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Introduction

An estimated 1 in 1,000 of the US population is born deaf or displays profound hearing loss early in childhood (Cotton and Myer). Of these, half are acquired prenatally while the remaining half will exhibit hearing loss as a result of hereditary-genetic factors. Approximately one-third of children with genetic hearing loss will display phenotypic characteristics of a syndrome while two-thirds will be nonsyndromic (i.e. hearing loss in the absence of other features). Whether the hearing loss is syndromic or nonsyndromic, it is of the utmost importance to identify these patients early so that the proper auditory rehabilitation and corrective measures can be implemented in time to provide the best prognosis. The discussion below will focus on syndromic forms of hearing loss as there are a plethora of syndromes that manifest an auditory phenotype.

Embryology of the Ear

Most deformities that present congenitally are often the result of some insult that occurs during the gestational development of the fetus. Knowledge of the embryology of the ear will serve as a good foundation with which to understand some of the syndromic malformations that display ear abnormalities and hearing loss.

Mesenchymal tissue from the first and second branchial arches contain the Hillocks of His which organize to form the auricle at 4 weeks gestation. The auricle is completely formed by 12 weeks with deformities and/or absence traceable as early as 7-8 weeks. Generally speaking, the earlier the insult in the developmental timeline, a more severe deformity can be expected. This holds true for most embryologic processes.

The external auditory canal (EAC) begins forming at 8 weeks when the ectoderm from the first branchial cleft joins the developing tympanic ring. The tympanic ring begins ossification at 12 weeks giving way to the bony EAC. At 28 weeks, the EAC begins to canalize producing a three layered tympanic membrane, thus abnormalities of the EAC are usually in conjunction with tympanic membrane abnormalities. Atresia occurs as a result of failure of the EAC to canalize and stenosis as a failure of complete canalization. Both atresia and stenosis can be traced to approximately 28-30 weeks gestation.

The formation of the stapes initializes ossicular development at 4 ½ weeks. The footplate begins to form at 7-9 weeks and uninterrupted development is crucial to avoid malformations or absence of the oval window. At 12 weeks the anterior and posterior crura of the stapes become bowed and their ossification takes place between 18-24 weeks. Deformities of the stapes footplate and/or superstructure can be linked to the 12 week point on the embryonic timeline. The development of the malleus and incus begins at 5 weeks from Meckel's cartilage of the 1st arch and Reichert's cartilage of the second arch. A fused malleus-incus mass occurs when the middle ear mucosa fails to develop and separate the undeveloped ossicles from the tympanic cavity. The incus is the first ossicle to ossify at 15 weeks followed by the malleus at 16 weeks and is complete by 24 weeks.

The inner ear exists as the otic vesicle embryonically which appears approximately week 4. The otic vesicle then splits into a pars inferior and a pars superior (week 5) which will be the precursors of the semicircular canals (SCC) and utricle (pars inferior) as well as the cochlea and saccule (pars superior). Differentiation of the pars inferior and superior into the SCC, utricle, cochlea and saccule occur in weeks 6-7. The cochlea develops its basal turn, 1.5 turns and complete 2.5 turns by weeks 7, 8 and 10 respectively. Interruptions at this point are responsible for malformations such as Mondini's dysplasia. During the same time period as the division of the otic vesicle into the pars superior and inferior, the acousticofacial ganglion divides into the acoustic ganglion and the facial ganglion. At week 5, the acoustic ganglion separates into a superior and inferior division with the superior division innervating the neuroepithelium of the superior portion of the otic vesicle (utricle, superior and lateral SCC). The inferior division of the acoustic ganglion will innervate the neuroepithelium of the saccule and the posterior SCC. Meanwhile, the facial ganglion will innervate the structures of the second branchial arch.

Basic genetics and definitions

In continuity with establishing a foundation for understanding the pathology of syndromes, a brief discussion of inheritance patterns as well as definitions to some frequently used terminology will be addressed.

Hereditary Patterns

Autosomal Dominant: Disorders with this mode of inheritance are usually expressed with alteration of only one gene in a gene pair. Males and females are equally affected and male-to-male transmission occurs. There is a 50% risk of an affected parent's offspring being affected (male or female). Several factors may influence the clinical presentation such as decreased penetrance, variation in expressivity and age of onset.

