Syndromes Related to Pediatric Otolaryngology

Renata C. Di Francesco

Otolaryngologists must have experience in how to approach syndromic children. About 2% of children present some congenital anomaly, and about 70% of them are located in the head and neck[1]. Children with craniofacial abnormalities are more prone to ear nose and throat (ENT) problems[2]. The physician may be presented with two distinct situations: a patient with a known syndrome that presents an ENT problem that requires an appropriate investigation and management of the child, or a suspicion that a child must have a syndrome that has not yet been diagnosed[1].

Sleep disordered breathing is about 9 times higher in children with craniofacial abnormalities than in normal ones. Upper airway obstruction occurs in the presence of an anatomically narrow nasopharyngeal space, sometimes in association with some degree of stenosis or atresia of the choanae.

Many airway abnormalities can be diagnosed by physical examination and a simple nasopharyngeal endoscopy or computed tomographic scan or magnetic resonance imaging of the head and neck[2]; as well as by a bronchoscopy that may also approach the lower aiways[3].

A frequent problem in syndromic children is laryngomalacia, a common cause of stridor in **infants, accounting** for up to 75% of all congenital laryngeal anomalies[4].

All children with craniofacial syndromes must have their hearing checked. Neonatal hearing screening is mandatory. Those patients must be followed up during their growing years due to a possible late onset of a hearing problem. They may present congenital sensorineural hearing loss or acquired ones; such as serous otitis media that is very common.

A description of the ENT features of more frequent syndromes is given below:

Down Syndrome (DS)

Down Syndrome is the most common congenital chromosome anomaly, occurring in 1 of 700 live births. Recent advances in surgery for the treatment of congenital heart defects have greatly enhanced the survival of these children. About 50% of children with DS see an otolaryngologist regularly because they usually present several morphologic abnormalities that predispose them to problems leading to ear, nose and throat diseases[5].

Their typical face shows midface hypoplasia that leads to malformation of the auditory tube and, consequently, to an increased number of ear infections and conductive hearing loss due to otitis media with effusion; and about 50% to 90% present hearing impairment. The stenotic external ear canal may hinder the ade-

quate examination of the ear by otoscopy. Routine audiologic screening is mandatory. Surgical intervention to place ventilation tubes is an effective strategy managing otitis media with effusion[5].

Sensorineural hearing loss (SNHL) is less common in children with Down Syndrome. However inner ear dysplasia was seen in three quarters of all cases, and in approximately half of the ears examined there was a **malformation** bone island of a lateral semicircular channel as defined by a measurement of 3 mm or less. Early presbycusis is also a causal factor of NSHL in adults[6].

About 79% of children have sleep disordered breathing and most of them sleep apnea7. They present a shortened palate, relative macroglossia, narrowing of the oropharynx and nasopharynx, and generalized hypotonia, which increase **greatly** the frequency and severity of obstructive sleep apnea. There is a small upper airway with superficially positioned tonsils and relative tonsillar and adenoidal encroachment. The efficacy of adenotonsillectomy is lower than in the general population[5]. **Obesity** strongly contributes to sleep disordered breathing.

Because of their preexisting learning difficulties, children with DS can be affected much more than typically developing children when they have a mild hearing impairment or chronic sleep disturbance. This is especially important when these problems occur during the early years of development[7].

Pierre Robin Sequence

Pierre Robin Sequence (PRS), a **clinically identified** anomaly containing mandibular hypoplasia, glossoptosis, and a U-shaped cleft palate, is the most common cause of syndromic micrognathia[8]. It occurs in 1:8500 to 1:14,000 births. The small mandible is thought to be a result of a genetic problem or a deformational problem where intrauterine growth is restricted or mandibular positioning is altered.

Airway obstruction is a result of the abnormal positioning of the tongue; it occludes the nasal and oral pharynx on inspiration, which can result in repeated oxygen desaturations. Prone or lateral positioning will solve the airway obstruction in 70% of PRS cases.

