ORPHAN DISEASES IN THE REPUBLIC OF NORTH OSSETIA–ALANIA: STRUCTURE, POPULATION GENETIC FEATURES, ISSUES AND PROSPECTS

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Currently, there are more than 8000–10000 rare disease (RDs), among which 75–80% are hereditary. In the Russian Federation (RF), patients are provided medical care in accordance with two lists: 17 chronic progressive and life-threatening diseases (RLTDs) and 14 high-cost nosologies (HCNs). The study was aimed to assess the range, prevalence, and genetic epidemiological characteristics of the RDs from the lists of RLTDs and HCNs in the Republic of North Ossetia–Alania and RF in general. We determined the number of patients from the RLTD (a total of 18,744 people in the RF, among them 8713 children; 129 and 42 people, respectively, in the Republic of North Ossetia–Alania) and HCN (28727 people/13454 children in the RF; 554 and 64 in the Republic of North Ossetia–Alania) lists and calculated the prevalence per 100,000 population. The global prevalence of RDs was estimated using the Orphanet database. The average prevalence of RLTDs in the whole population of the RF was 11.51 cases and that among children was 25.08. Similar data were obtained for the Republic of North Ossetia–Alania (19.38 and 29.44, respectively). It was found that idiopathic thrombocytopenic purpura, disorder of the complement system, maple syrup urine disease, porphyria were more common in the Republic of North Ossetia–Alania than in the RF in general, while galactosemia was less common. The analysis of disorders from the RLTD list has shown lower prevalence of hemophilia and pituitary dwarfism in the Republic of North Ossetia–Alania compared to the RF and Orphanet, along with the higher prevalence of type VI mucopolysaccharidosis, hemolytic uremic syndrome, and systemic juvenile rheumatoid arthritis. In the Republic of North Ossetia–Alania, the features of the range of genetic variation in the genes *PAH* (phenylketonuria) and *CFTR* (cystic fibrosis) have been identified. Thus, assessment of the RD prevalence in the regions is important and essential for raising awareness of medical personnel, as well as for expansion and improvement of medical care provision to patients with RLTDs and HCNs.

Keywords: rare (orphan) diseases, chronic progressive and life-threatening diseases, high-cost nosologies, prevalence, Republic of North Ossetia–Alania, Russian Federation

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ОРФАННАЯ ПАТОЛОГИЯ В РЕСПУБЛИКЕ СЕВЕРНАЯ ОСЕТИЯ – АЛАНИЯ: СТРУКТУРА, ПОПУЛЯЦИОННО-ГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ, ПРОБЛЕМЫ И ПЕРСПЕКТИВЫ

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В настоящее время известно более 8000–10000 редких болезней (РБ), 75–80% которых наследственные. В Российской Федерации (РФ) пациентам оказывают медицинскую помощь по двум перечням: 17 хронических прогрессирующих и жизнеугрожающих заболеваний (РЖЗ) и 14 высокозатратных нозологий (ВЗН). Целью исследования было оценить спектр, распространенность и генетико-эпидемиологические характеристики РБ из перечней РЖЗ и ВЗН в Республике Северная Осетия — Алания (РСОА) и в РФ в целом. Определено число пациентов из перечней РЖЗ (по РФ всего 18 744 человек, в т. ч. 8713 детей; по РСОА — 129 и 42 соответственно) и ВЗН (по РФ — 28727 /13454 детей; по РСОА — 554 и 64) и рассчитана распространенность на 100 000 человек. Распространенность РБ в мире оценивали по базе Orphanet. Средняя распространенность заболеваний их группы РЖЗ среди всего населения РФ составила 11,51 случаев и среди детей — 25,08. Схожие данные получены для РСОА (19,38 и 29,44 соответственно). Выявлено, что идиопатическая тромбоцитопеническая пурпура, дефект в системе комплемента, болезнь «кленового сиропа», порфирия в РСОА встречаются чаще, чем в среднем по РФ, а галактоземия — реже. Анализ заболеваний из перечня ВЗН показал более низкую по сравнению с РФ и Orphanet распространенность гемофилии и гипофизарного нанизма в РСОА, и более высокую для мукополисахаридоза VI типа, гемолитико-уремического синдрома и юношеского артрита с системным началом. В РСОА выявлены особенности спектра генетических вариантов в генах *PAH* (фенилкетонурия) и *CFTR* (муковисцидоз). Таким образом, изучение распространенности РБ в регионах является важным и необходимым условием для повышения настороженности медицинского персонала, расширения и совершенствования оказания медицинской помощи пациентам с РЖЗ и ВЗН.

