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REVIEW PAPER

Genetic hearing impairment

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Abstract
Introduction Three out of 1000 newborns are affected by a hearing loss, one of these being profound congenital deafness, whereas in the population of children treated in the intensive care unit, the incidence is 1:50. The purpose of this paper is to show in which genetic diseases and syndromes that hearing impairment can occur.
Discussion A large number of pathological conditions, (genetic, infectious, and metabolic) can manifest themselves in a conductive or sensorineural hearing loss. Nonsyndromic autosomal recessive hearing loss is found in 56 % of cases, syndromic recessive in 30 %, nonsyndromic autosomal dominant in 12 %, and nonsyndromic related to the X chromosome and mitochondrial in 2 % of the cases.
Conclusion To make a diagnosis, the knowledge of clinical features of genetic syndromes is of paramount importance. Complete evaluation includes pediatric examination, bone and soft tissue radiological visualization, i.e., computed tomography and nuclear magnetic resonance, and finally genetic tests in cases where a hereditary disorder is suspected or identified.

Keywords Hearing impairment · Sensorineural · Mitochondrial · Exsanguinotransfusion · Hypoplasia

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Introduction

From audiological aspect, deafness signifies the absence of auditory function [1]. Normal hearing requires anatomical integrity and functional compliance of all parts of the auditory system: the outer, middle, and inner ear; the cochlear nerve; and the central auditory pathways [2]. According to the site of the lesion, HI can be conductive, sensorineural, mixed, central, and psychogenic.

Classification of HI for partition of the threshold of hearing for tone on important speech frequencies includes mild, moderate, moderately severe, severe, and profound HI.

Conductive HI is the result of insufficient functioning of the conduction part, outer and middle ear. Sensorineural hearing impairment (SNHI) is the result of damaged membranous labyrinth, the organ of Corti, or some of the structures involved in the transmission of sound to the temporal cortex. Mixed HI involves dysfunction of both parts of the hearing organ, conductive and perceptive (3.4). With regard to duration, a HI may be transient or permanent, in relation to behavior, progressive or non-progressive.

In relation to the side on which the lesion is present, HI can be unilateral or bilateral. According to the origin, all HI in children can be divided into genetic (hereditary) and acquired [1, 3].

Depending on the time of onset, HI may be prenatal, perinatal, congenital, and postnatal [1, 2]. Depending on the time of HI manifestation in relation to speech function development, it can be divided into prelingual and lingual.

Epidemiology

Three out of 1000 newborn children are affected by a hearing impairment and one by profound congenital deafness in the entire population. In the population of children treated in the

intensive care unit, the incidence is 1:50 according to approximate estimates found in a number of studies [3–5].

Prevalence of sensorineural hearing impairment

The prevalence of congenital permanent SNHI is equivalent to the incidence standing at 112:100,000, while the prevalence of permanent SNHI with a threshold equal to or greater than 40 dB stands at 133:100,000 [4–8]. Congenital and acquired progressive SNHI occurs in 21:100,000 newborn children [7, 8].

The etiology of hearing impairment

Based on the examination alone, it is difficult to determine whether the child's HI is genetically conditioned or acquired. Acquired causes are believed to be more frequent and are found in 60 % of patients.

The formation of the ear structure and auditory pathways involves a large number of genes, over a hundred, which, in turn, makes diagnosing a very complex process. For this reason, there is no unique and precise division of genetic HI. To determine a HI etiology, it is necessary to take a detailed personal and family history. For a number of genetic disorders, there is a positive history. Furthermore, it is important to determine whether it is an isolated, "nonsyndromic" disorder, or a HI associated with other anomalies in case of which we need to consider the possibility of genetically conditioned syndrome. The isolated HI inheritance mode can be autosomal recessive (in 56 % of patients), autosomal dominant (in 30 % of patients), X-linked (in 12 % of patients), and mitochondrial (in 2 % of patients). Autosomal recessive HI is mostly prelingual, nonprogressive and deep (with a threshold of hearing speech frequencies above 90 dB), while the autosomal dominant is usually progressive and manifests itself later in life.

The differential diagnosis has to exclude possible HI risk factors such as: family history related to rubella and other intra utero infections, birth weight less than 1500 g, hyperbilirubinemia which demands exsanguinotransfusion and perinatal asphyxia with APGAR score under three.

Discovering the cause is important for rehabilitation planning, prognostic assessment, diagnosis of disorders in the context of genetic syndromes, and family planning [4–11].

