Sleep Apnea in Pediatric Neurological Conditions

Gabor Szuhay, MD, and Josh Rotenberg, MD

Corresponding author
Gabor Szuhay, MD
Department of Neurosciences and Behavioral Medicine, George Washington University of Medicine, Children's National Medical Center, 111 Michigan Avenue NW, Washington, DC 20010, USA.
E-mail: gszuhay@cnmc.org

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Sleep apnea in neurologically compromised children is common but underrecognized. It can be secondary to diseases at all locations on the neuroaxis and may independently alter their presentation, severity, and course. As a primary and secondary illness, it is associated with significant neurological morbidities. In its severe manifestation, it can cause life-threatening short- and long-term systemic morbidities. The authors review the most recent and relevant literature and provide the pediatric neurologist with a framework with which to identify children at risk.

Introduction

Disordered breathing in sleep is a common and treatable condition affecting children of all ages. While the presentation has a spectrum of severity, sleep apnea (SA) syndrome implies the presence of markedly abnormal breathing in sleep with disruption in daytime functioning, behavioral problems, and/or excessive daytime somnolence (EDS). Neurologically impaired children have additional unique and often multiple disease-specific risk factors for SA. Genetic susceptibility and treatment exposures also contribute to disease expression. SA can be difficult to appreciate in this group of children because patients and parents with cognitive limitations tend to underreport symptoms and signs. Furthermore, SA symptoms and signs may be falsely attributed to the underlying neurological disease. As SA is curable and its morbidities are at least partially reversible, pediatric neurologists must be able to identify patients at risk.

Anatomy and Physiology

Respiration

Efficient breathing relies on three intact compartments: the central and peripheral nervous system, the respiratory musculature, and the airway. The drive to breathe in sleep is largely automatic. Peripheral and central respiratory chemoreceptors and pulmonary mechanoreceptors all project to the nucleus of the solitary tract. Respiratory rhythm is generated by the medulla's ventral respiratory group and the pre-Botzinger complex. The carotid bodies are sensitive to hypoxia and project to the ventral respiratory column's and pre-Botzinger complex's glutaminergic neurons via the nucleus of the solitary tract. The serotonergic neurons in the medullary raphe and ventral surface are sensitive to carbon dioxide and hydrogen ions. These neurons mainly project to the phrenic nerve. The arcuate nucleus is the equivalent of the central chemoreceptors in animals and perhaps in humans [1••].

Pousielle's law describes the physics of laminar flow through a tube and specifies the direct relationship between flow and the fourth power of the tube's radius. As a result, a small decrease in airway diameter profoundly reduces the efficiency of breathing.

The airway stays patent through tonic activation of the upper airway musculature. In brief, during stage 1 and 2 sleep, voluntary control of respiration persists; automatic breathing occurs in non–rapid eye movement (NREM) and REM sleep. In NREM sleep, respiratory drive depends on input from peripheral chemoreceptors, the diaphragm, and other respiratory muscle groups to stay active. In REM sleep, muscle atonia involves all respiratory muscles except the diaphragm. Respiration depends more on central drive. In the progression to REM sleep, the activity of the tonic motor neurons is lowest; upper airway resistance (and therefore the risk of apnea) is highest. The amount and distribution of REM sleep and thus the apnea rate vary throughout the night in different age groups.

Sleep

Efficient sleep is important to protect vital functions of the developing brain such as memory consolidation and is maintained by minimizing sleep disruption from arousals. Arousal is necessary to resolve respiratory compromise by

restoring pharyngeal patency and ventilatory drive. The first type of arousal—cortical arousal—involves cholinergic projections from the brainstem to the cortex. Children more frequently respond with only an increase in peripheral and upper airway muscular tone, limb movement, or autonomic changes without evidence of cortical arousals. These represent the second type: subcortical arousals.

Biologic and clinical observations suggest that the developing brain may be more resistant to "arousal" as a protective mechanism. However, more accurate polysomnographic indices of "arousal" are needed. From a clinical persperctive, improvements in behavior and cognition are noted after treatment of obstructive sleep apnea (OSA) with even modest improvements in currently used measures of sleep disruption. This observation implies either that arousals are undetected in children [2••] or that the young brain is more vulnerable to sleep disruption [3••]. In preteens, the frontal lobe connections are not matured and the frontal electroencephalogram (EEG) leads show minimal additional cortical arousals only in snoring [4]. Other parameters to measure cortical and subcortical arousals are being substantiated in children, including the cyclic alternating pattern and changes in autonomic function, respectively [2••].

