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Characteristics of 26 patients with type 3 Gaucher disease: A descriptive analysis from the Gaucher Outcome Survey

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ABSTRACT

The Gaucher Outcome Survey (GOS) is an international disease-specific registry established in 2010 for patients with a confirmed diagnosis of Gaucher disease (GD), regardless of GD type or treatment status. Historically, there has been a limited understanding of type 3 GD (GD3) and its natural history in patients irrespective of their treatment status. Here, we describe the disease characteristics of patients with GD3 enrolled in GOS. As of October 2015, 1002 patients had been enrolled, 26 of whom were reported as GD3. The majority of patients with GD3 were from the US (13; 50.0%), seven (26.9%) were from the UK, three (11.5%) from Israel, and three (11.5%) from Brazil. No patients were of Ashkenazi Jewish origin. Median age of symptom onset was 1.4 (interquartile range: 0.5–2.0) years. The most common *GBA1* mutation genotype was L444P/L444P, occurring in 16 (69.6%) of 23 patients who had genotyping information available. Nine patients reported a family history of GD (any type). Of 21 patients with treatment status information, 20 (95.2%) had received GD-specific treatment at any time, primarily imiglucerase (14 patients) and/or velaglucerase alfa (13 patients). Hemoglobin concentrations and platelet counts at GOS entry were within normal ranges for most patients, and there were no reports of severe hepatomegaly or of splenomegaly in non-splenectomized patients, most likely indicative of the effects of treatment received prior to GOS entry. This analysis provides information on the characteristics of patients with GD3 that could be used as the baseline for longitudinal follow-up of these patients.

1. Introduction

Gaucher disease (GD) is a debilitating, autosomal recessive condition caused by deficient activity of the lysosomal enzyme β-glucocerebrosidase (glucosylceramidase; EC 3.2.1.45). It is characterized by the accumulation of glucocerebroside in the lysosomes of cells of the monocyte–macrophage system, primarily in the liver, bone marrow, and spleen, leading to multisystemic disease manifestations [1]. Although GD is generally considered to be a phenotypic continuum [2], patients are frequently classified into three disease types: types 1, 2, and 3, defined by clinical characteristics and disease course, to aid treatment and patient management decisions. Type 1 (non-neuronopathic) GD (GD1) is classically characterized by an absence of central nervous system involvement, while types 2 and 3 are neuronopathic forms of the disease, in which the central nervous system is primarily affected. Patients with type 2 (acute neuronopathic) GD (GD2) suffer rapid deterioration, with death usually occurring before 2 years of age, while patients with type 3 (chronic neuronopathic) GD (GD3) experience a slower disease course [3]. An estimated 5% of patients with GD in Europe, North America, and Israel are affected by type 3 disease [3,4], but much higher percentages have been reported in some countries, including Sweden, Egypt, China, India, Korea, and Japan [4–9].

The clinical presentation of patients with GD3 is diverse, ranging from aggressive systemic involvement, including enlarged liver and

Abbreviations: ERT, enzyme replacement therapy; GD, Gaucher disease; GD1, type 1 Gaucher disease; GD2, type 2 Gaucher disease; GD3, type 3 Gaucher disease; GOS, Gaucher Outcome Survey; IQR, interquartile range; MN, multiples of normal; SRT, substrate reduction therapy

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spleen, anemia, thrombocytopenia, bone manifestations including kyphosis, infiltrative lung disease [10], and early onset of horizontal supranuclear gaze palsy (type 3b), to predominant neurological involvement, including cognitive impairment, saccadic eye movement abnormalities, auditory processing defects, seizures, muscle weakness, ataxia and, in some cases, a progressive myoclonic epilepsy (type 3a) [10–12]. A distinct form of GD3 (type 3c) is linked to a particular genotype (D409H homozygosity) and manifests with corneal opacity and valvular heart disease with progressive calcification [13]. Neurological manifestations may arise at any age, although nearly half experience onset before 2 years of age [10]. Universal clinical findings include eye movement disorder, either presenting as oculomotor apraxia in younger children or as horizontal supranuclear gaze palsy and slowed saccades.