Autosomal recessive inheritance of hearing impairment

Autosomal recessive HI is usually a consequence of mutations in genes Connexin 26, 30, and 31; GJB 2 (C×26); GJB 3 (C×31); and GJB 6 (C×30) encoding the transmembrane protein which determines the creation of connections between the intermediate space and the opening of K+ channel. These mutations result in high levels of toxic K+ in hearing cells which causes irreversible damage [9, 12, 13]. Hearing impairment is manifested at birth or, rarely, a little later, but definitely in prelingual stage. It is not progressive and HI level varies in different families. The sense of balance is preserved. Mutated gene carriers have been registered in Europe, America, and parts of Asia. In the African American population, 4 % are heterozygous carriers of the mentioned mutations; in the Caucasus region, about 2–3 % are mutation carriers; and among Ashkenazi Jews, heterozygotes are present in about 4 % of the population.

Congenital genetic malformations of the inner ear

The pathological substrate of HI is often made by skeletal anomalies or membranous labyrinth with or without altered vestibular part. The type of inheritance is usually not known.

Michel dis/aplasia of the labyrinth, as a rule, causes profound HI.

The "common cavity" anomaly is clinically manifested by profound hearing loss. Cochlear aplasia with preserved vestibular part of the inner ear is manifested in the same way. Hypoplasia of the cochlea usually causes moderate HI. Incomplete division, i.e., the absence of interscalar partitions, usually results in moderate to heavy HI with preserved higher frequencies.

One of the most common findings on computed tomography of children with SNHI is Mondini dysplasia. It occurs in the seventh week of gestation. This dysplasia is characterized by hypoplasia of the cochlear basal turn, which leads to a progressive, sometimes fluctuating SNOS [8, 12].

In children with bilateral, progressive SNHI computed tomography can detect large vestibular syndrome aqueduct. This disorder begins gradually, "step by step", usually in childhood, sometimes with instability as the only symptom. There are descriptions of clinical cases of sudden onset after a head trauma, a strong blow in wind instrument, flying by plane, and other (5.8).

Deformities of the membranous labyrinth are very rare and not easily diagnosed by computed tomography if completely isolated from the bone labyrinth. Scheibe dysplasia affects pars inferior of the cochlea and sacculus. Alexander malformation implies cochlear aplasia of the ductus, whereby the basal bend of Corti and the neighboring ganglion cells are most affected. The damage is more pronounced at high frequencies, while the low ones are relatively well preserved [7, 8]. These malformations are diagnosed by means of nuclear magnetic resonance imaging with high resolution [7, 8, 12]. Each ear anomaly predisposes to the emergence of perilymphatic fistula. There are recorded cases of congenital perilymphatic fistula in oval, round window, and otic capsula. The existence of abnormal communication between the middle ear and the endocranium carries a high risk of recurrent labyrinthitis and bacterial meningitis development.

Syndromes with hearing impairment

So far, over 400 syndromes have been described covering HI of different nature and location.

Branchio-oto-renal syndrome (BOR syndrome, Branchio-oto-renal dysplasia, Melnick-Fraser syndrome) is an autosomal dominant disorder with manifestations in the hearing structures and the kidneys. The presence of clinical signs varies among and within affected families. Clinical manifestations of BOR syndrome are malformations of the outer, middle, or inner ear, hearing loss compounded by mild or serious anomalies of the kidney. Hearing impairment can vary from mild to profound degree; according to the site of the lesion conductive, sensorineural and mixed HI are distinguished. In the external auditory canal, stenosis of varying degree can occur, even atresia. The middle ear may be affected by various anomalies of malformation, malposition or fixation of the ossicles, and irregular size and shape of the tympanic cavity. Cochlear hypoplasia, cochlear and vestibular large aqueducts, or hypoplasia of the lateral semicircular channel can be found in the inner ear. The literature indicates a prevalence of BOR syndrome of 1:40,000, making this disorder responsible for about 2 % of the profound HI in children [8, 12, 14].

Pendred syndrome is inherited as an autosomal recessive trait, and the clinical picture comprises deafness and thyroid disease (euthyroid goiter). The pathological substrate of deafness in this syndrome is a large vestibular aqueducts or Mondini dysplasia.

Wolfram syndrome or DIDMOAD was described in 1938 for the first time. It includes diabetes insipidus, diabetes mellitus, optic atrophy, and HI. All patients have similar non-progressive SNHI with characteristic shape of audiometric curve which is slightly descendant.

