

Gaucher disease in Syrian children: common mutations identification and clinical futures

Diana Alasmar

From the Children's Hospital Damascus University, Damascus, Syria

Correspondence: Dr. Diana Alasmar · Endocrine and Metabolic Diseases Unit, Children's Hospital Damascus University, Syria · T: 963 11 6623650 F: 963 11 6623040 · dianaasmar11@yahoo.com

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BACKGROUND AND OBJECTIVES: Gaucher disease (GD) is caused by the deficiency of glucosidase beta acid (GBA). Three clinical forms of GD are available. Some mutations in the GBA gene have a high frequency in specific populations. The aim of this study was to analyze the characteristics of phenotypes and genotypes of GD in Syrian pediatric patients and assess whether a genotype-phenotype relationship could be helpful in treatment decision-making.

DESIGN AND SETTINGS: A cross-sectional clinical genetic study of 19 Syrian children admitted to Children's Hospital, Damascus University.

PATIENTS AND METHODS: Nineteen Syrian children with GD were enrolled in the study; DNA was extracted from peripheral blood leukocytes. The GBA gene was amplified by polymerase chain reaction, and the 9 most common mutations were studied using a Gaucher Disease Strip Assay (ViennaLab Diagnostics GmbH, Vienna, Austria).

RESULTS: The majority of children had an early age of onset. A total of 17 patients presented severe hematological and skeletal complications. Neurological involvement was encountered in 2 patients. Twelve patients (63, 2%) were homozygous for the L444P mutation, 1 patient (5.3%) was homozygous for the N370S mutation, and 1 patient (5.3%) was heterozygous for the N370S mutation. Five patients (26.3%) had unknown mutations.

CONCLUSION: L444P/L444P was the most common genotype in the studied patients. GD3 with severe visceral presentation in childhood was the dominant phenotype; N370S was found in the heterozygote state in 1 case and in the homozygote state in 1 case. This phenotype and genotype pattern is encountered in the Middle East. There was no genotype-phenotype correlation.

Gaucher disease (GD) is the most common sphingolipidosis.¹ Three clinical subtypes of GD are delineated by the absence or presence and progression of neurologic manifestations.² GD1, which accounts for more than 90%, has a high incidence in Ashkenazi Jews.^{2,3} The other 2 types are less common (GD2: 1%, GD3: 5%).³ and have no ethnic predilection.² All types are autosomal recessive traits.

GD phenotype is complex.⁴ GD1 or the adult non-neuropathic form is characterized by hepatosplenomegaly, anemia, thrombocytopenia, and bone involvement, with a broad range of severity and age of onset. GD2 or the acute neuropathic form is characterized by early onset of symptoms before the age of 6 months with a rapidly progressing brainstem dysfunction, associated with organomegaly, and leading to death before the age

of 2. GD3, the juvenile or sub-acute neuropathic form is characterized by severe visceromegaly and progressive encephalopathy (oculomotor apraxia, epilepsy, and ataxia). Signs appear during childhood or adolescence. The fetal form manifests with a decrease or absence of fetal movements or anasarca.^{5,6} Gaucher-like disease presents with progressive calcification of the aorta and the aortic and/or mitral valves as its main feature.⁷

GD is due to a deficiency in lysosomal glucosidase beta acid (GBA). It leads to the accumulation of glucosylceramide deposits in the cells of the reticuloendothelial system (Gaucher cells) of the liver, spleen, bone marrow, and cerebral gray matter.^{2,8}

The GBA gene, a 7-kb gene, is located on 1q21 with 11 exons.⁹ There is a highly homologous (96% identity) pseudogene (5 kb) located 16-kb downstream to the

GBA gene.¹⁰ The abnormal alleles include exonic missense and nonsense mutations, splice junction mutations, deletions and insertions of 1 or more nucleotides, and complex alleles resulting from gene conversion or recombination.⁸