Autosomal Recessive: Nearly one-third of mendelian disorders share this hereditary pattern. This pattern occurs when both parents are unaffected carriers. Each parent transmits either the normal or mutant gene to each of their offspring. As a result, there is a 25% risk of the children being affected. The risk of having siblings who are unaffected carriers is two-thirds. Consanguinity and reproduction among genetically isolated groups increases the risk of autosomal recessive disorders.

X-linked inheritance: X-linked recessive disorders are always expressed in males because they only have one copy of the X chromosome. In contrast, females are usually carriers since they possess two copies of the X chromosome. Females become carriers as a result of transmission from their affected fathers. Since males only receive Y chromosomes from their fathers, father-son transmission does not occur.

Mitochondrial Inheritance: All mitochondrial genes, located in the ovum at the time of conception, are inherited from the mother because sperm cells do not contribute mitochondria. conditions caused by mutations in the mitochondrial genome are described as following maternal inheritance and affect both male and female offspring.

Definition of commonly used terminology

Penetrance: This refers to the modification of traits by other genes and/or environmental factors they may render them clinically absent although the gene responsible for the trait is present.

Expressivity: The variation in expression of a gene's phenotype. The gene is present, but may express the phenotype in a mild, moderate or severe form which will correlate with disease severity.

Pleiotropy: The multiple phenotypic effects in an affected individual as a result of the mutant gene or gene pair.

Malformation: Results when an abnormal developmental process is responsible for anatomic defect in an organ, part of an organ or a region of the body.

Syndrome: The simultaneous presence of two or more malformations that are proven or assumed to be secondary to a single etiology.

Deformation: Occur due to extrinsic mechanical forces; not related to genetic information. An example would be plagiocephaly.

Disruption: This happens when processes such as ischemia, tissue breakdown, etc victimize a normal developmental process. Amputation of normally formed digits or limbs by free-floating amniotic bands as a result of early amnion rupture would be an example.

Sequence: A pattern of multiple defects that result from a single primary malformation. An example is Pierre Robin sequence in which micrognathia results in tongue displacement which results in cleft palate.

Association: A pattern of anomalies that occur in conjunction with one another more frequently than expected but have yet to be identified as a distinct syndrome or sequence. CHARGE association is an example (coloboma, heart anomalies, choanal atresia, retardation, genital and/or anomalies).

Practical approach to the syndromal child with hearing loss

As stated earlier, genetic hearing loss can either be syndromic or nonsyndromic. Physical exam and lab tests/investigations aim to detect those with syndromic hearing loss which account for 30% of genetically caused hearing loss. It is vital to identify cases that have an obvious genetic etiology in order to make a diagnosis and begin early and aggressive hearing rehabilitation as this affects prognosis in terms of speech and language development.

When taking an initial history for a pediatric patient with hearing loss, the physician should entertain the possibility of a genetic cause. When taking the family history, the physician should specifically inquire regarding the hearing status of the parents. Although the parents may appear to have no hearing deficits, the physician must bear in mind that one or both of the parents may be exhibiting variable expression of a mutant gene or reduced penetrance. This could especially be true of normal hearing parents who report having parents with early onset of hearing loss. Alternatively, the case may involve X-linked inheritance in which none of the parents themselves exhibit hearing loss despite a positive history in other family members. Often, this information is not volunteered and must be sought by the astute clinician.

The pregnancy and birth history are also important inquiries to make; especially the rubella status of the mother. In addition, attention should be paid to the developmental history of the patient. Isolated motor delay or global developmental delay could be clues to vestibular dysfunction or a syndrome diagnosis respectively. Also, reports of visual problems manifesting in the child could also point the physician toward a syndrome diagnosis.

A thorough physical exam is an important adjunct to the history and must not be confined only to the head and neck. Checking for birth marks on the trunk and limbs as well as limb deformities can prove helpful in trying to arrive at a syndrome diagnosis. It may be helpful to ask the parents to bring old photo albums of themselves and family members to help delineate normal familial traits from those that may be syndromic.