Long QT syndrome occurs with the clinical picture of sudden nonsyncopal episode, and when coupled with profound congenital SNHI, it is known as the Jervell and Lange-Nielsen syndrome. The mode of inheritance is autosomal recessive [14].

Usher syndrome is the most common cause of deafness associated with blindness. It is inherited in an autosomal recessive manner. Basic characteristics of the syndrome are progressive hearing and visual impairments and, sometimes, loss of the ability to maintain balance. Retinitis pigmentosa is at the core of visual loss. There are three types of the syndrome: type one implies profound HI and damaged sense of balance; type two, medium to hard SNHI (better preserved low frequencies); and type three, progressive SNHI and damaged sense of balance (the majority of registered patients live in Finland). Diagnosis involves audiometry, electroretinogram (tunnel vision), and balance testing [14].

Goldenhar syndrome (hemifacial microsomia, oculoauricular vertebral syndrome) has an incidence of 1:5000–25,000 live births. It is inherited in both autosomal recessive and autosomal dominant manner. Clinical features are deformities of the face, including the cleft lip, and the palate and various deformities of the ears (malformed ear, external auditory canal atresia, anomalies of the middle and inner ear, stria vascularis, and semicircular channels). Kidney and gastrointestinal tract anomalies may be encountered, albeit the latter ones rarely. Hearing impairment varies from mild, moderate conduction, and moderate to severe SNHI [14].

CHARGE syndrome is observed in 1:8500–10,000 newborns. It is transmitted in an autosomal dominant manner and is defined by the existence of following anomalies: coloboma, heart anomalies, atresia choanalis, stunted growth, genitourinary malformations, and anomalies of the ears, thus the acronym CHARGE. Not all the anomalies are necessarily present and may be of different degrees of severity. The earlobe is usually low set and malformed, while the external auditory channel is stenotic, most commonly resulting in severe to deeply asymmetric mixed HI. It is not uncommon to see bilateral cases of the syndrome. Hearing impairment is the result of secretion in the tympanic cavity associated with sensorineural lesions like Mondini dysplasia, hypoplasia or agenesis of the auditory nerve, as well as anomalies of semicircular channels. Ossicular anomaly, the absence of the oval window or stapedius muscle, may also be present. In some of the patients, asymmetrically fluctuating conductive HI with a decrease at lower frequencies is described, while the cochlear anomalies are accompanied by a decline at high frequencies [14].

Pierre Robin syndrome usually occurs sporadically, with an incidence of 1:10,000. It is clinically manifested by micrognathia, glossoptosis, cleft palate, and consecutive conductive HI.

Stickler syndrome occurs with a frequency of 1:7500–9000 newborns. It is a collagen disease that is transmitted in an autosomal dominant manner. It is characterized by flattened shape of the face due to less developed bony structures of the middle face massif. Vision is impaired with possible myopia, cataract, and glaucoma. Patients are usually with cleft palate, macroglossia, arthritis, kyphosis, scoliosis, mitral valve prolapse. Hearing impairment can be conductive, due to fixation of the stapes, or sensorineural, due to a defect in collagen building of basilar and tectorial membrane of the organ of Corti [14].

Waardenburg syndrome is a group of genetic disorders that occur with an incidence of 1:40,000. The manner of inheritance is autosomal dominant and covers 2–5 % of all congenital deafness. Children with this syndrome may have changes in iris pigmentation or hair; their eyes are sometimes of different colors, sometimes striking blue; a strand of hair is white or prematurely gray. Type III (Klein-Waardenburg syndrome) includes hand anomalies, while patients with type IV (Waardenburg syndrome Shahov) suffer from Hirschsprung's disease [14].

Treacher Collins syndrome occurs with an incidence of 1:50,000 newborns; it is inherited in an autosomal dominant manner. Patients with this syndrome have characteristic abnormalities of the face, eyes, and ears. Ear anomalies can be discrete earlobe and ossicle anomalies but even anotia is possible. Approximately 40–50 % of children have conductive hearing loss associated with SNHI at high frequencies. The middle ear ossicles hypoplasia or malformations occur frequently. The inner ear is usually healthy [14].