By comparison with GD1, there is limited understanding of GD3, its natural history, or the impact of GD-specific treatments. Enzyme replacement therapies (ERTs) and substrate reduction therapies (SRTs) specific for GD have been used successfully in patients with GD1 since the approval of the first ERT, alglucerase, in 1991, and clinical data suggest that these drugs also have the potential to alleviate systemic manifestations and improve quality of life for patients with GD3 [14,15]; however, these agents have no impact on the neurological manifestations of GD, and no treatments are currently available that address these features. Prospective clinical studies in patients with GD3 report increases in hemoglobin concentration and platelet counts, as well as decreases in liver and spleen volumes, following treatment with ERT [16–19]. Management recommendations published in 2009 by a task force of GD experts, as well as recommendations for the management of GD in children published in 2013, state that ERT should be commenced at a starting dose of 60 U/kg every other week as soon as possible after diagnosis in children with GD3, or at 30 to 60 U/kg every other week in adults [14,20]. Velaglucerase alfa was approved in Japan in 2014 for GD, including GD3, while imiglucerase is indicated in Europe for patients with GD3 who exhibit clinically significant non-neurological disease manifestations [21]; however, there are no approved GD-specific treatments for GD3 in the US.

Analysis of real-world outcomes from patient registries can thus provide valuable information on the disease characteristics and management of GD3. The Gaucher Outcome Survey (GOS) is an international GD-specific registry sponsored by Shire Human Genetic Therapies, Inc that was established in 2010 for patients with a confirmed GD diagnosis, regardless of GD type or treatment status. GOS collects real-world data from GD patients, including information on disease manifestations and treatment history [22], under the governance of GD experts from participating sites. The objective of GOS is to evaluate the safety and long-term effectiveness of velaglucerase alfa and other GD-specific treatments to gain a better understanding of the natural history of GD and to serve as a database for the evidence-based management of GD, as described previously [22,23]. Here, we describe the disease characteristics of all patients in GOS with GD3, regardless of treatment status.

2. Patients and methods

2.1. Patient population

Patients with a diagnosis of GD, confirmed by biochemical analysis of glucocerebrosidase activity and/or by *GBA1* genotyping, can be enrolled into the GOS registry regardless of their treatment status or type of treatment received. Patients are enrolled on a voluntary basis and are managed under the direction of their physician in accordance with routine clinical practice. Written informed consent is obtained from all patients taking part in GOS. For patients < 18 years of age (< 16 years of age in the United Kingdom), consent is obtained from a parent or legal representative, along with assent where appropriate. All patients in the GOS registry with a diagnosis of GD3 determined by their treating physicians at the time of data extraction on October 30, 2015 were included in this study.

Table 1
Treatment status definitions.

Status	Definition
Treated at entry	Patients reported as having started GD-specific treatment before entry into GOS and who either continued to receive treatment or stopped treatment ≤ 6 months before GOS entry
Treated at any time	Patients for whom there were one or more records of a GD-specific treatment and a treatment start date specified
Untreated at entry	Patients who either had no record of having received GD-specific treatment before entry into GOS or were reported to have received treatment but stopped > 6 months before GOS entry

GD = Gaucher disease; GOS = Gaucher Outcome Survey.

2.2. Data collection

Data on patient demographics, diagnosis, physical characteristics, hematological and visceral parameters, and GD-specific treatment history (including start and stop dates for each treatment received) were collected at the time of entry (enrollment) into GOS via the registry's web-based electronic case report form. Information on dose and adverse events was also obtained for patients receiving GD-specific treatments, defined as all ERTs (alglucerase, imiglucerase, velaglucerase alfa, and taliglucerase alfa), SRTs (miglustat and eliglustat), and the pharmacological chaperone ambroxol. Liver and spleen volumes were obtained by abdominal imaging (volumetric magnetic resonance imaging [MRI], computed tomography [CT] or ultrasound).

2.3. Analysis

This analysis included data for patients treated or untreated at entry, and for patients treated at any time, as defined in Table 1. Patients with missing treatment information were excluded from this analysis. Data on hematological and visceral parameters were analyzed overall and by splenectomy status. GD-specific treatment patterns were analyzed for patients who had received treatment at any time.

3. Results

3.1. Population demographics

As of October 30, 2015, 1002 patients were enrolled in GOS from 34 treatment centers specializing in the management of GD and other lysosomal storage diseases in 10 countries (Argentina, Brazil, France, Israel, Italy, Paraguay, Russia, Spain, the United Kingdom, and the United States). GD subtype data were available for 969 patients; 26 (2.7%) were reported as having GD3, compared with 940 (97.0%) with GD1 and three (0.3%) with GD2 (Fig. 1).

