Amursky St., 680000;
4. Kogut Boris Michailovich – Doctor of Medical Science, professor of the Department of normal and topographic anatomy with the course of operative surgery of the Far Eastern State Medical University Khabarovsk, 35, Muravyev-Amursky St., 680000;
5. Boiarintsev Nikolai Ivanovich – Doctor of Medical Science, professor of the Department of additional professional education of the Institute of continuous professional education and accreditation of the Far Eastern State Medical University Khabarovsk, 35, Muravyev-Amursky St., 680000;
6. Kosenko Pavel Mikhailovich, FGBOU VO "FGMU" of the Ministry of Health of Russia, Associate Professor of the Department of General and Clinical Surgery, Candidate of Medical Sciences, kosenko @ inbox.ru, 680000g. Khabarovsk, Muravyev-Amursky 35;
7. Melkonyan Gegam Genrikovich – doctor of surgical department of the 301 Military Clinical Hospital, Khabarovsk, 1, Seryshev St., 680028;
8. Ianovoi Valerii Vladimirovich – Doctor of Medical Science, head of the Department of hospital surgery with a course of pediatric surgery of the Amur State Medical Academy, Blagoveschensk, 95, Gorky St., 675000.

V.G. Pshennikova*, F.M. Teryutin*, N.A. Barashkov, N.N. Gotovtsev, A.A. Nikanorova, A.V. Solovyev, G.P. Romanov, O.L. Posukh, L.U. Dzhemileva, E.K. Khusnutdinova, S.A. Fedorova

POSTLINGUAL DEAFNESS IN EVENO-BYTANTAYSKY NATIONAL DISTRICT OF THE SAKHA REPUBLIC (YAKUTIA): AUDIOLOGICAL AND CLINICAL-GENEALOGICAL ANALYSIS

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ABSTRACT

In this paper we present for the first time the results of the audiological and clinical-genealogical research of the population of settlements Batagai-Alyta and Kustur of the Eveno-Bytantaisky National District (ulus) of the Sakha Republic (Yakutia) for studying the postlingual form of deafness of unknown etiology, which we for the first time have identified earlier in 3 Evens. As a result of an audiological examination of 72 people, 10 patients from 6 nuclear families who met the criteria of postlingual form of hearing loss were found. The segregation analysis carried out in these families confirmed the autosomal recessive type of inheritance of this form of postlingual hearing loss. The distant relationship of the examined patients with postlingual hearing loss living in two villages of the Eveno-Bytantaisky National District of the Sakha Republic can indicate to the role of the founder effect in the local prevalence of this pathology. The results of present study and obtained expedition material will be the basis for further research of the molecular genetic etiology of this form of deafness and the discovering of mechanisms of its accumulation in this region of Yakutia.

Keywords: postlingual deafness, audiological analysis, clinical-genealogical analysis, segregation analysis, Eveno-Bytantaisky National District, Sakha Republic (Yakutia).

Introduction. Mutations of the *GJB2* gene are the main reasons of congenitial and prelingual nonsyndromic hearing loss (HL) in many countries [5, 10]. Currently the territory of Eastern Siberia (the Sakha (Yakutia) Republic) is characterized by the spectrum and frequency of mutations of the *GJB2* (Cx26) gene on the large cohort of patients (n=393) with congenital hearing impairments and individuals with normal hearing (n=187) from Yakut and Russian populations [1, 9]. Recently it was shown that the pathogenic contribution of biallelic *GJB2* gene mutation to the etiology of HL in Yakutia was equal to 49%; and this rate was the largest in comparison with the earlier studied regions of Asia (10213 probands from 23 countries) [4]. In the spectrum of identified *GJB2* mutations, three mutations: c.-23+1G>A, c.35delG and c.109G>A were the most common. These mutations account for 98% out of all pathogenic *GJB2* alleles. The major *GJB2* mutations specific for the main ethnic populations of Sakha (Yakutia) Republic were identified: for the Yakuts - c.-23+1G>A and for the Russians - c.35delG. Nevertheless, the biallelic *GJB2* mutations were not detected in 51% of examined deaf patients (*GJB2*-negative patients), and the reason of their HL remained unknown. Considering the genetic diversity of known hereditary forms of deafness, there is a high probability that HL of some patients may be due to the mutations in other genes since about 100 genes are known in association with non-syndromic hearing impairments (Hereditary Hearing loss Homepage - http://hereditaryhearingloss.org).

Our detailed clinical-genealogical analysis of the sample of *GJB2*-negative patients from different districts of the Republic of Sakha (Yakutia) revealed 3 Evens with late onset HL from the village Batagay-Alyta (Eveno-Bytantaysky National District): 2 sibs (proband A and sibs A) whose HL became noticeable at 7 years in proband A and at 4 years in sibs A, and also one patient (proband B) with the same onset of HL (at 4 yrs).

