ORIGINAL ARTICLE

Gaucher Disease: Clinical phenotypes and GBA1 variants spectrum in Kazakhstani patients

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ABSTRACT

Background and Aim: Gaucher disease (GD) is a rare lysosomal storage disorder caused by mutations in the β-glucosidase (GBA1) gene, with more than 500 variants described. This study aimed to investigate the clinical features and spectrum of GBA1 variants in Kazakhstani patients with GD.

Methods: Medical records from the national referral center for GD in Kazakhstan were reviewed. Forty-five patients with confirmed GD were included. Diagnosis was confirmed by reduced β-glucosidase, glucocerebrosidase enzyme activity, and supported by elevated plasma chitotriosidase activity. The entire coding region of GBA1 was analyzed using bidirectional Sanger sequencing.

Results: Among 45 patients from 38 unrelated families, 15 variants were identified in 20 combinations, including 12 missense variants, 2 nonsense variants, 1 frameshift variant, 1 splice-site variant, and 1 recombinant variant. Of the missense variants, 10 were pathogenic, while 2 novel variants (A316L and F477R) were classified as likely pathogenic. The most frequent variants were L444P (28) and N370S (19). The N370S variant was predominant in GD type 1 (19), whereas L444P occurred in both type 1 (15) and type 3 (11) disease.

Conclusions: This study demonstrated that 28 of 45 patients with GD in the Republic of Kazakhstan have type 1 disease, with the N370S mutation being the predominant genetic variant (28). Among the 17 patients with

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type 2 and 3 GD who had central nervous system involvement, the most frequent finding was the L444P mutation. (www.actabiomedica.it)

Key words: Gaucher disease, variants, β-D-glucocerebrosidase, GBA1 gene

Introduction

Gaucher disease (GD) is a genetic disorder caused by mutations in the GBA1 gene. These mutations lead to a deficiency of the lysosomal enzyme glucocerebrosidase (GCase), which results in the intracellular accumulation of glycolipids. GBA1 gene variants impair the activity of the GCase enzyme, which normally catalyzes the hydrolysis of glucocerebroside into glucose and ceramide. The pathological accumulation of glucocerebroside is a key mechanism underlying the development of GD (1). Although GD is inherited in a monogenic pattern, its clinical manifestations are highly heterogeneous, ranging from asymptomatic forms to severe, life-threatening phenotypes. In its multisystemic course, GD may present with progressive enlargement of parenchymal organs, gradual bone marrow infiltration by lipid-laden macrophages leading to anemia and thrombocytopenia, hepatosplenomegaly, skeletal involvement (including bone pain, avascular necrosis, and osteoporosis), as well as central nervous system impairment. GBA1 gene is located on chromosome 1q22 and consists of 12 exons and 11 introns. According to the Human Gene Mutation Database (HGMD), about 560 GBA1 variants associated with GD have been reported. These include frameshift, missense, deletion mutations, and other genetic changes. Biallelic GBA1 variants lead to GD, whereas both biallelic and monoallelic GBA1 variants have been linked to an increased risk of developing Parkinson's disease (2). The spectrum of GBA1 mutations varies across different populations. For instance, the p.Leu483Pro (L444P) variant is predominant in India, whereas the c.84dupG (84GG) is very common among Ashkenazi Jews, accounting for up to 96% of cases. In other populations, its frequency is significantly lower, around 50–60%. The L444P and RecNciI variants are frequently observed in patients with neuropathic forms of GD (types 2 and 3) in China, Japan, and Korea (3–5). In the Republic of Kazakhstan, 46 patients with GD have been registered over the past 10 years. However, the present study is the first to provide a detailed description of the clinical characteristics and the spectrum of GBA1 mutations in Kazakhstani patients. The aim of this study was to investigate the clinical features, the spectrum of GBA1 variants, and their impact on the clinical and laboratory manifestations of GD in the Kazakhstani population.

Materials and Methods

This, retrospective and prospective cohort study included patients with GD registered at the Scientific Center of Pediatrics and Pediatric Surgery and the Scientific Center of Cardiology and Internal Medicine from 2011 to 2024. A total of 46 patients were registered in the population during this period; however, only 45 patients were enrolled in the study, as genetic testing had not yet been performed for one patient. Data were derived from the national GD registry's electronic health records. The diagnosis was established based on clinical evaluation, laboratory tests, genetic analysis, and imaging. Clinical, laboratory, and instrumental data were obtained from the patients' medical records at the time of diagnosis. Genetic analysis, determination

of glucocerebrosidase (GCase) activity, as well as measurement of glucosylsphingosine (Lyso-Gb1), chitotriosidase, osteocalcin, parathyroid hormone, and vitamin D levels were performed prospectively at the time of diagnosis.

Genetic analysis

The GBA1 gene was analyzed using amplicon-based next-generation sequencing (NGS), covering the full coding region and conserved exon–intron junctions, with a minimum coverage of >20×. Low-quality or missing regions were confirmed by Sanger sequencing to achieve complete coverage. Analyses were performed at the University Medical Center Hamburg-Eppendorf, Centogene (Germany), Archimed Life Genomics (Austria), and the Bochkov Research Centre for Medical Genetics (Moscow).

