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Non-syndromic congenital hearing loss

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Abstract

Non-syndromic congenital hearing loss is a global problem. It is the most common disorder at birth, occurring in 1-2/1000 newborns. Congenital hearing loss leads to delayed language development, impaired psychosocial interactions abnormal behavior and poor educational achievement. Genetic transmission is implicated in 50% of the cases of congenital deafness. Of these, about 70 % are non-syndromic. Genetic counseling is essential to making the parents aware of the most appropriate treatment. Classification and the rationale for screening of hearing loss in the newborn will be reviewed here.
Keywords: *non-syndromic congenital hearing loss, genetic diagnosis*

Introduction

Hearing loss in the first year of life can cause delays in speech, language and cognitive development.

Approximately 50% of cases are thought to be due to environmental factors and the remainder to genetic causes.

Deafness/hearing loss is a common congenital defect.

Approximately 1 of 500 newborns is affected by bilateral and permanent hearing loss[(1)].

The clinical classification divides hearing loss types in:

- According to the degree of the impairment - slight, moderate, severe and profound;
- According to the association with other manifestations - syndromic or non-syndromic;
- According to laterality - unilateral/bilateral; symmetrical/asymmetrical;
- After the moment of the apparition, prelingual (precedes the onset of speech)/postlingual;
- According to the impairment type - sensorineural/ of perception, conductive or mixed[(1,2)].

The classification after types of mutation transmission divides the nonsyndromic hearing loss in autosomal recessive, autosomal dominant, related to chromosome X or mithocondrial (i.e. aminoglycoside induced hearing loss).

Congenital hearing loss appears with a frequency of 1/1200-1/200 of newborns, the autosomal recessive type being the most common (approximately 75% of the cases of congenital hearing loss).

About 80% of the congenital hearing loss types are non-syndromic, without being accompanied by other clinical manifestations[(3)].

Most of the cases of non-syndromic hearing loss are caused by connexin mutations, for the human species at least 20 subtypes have been identified until now.

Genetic testing for these cases has the role of determining if the hearing loss is hereditary or to determine the status of the parents' heterozygous carrier.

The genes that are most frequently involved in determining this impairment are gap junction protein beta-2 (GJB2) and GJB6. The GJB2 is a small gene, having only one exon, but mutations in this gene are identified in approximately 50% of the patients with non-syndromic congenital hearing loss.

The disease is highly heterogeneous, but the mutations in the gene that encode for the connexin 26 appear at ~49% of the patients with congenital types and ~37% of the isolated cases.

The frequency of the carriers for the European population is between 1/20-1/31 of the individuals[(2,3)].

The genes for the connexin encode for the gap junctional channels that connect 2 adjacent cells, allowing the cytoplasm of ions and small mollecules up to 1.2 kDa.

The size of the gap junction and the types of particles that move through it are determined by the particular connexin proteins that make up the channel. Gap junctions made with connexin 26 transport potassium ions and certain small molecules. Connexin 26 is expressed with connexin 30 (encoded by the GJB6 gene) in the inner ear.

GJB2 gene mutations probably alter gap junctions, which may disturb the level of potassium ions in the inner ear. Levels of potassium ions that are too high may affect the function and survival of cells that are needed for hearing. Some mutations delete or insert DNA base pairs within or near the GJB2 gene.

The most common mutation, particularly in white populations, deletes one base pair between positions 30 and 35 in the GJB2 gene (35delG or 30delG). The second mutant allele was c.71G>A (p.W24X) found in homo- or hetero-zygotic forms as well, followed by c.-23+1G>A and c.380G>A (p.R127H) mutations with lower frequencies. Two deletions in the GJB6 gene, namely del (GJB6-D13S1830) encompassing 309 kb and del GJB6 spanning 232 kb, have been shown to be a common cause of hearing loss as well.

A previously published study about the mutations in GJB2 genes in hereditary deafness population with the c.35delG mutation showed a carrier rate in the Romanian population of 3.14%. The data about ethnic

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or geographic distribution and genetic epidemiology of the GJB2 gene and the incidence of congenital hearing loss in Romania was estimated to be 0.93 per 1,000 live births[3,4].

The most frequent types are those with autosomal recessive transmission, these majorly involve a few characteristics:

- neuro-sensorial affection;
- moderate-to-profound severity;
- congenital start;
- usually non-progressive;
- it does not associate with other clinical manifestations;
- the types with dominant transmission present, at their turn, the following characteristics:
- they are progressive;
- start between the II and IV life decade[5].

