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Demographic, clinical and genetic characteristics of child Gaucher disease patients in Russia: pediatric register data

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Background: *Registers are an effective tool for tracing the dynamics of patients with rare pathologies.* ***Objective:*** *Our aim was to examine the demographic, clinical and genetic features of child Gaucher disease patients in Russia.* ***Methods:*** *We held a retrospective survey of the pediatric register data with regard to children suffering from Gaucher disease. The period of data accounting was from 2006 to 2016.* ***Results:*** *115 children with Gaucher disease aged from 3 months to 17 years (the median age of diagnosis is 5 years) were registered; 62 them (53.9%) are girls. The prevalence of the disease was 0.32 cases for 100,000 children. 95 (82.6%) children had 1st type of Gaucher disease, 6 (5.2%) — 2nd, and 1 (12.2%) — 3rd. Maximum morbidity was in Central (27; 23.5%) and Volga (27; 23.5%) Federal Districts; minimal — in the Far East (3; 2.6%). By the time of diagnosis all the patients were suffering from splengomegaly. The genotype and phenotype correlations in 90 children with Gaucher disease were as follows: in case of 1st type (n = 77), in 21 (27.3%) cases, the p.N370S/p.L444P genotype was set, in 12 (15.6%) — the p.N370S/other mutation; in case of 2nd and 3rd types, in 13 children with neuropathic forms, in 9 (62.9%) cases — the p.L444P/p.L444P, in 3 (231%) — the p.L444P/p. D409H. The rest of genotypes were presented by other mutations, 13 of which were revealed for the first time. The p.W223R (p.W184R) mutation is specific for Russian patients. Enzyme replacement therapy was carried out for 109 patients (94.8%): in 105 (96.3%) children (1st and 3rd types of Gaucher disease) with imiglucerase, in 4 (3.7%) children with 1st type — with velaglucerase alfa. Pathogenetic treatment stops the main symptoms in most patients.* ***Conclusion:*** *The pediatric Gaucher disease register allows to systemize the data concerning the disease course in children and optimizing the approaches to its monitoring in Russia.*
Keywords: *children, Gaucher disease, register, molecular-genetic diagnosis, mutations, imiglucerase, velaglucerase alfa.*

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RATIONALE

Gaucher's disease is the most common lysosomal storage diseases of more than 50 known nosologies of this group [1]. The disease is inherited in an autosomal recessive manner. The absence or decrease in activity of the lysosomal glucocerebrosidase enzyme, characteristic for this disease, leads to the accumulation of glycolipid substrate (glucocerebroside) in cells of the monocyte-macrophage series of the reticuloendothelial system with lesions of the spleen , liver, bone marrow, central nervous system (1-10% of cases) [1, 2]. Gaucher disease prevalence in different parts of the world varies between 1:40 000-100 000, but in some ethnic groups (e.g. among Ashkenazi Jews) the index values can be significantly higher [3, 4].

In 1991, on the initiative of a group of experts studying Gaucher disease (International Collaborative Gaucher Group, ICGG), an international register of patients was created. It covered more than 6,000 patients from 62 countries, including the adult cohort of patients from the Russian Federation (RF) [5], by 2012. The purpose of the register was study of the peculiarities of Gaucher disease to determine the volume of health care and long-term effects of enzyme replacement therapy, as well as the development of clinical guidelines for optimizing the monitoring and treatment of patients, improving their quality of life.

On the basis of international experience, in a number of countries, taking into account the diagnostic and economic capabilities of the state, national registers are established. They allow developing clinical guidelines for accounting and monitoring the state of patients [5-7]. The result of the database analysis was production of treatment goals, standards of diagnosis, monitoring and treatment of patients [5]. Evaluation of demographic, clinical and genetic parameters and the effectiveness of treatment within one country and in comparison with international data helps to optimize the tactics of long-term management of patients with Gaucher disease. In 2015, Russia established the register of adult patients with Gaucher disease based on FSBI "Hematology Research Center" of Russian Health ministry (Moscow).

The purpose of this study is to study demographic, clinical and genetic features of Gaucher disease in children with the help of Russian Pediatric register.

METHODS

Study design

A retrospective study of data on patients with Gaucher disease, included in a pediatric register.

Eligibility criteria

The register included data obtained from the extracts and medical conclusions of patients under the age of 18 years with proven by results of enzyme diagnostics and/or molecular-genetic research diagnosis of "Gaucher disease".

