].

Night terrors (horrors) are night episodes of extreme terror and panic, followed by intense cheers, motions and high levels of vegetative manifestations, when a child sits down or gets up from the bed, usually during the first third of nocturnal sleep, with a panicky scream, does not respond to the words addressed to him/her, and any attempts to calm him/her down may increase fear or lead to resistance [16]. Memory of the incident, if any, is very limited (usually one or two pieces of mental imagination). The prevalence in children is 1-4%, reaching a peak at the age of 4-12 years. Most often episodes of night terrors occur when waking from the 3rd and 4th stages of slow wave sleep [16].

Nightmares - experiences in a dream, overloaded with anxiety or fear, bright and typically including topics related with threats to life, security or self-esteem, which tend to

repeat; herewith the patient remembers all the details of the dream [16]. During a typical episode of this disorder, there are vegetative manifestations, but no noticeable exclamations or movements of the body [16].

"Restless legs syndrome" is characterized by unpleasant and sometimes painful sensations in the legs that appear more often before the onset of sleep, growing to the middle of the night (sometimes during the day), and cause a strong desire to move the limbs. The symptoms facilitate by moving and can last from several minutes to several hours, delaying the onset of sleep. There are both idiopathic (probably hereditary) and symptomatic (due to iron deficiency, metabolic disorders, and so forth.) forms of the syndrome [4-6].

Movement disorders associated with sleep, in addition to the "restless legs syndrome" include night cramps, rhythmic movement disorder (group of stereotyped repetitive movements of the head, trunk and limbs), and bruxism [4-6].

Periodic limb movements in sleep are frequent series of movements in the limbs (extension of the thumb, ankle flexion, etc.), which are repeated periodically during sleep at intervals of 10-90 sec (while the patient does not know about the presence of such conditions) and can cause awakening that leads to fragmentation of sleep and daytime sleepiness [4-6, 12].

Sleep associated *nodding* appears as rhythmic head swinging (usually in the period immediately preceding sleep, less common during sleep), which may be associated with emotional overexcitation during the day, and, as a rule, is significantly reduced by 2-3 years of age [4-6, 12].

Bruxism - teeth grinding episodes during sleep often associated with daytime emotional situations and familial events, as well as a manifestation of various hyperdynamic disorders in the child (hyperactivity syndrome with attention deficit). Bruxism often occurs during the 2nd stage of sleep [4-6, 12].

Enuresis - a disorder characterized by frequent (for boys after 5 years - more than 2 episodes per month, for girls - 1) cases of involuntary urination during sleep. Children with this disorder, as a rule, experience a very deep sleep (delta sleep is increased), though episodes of enuresis can be observed at all stages of sleep. There are primary (from birth) and secondary (when disorders occur after the foregoing, at least one year, "dry period") forms of enuresis [4, 12].

Sleep apnea syndrome

A relevant and frequent (in pediatric practice) sleep disorder connected with breathing problems during sleep - sleep apnea and hypopnea, which develop only during REM sleep and can be [10, 17-19]:

1. Obstructive: caused by the collapse of airways in the continuing respiratory efforts, herewith the function of the respiratory center is saved;

2. central (Cheyne-Stokes respiration and other forms): caused by functional decrease or stopping of respiratory center and respiratory efforts, but herewith airways remain open;
3. mixed.

The obstructive sleep apnea syndrome (OSAS) is a condition characterized by the presence of snoring, periodic falling of the upper airway at the throat, and the termination of pulmonary ventilation in persistent respiratory efforts, reduction in the blood oxygen level, rough sleep fragmentation and excessive daytime sleepiness [10, 17-19]. The clinic of OSAS is characterized by cessation of breathing during sleep, followed by loud snores. It was shown that during severe OSAS (400-500 apnea per night) the risk of sudden death during sleep, hypertension, cardiac arrhythmias, myocardial infarction, and stroke significantly increase [10, 19].

