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Obstructive Sleep Apnea in Children: Implications for the Developing Central Nervous System

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Abstract

Recent increases in our awareness to the high prevalence of sleep disorders in general, and of sleep-disordered breathing among children, in particular, has led to concentrated efforts aiming to understand the pathophysiological mechanisms, clinical manifestations and potential consequences of such conditions. In this review, I will briefly elaborate on some of the pathogenetic elements leading to the occurrence of obstructive sleep apnea (OSA) in children, focus on the psycho-behavioral consequences of pediatric OSA, and review the evidence on the potential mechanisms underlying the close association between CNS morbidity and the episodic hypoxia and sleep fragmentation that characterize OSA.

Sleep Disorders In Children

Pediatric sleep continues to gain significant recognition due to both increasing evidence of a high prevalence of sleep disorders among children, and by virtue of the potential somatic and psycho-behavioral effects of disrupted sleep during early development. Obstructive sleep apnea (OSA) is by far the most frequently diagnosed pediatric sleep disorder, and has been reported to affect at least 1–3% of all pre-school and school-aged children. Furthermore, symptoms consistent with an increased risk for sleep-disordered breathing have been reported in 6–27% of children (1–8).

Brief Overview of OSA

OSA is characterized by repeated events of partial or complete upper airway obstruction during sleep. These upper airway changes induce disruption of normal alveolar ventilation and sleep structure, and lead to blood gas abnormalities and sleep fragmentation (9).

The primary symptom of OSA is habitual snoring, a symptom that may affect up to 27% of children with a median revolving around 10–12% (1,4,5–8,9–13). Prevalence rates of snoring similar to those of preschool and early school-age children have also been reported among infants. Indeed, habitual snoring was found in 5% of 2–4 month-olds (14) and 6–12 month-olds, (4) with higher rates among infants between the ages of 1 to 8 months (16%–26%) (15). Recently, we reported that habitual snoring was present in 1–9% of infants and toddlers (2–24

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months of age) (6). This relatively high frequency of habitual snoring usually decreases in 9–14 year-olds to around 3–5% (16).

Despite the fact that OSA and its associated manifestations were first described over 120 years ago (17,18), it was not until 1976 that Guilleminault reported OSA as a clinically relevant 4 entity in children (19). Furthermore, Osler (18) reported that children with “loud and snorting” respirations with “prolonged pauses” were often “stupid looking” and slow to respond to questions; yet, it took a century before Osler’s observations on neurocognitive decrements in pediatric OSA were investigated using objective methodology. Of particular emphasis is the fact that OSA in children is distinct from the OSA that occurs in adults, and such differences are particularly striking in relation to racial and gender distribution, clinical manifestations, and treatment (20). Nevertheless, more than one clinical phenotype have been recently proposed for OSA in children (for a more extensive review of this issue see reference 21)

Pathophysiology of OSA in Childhood

Transition to the sleep state will normally result in elevations of upper airway resistance (22, 23), primarily linked to reductions in airway diameter resulting from reduced tone of the pharyngeal dilator and constrictor muscles (24–26). In children, the primary abnormality associated with increased odds of OSA consists in the presence of adenotonsillar hypertrophy. This is not surprising, considering the obvious fact that anatomical impingement of the upper airway by enlarged lymphoid tissues will exponentially increase the airflow resistance, and ultimately culminate in recurring upper airway collapse, the latter being characteristic of OSA (27,28). Adenoids are located on the roof of the nasopharynx and enlarge from infancy through childhood, with progressive subsequent reductions in size during adolescence through adulthood. Similarly, tonsils will grow in early childhood. Previous observations suggested that tonsillar and adenoidal tissue enlarge at a faster rate than the bony structures of the nasopharynx during early childhood, and therefore would result in an overall reduction in the upper airway diameter during early childhood (29). However, in healthy non-snoring children, the growth of such tissues is actually proportionate to the somatic growth of the airway, and therefore any deviation from such anticipated growth trajectories would essentially be abnormal (30). In support of this recent work, magnetic resonance imaging of upper airway structures clearly established that children with OSA have significantly larger adenoids and tonsils than controls (31), and that the region in which these 2 lymphoid tissues overlap in the 3-dimensional space of the upper airway constitutes the site with the smallest airway diameter in these children, and therefore the likely location for upper airway collapse to develop. I should however emphasize that the presence of markedly enlarged tonsils and adenoids is not synonymous with the presence of OSA, and that complex interactions between the anatomical components and other elements such as upper airway tone, central and peripheral respiratory drive, and upper airway reflexes may all play a role of greater or lesser importance depending on the individual OSA patient. Genetic and ethnic factors have also been identified in the pathogenesis of OSA (32–39). For example, African Americans are at higher risk than Caucasians when controlling for age, sex and body mass index (40). While no specific genes have been thus far identified for OSA, it has become apparent that OSA is polygenic in nature, and that specific genes impacting on factors such as oral mucosa thickness and facial structure will play a deterministic role in OSA. The clustering of OSA in families further lends credence to the genetic hypothesis for OSA. Based on all aforementioned considerations, multiple medical conditions have emerged as being associated with an increased risk of OSA. Examples of such conditions include congenital or acquired craniofacial anomalies with fixed anatomical narrowing of the upper airway, the presence of neuromuscular dysfunction, prematurity, Down syndrome (41), achondroplasia (42), cerebral palsy, and myelomeningocele (43). In addition, and of particular importance, is the presence of obesity as a major and significant risk factor for OSA in children (44–49).

