CLINICAL PECULIARITIES OF THE NON-SYNDROMIC SENSORINEURAL HEARING LOSS IN CHILDREN OF BELARUS

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Abstract

Background: About 100 genes are determined to be involved in hearing loss in humans. Among them the major one is *GJB2* coding connexin 26. The deletion of any one of six G nucleotides at positions 30–35, so called *35delG* mutation, is most often found in *GJB2* gene in Europeans. The aim of the study was: 1) to analyze *35delG* mutation's rate in the large group of children with moderate-to-profound sensorineural hearing loss (SNHL); 2) to determine the influence of risk factors of non–syndromic SNHL.

Materials and Methods: 392 children (aged 3–17) with SNHL from moderate-to-profound were examined. A screening for 35*delG*, pure – tone audiometry and family interviews were performed. A comparative analysis of gender characteristics, degree of hearing loss and risk factors in three groups of children: 35*delG* heterozygous, 35*delG* homozygous and without this mutation were performed. The influence of risk factors of SNHL was statistically estimated by means of R-System.

Results: Among children with moderate and profound SNHL 45% were homozygous and 15% were heterozygous for *35delG GJB2.* The most significant risk factors leading to deafness in group of patients without mutation were perinatal risk factors.

Conclusions: Our study revealed that single-nucleotide deletion *35delG* in *GJB2* is the main genetic cause of SNHL in Belarus as it was detected in homo- or heterozygous state in 60% of the patients with SNHL. A molecular analysis for 35*delG* mutation should be performed in cases of positive family history, severe – profound congenital hearing loss, presence of perinatal risk factors.

Key words: Connexin 26 • GJB2 gene • 35*delG* mutation • non-syndromic hearing loss

Background

Since the last decade of the 20th century genetics of hearing impairment has been extensively moving ahead. At present about 100 *loci* are proven to be involved in the control of normal hearing located both in nucleus and mitochondria [Van Camp et al., 1997; Petersen, Willems, 2006]. The most intensively studied nuclear *loci* is the *GJB* family including *GJB2, GJB3* and *GJB6* genes encoding connexins – gap junction proteins [Van Camp et al., 1997; Schrijver, 2004]. Mutations in *GJB2*, encoding connexin 26 (Cx26) were found to be the cause of deafness in more than 50% cases of autosomal recessive nonsyndromic hearing loss in many world populations.

We report here the data of the rate of *35delG* recessive mutation in the large group of Belarus patients – children with SNHL (about 400 patients). In addition, we aimed to define the clinical features of SNHL due to above-mentioned mutation.

Materials and Methods

Subjects

A total of 392 hearing impaired children (aged 3–17), constantly living in Belarus, were included in this study. Exclusion criteria were: the presence of additional symptoms or malformations; unilateral SNHL; absence of cognitive defects.

Pediatric assessment

To determine the presence of prenatal and perinatal risk factors for hearing impairment, medical histories and parents were taken at family interviews. Details recorded included prenatal (abortion in anamnesis, rubella and toxoplasmosis during pregnancy, maternal exposure to alcohol, aminoglycoside antibiotics), perinatal (prematurity, low birth weight, hypoxia, neonatal mechanical ventilation, hyperbilirubinemia and admission to the neonatal intensive care) and postnatal (otitis media in anamnesis)

factors. Informed consent was obtained from all hearing impaired children's parents.

Audiological assessment

All hearing impaired children have passed otoscopic examination and pure tone audiometry. As determined by tympanometry, there were no conductive hearing loss. The air conduction thresholds were determined for each ear. The average threshold at 500, 1000, 2000 and 4000 Hz of the better ear defined the severity of hearing loss: mild (26–40 dB), moderate (41–55 dB), moderately severe (56–70 dB), severe (71–90 dB) and profound (>91 dB), according to the Classification of hearing loss taken WHO.

Molecular genetic tests

50–100 mcl of peripheral blood was taken. DNA was isolated with proteinase K and phenol-chloroform purification. *GJB2* mutation was detected by PCR-PDRF method using endonuclease MvaI.

Statistical analysis was performed by helping R-System.

Results

Genotyping *35delG* of the patients with SNHL

All 392 patients with SNHL were genotyped for the *35delG*. We found that 179 patients (45.5%) were homozygous for this mutation, 53 (14.8%) had only one mutant allele (heterozygous) and in 160 (40.7%) patients the major *GJB2* mutation was not found. *35delG* point deletion is the major cause of prelingual SNHL in Belarus patients, been detected in about 60% of the people studied.

Audiological findings

On comparison of 35*delG* homozygous with 35delG absent patients, the prevalence of severe-to-profound hearing loss was significantly (p value=0.086) higher in the group of 35 *delG* associated SNHL patients.

Clinical findings

Gender. Both boys and girls suffer from 35*delG*-associated SNHL with the same rate. Significant statistically differences between three groups are not revealed (p value=0.087).

The next stage of our research was a comparative analysis of the presence of various risk factors that play a role in the etiopathogenesis of sensorineural hearing disorders in children. 341 parent's questionnaires and medical history were analyzed.

Prenatal factors. The analysis found that prenatal pathology was equally common in all three groups (p value=0.079).

Perinatal factors. The frequency rate of prenatal pathology in the group of patients without 35*delG* was significantly higher (p value =0.08) than in groups of 35*delG* homozygous and 35*delG* heterozygous.

At the same time, further analysis found a significant difference (p value =0.08) in the groups with respect occurrence of perinatal pathology. Birth of a child with low birth weight significantly increases the risk of sensorineural hearing loss, as in a group of children without the mutation the number of children with low birth weight is prevalent.

Postnatal factors. At the same time, conditions such as acute otitis media were marked with equal frequency in all three groups (p value >0.05).

Family story. Our study shows that a positive family story (presence of deaf relatives) is present in 45% of cases with *35delG* homozygous children, while for group without this mutation the deafness was reported for only 15% of relatives.

Discussion

In this study it was shown that 35G- deletion in *GJB2* typically results in severe defect of sound transmission, and it is highly probable that genetic defects among patients with severe and profound deafness are more common than in the group with moderate hearing loss.

Our study has confirmed the view of researchers of the need to manage the risks of perinatal period in the etiopathogenesis of sensorineural hearing disorders in children. Established by us is evidence of appropriate accounting of these factors during the hearing screening. At the same time, relying only on account of these risk factors will be neglected group of children with hearing loss is genetic nature, which can be established only by molecular genetic analysis.

Conclusion

1. The presented study reveals that single-nucleotide deletion *35delG* in *GJB2* is the main genetic cause of *SHL* in Belarus as it is detected in homo- or heterozygous state in 60% of the patients with SNHL. Above-mentioned mutation is cause of more profound degrees of SNHL.

2. The rate of frequency of *35delG*-associated SNHL is the same for boys and girls.

3. Comparative analysis of risk factors for three groups of children depending on the presence of mutation 35 delG suggests that perinatal risk factors play significantly important role for children without 35*delG*.

4. The obtained data demonstrate both the perinatal risk factors and the genetic etiology of SNHL should be considered.

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