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REVIEW

Obstructive sleep apnea in patients with Down syndrome: current perspectives

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Abstract: For individuals with Down syndrome (DS), obstructive sleep apnea (OSA) is a complex disorder with significant clinical consequences. OSA is seen frequently in DS, and when present, it tends to be more severe. This increased prevalence is likely related to common anatomic abnormalities and a greater risk of additional comorbidities such as hypotonia and obesity. Because signs and symptoms do not often correlate with disease, all children and adults with DS should receive routine screening for OSA. Similar to the general population, polysomnography remains the gold standard for diagnosis. Because individuals with DS may be more susceptible to cardiovascular and neurocognitive sequelae, early diagnosis and treatment of OSA is becoming increasingly important. Treatment options generally involve upper airway surgery (primarily adenotonsillectomy) and continuous positive airway pressure (CPAP); however, various adjunctive therapies including intranasal steroids, palatal expansion, and oropharyngeal exercises are also available. Residual disease status post adenotonsillectomy is common, and further evaluation (eg, drug-induced sleep endoscopy [DISE]) is often needed. More advanced and directed airway surgery can be performed if additional sites of obstruction are observed. Novel therapies including hypoglossal nerve stimulation are emerging as effective treatments for refractory OSA. Due to the diversity among individuals with DS, personalized treatment plans should be developed. Within this arena, opportunities for research remain abundant and should include areas involving patient risk factors, alternative diagnostic methods, and outcome analysis.
Keywords: sleep-disordered breathing, pediatric, adenotonsillectomy, polysomnography, positive airway pressure, drug-induced sleep endoscopy

Introduction

Sleep-related breathing disorders encompass any abnormal respiration during sleep and include obstructive sleep apnea (OSA), central sleep apnea, sleep-related hypoxemia, and sleep-related hypoventilation. OSA is the most common of these disorders, affecting roughly 15% and 5% of adult males and females, respectively.[1] The prevalence of OSA in the general population has risen substantially in recent decades, likely in part due to increasing rates of obesity.[1] Likewise, OSA is not uncommon in children, affecting approximately 1–5% of all children.[2] Consequences of untreated OSA are wide ranging and include excessive daytime sleepiness, hypertension, cardiac arrhythmias, and cognitive deficits. Economically, untreated OSA may result in an additional 69 billion dollars of health care spending annually.[3]

Down syndrome (DS) is the most common inherited chromosomal disorder, occurring in roughly one in 700 live births, and is caused by the presence of an additional copy of chromosome 21.[4] Clinically, patients are characterized by several dysmorphic

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features and are at an increased risk of developing numerous conditions including intellectual disability, congenital heart disease, hearing and speech difficulties, hypothyroidism, obesity, celiac disease, etc. Importantly, OSA is one of the most common comorbidities in patients with DS. In this review, we discuss current perspectives regarding the diagnosis and management of OSA in this patient population.

Epidemiology

Is OSA common in patients with DS? Yes

Patients with DS are at an increased risk of developing OSA. Current estimates place the childhood prevalence around 50–100%,[5–9] with this prevalence nearing 100% in adulthood.[10] In a recent study by Maris et al[7] of a large (n>120) group of unselected patients with DS, 66% were found to have OSA on full night polysomnogram (PSG) and about half of these children presented with severe disease. Furthermore, the investigators found that even among those children with no history of snoring or witnessed apneas, the majority (53%) were found to have OSA on PSG and that traditional risk factors for OSA such as tonsil size or body mass index (BMI) *z*-score were not associated with the risk of OSA.[7] Hill et al[8] also found that tonsil size and BMI were unrelated to the presence of OSA among a large cohort of children with DS.

The high prevalence of OSA in individuals with DS likely reflects the presence of many risk factors contributing to airway obstruction. In addition to the common anatomic abnormalities often cited (macroglossia, adenotonsillar hypertrophy, midface hypoplasia), other associated conditions such as obesity, hypothyroidism, hypotonia, and gastroesophageal reflux[11–13] are also encountered at significantly higher rates. As a result, a combination of mechanisms impacting breathing during sleep may need to be addressed.

In recent decades, the average lifespan of patients with DS has improved drastically (roughly doubling since 1980), and individuals will often live into their 60s.[14] This improved longevity has contributed to an increased focus on quality of life, especially as these individuals approach later stages of adulthood. A heightened awareness of the pervasiveness of OSA in patients with DS is critical for early recognition, effective management, and ultimately, optimization of long-term outcomes.

