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Obstructive Sleep Apnea in Selected Genetic Syndromes

Obstruktivna apneja v spanju pri izbranih genetskih sindromih

ABSTRACT

KEY WORDS: obstructive sleep apnea, genetic disorder, craniofacial abnormalities, skeletal dysplasia, connective tissue disorders, Down syndrome

Obstructive sleep apnea is a common sleep breathing disorder affecting 2–4% of the middle-aged population. However, the reported prevalence between population sub-groups is highly variable. Epidemiological studies established several risk factors associated with obstructive sleep apnea, including age, sex, body mass index, craniofacial and upper airway abnormalities, use of sedatives and alcohol, familial history, and comorbidities. Obstructive sleep apnea is a prevalent complication in complex genetic disorders, particularly those with predisposing features, such as craniofacial abnormalities, macroglossia, narrow nasopharynx and/or oropharynx, obesity, and hypotonia. Sleep disorders are often overlooked in genetic syndromes, particularly during childhood, thus increasing the risk for further comorbidities, neurocognitive impairment, and cardiopulmonary complications. Early diagnosis and management of obstructive sleep apnea positively impact the quality of life of individuals with genetic disorders and their families. The review will briefly present obstructive sleep apnea in selected genetic syndromes, including achondroplasia, Osteogenesis imperfecta, Down syndrome, Prader-Willi syndrome, Ehlers-Danlos syndrome, Marfan's, mucopolysaccharidosis, and other common syndromes with craniosynostosis and specific facial features including orofacial cleft and Pierre Robin sequence.

IZVLEČEK

KLJUČNE BESEDE: obstruktivna apneja v spanju, genetski sindromi, kraniofacialne nepravilnosti, skeletne displazije, vezivnotkivne bolezeni, Downov sindrom

Obstruktivna apneja med spanjem je pogosta motnja dihanja, ki se pojavlja pri 2–4 % prebivalstva srednjih let, vendar je prevalenca med posameznimi podskupinami prebivalstva zelo različna. Epidemiološke študije so pokazale več različnih dejavnikov tveganja za pojav obstruktivne apneje v spanju, med njimi starost, spol, indeks telesne mase, kraniofacialne nepravilnosti in nepravilnosti zgornjih dihalnih poti, uporaba pomirjeval in alkohola, družinska anamneza in nekatere pridružene kronične bolezni. Obstruktivna apneja v spanju je poznan in pogost zaplet tudi pri kompleksnih genetskih motnjah, zlasti tistih

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z očitnimi dejavniki tveganja, kot so kraniofacialne nepravilnosti, nenormalno velik jezik (lat. *macroglossia*), ozek nazofarinks in/ali orofarinks, debelost in hipotonija. Pri genetskih sindromih so motnje spanja pogosto spregledane, zlasti v otroštvu, kar poveča tveganje za nadaljnje soobolevnosti, nevrokognitivne okvare in srčno-pljučne zaplete. Zgodnje odkrivanje in zdravljenje obstruktivne apneje v spanju pozitivno vpliva na kakovost življenja posameznikov z genetskimi motnjami in njihovih družin. S pričujočim pregledom bo na kratko predstavljena obstruktivna apneja v spanju pri izbranih genetskih sindromih, vključno z ahondroplazijo, osteogenesis imperfecto, Downovim sindromom, Prader-Willijevim sindromom, Ehlers-Danlosovim sindromom in Marfanovim sindromom, mukopolisaharidozami ter sindromi s kraniosinostozo in specifičnimi obraznimi potezami, vključno z orofacialnim razcepom in Pierre Robinovo sekvenco.

