Neurobehavioral Consequences of Obstructive Sleep Apnea Syndrome in Children

76

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76.1 Introduction

Obstructive sleep disordered breathing (SDB) is a common problem in children and includes many clinical conditions with variable severity of intermittent airway obstruction such as primary snoring, upper airway resistance syndrome (UARS), obstructive hypoventilation, and obstructive sleep apnea syndrome (OSAS) (obstructive, central, and mixed). Primary snoring is described by snoring over three nights a week, without oxyhemoglobin desaturation or sleep fragmentation. UARS is characterized by snoring with frequent sleep fragmentation and increased respiratory effort with upper airway resistance, in the absence of recognizable oxyhemoglobin desaturation. OSAS is characterized by persistent episodes of upper airway obstruction with oxyhemoglobin desaturation disruption and normal sleep pattern. Obstructive hypoventilation is considered as elevated end-expiratory carbon dioxide partial pressure without noticeable obstructive events [1–5]. Definition of obstructive hypoventilation is comprised in International Classification of Sleep Disorders [4], but American Thoracic Society [5] evaluated it within the definition of OSAS.

Knowledge on the epidemiology of obstructive SDB is limited and conflicting. Prevalence of obstructive SDB in the children differs from study to study due to a variety of methodologic issues (parent-reported snoring, parent-reported apneic events, parent-reported symptoms on the questionnaire, etc.), and heterogeneity in diagnostic criteria such as most of the studies did not estimate UARS and obstructive hypoventilation. Most studies reported the prevalence of OSAS between 1 and

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4% [6]; however, the conclusion of a meta-analysis which was given by Lumeng et al. [2] indicated the rate of snoring in children is 7.45% and while OSAS occurs in 0.1–13%. According to this meta-analysis, higher prevalence of obstructive SDB symptoms was found in boys. Also, African-American ethnicity and obesity are among high risk factors for SDB in children [2].

OSAS in children is associated with cardiovascular morbidity (severe pulmonary hypertension and cor pulmonale), morbidity from the central nervous system (excessive daytime sleepiness, inattention/hyperactivity, cognitive deficits/learning problems and behavioral problems), and nocturnal enuresis, delay of growth, decreased quality of life, and also increased health care utilization. These morbidity and conditions coexisting with OSAS emphasize the importance of recognition, detection, and treatment. The diagnosis should be considered and diagnosed with overnight polysomnography (PSG) in children with representative symptoms (e.g., signs of upper airway obstruction such as snoring, fragmented sleep, oral breathing, excessive daytime sleepiness, or hyperactivity) and risk factors (obesity, tonsillar hypertrophy, mandibular hypoplasia, neuromuscular/craniofacial/neurologic or genetic disorders). In this section, the neurobehavioral consequences of OSAS in children were summarized to draw attention to the presence of symptoms and concerns about a child's learning capacity and school performance, attention, memory, hyperactivity, or emotion regulation.

76.2 Neuropathogenesis of OSAS

OSAS is described by repeated events of partial or complete obstruction during sleep and induced deterioration of the gas exchange (hypoxemia and hypercarbia), sleep fragmentation, repeated arousals, inadequate sleep efficiency, and episodic cerebral perfusion alterations. Long-time repetition of these events leads to neuronal cell losses in selective brain regions, as well as affects the brain functional response, particularly in developing brain. Regional blood flow modification during sleep, recurrent hypoxia-re-oxygenation events with apneic episodes, that causes to elevated oxidative damage and inflammation process, lipid peroxidation, and ensuing neuronal damage might be responsible for neurocognitive deficits [7–11]. Genetic and environmental factors are also effective. In experimental animal models, subjected animal to repeated intermittent hypoxia has been shown to induce neuronal damage in regional brain regions, axons inside of white matter tracts, and nerve fibers in gray matter, just as in human model [10, 12]. Also, elevated inflammatory markers, lipid peroxidation products, and oxidative damage have been demonstrated in many brain regions [10, 11].

Previous studies indicated substantially reduced gray matter volume in the caudate nucleus, insular region, hippocampal region, the frontal and temporo-parieto-occipital cortices, and cerebellar regions [13, 14]. The other studies reported that children with OSAS showed tissue damage in white matter integrity and functional activation in anterior, mid, posterior corpus callosum [9, 15]. A number of axonal tracts among such brain structures would reduce integrity, and also modify the

function of these structures. The emotional expression could be affected due to injury to limbic areas (e.g., the anterior cingulate and insula, and interconnections to the amygdala and hippocampus). Damage in the limbic structure, as well as abnormal functional connectivity between hippocampus and cerebellum, may contribute to mood disorders and impaired memory process. Moreover, the possible cause of cognitive dysfunction in children with OSAS may be the structural changes in the anterior cingulate cortex, hippocampus, fornix, cerebellum, and frontal cortex [9, 16].