Definitions

SA is defined by respiratory alterations and sleep disruption on a single overnight polysomnogram (PSG) [5] and can be divided into three categories: central, obstructive, and mixed apneas. Central apnea is a pause of respiratory effort that lasts longer than 20 seconds or two missed breaths with an oxygen desaturation of at least 3% and/or arousal.

Sleep-disordered breathing (SDB) is a spectrum that covers primary snoring up to OSA. Primary snoring refers to audible snoring with arousals/awakenings. Upper airway resistance syndrome refers to snoring with increased upper airway resistance and cyclical arousals. Hypopneas refer to decrease in airflow for two respiratory cycles with at least 3% oxygen desaturation and/or arousals/awakenings. Obstructive apnea indicates a lack of airflow for two breathing cycles with intact respiratory effort and may be accompanied by oxygen desaturation or arousal. A mixed apnea is an obstructive event that starts with absent respiratory effort. An obstructive index of 1 or higher per hour or a combined apnea–hypopnea index of 1 or higher is considered diagnostic of pediatric OSA.

Sleep disruption consists of awakenings or arousals detected on EEG channels of the PSG. Arousals can be spontaneous or secondary to other events, such as respiratory compromise. Cortical arousals are scored on the EEG by an abrupt shift for at least 3 seconds, with 10 seconds of stable sleep preceding the event. Subcortical arousals may be revealed by subtle increases in muscular tone on electromyogram, frank movement, or autonomic changes [6].

Risk Factors and Clinical Presentation

Risk factors for SA

Several well-established risk factors exist for pediatric SA. Narrowing of the upper airway in sleep by adenotonsillar hypertrophy (ATH) is the most important and is more common in sickle cell disease and mucopolysaccharidoses. Certain craniofacial malformations may also restrict the upper airway. Obesity is becoming an increasingly prevalent risk factor [7••] and is more common in patients with pseudotumor cerebri, some genetic syndromes, and neuromuscular diseases. Common disorders such as atopy [8], asthma and allergies, reflux [9], or secretions [10] may also compromise airway patency. Hypotonia/weakness of the pharyngeal or respiratory musculature and inability to change body position [11] predispose neurologically impaired children to obstructive apnea. Maldevelopment (history of prematurity, apnea of prematurity, congenital central hypoventilation syndrome, myelomeningocele), destruction of central nervous system structures that control breathing, and desensitization of chemoreceptors from chronic alveolar hypoventilation seen with neuromuscular diseases are risk factors for central apnea. Risk factors frequently coexist, and SA often can be central and obstructive.

Risk factors for EDS

EDS is not as common in children as it is in adults with SA. Overt sleepiness may be less prevalent because of less sleep disruption from respiratory arousals [2••] or because of inherent developmental variation in the circadian pressure to manifest behavioral sleep. Pain [12], seizures [13], movement disorders (eg, tics [14]), restless legs syndrome/periodic limb movement disorder [15••], and bruxism [16] are important causes of secondary arousal. Spontaneous arousals in sleep disorders of arousal (sleepwalking, nightmares, night terrors), autism, attention-deficit/hyperactivity disorder (ADHD), and psychiatric comorbidities can disrupt sleep independently of SA [15••].

Clinical presentation

SDB presents most commonly with snoring, which is a good predictor of SDB, especially when accompanied by ATH. Important symptoms and signs that can indicate SA are apneas, coughing, choking, gagging or nocturnal dyspnea, mouth breathing, enuresis, and nighttime sweating in infants. Disrupted sleep in the absence of respiratory signs may manifest as anything from fidgety sleep to frequent awakenings and can indicate significant SDB [17•].