Measurement of glucocerebrosidase activity

The quantification of the enzymatic product, 4-methylumbelliferone, was performed by fluorometry on a microplate reader (Victor X2, PerkinElmer). This analysis was conducted for all patients at the laboratories of Centogene (Germany) and Archimed Life Genomics (Austria).

Lyso-Gb1 measurement

Blood samples (60 µl) were spotted onto CentoCard® filter paper, air-dried, and 3.2 mm diameter discs (~3.1 µl of blood) were punched from them. The analysis was performed by liquid chromatography using an ACE 3 C8 column on a Waters I-Class UPLC system. The study was conducted at the laboratories of the University Medical Center Hamburg-Eppendorf (Hamburg, Germany), Centogene (Germany), Archimed Life Genetics (Austria), and the Bochkovsky Medical Genetic Scientific Center and Laboratory (Moscow, Russia).

Chitotriosidase measurement

Chitotriosidase activity was determined by measuring its hydrolytic activity in serum using a fluorescent chitotriose analog. The analyses were performed at the laboratories of Centogene (Germany) and Archimed Life Genomics (Austria).

Osteocalcin measurement

Osteocalcin was determined by electrochemiluminescence immunoassay on a Cobas 6000 analyzer (Roche Diagnostics, Switzerland). The Elecsys N-MID Osteocalcin kit (Roche Diagnostics, Switzerland) was used as reagents. The study was conducted according to the instructions for the reagent kit.

Parathyroid hormone measurement (PTH)

PTH was determined by a solid-phase, enzyme-amplified, two-step chemiluminescent immunometric assay on a Cobas 6000 system (Roche Diagnostics, Switzerland). The Elecsys PTH (1-84) reagent kit (Roche Diagnostics, Switzerland) was used for the analysis. The study was conducted according to the instructions for the reagent kit.

Vitamin D (25-Hydroxycalciferol) measurement

The level of 25-hydroxyvitamin D was determined by an enzyme-linked fluorescent immunoassay (ELFA) using VIDAS family analyzers (bioMérieux, France). The VIDAS 25 OH Vitamin D TOTAL (VITD) reagent kit (bioMérieux, France) was used for the analysis. The study was conducted according to the manufacturer's instructions.

Measurement of ionized calcium

The concentration of ionized calcium was determined in blood plasma using an ion-selective electrode on an automated Cobas 6000 analyzer (Roche Diagnostics, Switzerland). The analysis was performed according to the manufacturer's instructions for the reagent kit.

Laboratory findings

In the complete blood count (CBC), levels of hemoglobin and platelets were evaluated. Anemia

was classified as severe for hemoglobin levels below 70 g/L, moderate for levels from 70 to 109 g/L, and mild for levels from 110 to 119 g/L. Thrombocytopenia was classified as severe for a platelet count below 50 x 10^9/L, moderate for a count from 51 to 100 x 10^9/L, and mild for a count from 101 to 150 x 10^9/L.

Radiological assessment

X-rays of the femur including the hip and knee joints in the anteroposterior view were obtained using a Philips PCR Eleva digital X-ray system (The Netherlands).

Ultrasound examination of the liver and spleen was performed in all patients upon hospitalization using a "Logiq P6" ultrasound machine (General Electric, USA). The following probes were used:

- Microconvex universal intracavitary probe, broadband, multi-frequency, 4.2–10.0 MHz;
- Linear broadband multi-frequency probe, 4.2–13.0 MHz;
- Convex broadband multi-frequency probe, 2.0–5.5 MHz.

Liver and spleen fibroelastometry

Liver and spleen fibroelastometry was performed using a FibroScan 502 device (EchoSens SA, France) with three probes corresponding to the patients' chest circumference: Small 1 (< 45 cm), Small 2 (45–75 cm), and Medium (> 75 cm). The study was conducted at the Institute of Gastroenterology, Hepatology and Metabolism, LLP, in Almaty, Kazakhstan.

Statistical analysis

Statistical analysis and data visualization were performed using the R 4.4.2 environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria), GraphPad Prism, and StatTech v. 3.1.10 (developed by StatTech LLC, Russia). Quantitative variables with a normal distribution were described using mean values (M) and standard deviations (SD). The precision of the mean values was reported using 95% confidence intervals (95% CI).

Results

By ethnicity, out of 45 patients, 32 were of Kazakh nationality, 4 were Russian, 3 were of mixed nationality, 1 was Uzbek, 1 was Uyghur, 1 was Tatar, 1 was Korean, and 2 were Ingush. The distribution of patients by GD type was as follows: 28 patients with type 1, 4 with type 2, and 13 with type 3. Analysis of the time to diagnosis revealed significant differences depending on the disease type, with the overall mean diagnostic delay being 5.3 years. A diagnosis was established within the first year of clinical symptom onset in only 3 patients with type 1. In most cases, the diagnosis of GD was established late. A diagnostic delay of 1 to 5 years was observed in 8 patients, 5 to 30 years in 13 patients, and in 3 patients, the diagnosis was made only after 30 years or more following disease manifestation. In patients with type 2 GD, the diagnosis was established within the first year of clinical symptom onset in 2 children and within 1 to 3 years in 2 children. For patients with type 3, the diagnosis was made within 1 year in 3 patients and from 1 to 3 years in 9 patients (Table 1).