Ключевые слова: редкие (орфанные) заболевания, хронические прогрессирующие и жизнеугрожающие заболевания, высокозатратные нозологии, распространенность, Республика Северная Осетия – Алания, Российская Федерация

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The disease prevalence in the country is the main criterion determining the fact that the disease entity belongs to rare (orphan) diseases (RDs). This indicator varies between 1:1250 and 1:10,000 or more in various countries of the world [1–6]. Among 8000–10,000 currently known diseases, treatment options have been developed for 5% of diseases only, and the treatment effectiveness is directly related to the timing of starting therapy [2, 7, 8].

Efforts are made in different countries of the world to optimize the diagnosis of RDs with the help of various state projects and programs. In 2008, the US National Human Genome Research Institute created the conditions for comprehensive examination of 964 patients with undefined diagnoses for the first time. A network that included a coordination center and seven clinical centers, exome and genome sequencing centers, metabolomics and modeling center, biobank was created in order to implement the project, and the program for undiagnosed disorders was developed by the National Institutes of Health. As a result, the vast majority of patients were diagnosed, numerous new associations between genes and diseases were identified [9–12].

Such a comprehensive approach to the diagnosis of RDs turned out to be successful in Spain [13], Japan [14], Korea [15], and China [16]. High effectiveness of whole-genome sequencing in the diagnosis of RDs was demonstrated during implementation of the 100,000 Genomes Project in the UK [17–21].

Of particular relevance are various genetic tests performed in the format of express diagnosis to detect RDs in the critically ill newborns staying in the intensive care units: whole-genome/exome sequencing. According to the literature data, 25–50% of such tests are informative in terms of RD diagnosis [8].

In recent years, much has been done in our country to optimize the diagnosis of RDs. Such institutions, as the Research Centre for Medical Genetics, Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Endocrinology Research Center, and some other federal medical centers have the option to conduct expensive genetic tests at the expense of budgetary funds, but the number of such tests is limited. The work of several Orphan centers, in which a multidisciplinary approach to the diagnosis of RDs is used, has been also organized.

Legislative consolidation of the RD treatment was achieved in the Russian Federation (RF). The list of 283 diseases belonging to the groups of RDs was published on the website of the Ministry of Health of the Russian Federation [22], in which 17 disease entities are in the list of chronic progressive and life-threatening diseases (RLTDs) [23] and 14 are in the list of high-cost nosologies (HCNs).

In January 2021, the Circle of Good foundation for support of children with severe life-threatening and chronic diseases, including RDs, was established by the decree of the Russian President to provide such children with pharmaceuticals and medical devices, in some cases with those not registered in the RF, as well as with the rehabilitation equipment not included in the federal list of the rehabilitation measures, rehabilitation equipment and services provided to disabled individuals. The Foundation created an information resource being part of the unified state system in healthcare together with the Ministry of Health of the RF. The information resource contains information about the children, requests from parents (children's legal representatives), requests for medical care provision, information about procurement of pharmaceuticals, pharmaceutical product balances, protocols of the expert and guardianship councils, lists of pharmaceuticals, diseases, and categories of children approved by the Foundation councils.

The study was aimed to assess the range, prevalence, and genetic epidemiological characteristics of the orphan diseases from the lists of RLTDs and HCNs among children and adults in the Republic of North Ossetia–Alania and RF in general, as well as to compare the data obtained with the data provided in the world's literature, determine the issues and prospects of the diagnosis and treatment of this group of diseases.

METHODS

The research object was represented by the pediatric (162,452 people) and adult (680,748 people) populations of the Republic of North Ossetia–Alania and patiens with RDs according to the end of the year 2022: children from birth to 18 years of age and adults.

The population and number of patients in the country were determined based on the data provided by Rosstat and the Ministry of Health of the RF as of 31 December 2022. The population of the RF was 146,447,424 adults and 27,300,000 children.

The Annual Bulletin of the Expert Council on RDs of the State Duma Committee on Health Protection (the so-called White Book) is the only source of information providing the summary of the main analytical materials on the prevalence of RDs from the list of RLTDs in our country. The Bulletin provides information about the number of patients having diseases from the list of RLTDs in the RF. The regional Ministries of Health of the constituent entities of the RF have been providing information about the number of patients annually since 2018 [24] in accordance with the Government Decree No. 403 dated 26 April 2012. The Department of Medical Care for Children, Obstetrics and General Health Services of the Ministry of Health of the Russian Federation is the registry holder. The State Duma Committee on Health Protection obtains the regional data through parliamentary inquiries annually.

