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Clinical Evaluation of Connexin-26 Gene Mutation in the Development of Hearing Loss in the Kazakh Population

Saule Kudaibergenova [1], Gulzakhira Djarkinbekova [1], Abdukhalil Musaev [2], Abdumannop Abdukayumov [1], Abdugani Musayev [1], Ayat Assemov [3*]

[1] Asfendiyarov Kazakh National Medical University, KAZAKHSTAN
[2] Republican Specialized Scientific Practice Medical Center of Pediatrics, UZBEKISTAN
[3] Groningen University, NETHERLANDS
***Corresponding Author:** ayat.asemov@gmail.com

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ABSTRACT

Introduction: Hearing loss is the most common sensory deficit in humans. Early diagnosis and intervention are important in the acquisition of hearing, speech, and linguistic skills, thereby contributing to the positive development of the child.

Aims: To study the state of hearing in children living in Kazakhstan, to identify the proportion of mutations in the connexin-26 gene in the event of sensorineural deafness.

Methods: prospective case-control analysis. In total, 454 participants were examined.

Results: It has been identified that for the Kazakh population with regard to the polymorphism of gene frequency GJB2 (35delG, 235Cdel, 167delT) the most characteristic is allele spectrum frequencies of 167delT polymorphism.

Conclusion: Thus, the population frequencies of the mutation were studied: 35delG (0.49±0.28), 235delC (0.66±0.33), 167delT (1.64±0.51) of the GJB2 gene in the Kazakh population, which makes a significant contribution to the study of the gene pool of Kazakhs.

Keywords: connexin-26, hearing loss, Kazakh, child, genetics of hearing loss

INTRODUCTION

Hearing loss is the most common sensory deficit in humans. It affects one out of every 500 newborns [1,2].

Thirty percent of newborns with genetically inherited hearing loss have associated clinical symptoms that constitute a known syndrome. The remaining 70% are related to non-syndromic congenital hearing loss [3-6].

Early diagnosis and intervention are important in the acquisition of hearing, speech, and linguistic skills, thereby contributing to the positive development of the child [7,8].

Identification of a genetic etiology has several benefits, as it can impact clinical management, direct further evaluation, refine genetic counseling, and improve patient outcomes. Genetic testing and results may preclude the use of imaging, which can be cost-saving and decrease radiation and sedation exposure.

Purpose of The Study

The purpose of the study is to study the state of hearing in children living in Kazakhstan and to identify the proportion of mutations in the connexin-26 gene in the event of sensorineural deafness.

Aim of the Study

The aims of the study can be listed, as follows:

1. To study the hearing conditions of children residing in Kazakhstan depending on the age, gender and the parents' seniority.
2. To identify the genetic share of ***connexin-26*** gene-mutation in case of the neurosensory deafness emergence.

METHOD AND MATERIALS

The survey was conducted using a prospective case-control analysis at the Center for Molecular Medicine and City Clinical Hospital No. 5 located in Almaty, Kazakhstan.

The data was collected between 2016 and 2019. All the examined individuals were ethnic Kazakhs, and the groups were correlated in terms of seniority and gender. In total, 454 participants were examined, including 150 children born between 2003 and 2020 with the diagnosis of ambilateral neurosensory deafness, who formed the primary group, and 304 people with no hearing function abnormalities, who comprised the control group.

Table 1. Assessment and comparison of anthropometric indicators of children and the age of their parents

Indicators	Primary group, n=150		Control group, n=304		t-Student criteria	p-average
	Average	±s	Average	±s		
Age (indicated in years)	8.92	3.76	7.93	3.50	0.19	>0.05
Height (in cm)	137.5	20.2	120.4	25.54	0.52	>0.05
Weight (in kg)	35.0	12.7	26.22	12.03	0.50	>0.05
At what age the deafness has been diagnosed	2.61	1.88	-	-	-	-
The father's age	39.9	3.9	31.27	1.1	2.12	<0.05
The mother's age	37.3	4.3	28.27	1.4	1.99	<0.05

