Clinical and molecular-genetic investigation of non-syndromic hearing disorders in children of the Uzbek population

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In order to observe for a mutation of 35 delG in gene Cx26 we carried out the screening observations in the special educational schools for children who have hearing loss and deafness. For the maximal involving of parents who have children with hearing disorders and for specification of the information about the family, specially worked out questionnaires were predominantly spread. By the results of DNA-diagnostic of gene Cx26 we have determined three types of patients. 39% of patients (146/374) belongs to the group of homozygote patients according to mutation of 35delG, genotype Δ/Δ. 14% of patients (57/374) belong to the group of heterozygote patients according to mutation of 35delG, genotype Δ/N. There were determined 23 cases with biallel inheritance of the mutation in gene Cx26 and 1 case of digenic inheritance mutation of 35delG in gene Cx26 and in a big deletion of gene Cx30.

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According to the data of World Health Organization (WHO), nowadays in the world there are more than 250 million people suffering from hearing disorders of different genesis, which makes up 4.2% of worldwide population. Such picture we can see in different countries of Europe and Asia (Bochkov, 2002; Koroleva et al., 1999; Markova et al., 2002; Bork et al., 2001).

The real break-through in the field of molecular and genetic knowledge about the hearing organ has brought to a qualitatively higher level approaches to determine the causes of hearing loss and to elaborate the effective methods of treatment (Bitner-Glindzicz, 2002). The possibilities of DNA-diagnostics of congenital hearing disorders open us new ways for the effective prevention. In that case, increases the role of medical and genetic consultations, prenatal and postnatal diagnostics of congenital hearing loss. It has become necessary to organize special dispenser registration of families that have menacing condition for the development of congenital hearing loss and to determine the risk group among children. Identification of pathologic mutation in families with different types of congenital hearing loss allowed us to illustrate the clinical manifestation of the changes in different genes (Bitner-Glindzicz, 2002; Petit, 2006).

Complex medical observations carried out in different regions of the world showed that in more than 6% of population changes in the hearing function were determined, and in 0.65-2% of them inadequate hearing function was determined. Congenital hearing disorders forming a significant part of all congenital forms of deafness and hearing loss can require a special approach regarding the specificity of preventive methods. Another important problem is genetic heterogeneity of the congenital hearing disorders. Research of the genetic heterogeneity is important not only to study the etiology of deafness and to work out, on this base, the approaches to pathogenic treatment, but also for the correct medical-genetic consultation (Bochkov, 2002; Stenton, 1999; Bork et al., 2001).

Known is relative influence of mutation in some genes for the development of the congenital and pre-speech hearing disorders: in some countries of Europe and the USA mutation in the gene of connesine 26 (Cx26) was observed in 59% of cases; in 5% of cases were determined mutations in gene Cx30 and caderine 23. In separate countries in
5% of cases was determined mutation of myosin 15, pendrin, stereosilin; in 3% of cases was determined mutation of otoferlin and mitochondrial gene 12S p-RNA. Significant genetic heterogeneity of hearing disorders is considered as the main problem of clear diagnostic hearing loss cases (Petit, 2006; Petersen and Willems, 2006).

However, at the dispensary are a much smaller number of patients due to a number of social causes. The role of the genetic factors in the development of hearing diseases in children at the early age is one of the least studied problems. This problem is especially important in our region where the fact of marriage of blood relatives still remains (inbreeding) (Bork et al., 2001). By the frequency of inbred marriages Uzbek population has occupied the second place in the world after Egypt, and the first place in the CIS countries. An important role in maintaining the high frequency of inbreeding is different national, religious, caste, social and economical factors. According to different authors (Stenton, 1999; Koroleva et al., 1999; Bochkov, 2002), as a result of blood related marriages increased the number of prenatal, postnatal and infant mortality, increases the frequency of genetic diseases and congenital ugliness.

The problem of diagnosis, treatment and rehabilitation of hearing loss and deafness was and is still important worldwide. The significant importance it has in children’s ENT diseases, because hearing condition in children depends on the development of speech. The consequences of children’s hearing loss and deafness can be different. They depend on the age when hearing disorders happened, determining duration of the defect and level of hearing disorders, degree of hearing loss and early rehabilitation (Bochkov, 2002; Markova et al., 2002; Bork et al., 2001).

It is known that in children conditions, that worsen the perinatal period of life, are the biological factors which can cause pathology of sound analyzer.

Inferiority of hearing gnosis stipulates underdevelopment of expressive aspects of speech: disorders in sound pronunciation, syllabic structure of words, phrases and construction of expressions (Markova et al., 2002; Bork et al., 2001). With significant hearing loss the development of speech is possible only for some part of children, and the necessary condition for this is to carry out early ear plastic and long term study with teachers of the deaf and dumb (Bochkov, 2002; Markova et al., 2002; Bork et al., 2001).

The aim of our research work was to investigate the condition of hearing function in children with neuro-sensor hearing loss in order to determine the heredity and further treatment strategy for their rehabilitation.

**Materials and methods of investigation**

Material for the investigation was received during the expedition work in schools and boarding schools No126 and No61 of Samarkand city. All patients underwent the investigation of ear, nose and throat (ENT) and genetic investigation. Was conducted a complex survey of children: consultation of children’s audiologist, teachers of the deaf and dumb, speech therapist, examination of ENT-organs, tonal threshold audiometry (audiometer MA-31) and impedancemetry investigations.