Apert syndrome occurs in 1:65,000–88,000 live births. The appearance of these patients is distinctive and includes the following: craniosynostosis, protruding frontal region and tucked in central massif of the face. Hydrocephalus is a common complication, a large number of patients have abnormalities of the corpus callosum and fusion of C5-C6 vertebrae, also syndactyly compounded by vision and hearing impairments. Usually, it is a bilateral conductive HI as a result of otitis media with effusion or fixation of the ossicular chain [14]. Sensorineural hearing impairment is rarely present at birth no more than in 3–6 % of patients; however, at the age of 20, it is registered in 50 % of patients with mild to moderate degree at low frequencies. Hearing impairment is the result of inner ear anomalies such as cochlear dysplasia, extension and lateral vestibular semicircular channel [14].

Crouzon syndrome was first described in 1912. Inherited in an autosomal dominant manner, it occurs in 1:50,000 live births in Europe. It is characterized by craniosynostosis, the development of hydrocephalus, broad face, a recessed central face massif, a high forehead, lagophthalmos, and HI. Thirty percent of patients with this syndrome have a conductive HI as a result of abnormalities of the outer ear (earlobe malformations and external auditory canal) and the Eustachian tube, secretory otitis media, and ossicular and oval window anomalies. SNHI is rarely seen [14].

Pfeiffer syndrome is very rare, the incidence is 1:100,000 representing the allelic form of Crouzon syndrome, inherited in an autosomal dominant mode. People with this syndrome have malformations of the head, limbs, short and broad fingers, and HI.

Sæthre-Chotzen syndrome is transmitted as an autosomal dominant type, with an incidence of 1:25,000–1:50,000. The appearance of these individuals is characteristic; they have brachycephaly, anomalies of the vertebrae and toes, and short stature. Hearing loss is usually due to the conductive anomaly of the external auditory hall, ankylosis of the stapes, fixation of the ossicular chain, microtia, the tympanic cavity anomalies, mastoid absence, and the brain stem anomalies [14].

Autosomal dominant, Townes-Brocks syndrome is rare, and the incidence is 1:250,000. It is characterized by the clinical triad of anus imperforatus (82 %), external ear abnormalities (85 %), and thumb anomalies (89 %), together with the records of urogenital system and kidney anomalies, congenital heart defects, malformed legs, and mental retardation.

Miller syndrome, acrofacial dysostosis, is very rarely seen; one in a million live births. In addition to craniofacial abnormalities, there are also limb abnormalities. Patients have conductive HI due to defects in the middle ear [14].

Nager syndrome or acrofacial dysostosis is rare, in respect to individual characteristics clinically similar to Treacher Collins syndrome, inherited in an autosomal recessive manner. The characteristics of this syndrome are facial and limb malformations, ear anomalies, with sensorineural HI more common than conductive [14].

Mitochondrial inheritance

Mitochondrial diseases commonly affect the nerve and muscle tissue; therefore, these patients often have damaged auditory pathway. Hearing loss occurs in the MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), Kearns-Sayre syndrome, and MERRF (myoclonic epilepsy with ragged red fibers). Sensorineural HI in patients suffering from these illnesses is bilateral, usually symmetrical, most pronounced at high frequencies.

Hypersensitivity to aminoglycosides, manifested in HI, is also inherited by mitochondrial DNA [15, 16].

Sex linkage

Alport syndrome involves kidney damage with hemorrhage and progressive HI. It is inherited in different ways, usually related to the X chromosome. Microscopic hematuria and proteinuria found in about 40 % of male children constitute a significant risk of developing into nephrotic syndrome 10 years later. In female patients, the disease progresses more slowly or not at all, and they do not develop a renal failure. Hearing impairment observed in most patients, progressive, bilaterally expressed at high frequencies, usually occurs before the age of 10. Eye damage, front lenticonus, cataract, and retinal damage, to name just a few, are also described. Diagnosis is based on clinical features, histological findings of renal tissue after biopsy, and genetic testing.

Mohr-Tranebjærg syndrome is inherited by recessive X-linked chromosome. As part of this syndrome, postlingual SNHI, progressive dystonia, spasticity, dysphagia, and optic atrophy are developed in childhood. The disease has similarities to the clinical Friedreich's ataxia, but without cardiomyopathy.

Anomalies in the skull development appear as a result of defects in embryogenesis first and second branchial arch that participate in the development of the skeletal (mandible, maxilla, and small bones of the middle ear), muscle, and nerve (*n. facialis*) structure of the skull [14].

Conclusion

In determining the causes of hearing impairment, the knowledge of clinical syndrome characteristics is of utmost importance. Usually, an extensive pediatric testing is required, including radiological imaging of both bony and soft tissue structures, such as computed tomography and nuclear magnetic resonance. The tests at the molecular level are necessary for a definitive diagnosis of genetically conditioned hearing impairment.

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