The prefrontal cortex is regarded as an important part of the cerebral cortex that contributes to a wide variety of executive functions such as higher cognition, planning, proper social behavior, and personality. Beebe et al. [17] proposed a model that linked to daytime cognitive and behavioral deficits in OSAS through disruption of prefrontal cortical processes. Sleep disruption, intermittent hypoxia, and hypercarbia modify the metabolism and neurochemistry of the prefrontal cortical region, and then lead to mentally manipulating information, emotional lability, poor decision-making, and deficit in attention and memory [17].

The results of the publications, mentioned above, indicate that various brain structures and their associated neuronal pathways are susceptible to OSAS complications. Disruption of the function and integrity of the related brain structures associated with neuronal damage may lead to the neurocognitive impairment in children with OSAS.

76.3 Excessive Daytime Sleepiness

Excessive daytime sleepiness (EDS), a sudden uncontrollable impulse to sleep, is an important symptom in children with OSAS. EDS is caused by a wide range of sleep-related causes and distinct conditions such as insomnia, nocturnal seizures, chronic pain, and movement disorders. Sleep-related causes of EDS are classified under four main headings, namely inefficient sleep duration (insomnia), disturbed/fragmented sleep (behavioral, SDB, movement disorder, medical problems disturbing sleep, environmental disturbances), circadian misalignment (Circadian rhythm disorder), and primary disorders that increased need for sleep (head trauma, increased intracranial pressure, hypersomnia, hypothalamic lesions).

EDS is the most frequent symptom among children and adolescents by a progressive increment with age and pubertal maturation. Female dominance occurs after mid-puberty [18]. Despite the exact prevalence of sleep-related causes of EDS in children with OSAS is unclear due to different assessment methods, studies have reported the prevalence of EDS, ranging from 10% to 20% in prepubertal children and 16% to 47% in adolescents [18, 19]. In studies conducted with Multiple Sleep Latency Test (MSLT), the prevalence of EDS was reported as 13–20% and was more prone to being obese [19–21].

EDS in children is rarely recognized by parents and physicians as sleepiness may not be verbalized by the child. They usually present to the physicians with different symptoms such as increased hyperactivity, mood disorders, behavioral

problems, impairments in neurocognitive function, diminished learning capabilities, or academic difficulties. Childhood and adolescence are characterized by major developmental changes in physiological, social, and psychological fields. Some learning, behavior, mood, or sleep disorders that occur in these constantly changing periods can lead children and adolescence to seek psychiatric care. It is then very important to accurately determine which symptoms are related to sleep disorders. Otherwise, some sleepy children may be mistakenly considered lazy, hyperactive, or depressed. For these reasons, diagnosis of EDS requires a detailed systematic approach in children. A comprehensive history and physical examination are of prime importance for evaluating these children. Screening instruments such as Epworth Sleepiness Scale, Pittsburg Sleep Quality Index, Pediatric Daytime Sleepiness Scale, and Children's Report of Sleep Pattern-Sleepiness Scale can help confirm the subjective EDS in children. In the history, sleep behaviors (daily sleep duration or patterns), sleep hygiene (bedtimes, use of mobile devices, or snacking before bed), past medical history (e.g., epilepsy, asthma, neuromuscular disorders, migraine, or autism), use of medications that may affect sleep, family history of sleep disorders, snoring, or pauses in breathing during sleep should be questioned. Physical examination should include assessments of growth and development, body mass index (BMI), neurologic function, presence of the genetic condition, and ear/nose/throat examination. Objective measures include actigraphy (indicating wakefulness or sleep and estimates total sleep time), PSG, and MSLT. Lateral neck X-rays or endoscopy helps to show adenoidal hypertrophy.

