DIAGNOSTIC AND TREATMENT METHODS

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ANALYSIS OF THE LEVEL OF THYROID HORMONES IN PATIENTS WITH HEARING DISORDERS IN THE REPUBLIC OF BURYATIA: SEARCH FOR PENDRED SYNDROME PHENOTYPES

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В статье представлены результаты диагностического поиска фенотипов, соответствующих клинической картине синдрома Пендреда (ceThe article presents the results of the diagnostic search of the hereditary autosomal recessive disease Pendred's syndrome (sensorineural deafness combined with thyroid disorders) in patients with hearing disorders in Buryatia using instrumental (threshold tone audiometry) and laboratory methods (ELISA analysis of FT3, FT4 and TSH). Threshold tonal audiometry and analysis of thyroid hormone levels were performed in 164 patients with hearing impairment. The analysis showed that 7.9% (13 out of 164 people) of patients with severe hearing loss and deafness can be assumed to have thyroid disorders (12 people – hypothyroidism, 1 person – hyperthyroidism). Overall, 7.3% of deaf patients with hypothyroidism (12 of 164) were formally consistent with the clinical features characteristic of Pendred's syndrome.

Keywords: Pendred's syndrome, hearing impairment, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), Buryatia.

Summary. The article presents the results of the diagnostic search of the hereditary autosomal recessive disease Pendred's syndrome (sensorineural deafness combined with thyroid disorders) in patients with hearing disorders in Buryatia using instrumental (threshold tone audiometry) and laboratory methods (ELISA analysis of FT3, FT4 and TSH). Threshold tonal audiometry and analysis of thyroid hormone levels were performed in 164 patients with hearing impairment. The analysis showed that 7.9% (13 out of 164 people) of patients with severe hearing loss and deafness can be assumed to have thyroid disorders (12 people – hypothyroidism, 1 person – hyperthyroidism). Overall, 7.3% of deaf patients with hypothyroidism (12 of 164) were formally consistent with the clinical features characteristic of Pendred's syndrome.

Keywords: Pendred's syndrome, hearing impairment, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), Buryatia

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Introduction. Congenital sensorineural deafness or severe hearing loss is registered with an average frequency of 1 per 1000 newborns [11]. About 20-30% of inherited hearing disorders are registered as part of various syndromes [12]. Finding out the etiology and correct diagnosis of syndromic forms of hearing loss and deafness are necessary conditions for proper consultation and choice of treatment tactics for such patients. One of the most common causes of syndromic hearing loss is Pendred's syndrome (OMIM #274600), which is observed in 10% of cases of congenital deafness [16, 20]. The prevalence of Pendred syndrome ranges from 7.5 to 10 cases per 100 000 people [8, 20]. Pendred syndrome is an autosomal recessive disease characterized by a combination of sensorineural hearing loss with or without hypothyroidism [20]. Given its autosomal recessive type of inheritance, the risk of inheritance from heterozygous parents is 25% [5, 20]. It is known that in most cases the syndrome is caused by biallelic mutations in the *SLC26A4* gene that lead to a defect in the pendrin protein [18]. The *SLC26A4* gene is located on chromosome 7 (7q22.3) and is expressed in many organs and tissues, including the inner ear, kidneys, thyroid, and bronchial epithelial cells [18, 20]. The product of the *SLC26A4* gene, the pendrin protein, is a multifunctional anion exchanger that has affinity for chloride, iodide, bicarbonate, and other anions [5, 20].

It should be noted that Pendred's syndrome does not always show abnormalities in the thyroid gland. Usually, they are observed in residents of regions with iodine deficiency. Iodine deficiency of various degrees of severity was detected almost throughout the Russian Federation [1]. In turn, the Republic of Buryatia belongs to the regions with the most tense situation in terms of the severity of natural iodine deficiency [1]. In such regions, there may be high rates of thyroid diseases.

In this regard, the purpose of this work is to analyze the level of thyroid hormones in patients with hearing disorders in the Republic of Buryatia, to search for phenotypes that correspond to the clinical picture of Pendred syndrome.

Materials and methods.

Patients

For this study, ELISA analysis of the level of thyroid hormones including free triiodothyronine (FT3), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) in patients with predominantly congenital pronounced hearing loss of un-

known etiology (n=164) was performed at the clinical and diagnostic laboratory of the N. A. Semashko Republican clinical hospital (Ulan-Ude, Republic of Buryatia). The age of the patients ranged from 18 to 82 years. The average age of women and men is 52.6 and 43.2 years, respectively (table 1). The share of Buryats and Russians by national composition was 47.5% and 46.3%, respectively. The majority of patients had bilateral deafness (70.7%) and early age (0-12 years) manifestations of hearing loss (97.5%). Individuals with a previously established diagnosis of thyroid pathology were not identified.