The majority of patients with GD3 were from the United States (13/26; 50.0%), seven (26.9%) were from the United Kingdom, three (11.5%) from Israel, and three (11.5%) from Brazil. None of the patients were of Ashkenazi Jewish origin. All patients included in this analysis were diagnosed with GD3 when < 18 years of age, with a median (interquartile range [IQR]) age at symptom onset of 1.4 (0.5–2.0) years. Patients' median (IQR) age at GOS entry was 17.1 (11.3–27.2) years; 15 (57.7%) were female and 11 (42.3%) were male (Table 2). At the time of data extraction, seven patients, all aged ≥ 18 years (7/26; 26.9%) were reported as having received a total splenectomy prior to GOS entry (Table 2). Subsequent to the 30 October 2015 data cut-off, it became apparent that one patient included in the 'non-splenectomized' group had undergone a total splenectomy prior to GOS entry. This patient received no GD-specific treatments and no data

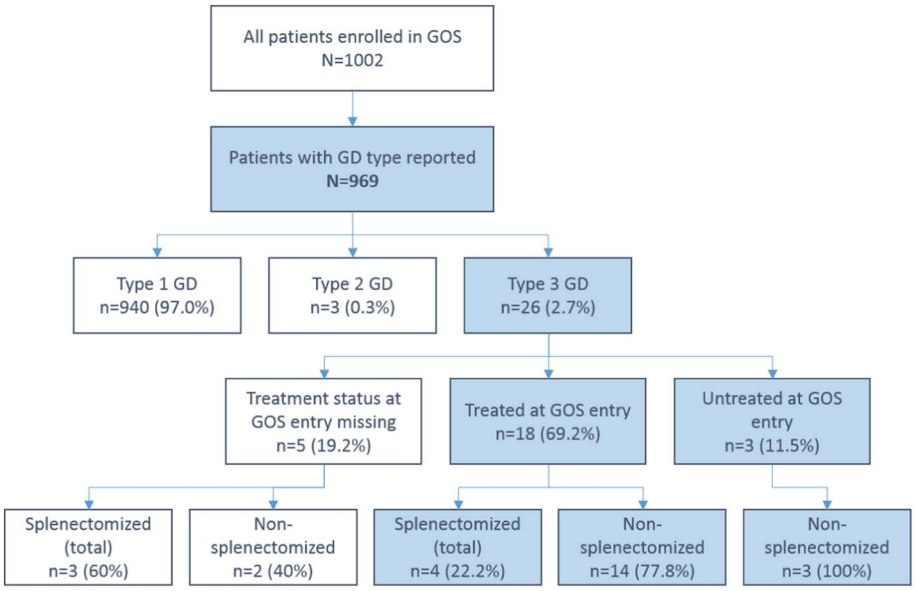

Fig. 1. Overall GOS population at the time of data extraction (October 30, 2015). GD = Gaucher disease; GOS = Gaucher Outcome Survey.

were gathered for liver and spleen size or skeletal abnormalities for this patient.

GD3 diagnosis was confirmed by genotyping for 23 of 26 (88.5%) cases, with the most common *GBA1* genotype being L444P/L444P (16/23; 69.6%; Table 2). The L444P/D409H genotype occurred in two patients (8.7%) and other mutations (L444P/F213I, L444P/RecNciI, R463C/D409H, R463C-10L-REC, and L444P/unknown) occurred in five patients (21.7%). Nine patients reported a prior history of GD (any subtype) in their families (9/21; 42.9%; data missing for five patients).

3.2. Treatment status

Of 21 patients with treatment status information, 20 (95.2%) had received GD-specific treatment at any time (before or after entry to

Table 2
Demographic and physical characteristics of patients with GD3 at time of entry into GOS (n = 26).