Terms of study

The study was conducted on the basis of the regenerative treatment of children with digestive system diseases department of the Scientific Center of Children’s Health (SCCH, Moscow) Scientific Research Institute of Pediatrics. Data of patients observed in the period from January 2006 to January 2016 was analyzed.

Methods of collecting information

Enzyme diagnostics to verify the diagnosis (determination of the activity of glucocerebrosidase and chitotriosidase) was carried out in laboratories of SCCH molecular

genetics and cell biology and of Medical Genetic Research Center (Moscow) hereditary metabolic diseases. Determination of mutations in the *GBA* gene (glucocerebrosidase gene) is carried out on the basis of the laboratory of SCCH molecular genetics and cell biology.

In order to create the "Register of children with Gaucher disease in the RF" database, employees of the department developed an electronic form of the individual patient card registration, which includes the following sections:

- "General information": personal data, address and contact information of the patient;
- "Diagnosis": data on the onset of the disease, diagnosis, methods of primary diagnostics and the type of disease, established according to the international classification;
- "Visits": according to the plan of the patient survey, this section includes a description of clinical symptoms, the results of physical examination (height, weight, liver and spleen size from the edge of the rib arc in centimeters) and laboratory-instrumental examinations (hemoglobin concentration, platelets number, linear dimensions liver and spleen according to ultrasound/ MRI and/or CT scan, bone mineral density according to osteodensitometry of lumbar spine);
- "Treatment": date of the start of therapy, the drug used for enzyme replacement therapy, the dosage, frequency and regularity of its administration to the patient, as well as methods of auxiliary treatment.

Demographic characteristics, used for description of patients, included gender, age of the disease debut, age of diagnosis, initiation of therapy, the debut of specific neurological symptoms and death. In addition, the ethnic groups, as well as the place of residence (federal district) were taken into account.

The clinical criteria of the disease included hepatosplenomegaly, bone pain and bone crises, hemorrhagic and asthenic syndromes, the central nervous system (CNS) lesion symptoms, delayed physical development, skin pigmentation.

Laboratory criteria included hemoglobin concentration and platelet number; glucocerebrosidase, chitotriosidase and liver transaminases activity; lipids, iron, and ferritin levels; prothrombin time, activated partial thromboplastin time.

Evaluation of the imiglucerase therapy effectiveness was carried out only in 35 patients with Gaucher disease of type 1, according to the inclusion criteria: regular treatment at a dose of 30-60 IU/kg for at least three years; the initial parameters of hemoglobin, platelets, liver and spleen size not corresponding the norm. The dynamics of the following indexes was evaluated: hemoglobin concentration and platelet number, liver and spleen linear dimensions (% of normal), bone mineral density (Z-score), physical development (the child's growth in percentiles). The degree of organs' enlargement was expressed as percentage of a normal linear parameters determined in accordance with the growth of the child [8]. In 17 primary patients with Gaucher disease of type 1 aged from 5 to 18 years, who had not received treatment previously, the quality of life was evaluated before and after 1 year from the start of pathogenetic therapy with the use of PedsQL (Pediatric Quality of Life) international pediatric questionnaire.

Register is created using the MySQL software (Oracle, USA).

Statistical analysis

Analysis of the results was performed using the IBM SPSS Statistics v. 21 (IBM Software, USA) software package. Description of quantitative data is in the form of absolute values, interests and the median (25th, 75th percentiles). Evaluation of differences is made simultaneously in three groups: quantitative traits were evaluated using the nonparametric variance analysis analogue — Kruskal–Wallis one-way analysis of variance (taking into account the difference of quantitative traits contrast values distribution from normal); qualitative (discrete) traits were evaluated using the chi-square test (with df = 2). If there were statistical

evidence of differences of groups, the subgroup statistical analysis using the Mann-Whitney test and χ^2 was carried out. Quantitative traits in the dependent (paired) samples were compared using the Wilcoxon test, qualitative traits — using the McNemar test. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Characteristics of patients

115 children with a diagnosis of "Gaucher disease", established on the basis of characteristic clinical picture, laboratory and instrumental examination data confirmed by the results of enzyme diagnostics and/or molecular genetic examination, were registered during the period from 2006 to 2016. 95 out of 115 children (82.6%) had the 1st type, 6 (5.2%) children had the 2nd type, and 14 (12.2%) had the 3rd type. The age of patients ranged from 3 months to 17 years 11 months (median of diagnosis age was 5 years), there were 53 boys (46.1%), and 62 girls (53.9%). Family history was burdened in 22 (19.1%) cases.

