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Clinical and Diagnostic Characteristics of Children with Gaucher Disease in the Republic of Kazakhstan -

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ABSTRACT

The article is devoted to the analysis of morbidity and diagnostics of Gaucher Disease (GD) in the Republic of Kazakhstan (RoK); Degree of incidence, distribution by type, ethnicity based on initial clinical and laboratory changes and analysis of genetic mutations of the GBA gene in patients with GD.

Keywords: Gaucher disease; epidemiology; Genetic analysis; Clinical symptoms; Children

TOPICALITY

Metabolic diseases in children are caused by genetic disorders of enzyme functions and are one of the complex, poorly known problems of modern pediatrics, as they relate to severe diseases difficult to diagnose.

Gaucher disease is based on a deficiency of the glucocerebrosidase enzyme causing a progressive enlargement of parenchymatous organs (liver, kidney, lungs, pancreas gland, and others) gradual infiltration of bone marrow by macrophages, profound disorders of hemopoiesis, and, in a small part of patients, damage of the central nervous system. GD is a pan ethnic disease, it occurs with incidence from 1:40 000 to 1:60 000 in representatives of all ethnic groups; in the Ashkenazi Jewish population, the incidence reaches 1:450. The variability of the clinical pattern of GD is associated with a multitude of mutations of the GBA gene. Currently, about 350 mutations have been identified [1,2].

This disease is especially difficult to diagnose when for a long period of time it can occur under the masks of other diseases. Over the past decade, a lot of work has been done in Kazakhstan to improve the GD diagnosing and to provide healthcare delivery to patients with this pathology. In 2010-2011, an enzymatic and molecular genetic diagnosing was established in the reference laboratories of Austria and Germany, patients began receiving free ERT paid from the Republican budget. In 2016-2017 a protocol of GD treatment and the GD patients pathway were developed, regional coordinators for orphan diseases, including GD, were appointed and trained. Every year, training workshops, seminars, and conferences dedicated to modern issues of GD diagnostics and treatment are held. Against the background of the work done, there is an increase in the growth of identified GD cases, but nevertheless, this index in our country remains several times less than the average oneV. Thus, 15 years of experience in managing patients with GD allowed us to identify certain features of clinical and laboratory signs of the disease in the population of children with GD in Kazakhstan, to evaluate the effectiveness of ongoing measures to improve GD diagnosis in our Republic, and to give recommendations for practical healthcare to improve early diagnosis verification in this cohort of patients.

THE PURPOSE OF THIS WORK

To inform medical specialists about the basic laboratory and instrumental methods of studying the Gaucher disease and the problematics in diagnosing the disease in the Republic of Kazakhstan.

MATERIALS AND METHODS

Based on a retrospective analysis and laboratory-instrumental examination, initial clinical and diagnostic features will be studied in 20 children with Gaucher disease in Kazakhstan.

For the first time, molecular-genetic studies will reveal the most common mutations based on the Kazakhstan population.

Based on the analysis, an algorithm for the early diagnosis of Gaucher disease will be proposed. It aims at early detection of GD in the child population, reduced mortality and prevention of disability, timely grounding and the initiation of pathogenetic Enzyme Replacement Therapy (ERT). These measures will consequentially improve the quality of life and social adaptation of patients.

RESULTS OF THE STUDY AND THEIR DISCUSSION

Over the past 18 years, with the improvement of doctors' knowledge of GD and the availability of methods for diagnosing the disease, the incidence of GD in Kazakhstan tends to increase. The average rate of annual increase in GD from 2001 to 2017 was 6.1% [Figures1,2].

The rate of incidence of GD in RoK for the period of 1999-2017 was 0.33 per 100 000 live births, which is significantly different from the global GD incidence. But account must be taken of that this indicator does not reflect the true incidence of GD in the RK, as in a number of cases the disease can remain undetected.