Characteristics	All patients (n = 26)	Treated at entry[a] (n = 18)	Untreated at entry[a] (n = 3)	Missing treatment information (n = 5)
Sex				
Male, n (%)	11 (42.3)	8 (44.4)	1 (33.3)	2 (40.0)
Female, n (%)	15 (57.7)	10 (55.6)	2 (66.7)	3 (60.0)
Country, n (%)				
United States	13 (50.0)	11 (61.1)	0	2 (40.0)
United Kingdom	7 (26.9)	1 (5.6)	3 (100.0)	3 (60.0)
Israel	3 (11.5)	3 (16.7)	0	0
Brazil	3 (11.5)	3 (16.7)	0	0
Ethnicity, n (%)[b]				
Ashkenazi Jewish	0	0	0	0
Caucasian	21 (87.5)	16 (88.9)	1 (50.0)	4 (100.0)
Asian	2 (8.3)	1 (5.6)	1 (50.0)	0
Black/African American	1 (4.2)	1 (5.6)	0	0
Missing information	2	0	1	1
Age at GOS entry, n (%)				
< 18 years	14 (53.8)	12 (66.7)	1 (33.3)	1 (20.0)
≥ 18 years	12 (46.2)	6 (33.3)	2 (66.7)	4 (80.0)
Age at GOS entry, median (IQR) years	17.1 (11.3–27.2)	13.0 (10.4–21.6)	18.2 (2.6–41.9)	44.7 (19.2–51.4)
Age at GD symptom onset, median (IQR) years	1.4 (0.5–2.0)	1.6 (0.8–2.3)	1.5 (1.1–1.8)	0.1 (0–0.5)
Age at GD diagnosis, median (IQR) years	1.8 (1.4–3.0)	2.0 (1.5–3.0)	1.5 (1.1–1.8)	0.5 (0–0.5)
GBA1 mutation alleles, n (%)[b]				
L444P/L444P (c.1448 T > C + c.1448 T > C)	16 (69.6)	12 (66.7)	2 (100.0)	1 (100.0)
L444P/other (c.1448 T > C + other)	5 (21.7)	4 (22.2)	0	0
Other/other[b]	2 (8.7)	2 (11.1)	0	0
Missing information	3	0	1	4
Family history of GD, n (%)[c]				
Yes	9 (42.9)	7 (41.2)	0	2 (66.7)
No	12 (57.1)	10 (58.8)	1 (100.0)	1 (33.3)
Missing information	5	1	2	2
Splenectomized, n (%)	7 (26.9)	4 (22.2)	0	3 (60.0)
Total	7 (100.0)	4 (100.0)	0	3 (100.0)
Partial	0	0	0	0

GD3 = type 3 Gaucher disease; GOS = Gaucher Outcome Survey; IQR = interquartile range.
[a] Information on treatment status at GOS entry was missing for five patients.
[b] Other/other genotypes: R463C/D409H and R463C-10L-REC.
[c] Percentages determined from number of patients with available data.

Table 3
Disease characteristics of patients receiving velaglucerase alfa (n = 13).

Characteristics	Velaglucerase alfa only[a] (n = 6)	Velaglucerase alfa + another GD treatment[a] (n = 7)
Sex		
Male, n (%)	1 (16.7)	2 (28.6)
Female, n (%)	5 (83.3)	5 (71.4)
Age at GOS entry, n (%)		
< 18 years	5 (83.3)	4 (57.1)
≥ 18 years	1 (16.7)	3 (42.9)
Age at GOS entry, median (IQR) years	11.4 (2.6–13.0)	15.3 (4.5–28.7)
Age at GD symptom onset, median (IQR) years	1.8 (1.1–5.0)	1.3 (0.6–2.3)
Age at GD diagnosis, median (IQR) years	1.8 (1.1–5.0)	1.8 (1.4–3.0)
GBA1 mutation alleles, n (%)[b]		
L444P/L444P (c.1448 T > C + c.1448 T > C)	1 (25.0)	5 (71.4)
L444P/other (c.1448 T > C + other)	3 (75.0)	1 (14.3)
Other/other[c]	0	1 (14.3)
Missing information	2	0
Splenectomized, n (%)	0	2 (28.6)
Total	0	2 (100.0)
Partial	0	0

GD = Gaucher disease; GOS = Gaucher Outcome Survey; IQR = interquartile range.
[a] Information on treatment status at GOS entry was missing for five patients.
[b] Percentages determined from number of patients with available data.
[c] Other/other genotype: R463C-10 L-REC.

GOS), and one (4.8%), who underwent successful bone marrow transplantation for GD3, had never received GD-specific pharmacological treatment. Information on treatment status was missing for five patients. Historic treatment status information for one patient became available subsequent to the 30 October 2015 data cut-off and was not included in this analysis.