N370S, the most common mutation in Ashkenazim, is also frequent in Caucasian populations. The second most frequent mutation, L444P, was first described in Norbotnian GD3.⁸

Genotype-phenotype correlations have been noted.² They are complex, and the molecular analysis has often shown a poor correlation between genotype and phenotype.¹¹ There is a high inter-individual variance in the severity of the clinical manifestations of the same genotype including N370S homozygote.^{12,13}

The L444P mutation is more frequently associated with GD2 and GD3.⁸ Complex alleles due to genetic rearrangements are more often associated with severe forms and perinatal lethal forms.⁸

Later-onset effects of Gaucher disease, such as Parkinsonism and peripheral neuropathies, have been described.¹⁴ Even heterozygosis for a GBA gene mutation may predispose to Parkinson disease.^{15,16}

The biochemical assay of GBA activity is the most reliable method to diagnose GD. However, it can be supplemented by molecular diagnosis.¹⁰ The unfolded protein response assay has been shown to correlate with disease severity.¹⁷

Enzyme replacement therapy (ERT) and substrate reduction therapy are 2 available treatments for GD1 and to some extent GD3; they are ineffective for GD2.^{8,18}

The prognosis is good in GD1, while death usually occurs before the age of 2 in GD2. Without a specific treatment, death progresses within a few years in GD3. ERT has no effect on the neurological manifestations.^{8,19} The magnitude and time course of responses to therapy are also variable.²⁰

This study is the first of the GBA gene mutations in the Syrian population. It aimed to analyze the characteristics of the phenotypes and the genotypes of GD in Syrian pediatric cohort, compare the results with those in the Middle East and the rest of the world, and assess if any genotype-phenotype relationship could be found. The national health system in Syria would refer to this study to introduce GD treatment in its policy in the near future.

PATIENTS AND METHODS

This study was carried out in Damascus University Children's Hospital. It comprised a cohort of 19 GD Syrian Children from unrelated families. They were recruited from the General Pediatrics Unit and Pediatric Hematology Unit in a period of 3 years. Diagnosis depended on clinical presentation and laboratory findings compatible with GD.⁷ These included the presence of organomegaly, neurologic signs, growth failure, blood cytopenia, and high level of acid phosphatase and ferritin. The histologic findings of typical Gaucher cells in bone marrow, liver, or spleen biopsy²¹ was the principal inclusion criteria. We excluded 4 patients negative for Gaucher cells from the study.

The clinical classification of the patients into GD1 or GD2 or GD3 was based on the presence of neurological signs and symptoms and the rate of disease progression.²²

A GBA gene study was performed in the Genetics research laboratory of the Damascus University by using a Kit of Vienna lab Gaucher Disease StripAssay (ViennaLab Diagnostics GmbH, Vienna, Austria). Genomic DNA isolation: DNA was prepared from peripheral blood leukocytes using the salting-out procedure (Miller et al, 1988). The assay includes 3 steps: (1) Polymerase chain reaction amplification using biotinylated primers. (2) Hybridization of amplification products to a test strip containing allele-specific oligonucleotide (ASO) probes immobilized as an array of parallel lines. (3) Bound biotinylated sequences were detected using streptavidin-alkaline phosphatase and color substrates. Affected alleles were detected by allele-specific oligonucleotide hybridization, which allows the identification of homozygote, heterozygote, and normal genotype (Figure 1).