When studying the incidence of GD by the regions of the Republic of Kazakhstan, it was revealed that the highest detection of patients with GD is observed in the North- Kazakhstan region. The incidence rate of GD in this area was 2.1:100,000, which corresponds to the world indices. The lowest incidence of GD was registered in the South-Kazakhstan region, the figure was 0.09:100,000. We do not consider this indicator to reflect the true picture, since we have

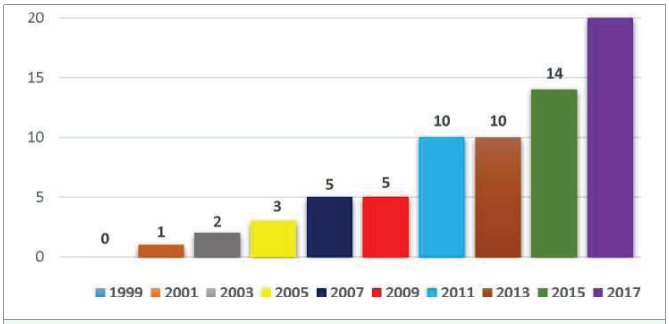

Figure 1: Dynamics of diagnosed GD cases from 1999 to 2017.

Figure 2: Rate of incidence of GD in the period of 1999-2017.

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the highest birth rate and population density in this region of the country. No GD cases in children were detected in Atyrau, Akmola, Mangystau, West Kazakhstan regions. Table 1 presents the incidence rate of GD by the regions of the Republic of Kazakhstan for the period of 2000-2016.

In accordance with the GD clinical classification in the RoK, Type I amounts to 60%, Type II - 15%, Type III - 25%.

In recent times, in connection with the improvement of GD diagnostics, children in the Republic of Kazakhstan are characterized by an earlier age of disease onset. It is related to earlier manifestation of the clinical pattern and a more severe course of the disease in comparison with the indicators for the general population. When considering the age composition at the time of diagnosis verification, it should be noted that all patients with Type II disease were diagnosed in early age, 2-4 months from birth. And at the time of diagnosis verification, the disease often had an aggressive course. The average age of patients at the time of disease onset was 1.1 years, and the average age at the time of laboratory confirmation of diagnosis was 3.5 years. On average, the diagnosis verification takes 2.5 years.

At the moment, the ratio of patients with GD by gender is 1:1, the same number of boys and girls is observed (10:10). According to ethnic distribution, 18 (90%) of 20 children were of Kazakh nationality, 1 (5%) of Russian nationality and 1 (5%) Korean.

The gold standard for the modern diagnosis of Gaucher disease is the biochemical determination of beta-glycosidase activity in blood leukocytes. The diagnosis is confirmed when the activity of the enzyme is lower than 30% of the normal value. In our study, all patients underwent a study of the activity of the glucocerebrosidase enzyme. The analysis was carried out in different laboratories; therefore, the results are presented are in different units of measurement. The results of the analysis in 14 children were 0.01 to 0.52 pmol/l/h (at a rate of > 2.5 pmol/l/h) and 6 children from 21.14 to 163.71 pmol/spot*20h at a rate of 200-2000 pmol/spot*20h).

At the first trial of an enzyme, the false-negative result that has affected the duration of the diagnostic study period was reported in two patients.

An additional method of diagnosis is molecular genetic testing, which allows identifying the root source of the development of any hereditary disease. The molecular genetic analysis carried out in 16 (80%) of 20 patients revealed that in 94% of cases GBA gene damage was represented by missense mutations, in 6% - by RecNcil recombinant mutation.

In the Kazakhstan population, the most common mutations were L444P 42% (13 mutations), and F213I 13% (4 mutations). Only in two cases the L444P mutation was determined in the homozygous state. The mutation N370S - 10% (3 mutations) is the third by incidence rate in Kazakhstan.

According to the literature, mutations L444P and F213I are associated with neuronopathic types of GD and are most typical for Asian countries [3,4]. The N370S mutation, on the contrary, protects against CNS damage in the course of GD, and is the most common mutation in the Ashkenazi Jewish population and in many European countries [5,6]. Table 2 compares the incidence rate of mutations L444P, F213I and N370S among Asian countries and in the general population. Data on the general population are taken from the published materials of the International GD Register [7].

