R E V I E W

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 post-operatively.[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.

References

1. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased Prevalence of Sleep-Disordered Breathing in Adults. *Am J Epidemiol*. 2013;177(9):1006–1014.
2. Marcus CL, Brooks LJ, Draper KA, Ward SD, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*. 2012;130(3):e714–e755.
3. Knauert M, Naik S, Gillespie MB, Kryger M. Clinical consequences and economic costs of untreated obstructive sleep apnea syndrome. *World J Otorhinolaryngol Head Neck Surg*. 2015;1(1):17–27.
4. Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol*. 2010;88(12):1008–1016.
5. Shott SR, Amin R, Chini B, Heubi C, Hotze S, Akers R. Obstructive sleep apnea: Should all children with Down syndrome be tested? *Archives of otolaryngology-head & neck surgery*. 2006;132(4):432–436.
6. Lal C, White DR, Joseph JE, van Bakergem K, Larosa A. Sleep-Disordered Breathing in Down Syndrome. *Chest*. 2015;147(2):570–579.
7. Maris M, Verhulst S, Wojciechowski M, van de Heyning P, Boudewyns A. Prevalence of Obstructive Sleep Apnea in Children with Down Syndrome. *Sleep*. 2016;39(3):699–704.
8. Hill CM, Evans HJ, Elphick H, et al. Prevalence and predictors of obstructive sleep apnoea in young children with Down syndrome. *Sleep Med*. 2016;27-28:9999–106.
9. Dyken ME, Lin-Dyken DC, Poulton S, Zimmerman MB, Sedars E. Prospective Polysomnographic Analysis of Obstructive Sleep Apnea in Down Syndrome. *Arch Pediatr Adolesc Med*. 2003;157(7):655–660.

10. Trois MS, Capone GT, Lutz JA, et al. Obstructive sleep apnea in adults with Down syndrome. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2009;5(4):317–323.

11. van Gameren-Oosterom HBM, van Dommelen P, Schonbeck Y, Oudesluys-Murphy AM, van Wouwe JP, Buitendijk SE. Prevalence of Overweight in Dutch Children With Down Syndrome. *Pediatrics*. 2012;130(6):e1520–e1526.

12. Bull MJ, the Committee on Genetics. Health Supervision for Children With Down Syndrome. *Pediatrics*. 2011;128(2):393–406.

13. Macchini F, Leva E, Torricelli M, Valadè A. Treating acid reflux disease in patients with Down syndrome: pharmacological and physiological approaches. *Clin Exp Gastroenterol*. 2011;4:19–22.

14. Glasson EJ, Sullivan SG, Hussain R, Petterson BA, Montgomery PD, Bittles AH. The changing survival profile of people with Down's syndrome: implications for genetic counselling. *Clin Genet*. 2002;62(5):390–393.

15. Friedman NR, Ruiz AG, Gao D, Ingram DG. Accuracy of Parental Perception of Nighttime Breathing in Children with Down Syndrome. *Otolaryngology-Head and Neck Surgery*. 2018;158(2):364–367.

16. Nehme J, Laberge R, Pothos M, et al. Predicting the presence of sleep-disordered breathing in children with Down syndrome. *Sleep Med*. 2017;36:104–108.

17. Vicari S, Pontillo M, Armando M. Neurodevelopmental and psychiatric issues in Down's syndrome: assessment and intervention. *Psychiatr Genet*. 2013;23(3):95–107.

18. Nikolakaros G, Virtanen I, Markkula J, Vahlberg T, Saaresranta T. Obstructive sleep apnea in psychiatric outpatients. A clinic-based study. *J Psychiatr Res*. 2015;69:126–134.

19. Kuroda H, Sawatari H, Ando S, et al. A nationwide, cross-sectional survey on unusual sleep postures and sleep-disordered breathing-related symptoms in people with Down syndrome. *Journal of Intellectual Disability Research*. 2017;61(7):656–667.

20. Senthilvel E, Krishna J. Body position and obstructive sleep apnea in children with Down syndrome. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine*. 2011;7(2):158–162.