EDS may present with a propensity to sleep in unusual situations, excessive napping, and/or externalizing behaviors. It is an important though insensitive indicator of sleep disturbance in neurologically impaired children. The Epworth Sleepiness Scale modified from the adult version was used in white and black children 2 to 18 years of age and did not differentiate OSA from primary snoring but correlated with mean nocturnal Sao_2. In Chinese children between 3 and 12 years of age, the same scale predicted a higher apnea-plus-hypopnea index (AHI) score [18].

For scores of 11 to 15, the Pediatric Daytime Sleepiness Scale can be used; from 13 to 17, the School Sleep Habits Survey is applicable; and from 11 to 17, the recently validated Cleveland Adolescent Sleepiness Questionnaire is available [19]. Many questionnaires aim to diagnose SDB by incorporating daytime behaviors. An example is the Pediatric Sleep Questionnaire. It is validated but has low sensitivity and specificity for SDB in children older than 2 years of age and PSG-defined OSA in older children [20]. In conclusion, medical history and physical examination underestimate SDB frequency in otherwise healthy children [17•] and may be even less sensitive when applied to children with cognitive or communication impairment.

Epidemiology

The prevalence of habitual snoring in children is approximately 10% and is even higher in infants. The prevalence of OSA is 2% to 3% in the general pediatric population and peaks between 2 and 8 years of age, corresponding to the peak of ATH. EDS is common in older children and adolescents because of their lifestyle choices; SA is a relatively infrequent cause. Even in severe OSA, EDS prevalence can range from as low as 8% to 84% in some studies [21••].

Neuropathology

Central nervous system

Intermittent hypoxia (IH) and sleep disruption can affect the central and peripheral nervous systems. In the central nervous system, IH affects the hippocampal CA1 region by activating apoptotic pathways, lipid peroxidation, inductible nitric oxide synthase expression, cyclooxygenase-2 activation, nitrosylation/carbonylation, platelet activating factor expression, and altered gene regulation. IH provokes apoptosis, glial proliferation, oxidative stress/inflammation, and cytoarchitectural disorganization (decrease in *N*-methyl-D-aspartate receptors and disorganized astroglial and oligodendroglial processes and dendritic arborization). Cytoarchitectural disorganization has been linked to decreased excitability of CA1 neurons, impaired synaptic plasticity of the CA1 neurons, and impaired long-term potentiation. IH has been linked to decreased myelination of the corpus callosum with a similar process in the basal forebrain. IH also affects the dopaminergic, cholinergic, and serotonergic systems [22••].

Sleep disruption may also cause some of the above changes [23]. Sleep maintenance is important for executive function and spatial and nonspatial memory formation. Impairment of long-term potentiation of CA1 hippocampal neurons is seen in mice deprived of REM sleep; the medial prefrontal cortex and the visual cortex have shown involvement in rats [24]. The combined effect of these alterations explains the impaired spatial working memory, hypersomnolence, and hyperactivity noted in children with OSA.

Peripheral nervous system

Resistance to ischemic conduction failure (RICF) has been demonstrated in the peripheral nerves of adults with OSA and is thought to indicate adaptive changes to ischemia through more efficient use of oxygen and anaerobic metabolism. Mainly axonal damage was noted in patients with OSA, with more nerve dysfunction in patients with the lowest nocturnal oxygen saturation. Complete correction of the RICF was achieved with nasal continuous positive airway pressure (nCPAP) without exerting an effect on axonal dysfunction [25]. Microvascular and diabetic conditions may be confounding, but OSA may also alter peripheral insulin resistance and endothelial function [26] and is relevant in the metabolic syndrome.

Cardiovascular and Other Morbidities

IH exerts its effects on the autonomic nervous system by producing elevated plasma and urine catecholamines and by decreasing the sensitivity of the baroreceptor reflexes during apneas in adults. Different measures of the autonomic nervous system showed improvement in all patients compliant with nCPAP for severe OSA, with reversal of adrenergic tone and autonomic nervous system response related to improvement in nocturnal oxygen saturation [27]. This may have implications for the development of short- and long-term cardiovascular complications. OSA has significant systemic complications, including dysrhythmias, pulmonary hypertension, reduced right heart ejection fraction, and cor pulmonale. Increased oxidative stress and inflammation make up the pathophysiologic model for the development of hypertension with important genetic susceptibility [28••].