Table 2. Clinical implications of statho-coordination impairments

Complaints	Main group, n=150		Control group, n=304		Relative risk	95% CI
	n	%±s	n	%±s		
Tinnitus	19	12.7±2.7	0	0	3.32	2.88-3.83
Dizziness	10	6.7±2	0	0	3.17	2.77-3.64
Equilibration dyscrasia	3	2.0±1.14	0	0	3.07	2.67-3.50
Gait disturbance	6	4.0±1.6	0	0	3.11	2.72-3.56
Chronic diseases	41	27.3±3.6	3	1.0±0.57	37.74	11.45-124.37
Allergic reactions	17	11.4±2.6	3	1.0±0.57	12.92	3.72±44.85
Has undergone the cochlear implantation surgery	50	33.3±3.8	0	0	4.04	3.41-4.79

Molecular genetic analysis was performed at the Center for Molecular Medicine in Almaty, Kazakhstan. For the study, peripheral blood was taken for DNA analysis from sick and healthy (control) children of Kazakhs. The method of blood sampling is standard, so that the blood does not clot, a solution of EDTA (ethylenediaminetetraacetic acid) was added. Analysis technique - real-time PCR. The used StepOnePlus ™ (Applied Biosystems™, USA) analysis instrument.

Also, from the peculiarities of collecting anamnesis, information about pregnancy and childbirth was taken, about the presence of NSHL in relatives. Objective data consisted of otorhinolaryngological examination of patients with a hearing test.

RESULTS

The average age of the examined individuals was about 8.92±3.76, which is not quite different from the control group, the age of which was 7.93±3.50 (t=0.19; p>0,05). Besides, statistically significant discrepancies have not been defined with regard to the following parameters such as: a child's average weight with neurosensory deafness 35.0±12.7и 26.2±12.03 in the control set (t=0.50; p>0,05); an average height was 137.5±20.2 in the main group as compared to the reference group – 120.4±25.54 (t=0.52; p>0,05).

Reliable differences have been identified based on the age of the parents whose children had hearing loss diagnosed. The average age of the fathers by the child's birth ranged 39.9±3.9 while the mothers' age was – 37.3±4.3 versus the parents' age in the reference group (the fathers' age was – 31.27±1.1, while the mothers' was – 28.27±1.4) (t=2.12; t=1.99; p<0.05, respectively) (**Table 1**).

According to the audiology data collected in Kazakhstan, due to the lack of properly equipped offices and trained specialists, the peak identification rate of hearing abnormalities still falls on the age of 6, which in the long run will decrease the efficiency of the further rehabilitation process. According to our records the average age of children with neurosensory deafness by the moment of diagnosing the acoustical disturbances ranges from the age of 2 up to 4 (an average value of this indicator is – 2.61±1.8).

The most characteristic implications of statho-coordination impairments include: tinnitus, equilibration dyscrasia, motion coordination dysfunction, and non-rotary vertigo (**Table 2**). Tinnitus was defined among 19 patients, which comprised 12.7%±2.7 (relative risk=3.32 [97% CI; 2.88-3.83]). The proportion of dizziness symptoms among the patients with neurosensory deafness was amounted to 6.7%±2.0 (relative risk=3.32 [97% CI; 2.77-3.64]), while equilibration dyscrasia and gait disturbance in our survey have been encountered not so frequently and comprised 2.0%±1.14 and 4.0%±1.6, respectively with relative risk 3.07 (97% CI; 2.97-3.50) and OP 3.11 (97% CI; 2.72-3.56).

While analyzing the etiological factors of emergence of neurosensory deafness among children in the primary group, it has been defined that in those groups there had been frequent infections revealed such as rubella, cytomegalovirus (CMV), etc. Furthermore, various acquired risk factors have been detected in the past medical histories of these children, specifically: acceptance of ototoxic antibiotics, etc. Only one child had auditory passage atresia, while 50 kids (1/3) in the primary group had previously had cochlear implantation surgery (CI) (**Table 3**).

At the Molecular Medicine Center, the population peculiarities of the frequency distribution gene polymorphism ***GJB2 (35delG, 235Cdel, 167delT)*** were surveyed, which was necessary for the identification of the clinical diagnostic significance in the Neuro-sensory Deafness (NSD) progressing. As a consequence of the performed molecular genetic testing, it has been identified that for the Kazakh population with regard to the polymorphism of gene frequency ***GJB2 (35delG, 235Cdel, 167delT)*** the most characteristic is allele spectrum frequencies of ***167delT*** polymorphism.