Neurobehavioral Consequences of Sleep Apnea in Children

One of the most important consequences potentially affecting the majority of children with mild to moderate sleep-disordered breathing involves psycho-behavioral co-morbidities. Studies on these specific issues have focused on the daytime effects of sleep-related breathing disorders (e.g., snoring and OSA)

Excessive Daytime Sleepiness

The predominant daytime consequence of sleep disturbance is “sleepiness” and as such, it is imperative to initially address the meaning of this rather ambiguous term. Originally described by Carskadon and Dement (50), one objective technique used to quantify sleepiness is the Multiple Sleep Latency Test (MSLT). This simple method involves a series of 20 to 30-minute polysomnographically recorded daytime ‘nap’ opportunities in a sleep-promoting environment (i.e., darkened and quiet room, comfortable bed and temperature). Under such standardized circumstances, the shorter the latency to sleep onset during these nap opportunities, the higher the degree of sleepiness (50). MSLT assessments are expensive, labor-intensive, and difficult to conduct in children, such that very few studies have objectively measured daytime sleepiness in children. Another problem in evaluating sleepiness is that similar to studies in adults, there seems to be a limited relationship between the sleepiness derived from a MSLT and the sleepiness based on subjective report in children (51). Moreover, it is important to note that behavioral sleepiness may display differently in children than it does in adults. For example, children with ADHD have greater objective daytime sleepiness (52), such that a state of “hyperarousability” may in fact underlie “sleepiness” in children.

The exact prevalence of excessive daytime sleepiness (EDS) in pediatric OSA is unclear, and likely secondary to the overall impaired perception of caretakers, both as surrogate reporters of EDS, and also because children are unlikely to verbalize such symptoms. Several studies have thus far examined this particular issue. Parental reports of children being evaluated for suspected OSAS initially indicated that only a small minority of these children (7%) presented with symptoms compatible with EDS (53), a rather surprising finding that would implicitly suggest that children would be relatively “protected” from OSA-induced EDS. Based on our accrued understanding of the impact of EDS on behavior in children, questionnaires were developed and included more specific questions on the presence of behaviors more likely to be associated with EDS. Despite their subjectivity, such questionnaires revealed that the frequency of EDS symptoms is probably much higher than originally reported in snoring children, and that EDS may be present in up to 40–50% (51). Using the MSLT, the prevalence of EDS in pediatric OSA was 13–20% (54,55), and appeared to be more prominent and frequent in obese children (54).

Behavioral consequences of general sleep disturbance

Intuitively, we would assume that sleep fragmentation should lead to adverse consequences on daytime performance. Sadeh and colleagues reported a high prevalence of sleep fragmentation in children (56), but the effects of sleep fragmentation on daytime functioning have yet to be examined in detail among pediatric populations. It is known that infants, toddlers, and school-age children who are reported by their parent(s) to be poor sleepers manifest increased incidence and severity of behavioral issues compared to children without reported sleep problems (57–61). These observations have been confirmed by objective assessments, in which the degree of sleep disturbance and the severity of behavioral changes are strongly linked (11,62–66). Moreover, 36% of young children with global reports of sleep problems present with significant behavioral problems (67), and conversely daytime hyperactivity, anxiety, and depressive symptoms have all been associated with prolonged sleep latency (58, 67). Pre-school children with shorter total sleep time exhibit more behavioral problems (68),

and the reciprocal of this observation holds true as well, since improvements in sleep are associated with improvement in daytime behavior (51,59,62). Thus, sleep and behavior exhibit dynamic interactions that can either interfere with each other, or synergistically interact, such that the outcome of such interactions is not always predictable. Sleep disorders may lead to sleep that is either inadequate, fragmented, or both. The association between sleep disorders in general, and OSA, in particular, and adverse effects on daytime functioning is now firmly established, and in fact, early treatment often reverses these effects.