Thus, in the overall cohort, a diagnosis was established within the first year of clinical symptom onset in only 9 out of 45 patients. Moreover, patients with type 2 and type 3 GD were diagnosed earlier compared with those with type 1, in whom the prediagnostic period could last for several years. In addition, the analysis demonstrated that enzyme replacement therapy (ERT) was not always initiated immediately after diagnosis: on average, patients started treatment 1.1 years after the diagnosis was established. The determination of β-glucocerebrosidase enzyme activity was performed in all 45 patients at the time of diagnosis. The median enzymatic activity in the overall cohort (n=45) was 0.89 μmol/L/h, whereas in type 1 it was 0.9 μmol/L/h, in type 2 – 0.5 μmol/L/h, and in type 3 – 0.8 μmol/L/h. Of the 45 patients, 43 had anemia of varying degrees, with a predominance of moderate and severe forms. Thrombocytopenia was observed in 42 patients, most often of moderate and severe degrees (Table 2).

The levels of the metabolic biomarkers Lyso-Gb1 and chitotriosidase were determined in 30 and 28 patients, respectively. The mean values of these markers

Table 1. Duration of the pre-diagnostic period in GD.

Time from symptom onset to diagnosis	N=45		Type 1 n=28	Type 2 n=4	Type 3 n=13
	abs	%	abs	abs	abs
less than 1 year	9	20	3	2	4
from 1 to 5 years of age	20	44.4	8	2	10
from 5 to 30 years of age	13	28.8	13	-	-
30 years and older	3	6.6	3	-	-

Table 2. Prevalence and severity of anemia and thrombocytopenia in patients with GD.

Indicator	M	Range	Number of patients by severity degree			
			mild	moderate	severe	a total of
Hemoglobin (g/L)	78,5	47-126	13	18	12	43(95.5%)
Platelets x10^9/L	89	32-256	6	32	4	42(93.3%)

were significantly higher than normal, which confirms metabolic disturbances (Table 3). To assess bone metabolism, levels of ionized calcium, parathyroid hormone, vitamin D, and osteocalcin were determined. Patients with GD showed hypocalcemia and vitamin D deficiency, which is associated with a high frequency of skeletal complications (Table 3).

Spleen elastography was performed in 16 patients at the time of diagnosis, with varying degrees of fibrosis detected in 12 of them. Splenic fibrosis was found in 2 patients with grade 1, 6 with grade 2, 5 with grade 3, and 3 with grade 4. Splenic fibrosis was identified with the following distribution by grade: Grade I (n=2), Grade II (n=6), Grade III (n=5), and Grade IV (n=3). Radiological changes in the musculoskeletal system included Erlenmeyer flask deformity of the bones (14 cases), rarefaction of bone tissue (19 cases), and signs of osteonecrosis (9 cases). Magnetic resonance imaging (MRI) of the femur in 16 patients showed infiltration of the bone marrow by Gaucher cells. Osteodensitometry performed in 10 patients revealed osteopenia (5 cases), osteoporosis (3 cases), and osteonecrosis (2 cases). These findings underscore the critical need for regular monitoring of skeletal complications in patients with Gaucher disease. Among 45 patients from 38 unrelated families who underwent molecular genetic testing, a total of 15 distinct mutations were identified, represented in 20 different allelic combinations. These included 12 missense variants, 2 nonsense mutations, 1 frameshift mutation, 1 splice-site mutation, and 1 recombinant mutation. Of the 12 missense variants, 10 were classified as pathogenic, while 2 previously unreported variants (A316L and F477R) were categorized as likely pathogenic, thereby warranting inclusion in the Human Gene Mutation Database (HGMD). In our study of GD patients in Kazakhstan, the most frequently identified variants were L444P (n=28) and N370S (n=19). The N370S variant was dominant in Type 1 GD ($p<0.001$), whereas L444P was found in both Type 1 and Type 3. The RecNcil variant was predominantly detected in patients with Type 2 GD ($p<0.001$), which confirms its association with more severe forms. The frequencies of other rare variants are presented in Table 4 and Figure 1.

The c.1448T>G (L444P) variant was the most common and was identified in 28 patients, of whom 22 were heterozygous and 6 were homozygous. In the heterozygous state, L444P was combined with F252I and RecNciI variants in 4 patients. The c.1448T>G (L444P) variant was the most prevalent and was detected in 28 patients, of whom 22 were heterozygous

Table 3. Biomarker surveillance in the investigated patient cohort.

