METHODS OF DIAGNOSIS AND TREATMENT

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SOME BIOETHICAL ISSUES OF MOLECULAR GENETIC DIAGNOSTICS OF AUTOSOMAL RECESSIVE DEAFNESS 1A IN THE YAKUT POPULATION

ABSTRACT

Autosomal recessive deafness 1A is one of the most frequent hereditary diseases in the Republic Sakha (Yakutia). The diagnosed features of spectrum and frequency of pathogenic variants in the GJB2 gene by the patients with congenital hearing loss allow applying routine DNA diagnostics in medical practice. In the article some bioethical issues of DNA testing of autosomal recessive deafness-1A are discussed.

Keywords: bioethical problems, autosomal recessive deafness 1A, DNA diagnostics, the Republic Sakha (Yakutia).

Introduction

Congenital deafness – one of the most frequent pathologies in the world(1 to 650-1000 of newborns), about 50-60% of all cases of congenital deafness have the hereditary reasons [14].

The general prevalence of the forms of hereditary hearing loss is 13.0:100000 in the Russian Federation. There are regions with higher frequency, for example, in the Chuvash Republic – 32.5:100000, in Rostov Oblast – 36.6:100000 [4,9]. The conducted epidemiological researches of hearing loss in the Republic of Sakha (Yakutia) note sufficiently high frequency of sensorineural hearing loss among children up to 14 years; its prevalence exceeds this figure across The Central Federal District of the Russian Federation by 1.85 times. Among pupils of hard-of-hearing schools the inherited causes of the disease are traced over 43%, and pupils of deaf schools - 31% [11].

Molecular genetic research of hereditary non-syndromic sensorineural hearing loss is carried out in the Republic Sakha (Yakutia) since 2005 [3]. For the first time in the Yakut population there is identified the molecular genetic cause of the hereditary congenital hearing loss form. It is revealed as splice donor site mutation c.-23+1G>A of the GJB2 gene (Cx26) and it is classified as the allelic variant of autosomal recessive deafness 1A (DFNB1A) according to the international OMIM catalog (Online Mendelian Inheritance in Men).

The prevalence of DFNB1A is 16.2 to 100000 of the Yakut population, and the frequency of the heterozygous carriage of mutation c.-23+1G>A varies from 3,8 to 11,7% among indigenous people of Yakutia (Evens, Evenks, Dolgana, Yakuts). The research results of splice donor site mutation of the GJB2 gene (Cx26) demonstrate existence some of the largest worldwide «endemic focus» of accumulation c.-23+1G>A in Eastern Siberia [3].

Whatever the reasons of hearing loss: congenital, hereditary or acquired, deafness is a socially significant disease. As the leading speech pathologist L. Vygotsky (1983) noted: «Deaf-muteness is an immeasurably great tragedy because it isolates a person from any communication with people. Deaf-muteness is a social deficiency mainly. It breaks social communications of person stronger than blindness» [2]. Communication of deaf people with the hearing ones can be different: from the need of help to restore the lack of auditory information to the avoiding communication with people around because of the fear of being misunderstood. Therefore people with the hearing disorder quite often prefer to be in the company with people of the same disorder [10]. Deaf persons have much more medical and psychological problems than hearing ones. Proceeding from this, a number of researches shows a marked decline of quality of life in various spheres of activity in society [15,16].

Care delivery for special group of people with hearing loss is a particular problem for a doctor since there is a set of questions, for example, how to hold medical consultation successfully taking into account tongue and cultural specifics of a patient, his associated diseases, psychosocial problems etc. [19,20]. In the research among various organizations 100 deaf were interviewed. It was shown that there is inequality in access to health care service. For example, deaf women faced insufficient awareness of medical personnel on how to communicate with them. The research confirmed these problems are of great importance for most of deaf women that results in inequality when they are compared to the hearing people [21].

Among people with hearing loss there are distinguished deaf, hard-of-hearing, deafened and implanted. We should talk about deafness when it is found a persistent bilateral (on both ears) substantial impairment of hearing, and the coherence in speech perception is impossible. Based on time of occurrence it is accepted to distinguish early onset deafness (aged up to 3 years) and late onset deafness (occurred after the speech developing). Deafness, congenital or acquired, without special training, deprives a child of an opportunity to learn speech. If speech already began to form, then early deafness leads to its breaking. However, it is necessary to know that for such or other cases of hearing disorder to use the term «deaf-mute» is unethical [10].

Deafened (late-deafened) – the people who lost hearing but kept the ability to speak. Condition of their speech depends on the time deafness onset and means for its development. Children, who became deaf aged from 3 up to 5 years and didn't receive the special help by the time of starting school, most often keep a small vocabulary and usually pronounce it in a wrong way. Children, who became deaf in later age, almost completely keep a word-stock (especially the children who already learned to read and write). Special pedagogical influence to the ability to speak can fully save it within early-onset hearing loss [5].

