

TITLE: The Syndromal Child

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As otolaryngologists, we are often involved in the management of children with congenital disorders that affect the head and neck, i.e., craniofacial syndromes. Our consultation is frequently required when inborn anatomic or physiologic problems affect respiration, swallowing, hearing, speech or facial appearance. Therefore, the otolaryngologist should be familiar with the basic terminology used in syndrome diagnosis and the specific otolaryngologic issues involved with congenital anomalies affecting the head and neck.

Definitions:

Malformations

A malformation is defined as a morphologic defect of an organ, part of an organ, or larger area of the body, which results from an intrinsically abnormal developmental process. Malformations can be relatively simple or complex depending on when the defect is initiated during development. If the defect is initiated early in development the consequences are far more severe. Examples of malformations include cleft palate, syndactyly, and renal agenesis.

Deformations

A deformation is defined as an abnormal form or position of a body part caused by nondisruptive mechanical forces. These abnormalities occur more frequently late in fetal development and may result from mechanical, malformational or functional causes. The common underlying pathology is a result of restricted movement by the fetus. The most common causes are a result of mechanical forces, such as unstretched uterine and abdominal muscles, small maternal size, amniotic tears, abnormal uterine anatomy and twin fetuses. Deformations may also result from malformations that affect fetal movement. When this occurs, the malformations usually involve the central nervous system and the urinary tract. An example of a complex malformation-deformation relationship is Potter or oligohydramnios sequence. The compression deformities of the face and limbs, pulmonary hypoplasia, and growth

restriction result from any condition that leads to oligohydramnios (i.e., bilateral renal agenesis, polycystic kidneys, urinary tract obstruction, or amnion leakage).

Disruptions

A disruption is defined as a defect of an organ, part of an organ, or a larger area of the body due to interference with an otherwise normal developmental process. Disruptions tend to occur sporadically and rarely, unlike malformations and deformations that tend to recur. An example of a disruption is the formation of amniotic bands, which may lead to digit/limb amputations, bizarre facial clefting, or large calvarial defects.

Sequence

A sequence may be defined as multiple defects that occur as a result of a single presumed structural anomaly. The primary defect starts a chain of events, which affects the subsequent development of an organ or larger body part. For example, mandibular deficiency seems to be the initiating factor in the Pierre Robin sequence. The relative retroposition of the mandible maintains the tongue high in the nasopharynx, which prevents normal fusion of the palatal shelves. Malformations and sequences are nonspecific and may occur as an isolated event or as a component of various syndromes.

Syndrome

A syndrome is a pattern of multiple anomalies believed to be pathogenetically related and not representing a sequence. Furthermore, a syndrome usually implies a single etiology for an associated group of anomalies. In syndromes, the pathogenesis of a group of malformations is frequently less understood than in a sequence. Also, because the malformations that are associated with syndromes occur in embryonically noncontiguous areas, they must be related at a more basic level. Hence, hereditary disorders are usually described as syndromes, because the phenotype is due to a single genetic defect.

Association

An association is the nonrandom occurrence in multiple individuals of a group of anomalies that are not known to be a sequence or syndrome. Examples include CHARGE (colobomas, heart defects, atretic choanae, retarded growth, genitourinary anomalies, and ear malformations) and VATER (vertebral defects, anal atresia, tracheo- esophageal fistula/atresia, and radial anomalies). Although associations are not specific syndromes or diagnoses, the mnemonics help to alert clinicians to search for associated anomalies in these patients.

Approach to Syndrome Diagnosis

There are over 3,000 genetic syndromes described to date, so it would be impossible for a clinician to recognize all but the most common. Therefore, one should always simplify things by beginning with a good history including a detailed medical pedigree. Information should be

solicited about maternal and paternal ages, parental consanguinity, previous abortions and maternal exposure to teratogens. It is also helpful to compare siblings and other family members when possible. During physical examination, one should search for both major and minor anomalies, especially of the auricles and facial features. It is always useful to search reference books, such as *Smith's Recognizable Patterns of Human Malformations*, to help identify a suspected syndrome. If a syndrome is strongly suspected, a geneticist should be consulted to evaluate the patient for appropriate laboratory tests and karyotyping. This will also ensure that the parents receive appropriate genetic counseling.