Biomarkers	**Indicators, M**
Lyso-Gb1 (ng/ml), Me (Q1-Q3) n=30	271 (121.2–560)
Chitotriosidase (nM/ml/hour), Me (Q1–Q3), n=28	541,5 (188.8–1459.2)
Ionized Calcium (μmol/L/h), Me (Q1–Q3), n=35	0.69 (0.47-0.99)
Osteocalcin, (ng/ml), Me (Q1-Q3), n=35	1.33 (1.2-1,8)
Parathyroid hormone, (pg/ml), M ± SD, n=35	8.34±3.59
Vitamin D, (ng/ml), Me (Q1-Q3), n=35	11.4 (7.45-15.6)

Table 4. Frequency of mutations identified based on the type of GD.

Mutation	**The entire patient cohort (n=45)**	**Type1 (n=28)**	**Type 2 (n=4)**	**Type 3 (n=13)**	**P**
L444P	28 (62.2%)	15 (54%)	2 (50%)	11 (85%)	0.120
N370S	19 (42.2%)	19 (68%)	0 (0%)	0 (0%)	**<0.001**
F213I	5 (11.1%)	2 (7,1%)	0 (0%)	3 (23.1%)	0.337
RecNcil	4 (9%)	0 (0%)	3 (75%)	1 (8%)	**<0.001**
E233D	4 (9%)	1 (3.6%)	1 (25%)	2 (15.4%)	0.159
R120W	3 (7%)	3 (11%)	0 (0%)	0 (0%)	0.654
W184R	2 (4.4%)	2 (7.1%)	0 (0%)	0 (0%)	>0.999
G85E	2 (4.4%)	2 (7.1%)	0 (0%)	0 (0%)	>0.999
V398L	1 (2.2%)	1 (4%)	0 (0%)	0 (0%)	>0.999
R87Q	1 (2.2%)	1 (4%)	0 (0%)	0 (0%)	>0.999
R285H	1 (2.2%)	1 (4%)	0 (0%)	0 (0%)	>0.999
N188S	1 (2.2%)	1 (4%)	0 (0%)	0 (0%)	>0.999
F477R	1 (2.2%)	0 (0%)	0 (0%)	1 (7.7%)	0.378
D315H	1 (2.2%)	1 (3.6%)	0 (0%)	0 (0%)	>0.999
A316L	1 (2.2%)	0 (0%)	0 (0%)	1 (8%)	0.378

and 6 were homozygous. In the heterozygous state, L444P was found in combination with the F252I and RecNciI variants in 4 patients. The L444P/F252I genotype was identified in one patient with Type 1, who had a high risk of progression to Type 3, as well as in one patient with Type 2. The L444P/N370S, L444P/E233D, L444P/G85E, L444P/N188S, and L444P/? (unknown allele) genotypes were found in 23 cases (85.1%) among patients with Type 1 disease. In the homozygous state, the variant was found in 5 patients with Type 3 and 1 patient with Type 1 disease. The second most frequent variant in the GBA1 gene, N370S, was found in 19 cases, of which 13 were in a heterozygous state in combination with the L444P, R120W, and W184R variants. In the homozygous state, it was found in 5 cases, exclusively in patients with Type 1 GD. The next most frequently identified variant in this study was the complex recombinant RecNcil allele in exon 11 (Table 5). This variant was detected in the homozygous state in 3 patients with Type 2 GD, as well as in a complex heterozygous genotype in 1 patient with Type 3 disease. The F252Ile variant was identified in a compound heterozygous state in 3 patients with Type 3 GD. Similarly, the E233D variant was detected in a heterozygous form in 3 patients in combination with another variant. In this study, new variants F477 and A316L were identified, associated with Type 3 GD. In a patient with the F477 variant, who