The prevalence of certain orphan diseases, diagnosed among pediatric and adult patients in the RF, in the Republic of North Ossetia–Alania was calculated based on the data from the White Book for the year 2022.

The data of the regional registries provided to the Ministry of Health of the RF were used to assess statistical data on the prevalence of orphan diseases from the list of HCNs.

The following formula was used to calculate the prevalence (P) of the disease entities:

$$P = \frac{\text{Number of patients in the RF or Republic of North Ossetia–Alania}}{\text{Population of the RF or Republic of North Ossetia–Alania}} \times 100{,}000$$

The global prevalence of orphan diseases was estimated using the database of the Orphanet international portal on RDs created in 1997 in France to collect scarce data on orphan diseases, improve the diagnosis of such diseases, and provide treatment to patients with RDs. Today, Orphanet is multilingual portal uniting 41 countries in Europe and around the world [25].

We determined the number of adults and children suffering with the diseases from the lists of RLTDs (a total of 18,744 patients in the RF, among them 8713 children; 129 and 42 patients, respectively, in the Republic of North Ossetia–Alania) and HCNs (a total of 28,727 patients in the RF, among them 13,454 children; 554 and 64 patients, respectively, in the Republic of North Ossetia–Alania). A retrospective analysis of the medical records of patients with orphan diseases registered with the medical genetic center at the Republican Children's Clinical Hospital of the Republic of North Ossetia–Alania for the

17-year period was carried out. The whole range of essential laboratory and instrumental tests was provided to patients with hereditary diseases, along with confirmatory diagnostic testing at various branches of the Research Centre for Medical Genetics. Some patients passed confirmatory diagnostic testing in the Genomed LLC on their own.

RESULTS

Analysis of data on the diseases from the list of chronic progressive and life-threatening diseases

Statistical data on the global prevalence of diseases from the list of RLTDs contained in the Orphanet database, the data on the number of patients and the prevalence of these diseases in the pediatric and adult populations of the RF and Republic of North Ossetia–Alania are provided in Table 1.

The analysis considering the molecular genetic diagnosis data was performed for all hereditary RDs. We determined the prevalence of the aromatic amino acid metabolism disorders (classic phenylketonuria (PKU), other hyperphenylalaninemias), which was 1–9/100,000 according to Orphanet, 3.87 in the adult population and 14.2 in the pediatric population of the RF (this corresponded to 1:7142). The prevalence of these disorders in the Republic of North Ossetia–Alania was as follows: 10.28/100,000 in the whole population and 9.23/100,000 among children. The diagnosis of phenylketonuria was confirmed by molecular genetic testing. Seven patients having classic phenylketonuria receive diet therapy in accordance with the federal clinical guidelines [26]. Other patients do not need any therapeutic diet. Predominance of two frequent genetic variants of the *PAH* gene (disease-associated alleles P281L and P211T) was the feature; in ethnic Ossetians, these two variants accounted for 60% of all identified mutations (P281L — 42.11%, P211T — 18.42%). The well-known genetic variants were identified in children with PKU (R408W, R261Q, F33S, M1R (c.2T>G), c.529G>A, c.1222C>T, E390G, c.47_48del (p.Ser16*), c.631C>A (p.Pro211Thr), V230I, c.529G>A (p.Val177Met)) [27].

According to Orphanet, the prevalence of homocystinuria is 1–9/100,000, no data on the prevalence of glutaric aciduria are provided. The prevalence of homocystinuria in the adult/pediatric population of the RF is 0.03/0.10, while the prevalence of glutaric aciduria is 0.05/0.22. One adult patient with homocystinuria has been identified in the Republic of North Ossetia–Alania, the disease prevalence is 0.15 per 100,000 population. The patient was first diagnosed at the age of 24 years. The search for pathogenic mutations was conducted by exome sequencing. The nucleotide sequence variant NM_000071.2(*CBS*):c.209+1G>A in the heterozygous state was identified, that had been earlier reported as pathogenic (HGMD: CS971640); the variant affected an invariant dinucleotide of the donor splice site in the intron 3 of the *CBS* gene encoding cystathionine β-synthase. Furthermore, the nucleotide sequence variant NM_000071.2:c.239T>C in the exon 4 of CBS in the heterozygous state was identified, that had not been earlier reported as pathogenic; the variant led to the nonsynonymous substitution p.(Ile80Thr) of the highly conservative position of this enzyme. No patients with glutaric aciduria were found in the region.