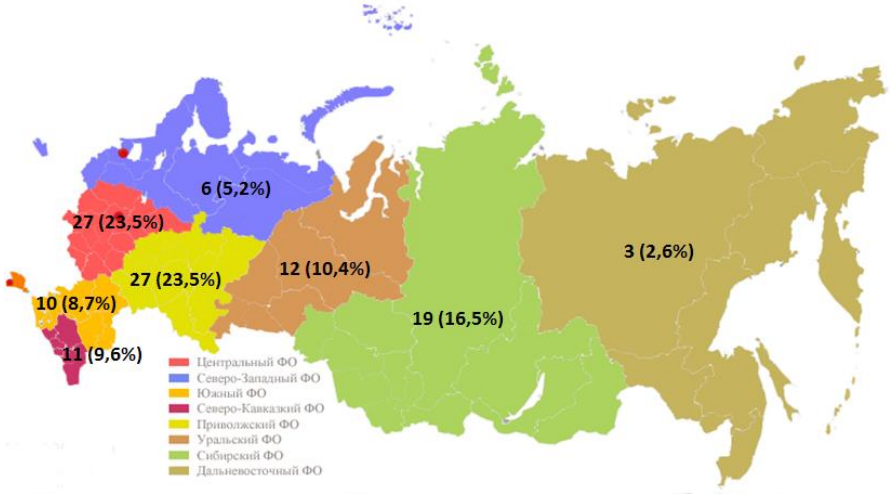
At the stage of diagnostic search, patients were counseled by doctors of at least three different specialties, including pediatrician (all children), hematologist (88; 76.5%), gastroenterologist (79; 68.7%), surgeon/orthopedist (27; 23.5 %), geneticist (25; 21.7%), neuropsychiatrist (23; 20.0%), otolaryngologist (11; 13.0%), endocrinologist (11; 9.6%), rheumatologist (2; 1.7 %), and dermatologist (2; 1.7%).

Epidemiology of Gaucher disease

During the period of data recording, the highest number of children diagnosed with "Gaucher disease" is registered in the Central (27; 23.5%) and Volga (27; 23.5%) Federal District, the lowest – in the Far Eastern (3; 2.6%) Federal District (***fig.1***).

For the calculation of the number of children with Gaucher disease, we used data of average child (under 18 years) population number at January 1, 2015 in each Federal District, received by the Federal Service of State Statistics [9]. To this date, according to SCCH data, 86 children with Gaucher disease were registered on the territory of the Russian Federation. Thus, the prevalence was 0.32 per 100 thousand of child population. The highest prevalence of the disease was registered in the North Caucasus and the Urals, the lowest — in the Far Eastern Federal District (***table 1***).

Fig. 1. Distribution of children with Gaucher disease by federal districts (data for 2006-2016).



Note: *(the regions in column from top to bottom) Central, Northwestern, Southern, North Caucasus, Volga, Ural, Siberian, Far Eastern*

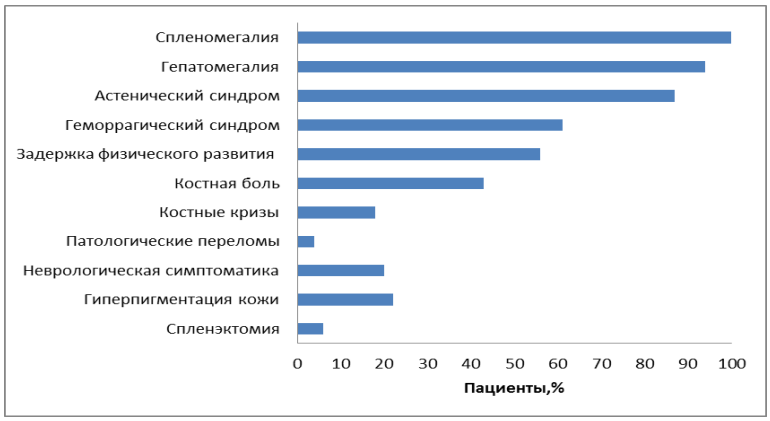
Table 1. The number of children with Gaucher disease in the territory of the Russian Federation (as of January 2015)

Federal district	Child population size	The number of cases, abs. (%)		The incidence per 100 thousand of child population
Volga	6213396	24 (25.3)		0.39
Central	6841417	18 (18.9)		0.26
Siberian	4312994	17 (17.9)		0.39
Uralian	2701259	11 (11.6)		0.41
North Caucasus	2736354	11 (11.6)		0.40
South	3237829	9 (9.5)		0.28
Northwestern	2513393	4 (4.2)		0.16
Far Eastern	1347722	1 (1.1)		0.07
Total	29904364	95 (100)		0.32