All collected data (medical history, the results of molecular-genetic and audiological analysis) for these 3 patients from the Eveno-Bytantaysky National District of the Sakha Republic allowed us to suggest the hereditary cause of this postlingual form of deafness.

The **objective** of this study is to conduct audiological and clinical-genealogical analysis of the families with postlingual form of deafness of unknown etiology from Eveno-Bytantaysky National District for the further confirmation of hereditary nature of this disease and clarification of its inheritance type.

Materials and methods of the research. During the field work in the Eveno-Bytantaysky National District of the Sakha (Yakutia) Republic (April, 2018) the staff of the Yakut Science Center of Complex Medical Problems (Yakutsk) examined 106 inhabitants of the villages Batagay-Alyta and Kustur. Among them, 72 individuals were selected for the study of the etiology of the postlingual form of deafness - 65 from Batagay-Alyta, 4 from Kustur, and also 3 previously examined *GJB2*-negative patients (proband A, sibs A, proband B) from Batagay-Alyta were taken for further examination. Among

* - These authors contributed equally to this work

them, males accounted for 34.7% (n=25), females - 65.2% (n=47). The average age was 44±17.21 years. Ethnic composition of the sample: Evens - 48 (66.6%), Yakuts - 22 (30.5%), one Evenk (1.4%), and one individual of mixed ethnicity (Even/Yakut) (1.4%).

Audiological examination

Complaints about the condition of hearing such as the presence of a discharge from the ear, noise in the ears, dizziness were clarified through an interview with patients. Medical and life histories including past illnesses, injuries and/or surgeries, contacts with industrial noise, and information about allergic reactions was ascertained for all examined subjects. The otologic examination was carried out by unified algorithms on the KaWe Combilight otoscope. A full audiological survey was conducted with the use of a tympanometer and an audiometer "AA222" ("Interacoustics", Denmark). Hearing thresholds were measured by air conduction at frequencies of 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 kHz and bone conduction at frequencies of 0.25, 0.5, 1.0, 4.0 kHz in 5.0 dB increments. Severity of HL was defined by hearing thresholds of better hearing ear in the voice frequency range (VFR) in accordance with international classification under which I degree is equal to 26-40 dB in VFR, II - 41-55, III - 56-70, IV - 71-90, deafness > 90 dB.

Clinical-genealogical analysis

We had developed an individual card, which included information about last name, first name, middle name of the participant and his parents and grandparents; age; ethnicity (up to the third generation); place of birth and residence as well as the profession was filled out for each participant. The information about otorhinolaryngologic diagnosis, potential cause of HL, onset of HL, presence or absence of relatives with HL, and concomitant diseases was also included in the individual patient's card. The pedigrees compiled on the basis of all obtained data were subjected to subsequent clinical-genealogical analysis.

To confirm the heritability of postlingual form of HL and ascertain the type of its inheritance we conducted a segregation analysis in six nuclear families selected through the proband (Table 1). All parents in these families were healthy that suggests a recessive type of the inheritance of this trait.

The Weinberg formula for a single choice was used for calculation of the segregation frequency (SF) of the trait in families [11]:

$$SF = (r - n) / (s - n), \quad (1)$$

where r - the number of affected subjects in all siblings, n - the total number of probands, s - the total number of descendants in the sample.

The standard deviation was calculated as:

$$\sigma = \sqrt{SF(1-SF)/(s-n)} \quad (2)$$

To test the hypothesis about the type of inheritance, a confidence interval (CI) was calculated as:

$$CI = SF \pm 1.96 * \sigma \quad (3)$$

The hypothesis is accepted if the expected value of the segregation frequency (0.25 for recessive inheritance) falls into this interval.

Table 1

Data for segregation analysis in families of patients with signs of postlingual form of deafness/hearing loss

Sibship's size (s)	Nuclear families/ probands (a)	Affected siblings (r)		
		1	2	3
2	2	2	-	-
3	2	1	1	-
7	1	-	-	1
9	1	-	1	-
Total	6	3	4	3

All examinations provided in this study have been conducted after written consent of all participants or their parents. This study was approved by the local Biomedical Ethics Committee of Federal State Budgetary Scientific Institution "Yakut Science Centre of Complex Medical Problems", Yakutsk, Russia (Protocol No. 16, April 16, 2009).