21. Jheeta S, Mcgowan M, Hadjikoumi I. Is oximetry an effective screening tool for obstructive sleep apnoea in children with Down syndrome? *Arch Dis Child*. 2013;98(2):164.

22. Skotko BG, Macklin EA, Muselli M, et al. A predictive model for obstructive sleep apnea and Down syndrome. *Am J Med Genet A*. 2017;173(4):889–896.

23. Elsharkawi I, Gozal D, Macklin EA, Voelz L, Weintraub G, Skotko BG. Urinary biomarkers and obstructive sleep apnea in patients with Down syndrome. *Sleep Med*. 2017;34:84–89.

24. Kirk V, Baughn J, D'Andrea L, et al. American Academy of Sleep Medicine Position Paper for the Use of a Home Sleep Apnea Test for the Diagnosis of OSA in Children. *J Clin Sleep Med*. 2017;13(10):1199–1203.

25. Fan Z, Ahn M, Roth H, Li L, Vaughn B. Sleep Apnea and Hypoventilation in Patients with Down Syndrome: Analysis of 144 Polysomnogram Studies. *Children*. 2017;4(7):55.

26. Mcdowell KM, Craven DI. Pulmonary Complications of Down Syndrome during Childhood. *J Pediatr*. 2011;158(2):319–325.

27. Paladini D, Tartaglione A, Agangi A, et al. The association between congenital heart disease and Down syndrome in prenatal life. *Ultrasound in Obstetrics and Gynecology*. 2000;15(2):104–108.

28. Laursen HB. Congenital heart disease in Down's syndrome. *Heart*. 1976;38(1):32–38.

29. Chi TL, Krovetz LJ. The pulmonary vascular bed in children with Down syndrome. *J Pediatr*. 1975;86(4):533–538.

30. Ingram DG, Singh AV, Ehsan Z, Birnbaum BF. Obstructive Sleep Apnea and Pulmonary Hypertension in Children. *Paediatr Respir Rev*. 2017;23:33–39.

31. Lott IT, Dierssen M. Cognitive deficits and associated neurological complications in individuals with Down's syndrome. *Lancet Neurol*. 2010;9(6):623–633.

32. Chapman RS, Seung H-K, Schwartz SE, Kay-Raining Bird E. Language Skills of Children and Adolescents With Down Syndrome. *Journal of Speech Language and Hearing Research*. 1998;41(4):861–873.

33. Lögdbergi B, Brun A. Prefrontal neocortical disturbances in mental retardation. *Journal of Intellectual Disability Research*. 1993;37(5):459–468.

34. Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. *Lancet Neurol*. 2010;9(8):793–806.

35. Sharma RA, Varga AW, Bubu OM, et al. Obstructive Sleep Apnea Severity Affects Amyloid Burden in Cognitively Normal Elderly. A Longitudinal Study. *Am J Respir Crit Care Med*. 2018;197(7):933–943.

36. Bliwise DL. Alzheimer's Disease, Sleep Apnea, and Positive Pressure Therapy. *Curr Treat Options Neurol*. 2013;15(6):669–676.

37. Ancoli-Israel S, Palmer BW, Cooke JR, et al. Cognitive Effects of Treating Obstructive Sleep Apnea in Alzheimer's Disease: A Randomized Controlled Study. *J Am Geriatr Soc*. 2008;56(11):2076–2081.

38. Breslin J, Spanò G, Bootzin R, Anand P, Nadel L, Edgin J. Obstructive sleep apnea syndrome and cognition in Down syndrome. *Developmental Medicine & Child Neurology*. 2014;56(7):657–664.

39. Brietzke SE, Gallagher D. The Effectiveness of Tonsillectomy and Adenoidectomy in the Treatment of Pediatric Obstructive Sleep Apnea/Hypopnea Syndrome: A Meta-Analysis. *Otolaryngology-Head and Neck Surgery*. 2006;134(6):979–984.