Management Issues of the Syndromal Child

Children with craniofacial abnormalities have multiple aesthetic, functional, and psychological concerns, which are best managed by a team of specialists. The otolaryngologist on the team is responsible for the assessment and management of the upper airway, hearing and speech in these children.

Airway Obstruction:

Children with craniofacial anomalies present a variety of airway challenges to the otolaryngologist. The effects of the airway obstruction may be related to age, and often change as the child grows. Often these children represent difficult airway maintenance during necessary surgical procedures, which can be a significant cause of morbidity and mortality.

Neonatal Nasal Airway Obstruction

Neonates are obligate breathers until about age 3 months. Therefore, when the nasal passages become obstructed, they experience respiratory distress, becoming cyanotic, when their mouths are closed or during feeding. This problem commonly occurs with bilateral choanal atresia and children with midface hypoplasia (Crouzon/Apert syndrome). The problem is usually relieved with a secured oral airway until at least 3 months of age.

Neonatal Oropharyngeal Airway Obstruction

Neonates can also experience respiratory distress when the tongue falls back into the oropharynx. This is common in neonates with retrognathia or micrognathia, and the resultant glossoptosis. This problem causes more problems when associated with a cleft palate, as in Pierre Robin sequence. This type of airway obstruction usually responds to nursing the infant in the prone position for the first few months of life. If symptoms persist, insertion of a nasopharyngeal airway or tracheotomy may be necessary. When the child approaches 6 months of age, mandibular growth is usually sufficient to decrease the glossoptosis and resolve the obstruction. Decannulation can be performed at this time or usually shortly after palatoplasty (with cleft palates).

Obstructive Apnea

Children with craniofacial anomalies may experience obstructive apneic episodes during sleep due to a variety of causes, including maxillary hypoplasia with a resultant narrow nasopharyngeal airway (Crouzon and Apert syndromes), retrognathia (Treacher Collins syndrome), and palatopharyngoplasty performed in a child with velopharyngeal incompetence (VPI) and glossoptosis (Pierre Robin, Treacher Collins).

Children with narrow nasopharyngeal airways, as in Crouzon syndrome, have benefited from adenotonsillectomy prior to three years of age. Patients with retrognathia and obstructive symptoms may benefit from tonsillectomy if the palatine tonsils are enlarged. Children with retrognathia or micrognathia and a history of airway obstruction are poor candidates for palatopharyngoplasty to correct VPI. It is probably a good idea to obtain a preoperative sleep study prior to pharyngeal surgery for VPI in any child with a clinical suspicion of OSA.

It is often necessary in children with craniofacial anomalies and OSA to perform a series of escalating operations to relieve the obstruction. Each is followed by a sleep study to determine effectiveness. These operative procedures may include, (adeno)tonsillectomy, laser reduction of the mid-base of tongue, uvulopalatopharyngoplasty, laser resection of redundant supraglottic structures or pharyngeal folds, sliding mandibular osteotomies (creating a class III malocclusion), and finally tracheotomy. It may be necessary to perform tracheotomy early in these patients to prevent asphyxiation.