Results and discussion

Audiological analysis

Among 72 examined individuals 35 subjects did not complain about HL and audiological examination has not revealed any objective otologic problems (normal hearing thresholds were detected). Unilateral or bilateral HL was observed in 37 individuals (the possible causes of HL are shown in Fig. 1). Among them, the pathology of the sound-conducting system and unilateral or bilateral

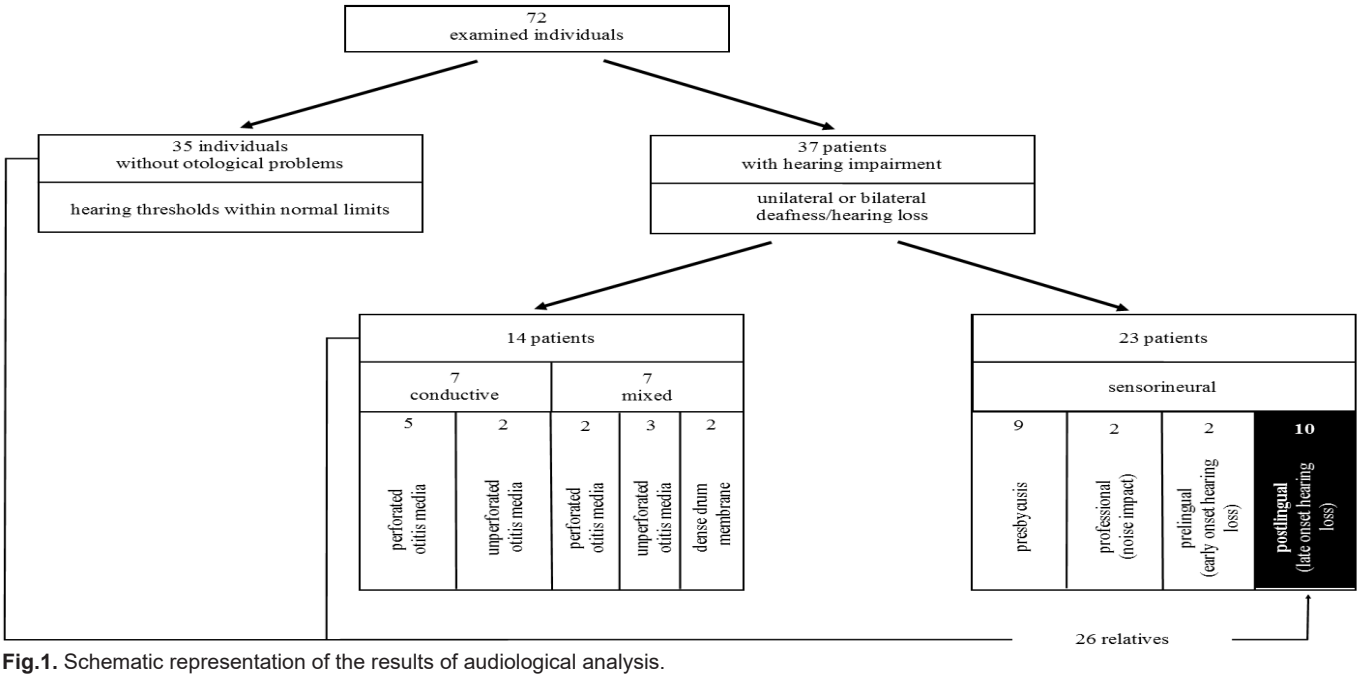

Fig.1. Schematic representation of the results of audiological analysis.

Note: 26 individuals from all examined subjects are relatives (of different degree of kinship) of proband A with postlingual form of deafness.

conductive or mixed HL were objectively detected in 14 patients. 23 patients had unilateral or bilateral sensorineural HL in the absence of a visual otological problem. Among these 23 patients with sensorineural HL, 12 patients had no opinion about causes of their HL, 2 patients supposed otitis media in childhood, 2 patients - possibly toxic exposure to antibiotics, 2 patients - head injury in childhood, 1 patient - hereditary HL, 1 patient - colds, 1 patient - age, 1 patient - industrial noise exposure. Among 23 patients with sensorineural HL, 9 patients showed signs of presbyacusis, 2 patients showed signs of noise exposure, 2 patients had a prelingual (before 1 year) HL, and 10 had signs of postlingual HL that had become noticeable at the age of 3 - 48 years. In total, as a result of the audiological analysis 10 patients (5 males and 5 females from 18 to 65 years old, whose average age at the time of the study was 43.3±13.7 years), showed the signs of postlingual form of HL which firstly detected by us in 3 patients (proband A, sibs A, proband B) (Table 2).

These patients were predominantly Evens (Evens - 8, Yakuts - 2) that probably indicates the ethnic specificity of investigated form of HL.