Feeding difficulties are common as infants struggle to breathe during eating.

Mandibular distraction is reserved for patients with tongue-base airway obstruction who experience failure with positioning and conservative measures[9].

CHARGE Syndrome

CHARGE (colobomata, heart defect, atresia of the choanae, retarded growth or development, genital hypoplasia, and ear anomalies or deafness) is the acronym of a multiple malformation syndrome, which ranges from 0.1–1.2/10,000 live births[10].

Thirty-five to 80% of these children present ear abnormalities, low-set hypoplasic pinnae and facial palsy. Middle and inner ear malformations include: Mondini deformity and absence of the oval window, hypoplastic incus and abnormal semicircular canals. Twenty percent of children have effusion in the middle ear[11]. Other malformations are choanal atresia10 and 38% show laryngotracheal abnormalities, such as laryngomalacia and subglottic stenosis[11].

Treacher Collins Syndrome

The Treacher Collins Syndrome (TCS) is an autosomal dominant disorder of the craniofacial development with an incidence of approximately 1 in 50,000 live births.

Features characterizing TCS include bilateral downward slanting palpebral fissures, frequently accompanied by colobomas of the lower eyelid with a paucity of eyelashes medial to the defect; abnormalities of the external ear, atresia of the auditory canal, and bilateral conductive **hearing loss.** They also present hypoplasia of the zygomatic complex and mandible and cleft and palate.

Delayed speech development is seen in many of the patients and seems to be caused by hearing loss. Hypoplasia of the mandible and zygomatic complex, cleft palate and choanal atresia are known contributors to the narrowing of the airway. In children with TCS, it is advisable to repeat the polysomnography throughout their childhood, as the size of the airways and the soft tissue (adenoids and tonsils) alters as the child develops [12].

Goldenhar Syndrome

Goldenhar Syndrome is also known as oculo-auriculo-vertebral spectrum, hemifacial microssomia and first and second arch syndrome[1].

These children present middle and internal ear malformations that may cause profound hearing loss. Bone-anchored hearing aids have been used to treat these patients[13].

Patients with Goldenhar Syndrome should also be screened for sleep apnea [14].

Velocardiofacial Syndrome (VCFS) / Di George

The 22q11.2 deletion syndrome occurs in approximately 1 in 4000 live births and is identified as Di George, velocardiofacial, and conotruncal anomaly face Syndromes. The majority of these patients have palatal anomalies, including palatal clefting and velopharyngeal insufficiency[15].

Major characteristics of VCFS include clefting of the secondary palate, hypernasal speech, pharyngeal hypotonia, structural heart anomalies, dysmorphic facial appearance, slender hands and fingers, and learning disabilities. Hypernasal speech caused by velopharyngeal insufficiency is characteristic of VCFS and is usually the first symptom that prompts families to seek treatment for their affected children[16].

At physical examination, a classic triad of findings characterizes overt submucous cleft palate, clefting of the secondary palate, and sometimes clefting of the hard palate.

However, occult submucous cleft palate is diagnosed by observing morphological changes on the nasal surface of the velum, and this observation must be made by nasopharyngoscopic examination[16].

A significant number of common otolaryngological problems are found within these syndromes such as structural anomalies including retrognathia, which may predispose them to obstructive sleep apnea. The prevalence of obstructive sleep apnea is about 10.2%, a percentage that exceeds by far its prevalence in the general pediatric population[15].

For VCFS patients, removal of adenoidal tissue worsens the velopharyngeal insufficiency because of their already deficient velum and poor movement of the lateral and posterior pharyngeal walls, thus making compensation highly unlikely. Adenoidectomy should be avoided[16].

There is a higher incidence of conductive hearing loss and also middle ear disease. Otitis media is a result of abnormal craniofacial anatomy, cleft palate, and associated Eustachian tube dysfunction instead of adenoidal hypertrophy. VCFS patients should receive complete audiological evaluation as well as early-stage myringotomy with tube placement[16].