Of the 20 patients who received treatment at any time, 18 (90.0%) were considered on-treatment at GOS entry (had received treatment at the time of or ≤ 6 months prior to entry into GOS). The median (IQR) time from starting treatment until enrollment into GOS was 11.1 (2.4–17.8) years, although treatment may not have been continuous for all patients. The mean duration of ERT at the time of the data cut-off (October 30, 2015) for patients on-treatment at GOS entry was 11.0 years (range 0.5–27.8 years); mean duration of ERT was higher for splenectomized patients (18.7 years, range 5.5–27.8 years; n = 4) than non-splenectomized patients (8.8 years, range 0.5–21.2 years; n = 14).

Over the course of their disease, 13 (65.0%) of the 20 patients treated at any time had received velaglucerase alfa (Table 3) and 14 (70.0%) had received imiglucerase (patients could have received more than one type of treatment). Twelve (60.0%) of the 20 treated patients had received a single GD-specific drug (six velaglucerase alfa and six imiglucerase). Eight patients had switched from one treatment to another, three of whom (37.5%) switched from imiglucerase to velaglucerase alfa. For the 13 patients who received velaglucerase alfa, treatment was given every other week at ≤ 60 U/kg (median 52 U/kg, range 15–60 U/kg) in 12 of 20 (60%) dose entries and at > 60 U/kg (median 90 U/kg, range 69–120 U/kg) in eight (40%) entries. At the time of data extraction, 12 patients were receiving velaglucerase alfa, seven were receiving imiglucerase and one was receiving eliglustat. No patient was reported to have received ambroxol.

3.3. Disease characteristics at time of GOS entry

All 20 patients with available data had normal hemoglobin concentrations (as defined using International Collaborative Gaucher Group [ICGG] registry cut-off values for anemia [24,25]) of ≥ 11.0 g/dL (females and patients ≤ 12 years of age) or ≥ 12.0 g/dL (males) at GOS entry, and 19 of 20 (95.0%) had platelet counts ≥ 120 × 10^9/L (Table 4). Median (IQR) hemoglobin concentrations were similar in splenectomized and non-splenectomized patients, at 12.0 (11.8–12.0) g/dL (n = 5) and 13.3 (11.8–13.8) g/dL (n = 15), respectively, while median [IQR] platelet counts were numerically higher in splenectomized patients (257 [174–349] × 10^9/L) than in non-splenectomized patients (190 [156–238] × 10^9/L) (Table 5).

Data for hemoglobin concentrations and platelet levels were available for 13 of 18 patients who were on-treatment at GOS entry, and for all three patients who were untreated at GOS entry. For non-splenectomized patients, median (IQR) hemoglobin concentrations were similar, regardless of treatment status at GOS entry, at 13.5 (12.0–13.7) g/dL for on-treatment patients (n = 10; data missing for four patients) and 13.0 (11.6–15.5) g/dL for patients untreated at GOS entry (n = 3). Median (IQR) platelet counts were numerically lower for non-splenectomized patients who were on-treatment at GOS entry (175 [156–200] × 10^9/L; n = 10) than for non-splenectomized patients who were untreated at GOS entry (242 [190–261] × 10^9/L; n = 3) (Table 5). For splenectomized patients, all of whom were on-treatment at GOS entry, median (IQR) hemoglobin concentrations and platelet counts were 12.0 (11.8–12.0) g/dL and 349 (257–456) × 10^9/L, respectively (n = 3).

All non-splenectomized patients with abdominal imaging data had liver volumes ≤ 2.5 multiples of normal (MN; n = 6) and spleen volumes ≤ 15 MN (n = 5; Table 4). At time of GOS entry, median (IQR) liver volumes by abdominal imaging were 1.1 (0.8–1.4) MN for non-splenectomized patients (n = 6; data missing for 13 patients) and 0.6 (0.6–0.6) MN for splenectomized patients (n = 2; data missing for 5 patients). Median (IQR) spleen volume at GOS entry was 9.2 (4.2–11.9) MN for non-splenectomized patients only (n = 5; data missing for 14 patients) at GOS entry (Table 5). No abdominal imaging data were available for the three patients who were untreated at GOS entry.