Clinical-genealogical analysis

Based on the initial analysis of personal data, we found that 72 examined individuals belonged to 24 families with 718 family members in total. Among them, 10 patients with signs of postlingual form of HL belonged to three extended pedigrees (355 relatives in total) (Fig. 2). At

Table 2

Characteristics of patients with signs of postlingual form of deafness/hearing loss

Patients	Code	Sex	GJB2 genotype	Ethnicity	Age	Diagnosis (otorhinolaryngological)	Onset of hearing loss	Subjective cause of hearing loss	Accompanying illnesses		Speech
									Otorhinolaryngological	Other	
1 Proband A	A - IV2	Female	c.[Wt];[Wt]	Even	19	Bilateral deafness	7	Not determined	Systemic hypoplasia of speech	Residual encephalopathy	Sign-dactylic language
2 Sibs A	A - IV1	Male	c.[79G>A];[Wt]	Even	20	Bilateral deafness	4	Not determined	Microtia and external auditory canal atresia	-	Sign-dactylic language
3	A - III7	Male	c.[Wt];[Wt]	Even	65	Bilateral deafness	7	Probably a trauma in childhood	Speech is absent	Glaucoma (Blindness)	Sign language
4	A - III13	Female	not investigated	Even	59	Bilateral deafness	9	Antibiotics	Dense eardrum; Chronic dystrophic rhinopharyngitis	Chronic gastritis	Sign-dactylic language
5 Proband B	A - III17	Male	not investigated	Even	57	Bilateral deafness	4	Not determined	Rinoskoliosis. Curved nasal septum	-	Sign language
6	A - III18	Male	not investigated	Even	29	Bilateral deafness	4	Colds; due to otitis media	Dense eardrum	Chronic gastritis; Neurodermatitis; Hepatitis B; Lumbar osteochondrosis	Sign-dactylic language
7	B - IV3	Male	not investigated	Yakut	38	Bilateral sensorineural hearing loss III degree	36	Not determined	Dense eardrum	Vegetative vascular dystonia according to the hypertonic type; Myopia	Intact
8	B - IV8	Female	not investigated	Yakut	42	Bilateral sensorineural hearing loss IV degree	30	Hereditary burdening	-	Chron. Pyelonephritis; Cholecystitis; Chronic pancreatitis	Intact
9	C - II7	Female	not investigated	Even	54	Bilateral sensorineural hearing loss III degree	8	Not determined	-	Arterial hypertension; Diabetes II; Psoriasis; Chronic pyelonephritis; Lumbar osteochondrosis; Goiter	Intact
10	C - II9	Female	not investigated	Even	50	Bilateral sensorineural hearing loss III degree	30	Not determined	-	Mental retardation	Intact
Total		Male - 5 (50%); Female - 5 (50%)	*GJB2-negative - 30%; not investigated - 70%*	Even - 8 (80%); Yakut - 2 (20%)	Middle age: 43,3± 13,7	Bilateral deafness - 6 (60%) Bilateral sensorineural hearing loss - 4 (40%)	Middle age: Juvenile - 5,6±1,9; Middle age: Mature - 36±6	Not determine - 6 (60%) Other - 4 (40%)	Three people report dense eardrum - 3 (30%)	-	Absent - 6 (60%); Intact - 4 (40%)

the first stage of pedigree's analysis, it was revealed that proband B (A-III17) was a paternal relative for proband A (A-IV2) and sibs A (A-IV1) (Fig. 2, A). It should be also noted that mothers (A-III1 and B-III1) of probands A-IV2 and B-IV3, respectively, are cousins (Fig. 2, A, B).

For segregation analysis we used the data on six nuclear families which included 10 patients with postlingual HL, their siblings and parents (Fig. 2). We assumed an autosomal recessive type of transmission of postlingual HL in these six nuclear families since all affected probands had hearing parents who did not complain about hearing impairment and also both deaf and hearing siblings (including cousins). To confirm or disprove the hypothesis about autosomal recessive type of inheritance of postlingual HL the segregation analysis was carried out in six siblings. Only siblings from each nuclear family were taken into account (without half-sibs and indirectly registered (on information from relatives) affected family members (Table 1). As a rule, the Weinberg proband method is used for calculation of the segregation frequency (SF) [2, 6-8, 11]. The essence of this method consists in calculating of the ratio of the total number of affected siblings to the total number of their unaffected siblings with correction for the number of probands (formula 1). The segregation frequency (SF), calculated from formula (1) with using the data from Table 1, was 0.20:

SF = (r – n) / (s – n) = 4/20 = 0.20

Subsequently, the obtained segregation frequency (0.20) was compared with the segregation frequency expected according to the recessive type of inheritance (SF_0 = 0.25). The confidence interval calculated using formulas (2) and (3) for the obtained estimation of the segregation frequency is equal 0.026 - 0.374. Theoretically expected value of segregation frequency (SF_0 = 0.25) falls into this interval that allows to accept the hypothesis about autosomal recessive type of inheritance of trait under study.