Airway Maintenance and Craniofacial Surgery

During surgical correction of craniofacial anomalies, the airway is maintained with endotracheal intubation (oral or nasal) or tracheotomy. The use of elective tracheotomy is less common today because of advances in intubation equipment and techniques and stabilization with rigid fixation of mandibular/maxillary osteotomies. However, tracheotomy should still be considered under certain circumstances. Tracheotomy is indicated:

1. if endotracheal intubation for the procedure is impossible, expected to be difficult or traumatic, or if postsurgical extubation distress is anticipated.
2. to facilitate surgery and postoperative care (as with extended midfacial procedures)
3. when extended nasotracheal intubation, which is necessary for mandibular osteotomies, is not possible secondary to a previous palatopharyngoplasty

In order to reduce morbidity and/or mortality rates, tracheotomy should be performed with the airway controlled by a bronchoscope or endotracheal tube in these patients. However, in patient's with severe mandibular hypoplasia (Pierre Robin, Treacher Collins, Goldenhar), intubation may be extremely treacherous, because the larynx may be impossible to visualize with standard intubation techniques. In such a case, it may be necessary to first perform direct laryngoscopy with a pediatric anterior commissure laryngoscope with insertion of the endotracheal tube through the laryngoscope. It may be necessary to use a small telescope as an optical stylet if visualization is still difficult.

Hearing Loss:

Children with craniofacial anomalies have a high risk of congenital and acquired hearing loss. Since even mild hearing losses can significantly delay the acquisition of language skills and intellectual development, these children require careful otologic and audiologic follow-up and management. The detection of hearing loss is often delayed by the erroneous belief that slower learning is somehow related to their syndrome.

Congenital Hearing Loss

In most craniofacial anomalies the congenital hearing loss is conductive. Sensorineural hearing loss is thought to be coincidental if present, except in the case of Waardenburg syndrome. Microtia with atresia of the external auditory meatus is frequently seen in Treacher Collins syndrome and hemifacial microsomia, and results in a congenital conductive hearing loss. Patients with bilateral microtia and EAC atresia often have obliteration of the middle ear cleft, which precludes surgery. These patients often do well with hearing aids. Surgery is usually not recommended in these patients with a normal hearing ear, and they do well with CROS (contralateral routing of signal) hearing aids.

If the child's ears appear normal, conductive hearing loss may be the result of ossicular deformity or fixation. Middle-ear surgery may improve hearing in this subset of patients, but caution is necessary to avoid damage to a dehiscence or abnormally located facial nerve. CT scans of the temporal bone should be obtained prior to any surgical intervention.

Acquired Hearing Loss

Acquired Hearing Loss in children with craniofacial anomalies is usually a consequence of eustachian tube dysfunction (ETD). ETD is common in children with secondary cleft palates, however, it may also be seen in patients with craniosynostosis and the associated anomalies of the midface and skull base. These children will usually require ventilation tubes, because the ETD does not respond to medical management or surgical repair. There have been reports of an increased incidence of unilateral jugular bulb dehiscence in children with craniosynostosis, so care must be taken when performing the myringotomy. Multiple tympanostomy tube placements is often the rule. Tympanoplasty procedures are usually unsuccessful until late adolescence due to persistent ETD.

Speech Disorders:

Hypernasality

Hypernasality is often a consequence of VPI after cleft palate repair. It may also be apparent as "deaf speech", observed in children with craniofacial anomalies and hearing loss greater than 30dB without VPI. This complication is often manageable with speech therapy alone. Palatopharyngoplasty may be necessary in children over 5 years old with persistent VPI despite speech therapy.

Hyponasality

Hyponasality is usually due to some form of nasal obstruction. This can occur in children with severe posterior displacement of the midface, bilateral choanal atresia and iatrogenic velopharyngeal atresia (over correction with pharyngopalatoplasty). Removal of nasal airway obstruction usually resolves the problem.

Hoarseness

Hoarseness occurs in 20 percent of children with VPI secondary to the development of vocal cord nodules. This is thought to be a response to compensatory laryngeal activity. With elimination of the VPI, the nodules usually resolve. Hoarseness may also develop after nasotracheal intubation.