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep breathing disorder characterized by recurrent episodes of upper airway obstruction, which can be complete (apnea) or partial (hypopnea). The number of apneas/hypopneas per hour of sleep represents the apnea-hypopnoea index (AHI), which is commonly used to classify the severity of the disorder, separating mild (AHI is 5–15), moderate (AHI is 15–30) and severe (AHI is > 30) OSA *(1).* These apnea/hypopnea episodes are often associated with intermittent hypoxemia, hypercapnia, swings in intrathoracic pressure, and increased sympathetic activity leading to nocturnal hypertension, sleep fragmentation, and nocturnal arousals *(2, 3).* OSA symptoms can manifest during sleep as snoring, choking attacks, awakenings due to gasping or choking, or witnessed breathing disturbances. Daytime symptoms are connected to excessive daytime sleepiness. Eventually, OSA may represent a risk factor for numerous neurocognitive and cardiovascular diseases, metabolic disturbances, and sleepiness-related accidents. There are also distinct age and sex-specific clinical presentation differences. Females are less likely to report snoring or witnessed apneas but are more likely to have morning headaches, fatigue, insomnia symptoms, anxiety, and depression *(4).* Children mainly present with mouth or noisy breathing, pauses in breathing, coughing or choking in sleep, restless sleep, sweating, and nocturnal enuresis and parasomnias are common *(5–7).* Excessive daytime sleepiness is not so obvious in children and may manifest as age-inappropriate daytime sleeping, often during short rides or in school. Untreated OSA in children is associated with substantial cardiovascular and neurobehavioral morbidities, including systemic hypertension, pulmonary hypertension, lat. *cor pulmonale*, and sudden death *(8).* Failure to thrive, behavioural problems resembling attention deficit-hyperactivity disorder, and learning and cognitive issues are commonly described.

Obstructive Sleep Apnea: Epidemiology and Risk Factors

In general, the prevalence of OSA in the adult population is reported to be up to 4%. However, there is a wide variation between population sub-groups in relation to various risk factors *(9).* Epidemiological studies established that older age, male sex, obesity, craniofacial and upper airway abnormalities, comorbidities, use of sedatives and alcohol, and positive family history, among other factors, are risk factors predisposing OSA *(10–12).* The prevalence of OSA increases with age, independent of other risk factors. Recent global estimates of adults between the ages 30–69 suggest

that 936 million people worldwide have OSA, whereas 425 million people worldwide have moderate to severe OSA. OSA is more common in men than women due to gender differences in hormones, body fat distribution, and pharyngeal anatomy and function. Obesity is a major predisposing risk factor for OSA because of increased weight in the upper airway. Craniofacial abnormalities, such as retrognathia, micrognathia, a high arched or narrow palate, macroglossia, tonsillar hypertrophy and nasal septal deviation also contribute to the development of OSA. Positive family history is an important risk factor for OSA *(13–15).* Around 40% of the variance in AHI has been shown to be explained by genetic factors *(13).* OSA was reported in 21%–84% of first-degree relatives of individuals with OSA *(14, 15).*

Obstructive Sleep Apnea in the Pediatric Population

The prevalence of OSA among the pediatric population was reported to be 1–10% *(5, 17).* In the pediatric population, OSA is defined as a »disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts normal ventilation during sleep and normal sleep patterns« *(18).* Symptoms like habitual snoring, difficulty breathing during sleep, observed apnea, arousals, restless sleep, enuresis, cyanosis, and frequent daytime sleepiness may be present. However, OSA in children may remain undetected, as learning, attention, and behavior issues may present instead *(5).* The pediatric OSA is mainly the result of disorders that cause upper airway narrowing or increased collapsibility. The upper airway narrowing is mostly associated with immaturity of the respiratory center in infants and adenotonsillar hypertrophy in children *(19).* Increased upper airway collapsibility is typically associated with the conditions that cause a decrease in muscle tone or inflammatory conditions affecting the upper airways. The standard criterion for diagnosis of OSA in children is polysomnography (PSG), but in practice, only a small percentage of children with suspected OSA actually undergo PSG, and the diagnosis is primarily clinical (20). The long-term sequelae of untreated OSA include failure to thrive, cardiorespiratory compromise, and even death.

OBSTRUCTIVE SLEEP APNEA IN GENETIC SYNDROMES

OSA is a highly prevalent complication in numerous genetic syndromes, particularly those with predisposing features, such as craniofacial abnormalities, macroglossia, narrow nasopharynx and/or oropharynx, obesity and hypotonia. Genetic disorders predisposing to upper airway obstruction that make treatment of OSA a priority include individuals with Achondroplasia, Osteogenesis Imperfecta (OI), Down syndrome (DS), Prader-Willi syndrome (PWS), Ehlers-Danlos syndrome (EDS), Marfan's, Mucopolysaccharidosis (MPS), and other common syndromes with craniosynostosis and specific facial features including orofacial cleft and Pierre Robin sequence (PRS) among others.