Craniosynostosis

Craniosynostosis refers to either prenatal or postnatal premature fusion of one or more cranial sutures, which results from either a primary defect of ossification (primary craniosynostosis) or from failure of brain growth (secondary craniosynostosis).

Syndromic craniosynostosis (SCS) can be associated with additional congenital anomalies such as choanal atresia, cleft lip or palate, maxillary hypoplasia, abnormalities of the tracheobronchial tree, hydrocephalus, and other central nervous malformations along with complex craniosynostosis. It includes, among others, Apert, Crouzon, and Pfeiffer Syndromes. Its incidence is 5 in 10,000 live births[17].

A high prevalence of sleep-disordered breathing has been noted in children with SCS, usually appearing as obstructive respiratory events and thus consistent with the associated craniofacial anomalies[17].

Around 75% of patients with SCS have abnormal polysomnography results and 50% severe obstructive sleep apnea. The advancement of the midface on Le-Fort III level significantly increases the airway volume of the nasal cavity, naso-, oro- and hypopharynx. The main increase of airway volume was detected at the level of the nasal cavity and nasopharynx [18].

Most patients with syndromic and complex craniosynostosis have recurrent otitis media with effusion, causing episodes of conductive hearing loss throughout their lives. Sensorineural hearing loss can occur but is rare. Thus, routine visits to the otolaryngologist are recommended in order to screen them for otitis media with effusion throughout their lives. We also advise early screening for sensorineural hearing loss among children and young adults with these syndromes[19].

Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann Syndrome is a congenital disorder manifested by organomegaly, omphalocele, hypoglycemia, and macroglossia.

A significant number of these children are at risk for upper airway obstruction during infancy or childhood. Patients may require tonsillectomy and adenoidectomy to relieve upper airway obstruction, although macroglossia seems to be the main cause of airway obstruction. Anterior tongue reduction is reserved for the correction of malocclusion, articulation errors, or cosmesis, whereas tonsillectomy and adenoidectomy may be indicated for obstructive symptoms[20].

Achondroplasia

Achondroplasia presents an incidence between 1:15 000 and 1:40 000 live births.

Patients with achondroplasia (see Achondroplasia chapter from Shah & Shah and Levi in this Manual) are recognized by their short stature, with short proximal limb segments, referred to as rhizomelia. In the head and neck region, they often display macrocephaly and a prominent forehead. The characteristic phenotype is a result of gene encoding for fibroblast growth factor receptor 3 (FGFR3).

Common otolaryngologic conditions are otitis media due to abnormalities of the auditory tube, **which** results to the characteristic craniofacial anomalies and also obstructive sleep apnea.

Midface hypoplasia and a depressed nasal bridge further characterize their appearance and can contribute to nasal and upper airway obstruction. The combination of narrow nasal cavities, midface hypoplasia, and hypotonia predisposes them to upper airway obstruction and obstructive sleep apnea quoted as high as 75% and can be exacerbated by concomitant adenotonsillar hypertrophy.

Adenotonsillectomy did not provide significant improvement of sleep apnea in this population, since they often had central sleep apnea, as well as coexistent small airway disease[21].

Prader Willi Syndrome

Prader-Willi Syndrome (PWS) is a classic genetic disorder characterized by central hypotonia with poor suck and feeding difficulties that is found in infancy and that is accompanied by failure to thrive, hypogenitalism/hypogonadism, and growth hormone deficiency. PWS occurs in 1 in 15000 live births and is estimated to affect around 400 000 people worldwide[22].

In early childhood, hyperphagia develops and leads to obesity if left uncontrolled. Additional findings include an IQ of around 65 and behavioral problems (rigidity, compulsions, temper tantrums, self-injury), as well as hypopigmentation, small handstand feet, short stature, and a characteristic facial appearance. It is considered the most common syndromic cause of **life threatening** obesity[22].