Table 1: Degree of GD incidence by RoK regions for the period of 2000-2016.

Region	Total number of live-borns	Total number of diagnosed cases of GD	The rate of GD, per 100 000 live- borns
Akmola	200468	0	-
Aktobe	257198	1	0,38
Almaty	636038	3	0,47
Atyrau	218413	0	-
West-Kazakhstan	184283	0	-
Zhambyl	417160	1	0,24
Karagandy	365840	3	0,82
Kostanay	203614	1	0,49
Kyzyl Orda	285151	2	0,7
Mangystau	223107	0	-
South Kazakhstan	1151737	1	0,09
Pavlodar	194652	1	0,51
North Kazakhstan	142255	3	2,1
East Kazakhstan	360516	3	0,55
Astana city	245655	0	-
Almaty city	428398	1	0,23

Table 2: Incidence rate of L444P, F213I, N370S mutations in different populations.

Mutation	RoK		Japan	Korea	China	International Register (*n* = 1698)
	абс.	%	%	%	%	%
L444P	13	42	41	60	55	18
F213I	4	13	14	N/A	14	N/A
N370S	3	10	almost does not occur	almost does not occur	3	53

The mutations E272D and RecNcil are on the fourth place of the incidence rate among the Kazakhstan population, each of which amounted to 6% (2 mutations). The literature reports that the RecNcil recombinant mutation is one of the most unfavorable in the prognostic context and is often found in Type II [8]. Two patients who were diagnosed with this mutation did not become an exception; during their lifetime, Type II was diagnosed; at the time of this study, one of the patients died in connection with the progression of the disease.

Also, G46E, N188S, D315H, W184R, V398F, R120W, R87Q mutations were detected, which were previously determined in other populations [5]. The percentage ratio of mutations of the GBA gene identified in the population of children with GD in Kazakhstan is shown in (Figure 3).

Among the patients, 10 different genotypes were identified, the most common of which was the genotype L444P/another mutation (25%). Table 3 presents genotypes and the number of cases of their detection in patients with GD in Kazakhstan in comparison with the general population.

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It should be noted that, at the stage of diagnostic study, patients were consulted by at least three different medical specialists, including pediatrician, neurologist, surgeon, hematologist, infectious disease specialist, pulmonologist, hepatologist, etc.; the disease onset was presented as clinical simulation of various diseases (Table 4).

When assessing the severity of GD course in children by the index proposed by A. Zimran [9], it was revealed that the disease was of medium severity in 11 patients (55%) and severe in 9 patients (45%). No patients were identified with a mild severity.

Analysis of anthropometric measurements, such as weight and height, revealed a failure to thrive in 18 children out of 20 (90%). The growth rate was within the norm in two children (10%), in two children it was below the average (10%), in the low range in 5 children (25%), in very low range in 11 children (55%). The weight index was within the norm in three children (15%), in the range below the average in two children (10%), in the low range in three children (15%), in the very low range in 12 children (60%).

Assessment of main clinical manifestations of GD in children in the RoK.

One of the most frequent manifestations of GD was hemorrhagic syndrome, which was noted in 12 (60%) children. In two children, hemorrhagic syndrome manifested itself as nasal bleeding and skin syndrome, in 10 children - only in the form of bleeding. Figure 4 shows the characteristics of hemorrhagic syndrome in children with GD.

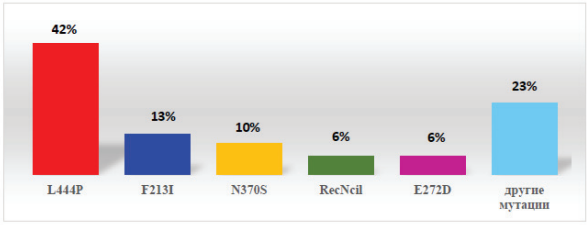

Figure 3: Mutations of the GBA gene in the population of children with GD in Kazakhstan.