Threshold tonal audiometry. To determine the type and degree of hearing loss in patients, threshold tonal audiometry was performed using a portable audiometer "MAICO ST 20" (Germany) for air conduction at frequencies 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 kHz and bone conduction at frequencies 0.25, 0.5, 1.0, 4.0 kHz in increments of 5.0 dB. The degree of hearing loss was assessed by the hearing thresholds of the better-hearing ear in the speech frequency range 0.5, 1.0, 2.0, 4.0 kHz according to the international classification, according to which I degree of hearing loss corresponds to 26-40 dB, II degree – 41-55 dB, III degree – 56-70 dB, IV degree – 71-90 dB, deafness >90 dB.

ELISA-analysis of circulating FT3, FT4 and TSH. To determine the concentration of TSH, FT3 and FT4 circulating in the blood, the following enzyme immunoassay kits were used: T3 free-ELISA-BEST (JSC "Vector-best") (sensitivity: 0.5 pmol/ml; measurement range: 0-20 pmol/ml); T4 free-ELISA-BEST (JSC "Vector-best") (sensitivity: 0.5 pmol/ml; measurement range: 0-80 pmol/ml); TTG-ELISA-BEST (JSC "Vector-best") (sensitivity: 0.05 mU/l; measurement range: 0-16 mU/l). The measured concentrations of TSH, FT3 and FT4 were carried out on a microtiter plate reader VICTORX5 Multimode Plate Reader (Perkin Elmer Inc., USA). Reference values of TSH and thyroid hormone levels (FT3, FT4) are given in the explanation to table 2.

Results and discussion. This paper presents for the first time the results of a diagnostic search for phenotypes corresponding to the clinical picture of Pendred syndrome (sensorineural deafness combined with thyroid disorders), conducted using instrumental (threshold tone audiometry) and laboratory methods (ELISA analysis of FT3, FT4 and TSH) in patients with hearing disorders in the Republic of Buryatia. Of the 164 examined patients with hearing impairment, 13 had clinically significant deviations from the reference levels of TSH, FT3, and FT4. 4 patients were diagnosed with manifest hypothyroidism, 8 with subclinical hypothyroidism, and one patient with subclinical hyperthyroidism (table 2, fig. 1). The Type and degree of hearing loss in 13 patients with clinically significant abnormalities in thyroid hormone levels are shown in table 2.

Table1

Characteristics of a sample of hearing impaired patients from the Republic of Buryatia

Characteristics of the sample	n	%
Gender		
Female	96	58.5
Male	68	41.5
Nationality		
Buryat	78	47.6
Russians	76	46.3
Other nationality*	10	6.1
Place of residence		
Republic of Buryatia	112	68.3
Chita region	10	6.1
Irkutsk region	7	4.3
Other region	35	21.3
Degree of hearing loss		
Bilateral deafness	116	70.7
Grade IV bilateral sensorineural hearing loss	12	7.3
Sanseverina bilateral hearing loss of II-III degree	6	3.7
Bilateral, conductive hearing loss of II-III degree	1	0.6
Sensorineural hearing loss of II, III, IV degrees on the right/left, deafness on the right/left	26	15.9
Mixed hearing loss	3	1.8
Manifestation age of deafness/hearing loss		
0 - 12 years	160	97.6
18 – 30 years	2	1.2
Unknown	2	1.2
Heredity		
Unencumbered	123	75.0
Burdened	39	23.8
Unknown (orphan)	2	1.2
Total	164	100.0
Middle age		
Female	52.6 years	
Male	43.2 years	

Note: * Mongols, Evenks, Nanais, Uzbeks, Chuvash and individuals with mixed ethnical origin.

The decreased TSH with normal levels of FT3 and FT4 was observed in one patient (Russian, 82 years old), which corresponds to the preliminary diagnosis of subclinical hyperthyroidism. For Pendred's syndrome, hyperthyroidism is usually not characteristic. It is possible that the hyperthyroid state in this patient is associated with concomitant age-related changes and chronic diseases.

For the clinical picture of Pendred's syndrome, the state of hypothyroidism is more specific. So, in 4 patients, we observed an increased level of TSH, with a reduced FT4 and the normal level of FT3, which corresponds to the preliminary diagnosis-manifest (explicit) hypothyroidism. By ethnicity, these patients were Buryats, female, middle-aged and elderly. There was no information about the previously established diagnosis associated with thyroid pathology in the anamnesis.

Table2

Types and degrees of hearing loss in 13 patients with clinically significant abnormalities in thyroid hormone levels