The prevalence of galactosemia in the pediatric population of the Republic of North Ossetia–Alania was 0.88 per 100,000. According to Orphanet, the prevalence of this carbohydrate metabolism disorder is 1–5 cases per 100,000 population, while in the RF the prevalence is 0.34 and 1.70 per 100,000 in the adult and pediatric populations, respectively. The DNA diagnosis revealed Duarte galactosemia resulting from the homozygous N314D mutation in the *GALT* gene (N314D/N314D genotype) in two cases and type 1 galactosemia (GALT enzyme deficiency) with the *GALT* Met142Lys/Lys285Aspn(p.K285N) mutations in one case; type 2 galactosemia (GALK1 enzyme deficiency) resulting from the homozygous genetic variant Q382X in the exon 8 of *GALK1* (Q382X/Q382X genotype) was diagnosed in two cases in sibling patients [28].

Tyrosinemia is a rare disease with the prevalence lower than 1:100,000 according to Orphanet. According to our data, the prevalence in the adult and pediatric populations of the RF is 0.04 and 0.21 per 100,000, respectively. No cases of this disease were reported in the Republic of North Ossetia–Alania during the studied period.

Furthermore, no patients having diseases associated with the fatty acid metabolism disorders were reported in the Republic of North Ossetia–Alania. The prevalence in the adult and pediatric populations of the RF was 0.08 and 0.28, respectively.

According to Orphanet, the prevalence of maple syrup urine disease and other disorders of the branched chain amino acid metabolism (isovaleric academia, methylmalonic academia, propionic academia) can be 1–9/100,000, however, the disease in far less common in the RF: 0.02–0.18/100,000. The prevalence of this disease in the Republic of North Ossetia–Alania was 0.15/100,000. Only one patient diagnosed with leucinosis (maple syrup urine disease) at the age of 2 months was identified for the entire group of disorders. When conducting molecular genetic testing of the target regions of 266 genes, the c.1196>T p.S399F pathogenic nucleotide variant in the homozygous state, that had not been reported earlier, was identified in the DBT gene. The patient is fed with the leucine-, isoleucine-, valine-free formula (Nutrigen 14-leu-val-ile). No patients having other diseases of this group were identified.

The prevalence of sphingolipidoses (Fabry disease, Niemann–Pick disease, and acute intermittent (hepatic) porphyria) in the adult and pediatric populations of the RF was 0.09/0.02, respectively. These disorders were not diagnosed in the region. According to Orphanet, the prevalence of these disorders is 1–5 and 1–9 per 100,000, respectively.

The prevalence of copper metabolism disorder (Wilson's disease) in the adult/pediatric populations of the RF was 0.68/0.49. The disease was not found in the pediatric population of the Republic of North Ossetia–Alania, while the prevalence among adults was 1.03/100,000, which was slightly higher compared to the average value for the country.

The prevalence of osteogenesis imperfecta in the adult and pediatric populations of the RF was 0.56/1.50, respectively, while in the Republic of North Ossetia–Alania it was 1.02/3.08, which was significantly higher compared to the values for the country in general. This feature resulted from the founder effect and the fact that there were 6 Kumyk patients, who were blood relatives in four generations. The NM_000088.3(COL1A1):c.1243C>T, p.(Arg415Ter) mutation in the heterozygous state (HGND:CM960321) was identified in all of them. The variant is associated with type IV osteogenesis imperfecta with the autosomal dominant pattern of inheritance. The patients' clinical manifestations vary between joint hypermobility, blue sclera, connective tissue dysplasia and multiple fractures. Four patients with severe disease were prescribed bisphosphonate therapy.

Five disease entities (paroxysmal nocturnal hemoglobinuria, idiopathic thrombocytopenic purpura, disorder of the

Table 1. Number of patients, data on the prevalence (per 100,000) of orphan diseases from the list of RLTDs in the world, RF, and Republic of North Ossetia–Alania