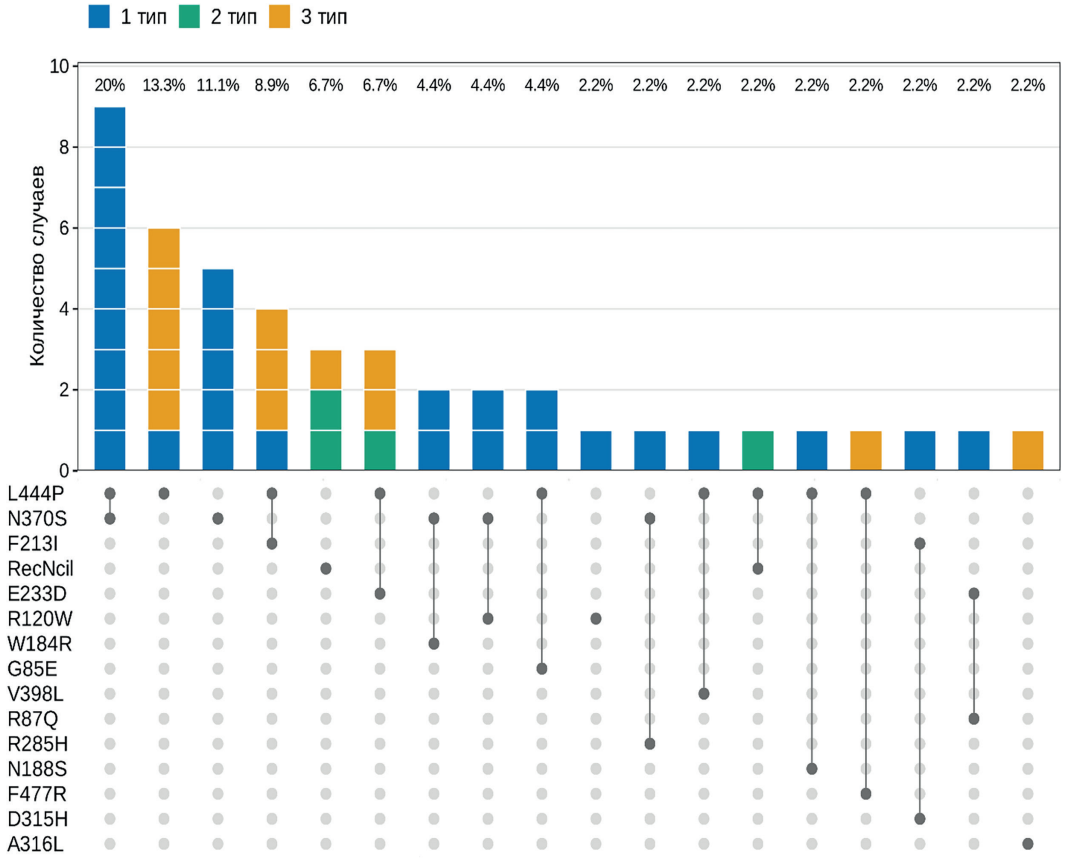

Figure 1. Spectrum of variants in GD in Kazakhstani patients.

phenotypically corresponded to Type 3, this variant was detected in a heterozygous state, with the second allele being L444P. A second patient with the A316L variant in a homozygous state phenotypically corresponded to Type 2 GD.

At the time of diagnosis, all patients exhibited hepatosplenomegaly. This was more pronounced in patients with Type 1 and Type 2 GD compared to those with Type 3. Subsequently, 14 of the 45 patients underwent splenectomy. At the onset of GD, a hemorrhagic syndrome was detected in 30 patients, primarily in the form of epistaxis and subcutaneous hematomas, more often in patients with Type 1 disease. Bone pain was observed in 28 patients, 3 of whom developed episodes of bone crises mimicking acute osteomyelitis. Over time, 12 patients developed severe skeletal complications, including avascular necrosis, pathological fractures, and compression fractures. At the time of GD diagnosis, fractures were detected in 9 patients, predominantly in those with Type 1 and Type 2 disease. Kyphoscoliosis was diagnosed in 3 patients with Type 3 GD. Respiratory system involvement was observed in 15 children, mainly as pneumonia, more frequently in Type 2 and Type 3 disease. Neurological symptoms (bulbar disorders, tetraparesis, oculomotor disturbances, parkinsonian syndrome) were observed in 17 children and occurred exclusively in Type 2 and Type 3. All patients with Type 2 GD were found to have the RecNciI variant, which is associated with an aggressive disease course. A comparison of clinical manifestations based on GD type is presented in Table 6.

Analysis of the clinical manifestations of GD depending on the disease type showed that hemorrhagic and bone pain syndromes with fractures were most pronounced in type 1, which is associated with

Table 5. Genotype-phenotype characterization of GD patients in Kazakhstan.

Patient	GD Type	Genotype	P*	P	gDNA	Zygosity	Exon
AT	I	c.1226A4G (N370S)	Asn409Ser	-	-	homozygous	9
BA	I	c.754T4(F213l[d]), c.1448T4C(L444P)	Phe252lle	Leo483pro	g.7319T4C	heterozygous	6/10
VA	I	c.1226A4G(N370S), c.667N4C(W184R)	Asn409Ser	Tr223Arg	g.434N4C	heterozygous	*9/6*
GB	I	c.1448T4C(L444P)	Leo483pro			homozygous	10
EP	I	c.1226A4G(N370S), c.475C4T(R120W)	Asn409Ser	Arg159Trp	g.394C4T	heterozygous	9/5
EE	I	c.1226A4G(N370S)	Asn409Ser			homozygous	9
GT	I	c.1226A4G(N370S), c.475C4T(R120W)	Asn409Ser	Arg159Trp	g.394C4T	heterozygous	9/5
GE	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	heterozygous	9/10
GE	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	heterozygous	9/10
IG	I	c.1060G>A(D213H), c.754T4(F213l[d])	p.Asp354His	Phe252lle	g.4430T4C	heterozygous	8/6
KH	III	c.754T4(F213l[d]), c.1448T4C(L444P)	Phe252lle	Leo483pro	g.7319T4C	heterozygous	6/10
KB	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	heterozygous	9/10
KD	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	heterozygous	9/10
KA	III	c.1448T4C(L444P)	Leo483pro			homozygous	10
KA	I	c.475C4T(R120W)	Arg159Trp			homozygous	5
KH	III	c.1448T4C(L444P), c.86A4C(E233D)	Leo483pro	p.Glu272Asp	g/504A4C	heterozygous	9/7
NT	I	c.1448T4C(L444P), c.680A4C(N188S)	Leo483pro)	p.Asn227Ser	g.4356A4G	heterozygous	9/6
TT	III	c c.754T4(F213l[d]), c.1448T4C(L444P)	Phe252lle	Leo483pro	g.7319T4C	heterozygous	6/10
TU	III	c.1448T4C(L444P)	Leo483pro			homozygous	10
TR	III	c.1448T4C(L444P)	Leo483pro			homozygous	10
AT	III	c.1448T4C(L444P)	Leo483pro			homozygous	10
AD	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	heterozygous	9/10
VS	I	c.1226A4G(N370S)	Asn409Ser	Leo483pro		homozygous	9
VT	I	c.1226A4G(N370S)	Asn409Ser	Leo483pro		homozygous	9
EB	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	homozygous	9/10
EG	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	heterozygous	9/10
ZE	I	c.970C4T (R285H), c.1226A4G(N370S)	Arg324His	Asn409Ser	6728F4G	heterozygous	7/10
KS	I	c.1226A4G(N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C		9/10
MB	I	?(R87Q), c.816A4C(E233D)	?	Glu272Asp	g.5047A4C	heterozygous	?/7
NB	I	c.1309G4C(V398L), c.1448T4C(L444P)	Val437Leu	Leo483pro	g.7319T4C	heterozygous	9/10