Bone abnormalities were reported in eight patients at GOS entry, five of whom were on-treatment at that time (mean 14.9 years duration, range 2.8–27.8 years; missing treatment information for three patients). These included four patients with avascular necrosis, one patient with bone marrow infiltration, and one patient with lytic lesions. Five of the eight patients were splenectomized, and between them experienced 16 bone abnormalities. Three non-splenectomized patients reported a total of six bone abnormalities. Two (14%) of 14 patients for whom data were available experienced bone pain at GOS entry, which was moderate for one patient (untreated) and severe for the other (on-treatment at GOS entry). Two of four patients for whom data were available reported abnormal pulmonary function at GOS entry, both of whom were receiving GD-specific treatment. One patient (age > 18 years) had mild restriction, and moderate restriction with nebulizer treatment, and one patient (age ≤ 18 years) had severe restrictive respiratory disturbance, and spirometry suggestive of severe restrictive ventilatory defect. Pulmonary function tests were not performed for 22 (84.6%) patients. Neurological abnormalities were reported in 4 patients at GOS entry, all of whom had received GD-specific treatment at any time. These included one case of seizures/epilepsy (treated with velaglucerase alfa at time of event), two cases of related eye movement disorders (one receiving imiglucerase and one receiving alglucerase at time of event), and one case of peripheral neuropathy (no GD-specific treatment at time of event).

3.4. Adverse events associated with GD-specific treatment

Six adverse events, none of which were serious, were reported in three of the 21 patients treated at any time. Four events in two patients were considered related to a GD-specific treatment, including a case of urticaria in a male adolescent treated with imiglucerase and three events (staring, catarrh, and cough) reported in a 3-year-old female treated with velaglucerase alfa, which were assessed as being possibly or probably related to treatment. All reported adverse events were mild in severity and all occurred in patients < 18 years of age.

Table 4
Hematological and visceral parameters in patients with GD3 at time of GOS entry (n = 26).

	All patients (n = 26)	Treated at entry[a] (n = 18)	Untreated at entry[a] (n = 3)	Missing treatment information (n = 5)
Non-splenectomized patients	n = 19	n = 14	n = 3	n = 2
Hemoglobin concentration, n (%)				
Below normal range	0	0	0	0
Within normal range	15 (100.0)	10 (100.0)	3 (100.0)	2
Missing information	4	4	0	0
Platelet count [$\times 10^9$/L], n (%)				
< 60	1 (6.7)	1 (10.0)	0	0
60 to < 120	0	0	0	0
≥ 120	14 (93.3)	9 (90.0)	3 (100.0)	2
Missing information	4	4	0	0
Liver volume, MN (abdominal imaging), n (%)				
≤ 1.25	4	4	0	0
> 1.25 to ≤ 2.5	2	2	0	0
> 2.5	0	0	0	0
Missing information	13	8	3	2
Spleen volume, MN (abdominal imaging), n (%)				
≤ 5	2	2	0	0
> 5 to ≤ 15	3	3	0	0
> 15	0	0	0	0
Missing information	14	9	3	2
Splenectomized[b] patients	n = 7	n = 4	n = 0	n = 3
Hemoglobin concentration, n (%)				
Below normal range	0	0	NA	0
Within normal range	5 (100.0)	3 (100.0)	NA	2 (100.0)
Missing information	2	1	NA	1
Platelet count [$\times 10^9$/L], n (%)				
< 60	0	0	NA	0
60 to < 120	0	0	NA	0
≥ 120	5 (100.0)	3 (100.0)	NA	2 (100.0)
Missing information	2	1	NA	1

GD = Gaucher disease; GOS = Gaucher Outcome Survey; MN = multiples of normal; NA = not applicable.
Hemoglobin: below normal range: < 11 (females, patients ≤ 12 years of age) or < 12 (males); normal range: ≥ 11 (females, patients ≤ 12 years of age) or ≥ 12 (males) [24,25]. All percentages in table determined from number of patients with available data.
[a] Information on treatment status at GOS entry was missing for five patients.
[b] All were total splenectomies.

Table 5
Hematological and visceral parameter medians and ranges at time of entry into GOS (n = 26).