Common Syndromes:

Down Syndrome (Trisomy 21)

The incidence of Down syndrome (DS) is about 1 in 700, which makes it the most common chromosomal anomaly. This incidence increases proportionately with maternal age, especially older than 35 years. It was first described in 1866 by John Landon Down, and is characterized by typical dysmorphic facies, flat nasal bridge, epicanthal folds, speckled irides, brachycephaly, various orofacial anomalies, a simian crease, learning disabilities and generalized hypotonia.

Airway:

An array of congenital airway anomalies occurs in DS patients. Because of midface hypoplasia, the nasopharyngeal and oropharyngeal regions are narrower and of smaller volume overall. OSA occurs in approximately 50% of DS patients. Given the generally small size of the adenoid pad in DS, adenotonsillectomy alone often fails to relieve upper airway obstruction. The addition of uvulopalato-pharyngoplasty (UPPP) has been shown to improve overall outcome. However, tracheotomy may be required in refractory cases. The incidence of subglottic narrowing has been found to be higher in DS than the general population. Because of this and the smaller airway commonly seen in DS, initial intubation should be made with an ET tube 2 sizes smaller than normally used. Another concern during anesthesia is the increased incidence of atlantoaxial instability in DS, which has been reported as high as 20%. Therefore, careful preoperative assessment of the cervical spine with radiographs should be obtained to avoid injury. All DS patients should be admitted to the hospital for postoperative observation following adenotonsillectomy.

Hearing:

Congenital and acquired otologic problems contribute to the relatively high incidence of hearing loss in DS patients. Conductive hearing loss may be a result of various anomalies including small pinna size, stenotic external auditory canals (predisposes to OE and CI), eustachian tube dysfunction (COME in 60%), and ossicular fixation. Sensorineural hearing is less common but may result from progressive ossification along the basal spiral tract, or other temporal bone anomalies (mondini's cochlea, shortened

apical cochlear turns, shortened organ of Corti, and decreased spiral ganglion cells). Management includes ventilation tubes for COME, frequent otologic and audiologic evaluation, and hearing aids for persistent hearing loss.

Velocardiofacial Syndrome

Velocardiofacial syndrome (VCFS) was delineated as a distinct multiple-anomaly syndrome in 1978. It may be the most common syndrome second to Down syndrome. It is characterized by congenital heart disease, hypernasal speech, cleft palate, learning disabilities, and a characteristic facial appearance. The transmission is by autosomal dominant inheritance, and the specific genetic cause is usually a deletion of chromosome 22.

The characteristic features of facial structure influenced by basicranial angulation include vertical maxillary excess, puffy upper eyelids, retrognathia, a prominent nasal root, and flat malar eminences. Although the mandible is typically structurally normal, it appears retruded because of the skull base angulation. Vascular anomalies are probably the most common structural malformation associated with VCFS and are present in all parts of the body. Anomalies of the major neck vessels are far more common, however, and have been found in almost all cases studied with magnetic resonance angiography.

Speech:

Palatal anomalies and consequent speech disorders are very common in VCFS. Of the palatal clefts found in the syndrome (75% of patients), fewer than 20% are overt. About 44% of the clefts of the secondary palate are typical submucous clefts with the classic bifid uvula, however, the remainder are occult. In fact, without endoscopic evidence, occult clefts in VCFS are nearly impossible to detect. In addition, the angulation of the skull base draws the posterior pharyngeal wall away from the palate which further contributes to the severe hypernasality observed in VCFS. Surgery for VPI is commonly applied to children with VCFS, but must be well planned to avoid injury to aberrant neck vessels. Speech evaluation and therapy must be conducted by a person with expertise in treating patients with VCFS.

Airway:

In infants with VCFS, airway obstruction is a common problem with multiple causes. Infants may exhibit any combination of generalized hypotonia, pharyngeal hypotonia, retrognathia, hypertrophic arytenoids, laryngomalacia, laryngeal webs, vascular rings, anomalous subclavians, and reactive airway disease. Endoscopic assessment of the airway is critical to determine the source or sources of obstruction. Flexible fiberoptic laryngoscopy and bronchoscopy are often employed to sort out the potential causes. Severe upper airway obstruction requiring tracheotomy in VCFS is rare. When there is the combination of retrognathia, cleft palate and airway obstruction in VCFS, the diagnosis of Robin's sequence is often mistakenly made (11%).