Craniofacial Abnormalities

Craniofacial abnormalities are a highly complex and heterogeneous group of disorders caused by the interruption of normal embryologic growth and differentiation of the face and skull *(21).* Children with craniofacial conditions, including orofacial clefts, micrognathia, midface hypoplasia, and craniosynostosis, are generally at increased risk for OSA *(5).* The reported prevalence of OSA in children with craniofacial syndromes ranges 7–67%, depending on the stringency of the diagnostic criteria and population under study *(22).*

Orofacial clefts

Orofacial clefts are the most common congenital disorders of the face, with a prevalence

of 1/700 live births *(23)*. Orofacial clefts are characterized by failure of normal fusion of the palate and lip at the midline during development. They may present as cleft lip, cleft palate, or both cleft lip and palate. While isolated orofacial clefts are not uncommon, approximately 30% of cleft lip and/or palate (CL/P) and cleft palate (CP) occur in the context of genetic syndromes, encompassing over 200 syndromes *(24)*. Namely, these defects are often an associated feature in PRS, Stickler syndrome, Treacher Collins syndrome, Goldenhar syndrome, and Nager syndrome. Nearly a third of patients with syndromic CL/P or CP presented with OSA, most likely due to maxillary or mandibular hypoplasia, macroglossia, or poor motor tone *(25, 26)*. Moreover, patients with orofacial clefts have an additional risk for OSA due to surgical correction procedures of the cleft. Thus, apart from the initial evaluation of respiratory issues after the birth of individuals with syndromic orofacial clefts, long-term evaluation of OSA is needed during the child's growth. If OSA persists, further interventions should be performed, such as adenotonsillectomy, turbinate reduction, and/or tongue reduction *(27)*.

Pierre Robin sequence

PRS occurs in 1/8,500–14,000 newborns per year (The Orphanet nomenclature of rare diseases, ORPHA: 718) *(29)*. The condition is classically characterized as a triad of mandibular hypoplasia or micrognathia, downward displacement of the tongue (glossoptosis), and a wide spectrum of phenotypes with varying degrees of airway obstruction at a different level. PRS may be isolated or syndromic, and CP is described in 80–90% of the PRS cases *(28–30)*. The reported prevalence of OSA in patients with PRS ranges between 12.5% and 100%, depending on the criteria used *(31–35)*. Infants with PRS usually present with OSA and respiratory distress, which requires an initial evaluation and immediate management of airway obstruction *(36–38)*. Symptoms usually include abnormal breathing sounds, increased use of respiratory accessory muscle, desaturations, difficulty feeding/swallowing, reflux, and aspiration. Over time, untreated OSA may lead to failure to thrive, difficulty speaking, neurological deficits, and ultimately pulmonary hypertension and cor pulmonale. As previously mentioned, PSG is the gold standard for assessing airway obstruction and decisions regarding conservative interventions, surgical procedures, or a combination of both *(18)*. By combining supplemental oxygen, positioning (feeding, sleep, and other positioning therapy) and nasopharyngeal airway placement (NPA), conservative management resolves up to 70% of cases with mild OSA. Nasopharyngeal stenting and continuous positive airway pressure are useful interventions that have shown great benefit. However, syndromic PRS is usually characterized with severe OSA and requires surgical management, such as tongue-lip adhesion (TLA), mandibular distraction osteogenesis (MDO), and tracheostomy *(28, 39)*. A cross-sectional study of PRS showed that approximately 50% of the children could not be managed with prone positioning and required respiratory support at an early age *(40)*. Those children needed surveillance until adulthood due to the high risk of developing OSA later. Children with PRS that had benefited from prone positioning as infants had a very low risk of obstruction at a later age.

