

Neurocognitive and behavioral morbidity in children with sleep disorders

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Purpose of review

This review examines in detail progress made regarding our understanding of the presence and pathophysiology of cognitive and behavioral morbidities among children with sleep disorders in general. Particular focus is given to pediatric obstructive sleep apnea.

Recent findings

In recent years, increased awareness of the morbid consequences of respiratory sleep disturbances in children has emerged. Evidence suggesting a causal association of intermittent hypoxia and sleep fragmentation with alterations in memory, attention, and intelligence has accumulated. Research has also identified a link between sleep disorders, and problematic and hyperactive behaviors and mood disturbances. Furthermore, there is considerable inter-individual variability in the presence and magnitude of neurobehavioral morbidity at any given level of disease severity. This further suggests that, in addition to the disease *per se*, both genetic (individual susceptibility) and environmental modifiers play a role in determining morbidity.

Summary

A more individually tailored approach to detecting morbidity associated with sleep disorders in children, employing biomarkers and gene-related single nucleotide polymorphisms, may ultimately be required to allow more rational prioritization of treatment.

Keywords

children, oxidative stress, sleep apnea, sleep fragmentation, systemic inflammation

Introduction

During the past three decades our awareness of pediatric sleep disorders, and their major implications for health and quality of life, has increased impressively. It is only in more recent years, however, that we have begun to understand how sleep disorders in general, and more specifically sleep-disordered breathing, can lead to substantial morbidities that affect the central nervous system (CNS), and cardiovascular and metabolic systems. Although many of these end-organ consequences undoubtedly share common pathogenetic mechanisms, here we focus our attention on neurobehavioral consequences of sleep disruption in pediatric populations, facilitating a comprehensive discussion of this important topic.

Sleep disturbances in children

Inappropriate sleep habits and resultant insufficient sleep duration have become highly pervasive in children and are a cause for major public health concern, particularly among westernized societies. As a corollary to progressive reductions in sleep hygiene, the prevalence of daytime sleepiness and its inherent consequences for behavior and academic performance in children have increased. Although the Multiple Sleep Latency Test is a well characterized method of assessing sleepiness and has been used in children and adolescent persons [1,2], it is labor intensive and potentially insensitive to specific disorders such as obstructive sleep apnea (OSA) [3]. Therefore, the Multiple Sleep Latency Test is overall a rather impractical method for extensive and frequent assessment of sleepiness in patient populations. In addition to voluntary or involuntary reductions in sleep duration, circumstances that lead to fragmented sleep also have the potential to exert an adverse effect on daytime functioning [4].

In this review we address recent evidence derived from clinical pediatric studies and animal models of OSA. We emphasize the potential pathophysiologic links between neurocognitive and behavioral dysfunction and the two major elements of OSA, namely intermittent hypoxia and sleep fragmentation.

Consequences of sleep restriction and sleep fragmentation in children

The effects of experimental sleep fragmentation on daytime functioning have not yet been examined in great detail in pediatric populations. Reciprocal relationships

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Abbreviations

CNS central nervous system
OSA obstructive sleep apnea

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have emerged between sleep – measured either subjectively or objectively – and behavior, in that a strong correlation has been found to exist between the degree of sleep disturbance and the degree of behavioral changes [5–9]. Daytime hyperactivity and inattention are associated with restless sleep, and conversely improved sleep ameliorates behavior [10,11]. Similarly, anxiety and depressive symptoms are associated with global sleep problems and sleep-onset and maintenance insomnia [11]. Therefore, sleep and behavior exhibit complex interactions that may either interfere with or promote each other in children. For example, acute sleep restriction for one night increased inattentive behavior [12], and more extended sleep restriction for 7 nights led to increases in parent-reported oppositional and inattentive behaviors [13].

Although total sleep duration may modulate behavioral patterns, we believe that it is disruption of the sleep process, rather than reduction in total amount of sleep, that may be the key determinant of the behavioral alterations that are so frequently observed in pediatric sleep disorders. In other words, sleep fragmentation appears to be the major factor that leads to impaired daytime functioning [14]. Thus, fragmentation by multiple arousals, such as is observed in OSA or in periodic limb movement disorder of sleep, would be expected to induce substantial neurobehavioral disturbances. This supposition recently received support from a study that identified significant relationships between arousals associated with periodic limb movements during sleep and attention deficit/hyperactivity disorder [15].