Other sequelae are reversible, such as failure to thrive [29], facial morphologic changes [30], and metabolic effects [26,31].

Genetic Implications

A significant familial risk exists for SDB symptoms, and genetic susceptibility may account for the variance in neurocognitive outcome. The risk of symptoms can increase fourfold when both parents are affected. A linkage peak was observed among younger adult Caucasians with OSA on chromosome 19 near the apolipoprotein E (ApoE) locus. ApoE is a lipoprotein that plays a role in toxic scavenging and redistributing lipids, with a potential neuroprotective role from toxic inflammatory and oxidative stress products. Children with SDB who show more cognitive deficits are more frequently carriers of the ε4 allele, arguing for increased neurocognitive susceptibility [32••].

Many genetic syndromes are associated with OSA. Age, hypotonia, multilevel upper airway obstruction [33], and obesity predispose individuals with Down syndrome to OSA. Approximately 30% to 50% of children with Down syndrome have OSA, and in one study, 81% showed evidence of hypoventilation [34]. Annual screening for OSA starting at 5 years of age is recommended [35]. Dementia

was present in 11% in their 40s and is more prevalent later with more cognitive impairment in patients with worse SDB. Carriers of ApoE ε4 have shorter life expectancy secondary to dementia [36]. DS, OSA, the ApoE4 ε4 allele, and dementia may have mutually reinforcing effects.

Learning and Cognition

SDB impairs cognition and learning, but the severity of OSA explains less than half of the neurocognitive effects, which implies genetic susceptibility [32••]. Although most children with SDB function in the average intellectual range, some memory processes may be more vulnerable, especially in younger children, which argues for a developmentally vulnerable period.

Poor learning in SDB has been documented, with the caveat that behavioral issues are frequent confounders. Habitual snoring independent of IH was associated with poor academic performance, hyperactivity, inattentiveness, daytime sleepiness, conduct problems, emotionality, and peer problems. Eighteen percent of 6-year-olds in the lower 10th percentile in academics had evidence of gas exchange abnormalities. Among 6- to 11-year-olds, respiratory events that are associated with even modest hypoxia (2% to 3% desaturations) were observed more frequently in children with snoring, EDS, and a learning disability. Among 6- to 12-year-olds with ATH, AHI/apnea index score and snoring predicted lower vocabulary scores and other factors. In 10- to 13-year-olds with ATH, decreased memory and learning disability and more severe language dysfunction were found. Low-performing 13- to 14-year-olds were more likely to have snored between 2 and 6 years of age. Some studies attest to improved working memory after adenotonsillectomy and academic performance in 1 year, but overall intellectual performance (IQ) remains the same [3••].

Behavior

Infants have been less systematically studied, but snoring 2- to 4-month-olds are "moodier." In children, the most common behavioral symptoms associated with SDB are hyperactivity, rebelliousness, and aggression [3••]. ADHD and sleep discontinuity may share a common pathophysiology of catechol-O-methyltransferase polymorphism [37]. EDS is a strong predictor of OSA in psychiatric patients; thus, more severe SDB does not necessarily correlate with ADHD severity, as evidence indicates that children with ADHD who snore but have no EDS have normal respiratory indices on PSG [38]. In addition, commonly comorbid behavioral sleep disorders and periodic limb movement disorder are important modifiers of EDS in SDB [15••]. Therefore, children with ADHD, combined type and ADHD with other comorbid psychiatric conditions have higher percentages of sleep-related symptoms; children with ADHD, inattentive type do not. Stimulant medications for ADHD may improve, have no effect on, or worsen sleep [39••]. They improve EDS and mask SDB. This can manifest by excessive sleeping during drug holidays or in the form of symptoms refractory to stimulants. Improvement in behavior over time after adenotonsillectomy also provides proof of an association [3••]. In conclusion, ADHD and aspects of abnormal sleep may share a common pathophysiology. The interaction of genotype with SDB may create a behavioral phenotype, with evidence that curing SDB will improve some of the behaviors in most children with time.