The implanted children and adults are the people who underwent a cochlear implantation procedure (lat. cochlea – a snail), i.e. an implantation of electrode systems in an inner ear (a cochlea), with the subsequent electrical stimulation of acoustical nerve that allows to send the signals causing acoustic sensation to a brain [5].

The purpose of the article is to

discuss the main bioethical issues of DNA diagnostics of autosomal recessive deafness 1A for the development of bioethical rules of using routine DNA testing of DFNB1A in medical practice. The bioethical rules developed with regional features are applied to the most widespread monogenic diseases in Yakutia, such as spinocerebellar ataxia type 1 (SCA1) and myotonic dystrophy.

Materials and methods of research

We considered a group of the most common form of deafness, so-called non-syndromic autosomal recessive deafness 1A. For identification of forms of deafness corresponding to clinical aspect of DFNB1A clinical genealogical analysis was carried out. At questionnaire we analyzed the answers of the hearing respondents which have children with the confirmed genetic etiology of hearing loss caused by GJB2 gene mutations. The respondents who aren't biological parents or having relatives of the remote degree of relationship (grandmothers, grandfathers, uncles and aunts) weren't included to the research. 91 hearing parents of 70 deaf of the children unrelated to each other and meeting the main clinical criteria of non-syndromic autosomal recessive sensorineural hearing loss were included in the research group. All 70 deaf patients had mutations in the GJB2 gene (in homozygous or compound heterozygous state) [6,7].

Clinical research of patients

Clinical research of patients was carried out with the organized visits of medical brigades of specialized departments to boarding schools. During medical inspection of each participant of the research it was completed the individual formalized map of inspection containing the code number, age at the time of the research and sample of a biological material, given about ethnic origin, the hereditary history, results of physical, laboratory and instrumental methods of diagnosis, the conclusion and references of the experts. Venous blood sample was taken from the median cubital vein of all participants of the research for release of DNA samples. The researches were carried out under the written informed consent of the parents. The work is approved by Local Committee on Biomedical Ethics FGBU "Yakut Science Centre of Complex Medical Problems" of the Russian Academy of Medical Science, Yakutsk, the protocol No. 16 of April 16, 2009.

Molecular genetic research

For molecular genetic research genomic DNA samples extracted from peripheral blood lymphocytes were used. DNA amplification was carried out by means of polymerase chain reaction (PCR) with use of the oligonucleotide primer sequences [13]. Determination of primary nucleotide sequence of the first and second exons of the GJB2 gene in the studied samplings was carried out by means of automated sequencing.

Results and discussion

For causation of deafness / bradyacusia in the family burdened by DFNB1A, patients can attend a genetic consultation with different genophenotypical status: individuals with a normal genotype without hearing disorder ([wt]; [wt]), heterozygous carriers with «normal hearing» (c.[-23+1G>A];[wt]), homozygous mutation with a serious degree of bradyacuasia (c.[-23+1G>A]; c.[-23+1G>A] [6]. Consequently, the approaches of genetic consultation and receiving of DNA testing informed consent for these groups of patients also must be different.

In most cases while genetic testing there can be contradictions between family members because of incorrect ideas of laws of heredity. The hearing parents consider themselves healthy people, so hearing disorder of their child - an accident. So, for example, the analysis of parents opinion about the possible reasons of their child hearing loss showed that most of the hearing respondents in Yakutia (86,1%), Tyva (73,8%) and Bashkortostan (76,2%) doesn't consider the hereditary is hearing loss of the child, and caused either environmental factors or unknown reason. It is some kind of psychoemotional protection from «unwillingness to be guilty of deafness of the child» [1]. When receiving the informed consent from the hearing parents for DNA testing of DFNB1A, it is possible to explain that the child inherits the damaged gene from each parent and, perhaps, some parents will see in it a balanced responsibility for illness. The familial clustering (presence of deaf relatives in family) considerably facilitates consultation and receiving consent to DNA testing as patients are psychologically ready to accept hereditaryburdeness in family. This fact was confirmed by our researches, it turned out that in the absence of deaf relatives parents denied hereditary character of a hearing loss at their child authentically more often ($p<0,05$), and in families where there was a hereditaryburdeness - reliable differences wasn't diagnosed [17].

DNA testing of DFNB1A can define a heterozygous carriage of the GJB2 gene mutation of the hearing patient (c.[-23+1G>A];[wt]). According to the researches of F. Teryutina (2016) it was established that the heterozygous carriage of DFNB1A mutation is associated with age-related hearing loss (presbycusis) with a conventional border of onset age ~ 40 years [6]. The results notification of DNA testing can deal a serious psychoemotional stress for the person. First of all, a tested patient is informed about risk of a child to be born deaf in family. In this case, under identification of DFNB1A heterozygous carriage of an individual it is necessary to recommend prospective genetic consultation or preconception care. Secondly, the heterozygous carrier needs to provide information about rather high risk of decreased hearing in older age. The statement of the fact can be complemented with references to maintain the corresponding way of life and work which would reduce a load by organs of hearing (to avoid the works with noise, etc).