Table 3: Genotypes of patients with GD.

Genotypes	Genotypes of patients with GD in Kazakhstan, *n* = 16		Genotypes of patients with GD according to the International Registry of GD for 2010, *n* = 3914 (%)
	abs	%	
N370S/ N370S	Does not occur		31
L444P/other mutation	4	25	3
L444P/ L444P	2	13	6
L444P/ F213I	2	13	N/A
N370S/other mutation	2	13	14
L444P/ N370S	1	6	15
L444P/ E272D	1	6	N/A
L444P/ RecNcil	1	6	N/A
F213I/ other mutation	1	6	N/A
F213I/ RecNcil	1	6	N/A
E272D/ other mutation	1	6	N/A

Table 4: Diagnosis in patients with GD at the stage of diagnostic study.

Medical specialist	Diagnosis of patients
Pediatrician	Anemia, rachitis, nosebleeds, frequent acute respiratory infections, pneumonia, protein-energy wasting
Neurologist	Residual-organic lesion of the CNS, astheno-neurotic syndrome, infantile cerebral paralysis, delayed psychomotor development
Surgeon	Portal hypertension, lymphadenitis, osteomyelitis, hypersplenism syndrome
Hematologist	Myelodysplastic syndrome, microspherocytic anemia, thrombocytopathy
Infectionist	CMV, opisthorchiasis
Ophthalmologist	Angiopathy of the retinal vessels
Pulmonologist	Pneumonia with respiratory failure, mucoviscidosis
Hepatologist	Reactive hepatitis, liver cirrhosis
Gastroenterologist	Banti's syndrome
Rheumatologist	Reactive arthritis

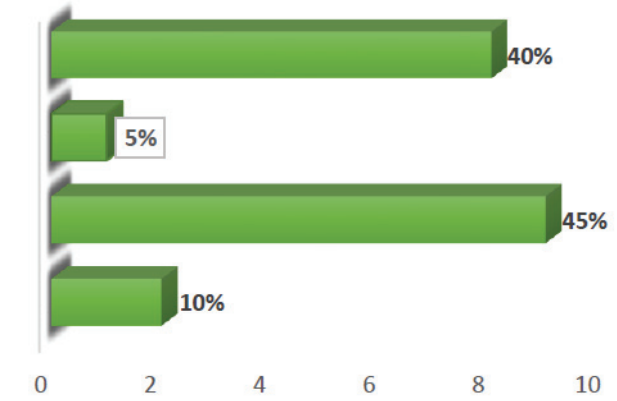

Figure 4: Shows the characteristics of hemorrhagic syndrome in children with GD.

Instrumental examination of the bone system was performed on 12 children, and a deformity in the form of an Erlenmeyer's flask, fine-focal ablation, osteopenia, and osteoporosis were revealed in 8 (67%) patients on the roentgenogram of the femoral bones. Also, kyphoscoliosis was diagnosed in two children (10%) with Type III GD (Figure 5). Besides the revealed changes in the femoral bones, three children (15%) additionally had pathological fractures in the thoracic and/or lumbar spine, pathological fracture of the femoral neck. In 4 (33%) cases, there was no pathological changes in the bone system.

Osteal aches were felt by 7 (35%) of 20 children. Three of them (15%) had episodes of bone crisis in the form of severe pains in knee and ankle joints, oedema, hyperemia and temperature rise. In 2 (10%) patients, bone crises were regarded as the course of osteomyelitis, and, therefore, they underwent surgical treatment.

Pathological symptoms from the CNS were registered in 8 (40%) of 20 children. On this basis, the children were diagnosed a neuronopathic form of GD. In children with Type II in the disease

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onset, the development of strabismus, delay in motor development, ataxia, retroflexia of the neck, general hypotension, and dysphagia were registered. They led to frequent RDS and prolonged pneumonia.

