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Egyptian Gaucher disease type 3 patients: a large cohort study spanning two decades

Amal El-Beshlawy[1], Khaled Abdel-Azim[1], Amina Abdel-Salam[1], Yasmeen M. M. Selim[1], Fadwa Said[2*], Nadine A. Gebril[1], Ekram Fateen[3] and Pramod Mistry[4]

Abstract

Background Gaucher disease (GD) has been the subject of genotype/phenotype studies as well as therapeutic innovation. A cohort of ethnically homogeneous Egyptian patients suffering from GD type 3 (GD3) is described here, with the effects of enzyme replacement therapy (ERT) highlighted.

Methods We studied the long-term outcome after 20 years of ERT in 85 patients with GD3 registered at the Pediatric Hematology Clinic of Cairo University since 1998. We obtained organ volumes, growth parameters, and neurological assessment at baseline and during ERT.

Results Of the total sample, 77.6% of patients were diagnosed before the age of 2 years. Our patients were highly consanguineous, and 51% had a family history of GD. The most prevalent genotype was homozygous p.Leu483Pro (75.7%), followed by homozygous p.Asp448His (11%). Hemato-visceral aspects of disease included anemia (75.6%), moderate to severe thrombocytopenia (21.7%), severe splenomegaly (49.2%), and severe hepatomegaly (10.8%). One patient had liver cirrhosis with hepatopulmonary syndrome. Oculomotor apraxia, squint, and bulbar symptoms were reported in 48.6%, 30.6%, and 29.4% of patients, respectively. Imiglucerase (Cerezyme) was administered to all patients for reversal of hemato-visceral and growth parameters. The overall survival rate was 71% at 20 years; 20 patients died of pulmonary and neurological diseases.

Conclusion This is the largest single-center study of GD3 patients with predominant homozygous p.Leu483Pro genotype. The patients had a very early onset of disease and severe disease parameters. The renunciation of hemato-visceral disease was achieved effectively by ERT with 71% OS, and one third of patients developed complications.

Keywords Gaucher, Type 3, Pediatrics

Introduction

Gaucher disease (GD) is a recessively inherited error of metabolism caused by a deficiency of glucocerebrosidase [1]. GD patients are classified into three recognized clinical types; nevertheless, GD is considered a phenotypic continuum due to its highly variable clinical picture [2]. Organomegaly, anemia, and thrombocytopenia are the typical features of type 1 GD (non-neuronopathic type), which is considered the most prevalent form and affects 90% of patients diagnosed in Europe, North America, and Australia [3]. The neuronopathic kinds (GD types 2 and 3) are characterized by central nervous system affection. GD type 2 patients (acute neuronopathic) (GD2) suffer rapid deterioration, with death usually occurring before the age of 2 years, while GD type 3 patients (chronic neuronopathic) (GD3) experience a slower disease course [4]. The hallmark clinical abnormality seen in type 3 GD consists of markedly slow horizontal saccades

*Correspondence:
Fadwa Said
f2said@yahoo.com
[1] Department of Pediatrics, Pediatric Hematology and BMT Unit, Faculty of Medicine, Cairo University, Cairo, Egypt
[2] Department of Clinical Pathology, Cairo University, Cairo, Egypt
[3] Department of Clinical Pathology, National Research Centre, Giza, Egypt
[4] Yale School of Medicine, New Haven, USA

[5]. Type 3 GD consists of three different subtypes: type 3a is characterized by progressive dementia, ataxia, and myoclonus and there appears to be variability in the age of presentation as well as the rate of disease progression in affected individuals. Supranuclear gaze palsy, as well as significant bone and visceral involvement, characterize type 3b (Norbottnian Gaucher). Type 3c is characterized by supranuclear gaze palsy, corneal opacity, and cardiac calcification, with little visceral involvement. Neurologic involvement can appear later in life and progress in a variety of ways.

The genotype–phenotype correlation in GD is not absolute, p.Asn409Ser (N370S) is the most common and the mildest GBA mutation. The presence of at least one N370S mutation accurately predicts GD1, while homozygosity for the mutation p.Leu483Pro (L444P) is accurately predictive of neuronopathic GD, although it is not possible to establish whether the patient has GD2 or GD3. Patients with cardiovascular involvement are invariably homozygous for the mutation p.Asp448His (D409H). Homozygosity for the mutations 84GG or IVS2 + 1 are presumed to be lethal.