Syndromic PRS has been recently reported to account for 60% of PRS, including Treacher Collins syndrome (TCS), 22q11.2 deletion syndromes (22q11.2DS), and Stickler syndrome *(24, 29)*. The most common syndrome associated with PRS is Stickler syndrome, a connective tissue disorder caused by pathogenic variants of COL genes (*COL2A1, COL11A1, COL11A2, COL9A1, COL9A2, COL9A3*), affecting col-

lagen formation. Typical craniofacial clinical features are PRS, cleft palate, myopia, cataract, and retinal detachment. Other typical signs include conductive and sensorineural hearing loss, joint hypermobility, mild spondyloepiphyseal dysplasia, and/or precocious arthritis *(36)*. Tracheostomy may be needed to ensure a competent airway but can be removed over time if micrognathia becomes less prominent. If micrognathia persists, a mandibular advancement procedure is often required. Treacher Collins syndrome is characterized by downslanting palpebral fissures, malar hypoplasia, micrognathia, and external ear abnormalities *(41)*. Less common abnormalities include cleft palate and unilateral or bilateral choanal stenosis or atresia. Conductive hearing loss and hypoplasia of the middle ear cavities may also be present. In newborns with Treacher Collins syndrome, airway obstruction results from extreme shortening of the mandible with severe micrognathia, glossoptosis, and choanal atresia or stenosis, which may lead to severe OSA and neonatal death. Airway management in neonates may require special positioning of the infant with oral intubation or tracheostomy during birth by cesarean section. Long-term periodic assessment of OSA, as well as growth and development, is recommended. 22q11.2 deletion syndrome describes different phenotypes, including DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, autosomal dominant Opitz G/BBB syndrome, Sedlackova syndrome, and Cayler cardiofacial syndrome *(42)*. In general, palatal abnormalities are present in 67% of 22q11.2 deletion syndrome patients and may include velopharyngeal incompetence, submucosal cleft palate, bifid uvula, and cleft palate. Other common craniofacial features include prominent nasal bridge, bulbous nose, micrognathia and craniosynostosis. Laryngotracheoesophageal abnormalities, like the vascular ring, laryngeal web, laryngotracheomalacia, and subglottic stenosis are also frequent. Other major clinical manifestations of 22q11.2 deletion phenotype include congenital heart disease, immune deficiency, sensorineural and/or conductive hearing loss, gastrointestinal, ophthalmologic, central nervous system, skeletal, and genitourinary anomalies, characteristic facial features, and learning difficulties. More than 50% of all 22q11.2 DS patients had OSA detected by PSG, and OSA persisted or was even worse after adenotonsillectomy or after surgery for velopharyngeal insufficiency correction *(42)*. Thus, close monitoring for OSA in 22q11.2 DS patients is needed. Clinical practice guidelines for the evaluation and treatment of individuals with 22q11.2 deletion syndrome have been published *(43)*.

Craniosynostosis

Craniosynostosis (CS) results from the premature fusion of one or more cranial sutures, with the estimated prevalence of 1/2,000 to 1/2,500 live births *(44, 45)*. Approximately 70–75% of all craniosynostosis are nonsyndromic, isolated findings *(45, 46)*. Those are mainly sporadic, but underlying genetic causes have been established in a substantial fraction of nonsyndromic craniosynostosis cases *(47)*. Syndromic CS represents approximately 25–30% of all cases, whereas pathogenic variants of several genes, including *FGFR1, FGFR2, FGFR3, TWIST1*, and *EFNB1* genes, have been frequently associated with various syndromic craniosynostosis cases *(48)*. Among identified genetic causes, pathogenic variants in the fibroblast growth factor receptor (FGFR) genes are linked to some of the most common craniosynostosis, including Pfeiffer (Online Mendelian Inheritance in Man, OMIM: 101600), Apert (OMIM: 101200), Crouzon (OMIM: 123500), Muenke (OMIM: 602849), Antley-Bixler (OMIM: 207410, 201750), Beare-Stevenson (OMIM: 123790), and Jackson-Weiss (OMIM: 123150) syndromes.

The FGFR-related craniosynostosis syndromes usually follow an autosomal dominant inheritance pattern. Apert syndrome is characterized by coronal craniosynostosis, bilateral symmetrical complex syndactyly of the hands and feet, a fusion between the phalanges of the digits, radiohumeral fusion, and variably present mental retardation. There is wide variation in the craniofacial phenotype, which typically includes moderate to severe midface retrusion, cleft palate, proptosis, strabismus, refractive error, anisometropia, dental anomalies, and conductive hearing loss. Narrow pharynx and midface retrusion are the frequent causes of airway compromise. Crouzon syndrome is typically the mildest FGFR2--associated CS, characterized by a high and flat forehead, proptosis, and midface hypoplasia. In general, facial anomalies are milder than those of Apert syndrome. Cleft palate is rarely present, and individuals typically have normal intelligence, hands, and feet. Most patients with Apert and Crouzon syndrome have *de novo* mutations, which mainly originate from the paternal DNA copy.