Obstructive sleep apnea prevalence rates range between 44% and 100% in the published reports 79.91%, equally distributed between the two genders. **However several** risk factors may help to explain this relationship, including obesity leading to fatty deposition around the neck and subsequent airway narrowing. A polyssomnography is recommended in cases of severe obesity, chronic respiratory infection, asthma, snoring or witnessed apnea[23].

ENT consultation should be requested if breathing disorders during sleep, snoring, enlarged tonsils and adenoids are present. Tonsillectomy and adenoidectomy (AT) should be performed if indicated[24].

Several studies have found either partial or a complete lack of response to AT. Additionally, one study suggests weight gain after AT, a major correlate to worsening of obstructed sleep apnea. Weight loss can lead to improvement of obstructive sleep apnea in some patients[23].

Growth hormone therapy is now frequently prescribed, often in early infancy

or by early childhood once the diagnosis of PWS has been confirmed. Growth hormone (GH) treatment can lead to improved changes in body composition, physical activity, and growth velocity[22]. Presence of sleep apnea should be assessed by polysomnography before starting the GH therapy. It may lead to adenotonsillar hypertrophy and obstructive apnea on the one hand and on the other,, it improves central hypoventilation via direct effect on hypothalamic function. Improvement was demonstrated in respiratory disorders and respiratory functions. **This** treatment should be started after an adenotonsillar surgery has been performed in children who have obstructive apnea before treatment [24].

Turner Syndrome

Turner Syndrome patients present a 45,X karyotype[25]. It affects up to one in 2000 live female births and is characterized by the total or partial loss of one X chromosome. Frequently observed manifestations of TS include short stature, lymphedema, gonadal dysgenesis, cardiovascular anomalies, renal abnormalities, hypertension, hypothyroidism, glucose intolerance and hyperlipidemia[26].

Otolaryngology manifestations are sensorineural hearing loss (SNHL), recurrent otitis media (OM), pterygium colli and craniofacial dysmorphism.

Commonly reported craniofacial findings include a low hairline, low-set ears, micrognathia, and oral palatal abnormalities[26]. Palatal dysmorphism, especially ogival morphology, is a key otolaryngologic marker for TS.

Girls that show isochromosomes with loss of the p-arm of the X chromosome have a greater risk of developing hearing loss than patients with mosaicism. There was a linear association between hearing loss and age in these patients[26].

Mucopolissacaridosis (MPS)

MPS is characterized by deficiency of one of the lysosomal enzymes involved in the breakdown of glycosaminoglycans (GAGs). Seven types of one-enzymatic defects have been described. This metabolic block leads to the accumulation of GAGs in lysosomes, resulting in cell, tissue and organ dysfunction.

The ubiquitous nature of GAGs in the body's connective tissues gives rise to a wide phenotypic spectrum usually characterized by coarse facial features, liver and spleen enlargement, bone deformities with subsequent reduction of joint mobility, variable mental retardation and cardiac and ophthalmologic involvement[27].

Ear, nose and throat disorders are extremely frequent, mostly in MPS I, II and VI, and are often the earliest clinical manifestations of these diseases. MPS patients display an increased risk of otitis media with effusion due to the pathologic deposition of GAGs in the post-nasal space, auditory tubes and middle ear; sensorineural hearing loss, whose etiology remains unclear, is believed to result from infiltration of the cochlear duct, stria vascularis and cochlear nerve.

Other common ENT disorders are: adenotonsillar hypertrophy, almost universal in MPS 5, chronic recurrent rhinitis and persistent copious nasal discharge. These conditions, in addition to nasal dysmorphism, mandibular abnormalities, tracheomalacia, thickened vocal cords, macroglossia and redundant tissue in the upper airway can contribute to its obstruction and also **to** sleep apnea[27].

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