The Wisconsin cohort study (USA) showed an increased risk of cardiovascular mortality by 5.2 times during 18 years of observing untreated patients with OSAS [18].The main neurocognitive complications of OSAS in adults are severe daytime sleepiness, irritability, depressed mood, apathy, loss of memory and attention, intellectual degradation [20-23]. Among the children, snoring is found in 10-14% under the age of 2-6 years, OSAS - 1-3%, with a peak of incidence between 2-8 years of age [24, 25]. Premature morbidity risk of OSAS is 3-5 times higher than that in full-term infants. Other risk factors are adenotonsillar hypertrophy, allergies, diseases of the upper and lower respiratory tract, choanal stenosis, displacement of the nasal septum, hereditary pathology (frequency of OSAS in Down syndrome is up to 80%), hypotension (especially in muscular dystrophy), obesity, and illnesses and injuries of the central nervous system [24-26].

Universally recognized criteria of the OSAS severity is the frequency of apnea and hypopnea per hour (apnea / hypopnea index, AHI). In children with mild OSAS, AHI is 1-5, with moderate OSAS - from 5 to 15, with severe - more than 15 [10, 27].

The reasons for the formation of OSAS in children are adenotonsillar hypertrophy, deformation of the facial skeleton, obesity, allergic rhinitis, diseases of the nervous system (neuromuscular diseases, amyotrophic lateral sclerosis, etc.) causing disruption of the muscles responsible for keeping the airways open during sleep [25].

The main clinical psychopathologic manifestations of OSAS in children are attention deficit and hyperactivity, daytime sleepiness, aggression, somatization complaints, depression, and retarded physical and mental development [28]. Disturbances of behavior and school performance in children with OSAS are found 3 times more often than in others [28].

In case of severe OSAS, obesity develops, as well as violation of the production of growth hormone (HGH) and testosterone secretion, the peaks of which are observed in the deep stages of sleep, which are practically absent with OSAS [29].

The main method of OSAS diagnosis is polysomnography, the main screening method - computer pulse oximetry [11, 30, 31]. According to the recommendations of the American

Academy of Pediatrics (2000), a screening study of OSAS is necessary for all children with snoring [27].

Computer monitoring pulse oximetry is a method of long-term monitoring of oxygen saturation and heart rate using special hand-held devices - pulse oximeters [30, 31]. Computer oximeters, which provide signal registration with increments of once every few seconds (from 1 to 10 s), are used for monitoring. Counting the number of desaturations (decrease in blood oxygen saturation) in 1 hour (desaturation index) gives an indication of the frequency of episodes of apnea / hypopnea in 1 hour - AHI [11, 30, 31].

The algorithm for OSAS diagnosis involves several stages [11].

Stage I. On the basis of complaints, medical history, physical examination and the presence of somatic diagnoses in which there is a high probability of obstructive sleep apnea syndrome, the risk group is formed with suspected obstructive sleep apnea syndrome.

Stage II. Taking a computer pulse oximetry in patients of the risk group. In case of the desaturation index being < 5 per hour, diagnosis of obstructive sleep apnea syndrome is unlikely, and further evaluation is not required. When desaturation index is from 5 to 15 per hour, diagnosis of obstructive sleep apnea syndrome is possible, but requires specifying research (cardiorespiratory monitoring, polysomnography). When desaturation index is > 15, the diagnosis of obstructive sleep apnea can be considered confirmed.

Stage III. Clarifying method of diagnosis according to the recommendations of the American Medical Association (polysomnography, cardiorespiratory monitoring, respiratory monitoring) [11, 27].