№	Disease	ICD-10 code	Prevalence per 100,000 according to Orphanet	Russian Federation				Republic of North Ossetia–Alania				*p*-value Russian Federation and Republic of North Ossetia–Alania	
				total 146,447,424/total 27,300,000				total 680,748/ children 162,452					
				Patients		Prevalence per 100,000		Patients		Prevalence per 100,000			
				Total	Children only*	Total	Children only*	Total	Children only*	Total	Children only*	Total	Children only*
1	Paroxysmal nocturnal hemoglobinuria (Marchiafava–Micheli syndrome)	D59.5	1.9	485	19	0.33	0.07	4	0	0.59	0.00	0.247	0.737
2	Idiopathic thrombocytopenic purpura (Evans syndrome)	D69,3	1.9	5638	1224	3.85	4.48	70	14	10.28	9.23	1.9E-17	0.013
3	Disorder of the complement system	D84,1	>1	631	93	0.43	0.34	6	4	0.88	2.64	0.075	5.7E-6
4	Central precocious puberty	E22,8	–	1990	1892	13.59	6.93	10	10	1.47	6.59	0.806	0.708
5	Aromatic amino acid metabolism disorders (classic PKU, other HPA)	E70,0	1.9	5666	3894	3.87	14.26	21	15	3.08	9.89	0.299	0.090
		E70,1											
6	Tyrosinemia	E70,2	>1	64	57	0.04	0.21	0	0	0.00	0.00	0.585	0.560
7	Maple syrup urine disease	E71,0	1.9	28	27	0.02	0.10	1	1	0.15	0.66	0.018	0.045
8	Other branched chain amino acid metabolism disorders (isovaleric academia,	E71,1	1.9	50	48	0.03	0.18	0	0	0.00	0.00	0.630	0.593
	methylmalonic academia		>1										
	propionic academia)		1.9										
9	Fatty acid metabolism disorders	E71,3	–	111	76	0.08	0.28	0	0	0.00	0.00	0.473	0.501
10	Homocystinuria	E72,1	1.9	44	28	0.03	0.10	1	0	0.15	0.00	0.082	0.683
11	Glutaric aciduria	E72,3	–	61	54	0.05	0.22	0	0	0.00	0.00	0.594	0.571
12	Galactosemia	E74,2	1.5	503	468	0.34	1.70	6	5	0.88	3.30	0.017	0.187
13	Other sphingolipidoses: Fabry disease,	E75,2	1.5	251	69	0.17	0.25	0	0	0.00	0.00	0.280	0.522
	Niemann–Pick disease		–										
14	Acute intermittent (hepatic) porphyria	E80,2	1.9	135	5	0.09	0.02	3	0	0.44	0.00	3.1E-3	0.863
15	Copper metabolism disorder (Wilson's disease)	E83,0	–	998	133	0.68	0.49	7	0	1.03	0.00	0.275	0.374
16	Osteogenesis imperfecta	Q78,0	1.5	824	410	0.56	1.50	7	5	1.02	3.08	0.107	0.103
17	Primary idiopathic pulmonary hypertension	I27,0	1.9	1265	216	0.95	0.94	6	1	0.88	0.66	0.961	0.802
Total				18744	8713	11.51	25.08	129	42	19.38	29.44	0	0.172

Note: * — children under the age of 18 years.

complement system, central precocious puberty, and primary idiopathic pulmonary hypertension) are not considered to be genetically determined. According to Orphanet, the prevalence of paroxysmal nocturnal hemoglobinuria is 1–9/100,000, while in the RF it is 0.33 and 0.07 in the whole population and among children, respectively. Four adult patients were identified in the Republic of North Ossetia–Alania: the prevalence was 0.59 and 0, respectively. A total of 70 patients suffering from idiopathic thrombocytopenic purpura were identified in the Republic of North Ossetia–Alania, among them 14 were children; the prevalence was 10.28 and 9.23, respectively, while the in the RF it was 3.85 and 4.48/100,000. According to Orphanet, the prevalence of this disease is 1–9/100,000. A total of 6 patients diagnosed with the disorder of the complement system were identified in the Republic of North Ossetia–Alania, among them four children. The prevalence was 0.88/100,000 in the whole population and 2.64/100,000 among children. Furthermore, the disease prevalence in the RF is 0.43 and 0.4, which is consistent with the global data provided in the Orphanet >1 database. Central precocious puberty was revealed in the RF; the prevalence was 13.59/100,000 in the whole population and 6.93/100,000 among children. A total of 10 pediatric patients were identified in the Republic of North Ossetia–Alania, the prevalence was 1.47 and 6.59, respectively. No Orphanet data

were provided. A total of 6 patients with primary idiopathic pulmonary hypertension were identified in the Republic of North Ossetia–Alania, among them one child; the prevalence was 0.88 and 0.66, respectively. The results obtained are consistent with the data for the RF (0.95 and 0.94 per 100,000 of surveyed individuals, respectively) and the Orphanet data (1–9/1,000,000).

Analysis of data on the diseases from the list of high-cost nosologies

The regional component of the Federal Registry of HCNs for the Republic of North Ossetia–Alania contains information about 554 patients, including 64 children (11.55%).

Information from the patients' genetic records about the diseases included in the list of HCNs is provided below (Table 2). Statistical data on the prevalence without any etiological structure analysis is provided for some diseases/conditions that are not genetically determined, such as organ and tissue transplant, hemolytic uremic syndrome. There are no statistics for some of them provided for the RF or deposited in the Orphanet database. As for diseases of genetic etiology, the more thorough analysis was performed in the Republic of North Ossetia–Alania considering molecular genetic testing, clinical features, and therapeutic interventions. The average prevalence was not calculated for this group of diseases.