The clinical manifestations of Gaucher disease

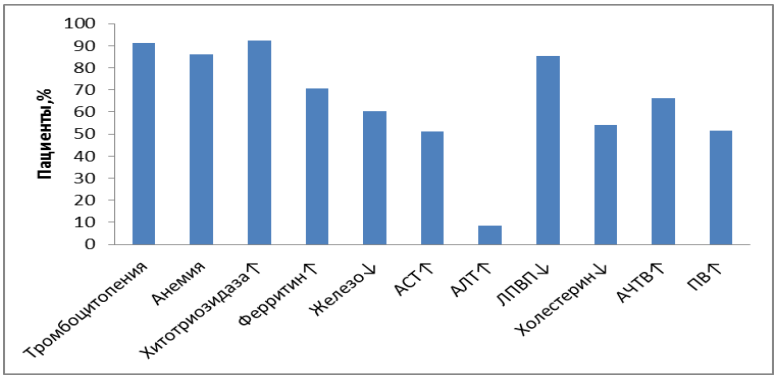
In most cases, clinical picture of Gaucher disease manifested by enlarged spleen and liver (***Fig. 2***). Among other laboratory markers, there are thrombocytopenia and anemia (***Fig. 3***). Characteristic for Gaucher disease changes in biochemical indicators were established: reduction of cholesterol, high-density lipoprotein and iron levels, and increased levels of AST and ferritin. Coagulogram revealed prolonged prothrombin and activated partial thromboplastin time.

Fig. 2. Clinical signs of Gaucher disease in children at the stage of diagnostics



Note: *(in column from top to bottom)* Splenomegaly, Hepatomegaly, Asthenic syndrome, Hemorrhagic syndrome, Delay of physical development, Bone pain, Bone crises, Pathologic fractures, Neurological symptoms, Dermatomelasma, Splenectomy

Fig. 3. Laboratory signs of Gaucher disease in children at the stage of diagnostics



Note. ↑ / ↓ - heightened/reduced level of laboratory marker.
(in line from left to right) Thrombocytopenia, Anemia, Chitotriosidase, Ferritin, Iron, Aspartate aminotransferase, Alanine aminotransferase, HDL, Cholesterol, APTT, PT

Medical errors at the stage of diagnosis

During the differential diagnostic search, in the majority of children with Gaucher were misdiagnosed and assigned to the wrong treatment. So, in 35 (30.4%) children, decrease in hemoglobin concentration was regarded as a manifestation of iron deficiency anemia, and therefore iron supplements have been recommended for the treatment — without effect. In 11 (9.6%) children, bone crises were treated as osteomyelitis, so surgical treatment envisaged antibacterial support. The presence of hepatosplenomegaly and/or pancytopenia in 58 (50.4%) children was seen as hematologic malignancies. Cirrhosis of the liver with portal hypertension was wrongly diagnosed in 15 (13.0%) children, hepatitis of infectious etiology — in 49 (42.6%). Most patients (74; 64.3%) underwent the bone marrow puncture, and in 12 (10.4%) cases — repeatedly. Due to the unknown cause and significant severity of splenomegaly, 6 (5.2%) patients underwent splenectomy domiciliary by mistake.

Features of clinical types of Gaucher disease

Analysis of the distribution of children in groups by gender indicated a higher proportion of girls among patients with neuronopathic Gaucher disease forms compared with not neuronopathic 1st type ($p = 0{,}038$). In the clinical picture of Gaucher disease of type 1 (not neuronopathic form of disease), hematologic and visceral symptoms, coupled with bone manifestations ($p^{types\ 1/2} = 0.040$), determining the severity of the disease, prevails. On the opposite, in neuronopathic forms of Gaucher disease (2nd and third 3rd types of the disease), the severity of disease is caused by central nervous system lesions ($p^{1/2}$ and $p^{1/3} = 0.010$) (***table 2***). Later debut ($p^{1/2} < 0.001$; $p^{1/3} = 0.012$) and maximum period of observation from the moment of manifestation until the diagnosis are marked in the 1st type of Gaucher disease ($p^{1/2}$ and $p^{1/3} < 0{,}001$) **—** 40 months (26; 58). Therefore the prescription of therapy was delayed by comparison with the 3rd type of Gaucher disease ($p = 0.001$). In Gaucher disease of type 2, there are the early debut ($p^{2/3} < 0.001$) and diagnosis ($p^{2/3} < 0.001$) due to severe neurological symptoms, noted from the first months of life. The presence of aspiration syndrome predetermined the patients' death from respiratory failure before the age of 1 year. Gaucher disease of type 3 is characterized by a combination of symptoms of 1st and 2nd types with delayed debut of neurological symptoms ($p^{2/3} = 0.001$). The early and most characteristic manifestation of CNS involvement in this type was oculomotor apraxia (in 14, 100%), which debuted at the age of 38 months (21; 113).