Enzyme replacement therapy (ERT) and substrate reduction therapy (SRT) have considerably altered the course of GD patients' conditions, resulting in a large reduction in morbidity [1], but these treatments have little effect on the disease's neurological characteristics due to lack of/reduced penetrance of the blood–brain barrier. After therapy with ERT, prospective clinical trials in GD3 patients reveal improvements in hemoglobin and platelet counts as well as a decrease in organ sizes [6].

In our center, the most common type of Gaucher disease was GD type 3. The general illness parameters (demographic, clinical, molecular, and treatment status) of an ethnically homogenous cohort of GD3 patients in Egypt are described here, with a particular emphasis on the impact of ERT on the growth, visceral, and hematological components of the disease.

Methods

Since 1998, 156 GD patients have been managed at the Pediatric Hematology Outpatient Clinic, Faculty of Medicine, Cairo University. The information was gathered after an IRB approval was obtained. Clinical features, biochemical investigation of glucocerebrosidase and chitotriosidase activities in peripheral blood leukocytes and plasma, and GBA gene analysis accomplished by DNA isolation and whole-exome sequencing were used to identify all patients as GD3. We reviewed the data of 85 individuals with GD3 registered in 1998 who had a long-term prognosis following a 20-year course of enzyme replacement therapy in the current investigation. Patients were classified as GD3 based on GBA1 genotyping ($n = 37$) or the appearance of variable CNS manifestations during the follow up period ($n = 48$). However, 22 patients had no neurological manifestations at diagnosis.

At baseline and during ERT, clinical phenotypic indicators such as organ volumes, growth parameters, neurological assessment, and bone affection were acquired. Diagnostic laboratory findings at presentation including hemoglobin levels, platelet counts, bone marrow aspirate (BMA), and enzyme assay at diagnosis were recorded. All patients had been tested for peripheral blood leucocyte acid β-glucosidase activity and plasma activity of chitotriosidase, which showed acid β-glucosidase enzyme activity below the normal level, while the level of chitotriosidase enzyme was above the normal level.

Hemoglobin levels and platelet counts during follow-up visits were also recorded. The hemoglobin level was analyzed as a binary variable, and anemia was defined as below the reference age- and sex-adjusted value as follows [7]:

Platelet counts were used to classify thrombocytopenia into the following groups: severe ($< 60 \times 10^3/\mu L$), moderate ($60 \times 10^3/\mu L$ to $120 \times 10^3/\mu L$), and mild/normal ($> 120 \times 10^3/\mu L$) [7].

Organ volumes were measured using abdominal ultrasonography and expressed as multiples of the normal size predicted for body weight (MN) [8]. The formula devised by Elstein et al. was used to convert ultrasound readings to volumetric equivalents [9]. Splenomegaly was classified into the following groups [7]:

Hepatomegaly was classified into the following groups [7]:

Additional data obtained in the current analysis included orthopedic imaging including plain X-ray images for long bones and chest and dual-energy X-ray absorptiometry (DEXA). Dual-energy X-ray absorptiometry scanning of the lumbar spine was used to assess bone mineral density in patients with GD. Brain imaging including electroencephalogram (EEG) and brain CT; bone marrow aspirate (BMA) data, which was an old technique used in GD diagnosis performed for selected patients; GD treatment information; and adverse event data, all were also obtained in the current analysis.

The data was compiled and significance was determined using SPSS version 24 (Statistical Package for the Social Sciences). Quantitative data were expressed as mean, median, standard deviation, minimum, and maximum, while categorical data were expressed as frequency (count) and relative frequency (percentage). The non-parametric Friedman test and Wilcoxon signed-rank test were used [10]. Survival analysis was performed by Kaplan–Meier analysis. The term "overall survival" refers to the time span between when a patient is diagnosed and when they die. Patients alive or lost during follow-up

Table 1 Classification of anemia according to age and sex [7]

Age	Hemoglobin level
< 6 months	< 9.1 g/dL
6 months to < 2 years	< 8.5 g/dL
2 years to < 12 years	< 9.5 g/dL
≥ 12 years	
Boys	< 11 g/dL
Girls	< 10 g/dL

Table 2 Classification of splenomegaly according to organ volume assessed by abdominal ultrasonography [7]

Splenomegaly	Organ volume expressed in multiples of normal
Mild/normal	≤ 5 MN
Moderate	> 5 to 15 MN
Severe	> 15 MN

MN multiples of normal

were considered censored until the last date of follow-up. Statistical significance was defined as a *P* value of less than 0.05.