PSG is the gold standard tool for evaluating OSAS and EDS [1]. PSG includes: (1) description of total sleep time, sleep latency, arousals, leg movements; (2) electroencephalography (EEG) to record sleep stages with brain wave activity, and also record seizures; (3) electromyography (EMG) to record skeletal muscle movement and electrooculography (EOG) for eye movements to determine rapid eye movement (REM) sleep; (4) monitors oxygen, CO2, and gas exchange via pulse oximetry and end-tidal CO2; and (5) monitors respiration including nasal and mouth breathing. Sleep-related breathing disorders are generally associated with hypertrophic tonsils and adenoids and sometimes incorporated with increased BMI in children, as well as chronic wheezing, nasal allergies, sinus problems, and craniofacial disorders. In accordance with the International Classification of Sleep Disorders [22], symptoms and evidence of pediatric OSAS associated with nocturnal symptoms such as snoring, oral breathing, snorting, gasping, pauses in breathing, and daytime outcomes (sleepiness, hyperactivity, inattention) should be existing. The criteria of PSG for pediatric OSAS requires either (1) $\geq$1 obstructive event (apnea or hypopnea) per hour of sleep or (2) obstructive hypoventilation, represented by $PaCO_2 > 50$ mmHg for more than 25% of sleep time [22].

The management of SDB-related EDS includes optimization of sleep hygiene and treating the cause of SDB, efficiently. Positive airway pressure (PAP) is an effective treatment choice in improving EDS for children with persistent sleepiness despite therapy [23].

76.4 Neurobehavioral Consequences of OSAS

Untreated OSAS symptoms in children are associated with a number of cognitive and behavioral effects which are generally described as "neurobehavioral." Neurobehavioral consequences of OSAS are thought to be the outcome of long-term intermittent hypoxemia with apneic events and sleep deprivation. While behavioral results are associated with inattention/hyperactivity symptoms, emotional lability, mood disorders, anxiety, and depressive symptoms, cognitive results are associated with intelligence, learning and academic difficulties, attention, executive function, memory, and language. These morbidities affect the physical health of the child, and also the quality of life for both the child and family.

Interest in neurobehavioral effects has been accelerated in recent years. Although meta-analyses on this topic frequently criticized the methodologic and conceptual issues of some researches, a number of studies have linked significant association with habitual snoring and OSAS to behavioral deficits such as emotional lability, anxiety, and depressive symptoms, especially to symptoms of attention deficit/hyperactivity disorder (ADHD) [1, 6, 17, 24–30].

ADHD is the most common behavioral disorder in children, and characterized by hyperactivity, attention deficit, and impulsivity. Children with OSAS are frequently misdiagnosed as ADHD, due to the overlap symptoms. Hyperactive and inattentive behaviors occur in almost 30% of children with habitual snoring and OSAS [20, 31]. According to parent-reports, sleep disturbances have been reported in more than 70% of children with ADHD. However, when evaluating the ADHD children by PSG, only 20% of children have reported sleep disturbance [20]. Additionally, ADHD children usually have persistent behavioral sleep problems, such as bedtime resistance, longer time to falling asleep, easily aroused sleep, and difficult to fall asleep. Several studies have demonstrated that the rate of SDB is higher in ADHD children, and also symptoms of ADHD are improved following treatment for OSAS [27–30]. A prospective and longitudinal population-based cohort study by Perfect et al. [32] indicated that children with SDB may show symptoms comparative with ADHD-like symptoms and disruptive behaviors, unless they are not treated. Wu et al. [31] reported that approximately 30% of children accompanying ADHD, and the prevalence of ADHD is increasing with age, and also the incidence of ADHD in boys with OSAS is higher than in girls. The effects of fragmented and restricted sleep have been assessed in several systematic reviews and meta-analyses. They reported that the OSAS could lead to neurobehavioral deficits associated with ADHD, and also SDB could be manifested or misdiagnosed as ADHD in some children [24–26]. Hypoxia may be an important causing factor for ADHD; therefore the assessment of sleep remains a crucial component from the perspective of clinicians in the evaluation of ADHD [25, 31].

Data on the emotional functioning of children with OSAS were based on self-reported and parent-reported symptoms, which may not be vulnerable to an objective mood [6, 33]. Degree of hypoxemia may point to the possible mechanism for increased depression in children [33, 34]. Hodges et al. [33] declared that children with OSAS have shown an increased risk for depressive symptoms, and revealed different

demographic variables such as race, BMI, and maternal education. Furthermore, they declared that the arterial oxygen desaturation is strongly associated with depressive symptoms [33]. A recent study which was directed by Geckil et al. [34] noticed that the REM-related OSAS which is related to frequent apneas and hypopneas have higher rates of anxiety and depression symptoms compared to non-REM-related OSAS.