The clinical spectrum of obstructive sleep apnea in children

The clinical condition termed OSA is estimated to affect 1–3% of the younger (<8 years old) pediatric population [16]. Habitual snoring, even in the absence of obstructive apneic events, is extremely frequent (affecting a median of 11–12% of all prepubertal children). It may lead to sleep fragmentation through respiratory effort-induced arousals, even if hypoxemia is absent. Conversely, intermittent oxyhemoglobin desaturations can occur without arousals, such that separation of these two disruptive elements, namely hypoxia and arousals, within the context of their respective consequences constitutes a rather futile enterprise. Furthermore, we do not know whether it is important to quantify these events, particularly as they relate to outcomes (see below). Therefore, until we know better we must continuously monitor through the night as many potentially relevant physiologic parameters as possible.

Despite the fact that OSA and its associated manifestations were first described as long ago as 1880 [17], it was only in 1976 that Dr Christian Guilleminault and colleagues ‘rediscovered’ OSA as a clinical pediatric

condition [18]. OSA in nonobese children differs greatly from the prototypic presentation in adults, and it is frequently diagnosed in association with adenotonsillar hypertrophy [19]. The evolving epidemic of obesity in Western societies, however, has generated a phenotypic pattern of OSA in children that is remarkably similar to that found in adults, and in which significantly lesser contributions from upper lymphadenoid tissue are needed to elicit airway obstruction/increased upper airway resistance during sleep [20]. Notwithstanding such considerations, both obese and nonobese children with OSA exhibit increased upper airway collapsibility [21], and surgical removal of hypertrophic adenotonsillar tissues is ‘curative’ in only a fraction of pediatric OSA patients [22^{**},23]. Hence, milder residual OSA is not infrequent after surgery and appears to respond favorably to anti-inflammatory therapy [24^{*}].

Behavioral and cognitive issues

To make matters more complicated, ‘primary snoring’ (i.e. the presence of habitual snoring in the absence of gas exchange abnormalities or impaired sleep macroarchitecture) may not be as benign a condition as was previously believed. Indeed, we and others recently showed that primary snoring may in fact be associated with disrupted sleep microarchitecture, the latter being assessed using the more refined approach consisting of quantification of the cyclic alternating pattern [25^{*},26^{**}]. Consistent with these findings, we also reported that there is increased probability of neurobehavioral deficits in primary snoring children, albeit of lesser severity than those found in children with OSA [27]. Furthermore, daytime parental reports of child sleepiness, behavioral hyperactivity, learning problems, and restless sleep are all significantly more common in habitual snorers as well as in children with frank OSA [28–31]. In addition, both pediatric OSA and habitual snoring are associated with poor quality of life [32,33], depressed mood [33], and increased health care utilization [34^{*}].

In support of a causal relationship between neurobehavioral manifestations and sleep disordered breathing in children, improvements in behavior and cognition have been reported following treatment [35–37], suggesting that timely treatment will lead to reversibility of such deficits [38]. Also, a dose-dependent response has emerged from large cohort studies, with the degree of hypoxemia correlating preferentially with deficits in executive function, whereas the magnitude of sleep fragmentation (measured using the Sleep Pressure Score [39]) appears to account more for the variance in attention [40]. Taken together, polysomnographic measures account for approximately 40% of the neurobehavioral phenotypic variance (Gozal D, unpublished observations, 2006). This raises the possibility that other factors may modulate the mechanisms whereby intermittent

hypoxia and sleep fragmentation operate and effect CNS dysfunction.

The deficits in executive performance found in children with OSA could reflect frontal lobe dysfunction [40], although many other brain regions are likely also to be affected [41]. Anatomic evidence supporting ‘neurodegenerative’ processes within the context of pediatric OSA is now emerging [42^{••}]. Furthermore, evidence for abnormal vascular reactivity in the brains of children with mild OSA but with cognitive deficits implies that the interaction between endothelial and neuronal compartments elicits functional alterations [43[•]]. When several functional domains are assessed, the global conclusion that emerges from the cumulative datasets is that pediatric OSA is associated with deficits in behavior and emotional regulation, academic performance, and problems with sustained and selective attention, as well as alertness [44^{••}]. There is also evidence that sleep disordered breathing has minimal association with expressive language skills, visual perception, and working memory, while findings are thus far inconclusive regarding some aspects of intelligence, memory, and executive functioning [44^{••}]. We are hopeful that thorough assessments of larger pediatric cohorts with a wide spectrum of disease severity, along with carefully designed interventional studies, we will ultimately decipher the code governing the precise magnitude of the link between disturbances in polysomnographic measures and neurobehavioral manifestations.