The assay covers 9 common GBA mutations: 84GG

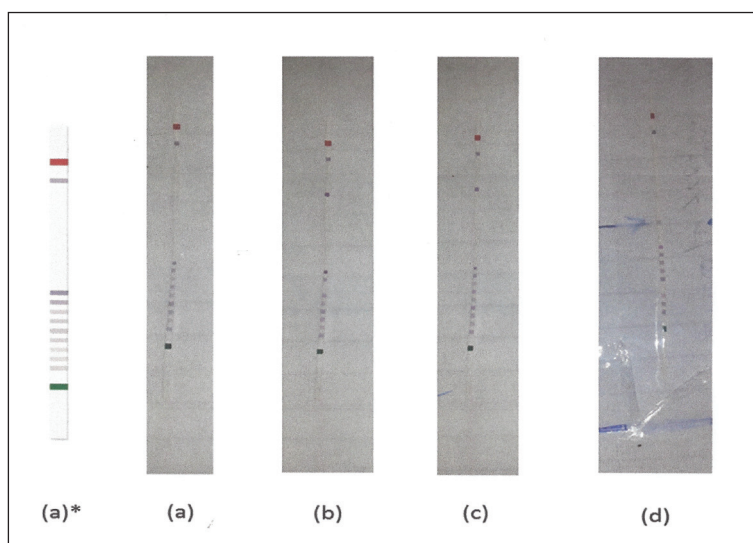


Figure 1. Gaucher Disease Strip Assay results from Dr. A. Ajlouni's collection in Damascus. (a) Unknown mutations (b) N370S/N370S (c) N370/Unknown mutation (d) L444P/L444P.

[452 +G], IVS2+1 [484 G>A], N370S [1226 A>G], V394L [1297 G>T], D409H [1342 G>C], L444P [1448 T>C], R463C [1504 C>T], R496H [1604 G>A], as well as 2 recombinant alleles derived from crossover between the GBA functional gene and pseudogene (*rec NciI*, *rec TL*).

The protocol was reviewed and approved by the Faculty of Medicine Ethics Committee. A written Informed consent was taken from subjects primary caregivers prior to inclusion in the study.

Statistical study

The statistical analysis of data was done using SPSS, version 14.0 (SPSS Inc., Chicago, IL USA). Qualitative data were presented as frequency and proportions, whereas quantitative data were presented as mean

(standard deviation). The Spearman rho correlation coefficient test was used to measure the strength of association between the detected genotypes and disease phenotypes. Results were considered significant at the 0.05 level (2-tailed).

RESULTS

This study includes 19 unrelated Syrian patients comprising 12 females and 7 males. The effect of parents' consanguinity was observed in 16 cases, out of which, 13 parents were first cousins. The family history of GD was positive in 2 cases, and the occurrence of unexplained deaths in infants was observed in 2 of these families (Table 1). The mean age of diagnosis was 19.3 (12.4) months.

A total of 15 patients were presented with the chief

Table 1. Detailed clinical and genotype finding in 19 children with Gaucher disease.

Genotype	Gaucher typical cell (+)	Consanguinity	Familial history	Symptoms and signs (main presentations)	Age at study (Y m/12)	Age at diagnosis (Y m/12)	Sex	Patient's number
L444P/L444P	BM, L, S	+ ^b	+ ^{a1}	Severe visceral ^d	4	10/12	M	1
L444P/L444P	BM, L	+ ^c	-	Severe visceral	1 6/12	1 6/12	F	2
L444P/L444P	BM	+ ^c	-	Severe visceral	2 6/12	2 6/12	F	3
L444P/L444P	BM	-	+	Severe visceral	1 6/12	1 6/12	F	4
L444P/L444P	BM	+ ^b	-	Severe visceral	2	2	F	5
L444P/L444P	BM	+ ^c	+ ^{a2}	Severe visceral	1 2/12	1 2/12	M	6
N370S/ Unknown mutation	BM, L	-	+ ^{a3}	Early severe visceral	2 6/12	2 6/12	F	7
L444P/L444P	BM, S	+ ^b	-	Severe visceral ^d Bone pain	3	1 4/12	F	8
L444P/L444P	BM, L, S	+ ^b	-	Severe visceral ^d	1 6/12	1 6/12	F	9
L444P/L444P	BM, L	+ ^b	-	Severe visceral	2	2	F	10
Unknown mutations	BM	+ ^b	-	Severe visceral	1	1	F	11
Unknown mutations	BM	-	+ ^{a3}	Psychomotor regression Mild visceral	2	2	F	12
Unknown mutations	BM	+ ^b	-	Severe visceral	7/12	7/12	M	13
N370S/N370S	BM	+ ^b	-	Severe visceral ^d Bone pain	9	5	F	14
Unknown mutations	BM	+ ^b	-	Severe visceral Interstitial pneumonia	6/12	6/12	F	15
L444P/L444P	BM	+ ^b	-	Severe visceral	6/12	6/12	M	16
L444P/L444P	BM, L	+ ^b	-	Severe visceral	1 2/12	1 2/12	M	17
L444P/L444P	BM	+ ^b	-	Early visceral	8/12	8/12	M	18
Unknown mutations	BM	+ ^b	-	Early psychomotor regression Spastic palsy Death	2	2	M	19

