Novel methods to diagnose obstructive sleep apnea in children

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Sleep-disordered breathing encompasses a spectrum of disorders that increase in severity from snoring to obstructive sleep apnea (OSA). OSA is a clinical disorder that requires a polysomnogram (PSG) to make the diagnosis. The PSG is the gold standard to confirm OSA. Alternative diagnostic tests are presented to supplement the clinical evaluation with objective information when evaluating the snoring child. Diagnostic tests to identify the anatomical site of obstruction are also discussed.

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Sleep-disordered breathing (SDB) is a spectrum of obstructive breathing disorders in children. It ranges in severity from primary snoring, to upper airway resistance (UARS), partial obstructive hypoventilation and, at its most severe, to obstructive sleep apnea (OSA). The cardinal symptom of SDB is nightly snoring. Intuitively, one would expect a comprehensive history and physical examination to reliably predict the presence of OSA. Unfortunately, a meta-analysis, which combined the results from 10 studies, revealed that only 55% of all children suspected to have OSA by clinical evaluation had OSA confirmed by polysomnogram (PSG). This article will specifically address OSA, the most severe form of SDB. When SDB is mentioned, it is to refer to the entire spectrum of obstructive breathing disorders.

Although a history and physical examination cannot reliably predict the presence of OSA, certain conditions should heighten one’s suspicion for the presence of OSA: craniofacial anomalies, Down’s syndrome, neuromuscular disorders, and obesity. The risk of OSA increases by 12% for each increase of 1 kg/m² of body mass index (BMI) greater than the mean. Of note, obese children with OSA may not have as much adenotonsillar hypertrophy as nonobese children. The siblings of children who have been treated for SDB are more likely to have SDB as well as adenotonsillar hypertrophy. These findings could be related to both genetic and environmental influences. Research also suggests that African Americans, ex preemies and males especially after puberty have a higher risk of OSA.

Because clinical examination cannot reliably detect the presence of OSA, clinicians are dependent upon technology. The American Academy of Pediatrics states that the gold standard to diagnose OSA is an overnight PSG.

Polysomnogram

A PSG has multiple components: electroencephalogram (EEG) leads to distinguish sleep from wakefulness; electrocardiogram leads to assess chin tone; electrooculograph leads to capture eye movements and identify rapid eye movement sleep; leg leads to detect limb movements; airflow and respiratory effort belts to detect respiratory events; oxygen and CO₂ probes to assess gas exchange.

The specific sensors used during a PSG determine which components of SDB can be detected. The best method to quantify airflow is a pneumotachograph; almost all sleep laboratories use a nasal thermistor, and most pediatric lab-
oratories also use nasal pressure cannula. The thermistor is a qualitative measurement that detects temperature fluctuations with respiration. It will detect any air movement. The nasal pressure cannula is quantitative and provides a linear approximation of airflow, which facilitates the scoring of hypopneas (partial pauses in breathing). A study may fail to identify OSA if it does not include measurements from a nasal pressure cannula. (It is important to note that the nasal pressure is not accurate while the child is mouth breathing.)

Many adult laboratories do not use a CO₂ monitor. Without end-tidal CO₂ monitoring, one cannot know whether partial obstructive hypoventilation is present. To detect UARS, an esophageal pressure transducer is considered necessary but few laboratories consistently use esophageal pressure monitoring. Alternatively, to detect UARS, flattening of the nasal pressure signal is used to assess for flow limitation.⁶

The International Classification of Sleep Disorders (ICSD) states that pediatric OSA exists when one or more scoreable respiratory events an hour is present. The duration criteria to qualify as a respiratory event is 2 missed breaths rather than the 10 seconds that is required to score a respiratory event in adults. The rationale for this difference is that children have a faster respiratory rate and therefore a 10-second apnea would be more severe in a child.⁷

The ICSD criteria are limited in that they define what is statistically abnormal but not necessarily what is clinically relevant. The Tucson Children’s Assessment of Sleep Apnea Study (TuCASA) group demonstrated that those children with an apnea hypopnea index (AHI) of greater than 5 events an hour were more likely to have parental reported snoring, excessive daytime sleepiness and learning problems. A subanalysis of the data, which evaluated gas exchange problems, revealed the clinical relevance threshold dropped from five to one event an hour if the respiratory events were associated with a 3% oxygen desaturation. These findings suggest that gas exchange abnormalities contribute to the morbidity of SDB. A follow-up prospective study, in which the authors use formal cognitive testing, supports the TuCASA group’s initial findings.⁸

In summary, any child with an AHI of greater than 5 events an hour appears to have clinically significant OSA. However, a lower AHI may be clinically relevant if the events are associated with oxygen desaturations. The authors of another study demonstrated an elevated systolic and mean arterial blood pressure if the AHI was greater than or equal to 5. Unfortunately, there were only a few patients that had this degree of obstruction.⁹ The clinical relevance of an AHI >5 is supported by another study in which the authors demonstrated that the group of children with an AHI >5 had more cardiac dysfunction than the group of children with an AHI <1 or an AHI between 1 and 5 events an hour.¹⁰