Lastly, once the history and physical exam are complete, there are certain lab tests and investigations that may prove useful. Audiometry of first degree relatives in addition to the patient, ophthalmology evaluation, serology for congenital infections (TORCHs), urinalysis (Export's syndrome), EKG (Terrell and Lange-Nielsen syndrome), chromosome analysis and CT scans for profound or progressive hearing loss.

Syndromic Hearing Loss

Autosomal Dominant Syndromes

Waardenburg syndrome: Characterized by sensorineural hearing loss, abnormal pigmentation of the skin and hair, dystopia canthorum (eye inner canthi are displaced laterally),

heterochromia iridis (iris colors do not match), and pinched nose. This syndrome occurs anywhere from 1 in 20,000 to 1 in 40,000 and accounts for 1-2% of people with profound hearing loss. The hearing loss can be unilateral or bilateral of varying severity. The syndrome has 4 subtypes classified according to the presence or absence of other abnormalities. In Type 1, every patient exhibits dystopia canthorum. The Type 2 phenotype is void of dystopia canthorum while Type 3 exists with upper extremity abnormalities in conjunction with Type 1 characteristics. Type 4 exhibits pigmentation abnormalities, Hirschsprung's disease, plus findings shown in Type 2. Types 1 and 3 are linked to gene mutations in the PAX3 gene, while Types 2 and 4 are linked to the MITF and EDNRB genes respectively.

Branchio-oto-renal syndrome: This syndrome is estimated to be present in 2% of profoundly deaf children. The syndrome displays high penetrance although variable expressivity has been shown in families. Hearing impairment is estimated to be present in 70-93% of affected people but the age of onset ranges from early childhood to young adulthood. Likewise, there is varied severity ranging from mild to profound and the nature can be conductive, sensorineural or mixed. Common characteristics of the BOR phenotype include cup-shaped pinnae, preauricular pits, branchial cleft fistulae and bilateral renal anomalies. Other features displayed are preauricular tags, lacrimal duct stenosis, deep overbite and a long, narrow face. Inner ear anomalies like Mondini's dysplasia and stapes fixation can also be present. The genetic etiology of this syndrome can be traced to the EYA1 gene. Based on the phenotypic anomalies, criteria have been developed for EYA1 testing: affected individuals must have at least 3 major criteria; two major criteria and at least two minor criteria; or one major criterion with one first-degree family member meeting BOR criteria (see accompanied POWERPOINT SLIDE SHOW presentation for table of criteria).

Stickler Syndrome (STL): In addition to having sensorineural hearing loss that is progressive, these patients usually display a cleft palate, abnormal development of the epiphysis, vertebral abnormalities and osteoarthritis. There are three clinical subtypes that exist. Type 1 develops progressive myopathy, retinal detachment and vitreoretinal degeneration. Retina detachment is nonexistent in type 2 due to lack of the COL11A2 gene in the retina. In Type 3 shares eye and ear findings present in type 1 but has facial abnormalities. The absence of COL11A2 in the vitreous humor is the reason for the differing ocular phenotypes between Stickler types 1 and 3, and Stickler type 2. The genes with loci responsible for STL 1, 2 and 3 are COL2A1, COL11A1, and COL11A2 respectively.

Treacher Collins (TC): Also known as Franceschetti-Zwahlen-Klein Syndrome or Mandibulo-Facial Dysostosis, this autosomal dominant entity is linked to mutations on chromosome 5q11 and some reports mention an association of maternal vitamin A hypersensitivity.

Diagnostic criteria include microtia and malformed ears, midface hypoplasia, downslanting palpebral fissures, coloboma of outer 1/3 of lower eyelids, and micrognathia. The upper airway narrowing can be a major issue in infancy. The size of the nasopharynx is 50% smaller than normal and affected infants are more prone to OSA and SIDS. Hearing loss in this syndrome is usually conductive with a wide array of middle ear anomalies present such as monopodal stapes, ankylosed foot plate, malformed incus, cochlea and vestibule abnormalities.

The EAC may be absent or stenosed. If sensorineural hearing loss is present, it usually occurs at high frequencies.