Similar to the obstructive sleep apnea syndrome, the clinical picture can produce a syndrome of central sleep apnea (Cheyne-Stokes respiration), in which cyclic respiratory stoppages can also be observed [10, 11, 32, 33]. It is necessary to differentiate between the above disorders, since they require different therapeutic approaches. The cardinal differential-diagnostic sign of obstructive sleep apnea and Cheyne-Stokes respiration is the presence or absence of respiratory movements during an episode of sleep apnea, as in the syndrome of obstructive sleep apnea, where, despite the absence of nasal-oral airflow, respiratory efforts are saved [11]. In case of Cheyne-Stokes respiration, cessation of ventilation is caused by an impulsion violation of the respiratory center and the lack of movement in the chest and the abdominal wall. The presence of severe heart failure, stroke or severe head trauma in a patient's history is more likely to indicate the possibility of Cheyne-Stokes respiration, although it does not exclude the concomitant obstructive sleep apnea syndrome [11]. Obstructive sleep apnea is diagnosed about 20 times more often than Cheyne-Stokes respiration [11].

The OSAS syndrome in children requires differentiation with periodic (irregular) breathing of newborns due to immaturity of the respiratory center, especially in preterm children [4, 10, 11]. Periodic breathing appears as a uniform alternation of respiratory movements (less than 80 per min) and a drop in the level of oxyhemoglobin. Though periodic breathing is considered to be a benign phenomenon in newborns, even short breaks can cause significant bradycardia and desaturation of oxygen. Unlike OSAS, periodic breathing may occur in both

REM and slow wave sleep, with relatively regular intervals of breathing and apnea. Some experts consider OSAS as a sign of cardiorespiratory instability, indicating the possibility of sudden infant death syndrome, but this issue requires further study [4, 10, 11].

According to the international standards for the majority of children with OSAS, adenotonsillectomy is identified as first-line treatment; moreover, the combination of OSAS and enlarged tonsils is an absolute indication for its conduction [34, 35]. The effectiveness of this method is observed in more than 80% of the children: a significant improvement in behavior, mood, attention, daily activities and learning abilities are observed after 6 months after surgery [34, 35]. Although the efficacy of tonsillectomy is high, it cannot guarantee a lifelong cure; moreover, the frequency of perioperative complications can reach 30%. In young children there can be a postoperative improvement, which at a later age would be replaced by the development of OSAS, herewith the risk factors are craniofacial anomalies (retrognathia and micrognathia), muscular hypotonia, obesity [34, 35].

In case of a combination of snoring and OSAS with allergic rhinitis, nasal obstruction and adenotonsillar hypertrophy, drugs of choice would be topical corticosteroids [36-39]. While using these drugs, a reduction in the size of the adenoids and tonsils is marked, breathing parameters during sleep improve [36, 37]. Mometasone furoate is approved for use from the age of 2 years in children with allergic rhinitis, adenotonsillar hypertrophy, snoring and sleep apnea, when topical corticosteroids are used as first-line therapy [39]. It is shown that the use of mometasone in patients with snoring for 3 months at a dose of 200 mg/day results in a substantial reduction of snoring and sleep improvement [39].

In children with OSAS, topical corticosteroids should be prescribed for a minimum of 40 days with further re-estimation of the OSA severity and the definition of further tactics of treatment: in the case of SDB elimination or significant relief of OSAS (reduction of AHI to < 5) it is possible to continue conservative treatment; while maintaining the $\underline{\text{AHI} \geq 5}$ it is recommended to remove the adenoids and enlarged tonsils surgically [11, 33, 39].

In adult patients, the main treatment for OSAS is a non-invasive assisted lungs ventilation which is done by creating a continuous positive airway pressure [5, 40-42]. In English literature, this method is called CPAP (Continuous Positive Airway Pressure) [11, 40, 41]. With CPAP-therapy, continuous positive airway pressure is maintained during the entire respiratory cycle, which prevents its dropping and removes the basic mechanism of the disease consisting of the airway cyclically overlapping the throat. To create positive pressure, a small compressor is used, which delivers a constant airflow under a predetermined pressure to the respiratory tract via a flexible tube and a nose mask, [11, 40, 41].