Despite recent efforts to determine the severity of OSA that is clinically relevant, the quandary remains that PSG outcome measures (specifically the AHI) is unreliable at predicting morbidity. In one investigation, children who had symptoms suggestive of OSA but a normal PSG improved as much or more in a behavioral hyperactivity and cognitive attention index post adenotonsillectomy than children with PSG-documented OSA who also had an adenotonsillectomy.¹¹ Another study did not show any correlation between the severity of OSA and degree of sleepiness or hyperactivity.¹²

Oximetry

Oximetry would have a greater role in the diagnosis of OSA if all obstructive respiratory events were associated with oxygen desaturations. Because an obstructive apnea does not require an associated oxygen desaturation, an oximetry study may mistakenly classify a child with SDB as normal. Abnormal oximetry studies have been shown to have a high positive predictive value to detect OSA.¹³ However, the low sensitivity at detecting OSA makes an oximetry study a poor screening test for SDB. To rule out a clinical disorder, a diagnostic study should have a high sensitivity (not many false-negative results) otherwise the clinician would falsely assume that their patient is healthy.

New technology to detect sleep disruption

A major issue in pediatric sleep medicine is whether PSG sensors can reliably detect physiological changes in children secondary to obstructive respiratory events. For adults, obstructive respiratory events are typically associated with an EEG arousal. Arousals disrupt the sleep architecture and are associated with daytime symptoms. For children with OSA, the sleep architecture is reportedly preserved making this less useful than for adults.

Cyclic alternating pattern

The cyclic alternating pattern (CAP) is a newer method to analyze the EEG pattern to detect sleep disruption. Currently, CAP analysis is a research tool. CAP is divided into 2 phases: A and B. CAP is characterized by a sequence of transient EEG events that are distinct from the background EEG. Phase A has a greater arousal level and phase B signifies a recovery to baseline activity. All CAP cycles begin with phase A and conclude with phase B. After 1 minute of no CAP activity, the CAP sequence is completed. The CAP rate is the summation of all the CAP sequences during the study divided by the total sleep time. The greater the CAP rate, the poorer the sleep quality. A small study in healthy adults did show a correlation with different CAP rates and performance on neuropsychological tests.¹⁴

Peripheral arterial tonometry

Peripheral arterial tonometry (PAT)¹⁵ is a noninvasive tool to detect disruption of the sleep architecture. Because EEG (cortical) arousals occur less frequently in children with SDB, recent research is being directed at autonomic (subcortical) arousals. Typically, in response to obstructive respiration, the body has in increase in sympathetic nervous
activity. PAT indirectly measures sympathetic activity by noninvasively assessing vasoconstriction in the finger. With an increase in sympathetic discharge, peripheral vasoconstriction occurs and peripheral arterial tone signal at the distal finger attenuates. Although there a good correlation between arousals and PAT-signal attenuations has been demonstrated; the inability for PAT to distinguish between spontaneous, limb-related, or respiratory-related arousals limits its usefulness. Another limiting factor is that PAT will be altered by any event that increases sympathetic tone such as hypoxemia.

**Pulse transit time**

Similar to PAT, the pulse transit time (PTT)\(^{15}\) is another noninvasive tool to detect autonomic arousals associated with respiratory events is. PTT is a marker of sympathetic activity and an indirect measure of arterial wall stiffness. It measures the time for an arterial pulse pressure wave to travel from the heart to a peripheral site. PTT is inversely proportional to arterial stiffness. When an individual has obstructive respirations, they have an increase in respiratory effort. Pulsus paradoxus occurs when a more negative intrathoracic pressure produces a decrease in the systemic blood pressure. With a lower blood pressure, there is a decrease in arterial wall stiffness and a prolonged time for the pulse signal to reach the finger monitoring sensor. A PTT arousal occurs when there is a sympathetic discharge that stiffens the arterial wall and shortens the PTT. A PTT arousal may occur during the recovery from an obstructive respiratory event. In a comparison study of PTT arousals and EEG arousals, the PTT were more commonly associated with obstructive respiratory events. The PTT arousal index was also able to distinguish a child with primary snoring from one with a mild form of SDB known as UARS. These findings suggest that PTT may be able to detect subcortical or autonomic arousals which are disruptive to a child’s sleep.

**Other diagnostic tests**

Because the severity of OSA does not always correlate with morbidity, other mechanisms must be involved. Recent research has focused on the body’s response to SDB. Capdevila and colleagues\(^ {16}\) support the “triple-risk” model for OSA: OSA severity, environmental/lifestyle factors, and individual susceptibility. For genetically susceptible individuals, oxidative stress and activation of inflammatory pathways especially under certain environmental conditions will make these children more predisposed to the morbidity associated with OSA.