Headache

The relationship between OSA and headaches is complex. Most experts agree that sleep symptoms are common in headache patients. Morning headaches (and nausea) or headaches that wake children from sleep can be associated with OSA, whereas most migraine syndromes are not closely linked to SA. EDS may be the most important marker of a sleep disturbance in pediatric headache and migraine patients, although insomnia and narcolepsy symptoms are also important [40]. Behavioral disorders are commonly seen in individuals with migraines [41] and can be independently associated with sleep resistance and EDS. One recent study using PSG showed increased sleep latency, upper airway resistance syndrome, and very mild OSA with migraines and nonspecific headaches [42••]. Low brain serotonin and melatonin levels may be the common link.

The association between pseudotumor cerebri (PC) and OSA is increasingly recognized in children. They share obesity as a risk factor. Increased intracranial pressure (ICP) has been described in sleep with OSA and papilledema. Several mechanisms may play a role—specifically hypercapnia, hypoxia, increased venous pressure, and polycythemia. In healthy men, OSA was common in PC, and it was also common in patients with idiopathic increased ICP without papilledema. One study documented remission from PC in patients with OSA on nCPAP alone [43]. In infants with complex or nonsyndromic single-suture craniosynostosis, elevated ICP and obstructive respiratory events in sleep (frequently with no signs of SDB) interact to decrease cerebral perfusion pressure and may lead to optic atrophy and worse developmental outcome [44].

Epilepsy

Children with epilepsy are sensitive to sleep disruption and may be predisposed to OSA. Prolonged sleep deprivation (48 hours) can elicit seizures in healthy adults, and a few hours of sleep deprivation can activate epileptiform discharges in children. Sleep deprivation is one of the most frequent causes of breakthrough seizures [45], and OSA was found in most sleepy epileptic children. Conversely, children with OSA and epilepsy may have higher body mass indices, worse desaturations, and sleep disruption from interictal discharges [46]. Vagus nerve stimulation causes sleep apnea in 8% of patients, and many neurologists test for OSA before implantation. OSA is an established cause of intractable epilepsy in children, and even partial treatment may significantly improve seizure control [13,47].

Cerebral Palsy

A case series of 173 children with cerebral palsy showed sleep breathing problems in 14.5%, EDS in 11%, and multiple symptoms in 14%. OSA may be more common in children with spastic quadriparesis, in whom impaired corrective body repositioning may lead to more airway obstruction. In addition, epilepsy may be an important contributor to nocturnal arousals. EDS was more common in the epilepsy group regardless of whether children were treated with antiepileptics [11,48]. Most children with cerebral palsy and OSA can be treated with adenotonsillectomy alone; however, nCPAP is also an option prior to invasive solutions. Treatment of SDB may improve seizures and behavior in patients with cerebral palsy and improve the quality of life of patients and their families [49].

Brain Tumors

OSA has been observed in children with brain tumors. Brainstem gliomas may present with sleep apnea. OSA can be seen in patients treated for central nervous system tumors outside the brainstem. It is usually accompanied by EDS or even narcolepsy (not necessarily with hypothalamic involvement) [50].

White Matter Disorders

Canavan disease can be associated with upper airway abnormalities, and severe OSA [51] is observed in Pelizaeus-Merzbacher disease [52]. In a case series of adults with Alexander disease with brainstem (mainly medullary) involvement, OSA was common [53]. Mitochondrial disorders generally show a mixed pattern of obstructive and central events from brainstem involvement, phrenic nerve involvement, or diaphragmatic and intercostals muscle weakness; they can be life-threatening, especially during exacerbations [54]. Decreased sleep efficiency and more awakenings were noted commonly in adults with multiple sclerosis with high subtentorial lesion burden, especially during exacerbations [55].

Diseases at the Cervicomedullary Junction and Spinal Cord

Mixed types of sleep apnea can be severe in 20% of children with myelomeningocele. It has been observed without Chiari type 2 or MRI evidence of brainstem malformation [56]. In Chiari type 1 malformations, OSA is present but is rarely severe. Syrinx can develop in Chiari type 1 disease and progress to involve lower brainstem breathing centers. Syringobulbia can present in children, and OSA is a prominent symptom. Intermittent increases in nocturnal ICP from OSA can cause syrinx progression even where surgical decompression has been achieved. Fatal respiratory failure can occur in sleep without prior warning symptoms or signs noted by patients or their cohabitants [57]. In achondroplasia, dynamic changes at the foramen magnum with neck flexion can result in apnea [58]. In mucopolysaccharidoses, in addition to adenotonsillar hypertrophy, C1 to C2 subluxation (also seen in Down syndrome) can lead to severe OSA and respiratory failure. However, AHI normalized in a few weeks on enzyme replacement [59].