In children with Type III, neurologic symptoms appeared a little after the organomegaly, the injury of CNS had a progressive course. In Type III, children developed oculomotor apraxia, strabismus, mental impairment, hyperkinesis, convulsive syndrome, progressive respiratory disorders (Table 5).

All children at the time of diagnosis verification were diagnosed with hepatosplenomegaly (Figure 6). According to ultrasound investigation data, the enlargement of liver size in all cases did not exceed more than 2 times. An enlargement in the right lobe of the liver in 16 (80%) patients was 1.5-2 times. In 4 (20%) patients, it was less than 1.5 times. An enlargement in the left lobe of the liver was 1.5-2 times in 10 (50%) children, less than 1.5 times in 4 (20%) patients. In 6 (30%) patients this parameter remained within the normal range.

Splenomegaly was more pronounced. In 5 (25%) children the spleen was enlarged by 1.5 times, in 8 (40%) patients by 2-2.5 times, in 7 (35%) patients by 3-3.5 times. According to the clinical examination, in 16 (80%) children the lower pole of the spleen was in a small pelvis. In 4 children the spleen was palpated 4.0-6.0 cm below the edge of the left costal arch. 4 (20%) patients underwent a splenectomy prior to verifying GD.

95% (19) of patients with GD had a change in hematologic parameters. Almost half of the children (45%) had IId anemia at the time of diagnosis verification. Anemia of the I degree was detected in 30% (6) patients, anemia IIId in 20% (4) patients. The hemoglobulin index was within the norm only in one child (5%). Anemia was hypochromic in all cases. Color Index (CI) in the range of 0.56-0.8. Initial hemoglobulin indices in children with GD is shown in (Figure 7).

Most children (65%) had mild thrombocytopenia. Three children (15%) had thrombocytopenia of moderate degree, and one child (5%) had severe thrombocytopenia. The platelet counts were within the normal range in three (15%) children out of 20. The initial platelet counts in children with GD are presented in (Figure 8).

Blood leukocyte counts were within the normal range in 10 (50%) of 20 patients. Leukopenia Id was recorded in 9 (45%) children. One child was diagnosed with moderate leukocytosis in the blood (Figure 9).

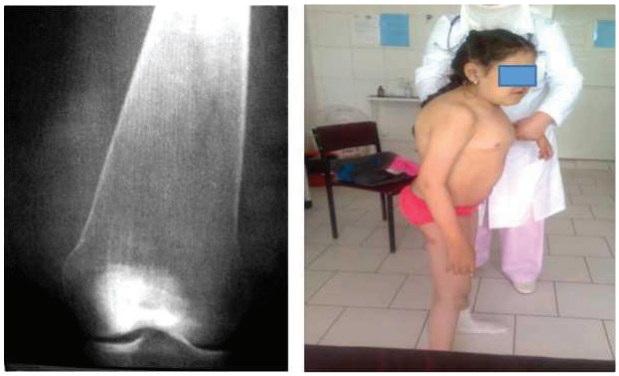

Figure 5: Changes in the bone system in Gaucher disease (Erlenmeyer's flask deformity, fine-focal ablation, osteopenia, osteoporosis, kyphoscoliosis in the female patient with Type III GD).

Table 5: Pathological changes in the nervous system in children with a neuronopathic form of GD.

Patholo gical manifestations of the nervous system	Number of patients (*n* = 8)	
	abs	%
Strabismus	8	100
Oculomotor apraxia	5	63
Delay in motor development	6	75
Mental development delay	2	25
Hyperkinesis	4	50
Convulsions	3	38
Retroflexion of the neck	3	38
Respiratory disorders due to dysphagia	8	100

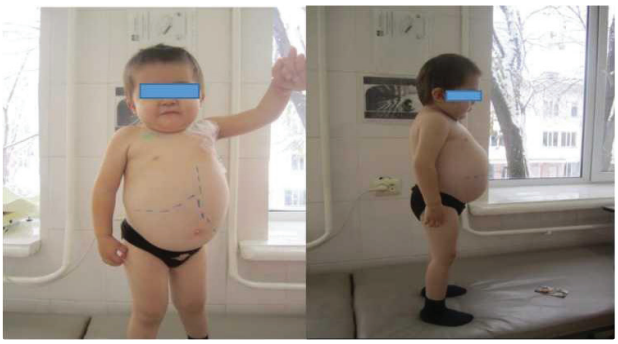

Figure 6: Hepatosplenomegaly in a patient with Type III BH.