Children with OSAS may have cognitive impairments such as intelligence, learning, memory, language, attention, as well as school performance and academic difficulties [1, 35–39]. Some studies which did not evaluate the PSG findings revealed that the children with have an increased incidence of cognitive impairment and academic difficulties [37, 39]. Bourke et al. [35] reported that although the neurocognitive deficits are higher in children with OSAS compared with normal controls, they did not find the relationship between the severity of SDB and neurocognitive impairment. Furthermore, they suggested that hypoxic brain injury and sleepiness are critical factors in decreasing cognitive and academic function in these children [35]. On the contrary, Brockmann et al. [39] investigated the association of primary snoring and neurocognitive impairments and indicated that significant neurocognitive impairment may exist in children with non-hypoxic and non-apneic. The results of a large population-based cohort study conducted by Calhoun et al. [40] demonstrated that there is no significant impairment in intelligence, attention, executive functioning, and memory compared with children without OSAS although these associations were not controlled for variables known to be incorporated with learning problems such as parent education, socioeconomic status, environmentally changes, or individual genetic factors. Alchanatis et al. [41] and Olaithe et al. [42] declared that individual differences in cognitive reserve, which reflect that innate intelligence or inter-individual differences allow some individuals to deal with progressive brain damage and cognitive stressors better than other patients, may clarify the discrepancy of results in previous studies related to neurocognitive impairment in children with OSAS. According to this theory, high intelligence children with OSAS have a preventive effect against OSAS induced neurocognitive morbidity, by allowing a greater tolerance for brain injury and maintaining better cognitive and behavioral tasks [41]. Therefore, OSAS effects may differ from child to child due to the different functional plasticity of the brain.

Some cross-sectional studies revealed that the emergence of specific SDB-related neurobehavioral impairments may modify according to the child age. In a long-term SDB, children aged 3–5 years showed behavioral deficits, but no neurocognitive deficits, while children aged 7–12 years showed reduced neurocognitive skills [35, 43]. These studies demonstrated that the children with any severity of PSG defined SDB which may affect neurobehavioral condition is important to identify and treat, timely.

76.5 Effects of OSAS Treatment on Morbidity from Central Nervous System

There are many treatment methods for OSAS, depending on the age of the child, underlying medical problems, and the main cause of the upper airway obstruction such as adeno-tonsillar hypertrophy, craniofacial abnormalities, or neuromuscular disorders. Hypertrophy of the tonsils and adenoids is the most common cause of

OSAS in childhood. This incidence of this condition is higher in the preschool years, when the lymphoid tissue is largest relatively to upper airway size [44]. If adeno-tonsillar hypertrophy is present, adenotonsillectomy (AT) is the first-line treatment option for OSAS with the remarkably improved symptoms and PSG parameters of OSAS. Obesity in children is an independent risk factor for OSAS. Weight reduction in obese children is consolidated with improved metabolic effects and potential benefits concerning OSAS. Furthermore, obesity is a substantial risk factor for moderate to severe OSAS persistence after AT [1]. PAP which maintains the upper airway patency is a good alternative choice for treatment of children with moderate to severe OSAS as well as residual OSAS after AT. PAP therapy reduces snoring, arousals associated with obstructive events and the obstructive apnea hypopnea index (AHI), and also normalizes the oxygen saturation. Adherence to PAP therapy in childhood is a very common problem especially in children with developmental delays or behavioral problems. Further surgical treatment such as uvulo-palato-pharyngoplasty, tongue-lip adhesion, or mandibular advancement may be considered, but it has shown poor efficacy so far [45]. It should be remembered that upper airway dimensions may improve over time in children. For this reason, advanced surgeries, which have relatively lower success and higher complication rates, may be postponed to later times. Tracheostomy, which has the highest efficiency in the treatment of OSAS, is usually used only in severe OSAS, particularly in the presence of severe craniofacial anomalies, neuromuscular diseases causing severe hypotonia, or other surgical and nonsurgical interventions are contraindicated. Tracheostomy remains permanent in many of these children. But sometimes it can be used temporarily until awaiting appropriate surgical treatment.

Neurobehavioral impairments may notably improve with convenient OSAS management [1, 15, 27–30, 46–49]. Continues positive airway pressure (CPAP) is frequently used in children for whom surgical treatment is inappropriate or insufficient, such as craniofacial anomalies or neuromuscular disorders. Additionally, residual OSAS after AT, especially children with obesity, craniofacial anomalies, or neuromuscular disorders, leads to an increased number of children requiring CPAP. Complications of CPAP are including nasal congestion, epistaxis, facial erythema and ulcer, and rarely midface deformity. Nonetheless, the most important problem in children is patient adherence. Previous studies demonstrated the positive effects of PAP on neurobehavioral outcomes, sleepiness, school performance, quality of life, besides being improvements in gas exchange [1, 27, 46]. Marcus et al. [27] reported the significant amelioration in neurobehavioral function, excessive daytime sleepiness, and quality of life in children who were treated for 3 months with PAP therapy. Bee et al. [46] emphasized the importance of PAP adherence in adolescents and reported that adolescents with an average of 57% PAP adherence demonstrated improved attention and school performance while non-adherent group showed a tendency to decline in academic and school performance. Management of complications, behavioral modification, parent-directed care, and proper device usage may improve patient adherence. However, there is still insufficient evidence in the literature, regarding hours of per night of CPAP use and its effect on daytime sleepiness, further strategies to improve poor adherence in children.