Table 2. Demographic, molecular-genetic, clinical and laboratory characteristics of 1-3 types of Gaucher disease in children

Indicators	Types of Gaucher disease			p
	1st n = 95	2nd n = 6	3rd n = 14	
Demographic indicators				
Girls abs. (%)	47 (49)	5 (83)	10 (71)	0,100
Age of the disease debut (Me), month	32.0 (13.0; 62.0)	1.0 (0.8, 4.0)	12.0 (8.0; 28.5)	0,001
Age of diagnosis (Me), month	72 (39; 120)	7.0 (5.3; 8.5)	21.5 (15.5; 35.0)	0,001
Age of onset of therapy (Me), month	89 (52; 131)	-	23 (18; 47)	-
Age of death (Me), month	-	9 (3; 10)	-	-
Age of debut of neurological symptoms (Me), month	-	2.0 (0,8; 3,3)	38 (21; 113)	-
Federal District with a maximum incidence	Central and Volga	Far Eastern	North Caucasus	-
***Molecular genetic indicators* ***				
Genotyped, n (%)	77/95 (81)			
p.N370S/p.L444P	21/77 (27)			
p.N370S/p.W184R	10/77 (13)			
p.N370S/p.N370S	2/77 (3)			
p.L444P/p.L444P	2/77 (3)	2/6 (33) 0 (0)	11/14 (79)	
p.L444P/p.D409H	0/77 (0)	0 (0)	0 (0)	0,023
p.N370S/other allele	31/77 (40)	0 (0)	0 (0)	0.192
p.L444P/other allele	8/77 (10)	2/2 (100)	0 (0)	0.731
Other genotypes	3/77 (4)	0 (0)	7/11 (64)	0,010
		0 (0)	3/11 (27)	0,002
		0 (0)	0 (0)	0,002
		0 (0)	0 (0)	0.271
		0 (0)	1/11 (9)	0.470
Clinical and laboratory and instrumental indicators at the time of diagnosis				
Anemia, abs. (%) Hemoglobin (Me), g/l	82/95 (86) 104 (93; 113)	5/6 (83) 105 (99; 114)	12/14 (86) 91 (80; 102)	0,9750,097
Thrombocytopenia, abs. (%) Platelets	86/95	6/6	13/14 (93) 96 (75;	0,7500,867

(Me), 10^9/l	(91) 93 (65; 123)	(100) 97 (56; 120)	129)	
β-D-glucosidase (Me) nM/mg / hr	1.20 (0.60; 1.90)	0.98 (0.47; 2.74)	1.35 (1.00; 1.93)	0.869
Chitotriosidase (Me) nM/ml/hr (N = 90/6/10)	9386 (5113; 14011)	15540 (11,850; 22,620)	8262 (5077, 13, 314)	0,150
Delay of physical development, abs. (%)	30/73 (41)	6/6 (100)	10/14 (71)	0,010
Splenomegaly, abs. (%) The increase from the norm (Me): •Length •width	95/95 (100) 79 (53; 113) 55 (32; 92)	6/6 (100) 97 (73; 107) 78 (51; 101)	14/14 (100) 115 (73; 147) 73 (35; 117)	- 0,0730,298
Splenectomy, abs. (%)	6 (6)	0 (0)	0 (0)	0,500
Hepatomegaly, abs. (%) The increase from the norm (Me): •Right lobe •left lobe	89/95 (94) 22 (12; 31) 0 (0 3)	6/6 (100) 33 (17; 45), 35 (23, 54)	14/14 (100) 38 (28; 46) 8 (0; 22)	0,500 0.008 <0.001
Bone pain abs. (%)	41 (43)	0 (0)	3 (21)	0,038
Bone crises, abs. (%)	17 (18)	0 (0)	0 (0)	0,100
Bone mineral density (Z-score, Me)	- 0.9 (- 1.7, - 0.3)	-	-0.9 (- 1.3, - 0.6)	-
Specific CNS symptoms, abs. (%)	0 (0)	6 (100)	14 (100)	0.01

Note. * - Statistical analysis included comparison of groups with 1st and 2/3 types of Gaucher disease. CNS - central nervous system.