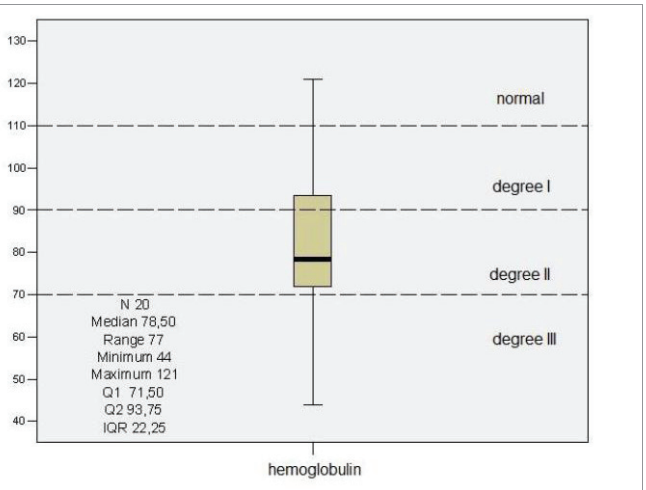

Figure 7: Initial hemoglobin indices in children with GD.

According to Niederau S, in 30-50% of patients with GD, serum aminotransferase levels increased only to 2 norms. Only in some patients, the activity of GPT, AST increased to 7 norms [11]. In our study, 19 (95%) children had a normal ALT level. The GOT level in 10 (53%) patients was increased 1.5 times from the norm, in one child (5%) in 2 times. In 8 (42%) patients this indicator was within the norm. In one patient with GD, hepatitis C was diagnosed. That is why the ALT and GOT levels of this patient were not taken into account

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when interpreting the initial indices of the biochemical blood test in the study.

The study of serum iron level was conducted in 11 (55%) patients. According to the results of the study, it was within the norm in 5 (45%) patients. It increased by 2.5 times in one child (10%), and a decrease in this indicator was revealed in 5 children (45%). The level of ferritin was analyzed only in three children (15%). And, in one of the patients, this indicator was higher than the reference values more than 7 times.

As is known, the pathomorphological substrate of the disease is the detection of specific Gaucher cells in the bone marrow biopsy. Morphological examination of the bone marrow allows revealing these cells and, at the same time, excluding the hemoblastosis or other lymph proliferative disease in patient as a cause of the cytopenic syndrome and hepatosplenomegaly. In our study, bone marrow puncture was performed in 17 (85%) children. Gaucher cells were found in the biopsy specimen in 71% (12) cases (Figure 10).

CONCLUSION

Thus, when assessing the initial clinical and laboratory-instrumental indicators in the population of children with GD in Kazakhstan, it was revealed that:

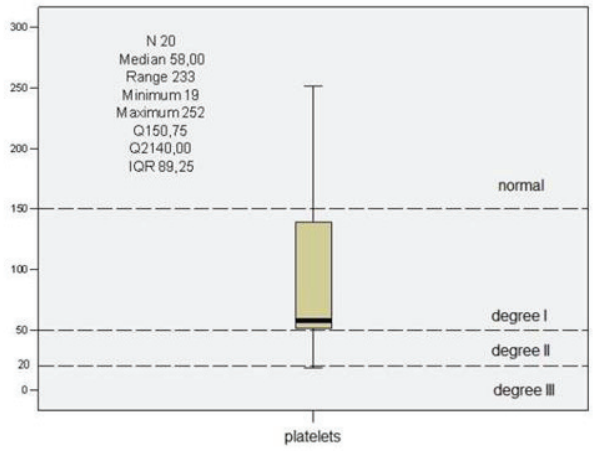

Figure 8: Initial platelet counts in children with GD.