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SA	I	c.2554G4C(G46E), c.1448T4C(L444P)	Gly85EGlu	Leo483pro	g.7319T4C	heterozygous	3/9
SY	I	c.1448T4C(L444P), c.2554G4C(G46E)	Leo483pro	Gly85EGlu	g.2632G4A	heterozygous	9/3
AA	II	c.2554G4C(G46E), c.1448T4C c.1483 G4C c.1497G4C(RecNcil)	Gly85EGlu	(p.Leu483Pro p.A495Pro p.Val499Pro)		heterozygous	9/11
IN	II	c.1448T4C c.1483G4C c.1497G4C	RecNcil	p.Leu483Pro p.A495Pro p.Val499Pro		heterozygous	11
KZ	I	c.1226A4G (N370S), c.1448T4C(L444P)	Asn409Ser	Leo483pro	g.7319T4C	heterozygous	9/10
KR	III	c.1448T4C(L444P)	Leo483pro			homozygous	10
KA	II	c.1448T4C(L444P), c.86A4C(E233D)	Leo483pro	p.Glu272Asp	g/504A4C	heterozygous	10/7
MA	I	c.1226A4G(N370S)	Asn409Ser			homozygous	10
RA	I	c.1226A4G(N370S), c.667N4C(W184R)	Asn409Ser	Tr223Arg	g.434N4C	heterozygous	10/6
SA	III	c.754T4(F213l[d]), c.1448T4C(L444P)	Phe252lle	Leo483pro	g.7319T4C	heterozygous	9/10
TA	III	c.1448T4C, c.1483G4C, c.1497G4C(RecNcil)	p.Leu483Pro p.A495Pro p.Val499Pro			homozygous	11
TE	III	c.816A4C(E233D), c.1448T4C(L444P)		Leo483pro	g.7319T4C	heterozygous	7/10
TA	III	?(F477R), c.1448T4C(L444P)	?	Leo483pro	g.7319T4C	heterozygous	7/?
ND	III	c.947G4T (Arg316L),?	?π	He oπp.	He oπp.	heterozygous	He oπp.
IE	II	c.1448T4C, c.1483G4C, c.1497G4C(RecNcil)	p.Leu483Pro p.A495Pro p.Val499Pro			homozygous	11

† Genomic DNA (gDNA) nucleotide positions (designated as "g.") are numbered starting from nucleotide 11, according to the reference sequences for GBA (GenBank J03059.1) and the pseudogene GBAP (GenBank J03060.1).

‡ Amino acid changes (designated as "p.") are described based on the primary translation product of the GBA gene, including the 39–amino acid signal peptide.

marked thrombocytopenia and infiltration of the skeletal system by Gaucher cells. CNS and respiratory system involvement were characteristic of types 2 and 3 (neuronopathic forms) of the disease.