The prevalence of OSA in children with syndromic CS was reported to be up to 74%, and it was more prevalent and severe in children with midface hypoplasia (Apert syndrome, Crouzon syndrome and Pfeiffer syndrome) than in those without hypoplasia (e.g., Muenke syndrome or Saethre–Chotzen syndrome) *(49–51)*. The highest prevalence of OSA was reported in patients with Apert syndrome, followed by Pfeiffer, Crouzon with acanthosis nigricans, and Crouzon syndromes. Severe OSA was detected primarily in patients with Pfeiffer syndrome, while patients with Apert and Crouzon syndromes were more likely to have moderate OSA. Contributing factors for OSA include narrowed nasal passages due to bony atresia/stenosis, tongue-based airway obstruction, and tracheal anomalies, which may represent a significant risk of sudden death during illness *(52)*. However, a predominant contributing factor is midface hypoplasia, associated with more severe OSA and less likely improvements *(53)*. Syndromic CS typically requires surgical intervention to improve the main functional issues resulting from the CS, including a correction of nasopharyngeal airway obstruction, which is present in most individuals. Roughly half of all children with syndromic craniosynostoses, such as Crouzon, Apert, and Pfeiffer syndrome, develop OSA within the first six years of life *(53)*. However, OSA may also develop or worsen during childhood or adulthood. Clinical assessment of the craniofacial region, and airway obstruction symptoms, followed by imaging modalities, are valuable for identifying OSA *(54)*. As previously mentioned, PSG is the gold standard, but endoscopic examination is often needed to detect the airway narrowing and decide on surgical intervention. Respiratory difficulties may require either supplemental oxygen via nasal cannula, continuous positive airway pressure support, nasal stenting, tonsillectomy/adenoidectomy, choanal dilatation, early midface advancement or tracheostomy, depending on the anatomical cause. If possible, continuous positive airway pressure support should be avoided since pressure on the midface aggravates midface retrusion. Clinical evaluation for OSA should be performed at least every three months during the first year and annually after that. PSG should be performed in the presence of clinical symptoms. In the case of central apnea brain, MRI should be considered in order to evaluate for Chiari I malformation.

Skeletal Dysplasia

Skeletal dysplasia is a large group of over 400 clinically and genetically heterogeneous disorders, with an approximate incidence of 1/5,000. Apart from already discussed craniosynostosis, OSA is known to be a common complication in other skele-

tal dysplasia disorders, such as achondroplasia (AH) (OMIM: 100800). AH is a bone growth disorder most noticeable in very short long bones of extremities (rhizomelia). It is caused by a pathogenic variant in the fibroblast growth factor receptor 3 (FGFR3) gene and has an autosomal dominant inheritance. Patients present with macrocephaly, midface hypoplasia, dysplasia of the skull base, foramen magnum stenosis with cervical spinal cord compression, and some other bone deformities. The upper airways are narrow, the chin is retruded, and the mandibular angle is increased. In addition, enlarged tonsils and adenoids are common, contributing to upper airway obstruction. OSA has been reported in 50–80% of children with AH and in 60% of adults *(55–58).* Guidelines for the management of AH-related OSA recommend early intervention, in the form of early overnight PSG and sleep study, which should be performed as soon as possible after the diagnosis/birth (in the first year of life or at the first signs of sleep-disordered breathing, whichever comes earlier); in any case, no later than at 2 years of age, and after that regular check-up for the prevention of OSA *(59).* Significant improvement has been shown in children after adenotonsillectomy, with fewer sleep respiratory disturbances *(60).* Other treatments for achondroplasia-associated OSA include positive airway pressure, tracheostomy for extremely severe cases, and weight reduction.