Results

Our cohort consisted of 85 patients classified as type 3a GD (7%), type 3b GD (64.7%) and type 3c GD (28.2%) based on assessment by the treating physician ± molecular genetic studies.

The median age of diagnosis was 1 year (IQR 0.08–15 years), with the majority of patients (77.6%) diagnosed before the age of 2 years (IQR 0.5–2 years). Consanguinity was detected in 85.9% of our patients, and 51% had family history of GD (Table 1).

Homozygous p.Leu483Pro was the most prevalent GBA genotype (75.7%) detected in our patients followed by homozygous p.Asp448His (11%) among the 37 patients who underwent GBA gene analysis. Other mutations are illustrated in (Table 2).

Patients' hematological characteristics revealed anemia at the time of diagnosis in 75.6% of patients and moderate to severe thrombocytopenia in 21.7% of patients. Thirty (35.2%) of our patients received packed RBCs, plasma, or platelet transfusion around the time of diagnosis. Massive splenomegaly (15 MN by abdominal ultrasonography) was detected in 49.2% of patients, four patients were splenectomized, and two (2.3%) patients had splenic infarctions and calcifications. Severe hepatomegaly (˃ 2.5 MN) was detected in 10.8% of patients (Table 3). Only one patient had liver cirrhosis complicated with hepatopulmonary syndrome.

Table 3 Classification of hepatomegaly according to organ volume assessed by abdominal ultrasonography [7]

Hepatomegaly	Organ volume expressed in multiples of normal
Mild/normal	≤ 1.25 MN
Moderate	> 1.25 to 2.5 MN
Severe	> 2.5 MN

MN multiples of normal

Table 4 Neurological manifestations of patients with GD3

Neurological manifestations	Number	Percentage
Oculomotor apraxia	41	48.2%
Squint	26	30.6%
Dysphagia	14	16.5%
Chocking	11	12.9%
Convulsions	7	8.2%
Spasticity	3	3.5%
Hypotonia	2	2.4%
Nystagmus	1	1.2%
Tremors	1	1.2%
Hypertonia	1	1.2%

Multiple fractures were discovered in three patients, as well as kyphosis in three others. Twenty-six patients (30.5%) with bony symptoms underwent a DEXA scan examination that showed normal BMD in 8 patients (30.8%), 1 patient (3.8%) had osteoporosis of the lumbar spine, and 17 patients (65.4%) had osteopenia.

Oculomotor apraxia, squint, and bulbar symptoms were the most common neurological signs (48%, 30.6%, and 29.4%, respectively) (Table 4). CNS structural changes as detected by brain CT ($n = 16$) included central and cortical brain atrophic changes in four patients (25%), prominent space at the frontoparietal region at both sides suggesting external hydrocephalus in two patients (12.5%), and periventricular white matter hypodensity likely related to leukoencephalopathy in one patient (6.25%). Brain CT results were normal in nine patients (56.25%). Out of 59 patients who underwent an EEG, 20 (33.8%) had abnormal findings (Table 5).

A bone marrow aspirate was performed in 49 patients (57.6%) to rule out other bone marrow dyscrasias. Thirty-seven patients (75.6%) showed the typical large mononuclear cell with the "wrinkled tissue pattern" of cytoplasm and eccentrically placed nucleus (Gaucher cells) [11]. The rest of the cases showed a non-conclusive picture.

Table 5 EEG findings of patients with GD3

Findings	Number	Percentage
Epileptic focus	7	11.8%
Depressed waves indicating diffuse brain insult	6	10.1%
Bilateral frontotemporal epileptogenic dysfunction more on the right side with secondary generalization	2	3.4%
Asynchronous rhythm spindles (a disturbance involving the thalamocortical pathway)	2	3.4%
Mild diffuse non-specific cerebral dysrhythmia	1	1.7%
Lt centro-temporal epileptic activity	1	1.7%
Diffuse episodes of frequent spikes and slow waves	1	1.7%

Table 6 Effect of visceral parameters

	Basal Mean ± SD	Last, follow-up Mean ± SD	*P* value
Liver (MN)	1.34 (0.4–4.6)	0.52 (0.18–1.89)	< 0.001
Spleen (MN)	15.8 (2.2–59)	4 (1.5–48.7)	< 0.001

HB Hemoglobin, *PLT* Platelet, *MN* Multiples of normal, *SD* Standard deviation

Treatment status

Imiglucerase (Cerezyme®) was given to all of the patients, and the dose was adjusted based on the severity of the condition at the start (range 30 to 120 U/kg) with the majority (94%) starting at a dose of 60 U/kg every 2 weeks. No serious adverse events were recorded from ERT. Debilitating and potentially life-threatening hemato-visceral and growth features were reversed with ERT (Table 6). On high-dosage ERT, the patient with hepatopulmonary syndrome exhibited complete reversal of clinical symptoms. Observer-reported outcomes for neurological abnormalities, including oculomotor apraxia, showed slight improvement (by clinicians and parents). Splenectomized patients ($n=4$) did not show significant differences in the neurological evolution compared to non-splenectomized patients.