Discussion

This study aims to present the GBA1 gene variants and their association with the clinical manifestations of GD in Kazakhstani patients. Of the 45 patients included in this study, the disease manifested during childhood in 91.1%. The most prevalent phenotype in the Kazakhstani population was Type 1 GD, which was detected in 62.2% of patients; Type 3 was observed in 29% of patients, and Type 2 was recorded in only 9%. Thus, the non-neuronopathic form of GD (Type 1) was predominant among the studied cohort. These results are consistent with previously published global studies (6), confirming that Type 1 GD remains the most common disease phenotype. This study aims to present the GBA1 gene variants and their association with the clinical manifestations of GD in Kazakhstani patients. Of the 45 patients included in this study, the disease manifested during childhood in 91.1%. The most prevalent phenotype in the Kazakhstani population was Type 1 GD, which was detected in 62.2% of patients; Type 3 was observed in 29% of patients, and Type 2 was recorded in only 9%. Thus, the non-neuronopathic form of GD (Type 1) was predominant among the studied cohort. These results are consistent with previously published global studies (6), confirming that Type 1 GD remains the most common disease phenotype. Genetic analysis revealed that the L444P variant was present in 62.2% of patients. The frequency of this variant varied, ranging from 54% in patients with Type 1 GD to 85% in those with Type 3. This distribution aligns with trends previously reported in the literature. For instance, according to Tylki-Szymańska et al. (7), the L444P variant is predominant in patients with neuronopathic forms of GD, reaching 70–90% of cases. Similar data were also presented in the work by Wang et al. (8), where the frequency of L444P was 61.5% in patients with Type 3 disease. The N370S variant was found in 42.2% of patients in the present study, which is expected for populations with a predominance of non-neuronopathic forms of the disease. This is consistent with data from Western European and Jewish populations (45% to 70%) as reported by Beutler et al. (9) and Horowitz & Zimran (10). The high frequency (75%) of the RecNcil variant in Type 2 patients within our study cohort deserves special attention. This significantly exceeds the data from the global ICGG registry, where it is found in 10–30% of Type 2 cases (11). This finding may indicate specific features of the variants distribution within this population or may be due to the limited size of our sample. The F213I variant, found in 23.1% of patients with Type 3 GD, is also of interest, as it is mentioned as being extremely rare in most studies, such as that by Nalysnyk et al. (12). Such an increase in frequency may be related to regional or ethnic specificities. The R120W genotype was found in 3 (7%) patients with Type 1 disease in our study. Although it has been previously reported in the literature that the R120W variant is associated with Type 2 GD (5), in this study it was identified among 6 (13.3%) rare alleles and was found in combination with the neuroprotective N370S variant, predominantly in patients with Type 1 disease. The rare variants A316L and F477R, found in two of our GD patients, have not been previously described in the literature. CNS involvement in these patients was observed from the age of 1.5 years, manifesting as severe epilepsy and oculomotor apraxia. Both patients also had visceral and hematological manifestations, with a fatal outcome before the age of 4. In a study by Hruska et al. (13), it is noted that rare variants in the GBA1 gene can influence the clinical course of GD, including more severe forms that present in infancy with rapid progression of neurological deficits. This may also be associated with variants such as A316L and F477R. The observed frequency of the rare variants (W184R, G85E, V398L, R87Q, R285H, N188S, F477R, D315H, A316L) is within the range of 2.2–7%, which is comparable to data in the literature. For instance, according to Koprivica et al. (14), the total frequency of rare alleles accounts for approximately 10% of all GBA1 gene mutations. Thus, we conducted a literature review, the results of which are presented in a comparative table (Table 7). According to our study, the frequently found L444P alleles in the Kazakhstani population are

Table 6. Comparison of clinical manifestations based on GD type.

	General population, n=45		Type 1, n=28	Type 2, n=4	Type 3, n=13
Clinical manifestations	абс	%	абс	абс	абс
Hemorrhagic syndrome	30	66.6	25	-	5
Bone pain syndrome	28	62.2	22	2	4
Bone crises	3	6.7	3	-	-
Fractures	9	20	8	1	-
Respiratory system engagement	15	33.3	5	3	7
Central Nervous System involvement	17	37.7	4	4	9

Table 7. A comparative study of the most common GD variants in Kazakhstan and other populations.

P	**Commonly observed mutant alleles**							**Other alleles***		
Kazakhstan	L444P	N370S	F213l	Rec	G85E	W184R	E233D			
Japan (19)	L444P	-	F213l	-	-	-	-	D409H		
China (20)	L444P	-	F213l	-	-	-	-	R353W	N382K	L383L
Korea (5)	L444P	-	F213l	-	G85E	-	-	R296Q	N227S	
Turkey (21)	L444P	N370S	-	-	-	-	-	L385R		
Israel (22)	L444P	N370S	-	-	-	-	-	84GG- Ashkenazi ; L29Afs18		
Eyrope (23)	L444P	N370S	-	Rec	-	-	E233D	D409H	G377S	P266l
Russia (24)	L444P	N370S	-	-	-	W184R	-			
India (25)	L444P	-	-	-	-	-	-			

*Mutations characteristic of these countries, not found in the Republic of Kazakhstan.

characteristic of almost all countries, including those in Asia, Europe, Israel, Turkey, and India. In addition, the N370S allele found in our population in 42.2% of cases was also characteristic of patients in Turkey, European countries and Russia. The F213I variant, which is characteristic of the Kazakhstani population, is also found in Japan, Thailand, and Korea, but not observed in other countries. The G85E variant, most characteristic of the Korean population, was also found in one patient of Korean ethnicity in our study. The W184R allele has been described in Russian studies, and the E233D variant in studies from Europe.