Osteogenesis imperfecta

OI combines a group of genetic disorders 1/15,000–20,000 births. They all share a common disease mechanism – pathogenic change in the genes encoding type I collagen (COL1A1 and COL1A2) that results in the disturbing production, synthesis, folding, assembly, secretion or structure of type I collagen. Typical signs and symptoms include bone fragility, short stature, progressive skeletal deformity of cranial, spinal and long bones, hyperextensibility of ligaments, and other features. There are several subtypes, from prenatally lethal to mild, adult, non-deforming type. Until recently, OSA has not been recognized as frequent in these patients, but a cross-sectional study showed that up to 52% of OI patients suffer abnormal apnoea and hypopnea index according to overnight PSG *(61).* OSA prevalence seems to be higher in children with OI than in healthy children *(62).* The basis for OSA in OI has not been fully elucidated. The contributing factors include vertebral and other chest wall deformities, skull base abnormalities, and restricted lung function due to skeletal disease. In addition, patients are less active due to bone fragility and deformities, leading to overweight and further progressive deformities. The decreased mobility also leads to loss of muscle mass, increasing daily fatigue. There are no clear guidelines for OSA evaluation within the group of OI patients, but it is increasingly recognized as an important factor contributing to other disease-associated complications *(63).*

Connective Tissue Disorders

Marfan syndrome

Marfan syndrome is a complex, clinically heterogeneous disorder resulting from fibrillin-1 mutation. It is one of the most common genetic disorders, with a prevalence of 1/3,000–5,000 individuals. It predominantly affects skeletal, cardiovascular, and ocular systems. Interestingly, it has been shown that almost 60% of adults and 80% of children with the syndrome experience OSA. This has been speculated to be due to craniofacial characteristics and dysmorphic facial features, the most commonly present among them are dolichocephaly, retrognathia, temporomandibular joint disorders, crowded teeth, and specific palatal morphology including high arched palate and narrow posterior maxillary region *(64, 65).* The leading cause of mortality and morbidity in

Marfan syndrome is aortic disease and its complications. At the same time, individuals with OSA generally have a higher risk for cardiovascular diseases. The underlying biological factor has been attributed to intermittent hypoxia during OSA that further causes oxidative stress and systemic inflammation, and to the changes in intrathoracic pressure resulting in additional mechanical stress on the heart and large artery walls. The correlation between OSA severity and arterial disease complications has not been established in individuals with the syndrome, therefore, other factors predominantly contribute to aortic disease in patients with Marfan syndrome.

Ehlers-Danlos syndrome

EDS is another group of rare connective tissue disorders relatively common from the perspective of the rare disease, with a prevalence of 1/5,000 individuals. There are several subtypes, including classical, hypermobile, vascular, kyphoscoliotic, and some less frequent, with manifestations ranging from practically asymptomatic or mild skin and joint hyperextensibility to severe clinical presentation and early death. Genetic defects in several collagen subtypes or their synthesis and structural characteristics lead to multisystem involvement with the skin, ligaments, joints, blood vessels, and internal organs. Breathing during sleep might result from specific defects, predominantly high arched palate, mandibular retrognathia, cartilaginous defects of the nasal and maxillary cartilages, vocal cord abnormalities, scoliosis, and kyphosis. A meta-analysis showed that OSA prevalence in EDS patients is almost 40%, meaning that EDS patients are at 6 times higher risk of developing OSA than the general population. These patients typically complain of fatigue, daytime sleepiness, and increased pain, leading to impaired quality of life *(66)*. Clinical guidelines recommend the exclusion of sleep-disordered breathing in all patients with EDS complaining of fatigue *(67)*.

Mucopolysaccharidosis

These rare inherited lysosomal storage diseases are each caused by the deficiency of a specific lysosomal enzyme and are associated with the progressive accumulation of glycosaminoglycans in several organs. Diseases progress with age and result in severe morbidity and premature death. With the focus on the ear-nose-throat phenotype, upper and lower airway obstruction and restrictive pulmonary disease are typically present and lead to further complications – chronic rhinosinusitis, recurrent ear, upper and lower respiratory tract infections, obstructive sleep apnoea, and ultimately also respiratory failure. There are several prominent disease characteristics – flattened nasal bridge, short neck, high epiglottis, mandibular abnormalities, glycosaminoglycans deposition in the mouth, nose, and throat, and adenotonsillar hypertrophy. Sleep disordered breathing occurs in more than 80% of patients and no significant difference exists between different MPS subtypes. Multiple studies confirmed that children benefit from adenotonsillectomy, after which OSA significantly improves. In some cases, the hypertrophy of lingual tonsils causes persistent OSA after adenotonsillectomy. It is recommended that children with MPS are monitored with PSG and surgically treated when OSA is confirmed *(68, 69)*.