Information about 13 patients diagnosed with hemophilia is available from the medical genetic center at the Republican Children's Clinical Hospital of the Republic of North Ossetia–Alania. All the patients receive specific coagulation factor replacement therapy. Currently, molecular genetic testing of children is conducted at the Research Centre for Medical Genetics. Mutations in the F8 gene typical for hemophilia A have been identified: c. 1630G>A (p.Asp544Asn) in two Ingush siblings; del(GRCh37/hg19) in two patients (Russian and Georgian), c.3637del (p.Ile1213Phefs*5), inv22, NC_000023.10:g.(?_154128143)_(154129718_?) del (GRCh37/hg19) deletion that includes exons 20 and 21 of the gene F8 in the hemizygous state, F8 inv 22 mutation in the hemizygous state, c.3637del (p.Ile1213Phefs*5) variant in the hemizygous state, etc. Mutation in the intron 5 of F9 (chrX:138630651G>A) in the hemizygous state affecting the conventional splice donor site that was typical for the disease was identified in patients with hemophilia B.

Twelve patients suffering from pituitary dwarfism are registered in the Republic of North Ossetia–Alania, among them 11 are children; the prevalence in the Republic of North Ossetia–Alania is 5.14 and 8.00/100,000, respectively. According to the all-Russian registry, the prevalence is 7.92 and 12.74 (Table 2). The patients receive hormone replacement therapy. The molecular genetic assessment of the candidate genes in patients with pituitary dwarfism has revealed no genetic variants causing the disease. The results obtained are consistent with the average data for the RF (5.40 and 18.15 per 100,000 surveyed people, respectively) and the Orphanet data (10–50/1,000,000).

The prevalence of cystic fibrosis in the RF is 2.97/100,000 for the whole population and 10.99/100,000 for the pediatric population, which is consistent with the Orphanet data. In the Republic of North Ossetia–Alania, 12 patients were diagnosed with cystic fibrosis during the studied period, among them 11 were children (prevalence of 2.20 and 6.77, respectively). DNA testing revealed well-known mutations in the gene CFTR: W1282X, 1677delTA, F508del, 2184insA, 2118del4, 1248+1G>A, R334W,359insT. It should be noted that the W1282X mutation accounting for 37.5% of all pathogenic alleles in affected individuals was most common in ethnic Ossetians [29]. This mutation is a class 1 mutation associated with cystic fibrosis, for which no target therapy has been developed. The patients receive symptomatic treatment in accordance with the federal clinical guidelines [30, 31].

Mucopolysaccharidoses, the group of glycosaminoglycan metabolism disorders, are represented by two forms in the Republic of North Ossetia–Alania: type I and VI mucopolysaccharidosis. The child was diagnosed with type I mucopolysaccharidosis based on the phenotypic traits, pronounced decrease in α-L-iduronidase activity, high urinary glycosaminoglycan levels, and molecular genetic testing data: the c.1A>C (p.M1?) nucleotide sequence variant in the heterozygous state reported in the HGMD database as pathogenic was found in the exon 1 of the gene *IDUA*; c.510delinsAAGTTCCA (p.His171Serfs*14) in the heterozygous state was found in the exon 5 of *IDUA*. The council decided to prescribe enzyme replacement therapy (Laronidase), treatment was satisfactorily tolerated. In 2022, bone marrow transplant was performed, however, the child died in June 2022 in the intensive care unit due to graft-versus-host disease.

The child born in 2009 was diagnosed with type VI mucopolysaccharidosis based on the phenotypic traits, pronounced decrease in lysosomal arylsulfatase activity, high urinary glycosaminoglycan levels, and DNA testing data: the c.691-1 G>A (IVS as G-A-1; IVS3 — 1g>a) mutation in the homozygous state was found in the *ARSB* gene. The Federal council decided to prescribe enzyme replacement therapy (Galsulfase). Therapy is satisfactorily tolerated.

According to the regional registries, the average prevalence of type I mucopolysaccharidosis in the RF is 0.06/100,000 in the whole population and 0.26 among children, while that of type II mucopolysaccharidosis is 0.09 and 0.38, type VI mucopolysaccharidosis — 0.04 and 0.10, respectively. According to Orphanet, the prevalence of type I and II mucopolysaccharidosis is 1–9/100,000, which is higher compared to the values for the RF and the Republic of North Ossetia–Alania, while the prevalence of type VI mucopolysaccharidosis is similar to the data obtained in our study: <1/100,000.