Indications for CPAP therapy is moderate or severe OSAS regardless of the presence / absence of clinical symptoms, as well as mild OSAS in the presence of documented symptoms of daytime sleepiness, cognitive impairment, mood, insomnia or documented hypertension, coronary heart disease or disorders of cerebral circulation in history [11, 40, 41]. Absolute contraindications for the CPAP-therapy are not revealed; however, this method should be used with caution, weighing the possible risks and benefits, in patients with such conditions as bullous

lung disease, recurrent sinusitis and eye infections, severe respiratory insufficiency, severe hypotension, dehydration, a history of pneumothorax, pneumomediastinum, pneumocephalia, respiratory distress syndrome, previous brain, middle ear, inner ear, pituitary or gland surgery and frequent nosebleeds [11, 40]. Adequate treatment acceptability is defined as regular CPAP therapy more than 4.5 hours per night. The use of CPAP results in normalization of cerebral and systemic circulation after the first night of treatment [40]. To achieve the maximum beneficial effect on neurocognitive symptoms, up to two months of CPAP therapy may be required [41]. In recent years, researchers have described a successful experience of CPAP in children of all age groups, but especially recommended with concomitant obesity, as well as in patients with craniofacial anomalies [40, 41].

MELATONIN AND SLEEP DISORDERS IN CHILDREN

According to some researchers, one of the important determinants of sleep disorders may be the violation of melatonin synthesis [42, 43].

Melatonin is involved in virtually all life processes, and controls many bodily functions: sleep, cardio-vascular, endocrine and immune systems' activity. It is known that melatonin is the main hormone produced by pinealocytes in the epiphysis (80%), the retina and the intestine, thymus, and pancreas [42, 43]. The synthesis of melatonin in the pineal gland is effective only at nightfall, during sleep, and is reduced in the light phase of the day. Its concentration in the blood increases with the onset of darkness and reaches its maximum for 1-2 hours before waking. In humans, melatonin secretion by the pineal gland is the same with the usual hours of sleep. Melatonin has a short half-life (about 30 min), as 6-hydroxymelatonin-sulphate is excreted in urine [42, 43].

In healthy children, the level of melatonin in the blood gradually increases up to 1 year of life and is retained at a high level to puberty. The highest peak nocturnal melatonin concentration (about 325 pg/ml or 1400 pmol/l) is observed between the ages of 1-3 years (wherein nocturnal melatonin levels are about 40 times higher than daytime ones), then it gradually decreases [42]. In young children, this hormone performs two functions: it increases the duration of sleep and inhibits the secretion of hormones. At puberty, the amount of hormone circulating in the blood is reduced, the amplitude of the circadian rhythm of secretion by the pineal gland reduces, the difference between night and day level is cut to 6-10 times. Young people have an average amount of melatonin in the afternoon and peak - in the middle of the night of 10 and 60 pg/ml (40 and 260 pmol/l), respectively, [42, 43]. It is known that melatonin has an anti-gonadotropic action, and reducing its level accelerates sexual maturation [42]. Over the past few years, receptors for melatonin in many organs (brain, retina, intestine, ovaries and blood vessels) have been identified. There are two types of known melatonin receptors:

- cytoplasmic (MT1, MT2, TM3), found at the suprachiasmatic nucleus, hypothalamus, hippocampus, cerebral cortex brings and cerebellum;

- nuclear receptors found in various hypothalamic nuclei, retina, pineal gland, and epiphysis which belong to a new subclass of family of so-called orphan nuclear retinoid receptors ROR / RZR [42, 43].