The activity of enzyme markers (glucocerebrosidase and chitotriosidase) did not differ in the single-step group analysis, however, significantly higher value of chitotriosidase was received when compared between the 2nd and 3rd types of Gaucher disease (p = 0.020). Median of hemoglobin concentration and platelet number did not differ between patients groups. There were some features of parenchymal organs lesions: a marked increase in the length and width of the spleen was the same for different types of Gaucher disease. However, it was noted that the degree of increase of right ($p^{1/3}$ = 0,003) and left ($p^{1/2}$ = 0,002; $p^{1/3}$ = 0,006) liver lobes is more expressed largely in neuronopathic forms than in neuronopathic form, wherein in the 2nd type of Gaucher disease, the degree of the left liver lobe increase even prevails that of the right liver lobe. Splenectomy was in history of patients with Gaucher disease of type 1 only, with a median age of surgery 93 months (67; 111). The delay of physical development occurred more often in neuronopathic forms (2nd and 3rd types) of Gaucher disease compared to the 1st type ($p^{1/2}$ = 0,007; $p^{1/3}$ = 0,036). The indicator of bone mineral density (Z-score) did not differ between the 1st and 3rd types of Gaucher disease (p = 0.931).

The results of the molecular genetic analysis

Molecular genetic analysis was performed in 90 (78.3%) patients. 180 mutant alleles have been identified, of which 13 are new (not previously described) in 15 (16.7%) children. Among the new — 11 missense mutations: *p.Ser81Arg (c.243T>A), p.Gln115Arg (c.344A>G), p.Thr125Ile (c.375C>T), p.Arg209Cys (c.625C>G), p.Phe298Val (c.892T>G), p.Ala308Pro (c.922G>C), p.Phe386Cys (c.1157T>G), p.Ala423Asp (c.1268C>A), p.Leu459Arg (c.1376T>G), p.His461Tyr (c.1381C>T), p.Ile347Phe (c.1039A>T*; one nonsense mutation - *p.Tyr61X (c.183C>A)* and one deletion — *p.Ile158_Pro161del (c.474-485del)*. In 12 (13.3%) cases, structural rearrangements of *GBA* gene were revealed. The most common mutations were *p.N370S* and *p.L444P*, third in frequency of occurrence was *p.W184R* mutation, detected in 10 (11.1%) children (***table 3***).

Table 3. Mutations in the *GBA* gene, encoding glucocerebrosidase

mutation *	**n = 90, abs. (%)**	**Gaucher disease type**
p.N409S (p.N370S)	64 (71)	1
p.L483P (p.L444P)	42 (47)	1, 2, 3
p.W223R (p.W184R)	10 (11)	1
p.D448H (p.D409H)	3 (3)	3
Rare mutations	19 (21)	13
New mutations **	15 (17)	1
Structural reorganization	12 (13)	1

Note. * — Before the brackets there is the nomenclature recommended by the Human Genome Variation Society (HGVS) and a number of top-rated journals, in brackets — the traditional nomenclature; ** - Mutations that were not previously described in the literature.

Genotype and phenotype correlation are established: *p.N370S* mutation is typical for not neuronopathic form of Gaucher disease even in the heterozygous state; *p.L444P* mutation in the homozygous state is associated with damage to the nervous system and is characteristic for neuronopathic forms of Gaucher disease; *p.D409H* mutation is found only in children with Gaucher disease of type 3, *p.W184R* mutation — only with Gaucher disease of type 1. The most common genotypes in not neuronopathic form of the disease were *p.N370S/other mutation, p.N370S/p.L444P*, *p.N370S/p.W184R,* in neuronopathic forms **—** *p.L444P/p.L444P* и *p.L444P/p.D409H* (see table 2).

Treatment of children with Gaucher disease

According to the register data, the underlying disease treatment receive all patients with Gaucher disease, except for children with acute neuronopathic form (type 2)[*]. Median age at start of treatment was 75 months (35; 127). Enzyme replacement therapy was conducted using two registered in Russian Federation drugs for Gaucher disease treatment in children – imiglucerase and velaglucerase alpha. The effectiveness of treatment was assessed on the basis of relief of hematological, visceral and bone manifestations of the disease, as well as changes in patients' quality of life according to the result of the survey using pediatric questionnaire PedsQL.