Osteogenesis imperfecta (OI): This is an autosomal dominant disorder displaying the triad of bone fragility, blue sclerae and hearing impairment. Other characteristics include triangular face, short stature, hypermobile mobile joints, cardiovascular abnormalities and skin disorders. The incidence is estimated to be 1 in 20,000 to 1 in 30,000. Causative mutations involve the COL1A1 or COL1A2 gene which regulate formation of type I collagen. Hearing loss is usually mixed and has a prevalence ranging from 26-78%. The hearing loss usually presents itself during the late 20s or early 30s. The conductive component of the hearing loss is attributed to the thickened and fixed stapes footplate, similar to what is seen in otosclerosis. The sensorineural component usually results from cochlear hair cell atrophy and atrophy of the stria vascularis. Also, anomalous bone formation in and around the cochlea may contribute to the sensorineural component of the hearing loss.

Neurofibromatosis Type II (NF 2): Bilateral vestibular schwannomas are the hallmark of this disease with a prevalence of 1 in 210,000 people. Other features include meningiomas (intracranial and spinal), ependymomas, gliomas, presenile lens opacities, and schwannomas located in the cranial, spinal and peripheral nerves. The skin can also manifest café-au-lait spots but not to the extent found in neurofibromatosis type I. This disease is caused by an NF 2 tumor-suppressor gene mutation on chromosome 22. Affected patients usually present in the 2nd and 4th decade. Up to 41% present with unilateral sensorineural hearing loss rather than bilateral sensorineural hearing loss due to the fact that this percentage of patients do not present with bilateral vestibular schwannomas. Patients can also have tinnitus, disequilibrium, headache and cranial nerve symptoms. Children < 15 years old may commonly present with skin or spinal tumors prior to the onset of hearing loss or development of vestibular schwannomas. In addition to the Manchester criteria for diagnosis (see accompanied power point presentation) patients who are suspicious for having NF 2 should undergo audiometry and MRI with gadolinium enhancement of the internal auditory canals.

Autosomal Recessive Syndromes

Usher Syndrome: Usher syndrome is the most common cause of autosomal recessive hearing loss. The incidence of Usher syndrome is approximately 3-5 per 100,000 in the general population and 1-10% among profoundly deaf children. The syndrome has several subtypes based on severity of the deafness and the onset of retinitis pigmentosa (gradual retinal degeneration leading to decreased night vision, loss of peripheral vision, and blindness). Type 1 has severe hearing loss and vestibular dysfunction. The onset of retinitis pigmentosa is in childhood as opposed to type 2 where it begins after childhood. Mild to moderate hearing loss characterizes type 2 along with normal vestibular function. In type 3, hearing loss is progressive as is the vestibular dysfunction. Retinitis pigmentosa can occur anytime in life.

Pendred syndrome: Characterized by hearing impairment associated with abnormal iodine metabolism. The responsible gene is SLC26A4 (PDS). This encodes a protein named pendrin which helps regulate iodine and chloride ion transport. Most patients have a euthyroid goiter which is sometimes detected at birth but often is not clinically evident until 8 years of age. Diagnosis of the thyroid abnormality used to depend on perchlorate discharge tests (indicates

abnormal organification of nonorganic iodine) but this test is not specific for Pendred syndrome and the sensitivity is unknown. Instead, thyroid function tests are used. The hearing loss in this syndrome is severe and can be present at birth or progress with age. In addition, CT scans have revealed cochlear dysplasia (Mondini's) an enlarged vestibular aqueduct or both.

Jervell and Lange-Nielsen Syndrome: This syndrome, although rare, should be suspected in a child with hearing loss and seizures of unknown origin and/or a family history of sudden death. Patients are characterized by severe-profound hearing loss and prolongation of the QT interval EKG. The syncopal episodes are due to a cardiac conduction defect which can manifest as early as the 2nd or 3rd year of life. The cardiac conduction defects can be attributed to mutations in potassium channel genes traced back to loci on the KVLQT1 and KCNE1 genes located on chromosomes 11p15.5 and 21q22 respectively.

Biotinidase Deficiency: Infants with severe biotinidase deficiency will display skin rashes, seizures, hair loss, hypotonia, emesis and acidosis in the first few months of life. This syndrome occurs because the infant lacks the enzyme responsible for proper biotin metabolism. Approximately 75% of affected infants will develop hearing loss if left untreated. The significance of this disorder is that if it is recognized, all the sequelae can be avoided with biotin supplementation.