Evaluation and diagnosis

Can OSA be diagnosed based on signs and symptoms alone? No

Much like other comorbidities associated with DS, it can be difficult to recognize and accurately attribute the clinical features which accompany OSA. As difficult as it can be for clinicians to investigate sleep-related concerns, studies have shown that parents of children with DS also struggle with accurate perceptions of the quality of their child's sleep. Prior research has shown that up to 50% of children with DS without any sleep-related symptomatology per parental report will have abnormal PSG.[15] Likewise, subsequent research has also demonstrated that symptoms do not predict the presence or absence of OSA by PSG in this population.[16] Due to the combination of high prevalence of OSA in individuals with DS and the inability to predict its presence based on clinical symptoms, in 2011 the American Academy of Pediatrics began recommending PSG routinely for all children with DS by 4 years of age, regardless of symptom history.[12] The presentation of OSA in adults with DS may also be atypical, possibly due to an increased prevalence of psychiatric disease.[17,18]

While baseline screening has certainly improved the diagnostic reach within this population, early recognition of specific signs and symptoms remains an integral part of any workup for sleep-disordered breathing. Typical symptoms such as snoring, gasping, and excessive daytime sleepiness remain common in DS patients with OSA. In addition, behavioral complaints (eg, irritability, impulsivity, and poor concentration) may reflect previously undiagnosed OSA. Parental reports of uncommon or abnormal sleeping positions, such as sleeping bent forward at the waist in a sitting position, should raise suspicion of an underlying sleep disorder.[19,20] Clinical examination findings in OSA involve factors that may result in upper airway airflow limitation. Each patient should be evaluated for adenotonsillar hypertrophy, relative macroglossia, enlarged or swollen nasal turbinates, poor muscle tone, and elevated BMI. The majority of factors that contribute to OSA are in some way modifiable (medically or surgically), and working to create a multifaceted and personalized approach by addressing each variable may help maximize the chances of successful treatment.

Is polysomnography required to diagnose OSA in patients with DS? Yes

Similar to the general population, PSG remains the gold standard for the diagnosis of OSA in patients with DS. As discussed earlier, signs and symptoms alone are insufficient to make a formal diagnosis. Other modalities such as overnight pulse oximetry and capnography have shown poor sensitivity in diagnosing OSA in DS patients.[21] Investigators are currently working on more advanced predictive models combining several history/examination/radiographic measures. For example, Skotko et al[22] developed a model using a Logic Learning Machine that included data from survey questions, medication

history, anthropometric measurements, vital signs, age, and physical examination findings that had a negative predictive value of 73% for mild OSA and 90% for moderate/severe OSA, although the positive predictive values were 55% and 25%, respectively. The same group has investigated urinary biomarkers of OSA among children with DS with mixed results; no one biomarker level could differentiate those children with OSA vs no OSA, but a combination of four urinary biomarkers had a positive predictive value of 90% and negative predictive value of 68%.[23] Cardiorespiratory polygraphy has been utilized in research settings to evaluate for sleep apnea in children with DS,[8] but currently the American Academy of Sleep Medicine recommends full PSG.[24] Although investigational tools such as these likely represent the future of sleep apnea diagnostics, the current data are insufficient for them to supplant traditional PSG in this patient population at this time.

Are children with DS at risk for other sleep-related breathing disorders besides OSA? Yes

As stated earlier, compared to the general population, PSG for children and adults with DS reveals higher rates of OSA. In addition to higher overall prevalence, patients with DS also tend toward more severe disease.[6] A retrospective review of 144 sleep studies performed over a span of 10 years found that 78% of DS patients undergoing PSG demonstrated OSA (with a mean apnea–hypopnea index [AHI] of 9.8), and nearly half (45%) had OSA which qualified as moderate to severe.[25] Beyond OSA, the authors also found an increased propensity for central apnea in younger children with DS, which they speculated that it is due to hypotonia and immature respiratory control. Patients with DS also exhibited greater rates of hypoventilation, with roughly one-quarter (22%) of subjects demonstrating significant hypercapnia by end tidal or transcutaneous measurements, which was significantly related to BMI. While hypoventilation can be obstructive in etiology, it may also be due to underlying restrictive lung disease or hypotonia. Finally, the review found an increased prevalence of sleep-related hypoxemia, which may be due to lower functional reserve capacity, pulmonary hypertension, lung injury from recurrent pneumonia and/or aspiration, or interstitial lung disease.[25,26]

Morbidity and management

Does untreated OSA lead to significant morbidity in patients with DS? Yes

Considering that, by itself, OSA is associated with significant morbidity, it is not surprising that patients with DS can experience serious clinical consequences as a result of untreated OSA. Although the sequelae encountered are potentially far reaching, the current research has focused heavily on the cardiovascular and neurocognitive effects.