A common characteristic for all patients is later (in comparison with congenital HL) onset of this form of HL that occurred after the end of a sensitive period of speech development (after 4-5 years and older). In this period of sensory ontogeny, verbal speech is already formed, and the thinking development of young patients approximately corresponds to the level of their hearing peers [3]. However the earlier debuts of the HL cause the sooner complete degradation of verbal speech. HL in 6 patients from our sample occurred in juvenile age (on the average 5.6±1.9 years), and in 4 patients with verbal speech without any special distortions - at adulthood (on the average 36±6 years). Patients with different onset of HL are characterized by different degree of HL. Profound HL (up to deafness) (in the range from 98 to 108 dB in VFR) is common in patients with juvenile onset of HL while III-IV degree of HL (in the range from 58 to 75 dB in VFR) is detected in the patients having HL with onset in adulthood (Fig. 3). In addition, a comparative analysis of the audiometric data available for proband A-III2 for six years, from the first audiometry (at the age of 10 years) to the latest (at the age of 16 years), revealed significant deterioration of hearing (from II-III to IV degree of HL) that allowed us to suggest the progressive nature of this form of HL (Fig. 4). It is also interesting to note that the majority of patients (6 out of 10) could not determine the possible cause of their HL. They denied the hereditary cause despite the fact that some of them had deaf close relatives (Table 2). Most likely, this fact is due to that hearing problems of these patients began against a background of preserved hearing and developed speech. In addition, 3 cases of observation of a dense eardrum in adult patients are of interest since this peculiarity is mainly found only in children (Table 2).

To confirm the hereditary nature of this postlingual form of HL and ascertainment of its type of inheritance, a segregation analysis was carried out. The segregation frequency (SF), estimated using Weinberg's proband method, was 0.20 and matched the expected one for auto-

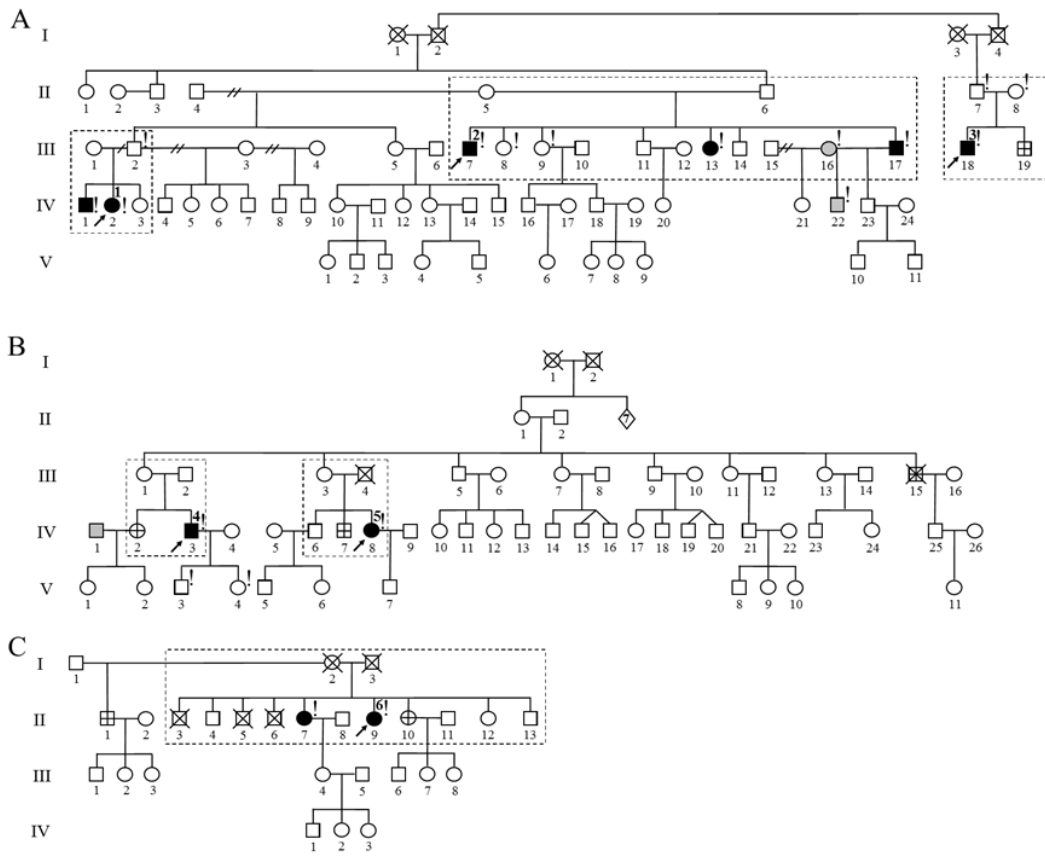

Fig.2. Pedigrees of probands with signs of postlingual form of hearing loss: A - pedigree of probands 1, 2 and 3, B - pedigree of probands 4 and 5, C - pedigree of proband 6.
Family members with signs of hereditary postlingual form of deafness are indicated by black symbols; family members with other forms of deafness/hearing loss (congenital or conductive) – by gray symbols; family members who have signs of postlingual hearing loss (on information from close relatives) - by plus into symbols; nuclear families are highlighted by dotted lines; probands in nuclear families are denoted by arrow and number on the top.