Laboratory analysis showed that the mean level of β-glucocerebrosidase activity was 0.89 μmol/L/h, compared to a normal value of 4.1 μmol/L/h. This finding is consistent with data from other studies. A reduction in activity to less than 15% of the normal value is considered the "gold standard" for diagnosing Gaucher disease and is typically accompanied by an increase in chitotriosidase (22). In the examined patients, chitotriosidase activity ranged from 188.8 to 1459.2 nM/ml/h, which was significantly higher than the normal range. An increase in Lyso-Gb1 was also detected (median 271 ng/ml), which is considered a reliable biomarker for the severity and prognosis of Gaucher disease in international studies, especially in patients with Type 3, who have a high risk of neurodegenerative complications, including Parkinson's disease (23). The phenotypic manifestations of GD in our cohort were highly variable, ranging from an asymptomatic course to severe forms with pronounced cytopenia, hepatosplenomegaly,

and osteoarticular complications. The severity of the laboratory and instrumental findings can likely be explained by the late diagnosis. For instance, in the majority of children, anemia and thrombocytopenia were moderate to severe, which led to the development of hemorrhagic syndrome (67%), while bone pain was noted in 62% and hepatosplenomegaly was present in all 100% of patients. Similar results are consistent with data from Korean authors, who also noted more pronounced bone complications in patients after splenectomy (24). In our cohort, 31% of children underwent splenectomy before the start of enzyme replacement therapy (ERT), and a third of them later developed severe skeletal complications, including the need for joint replacement. Respiratory system involvement was observed in a third of the patients, most often in the form of pneumonia and broncho-obstructive syndrome. Similar data are provided by Gawad et al. (25), who noted respiratory manifestations in 33% of GD patients, as well as by Beutler and Grabowski (9), who associate them with a predisposition to infections and aspiration in Type 2 and 3 of the disease. Neurological involvement in our patients was also characteristic of Types 2 and 3. In three cases, the initial diagnosis of Type 1 was revised to Type 3 due to the development of CNS symptoms. Similar observations have been described in Japanese cohorts, where the diagnosis was reclassified from Type 1 to Type 3 in 43% of patients as neurological manifestations progressed (26).

Conclusion

In the Kazakhstani cohort, 62% of patients with GD were classified as type 1, whereas 38% demonstrated CNS involvement (types 2–3). Notably, 7% of children initially diagnosed with type 1 subsequently developed neurological manifestations and were reclassified as type 3, suggesting that the prevalence of type 3 GD may increase with age. This may suggest that the prevalence of Type 3 GD may increase with age. This suggests that the prevalence of Type 3 GD may increase with age. Molecular genetic analysis revealed the presence of alleles commonly observed in both Caucasian (N409S, L444P) and Asian (L444P, F213I, G85E) populations. Furthermore, our findings provide novel evidence that the A316L and F477R variants of the GBA1 gene may be pathogenic and contribute to the neuropathic phenotype of GD. These results expand the known phenotypic and mutational spectrum of the disease and may serve as a valuable resource for future GBA1 genetic investigations in GD patients. Long-term, detailed clinical follow-up is required to clarify the neuronal effects of the A316L and F477R alleles and to elucidate the mechanisms underlying these associations. Long-term and detailed clinical observation is required to clarify the neural effects of the A316L and F477R alleles and to elucidate the mechanisms underlying these associations. The delay in diagnosis and the initiation of ERT in Kazakhstani patients led to severe hematological, visceral, and skeletal complications, many of which could have been avoided with timely treatment. These results underscore the genetic and phenotypic heterogeneity of GD in Kazakhstan and provide the first detailed description of its molecular spectrum in this population. This is important for increasing the accuracy of diagnosis, ensuring more precise prognostication, and providing informative genetic counseling for affected families, which will lead to improved long-term outcomes for GD patients in Kazakhstan.

Strengths and limitations

This study represents the first comprehensive description of the clinical and genetic spectrum of GD in Kazakhstan. Its strengths include the identification of new GBA1 gene variants (A316L and F477R) and the emphasis on the importance of early diagnosis. Furthermore, a key strength of the work is its comprehensive approach, combining clinical, biochemical, and molecular methods. However, the study has limitations: a relatively small sample size, the retrospective nature of some data, and incomplete information on certain parameters. Furthermore, the majority of patients belonged to a single ethnic group, which limits the generalizability of the results.

Ethic approval: This study was approved by the Institutional Review Board of S.D. Asfendiyarov Kazakh National Medical University IRB No. 916 dated 24.12.2019. The study adhered to the ethical principles, ensuring the protection of participants' rights and confidentiality.

Conflict of interest: Each author declares that he or she has no commercial relationships (e.g., consultancy, stock ownership, equity interest, patent/licensing arrangement, etc.) that could be construed as a potential conflict of interest in connection with this study.

Author contributions: AA: conception/design, drafting, critical revision; RB: drafting, critical revision, final approval; GK: accountability for accuracy and integrity of the work; IJ: drafting, critical revision, financial approval; DI: final approval; All authors contributed to the article and approved the submitted version

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