Children born with DS are at an increased risk of cardiovascular complications, regardless of sleep-disordered breathing. Congenital heart disease (with atrial and ventricular septal defects being the most common types encountered) exists in up to 56% of DS patients.[27] Left-to-right cardiac blood flow leading to pulmonary over-circulation places these children at increased risk for pulmonary hypertension. One particular study demonstrated that, of 24 DS patients with ventricular septal defects, all 24 also had pulmonary hypertension.[28] In addition, children born with DS tend to have higher baseline pulmonary resistance.[29] Multiple case series have documented the important interaction of OSA and pulmonary hypertension in children with and without DS and either resolution or improvement in pulmonary hypertension with proper treatment of the OSA.[30] Due to increased baseline risk for pulmonary hypertension, clinicians who are vigilant for OSA in this population may recognize early opportunities to intervene and improve health outcomes.

Children with DS have a wide spectrum of neurodevelopmental outcomes. Prior research has demonstrated baseline deficits in various categories such as short-term and long-term memory, language impairment, and visual perception skills [31,32]. It is believed that diminished executive function (associated with underlying abnormalities in the prefrontal and frontal cortex) plays a large role in these findings.[33] In addition, early-onset Alzheimer's disease (AD) is encountered at higher rates than the general population, with postmortem AD-associated changes found almost universally.[34] It is, therefore, not surprising that subsequent research has shown that DS patients with OSA tend to have worse cognitive outcomes than those without. Interestingly, among cognitively normal elderly adults, OSA has been associated with markers of increased amyloid burden.[35] Treating OSA in patients with AD may improve cognitive function, hypersomnolence, napping, and lethargy.[36,37] Breslin et al[38] examined a sample of 38 children with DS and found that the presence of PSG-confirmed OSA was associated with a verbal IQ that was 9 points lower compared to those without OSA. This verbal IQ difference likely represents a functional impairment in everyday language use for these children at lower baseline cognitive levels, making intervention even more important. There is clearly a need for additional research to more fully elucidate additional sequelae of OSA in this population including neurocognitive, metabolic, psychiatric, quality of life, health care utilization/cost, and mortality.

Is adenotonsillectomy curative for OSA in patients with DS? Sometimes

While outcomes for children undergoing adenotonsillectomy for OSA vary considerably, uncomplicated and otherwise healthy patients have historically shown significant improvement with adenotonsillectomy, with cure being achieved in up to 80% of cases.[39] Unfortunately, this level of success has not been replicated in the DS population. As discussed earlier, patients with DS often have multiple comorbidities that can affect airway obstruction and gas exchange through several mechanisms. Craniofacial/airway abnormalities such as midface hypoplasia, lingual tonsil hypertrophy, and macroglossia may create additional sites of airway obstruction. Obesity and hypotonia, depending on the severity, can also cause airway obstruction and contribute to hypoventilation. In short, because children with DS often have multiple factors contributing to sleep-disordered breathing, addressing only one of those factors is less likely to result in cure. Recent data have shown that between 50% and 75% of patients with OSA and DS will have clinically significant residual disease postoperatively.[40,41] Although this information may be somewhat discouraging, it should be noted that most patients with DS who undergo adenotonsillectomy for OSA still demonstrate substantial improvement in respiratory parameters on PSG, even if they do not achieve cure. In fact, on average, DS patients can see about a 50% reduction in their AHI after tonsil and adenoid removal.[40] So, if a hypothetical child with DS has an obstructive apnea-hypopnea index (OAHI) of 15 per hour (severe OSA) at baseline and undergoes adenotonsillectomy, and postoperative sleep study demonstrates an OAHI 7 per hour (moderate OSA), they have clearly benefited from the surgery in that they decreased disease severity from severe to moderate, but, on the other hand, they have not achieved surgical cure and will still likely require continuous positive airway pressure (CPAP). As a result, surgical management, specifically adenotonsillectomy, should routinely be explored as a therapeutic option for OSA in patients with DS, but with appropriate family education regarding effectiveness of adenotonsillectomy (T&A) in this population and the possible need for additional intervention (CPAP or advanced sleep apnea surgery) despite T&A. Finally, patients who are obese and/or sedentary should be counseled regarding fitness and nutrition to optimize weight status.