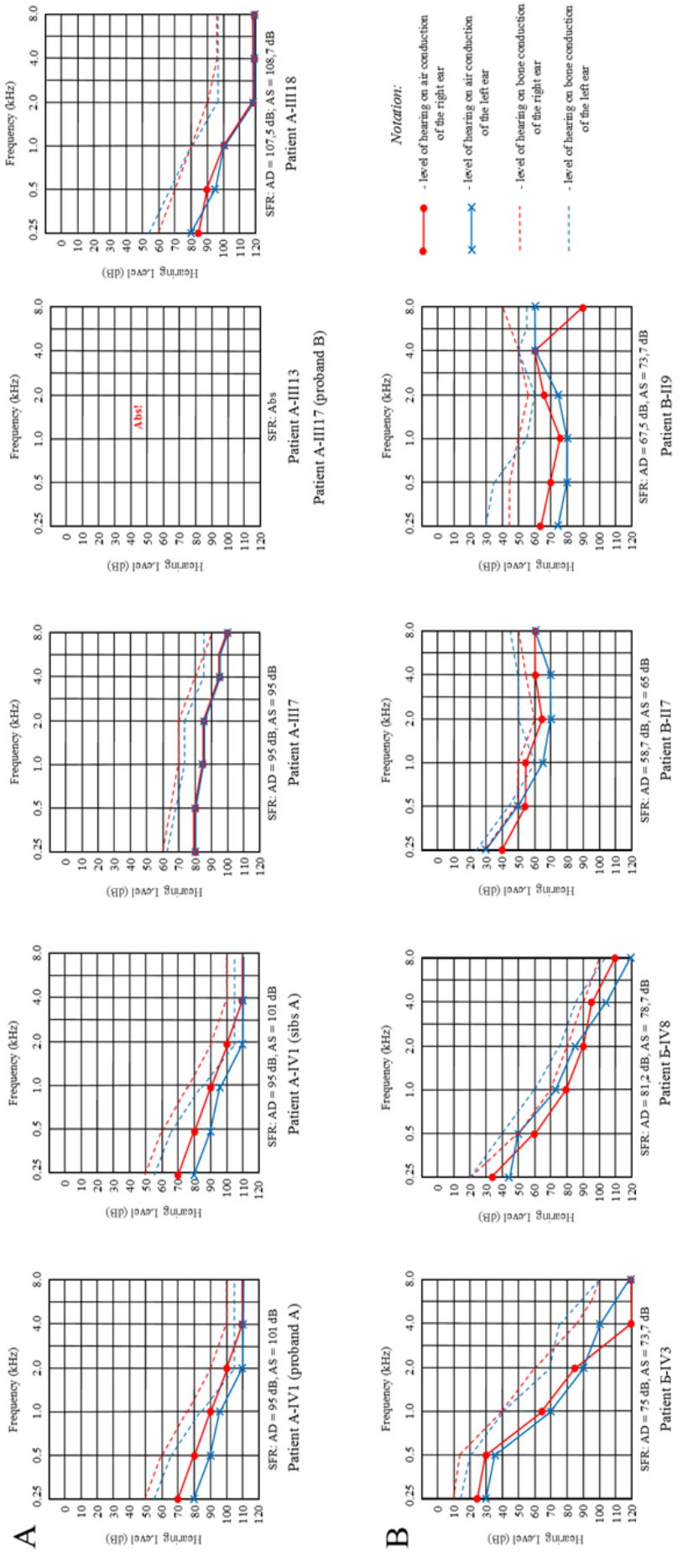

Fig.3. Audiograms of patients with signs of post-lingual form of deafness/hearing loss.
A - patients with juvenile onset of hearing loss;
B - patients with onset of hearing loss in adulthood.