DISCUSSION

Hearing loss is a well-known prominent risk for speech and language developmental delay. The provision of hearing aids and cochlear implants early in life has demonstrated to help

Table 3. The reasons causing the Neuro-sensory Deafness (NSD)

Reasons that caused NSD	Main group, n=150		Control group, n=304		Relative risk	95% CI
	n	%±s	n	%±s		
Meningitis	10	6.7±2.0	4	1.3±0.6	5.36	1.65-17.38
Epidemic roseola	6	4.0±1.6	1	0.3±0.3	12.63	1.51-105.84
Cytomegalovirus	5	3.3±1.5	1	0.3±0.3	10.45	1.21-90.25
Prematurity	20	13.3±2.8	9	3.0±0.98	5.04	2.23-11.37
Ototoxic antibiotics	50	33.3±3.8	0	0	4.04	3.41-4.79
Idiopathic deafness	97	64.7±3.9	0	0	6.74	5.25-8.64
External auditory passage atresia	2	1.3±0.9	0	0		

many children attain near-normal speech and language trajectories, as measured by growth curves using standardized language scores [9-11].

Hearing loss has also been found to affect a child's quality of life, particularly in the school and social domains, as well as behavior and behavioral disorders [12,13].

The authors in [14] reported unquantified but increased associations between hearing loss and internalizing behaviors, conduct and hyperactivity disorders, and other emotional problems. One study found the prevalence of the psychiatric disorder in a group of deaf and hearing-impaired children to be as high as 50% [15].

In the majority of hearing-impaired children, hearing loss is due to genetic factors, most often a single gene defect [16]. In our work, we provide molecular genetic analysis for the Kazakh population in terms of the frequency of gene polymorphisms.

Findings help create new therapeutic options for the treatment and management of hearing impairment, particularly in children.

Overall high involvement of connexin-26 mutations in autosomal recessive non-syndromic forms of deafness, and even in sporadic cases, makes mutation analysis distinctly worthwhile. Connexin-26 mutation analysis has therefore secured a place as a useful tool in clinical practice. So far, many different mutations in the connexin-26 gene causing DFNB1 have been identified [17]. The uncertainty about the pathogenicity of the mutation demands close collaboration with geneticists who are familiar with deafness [18]. Nevertheless, connexin-26 mutation analysis provides a good starting-point in the molecular diagnosis of patients with non-syndromic congenital deafness [18-21].

Mutation c.35delG in the GJB2 gene in homozygous and compound-heterozygous conditions is the major cause of non-syndromic recessive hearing loss in most European populations. It accounts for approximately 40–50% of overall mutant alleles of the GJB2 gene in deaf patients [22]. Earlier, the large-scale research covering 17 European countries demonstrated that the average carrier frequency of 35delG in Europe was 1.96% (1 of 51), with a variation from 1.26% (1 of 79) in Central and northern Europe to 2.86% (1 of 35) in southern Europe [23]. Further, the gradient of increase in 35delG frequency from north to south has been confirmed in the meta-analysis of the carrier frequency of 35delG in various European populations [24]. High carrier frequency of 35delG has been shown in Mediterranean populations: Greece (3.5%), southern Italy (4.0%), and France (3.4%) [25].

CONCLUSIONS

There are numerous data on carrier frequencies of basic GJB2 mutations 35delG, 167delT, and c.235delC in various populations of the world. However, until recently, such data with regard to populations on territories of the Former Soviet Union have been limited. The data obtained in this study allow, to a certain extent, to fill the gap in information on the prevalence of the c.35delG, c.167delT, and c.235delC mutations of the GJB2 gene on the vast territories of Eurasia.

Thus, the population frequencies of the mutation were studied: ***35delG*** (0.49±0.28), ***235delC*** (0.66±0.33), ***167delT*** (1.64±0.51) of the ***GJB2 gene*** in the Kazakh population, which makes a significant contribution to the study of the gene pool of Kazakhs and creates a molecular genetic basis for determining their clinical and diagnostic significance in the development of hearing loss.

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