Is adenotonsillectomy safe in children with DS? Yes (in the right setting)

As is the case with any surgical procedure, care should be taken to ensure that the potential benefits outweigh the risk of any possible complications. Because patients with DS exist on such a diverse spectrum, each case should be addressed individually to ensure that surgery is in the best interest of the patient. For patients with DS, types of complications encountered as a result of adenotonsillectomy are similar to ones seen in the general population. Postoperative respiratory insufficiency and hemorrhage are the most common, but cardiac arrhythmias (especially in patients with underlying heart disease) as a result of anesthesia can also be observed.[42] Although prior work has shown higher rates of respiratory difficulty postoperatively,[43] a more recent review involving more than 350 children with DS undergoing T&A did not show any increased risk of respiratory compromise compared to patients without DS. This same cohort, however, did demonstrate increased rates of postoperative hemorrhage on initial admission (2.8% vs 1.2%).[44] A separate retrospective review comprising 30 individuals with DS undergoing T&A showed that 10% of patients developed late-onset hemorrhage between 7 and 10 days.[42] As a result, DS patients receiving adenotonsillectomy should be referred to a center with expertise in medically complex individuals and who have the resources to address complications should they arise.[42] Although the risk associated with surgery does appear to be somewhat higher in patients with DS, adenotonsillectomy is still considered a relatively safe and worthwhile procedure for patients with comorbid OSA.

Are treatment options available for children with DS who have residual OSA status post T&A? Yes

Due to high rates of residual OSA after adenotonsillectomy, patients with DS will often require additional treatment. CPAP is a noninvasive and effective option for these patients (as well as for patients who are poor surgical candidates). While data regarding CPAP usage in DS are somewhat limited, a recent randomized controlled study by Hill et al[45] involving 28 individuals showed significant improvements in daytime sleepiness, depression, and cognitive function with CPAP treatment. Perhaps even more interesting is that the average nighttime usage was moderate at best (roughly 3 hours). Along these lines (and similar to many patients using CPAP), compliance issues are frequently encountered. Fortunately, compliance tends to be a greater issue when beginning therapy, and consistent usage can often be achieved with time. Roughly two-thirds of patients in the cohort just mentioned continued to use CPAP after the 12-month trial ended.[45] A separate study with data available on eleven DS individuals showed that 81% of patients had CPAP usage >4 hours per night 1–3 years after starting therapy.[46]

Because patients with DS frequently have multiple sites of upper airway obstruction, additional surgical intervention is sometimes beneficial. Tongue base reduction, lingual tonsillectomy, and turbinate coblation are some of the more common surgical procedures performed for persistent OSA. More invasive procedures such as uvulopalatopharyngoplasty (UPPP) and midface advancement may also be pursued. To determine which procedure(s) will be of greatest benefit, drug-induced sleep endoscopy (DISE) is often performed. In surgically naïve children with DS, DISE frequently reveals adenotonsillar hypertrophy; however, multilevel airway obstruction is also regularly encountered. In a prospective study performed by Maris et al[47] involving 41 children with DS undergoing DISE, tongue base obstruction and epiglottic collapse were present in 24.4% and 48.8% of patients, respectively. For patients with persistent OSA after adenotonsillectomy, information obtained from direct visualization of the airway while asleep can be invaluable when considering additional treatment options. In these situations, referral to a specialist and/or center with DISE capabilities should be considered.

In addition to CPAP and surgery, adjunctive therapies are often incorporated into a patient's treatment plan. Intranasal steroids and leukotriene receptor antagonists have shown efficacy in milder forms of OSA.[48,49] Recent data involving non-syndromic pediatric patients demonstrated a reduction in AHI with montelukast use, even after adenotonsillectomy.[50] Rapid maxillary expansion (RME) has been shown to significantly increase upper airway volume in patients with DS and provide long-term benefits in adolescents with isolated maxillary narrowing.[51,52] Accumulating evidence in both adult and pediatric patients demonstrates that oropharyngeal exercises, also known as myofascial reeducation, may reduce both subjective and objective measures of OSA, although this has yet to be studied in children with DS.[53–55] Newer treatment modalities are also emerging for refractory OSA in DS. Hypoglossal nerve stimulation (HNS) involves an implantable device which relieves upper airway obstruction in response to specific variations in respiration. In a recent study performed by Diercks et al,[56] adolescents with comorbid DS and OSA demonstrated improvements in AHI (56–85% reduction) and quality-of-life scores after 6–12 months of HNS use. It is important to note that nonsurgical management of OSA in patients with DS requires varying levels of time and commitment. Individual patient factors such as overall health, cognitive function, and socioeconomic status may affect the feasibility and efficacy of each treatment choice.

Conclusion

Based on the literature reviewed in this article, OSA is seen at increased rates and with greater severity in the DS population. Baseline screening has led to earlier diagnosis and treatment, with significant clinical improvements being reported. Multiple treatment options are available, each with varying levels of success, and treatment decisions should be based on individual patient-level factors as well as caregiver preferences. Larger studies are needed to further explore the scope of OSA in patients with DS. Areas for further research include the following: improved screening models optimizing the identification of individuals with OSA, continued research into the utility of DISE-directed sleep apnea surgery, investigation of efficacy of adjunctive treatment measures (such as myofunctional therapy), and continued efforts at studying outcomes to better match individual patients with personalized treatment plans to optimize outcomes.

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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