M, male; F, female; BM, bone marrow; L, liver, S, spleen. ^{a1}Three cousins with Gaucher disease; ^{a2}One cousin with Gaucher disease diagnosed at 6 months of age; ^{a3}Unexplained early deaths in the fraternity; ^bConsanguinity degree III; ^cConsanguinity degree IV or more; ^dSplenectomy.

Table 2. Symptoms and signs in 19 Gaucher disease patients.

Symptoms and signs	Number of patients	Percentage (%)
Hepatosplenomegaly	19	100
Large abdomen	15	79
Failure to thrive	8	42
Underweight	8	42
Splenectomy	4	21
Recurrent fever	3	15.7
Respiratory distress	2	10.5
Bone pain	2	10.5
Interstitial pneumonia	1	5.2
Osteonecrosis	1	5.2
Psychomotor regression	2	10.5
Spastic palsy	1	5.2
Pyramidal signs	1	5.2
Severe malnutrition	1	5.2
Chronic diarrhea	1	5.2
Osteonecrosis lesion	1	5.2
Adenopathy	1	5.2
Death	1	5.2

complaint of large abdominal mass. All the 19 patients had hepatosplenomegaly; it was considered to be extremely large in 8 cases, large in 5 cases, moderate in 4 cases, and mild in 2 cases. Complications such as underweight and/or failure to thrive were found in 8 cases. One patient presented with bone complications after undergoing splenectomy with an osteonecrosis lesion. Four patients needed splenectomy at different ages (1.5, 3, 4, and 9 years), and 1 patient presented with interstitial pneumonia.

Only 2 patients displayed neurological involvement, resulting in early childhood death in 1 case.

Neurological abnormalities were spasticity, squint, and swallowing difficulties in 1 patient and developmental delay in 2 patients (Table 2).

Hypochromic microcytic anemia was found in all patients, with the hemoglobin concentration of 8.4 (1.79) g/dL, platelet count of 115 157.8 (86 113.7) cells/mm², and ferritin concentration of 166 (84.1) ng/mL (Table 3). The level of acid phosphatase was found to be elevated in 18 patients. Nineteen patients were found to be Gaucher cell positive (Table 1).

Clinically 17/19 patients (89.5%) presented with an early severe visceral form. They did not display any neurologic symptoms; phenotype classification of these cases remained uncertain (GD1 or GD3). One patient (5.3%) presented with acute neuropathic form (GD2), and 1 patient (5.3%) presented with chronic neuropathic form (GD3).

L444P was found in 24/38 studied alleles (63.1 %) for a GBA gene mutation assay, N370S was found in 3/38 studied alleles (7.9%), and 11/38 studied alleles (28.9%) remained unknown (Figure 1).

One patient (5.3%) was heterozygous for N370S mutation, and 12/19 patients (63.2%) were homozygous for L444P mutation. They presented no neurologic manifestations at the time of the study. One patient (5.3%) was homozygous for N370S; he was presented with a severe non-neuropathic form. The genotype assay was negative in 5 patients (26.3%): 3 had a severe visceral non-neuropathic presentation, 1 had a chronic neuropathic form, and 1/5 patient had an acute neuropathic form (Tables 1 and 4).