[*] In the 2nd type of Gaucher disease, treatment is not prescribed because of the inefficiency and inconvenience of therapy

In 35 patients with Gaucher disease of type 1, on the background of the three-year imiglucerase therapy at a dose of 30-60 IU/kg intravenously every 2 weeks, there was an increase in hemoglobin concentration from 105 (99; 113) to 126 (123; 134) g/l (p <0,001) and the number of platelets from 86 (59; 105) to 158 (148; 210) × 10^9/l (p <0,001). There was also a reduction of linear dimensions of length and width of the spleen by 54 (47, 51) and 35% (31; 52), respectively (p <0,001); the right lobe of the liver reduction by 15% (in 9, 13%; p <0,001); reduction in the number of children with growth retardation from 14 (40%) to 2 (6%) (p <0,001), an increase in bone mineral density (Z-score) from -1.3 (-1.7, -0.5) to -0.3 (-0.6; 0.2) (p <0.001). In assessing the quality of life in 17 primary patients (previously untreated with enzyme replacement therapy) after 1 year from the start of pathogenetic therapy, there was an improvement of parameters of physical, emotional and social functioning, as well as improvement of the overall quality of life assessment (***table 4***).

Table 4. Dynamics of parameters of children with Gaucher disease quality of life between the ages of 5 and 18 years after 12 months from the start of enzyme replacement imiglucerase therapy (n = 17)

Parameter	According to the children		p	According to the parents		p
	Prior to ERT	After ERT		Prior to ERT	After ERT	
Physical functioning	62 (53; 83)	81 (65; 93)	0,001	62 (50; 77)	71 (66; 87)	0,002
Emotional functioning	70 (60; 83)	75 (68; 83)	0.01	50 (48; 68)	60 (53; 78)	0,042
Social functioning	80 (73; 95)	90 (83; 95)	0,035	70 (55; 93)	80 (73; 95)	0,001
Functioning in the kindergarten / school	70 (58; 75)	70 (60; 80)	0,625	50 (43; 66)	60 (50; 68)	0.928
Overall score	75 (62; 78)	79 (71; 87)	0,002	60 (52; 77)	67 (63; 80)	0,002

Note. ERT - enzyme replacement therapy.

DISCUSSION

Summary of key findings

The results of the analysis of demographic, clinical and genetic features of Gaucher disease in children, made on the basis of the pediatric register data, are presented for the first time. It was found that, despite the existence of certain regularities between the genotype and the nature of the disease clinical manifestations, even in the presence of the same mutations in different individuals, Gaucher disease is characterized by a wide spectrum of symptoms, requiring from the clinician their timely detection and evaluation. Diagnosis and appointment of a regular enzyme replacement therapy in the early stages will help to prevent complications, reduce the number of unwarranted procedures and appointments and thus to achieve the key objectives of the treatment.

Key findings discussion

Historically, the Gaucher disease classification is based on the presence or absence of specific neurological symptoms and the rate of its progression [10]. All patients were divided into 3 groups according to the types of Gaucher disease: type 1 — not neuronopathic, type 2 —

acute neuronopathic, type 3 — chronic neuronopathic. The obtained data comply with international statistical indicators, according to which, the most common is the 1st type of Gaucher disease — it takes about 80-90% of the total number of cases of the disease, type 2 takess about 1-5%, type 3 — 5-10% [10, 11].

Children with not neuronopathic form of Gaucher disease (Type 1) did not differ by gender. Among patients with neuronopathic forms (2nd and 3rd type), prevalence of the female gender is stated, which may be caused by features of the children distribution by gender in federal districts with the greatest their detection — the Far Eastern and the North Caucasus. North Caucasus (peoples of Dagestan, Chechens, Ingush) and Turk (Turks, Bashkirs, Azeri) ethnic groups prevailed. The obtained result is presumably caused by the peculiarities of the geographical migration of Gaucher disease, cumulative effect of the gene pool, and a high frequency of closely related marriages in these populations.

The prevalence of Gaucher disease in the Russian children calculated by us did not conform to international data due to certain limitations of the study. The obtained result reflects more the number of children with Gaucher disease in different federal districts and generally in Russia, than the true prevalence of the disease. The difficulty of obtaining specific laboratory verification of Gaucher disease in remote administrative districts, lack of awareness of doctors and the public about rare hereditary metabolic diseases and often low qualification of histologists, leading to an underestimation of the clinical symptoms and laboratory and instrumental indexes may possibly affect the low detectability.

Due to the high variety of clinical manifestations of Gaucher disease, its diagnosis requires knowledge of key clinical symptoms. Phenotypic heterogeneity of manifestations at the Gaucher disease debut causes primary uptake of the patient to specialists in different fields. Our results are comparable with international and show a preferential emptive counseling of children by pediatrician and hematologist, which is probably caused by the manifestation of the disease in the form of hematologic and visceral manifestations [12].