A word of caution is necessary, however; it is possible that delayed diagnosis and treatment of OSA may not lead to complete reversibility of the deficits associated with OSA. To examine this possibility further, we surveyed a large population of middle school students (age 13–14 years) for the presence of habitual snoring during early childhood, and specifically focused on two groups of students who were closely matched and who only differed in scholastic performance (i.e. either in the upper or lower quartile of their class) [38]. We found that those children who reported early childhood habitual snoring were at significantly greater risk for lower academic performance. This suggests that components of OSA-induced learning deficits may not be fully reversible, or that partial recovery may reflect a ‘learning debt’ that can be palliated only through supplemental teaching assistance [38]. Based on our findings in a rodent model of OSA, we now believe that the processes that underlie the learning deficits induced by OSA will somehow permanently modify selective neuronal pathways [45], thereby restricting particular learning skills.

What have we learned so far from animal models?

Deficits in cognitive functioning correlate with both sleep fragmentation and with hypoxemia. Reliable distinction

between the individual effects of these two hallmark characteristics of OSA on behavior and cognition is unfeasible in patients. To overcome such limitations, we and others have developed animal models that should permit improved definition of the specific effects on the CNS of intermittent hypoxia and sleep fragmentation. This approach has thus far contributed greatly to our understanding of the contribution made by intermittent hypoxia to prefrontal cortex and hippocampal anatomic and functional deficits throughout life [46–49,50[•]]. Interestingly, male rats exposed to intermittent hypoxia during sleep also exhibit increased locomotor activity and reduced duration of social interactions, which may represent a form of hyperactivity and lack of sustained attention, both of which are exhibited by children with OSA.

The mechanisms that underlie CNS vulnerability to either intermittent hypoxia or sleep disruption are now beginning to unravel. For example, oxidative stress as induced by intermittent hypoxia during sleep promotes neuronal cell loss and decreased cognitive function [51–53]. Similarly, activation of inflammatory cascades occurs, involving platelet-activating factor, cyclo-oxygenase-2, and inducible nitric oxide synthase, all of which ultimately modulate neuronal cell loss [54–56]. Apolipoprotein E is an additional factor that has been found to modify susceptibility to sleep fragmentation or hypoxia during sleep [57], probably through complex raft signaling pathways within cellular membranes. Other factors include activation of survival transcription factors [58,59], as well as capacity for stem cell migration and differentiation into damaged brain regions [60]. It is therefore likely that gene polymorphisms within multiple genes of interest may underlie the differential susceptibility to cognitive dysfunction in children with OSA. In support of these assumptions, the magnitude of the C-reactive protein response to OSA or the presence of the apolipoprotein E ϵ 4 allele have emerged as important modifiers of cognitive dysfunction in children with OSA [61^{••},62^{••}].

In addition to the aforementioned intrinsic factors of vulnerability, we should also pay attention to extrinsic factors that may modify end-organ susceptibility. Thus far, the degree of intellectual environmental enrichment [63], nutritional intake characteristics, and physical activity patterns [64^{••}] all appear to be important players in the complex interactions between disease and morbidity. Thus, in addition to OSA severity, the extent of neurobehavioral morbidity may be dictated by specific gene polymorphisms or by lifestyle patterns and environmental conditions.

Conclusion

Sleep disorders in general, and more specifically OSA, are accompanied by sizeable behavioral and neurocognitive

dysfunction in children. Both sleep fragmentation/restriction and intermittent hypoxia are probably involved in the pathophysiology of neurobehavioral morbidity. The mechanisms recruited appear to involve multiple biologically plausible pathways, especially oxidative stress and inflammation. Despite evidence for reversibility after effective treatment, the ultimate prognosis remains uncertain, particularly if delays occur in the recognition and management of this frequent pediatric disorder.

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 550).

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