Hearing:

Minor abnormalities of the ear are common in VCFS, the most consistent variation being overfolding of the helix. Also, the pinnae and ear canals tend to be small making

otoscopic examination difficult. Chronic middle-ear disease is common in VCFS with conductive loss in approximately 75% because of middle ear effusion. This is related to the palatal anomalies and the frequent immunopathy that tends to occur in these patients. In fact the course and duration of otitis in VCFS patients is typically more severe than in other patients with cleft palates. Sensorineural hearing loss occurs in approximately 15% of patients, but unlike other genetic disorders, it is typically unilateral and mild.

Pierre Robin Sequence

The triad of cleft palate, micrognathia, and glossoptosis (causing airway obstruction) is known as the Pierre Robin sequence (PRS), credited to a French stomatologist who reported the association of micrognathia with glossoptosis in 1923, later adding cleft palate to the sequence in 1934. The incidence most widely accepted among clinicians today is 1 in 8500. The sequence results from a series of events leading to the triad. The initiating event seems to be mandibular deficiency or hypoplasia which may have a variety of causes, including positional malformation (oligohydramnios, multiple births), intrinsic hypoplasia (genetic or teratogenic syndromes), neurologic or neuromuscular abnormalities (decreased movement), or connective tissue disorders. Children born with PRS have either nonsyndromic PRS (80%) or syndromic PRS, which carries a poorer prognosis. Syndromes most commonly associated with PRS include Stickler (severe ocular anomalies), VCFS, Fetal alcohol syndrome, and Treacher Collins syndrome.

Airway:

The cause of airway obstruction in PRS is multifactorial in nature, with both anatomic and neuromuscular components. Sher describes a classification scheme based on the four different processes he was able to identify with flexible fiberoptic nasopharyngoscopy:

Type 1: obstruction is due to posterior movement of the tongue contacting the posterior pharyngeal wall (true glossoptosis - 59%)

Type 2: the tongue moves posteriorly but the palate becomes sandwiched between the tongue and velum causing nasopharyngeal obstruction (21%)

Type 3: the lateral pharyngeal walls move medially, apposing one another (10%)

Type 4: pharynx constricts in a sphincteric manner (10%)

There are many proposed management strategies for airway obstruction in PRS on the basis of a type 1 obstruction (e.g., positioning, mandibular traction, glossopexy, mandibular distraction osteogenesis, subperiosteal release of the floor of mouth, nasopharyngeal airway, and tracheotomy). However, it is clear that types 2, 3, and 4 in the classification scheme of airway obstruction will only respond to a nasopharyngeal airway or tracheotomy, if this fails. The nasopharyngeal airway may be left in place for up to 8 weeks when used as definitive therapy. While the tube is in place, gavage feeding through an orogastric tube is recommended.

Hearing:

Otitis media with effusion is common in these patients, due to eustachian tube dysfunction from the palatal anomalies.

Treacher Collins Syndrome (Mandibulofacial dysostosis)

Treacher Collins Syndrome occurs in approximately 1 in 25,000 to 1 in 50,000 live births. Inheritance is autosomal dominant with variable expressivity. The syndrome is characterized by bilateral, symmetric abnormalities of first and second branchial arch structures. The disorder is characterized by hypoplasia of the maxilla, zygoma and mandible with a prominent nasal dorsum, giving them a convex facial profile. The eyes have a downward slant, and the lower eyelids typically have colobomas and an absence of eyelashes. The auricles are malformed or absent with varying degrees of middle ear cavity hypoplasia and ossicular malformation. Cleft palate, cleft lip, and choanal atresia may also be present.