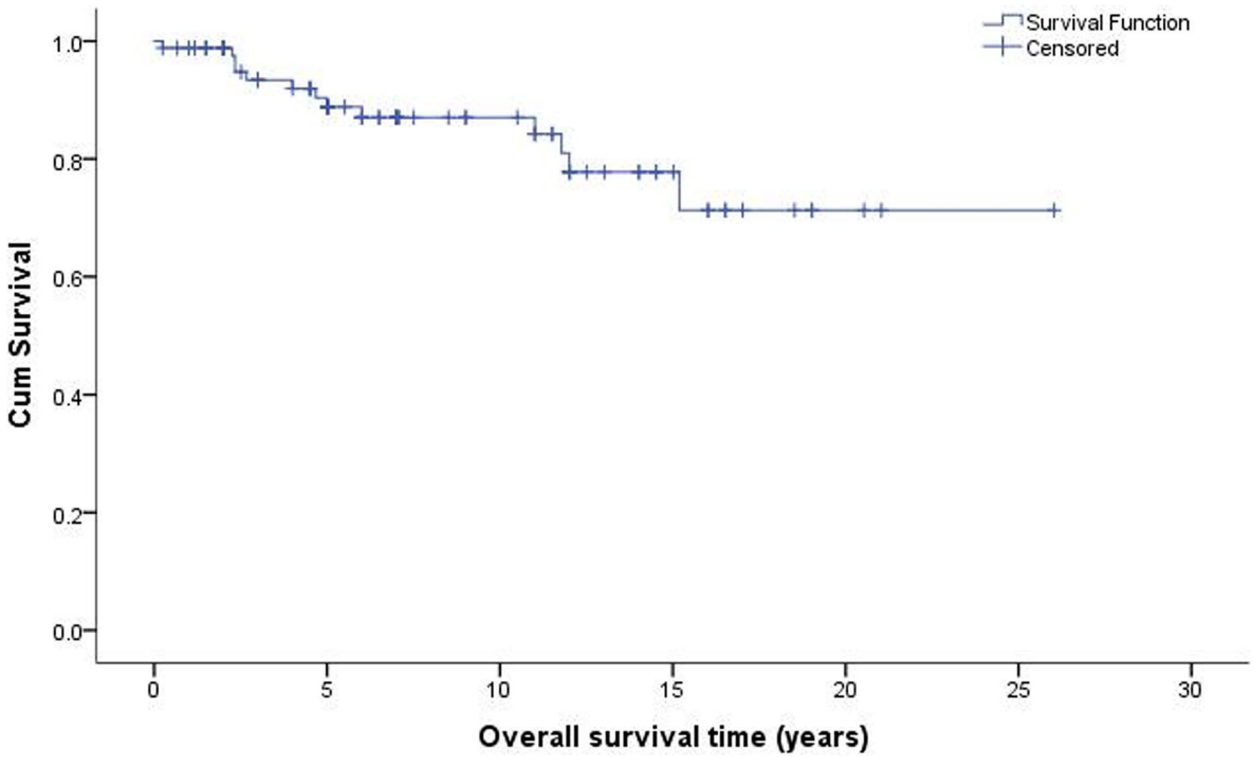

Fig. 1 OS over 20 years ($n=85$)

Survival analysis and outcome of patients

Overall survival (OS) was 71% after 20 years (Fig. 1), with 20 patients succumbing to pulmonary and progressive neurological disease. When the OS was compared to the variables studied, it was determined that none of the variables had an impact on OS ($p > 0.05$).

Discussion

Here, we investigate the disease characteristics and treatment options of 85 patients with GD3 treated at the Hematology Outpatient Clinic, New Children's Hospital, Cairo University, Cairo, Egypt, from 1998 to 2017, who received the GD-specific treatment imiglucerase (Cerezyme®).