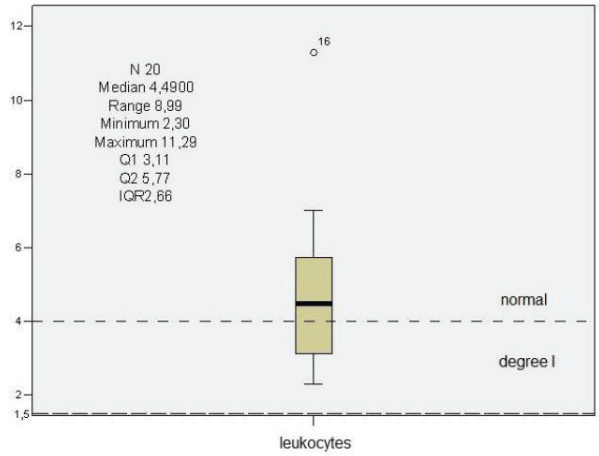

Figure 9: Initial indices of blood leukocytes in children with GD.

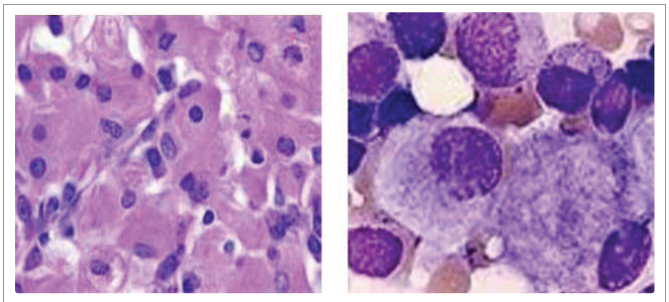

Figure 10: Gaucher cells in the bone marrow.

- The incidence rate of GD in the RoK was 0.33 per 100,000 live births, with an uneven incidence in the regions.
- In the studied patients with GD, L444P, F213I, RecNcil (61%) mutations and genotypes (63%), indicative of the neuronopathic form of GD, prevailed.
- In the population of children with GD in Kazakhstan, there was a higher proportion of neuronopathic types (40%) compared with the general population (7%) with an early onset of clinical manifestations of the disease (up to 3 years).
- Diagnosis is conducted only for the moderately severe (55%) and severe forms of GD (45%).
- At the time of GD verification in children, despite the fairly early age (3 years 6 months), there is a formed symptom complex in the form of anemia (95%), more often of moderate severity (45%), thrombocytopenia (85%) and leukopenia 50%), expressed splenomegaly (100%), moderate hepatomegaly (100%), failure to thrive (90%), hemorrhagic syndrome (60%), bone pain (35%), bone crises (15%).

The comparative analysis of a number of diagnosed cases of the disease in our country with the data of foreign researchers indicates insufficient diagnosing and presence of certain difficulties in the early verification of the diagnosis. First of all, this is due to the pronounced clinical polymorphism and diversity, which makes it difficult to recognize diseases at the clinical level. Also, the low incidence of this nosology in the population does not allow the practitioners to accumulate personal experience for the timely diagnosis.

It should be noted that the results of the analysis of the epidemiological, clinical and laboratory-instrumental indicators of GD among children in Kazakhstan, showing a lower incidence, is associated not so much with ethnic characteristics as with the alertness and awareness of doctors in the field of this pathology.

At present, the Republic of Kazakhstan is doing a lot of work aimed at early diagnosis of orphan diseases at all levels of medical care for the children. A good help in solving this problem is the widespread implementation of the Algorithm for the early diagnosis of Gaucher disease in children, taking into account the patients pathway, in the practical public healthcare of the country (Figure 11). Timely verified disease and timely treatment will improve the outcome of the disease, improve the quality of life of patients, their socialization, will help reduce mortality and prevent early disability.