This family includes the products of gene expression *of* alpha-ROR, *beta-ROR* and gamma-ROR. Receptors in the suprachiasmatic nuclei of the hypothalamus, apparently regulate the circadian rhythm, and receptors that are found in epithelial tissues (e.g. endothelium of arteries), regulate the cardiovascular function (it is known that melatonin has a relaxing effect on vascular smooth muscles, thus improving microcirculation) [42, 43]. Melatonin in the body carries out such tasks as biorythmological function (regulation of circadian rhythms); thermoregulation, sleep induction; antioxidant effect; anti-stress effect; regulation of sexual development, immunomodulatory effects [43-46]. Violation of quantitative production and rhythm of melatonin is the starting point, resulting on the initial stages in the appearance of DS, followed by organic pathology [42-45]. It is known that melatonin inhibits the proliferative activity of the cells and increases the level of apoptosis, preventing the emergence and development of tumor processes, slowing down the growth of certain tumor cell lines that may be caused by oncostatic and immunomodulatory effects [42, 43]. The immunomodulating effect of melatonin includes an enhancement of the immune response, increasing the activity of T- and B-immune cells, increasing the synthesis of gamma-interferon and interleukin in lymphocytes-helpers, and the tumor necrosis factor [42, 43].

In recent years, much attention is paid to the anti-stress function of melatonin, which is based on a decrease in the activity of sympathetic nervous system tone and the pituitary-adrenal system activity, reduction of corticosteroids, increasing in synthesis of endorphins [44, 47], as well as the ability of melatonin to restore and preserve the natural sleep pattern in patients with insomnia by acting as a chronostabilizer (sleep-wake cycle phase controller) [48]. The results of current research suggests that melatonin is not only a safe and effective treatment for sleep disorders in adults and children, but also has a positive effect on cognitive function in patients with neurodegenerative diseases [47, 49, 50]. The synthesized from amino acids of vegetable origin analogue of melatonin promotes normalization of nocturnal sleep: makes falling asleep faster, improves sleep quality, normalizes circadian rhythms; is not addictive; is taken as a hypnotic orally in 30-40 minutes before sleep [50].

MODERN APPROACHES TO THE COMPREHENSIVE TREATMENT OF SLEEP DISORDERS IN CHILDREN

Methods of non-pharmacological correction of sleep disorders in children should precede and accompany drug therapy [4-6, 12]. "Sleep hygiene" includes activities such events as respect for the sleep and waking regimen, waking up and laying the baby at the same time, limitation of mental and physical activity as well as of receiving stimulating drinks (especially caffeine because caffeine reduces the production of melatonin) before bedtime, restriction in heavy meals and liquid; providing comfortable sleep (minimum level of illumination, cool air temperature, since lowering the temperature of the environment and the body initiates the onset of sleep).

There are special methods of behavioral therapy of children's insomnia, including tactics of "checks and exposure" or "gradual redemption" [4, 6]. When using the first method, the child is placed to sleep only in his bed, parents ignore the related protests within a certain time, and then come, correct the bed and return to their bed, which contributes to a change in the 'wrong' falling asleep associations with the "right" (sleep in own crib). In another method, parents left the child to sleep in the room alone, but say that they will "come out and will be back soon," thus preventing the protest behavior, and gradually lengthen the periods of absence [4, 6].

For the treatment of sleep disorders in children, sedative properties of various herbs (valerian, motherwort, lemon balm, hops, camomile, peony) in various combinations are widely used [2-4]. From the standpoint of evidence-based medicine, the results of fundamental studies of the effect of herbal medicine for sleep are interesting, conducted by Chinese scientists in Heilongjiang University of Traditional Chinese Medicine (Harbin, China) [51-55]. Several double-blind, placebo-controlled randomized trials have shown the high efficacy of complex herbal medicines that are based on traditional Chinese recipes used in case of sleep disorders. It is shown that the Sini Sun preparation, widely used in China for the treatment of sleep disorders, established on the basis of traditional Chinese recipes and including such vegetable ingredients as *Radix Bupleuri* (root of thoroughwax), *Radix Paeonae Alba* (root of white peony), *Radix Glycyrrhizae* (licorice of root), *Fructus Aurantii Immatures* (fruits of bitter orange), affects the functioning of the serotonergic system [51].