The 85 patients with GD3 included in this analysis were all diagnosed at < 18 years of age and first experienced GD symptoms early in life (median age 1 year). The majority of the patients had the p.Leu483Pro homozygous GBA1 genotype (28/37, or 75.7%), which has been linked to neuronopathic GD in previous ICGG Gaucher registry reports [12, 13]. Although there are no absolute genotype–phenotype connections, and many individuals with the p.Leu483Pro mutation have phenotypic similarities to GD1, it is associated with higher disease severity and can help distinguish between type 1 and type 3 disease [14]. It is to be mentioned that great efforts are underway to spread simple information about the genetic background of Gaucher disease among the community via websites, pamphlets, and individual or group information sessions. Moreover, genetic counseling for all affected families regarding future pregnancies is provided on regular basis.

GD3 refers to a range of clinical characteristics. In some patients, slow horizontal saccadic eye movements may be the only neurological symptom. Other patients have a slower progression of neurological disease and less organ involvement, whereas others have extensive skeletal and organ involvement. Only a small percentage of patients develop the progressive neurological disease, aside from the early development of horizontal supranuclear palsy. There have been reports of developmental delays, language issues, dementia, and learning deficits in certain GD3 patients [15]. Anemia was the most common disease manifestation, occurring in more than 70% of our patients. Moderate to severe thrombocytopenia was present in more than 20% of patients, severe hepatosplenomegaly was present in more than half of our patients, and oculomotor apraxia, squint, bulbar symptoms, and convulsions were the most common neurological manifestations. Skeletal manifestations included multiple site fractures, skeletal deformities, osteopenia, and osteoporosis.

Enzyme replacement therapy is indicated in every patient with symptomatic GD. All our patients received ERT, and the main indications for treatment included early presentation of symptoms, severe anemia, L444P/L444P genotype, massive spleen/liver volume, decreased growth velocity, symptomatic bone disease, and thrombocytopenia. Although the recombinant enzyme is accessible, it is quite costly. As a result, reimbursement procedures, timetables, and starting treatment doses vary by area [14]. The 85 patients in our study were given imiglucerase (Cerezyme®, Genzyme Corporation) at diagnosis in doses ranging from 30 to 120 U/kg depending on the severity of their condition.

In the literature, individualization of the dose according to the clinical and molecular status of the patient was mentioned. Generally, it was recommended to maintain severely affected children on 60 U/kg every 2 weeks. While moderately affected children can receive at least 30 U/kg, when treatment goals are not met (Improvement of anemia and thrombocytopenia, reduction of organ volumes, achievement of normal growth and improvement of bony pains and bone mineral density), the dose should be increased up to 90 or 120 U/kg [14]. The bulk of our patients (94%) began with a 60 U/kg dosage, and a few patients started with 45 U/kg or 30 U/kg. However, higher starting doses of 90 to 120 U/kg were indicated in two patients. This was implemented according to the international recommendations [14, 16, 17]. Adverse events from ERT among our population were almost absent. After ERT, there were significant improvements in weight, height, anemia, and organ volumes ($p < 0.05$). It is crucial to keep in mind that the various aspects of GD do not necessarily respond to ERT at the same rate or to the same extent and that the extent of change in one parameter may or may not be reflective of changes in other parameters [18].

Conclusion

This is the largest single-center study of GD3 patients with the predominant homozygous p.Leu483Pro GBA genotype. Patients had very early onset of disease with devastating disease parameters. After 20 years of follow-up, reversal of hemato-visceral disease was achieved effectively by ERT as well as improvement in growth parameters with 71% OS, and one third of patients progressed to complications of GD3. OS was not correlated with the severity of baseline disease, underscoring the potential role of modifier genes.

Abbreviations

GD	Gaucher disease
GD3	Gaucher disease type 3
ERT	Enzyme replacement therapy

SRT	Substrate reduction therapy
BMA	Bone marrow aspirate
DEXA	Dual-energy X-ray absorptiometry
EEG	Electroencephalogram

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Authors' contributions
El-Beslawy A (in addition to revising of the manuscript) and Abdelazim K and Abdel salam A (in addition to writing the manuscript) and Selim Y and Gebril N: All did the recruitment of the patients, the clinical diagnosis and management. Said F did the initial labs for diagnosis of the patients and corresponding author. Fateen E did the enzyme assay. Mistry P did the genetics for Gaucher gene. All authors read and approved the final manuscript.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
The study protocol was approved by Investigational Review Board of Kasr Alainy School of Medicine-Cairo University in January 2017. The study followed the tenets of the Declaration of Helsinki including 2013 amendments. Informed consent from the legal guardian was taken with child assent taken when applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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