X-Linked syndromes

Alport syndrome: As a result of the mutation in type IV collagen gene COL4A5, patients with Alport syndrome exhibit renal disorders and ocular abnormalities in addition to progressive sensorineural hearing loss. Renal disorders include glomerulonephritis, hematuria ("red diaper"), and renal failure. Early diagnosis is essential because the renal disease is usually more severe in males causing death secondary to uremia prior to 30 year old. Congenital cataracts are also common. The progressive sensorineural hearing loss mentioned earlier usually has an onset beginning in the 2nd decade of life.

Non-genetic Syndromes

Down's syndrome: This is the most common of the chromosome abnormality syndromes typified by a wide range of abnormalities. Otolaryngologic findings are numerous in these patients and can affect every region of the head and neck. This includes small ears with overfolding of the superior helix, stenotic EAC and eustachian tube dysfunction. There is also an increased incidence of chronic ear disease in affected children due to increased incidence of upper respiratory infections, reduction of B and T cell function (immune system immaturity), and eustachian tube dysfunction. The hearing loss in DS is usually conductive secondary to the chronic middle ear disease but can also be due to ossicular chain abnormalities, especially the stapes. Upper airway obstruction and OSA are also problems encountered by children with DS due to the midface hypoplasia, and relative enlargement of the tongue, tonsils and adenoids in a constricted naso/oropharynx. Other systems affected include cardiovascular (ventricular-septal defect, tetralogy of Fallot, patent ductus arteriosus), genitourinary (micropenis, low testosterone, infertility), musculoskeletal (atlanto-axial instability, short metacarpals and phalanges) and ocular (speckled iris; Brushfield spots). In terms of speech and behavior, most Down's

syndrome patients exhibit dysarthria and articulation deficits in conjunction with some degree of mental retardation (IQ 30-50).

Fetal Alcohol Syndrome (FAS): Of children born to alcoholic mothers, 30-40% suffer this syndrome. The amount of alcohol intake required to cause FAS has not been clearly established. Alcohol and its major metabolite, acetaldehyde, may be teratogenic. The alcohol induced developmental abnormalities can be the result of restriction of cell growth during critical periods. Characteristics of the syndrome include prenatal and postnatal growth deficiency, microcephaly, and mental retardation (average IQ of 63). Behavior is also affected as irritability and hyperactivity are common. Neural tube defects and seizure disorder may also be present. From an ophthalmology perspective, this syndrome causes hypoplasia of the optic nerve, increased tortuosity of the retinal vessels, severe microphthalmia and colobomas. Almost no system is guaranteed to be spared as cardiac, renal and skeletal anomalies may manifest themselves as well as malignant neoplasms of embryonal origin. Common facial dysmorphisms include narrow forehead, short palpebral fissures, ptosis of eyelids, midface hypoplasia, short nose, smooth philtrum, thin upper lip and hypoplastic mandible. In addition, cleft palate or cleft lip may exist. Ten percent of patients have hearing loss that may be either conductive or sensorineural.

Goldenhar's Syndrome: Also referred to as facioauriculovertebral dysplasia (FAVD) and hemifacial microsomia (HFM), this disorder results from aberrant development of the first and second branchial arches. HFM is estimated to occur in 1 in 5600 live births, perhaps making it the most significant asymmetric craniofacial disorder. Otologic manifestations include microtia/anotia, preauricular tags, ossicular abnormalities, abnormal facial nerve course, and hearing loss (conductive > sensorineural). The hearing loss is predominantly conductive secondary to the abnormal development of the structures derived from the first and second branchial arches. Facial abnormalities include unilateral hypoplasia of the maxilla, malar and temporal bones in addition to mandibular ramus and condyle hypoplasia. Macrostomia or pseudomacrostomia (lateral cleft-like extension of the oral commissures), cleft lip or palate and delayed dental development. Lastly, the mastoid is poorly pneumatized and there may exist agenesis of the parotid gland or displacement of the gland. In terms of non-head and neck features, affected individuals can also have cardiac abnormalities such as coarctation of the aorta, ventricular septal defect, tetralogy of Fallot, and patent ductus arteriosus. Renal ectopia and hydronephrosis can encompass the renal abnormalities. Limb deformities can be present as well as cerebral malformation and mental retardation. Ocular abnormalities include blepharoptosis, microphthalmia, epibulbar tumors, and retinal abnormalities leading to reduced visual acuity.