DISCUSSION

This study highlights the pattern of possible GBA gene mutations present in a Syrian pediatric cohort. It is known that 9 common mutations promise the genetic diagnosis in only 50% to 70% of non-Jewish people.^{23,24} Although the L444P mutation is most common worldwide,²⁵ some studies of the rest of world demonstrate the highest prevalence of N370S compared with L444P like in Brazil,²⁶ Mexico,²⁷ Colombia,²⁸ Argentina,²⁹

Romanian,³⁰ and France.³¹ L444P was encountered in more than the half of the muted allele in Egypt¹¹ and Saudi Arabia.³² Furthermore, homozygous for L444P mutations was present in more than half of the patients in a pediatric Egyptian study.³³ Other known common mutation such as RecNcil that was encountered in high frequency in some population like Egypt,¹¹ Tunisia,³⁴ and Argentina²⁹ was not encountered in our study.

The sequencing of GBA gene is needed for all negative results. It is important to define if other rare mutations or some new mutations could be found,²⁴ which are expected in Non-Ashkenazi people.³⁵

Although many studies reported early severe visceral GD with the absence of neurological signs in L444P/L444P genotype.^{30,34} it is accepted that the onset of neurological findings is delayed in GD3. The 12 patients homozygous for L444P who succumbed to early severe visceral GD could be first classified as having GD1.^{36,37}

Furthermore, the prevalence of neuropathic GD appears to be higher in those who are not of European origin including the Middle East, India, China, Japan, and Korea.^{22,38} However, subtle neurological abnormalities can make the diagnosis of neurologic GD difficult.³⁹ Therefore, among the 17 patients with early isolated visceral presentation, only the patient with N370S/N370S genotype could be considered as GD1; the other 16 patients (12 patients with L444P/L444P and 1 patient with N370S/Unknown mutation Genotypes) may need to be reclassified as GD3.⁴⁰

The Spearman rho factor to assess genotype-phenotype correlation showed no significance ($r: -0.358$, 2-tailed: 0.133 , P value $>.05$). Anyway, the ability to predict patient outcome on the basis of DNA studies is often limited.¹

These Syrian genotype-phenotype pattern results could not be considered for the therapeutic judgments.²⁴ Otherwise, ERT may have some benefits in GD3.8 This treatment is well indicated when patients have a progressive visceral form.⁴¹

Table 3. Laboratory finding in 19 children with Gaucher disease.

Descriptive statistics	Minimum	Maximum	Mean	STDV
Age (mo)	6	60	19.3	12.4
Ferretin (ng/mL)	65	380	166	84.1
PLT (Cells/mm ³)	8000	289 000	115 157.8	86 113.7
WBC (Cells/mm ³)	1900	12 700	6040.5	3219.7
HB (g/L)	4.3	11.4	8.4	1.7

PLT, Platelet count; WBC, white blood count; HB: hemoglobin; STDEV, standard deviation.

Table 4. Genotypes and phenotypes in 19 Syrian children with Gaucher disease.

Genotype	Number of patients	Phenotype ^a		
		Type 1	Type 2	Type 3
L444P/L444P	12	-	-	12
N370S/Unknown mutations	1	-	-	1
N370S/ N370S	1	1	-	-
Unknown mutations	5	-	1	4
	19	1	1	17

^aCorrelation value of phenotype and genotype; $r=-0.358$, $P=.133$.

In conclusion, GD3 is the most encountered phenotype, L444P is the most common allele, and L444P/L444P genotype is the most common genotype in studied Syrian children with GD. This phenotype-genotype pattern is encountered in the Middle East. No genotype-phenotype correlation was found; further advanced studies of the GBA gene are needed.

In addition, the treatment decision in the early visceral presentation of GD3 will depend on the clinical course of the disease, and genotype should not interfere in the decision of treatment.

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