№	Patient ID	Gender	Age	Nationality	Type / degree of hearing loss	Age onset of hearing loss	Heredity	TSH (mU/l)*	FT3 (pmol/ml)**	FT4 (pmol/ml)***
Overt hypothyroidism										
1	2119	female	57	Buryat	Bilateral deafness	0	burdened	**8.16**	5.17	**10.84**
2	2131	female	69	Buryat	Grade IV bilateral mixed hearing loss	30	-	**8.5**	4.82	**11.4**
3	2190	female	53	Buryat	Bilateral deafness	0	burdened	**5.52**	4.25	**10.49**
4	2240	female	56	Buryat	Bilateral deafness	0	-	**15.42**	3.46	**9.19**
Subclinical hypothyrosis										
5	2152	female	42	Buryat	Grade II sensorineural hearing loss on the right, deafness on the left	0	-	**5.12**	5.4	13.71
6	2178	female	40	Russian	Bilateral deafness	0	burdened	**4.85**	6.72	15.21
7	2199	female	75	Buryat	Bilateral deafness	unknown	-	**4.86**	4.6	13.9
8	2203	female	65	Russian	Grade III sensorineural hearing loss on the left, deafness on the right	2	-	**13.64**	4.36	12.22
9	2116	male	69	Russian	Grade IV bilateral sensorineural hearing loss	4	-	**4.68**	4.3	15.14
10	2187	male	38	Buryat	Bilateral deafness	0	-	**4.72**	5.23	17.97
11	2238	male	23	Buryat	sensenvral hearing loss of II-III degree	3	-	**8.11**	6.01	14.02
12	2241	male	23	Buryat	CAE ,Bilateral, conductive hearing loss of II degree on the right, III degree on the left	0	burdened	**5.61**	5.1	15.1
Subclinical hyperthyroidism										
13	2193	male	82	Russian	Bilateral deafness	3	-	**0.239**	5.09	14.12

Note: * - reference value of TSH level-0.24-4.3 mU/l; * * - FT3-3.1-6.8 pmol / ml; * * * - FT4-12-22 pmol/ml. Bold text indicates deviations from the reference values, dash - heredity is not burdened, CAE - Congenital Artesia of Ears

Subclinical hypothyroidism was detected in 8 patients (5 Buryats, 3 Russians). When divided by age, 5 patients belonged to the young age group, 3 patients to the elderly age group. The clinical characteristics of patients are presented in table 2. Thus, the proportion of cases of hypothyroidism among patients with hearing disorders in Buryatia corresponding to the clinical picture of Pendred's syndrome was 7.3% (67.7% - subclinical hypothyroidism, 33.3% - manifest hypothyroidism) (Fig. 1).

As a rule, patients with Pendred syndrome have a violation of iodine organification in the thyroid tissues, mediated by a violation of the normal conformation of the pendrin protein (anion exchanger) on the apical membrane of thyrocytes, which should transport iodine from the thyrocyte to the follicle. Apical iodine outflow is stimulated by TSH [17]. Under conditions of sufficient dietary iodide intake, most people with Pendred syndrome are clinically and biochemically euthyroid (thyroid hormone levels are in reference values) [4, 10, 12, 19], however, if dietary iodide is not sufficient, patients with Pendred syndrome may experience subclinical or manifest hypothyroidism [2, 9]. For example, patients with documented biallelic mutations in the *SLC26A4* gene from countries with high iodine intake, such as Japan and Korea are always euthyroid [3, 6, 13]. Currently, goiter is not considered a permanent feature in Pendred syndrome, since it is present in 60-80% of patients [14, 18]. It is possible that the apparent and subclinical hypothyroidism in 12 deaf patients is mediated by age or insufficient iodine intake, however, it is possible that the cause of hypothyroidism in these patients may be a defect in the pendrin protein, which disrupts the organization of iodine in thyroid tissues and causes Pendred syndrome. For this group of patients requires further studies using computed tomography of the temporal bone (syndrome-specific anomalies of the inner ear according to the type EVA / Mondini), perchlorate test (to determine the defect iodides organification of the thyroid gland) and molecular genetic studies to search for variants katatelnyh responsible for the development of Pendred syndrome (*SLC26A4* gene).

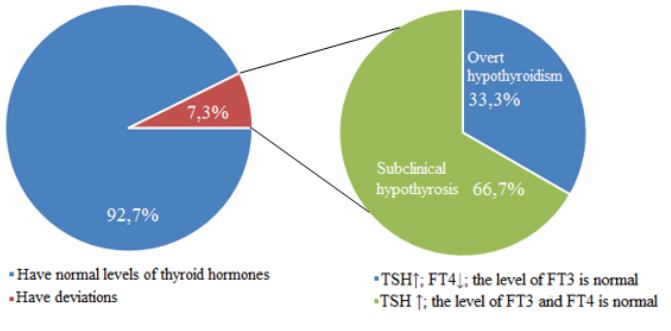

Figure 1. The proportion of cases of hypothyroidism among patients with hearing loss in the Republic of Buryatia (phenotypes of Pendred's syndrome).
Note: TSH – thyroid-stimulating hormone, FT3 – free triiodothyronine, FT4 – free thyroxine, ↑ - level above the reference values, ↓ - level below the reference values.

CONCLUSIONS

1. Analysis of the level of thyroid hormones in patients with hearing disorders from the Republic of Buryatia showed that 7.9% (13 out of 164) of patients can be assumed to have a deviation of the normal functioning of the thyroid gland;

2. Overall, 7.3% of deaf patients with hypothyroidism (12 out of 164) formally corresponded to the clinical features of Pendred's syndrome.

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