Results of a polysomnographic study on the popular traditional Chinese medicine preparation Zhusha Anshen Wan, which is composed of *Rhizoma Coptidis* (rhizome of Chinesegoldthread), *Radix Glycyrrhizae* (licorice root), *Radix Angelicae Sinensis* (Chinese angelica root), *Cinnabaris* (cinnabar, sulfurous mercury), *Rehmannia Rhizome* (rhizome of Reimann, Chinese foxglove) show a dose-dependent effect of the drug: when used in low doses, it was noted to provide an increase in the representation of SWS2 phase of sleep, in average doses - an increase in total sleep time due to the representation of the slow phase SWS1, SWS2, and in high doses - an increase in not only the total sleep time and representation of SWS1 and SWS2 phases, but also in the fast REM-phase. That indicated a more pronounced effect of this preparation on the duration and structure of sleep, compared with chemically synthesized drugs in the absence of significant side effects [52]. The results of this study demonstrate the possibility of differentiated treatment of insomnia, are important in terms of correcting cognitive disorders arising from sleep disorders, because studying the cognitive function under conditions of sleep deprivation showed that elimination of paradoxical REM-sleep phase leads to a significant reduction in memory, learning ability [53], attention, and increased aggression [56].

The high efficiency of the use of *Rhodiola sachalinensis* (Rhodiola Sakhalin) as a sedative preparation improving sleep was also demonstrated as the researchers of Heilongjiang University of Traditional Chinese Medicine identified both an increase in sleep duration and the normalization of its structure, which is associated with the possible influence of salidroside on the serotonergic system [54] .

Representatives of the valerian family, which includes about 200 species growing in North America, Asia and Europe, are widely used in traditional herbal medicine of various diseases of the nervous system in children and adults [55]. The researchers found that valerian, which is most commonly used as a sedative means, contains more than 150 active ingredients that define a wide range of its activities and provide anxiolytic, anticonvulsant and antioxidant effects [55]. A study cunducted in Heilongjiang University of Chinese traditional medicine concerning the isolation and study of active components of *Valerianae amurensis* (valerian Amur), which is mostly common in Heilongjiang (China), showed that the sedative effects of valerian, as well as its positive impact on the length and structure of sleep, are provided by compounds belonging to the group of sesquiterpenes (including derivatives of valeric acid), and 11 of already known sesquiterpenes were revealed. Their new representatives (caryophyllene derivatives) were also allocated, with a high biological and pharmacological activity [55 were].

One of the most effective and safe drugs used in children for the purpose of correction of the autonomic dysfunction syndrome, including sleep disorders, is hopantenic acid, which relates to the nootropic agents with a broad spectrum of clinical activities, combining neurometabolic, neuroprotective and neurotrophic effects [57-60]. A study of the drug's effect on the length and structure of sleep (using daily EEG monitoring) in 71 newborn with perinatal hypoxic-ischemic central nervous system damage has shown that before the treatment, a sleep cycle shortening was observed in 78.8% of children, the duration of the transitional sleep of more than 1 min was observed in 78.9%. After a course of treatment with hopantenic acid, the frequency of sleep disorders has decreased to 52.6%, the sleep transitional period frequency duration of more than 1 minute and latency period of 2 phase of restful sleep decreased to 45.5%, which demonstrates the high efficacy of the drug in the correction of sleep disorders in children [61]. Another clinical study showing the results of using hopantenic acid in children aged 3-5 years, patients with epilepsy with cognitive impairment and attention deficit hyperactivity disorder, testified that before the treatment sleep disorders were observed in 70% of patients, tics and fatigue - in 25 %, increased anxiety and fear – in 30%. After a 1-month course of the drug, a significant decrease in anxiety; improvement of sleep, focus, mechanical and dynamic memory, structure of the EEG background rhythm were observed in patients with the normalization of the zonal differences [62]. A study on the use of hopantenic acid in the treatment of children with rolandic epilepsy, showed that after 2 months of treatment, fatigue decreased from 66.7 to 23.8%, headache - from 38 to 14.3%, loss of memory, attention - from 71.4 to 42.9%, motor disinhibition - from 57.1 to 23.3% [63].