**Genetic analysis**

An elaborate investigation by Khalyfa and colleagues\(^ {17}\) demonstrated altered gene expression patterns in circulating white blood cells. Three genes were identified—growth factor receptor-bound protein two, RAS-related C3 botulinum substrate one, and cytochrome c. These genes had the greatest number of interactions with inflammatory pathways for the nonobese children with OSA. The ability to detect altered gene expression by a serum blood draw may facilitate identification of children who are at higher risk of OSA associated morbidity.

Gene polymorphisms have been associated with OSA. Apolipoprotein E is a lipoprotein made in the liver and brain that is involved in cholesterol deposition and transport. An apolipoprotein E polymorphism in nonobese children increased one’s odds for developing OSA as well as associated neurocognitive dysfunction.\(^ {18}\) Tumor necrosis factor alpha gene (TNF-\(\alpha\)) has been noted to be elevated in children with SDB. A specific polymorphism in the TNF-\(\alpha\) gene is not only associated with an elevated concentration but also with elevated sleepiness scores.\(^ {19}\)

**Biomarkers**

A noninvasive method to detect OSA by gas analysis is a possibility. Severity dependent increases in exhaled breath condensate for several leukotrienes has been documented for adults.\(^ {20}\)

Urinary protein expression patterns may also allow one to diagnose OSA without the use of PSG. A preliminary study demonstrated an increased amount of 2 urinary proteins (gelsolin and perlecan) in children with SDB and episodic hypoxemia. These findings also suggest that OSA may affect the kidney.\(^ {21}\)

Up-regulation of serum markers occurs for a variety of inflammatory mediators in children with OSA. Some of these mediators have been implicated in end organ morbidity: neurocognitive, behavioral cardiovascular. Leptin, the satiety protein that is produced in fat cells, is elevated with obesity as well as OSA even after controlling for BMI. Of note, leptin elevation is an independent risk factor for cardiovascular disease.

In a recent investigation researchers demonstrated that the proinflammatory cytokine IL-6 was elevated and the anti-inflammatory cytokine IL-10 was lower in nonobese children with OSA compared with control patients.\(^ {22}\) The presence of systemic inflammation potentially places these children at a greater risk of developing atherogenesis. The same group has also shown a greater concentration of leukotriene and leukotriene receptors in the tonsil tissue of children with OSA.\(^ {23,24}\) Other investigations have demonstrated an elevated C-reactive protein level for children with OSA compared with controls, especially if neurocognitive deficits were detected.\(^ {25}\) As previously mentioned, an elevation of TNF-\(\alpha\) gene is associated with elevated sleepiness scores. These findings suggest a causative role of systemic inflammation and end-organ OSA morbidity.
Identification of abnormal airway anatomy

The treatment of choice for children with pediatric OSA is an adenotonsillectomy. Success is as high as 97% by parent report or as low as 80% by PSG variables. Success also depends upon the definition of OSA. The authors of a recent meta-analysis determined that only 27% of children were cured if cut off for normal was an obstructive AHI of <1 event an hour. Adjusting the cure cut off to <5 obstructive events improved success to 78%.26 Regardless, if there is residual obstruction after an adenotonsillectomy, a surgeon needs to be able to identify where the obstruction is especially if the child is unable to tolerate noninvasive ventilation.

Cine magnetic resonance imaging

Whereas static films of the upper airway do not provide a dynamic analysis of the upper airway during sleep, sedated cine magnetic resonance imaging (MRI)27 scans in the supine position may reproduce those conditions more closely. Specific areas of interest include posterior displacement of the tongue and mandible, forward movement of retropharyngeal tissue, inferior and posterior displacement of the tonsils, and narrowing of the nasopharyngeal airway between the soft palate and the adenoid pad. Lingual tonsil hypertrophy and adenoid regrowth may also be readily identified.

Sleep endoscopy

Sleep endoscopy28 is becoming more popular to detect residual OSA. In contrast to cine MRI, sleep endoscopy allows the surgeon to directly examine the airway. One may use a similar sedation protocol as the cine MRI. The advantage of direct visualization is that one can better evaluate the hypopharynx for lingual tonsil hypertrophy, tongue position and laryngeal abnormalities. Also, one has a better view of the laryngeal dynamics. General anesthesia does not reproduce normal sleep, but some agents may closely approximate it. Sleep endoscopy may enable the surgeon to diagnose anatomical obstruction in the pharynx and formulate a treatment plan.

Conclusions

In summary, the future diagnosis of OSA may rely on more accurate and less intensive methods than attended PSG. Clinical examination, genetic testing, and measurements of markers in blood or urine may suffice to direct treatment. One may need to rely on specialized diagnostic procedures to tailor the surgical procedure to the obstructing anatomy. A genetic profile may determine which children are at increased risk for the end-organ morbidity associated with OSA. Measurement of inflammatory markers could become the outcome measure for successful treatment of OSA. A combination of diagnostic tests may enable clinicians to stratify OSA better than current PSG outcome measures of the AHI and oxygen saturation and to identify those children who require additional intervention for mild OSA.

References