In order to find mutation of 35 delG in gene Cx26 we carried out the screening examinations in the special educational schools for children who have hearing loss and deafness. For the maximal involving of parents, who have children with hearing disorders, and for specification of information about the family, specially worked out questionnaires were predominantly distributed.

Upon initial examination of children was carefully studied the history of child’s development, including the period of pregnancy, childbirth, transferred diseases; attention was drawn to speech, vocabulary, level of mental development. Investigation with tuning fork was used to determine the presence or absence of reaction of a child to sound which was evaluated by the movement of head, eyes and by the changes of face expressions.
The next stage was to analyze the character and level of hearing disorders. Was studied the etiological structure of the investigated persons before and after the screening of changes in gene Cx26.

Genetic investigations included clinical-genealogical and polymerase-chain reaction (PCR) diagnostics. Genealogical methods determined the type of blood relation or endogamy marriage, and also the type of inheritance, by means of cardio-typing were analyzed chromosomes (Konigsmarc and Gorlin, 1980).

For children and adolescents with hearing loss and deafness in Samarkand city of the Republic of Uzbekistan were organized two specialized secondary schools - boarding school and kindergarten, which receive pupils from all over the Republic. In general in the specialized educational institutions of Samarkand they have 560 children with congenital and hereditary hearing loss, and 105 children with mild type of hearing loss.

The results of investigation and discussion

By the result of investigation we have identified 560 children with different types of neuro-sensor hearing loss. The studied area in terms of numbers is mainly urban population. It was noted that the number of patients in towns and villages varied significantly. The index of morbidity with hearing pathology in the city population was 0.09% (504), in rural area - 0.01% (56). Thus, the morbidity of the city population was several times higher than the morbidity index of the rural population. Such high rate of morbidity in both rural and city population was not detected in any studied area. Most children with congenital hearing pathology have hearing parents. Lack of information about other relatives who have hearing disorders does not exclude the possibility of the genetic background of the disease. In the absence of molecular methods of investigation, the correct consultation of families of such patients is practically impossible.

There are 286 deaf and dumb children (165 boys and 121 girls) with the diagnosis of congenital deafness in the boarding school No61. In the personal cards of 175 patients we can see the diagnosis of congenital neuro-sensor hearing loss. There are 105 pupils (62 boys and 43 girls) in the boarding school No 126 for children with mild hearing disorders. In most patients was observed the congenital hearing loss of II-III degree of mixed type. There are 33 children (23 boys and 10 girls) in the registered kindergarten for children of pre-school age and 23 of them have the diagnosis of neuro-sensor hearing loss, 5 children have mixed type of hearing loss and 5 children were deaf and dumb.

In the life history of 552 (98.7%) children whose parents were family relatives, hearing loss and deafness had a congenital character, significantly inherited by autosomal-recessive type.

The need for medical-genetic counseling stressed only 35% of interrogated families, 13% of them needed a retrospective and 22% of them prospective consultations. The negative answer to the question regarding the necessity of genetic consultation for family was obtained in 55%.

Thus, the frequency of congenital and hereditary hearing disorders in the population of Samarkand city and its suburbs was 0.1%, which does not exceed the indices of other cities. In morbidity structure the number of patients with congenital and hereditary types of deafness (59.7%) was significantly higher than with other types of hearing loss. Investigation of age-sex composition of patients with congenital and hereditary types of hearing disorders showed that the number of boys was higher than the number of girls (248 and 164 accordingly).

Thus, the total number of congenital and before speech cases of hearing loss largely consist of hearing disorders in children with hearing parents, and from non-syndromic types, which is consistent with data from other studies.

According to the results of DNA-diagnostic of gene Cx26 we identified three types of patients. 39% of patients (146/374) belong to the group of homozygote patients in
accordance with mutation of 35delG, genotype Δ/Δ. 14% of patients (57/374) belong to the group of heterozygote patients in accordance with mutation of 35delG, genotype Δ/N. Were identified 23 cases with biallel inheritance of mutation in gene Cx26, 1 case with digenic inheritance of mutation of 35delG in gene Cx26 and Cx30 large gene deletions.

The results of population-genetic investigations of Samarkand population showed that 330 (59.1%) patients had a genetic factor with the predominance of autosomal recessive type of inheritance and the presence of blood relation marriages.

The statistical index of authenticity was p<0.001, for the separated types of hereditary and acquired deafness was p<0.05, for investigation results of hearing loss the statistical index proved to be unreliable (p<0.05).

**Conclusion**

1. The frequency of congenital and hereditary forms of hearing disorders among population of Samarkand city was 0.1%.

2. Prevalence of 35delG mutation depends on a number of characteristics of the investigated groups: the age of the primary diagnostics, severity level of hearing loss, history of the disease, family history and background. In the aggravated family history the type of family was important. In group of children with hearing disorders in both parents mutation was detected in 96%.

3. In the morbidity structure dominates the number of patients with congenital and hereditary forms of deafness due to the high percentage of inbred marriages in the country.

4. Basic group of people who needed the genetic consultation and DNA-diagnostics are parents of deaf children and adults with changed genotype, mutation carriers, children with hearing loss and their relatives. Providing true prevention for patients with hereditary hearing loss is possible only by using system approach to determining risk groups.

5. In the case history of the most patients (59.7%) was predominated the hereditary factor with the significantly autosomal-recessive type of inheritance.

**References**