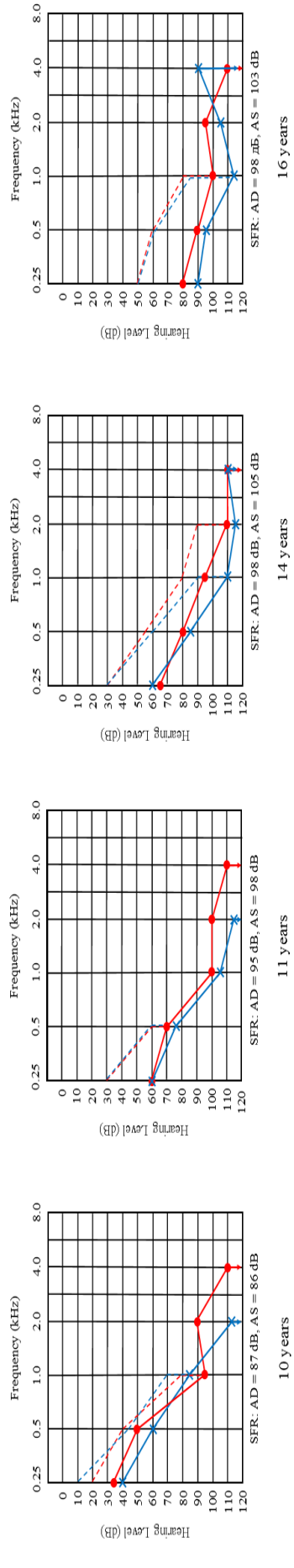

Fig.4. The progression of hearing loss by the example of audiograms of patient A-IV2 (proband A) with postlingual form of deafness.

somal recessive type of inheritance (SF_0 = 0.25) (CI 0.026 - 0.374).

Thus, we revealed 10 patients (mostly Evens) with postlingual bilateral sensorineural form of HL of unknown etiology which inheriting as autosomal recessive trait. Moreover, the distant relationship of the examined patients with postlingual HL living in two villages of the Eveno-Bytantaisky National District of the Sakha Republic may indicate the role of the founder effect in the local prevalence of this pathology.

We hope that the results obtained during this work will allow us not only to further reveal the molecular and genetic cause of postlingual form of HL in examined families, but also to uncover the mechanism of its accumulation in Eveno-Bytantaysky National District of Yakutia.

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The authors

Title of the manuscript **«Postlingual deafness in Eveno-Bytantaysky National District of the Sakha Republic (Yakutia): audiological and clinical-genealogical analysis»**

1. VERA G. PSHENNIKOVA - Ph.D., Head of laboratory, Yakut Scientific Center of Complex Medical Problems, 4, Sergelyakhskoe shosse, Yakutsk, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 32-19-81, e-mail: psennikovavera@mail.ru;

2. FEDOR M. TERYUTIN - Ph.D., Researcher, Yakut Scientific Center of Complex Medical Problems, 4, Sergelyakhskoe shosse, Yakutsk, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 32-19-81, e-mail: rest26@mail.ru;

3. NIKOLAY A. BARASHKOV - Ph.D., Head of laboratory, Yakut Scientific Center of Complex Medical Problems, 4, Sergelyakhskoe shosse, Yakutsk, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 32-19-81, e-mail: barashkov2004@mail.ru

4. NYURGUN N. GOTOVTSEV - Researcher, Yakut Scientific Center of Complex Medical Problems, 4, Sergelyakhskoe shosse, Yakutsk, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 32-19-81, e-mail: donzcrew@mail.ru

5. ALENA A. NIKANOROVA - Researcher, Yakut Scientific Center of Complex Medical Problems, 4, Sergelyakhskoe shosse, Yakutsk, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 32-19-81, e-mail: nikanorova.alena@mail.ru

6. AISEN V. SOLOV’EV - Postgraduate, Ammosov Institute of Natural Sciences, North-Eastern Federal University, 46, str Kulakovskogo, Yakutsk, Russian Federation, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 49-68-42, e-mail: nelloann@mail.ru

7. GEORGII P. ROMANOV - Postgraduate, Ammosov Institute of Natural Sciences, North-Eastern Federal University, 46, str Kulakovskogo, Yakutsk, Russian Federation, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 49-68-42,e-mail: gpromanov@gmail.com

8. OLGA L. POSUKH - Ph.D., Researcher, Federal Research Center Institute of Cytology and Genetics, Siberian Branch, Russian Academy of Sciences, 10, Ave. Lavrentieva,

Novosibirsk, 630090, Russian Federation. Phone: +7 (383) 363-49-63*3413, fax 8-(383) 333-12-78, e-mail posukh@bionet.nsc.ru

9. LILYA U. DZHEMILEVA - Ph.D., Researcher, Institute of Biochemistry and Genetics, Ufa Scientific Centre, Russian Academy of Sciences, 71, Octyabrya Ave., Ufa, Bashkortostan Republic, 450054, Russian Federation. Phone: +7 (3472) 35-60-88, e-mail: dzhemilev@mail.ru;

10. ELZA K. KHUSNUTDINOVA - Ph.D., Director, Institute of Biochemistry and Genetics, Ufa Scientific Centre, Russian Academy of Sciences, 71, Octyabrya Ave., Ufa, Bashkortostan Republic, 450054, Russian Federation. Phone: +7 (3472) 35-60-88, e-mail: e-mail: elkh@anrb.ru

11. SARDANA A. FEDOROVA - Ph.D., Head of Laboratory of Molecular Biology, Ammosov Institute of Natural Sciences, North-Eastern Federal University, 46, str Kulakovskogo, Yakutsk, Russian Federation, Sakha Republic, 677010, Russian Federation. Phone: +7 (4112) 49-68-42, e-mail: sardaanafedorova@mail.ru.