In the assessed period the diagnosis of Gaucher disease type 3 was established in a child born in 2016 at the age of 1.5 years in the Republic of North Ossetia–Alania. Molecular genetic testing revealed the p.L444P variant in the homozygous state in the *GBA* gene, which was confirmed by Sanger sequencing. The lifelong enzyme replacement therapy (Imiglucerase in a dose of 60 U/kg — 1200 U) was prescribed. However, the therapy conducted was followed by severe allergic reaction, anaphylaxis and angioedema. Imiglucerase therapy in accordance with the rapid drug desensitization scheme was initiated since the beginning of 2022 due to progression of complications. Furthermore, considering the IgE-mediated mechanism of allergy in this particular patient, the IgE antagonist, omalizumab, was added to premedication. During the period of 10 months physicians managed to administer 800 U with a 2-week interval. However, the child died in October 2022 due to secondary intercurrent disease [32]. The average prevalence in the RF was 0.31/100,000 in the whole population and 0.38 among children, which was lower compared to the Orphanet data (1–9/100,000).

DISCUSSION

Comparative analysis of the data on orphan diseases in the Republic of North Ossetia–Alania was conducted, the previously

Table 2. Number of patients, data on the prevalence (per 100,000) of orphan diseases from the list of high-cost nosologies (HCNs) in the world, RF, and Republic of North Ossetia–Alania

№	Disease	ICD-10 code	Prevalence per 100,000 according to Orphanet	Russian Federation				North Ossetia–Alania				*p*-value Russian Federation and Republic of North Ossetia–Alania	
				Patients		Prevalence per 100,000		Patients		Prevalence per 100,000			
				Total	Children only*	Total	Children only*	Total	Children only*	Total	Children only*	Total	Children only*
1	Hemophilia	D66	1.9	11601	3479	7.92	12.74	35	13	5.14	8.00	0.010	0.091
2	Pituitary dwarfism	E23,0	10.5	7915	4955	5.40	18.15	12	11	1.76	6.77	4.4E-5	6.7E-4
3	Cystic fibrosis	E84,0	10.5	4352	2945	2.97	10.79	15	11	2.20	6.77	0.246	0.127
4	Mucopolysaccharidosis I	E76,0	1.9	90	70	0.06	0.26	1	1	0.15	0.62	0.371	0.369
5	Mucopolysaccharidosis II	E76,1	1.9	139	104	0.09	0.38	0	0	0	0	0.421	0.431
6	Mucopolysaccharidosis VI	E76,2	<1	52	27	0.04	0.10	1	1	0.15	0.62	0.127	0.040
7	Gaucher disease	E75,2	1.9	455	105	0.31	0.38	1	1	0.15	0.62	0.444	0.637
8	Multiple sclerosis	G35,0	–	–	–	–	–	1	1	0.15	0.62	–	–
9	Hemolytic uremic syndrome	D59,3	1.9	502	312	0.34	1.14	6	2	0.88	1.23	0.017	0.916
10	Systemic juvenile rheumatoid arthritis	M08,2	1.9	1846	1148	1.26	4.21	22	11	3.23	6.77	5.3E-6	0.112
11	Aplastic anemia	D61,9	–	1420	142	0.97	0.52	5	1	0.73	0.62	0.534	0.867
12	Organ and tissue transplant	Z94	–	–	–	–	–	84	10	12.34	6.16	–	–
13	Malignant neoplasms of the lymphoid, hematopoietic and related tissues	C81-C96	–	–	–	–	–	372	1	54.65	0.62	–	–
14	Hereditary coagulation factor deficiency	D68,2		355	167	0.24	0.61	2	0	0.29	0	0.786	0.319
	II (fibrinogen),		<1										
	VII (labile factor),		1.9										
	X (Stuart–Prower factor)		1.9										
Total				28727	13454	19.62	49.28	554	64	81.38	39.40	0	0.073

Note: * — children under the age of 18 years.

unpublished data on the diseases from the list of RLTDs in the RF were provided. The average prevalence of RLTDs in the RF was 11.51/100,000 in the whole population (1 : 8688 people), 25.08/100,000 among children (1 : 3987 children). Similar data were obtained for the Republic of North Ossetia–Alania: 19.38/29.44 (1 : 5160 people/1 : 3396 children). No significant differences were revealed (Table 1).