Peripheral Nervous System

SDB is common in spinal muscular atrophy, and the quality of life and chances for survival are significantly improved with early identification of impending respiratory failure by screening for SDB. Patients' symptoms are more reliable indicators of OSA. Ethical considerations in treatment are very important because ventilated children may survive into adulthood in a locked-in state [60•,61•].

Hereditary sensory motor neuropathy (HSMN) type 2C can cause vocal cord paralysis. SDB is secondary to pharyngeal weakness in slightly overweight adults with hereditary sensory motor neuropathy type 1A [62]. Phrenic nerve dysfunction can be seen in many conditions (eg, Erb's palsy). Diseases of the neuromuscular junction also can be associated with OSA. Respiratory failure is a feature of acute myasthenia gravis (MG) exacerbation and occurs in one MG variant [63]. In adults with stable myasthenia gravis, obesity is the determining risk factor [64], and obese children also may be at risk.

Children with childhood onset myotonic dystrophy have the craniofacial features that predispose to OSA. Sleepiness is commonly reported by parents, and most children are unaware of their symptoms. OSA was common but did not account for all children with sleepiness. The loss of serotonergic neurons in the dorsal raphe may also explain hypersomnia. Periodic limb movement disorder may be the more important cause of EDS [65•]. Nocturnal reflux has not been studied [9].

Although respiratory failure is well-known in Duchenne's muscular dystrophy, patients develop SDB and nocturnal alveolar hypoventilation before evidence of daytime respiratory insufficiency. Alveolar hypoventilation is more prevalent in the second decade of life. Objective predictors of SDB are important, as Duchenne's muscular dystrophy patients of all ages are frequently unaware of their SDB symptoms. Adenotonsillectomy improves SDB in most patients, but its success is short-lived. When noninvasive ventilation was offered early, it relieved OSA, corrected sleep efficiency, and prevented a rise in mean nocturnal $PaCO_2$ on follow-up. Annual screening for SDB is recommended when clinically indicated, the child becomes wheelchair bound, or when the child reaches 12 years of age [66].

Treatment

When OSA is present in the supine position, patients can be repositioned to avoid obstructive events. Adenotonsillectomy is highly but incompletely curative in those without other significant and persistent risk factors. Pulmonary edema can be seen in the immediate postoperative period, mainly in children

with severe OSA. Mortality after adenotonsillectomy has been observed. History, physical examination, and screening tools are inadequate in identifying children with severe OSA. Consequently, the American Academy of Pediatrics recommends preoperative polysomnography in all children.

Treatment with positive airway pressure devices such as CPAP and bilevel positive airway pressure is second line for OSA. Tolerance varies (it is generally lower in neurologically compromised children), but desensitization programs can be effective. Oxygen can be used until other treatments are available. Medical therapies with nasal steroids and anti-inflammatory medications relieve nasal congestion and even shrink adenoid tissue; amitriptyline has not been systematically studied in children. Orthodontic maxillary expansion and other types of surgeries can provide definitive relief in selected cases. Tracheostomy may be appropriate as a last resort in selected cases.

Conclusions

Sleep apnea in children with neurological disorders has unique and multiple risk factors, atypical presentations, disease-specific treatments, and complications. The treating physician must know the pathophysiology and course of the underlying neurological disease to make ethical treatment decisions and to monitor response, because many patients remain at risk for life.

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Dr. Rotenberg can be contacted at Neurology and Sleep Specialists, 535 Oak Centre, Suite 400, San Antonio, TX 78258, USA; pedzzz@gmail.com.

Disclosures

Dr. Rotenberg is a consultant for Athena Diagnostics and has served as a speaker for Cephalon, UCB Pharma, and Cyberonix. He has served as president of Academy Diagnostics LLC Sleep Center.

No other potential conflicts of interest relevant to this article were reported.

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