Evaluation of the patients

The evaluation of patients with congenital hearing loss is complex, must be performed by a multidisciplinary team made of ear, nose and throat doctor, audiologist, neurologist, genetics physician.

The evaluation involves determining the family history (i.e. pedigree performance), physical ear, nose and threat, neurologic and genetics specialized in dysmorphology and must set out the type of hearing loss, the transmission modality and if it's syndromic or non-syndromic[3,4,5].

The autosomal recessive types represent 80% of the non-syndromic types and have some characteristics: the hearing loss is of perception, moderate or profound, had a congenital start and usually is non progressive and is not associated with other clinical manifestations[6].

Approximately 19-20% of the patients with non-syndromic hearing loss have dominant transmission types, usually progressive, starting in the 2nd or 3rd life decade. Over 100 loci have been described and 46 genes as being involved in nonsyndromic congenital hearing loss (NCHL).

The genes encode for the proteins involved in the development and functioning of the auditory system. The loci are named with the letters DFN (from DeaFNess) followed by a number that shows the chronological order of identification of these.

DFNA is the short term for loci with dominant transmission and it includes 21 genes, in which the most frequently involved are KCNQ4, WSF1, DFNB for loci with recessive transmission - it has 24 genes.

DFNX X linked transmission. The genetic loci where mutations associated with NCHL are marked with the letters DFN and NCHL is determined by mutations that appear in the genes GJB2 and GJB6 that encode for connexin 26 and 30, respectively. The B1 type of NCHL is determined by recessive transmitted mutations, most of them (>99%) in the GJB2 gene (over 150 described mutations), 1% in the GJB6 gene. Until present, over 400 different mutations have been described known to be associated with NCHL[6,7,8].

The rate of the healthy carriers in the general population for recessive mutations in the GJB2 gene is of approximately 1/33 of the individuals, some mutations being more frequent in certain ethnic groups.

The mutations in the GJB2 gene have impact on the expression of the protein of connexin 26 and in most of the cases it determines prelingual hearing loss, but not necessarily congenital.

Different mutations in the GJB2 gene can present a high phenotypic variation, but it has been proven that a correlation between the type of hearing loss and the molecular defect is possible[9,10].

Mutations in the GJB6 gene represent the second most frequent cause of NCHL, and it affects the expression of the protein connexin 30.

In rare cases, NCHL is caused by pathological mutations in other genes: ACTG1, CDH23, CLDN14, COCH, COL11A2, DFNA5, DFNB31, DFNB59, ESPN, EYA4, GJB2, GJB6, KCNQ4, LHFPL5, MT-TS1, MYO15A, MYO6, MYO7A, OTOF, PCDH15, POU3F4, SLC26A4, STRC, TECTA, TMC1, TMIE, TMPRSS3, TRIOBP, USH1C and WFS1[4,11,12].

Due to the existence of a large number of genes associated with NCHL there are various genetic testing panels that use the Next Generation Genetic Sequencing, a technology that allows simultaneous sequencing of several genes, at a low cost.

An adequate genetic screening has many benefits for the patient and his family.

Useless, expensive tests are avoided, for example electroretinography, temporal bone, computed tomography, etc[12,13].

Determining the causes of hearing loss can dissipate the misinformation and offer an emotional support for soothing the partent's guilt feeling.

The etiologic diagnosis offers a basis for determining the recurrence risk in the family, allows the anticipation of potential associated health problems and gives the recommendation for other adequate therapeutic options[12,14].

The optimal time for the genetic counseling of the family, for determining the genetic risk, identifying the status of the healthy carrier (i.e. for the recessive types) and discussing for the possibilities of prenatal genetic screening is before pregnancy (i.e. preconception).

The identification in the family of the molecular defect responsibile for hearing loss allows the correct performance of the prenatal diagnosis for the high risk pregnancies[5,14,15].

The benefits of genetic screening:

- determining the etiology of hearing loss;
- excluding the necessity of performing invasive, expensive, useless tests;
- offers the basis for establishing the clinical prognosis and anticipating the possible complications;
- correct guiding of the medical management;
- offering an adequate genetic advice for the pacient and his/her family[13,16].

The diagnosis of NCHL/deafness needs a specialized medical staff, experienced in genetic types of hearing impairment and in dysmorphology.

The clinical diagnosis is non-specific because there is a variable number of etiologic causes, many times is not possible to specify with certainty if there also is a genetic component[16,17].

Conclusions

Genetic counseling can provide a patient and/or family members with the natural history of the condition, identify at-risk family members, provide reproductive risks, explain preconception/prenatal options, and ensure appropriate referral for patient support and access to information resources. ■

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