AT is considered a suitable treatment choice for most cases of children with OSAS. Normalization of PSG parameters is more frequent in children with moderate to severe OSAS than in children with mild OSAS. Also, reduction in central apnea index has been shown in children with OSAS and mild central sleep apnea after AT [1, 45]. A number of studies demonstrated that the neurobehavioral morbidity tends to greatly improve 6–12 months after AT [27–29, 44–46]. Friedman et al. [48] who organized a prospective study to assess the neurocognitive function of children with OSAS before and after AT and to compare the results with healthy controls reported that neurocognitive function improved considerably 6–10 months after AT, reaching the levels of the control group; thus, they indicated that deterioration of neurocognitive function is mostly reversible. In a meta-analysis on neurophysiological functioning including attention-executive function, memory, and verbal ability after AT, Yu et al. [47] demonstrated a significant effect in children with OSAS when compared to their baseline level. But no significant effect was observed in attention-executive function and memory between children with OSAS and healthy ones. Studies concerning the PSG parameters of baseline OSAS and its following improvement after AT did not associate clearly with behavioral problems, cognitive deficits or sleepiness and they do not clarify the improvement neurobehavioral outcomes after AT [1, 28, 50, 51]. The Childhood Adenotonsillectomy Trial (CHAT) which was a randomized controlled study to evaluate a large of the cohort of school-aged children either early tonsillectomy (eAT) or seven months of watchful Waiting with Supportive Care (WWSC), reported that convalescence in the attention and executive function objective scores from baseline to follow up did not significantly differ between eAT and WWSC group after a period of 7 months as measured by psychometrician-measured neurocognitive testing, but improved the secondary outcomes of the teacher-reported behavior, caregiver-reported measures of executive function, quality of life and PSG parameters [50]. According to Cochrane systematic reviews [52], there is high-quality evidence that AT is beneficial for PSG parameters in 5–9 aged children with mild to moderate OSAS; however, the evidence in terms of quality of life and behavior is moderate quality. Additionally, high quality of evidence has shown no efficacy in regarding objective attention and measures of cognitive function compared to watchful waiting. They suggested that clinicians and parents carefully evaluate the benefits and risks of AT in these children, as PSG parameters of nearly half of children undergoing no-surgical treatment return to normal limits within 7 months [52].

Two systematic reviews concluded a significant deterioration in sleepiness, behavioral problems, attention deficit and hyperactivity symptoms, neurocognitive skills and quality of life scores of patients irrespective of preoperative OSAS severity [53, 54]. The parents completed 22 item SDB scale of Pediatric Sleep Questionnaire (PSQ) may be a useful tool since it may predict neurobehavioral morbidity from OSAS and its improvement after AT better than the AHI [1, 55]. Washtenaw Country Adenotonsillectomy Cohort [53] evaluated the effectiveness of SDB scale of PSQ by comparison with polysomnographic findings in the prediction of OSAS-related treatment responsive neurobehavioral morbidity and reported that its sensitivity and specificity for the diagnosis of OSAS are 78% and 72%,

respectively. They suggested that SDB scale of PSQ provides greater clinical benefit than the more detailed PSG in terms of clinically relevant neurobehavioral health outcomes [55].

Although other surgical interventions such as maxillary or midface advancement, uvulo-palato-pharyngoplasty, and tongue-hyoid advancement are used in the treatment of severe OSAS, they have not been studied extensively in terms of neurobehavioral outcomes in the literature [1].

76.6 Conclusion

Neurobehavioral deficits which are associated with OSAS may well be multifactorial in origin with individual genetic factors, environmentally changes, socioeconomic status, parent education, age of the child, and also the severity of nocturnal events. Evidence on literature reinforces the need for increased awareness, early detection, and timely intervention by physicians and parents in pediatric OSAS to minimize the damage and optimize the neurobehavioral outcomes.

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