Behavioral Implications of Snoring

First and foremost, we should emphasize that the presence of snoring needs not be viewed as a normal feature of sleeping children, since it indicates the presence of increased upper airway resistance. As mentioned above, a substantial percentage of snoring children may have primary snoring (i.e., habitual snoring without visually-recognizable disruptions in sleep architecture, alveolar ventilation and oxygenation). Notwithstanding the traditional view that primary snoring is essentially a benign condition, we have recently reported that primary snoring is in fact associated with a higher risk for neurobehavioral deficits, albeit less severe than the deficits found in children with OSA (69,70). Of note, daytime sleepiness, behavioral hyperactivity, learning problems, and restless sleep are all significantly more common in habitual snorers (11,71). Furthermore, infants with higher snore-related arousal indices exhibit lower scores on standardized mental developmental assessments, thereby providing further evidence that snoring is not just an innocent noise during sleep in infants or young children. We further propose that habitual snoring may in fact represent the low end of the disease spectrum associated with sleep-disordered breathing (72).

The consequences of snoring and OSA with their associated hypoxemia and sleep fragmentation in children reveal complex pathophysiological mechanisms (73; see also below). If left untreated or treated late, pediatric OSA may lead to significant morbidity affecting multiple target organs and systems, and such injurious consequences may, under certain circumstances, be partially irreversible despite appropriate therapy.

Psycho-Behavioral Consequences of OSA

Behavior

Both habitual snoring and OSA are associated with behavioral problems, particularly hyperactivity and ADHD (1,2,11,66). Hyperactive and inattentive behaviors occur frequently in children with OSA (63,71,74) and with habitual snoring (1,11,61,71,73,75). Furthermore, approximately 30% of all children with frequent, loud snoring or OSA manifest parentally-reported hyperactivity and inattentive symptoms (1), with improvements noted following surgical treatment of OSA (62,76,77). Interestingly, although children with ADHD appear to exhibit more sleep disturbances than normal children (78,79), we found that despite parental reports of increased sleep disturbances in ADHD children (>70%), only 20% of these children with ADHD actually exhibited objective sleep disturbances when assessed by polysomnographic criteria (81,82). In this study, OSA was not more likely to occur among children with true ADHD (i.e., when the diagnosis was established using the stringent criteria recommended by the Academy of Pediatrics and the Academy of Psychiatry). However, OSA was significantly more prevalent among children with parent-reported hyperactive behaviors that did not fulfill strict ADHD criteria, suggesting that disruption of sleep in the presence of OSA is associated with significant behavioral effects.

Neurocognition

In the context of SDB, the magnitude and probability of neurocognitive dysfunction in children with OSA is more pronounced than in those children with primary snoring (69–71).

Furthermore, hypoxemia is closely correlated with deficits in executive function, whereas sleepiness is preferentially associated with attention loss (82,83). The frequently reported deficits in executive performance in adults with OSA may emanate from hypoxemia-induced frontal lobe dysfunction (84). Several groups of investigators have posited that sleep disturbances are associated with dysfunction of the prefrontal cortex (PFC) in adults, and the same principles should be applicable to children (85). We have introduced a theoretical model, whereby sleep apnea induces daytime cognitive deficits via disruption of PFC-dependent processes (84), and this model provides the foundation for a recently proposed heuristic model for interpreting the prolific and dynamic research on both animal models and humans (86).

Attention

The ability to remain focused on a task and respond appropriately to extraneous stimuli in the environment plays an important role in learning, and consequently in social and academic development. Inattentive behaviors have been reported in children with OSA and in those children with habitual snoring (1,69–72). Furthermore, a dose response has emerged in the scores obtained using attention-impulsivity scales in the presence of OSA in children (87). Blunden and colleagues also reported that children with mild OSA demonstrated diminished selective and sustained attention compared with control children (71). Studies from our laboratory have further supported the concept that children with primary snoring (69) as well as those with OSA (11,70) are at higher risk for deficits in attention compared to control children when measured on parental report scales, and that such deficits are substantially improved following treatment with adenotonsillectomy (62,63,88).

Memory

In children with OSA, memory performance on standardized psychometric tests is significantly affected compared with control children (71), with children with higher respiratory disturbance indices showing greater memory deficits (89). These findings are not consistent however. Indeed, Owens and colleagues (87) and O'Brien and colleagues (11,69,70) found no evidence for the presence of any measurable differences in memory performance in children with varying degrees of OSA severity when compared to control children.

Intelligence

Several studies have now extensively documented the presence of significantly reduced IQ scores compared with control children (70,71,89). In these studies, the probability for lower normal or borderline range performance was much higher in children with OSA. Our group has also reported on the significantly impaired General Conceptual Ability scores (a measure of IQ obtained from the Differential Ability Scales; DAS) in school-age (70) and preschool-age (90) children with OSA when compared with control children, and also demonstrated the complete reversibility of cognitive deficits following timely treatment (90). Thus, these studies suggest that early diagnosis and intervention may lead to overall favorable outcomes (76). Of note, not all children with OSA will exhibit intellectual or behavioral deficits, raising the possibility that individual genetic susceptibility and environmentally dictated changes in the vulnerability to disease may play a significant role in the phenotypic presentation of any given child (91).