The average prevalence of idiopathic thrombocytopenic purpura in the Republic of North Ossetia–Alania is higher than the average prevalence in the RF, both in the whole population ($p = 1.9 \times 10^{-17}$) and among children (p = 0.013). Comparison with the Orphanet data has revealed no differences considering variability of the prevalence in different countries. The prevalence of the disorder of the complement system turned out to be higher only among children ($p = 5.7 \times 10^{-6}$), which is in line with the data reported for Europe. Maple syrup urine disease is more common in the Republic of North Ossetia–Alania, than in the RF ($p = 0.018$ and $p = 0.045$, respectively), which is consistent with the Orphanet data. The prevalence of galactosemia in in the whole population of the Republic of North Ossetia–Alania is lower ($p = 0.017$), than the average prevalence in the RF and Europe, which can be associated with low detection rate of the disease in the Republic due to milder course. At the same time, acute intermittent porphyria is characterized by higher prevalence ($p = 3.1 \times 10^{-3}$), than in the RF, and similar to the values reported for Europe. Such disease entities, as fatty acid metabolism disorders, glutaric aciduria, tyrosinemia, other amino acid metabolism disorders, have not been reported in the Republic of North Ossetia–Alania.

The differences were also revealed for the group of orphan diseases from the list of HCNs. The prevalence of hemophilia ($p = 0.010$ for the whole population) and pituitary dwarfism ($p = 4.4 \times 10^{-5}$ for the whole population, $p = 6.7 \times 10^{-4}$ for children only) in the Republic of North Ossetia–Alania turned out to be lower compared to the average prevalence in the RF and the Orphanet data. At the same time, the prevalence of type VI mucopolysaccharidosis ($p = 0.040$ for children), hemolytic uremic syndrome ($p = 0.017$), and systemic juvenile rheumatoid arthritis ($p = 5.3 \times 10^{-6}$) is higher than in the RF and is consistent with the Orphanet data.

All other diseases in the groups of RLTDs and HCNs showed the values that were statistically similar to the data for the RF and the Orphanet data.

Attention should be also paid to the specific range of mutations:

– in the *PAH* gene associated with phenylketonuria — predominance of two frequent genetic variants of the *PAH* gene (P281L and P211T), not typical for both RF and all world's populations. In ethnic Ossetians, these two variants together account for 60% of all the mutations identified (P281L — 42.11%, P211T — 18.42%). The P211T variant is a mild genetic variant with the residual phenylalanine hydroxylase activity of 72%, which results in milder clinical features of the disease and no need for replacement diet therapy;

– in the CFTR gene associated with cystic fibrosis — predominance of the W1282X class 1 mutation, which limits the target therapy options available for patients.

CONCLUSIONS

Today, there is no universal approach to improvement of the diagnosis, treatment, and drug provision to patients with

orphan diseases that might be replicated all over the world. At the same time, a rather big experience of dealing with the issues related to RDs has been accumulated. There are also certain achievements in Russia. Thus, the federal registries of various orphan diseases have been compiled and are regularly updated, the budget to support treatment that is often expensive has been determined. In our study we determined the structure and population genetic features of the RDs from the lists of RLTDs and HCNs in the Republic of North Ossetia–Alania and the RF. The features of prevalence were demonstrated for a number of diseases, along with the statistical similarity of values to the data reported for the RF and the Orphanet data for the vast majority of diseases. Despite significant breakthroughs in the field of diagnosis and treatment of orphan diseases, the detection rate of the discussed disease entities in both the region and the country is still inadequate. This results in the need to use the world's experience of organizing transregional orphan centers, wider adopt the confirmation diagnosis methods, exome/genome sequencing at the expense of budgetary funds. A separate problem is the limited range of options of free DNA diagnosis for adults. Establishment of the Circle of Good foundation contributed enormously to increasing the availability of pharmaceuticals and the earlier start of therapy. The system for communication with the Foundation has been worked out in the region. Every year, when drafting the budget, the Ministry of Health of the Republic of North Ossetia–Alania includes the demand for funding of preferential drug provision to the discussed category of patients calculated in accordance with personal prescriptions for each patient. As for the end of 2022, the republican segment of the Circle of Good information resource contains 22 patients suffering from RDs. All the patients are provided with pharmaceuticals and therapeutic food products in full. There are no interruptions of the ongoing therapy in the patients using drugs at the expense of the Foundation. Pharmaceuticals worth 369,165,971.70 rubles have been received since November 2021. A total of 188 prescriptions worth 210,304,075.10 rubles have been dispensed. Expansion of the range of screened diseases will contribute to optimization of the RD detection at the preclinical stage. Certainly, we are at the beginning of the completely new era, when the early diagnosis of such diseases can become a routine, and expansion of the gene therapy capabilities will make it possible to optimize the course of a large number of diseases, that have been earlier considered incurable.

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