Rubella: Consists of a triad characterized by deafness, congenital cataracts and heart defects. This disease is caused by an RNA togavirus and is transmitted postnatally via respiratory secretion, saliva, or direct contact. Transplacental transmission is the route responsible for congenital infection which can involve more sequelae if infection is present during the first trimester. In terms of diagnosis, positive viral culture must be obtained, rubella-specific IgM antibody, or demonstration of significant rise in IgG antibody in acute (7-10 days) and convalescent phase (2-3 weeks later). The virus can be cultured from blood, nasal secretions, urine, throat swab or CSF. In addition to the above listed triad, other abnormalities that may manifest are microcephaly, motor and neural retardation, hepatosplenomegaly, thrombocytopenia, encephalitis and interstitial pneumonitis. The hearing loss in rubella is

typically asymmetric and sensorineural with variable severity. The 500-2000 Hz frequencies are the most commonly affected. This hearing deficit usually manifests by 5 years of age and can be an isolated finding in 22%. Approximately 25% of patients will experience a progressive form of hearing loss.

Cytomegalovirus (CMV): CMV has an incidence of 0.2%-2.3% of live births making it one of the most frequently occurring viruses worldwide and the leading cause of congenital malformations and mental retardation in developed countries. Of all the TORCH infections, CMV is the most common. Microcephaly, intrauterine growth restriction (IUGR), petechiae, encephalitis, hepatosplenomegaly, and deafness are some of the physical characteristics of a congenital CMV infection. CMV is estimated to account for 1/3 of sensorineural hearing loss in young children. Hearing impairment in CMV can be delayed (occurring months-years after birth), or fluctuating and progressive. Interesting to note, infants with petechiae and IUGR are 2-3 times more likely to have sensorineural hearing loss. Post mortem temporal bone studies on infants who died from cytomegalic inclusion disease have revealed inclusion bodies in the stria vascularis, Reissner's membrane, saccule, utricle and semicircular canals. Endolymphatic hydrops was noted in the cochlear ducts.

Overall treatment goals in patients with syndromic hearing loss

The important fact to remember pertaining to syndromic hearing loss is that treatment of the hearing impairment is no different than treating a nonsyndromic patient with hearing loss. In other words, there isn't a special hearing treatment for the profound sensorineural hearing loss in Usher syndrome vs. the child who is profoundly deaf at birth without a syndrome. There have been studies documenting success in use of cochlear implants in syndromes manifesting sensorineural hearing loss such as Usher, Waardenburg, and Jervell and Lange-Nielsen syndrome. Likewise, when syndromic patients have conductive hearing loss or a significant conductive component contributing to mixed hearing loss, the appropriate surgical procedures should be performed. This can range from being as simple as a BM&T for the recurrent middle ear effusions in Down's to performing a stapedotomy/ossiculoplasty in osteogenesis imperfecta. Basically, the method of treatment should be selected to meet the individual needs of the patient to achieve the most benefit. In the end, the main purpose of arriving at a syndromic diagnosis is to identify those that will have hearing loss so that early and aggressive hearing rehabilitation can be initialized.

Discussion by Shraddha Mikerji, MD

Hearing loss associated with well-known syndromes is less common as compared to other non-syndromic causes of congenital hearing loss.

However, when hearing loss is a feature of a certain syndrome, babies and children tend to be evaluated early on for any hearing problems. Though the ultimate treatment of syndromic hearing loss does not differ from that of non-syndromic hearing loss, early identification of these children means early treatment and early rehabilitation with possible better outcomes.

Osteogenesis imperfect may present with conductive hearing loss which may be clinically indistinguishable from otosclerosis. However, other clinical features will correctly identify the children as have osteogenesis imperfect. Though the audiological pattern is similar for the two conditions, surgery is more complicated with less chances of post-operative improvement in hearing in children with osteogenesis imperfect. This is related to increased vascularity over the stapes foot plate. Also, even if the foot plate is thick it is more brittle, so can lead to floating foot plate and other complications including sensorineural hearing loss.

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