DNA testing of people hard-of-hearing / deaf is connected with a set of organizational and ethical problems. In communication with deaf people it must be kept in mind that they are members of socially isolated community of «deaf world» with their own language, culture and habits [18]. The quantity of assortative marriages among deaf grows; sometimes spouses can express an intention to have a deaf child regardless of injustice of such decision in relation to the child.

Anyway, comparing itself to the hearing people, the most part of deaf considers itself defective and socially deprived [20]. Use of DNA testing for mutations detection responsible for development of deafness can be dangerous because of psychological tension and aggravation and exacerbate sense of inferiority of the person. Therefore, it is necessary to create special conditions for consultation and receiving the informed consent for deaf. The informed consent for DNA testing of DFNB1A should be issued in a writing form and be the most available to understand. It is necessary to avoid difficult genetic terms and to use simple words and offers. Perhaps, it would be the correct decision to except the word «mutation» in the text of the informed consent for DNA testing, so that a tested patient can't decide himself that he is «mutant» in addition to the fact that he is deaf.

In oral communication with a deaf patient it is necessary to use a direct word order, enunciate a theme consistently, point by point; if communication conducts through an interpreter, it is needed to address a person you are talking to but not the interpreter.

DNA testing of DFNB1A carriage for children up to 14 years has to be carried out with the informed consent of parents or legal guardians. What is more, it is very important to inform parents well and in details about the genetic status of their

child and to give adequate psychological support with reporting results of DNA testing.

Conclusion

Detection of the whole range of the mutations which are the reasons of a hereditary bradyacuasia / deafness of a person is happened relatively recently, the results of these researches aren't introduced to public consciousness yet, and molecular genetic diagnostics of hearing loss isn't applied widely in medical practice [13]. In 2014 the DNA diagnostics algorithm of DFNB1A of the patients with congenital hearing loss in the Republic of Sakha (Yakutia) was developed for the first time [8]. It became possible to offer DNA testing of autosomal recessive deafness 1A for applied medicine as the routine analysis for diagnosis, differential diagnostics, identification of a heterozygous carriage, and, in the future, it is possible for population screening. The primary focus of DNA testing consists not only in identification of a mutation, but also in the differentiated approaches to genetic consultation of patients depending on their features: educational, cultural, age, etc. Development of ethical references and application rules of genetic technologies in medical practice is the most priority in modern medical genetics, because public consciousness often isn't in time behind the accelerating genetic technologies. Necessary increase of the levels of ethical standards gives to society security guarantees in the achievements of modern science.

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CHOLELITHIASIS AS A CAUSE OF ACUTE BILIARY PANCREATITIS

ABSTRACT
We studied the specific weight of biliary pancreatitis in the structure of patients with cholelithiasis. Based on the results of the studies, the cause of the occurrence of biliary pancreatitis -cholelithiasis and its diagnostic signs in the form of rapidly increasing hyperbilirubinemia and an increase in the level of ALT with a history for more than 20 years is proved.
Keywords:cholelithiasis, biliary pancreatitis, laparoscopic cholecystectomy,octreotide.

Introduction

Over the past 30 years, the incidence of acute and chronic pancreatitis has more than doubled worldwide. In Russia, there was a more intensive increase in the incidence of CP. Thus, the prevalence of pancreas diseases among adults over the past 10 years has increased 3 times, and among adolescents – more than 4 times [4].

Biliary pathology is the most frequent cause of acute and exacerbation of chronic pancreatitis. One of the reasons for the formation of biliary pancreatitis is gallstone disease (GD). The incidence of pancreatitis in patients with gastrointestinal tract, according to various estimates, is 25-90% or more [1, 3]. Every year, more than 1 million surgical interventions are performed in the world for gastrointestinal disorders, and cholecystectomy is the most common abdominal operation in General surgical practice. According to various authors, the incidence of biliary pancreatitis after surgery on the abdominal cavity reaches 20-25%, and after interventions on the biliary tract — 30 - 55% [2, 5]. According to the reporting data of the Republican hospital №2 – Emergency medical care center, cholelithiasis for 2014 amounted to 5.8% (118 patients) of all surgical pathologies. The problem of prevention of postoperative pancreatitis remains very relevant [6].

Research material and methods. The case histories of 20 patients admitted to the surgical Department of the Republican hospital №2 -Emergency medical care centerof Yakutsk with acute calculouscholecystitis, complicated in some cases by biliary pancreatitis, in the winter period from November to December 2014 were analyzed. Under the age of 35 years it was 4(25%) patients; under 50 years – 6 (37.5%) patients; over 50 years – 6 (37.5%) patients. The average age of patients was 45.5 years.

The proportion of patients with cholelithiasis: indigenous -16(80%), non-indigenous-4 (20%) (Fig.1).Duration of the disease: from 1 up to 20 years -3 (60%), 20-40 years -17 (40%).

Results and discussion

The number of patients with biliary pancreatitis among 20 patients with gastrointestinal tract is – 7(35%) patients, of them 4 (20%) – women, 3 (15%) – men, while indigenous-5(71.4%), non-indigenous-2 patients (28.6%). The last