Learning and school performance

School problems have been reported in multiple case-series of children with OSA, and such findings may underscore more extensive behavioral disturbances such as restlessness, aggressive behavior, excessive daytime sleepiness and poor test performances. Improvements in behavior emerge following treatment for OSA in children (62,74,92) suggesting that at least some of the deficits may be reversible. Lower school performance has also been described in

children with OSA, and the reciprocal has also been shown to be true, i.e., children with poor academic performance are more likely to have sleep disturbances such as snoring and breathing difficulties (74,75). Indeed, we found a 6–9 fold increase in the expected incidence of OSA among first grade children who ranked in the lowest 10th percentile of their class (74), and significant improvements emerged in school grades after those children with OSA were effectively treated. Since the optimal intellectual ability and academic performance for these children were unknown, we can not exclude the possibility that long-term residual deficits may be present after treatment. To further examine this possibility, we subsequently investigated the history of habitual snoring during early childhood in 2 groups of 13–14 year-old children who were matched for age, gender, race, school attended, and socioeconomic status, but whose performance was either in the upper or lower quartile of their class. We found that children who snored frequently and loudly during early childhood were at increased risk for lower academic performance later in life, well after snoring had resolved (93). These findings suggest that even if the major portion of OSA-induced learning deficits is reversible, there may be long-lasting residual deficits in learning capability. The latter could represent either the presence of a “learning debt”, i.e., the decreased learning capacity during OSA may have led to such a delay in learned skills that recuperation is only possible with additional teaching assistance, or alternatively could be indicative that OSA may have irreversibly altered the performance characteristics of the neuronal circuitry responsible for learning particular skills. Support for both these possibilities has emerged from our rodent models of OSA developed in our laboratory (94).

Potential Mechanisms of Neurobehavioral and Cognitive Dysfunction in Pediatric Sleep Disordered Breathing

Based on rodent models of OSA, we have thus far reported that increased oxidative stress is associated with increased neuronal cell loss and decreased spatial task learning and retention in rodents exposed to intermittent hypoxia during sleep (95–99). Similarly, we have shown that inflammatory pathways such as those mediated by cyclooxygenase 2, inducible nitric oxide synthase, and platelet activating factor are all pathogenetically involved in the neuronal cell losses associated with the presence of intermittent hypoxia during sleep (100–102). Additional factors that may modify susceptibility to sleep fragmentation or hypoxia during sleep include pathways associated lipid cellular processing such as apolipoprotein E (103), the ability to mount defense mechanisms within signaling cascades underlying cell survival (104,105), or pathways associated with neuronal cell repair or de novo neuronal cell generation (106). These tightly regulated factors raise intriguing questions as to the identity of a selected cluster of genes and their polymorphisms that may underlie the differential susceptibility to OSA in children. Supportive examples illustrative of the viability of such conceptual framework have recently been published by our laboratory. Indeed, children who exhibited an enhanced inflammatory response, as evidenced by increased morning plasma C reactive protein levels, were also more likely to manifest reduced cognitive functioning compared to children with a similar degree of OSA severity but in whom, C reactive protein remained within normal levels (107). Similarly, the presence of apolipoprotein E epsilon 4 allele was associated with an increased propensity to altered cognitive function in the presence of OSA in children (108). Finally, increased serum insulin growth factor 1 responses were linked to improved preservation of neurocognitive function in children with OSA (109). In addition to such considerations, we need to also account for potential extrinsic factors that may modify neuronal cell vulnerability. Examples of such factors could include the overall intellectual enrichment in which the patient lives (110), as well as their nutritional intake characteristics and physical activity patterns (111,112). Thus, in addition to OSA disease severity, the degree and magnitude of neurobehavioral manifestations of morbidity may be explained by genetic

variance in defense and injury pathways as well as by lifestyle patterns and environmental conditions.

Summary

In summary, sleep disturbance in children, whether due to poor sleep habits, developmental changes, or as emphasized in this article, the presence of OSA, is accompanied by rather profound behavioral and neurocognitive deficits. Both sleep fragmentation and intermittent hypoxia contribute to the neurobehavioral morbidity of pediatric OSA, and reversibility of such deficits is possible, particularly when treatment is implemented early and effectively. Increased awareness by physicians and parents to sleep-related issues, and early identification and treatment of conditions leading to altered sleep and nocturnal oxygenation should improve psycho-behavioral short-term and long-term outcomes.

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