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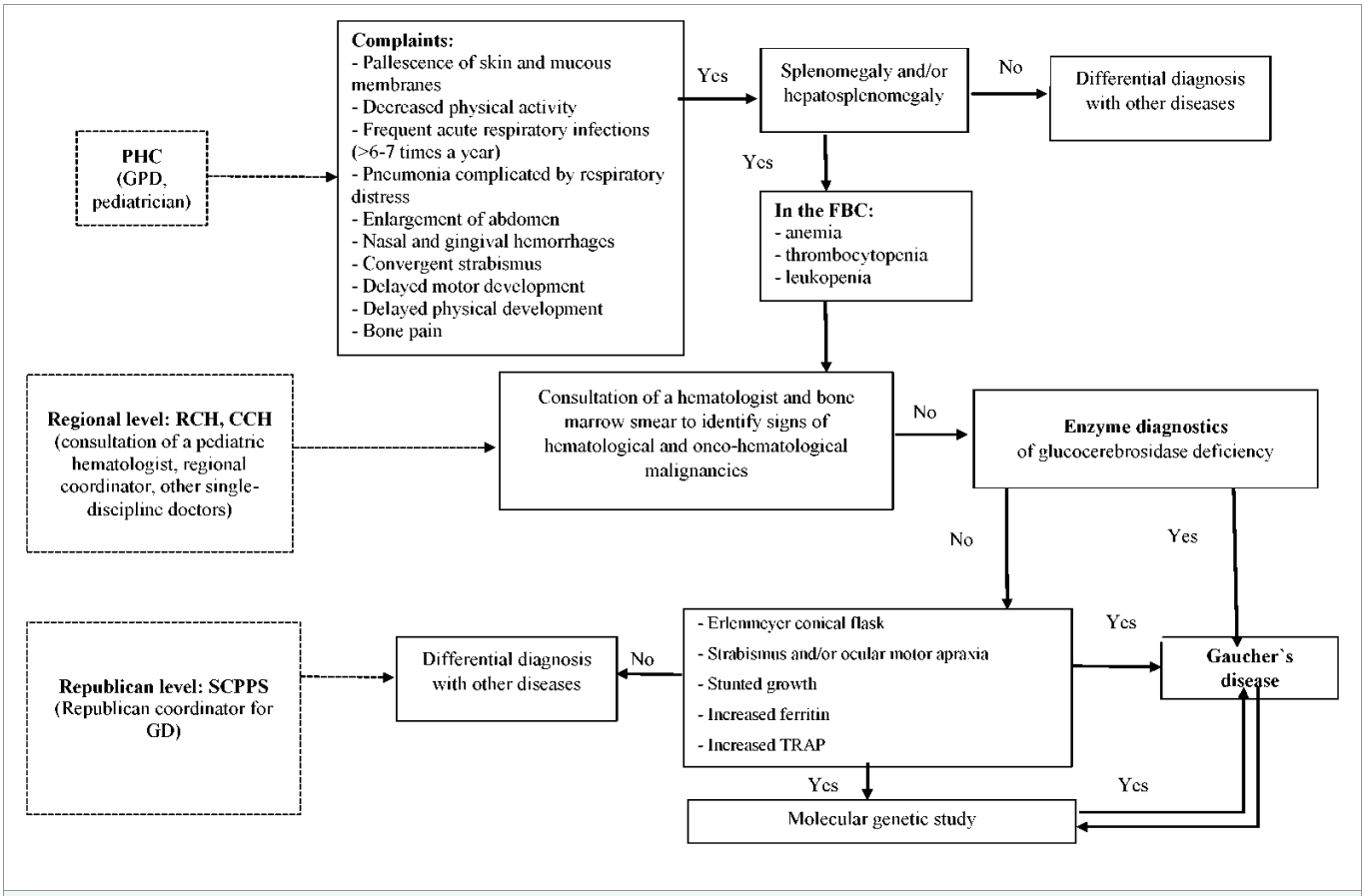

Figure 11: Algorithm for early diagnosis of GD in children, taking into account the patients pathway.

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