In children with sleep disorders caused by diseases of the nervous system, one of the leading problems of pathogenetic pharmacotherapy is to increase the energy potential of the brain using metabolically active energotropic levocarnitine drugs [64, 65]. In young children (in which sleep disorders are detected most frequently) the endogenous synthesis of carnitine is almost not performed, which makes them particularly vulnerable to the lack of receipt of exogenous carnitine with food. The significant efficacy of the levocarnitine drug in correcting

sleep disorders and other manifestations of autonomic dysfunction syndrome in children of different ages was demonstrated [64, 65].

Doxylamine can be used with a distinct sedative effect for the treatment of sleep disorders in adolescents from the age of 15 [66]; it is particularly prescribed for patients with complicated allergo anamnesis, and is the only drug with a soporific effect, which is approved for use in patients with sleep apnea [66].

Medications with an anxiolytic and neuroprotective effect: Phenibut, Noofen, Adaptol have a positive effect in the complex treatment of sleep disorders in children [67-69].

Noofen and Phenibut are derivatives of gamma-aminobutyric acid (GABA) and phenylethylamine (γ-amino-β-phenylbutyric acid hydrochloride) by their chemical structure. Noofen is an original tranquilonootrop, has clinically valuable combination of a nootropic and a mild tranquilizing effect, which is largely caused by its effect on GABA-B receptors, which differs from that of benzodiazepines, acting on GABA-A receptors [67, 68]. Experimental studies on the application of tranquilonootrops showed that the GABAergic neurotransmitter system is involved in the development and implementation of internal inhibition required for learning and effective adaptation. The drug stimulates memory and learning ability, improves physical performance, removes psycho-emotional stress, anxiety, fear, improves sleep, increases the duration of the phase of "slow" and "rapid" sleep [67, 68].

Adaptol relates to a non-benzodiazepine anxiolytics, has a pronounced anxiolytic, vegetal stabilizing effect, simultaneously possesses nootropic properties and causes practically no side effects [69]. It affects the activity of structures within the limbic-reticular complex, particularly in the emotiogenic areas of hypothalamus and acts on the main neurotransmitter systems: GABA, cholinergic, serotonergic and adrenergic, helping their balance and integration. It has a nootropic effect without causing muscle relaxation and impaired motor coordination, eliminates or reduces anxiety, fear, internal emotional pressure and irritability, helps normalizing the sleep. [69]

The intake of magnesium drugs in order to replenish magnesium deficiency can be considered a promising area of sleep disorders treatment. Magnesium increases the enzyme activity of serotonin N-acetyltransferase activity, involved in the biosynthesis of melatonin, which regulates the circadian rhythm of sleep-wakefulness. US researchers in their experimental work showed the reduction of melatonin levels by 1/3 in animals with magnesium deficiency as compared to those supplied with magnesium [70]. A lack of melatonin caused by magnesium deficiency can induce sleep disorders, primarily the reduction of night sleep or insomnia [71]. Disturbances and excitatory effects of magnesium deficiency also lead to sleep disorders. In several studies, the normalization of sleep has been noted as a positive result of Chronic Fatigue and stress disorders in adults magnesium drugs adjustment [72, 73].

CONCLUSION

Thus, sleep disorders in children are associated with an increasing risk of psychopathology and somatic disorders and lead to the deterioration of emotional status, cognitive function, health and school performance, which determines the need for timely diagnosis and comprehensive differentiated medical and psychological data correction of pathological conditions based on the neurophysiological and biochemical mechanisms of their development, as well as polymorphism of clinical manifestations in order to increase the effectiveness of treatment and quality of life of the child and his/her family.

CONFLICT OF INTEREST

The authors have indicated they have no financial support / conflict of interest relevant to this article to disclose.

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