Airway:

Respiration may be compromised by maxillary hypoplasia with choanal stenosis or atresia and by micrognathia and a retropositioned tongue. Airway management can be especially difficult in these patients, especially when the need for intubation or laryngoscopy arises. Careful coordination with a pediatric anesthesiologist is usually necessary. Obstructive sleep patterns may develop, which may respond to tonsillectomy or mandibular osteotomy procedures, during craniofacial reconstruction.

Hearing:

There is often a bilateral conductive hearing loss of 50 to 70 dB resulting from varying degrees of middle ear cavity hypoplasia and ossicular malformations. Early formal audiology testing is indicated. The inner ear structures are usually normal, however, successful surgical correction can be extremely difficult or dangerous. If the chance for a successful reconstruction is poor (based on temporal bone scans), rehabilitation with hearing aids is necessary.

Apert and Crouzon Syndromes

Apert syndrome (acrocephalosyndactyly) was credited by Apert's description in 1906. Six years later, Crouzon described a mother and daughter, who had the same malformation of the face and head, coining the term hereditary craniofacial dysostosis. Both are characterized by craniosynostosis, hypertelorism, exophthalmos, maxillary hypoplasia, and mandibular prognathism. Apert syndrome has the added feature of syndactyly. Inheritance of each is autosomal dominant, and the prevalence is similar, between 15 and 16 per 1 million births.

Airway:

Because of the cranial synostosis, the maxillary height, nasal cavity width, bony nasopharyngeal height, and the nasopharyngeal airway are all reduced. These malformations lead to severe compromise of the nasopharyngeal and oropharyngeal spaces, which pose a serious risk of impaired respiratory function, obstructive sleep apnea, cor pulmonale and sudden death. Treatment of respiratory distress is endotracheal intubation, followed by tracheotomy if the problem persists. Sleep apnea evaluation includes a sleep study, and if obstructive may require tracheotomy if severe. Central apnea can be caused by increased intracranial hypertension, and requires cranial vault

decompression. Forced mouth breathing in these children often causes feeding problems, which require nasogastric or gastrostomy feedings. Cervical spine anomalies (mostly vertebral fusions, C5-6) may occur, so cervical spine radiographs should be obtained prior to procedures requiring general endotracheal anesthesia.

Hearing:

Hearing loss is usually acquired from eustachian tube dysfunction, probably as a result of midface hypoplasia and decreased nasopharyngeal space. Treatment often requires the placement of ventilation tubes.

Goldenhar Syndrome (Oculoauriculovertebral spectrum)

Goldenhar syndrome is a unilateral craniofacial malformation characterized by facial asymmetry, unilateral external and middle ear deformities, and vertebral malformations. Most cases are sporadic, however autosomal dominant and recessive cases have been reported. The incidence is 1 in 5600 live births. Some believe that a vascular anomaly during fetal life causes hemorrhage into the 1st and 2nd branchial arches, thus producing the subsequent malformations. Other findings include upper eyelid colobomas and facial weakness (in 10 to 20%). These patients can present a challenging airway for surgical procedures, however, most of the concern is with hearing. Hearing loss is present greater than 50% of the time and is usually conductive, due to ossicular malformations or absences and external auditory canal atresia. Sensorineural loss is present occasionally.

C.H.A.R.G.E. Association

CHARGE is the association of 4 or more of the following anomalies: coloboma, heart defects (tetralogy of Fallot, ASD, VSD, PDA), atretic choanae, retardation of growth, genitourinary anomalies, and ear malformations. The most pressing otolaryngologic concern is with choanal atresia which is bilateral frequently. The neonate begins to have immediate respiratory distress, which should be relieved with an oral airway promptly. Other options include a McGovern nipple or intubation, if these fail. Repair may be delayed because of more serious anomalies associated with this condition, and if so, tracheotomy can be performed. The ear malformations may include any combination of the external, middle and/or inner ear. Deafness is usually of the mixed type with a characteristic "wedge"-shaped audiogram.

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