N.S. Arkhipova, E.K. Popova

ESTIMATION OF BODY MASS INDEX IN PATIENTS WITH CORONARY HEART DISEASE AGED OVER 60 IN THE CASE OF YAKUTIAN CITIZENS

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ABSTRACT

An analysis of the body mass index (BMI) revealed the ethnic, gender, age differences among the groups of hospital patients with coronary heart disease (CHD) aged over 60. Significantly higher value of BMI was identified in non-indigenous patients compared to Yakut group that was respective to the obesity of p <0,001. Maximum values of BMI were established in the older group aged between 60 and 74 years. The decrease in BMI can be observed with the age in the senile age group and more clearer dependency on age in the indigenous group. When comparing the BMI among the age groups: older, senile age and long-livers, the lower value of BMI was noted among long-livers (p <0,001). The obesity was identified significantly more often among women.

Keywords: body mass index, obesity, chronic coronary heart disease, non-indigenous, indigenous (Yakut), older, senile age, long-livers, Yakutia.

Introduction. Obesity is an independent risk factor of cardiovascular diseases, including arterial hypertension, coronary heart disease and heart failure, and is related to the increased risk of morbidity and mortality [4]. The prevalence of obesity increases with age [6] and there is enough evidence to consider the decrease in body mass as an important action preventing cardiovascular, endocrine and other diseases. The obesity is common among the patients with CHD and higher death rate is observed at values of BMI equivalent < 20 kg/m2 and ≥ 30 kg/m2 [5]. Epidemiological studies have proven the overweight and obesity to be the risk factors of increased human mortality [7].

The purpose of study - the examination of overweight and obesity prevalence on BMI in the group of patients with CHD aged 60 and older living in Republic of Sakha (Yakutia).

Material and research methods. The research included 354 patients under the age of 60 and older with verified diagnosis of CHD, who passed the examination and treatment in cardiological department of Geriatric center, Yakutsk city. The examined population consists of native group - Yakuts (100%) (n=205, average age 77,6±0,6) and European group – Russians (91,3%), Ukrainians, Tatars and Germans (8,7%) (n=149, average age 75,5±0,7). The studied groups were divided based on gender – men (n=187) and women (n=167), age – older (from 60 to 74 years old, n=154), senile (from 75 to 89 years old, n=149) and long-livers (90 years and older, n=51) (WHO, 1963). Body mass index (BMI) or Quetele II index was used to assess the ration of weight and height. BMI was calculated using the following formula: BMI (kg/m2) = weight (kg)/height (m2). Body weight was considered excessive with the BMI of ≥25 kg / m², and the presence of obesity was indicated with the BMI value of ≥30 kg / m² (European Guidelines for the III review, 2003).

The research was conducted as part of research work program "The contribution of metabolic syndrome to the development of coronary arteries atherosclerosis among Yakutian residents" of Yakut Science Center of Complex Medical Problems and was approved by the local committee on biomedical ethics at the YSC CMP. All the surveyed voluntarily gave the approval to take part in biomedical research.

Statistical processing of the results was performed using the methods of parametric and non-parametric statistics. Student's t-criterion was used to assess the intergroup differences in the values of indicators with the continuous distribution and Pearson's χ2-criterion was applied for the comparison of the frequency values. Methods of multiple intergroup differences, namely Kruskal – Wallis H-test and single-factor analysis of variance (ANOVA) were also used. The analysis of the dependence between the indicators was performed using the Pearson r-test, Spirmen's rs-test and the Pearson χ2-criterion. Statistical processing of the material was carried out on a computer using the standard software package of the statistical analysis (Statistica for Windows, v. 6.0). The critical level of validity of the null statistical hypothesis (about the absence of significant differences or factorial effects) was taken as 0.05.

Results and discussions. The probability of the development of cardiovascular disease increases with the rise of BMI [8]. Higher BMI was found in non-indigenous group compared with Yakut group (Table 1).

The estimation of BMI in patients (aged from 60 to 106 years old) revealed more frequent presence of obesity (p <0,001) in non-native patients while Yakut group had normal BMI (p <0,001) (Table 2).

An analysis of the dependence of BMI on age, taking into account ethnicity, was carried out in order to monitor the amount of body weight with age. It has been revealed that BMI decreases with age and most significantly traced in the Yakut group compared with non-indigenous people (r = –0.27, p <0.001 and r = –0.16, p = 0.058, respectively) (Figure 1).

The significant decrease in BMI was