40. Nation J, Brigger M. The Efficacy of Adenotonsillectomy for Obstructive Sleep Apnea in Children with Down Syndrome: A Systematic Review. *Otolaryngology-Head and Neck Surgery*. 2017;157(3):401–408.

41. Ingram DG, Ruiz AG, Gao D, Friedman NR, American Academy of Sleep Medicine. Success of Tonsillectomy for Obstructive Sleep Apnea in Children With Down Syndrome. *Journal of Clinical Sleep Medicine*. 2017;13(08):975–980.

42. Yumusakhuylu AC, Binnetoglu A, Demir B, Baglam T, Sari M. Is it safe to perform adenotonsillectomy in children with Down syndrome? *European Archives of Oto-Rhino-Laryngology*. 2016;273(9):2819–2823.

43. Goldstein NA, Armfield DR, Kingsley LA, Borland LM, Allen GC, Post JC. Postoperative Complications After Tonsillectomy and Adenoidectomy in Children With Down Syndrome. *Arch Otolaryngol Head Neck Surg*. 1998;124(2):171–176.

44. Baker AB, Farhood Z, Brandstetter KA, Teufel RJ, Larosa A, White DR. Tonsillectomy in Children with Down Syndrome: A National Cohort of Inpatients. *Otolaryngology-Head and Neck Surgery*. 2017;157(3):499–503.

45. Hill EA, Fairley DM, Williams LJ, Cooper S-A, Riha RL. A prospective, randomised, controlled trial of CPAP in adults with Down syndrome. *European Respiratory Journal*. 2015;46(suppl 59).

46. Dudoignon B, Amaddeo A, Frapin A, et al. Obstructive sleep apnea in Down syndrome: Benefits of surgery and noninvasive respiratory support. *Am J Med Genet A*. 2017;173(8):2074–2080.

47. Maris M, Verhulst S, Saldien V, van de Heyning P, Wojciechowski M, Boudewyns A. Drug-induced sedation endoscopy in surgically naive children with Down syndrome and obstructive sleep apnea. *Sleep Med*. 2016;24:63–70.

48. Goldbart AD, Greenberg-Dotan S, Tal A. Montelukast for Children With Obstructive Sleep Apnea: A Double-blind, Placebo-Controlled Study. *Pediatrics*. 2012;130(3):e575–e580.

49. Brouillette RT, Manoukian JJ, Ducharme FM, et al. Efficacy of fluticasone nasal spray for pediatric obstructive sleep apnea. *J Pediatr*. 2001;138(6):838–844.

50. Wang B, Liang J. The Effect of Montelukast on Mild Persistent OSA after Adenotonsillectomy in Children: A Preliminary Study. *Otolaryngology-Head and Neck Surgery*. 2017;156(5):952–954.

51. de Moura CP, Vales F, Andrade D, et al. Rapid maxillary expansion and nasal patency in children with Down syndrome. *Rhinology*. 2005;43(2):138–142.

52. Pirelli P, Saponara M, Guilleminault C, Expansion Rmaxillary. RME) for pediatric obstructive sleep apnea: a 12-year follow-up. *Sleep Med*. 2015;16(8):933–935.

53. Camacho M, Certal V, Abdullatif J, et al. Myofunctional Therapy to Treat Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. *Sleep*. 2015;38(5):669–675.

54. Chuang L-C, Lian Y-C, Hervy-Auboiron M, Guilleminault C, Huang Y-S. Passive myofunctional therapy applied on children with obstructive sleep apnea: A 6-month follow-up. *J Formos Med Assoc*. 2017;116(7):536–541.

55. Villa MP, Evangelisti M, Martella S, Barreto M, del Pozzo M. Can myofunctional therapy increase tongue tone and reduce symptoms in children with sleep-disordered breathing? *Sleep and Breathing*. 2017;21(4):1025–1032.

56. Diercks GR, Wentland C, Keamy D, et al. Hypoglossal Nerve Stimulation in Adolescents With Down Syndrome and Obstructive Sleep Apnea. *JAMA Otolaryngol Head Neck Surg*. 2017.