Prader-Willi Syndrome

PWS (OMIM 176270) is a rare genetic disorder with numerous metabolic, endocrine, neurological, behavioral, and intellectual issues. It results from the loss of the paternal gene expression within the PWS critical region on the 15q11.2-q13. Typical clinical features include global developmental delay, short stature, muscular hypotonia, poor feeding during early infancy,

severe obesity, and endocrine dysfunction in later childhood and adulthood. As individuals with PWS present with failure to thrive during infancy and then progress to morbid obesity during later childhood, sleep-related breathing disorders also change from central sleep apnea in infancy to OSA in older children and adults. The prevalence of OSA in children with PWS has been reported to be as high as 80% and the prevalence of moderate to severe OSA to be 22% in adults with PWS *(70, 71)*. PWS-related OSA is most likely the consequence of several factors like obesity, muscular hypotonia, mid-facial hypoplasia, and adenotonsillar hypertrophy *(72, 73)*. Treatment of PWS-related OSA is important in order to preserve cardiovascular health, limit the risk of severe respiratory events during sleep, and prevent sudden death. The treatment options are similar to those for the general population. However, behavioral issues may be challenging for some interventions. Some specific recommendations include consideration of adenotonsillectomy prior to initiating growth hormone treatment since GH may contribute to an overgrowth of lymphoid tissue resulting in OSA *(74)*. As hypothyroidism may contribute to OSA, yearly thyroid function testing is recommended. Weight loss through diet is important, but more recently, laparoscopic sleeve gastrectomy was also considered.

Down Syndrome

DS is the most common chromosomal abnormality in humans, resulting from the presence of a full or a part of the third copy of chromosome 21. It is characterized by mild to moderate intellectual disability, growth retardation, and typical craniofacial features. A recent meta-analysis established a high prevalence of DS-related OSA, ranging 60–95%, depending on the criteria used for diagnosis and the age of the patients *(75)*. Individuals with DS are at high risk of OSA, mainly due to hypotonia, midface hypoplasia, micrognathia, relative macroglossia, narrow nasopharynx, laryngomalacia, tracheomalacia, and hypertrophy of the adenoid and tonsillar tissue. Other risk factors include hypothyroidism and overweight/obesity *(75, 76)*. Regular screening for sleep-related breathing problems is recommended in routine clinical care for children with DS. The American Academy of Pediatrics recommends PSG in all children with DS around 4 years of age and in older children suspected of having OSA *(76)*. They also suggest regular PSG screening in the adult population with DS. Individuals with DS have an increased risk for cardiovascular and neurocognitive sequelae. Thus, diagnosing and treating OSA as soon as possible is important. First-line treatment options generally include adenotonsillectomy and continuous positive airway pressure, but these have shown only partial improvements in DS patients *(77)*. Conservative treatment options for DS include weight control and medical treatments with intranasal steroids or oral cysteinyl-leukotriene receptor antagonists. Other surgical interventions such as lingual tonsillectomy, tongue-based procedures, and hypoglossal nerve stimulation may be considered for cases with persistent OSA *(78)*. Adults with DS-related OSA may have an atypical presentation with psychological symptoms such as irritability, depression, paranoia, and other behavior changes. Therefore, periodic assessment of adult individuals with DS should include sleep studies.

CONCLUSION

OSA is one of the predominant complications in genetic syndromes affecting connective and skeletal tissue, craniofacial structures, genetic storage diseases, and morbid obesity. Nevertheless, it is frequently overt, resulting in significant neurocognitive, cardiovascular and metabolic homeostasis comorbidities, as well as behavioral issues with a potential long-term

impact. The widespread screening in these patients is reasonable, facilitating early diagnosis and management of OSA. Adenotonsillectomy is suggested in most cases; however, it often does not resolve the issue, requiring further interventions. PSG is recommended to be included in clinical practice before and after treatment interventions.

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