The high frequency of misdiagnosis and wrong manipulations in the primary stage by various specialists requires to raise awareness about this disease among physicians. The main clinical and laboratory manifestations of Gaucher disease in children in the Russian Federation were consistent with the generally known data [13-15]. Knowledge of such diagnostic criteria for the disease as spleno- and hepatomegaly, anemia and thrombocytopenia, may assist in the timely diagnosis [14]. The presence of splenectomy in history of a number of patients with Gaucher disease was associated with mistakes in diagnosis and the lack of effective treatment at the time of detection of symptoms. At the present stage due to the availability of effective treatment, the splenectomy for the purpose of cytopenic syndrome and abdominal discomfort relief is not justified and can be applied only in life-threatening cases [16]. Early diagnosis in the 2nd and 3rd types could have been caused by the presence of neurological symptoms in conjunction with the more pronounced, compared to Gaucher disease of type 1, degree of hepatosplenomegaly.

When studying geno- and phenotypic correlation, it was found that *p.N370S* mutation, even in the heterozygous condition, is associated with not neuronopathic form of Gaucher disease; *p.L444P* mutation in the homozygous state is associated with lesions of the nervous system and is characteristic for the 2nd and 3rd types of Gaucher disease; *p.D409H* mutation occurs in the 3rd type of Gaucher disease and, according to the literature, in the homozygous state is associated with cardiac disease and vascular calcification [17]. Specifically for Russian population of patients, in contrast to other countries, was the third by frequency of occurrence *p.W184R* mutation associated with the 1st type of Gaucher disease. Detection of the *p.L444P/p.L444P* genotype in two children with the 1st type of Gaucher disease, given their young age (1 and 3 years) and the lack of signs of CNS involvement, gives the opportunity to suppose subsequent development of the chronic neuronopathic form (3rd type) manifestations, which requires dynamic monitoring under the supervision of a neurologist. The findings are consistent with the analysis of mutations in European populations of patients of not Ashkenazi origin [17, 18].

In the early 90-ies of XX century, an effective pathogenetic enzyme replacement therapy was developed, which now is the "gold standard" of treatment for patients with Gaucher disease and which relieves the main symptoms of the disease [19]. Children with Gaucher disease were treated mostly with imiglucerase, because of its earlier registration in the Russian Federation and the restrictions on the use of veloglucerase alpha in children under 2 years of age and patients with Gaucher disease of type 3. According to international data, when using as an enzyme replacement therapy for Gaucher disease of type 1 of both imiglucerase and velaglucerase alpha, there was equal achievement of the key goals of therapy — relief of anemia, thrombocytopenia, hepatosplenimegaly, and bone crises and improvement in physical development, bone mineral density and quality of patients' life [19, 20]. Results of the effectiveness of imiglucerase therapy evaluation in 35 children with Gaucher disease of type 1, obtained by us, were comparable to foreign research data [19, 20].

Limitations of the study

In the calculation we take into account the prevalence of children with Gaucher disease, observed only in NTSZD, due to a lack of data on the total number of pediatric patients with this pathology cohort in the Russian Federation due to the failure to conduct neonatal screening and non-inclusion of adult cohorts. The calculation excluded patients that by 1 January 2015 was already 18 years of age, and children with Gaucher disease type 2, who died at the time of the survey. Molecular genetic analysis of the gene *GBA* was conducted only 90 children with Gaucher's disease due to the lack of biological material from 25 patients to the beginning of the study.

CONCLUSION

Register of patients with Gaucher disease is an important tool in the monitoring system, which allows to analyze the epidemiological, demographic and geno- and phenotypic peculiarities of the disease in children and to determine the scope of activities required to improve the efficiency of its diagnosis, monitoring and treatment. According to obtained data, it is possible to conclude that there is the lack of detection of Gaucher disease in children in the Russian Federation, which requires the organization of educational activities in the field of orphan pathology among physicians and the public and increase the availability of specialized diagnostic laboratories. Gaucher disease in children is characterized by polymorphism of clinical symptoms; however, knowledge of the key symptoms of the disease will help the clinician in a timely diagnosis. Determination of glucocerebrosidase gene mutations is expedient for optimization of the monitoring of patients with genotypes, characteristic for neuronopathic forms of Gaucher disease, and for more accurate prognosis of the disease in a particular patient. Timely administred enzyme replacement imiglucerase therapy with adequate dosing regimen allows achieving the key objectives of treatment in 3 years in most children with Gaucher disease of type 1.

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The authors have declared they have no competing interests to disclose.

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