	All patients (n = 26)		Treated at entry[a] (n = 18)		Untreated at entry[a] (n = 3)		Missing treatment information (n = 5)	
Non-splenectomized patients	n = 19		n = 14		n = 3		n = 2	
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Hemoglobin concentration, g/dL	15	13.3 (11.8–13.8)	10	13.5 (12.0–13.7)	3	13.0 (11.6–15.5)	2	12.8 (11.1–14.5)
Male	7	13.7 (13.3–14.5)	5	13.7 (13.3–13.7)	1	15.5 (15.5–15.5)	1	14.5 (14.5–14.5)
Female	8	11.9 (11.4–13.3)	5	12.0 (11.8–13.6)	2	12.3 (11.6–13.0)	1	11.1 (11.1–11.1)
Platelet count, $\times 10^9$/L	15	190 (156–238)	10	175 (156–200)	3	242 (190–261)	2	256 (235–277)
Liver volume,[b] MN	6	1.1 (0.8–1.4)	6	1.1 (0.8–1.4)	0	Missing	0	Missing
Spleen volume,[b] MN	5	9.2 (4.2–11.9)	5	9.2 (4.2–11.9)	0	Missing	0	Missing
Splenectomized patients	n = 7		n = 4		n = 0		n = 3	
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Hemoglobin concentration, g/dL	5	12.0 (11.8–12.0)	3	12.0 (11.8–12.0)	0	NA	2	13.0 (11.5–14.5)
Male	1	14.5 (14.5–14.5)	0	NA	0	NA	1	14.5 (14.5–14.5)
Female	4	11.9 (11.7–12.0)	3	12.0 (11.8–12.0)	0	NA	1	11.5 (11.5–11.5)
Platelet count, $\times 10^9$/L	5	257 (174–349)	3	349 (257–456)	0	NA	2	174 (173–174)
Liver volume,[b] MN	2	0.6 (0.6–0.6)	1	0.6 (0.6–0.6)	0	NA	1	0.63 (0.63–0.63)

GOS = Gaucher Outcome Survey; IQR = interquartile range; MN = multiples of normal; NA = not applicable.
[a] Information on treatment status at GOS entry was missing for five patients.
[b] Liver and spleen volumes determined from abdominal imaging. Liver volume of > 1.25 to ≤ 2.5 MN is considered moderate hepatomegaly and > 2.5 MN severe; spleen volume of > 5 to ≤ 15 MN is considered moderate splenomegaly and > 15 MN severe [10].

4. Discussion

Historically, there has been limited understanding of the natural history of GD3, and while studies have evaluated the efficacy and safety of ERT for treating non-neurological symptoms in patients with GD3 [14,15,26], there is little information on real-world treatment patterns and outcomes for patients with this subtype. Here, we report on the disease characteristics and management of 26 patients with GD3 enrolled in GOS, an international GD-specific disease registry, who were receiving a range of GD-specific treatments, reflective of real-world treatment practices.

The 26 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 1.4 years). Most were receiving ERT (primarily imiglucerase or velaglucerase alfa) at the time of GOS entry, in line with treatment guidelines [20]. One patient in this study was receiving only SRT (eliglustat). At the time of GOS entry, a third of treated patients had received both velaglucerase alfa and imiglucerase treatment. While this reflects real-world treatment practices, it means differences in disease parameters could not be attributed to any one drug; therefore, an evaluation of disease parameters by treatment type was not carried out.

Most of the patients with GD3 in this study had a *GBA1* genotype of L444P/L444P (16/23; 69.6%), which is associated with neuronopathic GD and is at a rate consistent with previous ICGG Gaucher registry reports [4,10,26]. Although genotype–phenotype correlations are not absolute, and many patients with the L444P mutation are phenotypically similar to GD1, its presence is associated with increased disease severity and can help differentiate between type 1 and type 3 disease [20].

Systemic GD parameters in the 26 patients with GD3 included in this analysis were generally mild, with hemoglobin concentrations and platelet counts within the normal range for nearly all patients, and no reports of severe hepatomegaly or splenomegaly. These findings could be indicative of the effects of GD-specific treatments received prior to GOS entry. However, although neurological abnormalities are a hallmark of GD3, no currently available GD-specific treatments are able to slow or reverse the progression of the neurological manifestations of GD3; data on these effects were not explicitly collected in GOS and are not described here. Agents such as the pharmacological chaperone ambroxol are being investigated to fulfill this unmet clinical need [27], but no patients in this cohort were reported to have received this treatment.

Skeletal manifestations in GD3 include severe bone pain, osteopenia, acute bone crises, and fractures [20]. In this evaluation, bone pain was reported at GOS entry in 14% of patients with GD3. This is similar to the frequency of 11% reported for patients with GD2 and GD3 in the Neurological Outcomes Subregistry of the International Collaborative Gaucher Group registry [10]. Bone abnormalities have been reported to occur at a higher frequency in GD patients who have had a total splenectomy, compared with non-splenectomized patients [28]; consistent with this, five (71%) of the seven splenectomized patients in this study experienced bone abnormalities, compared with three of 19 (15.8%) non-splenectomized patients.

While these data can provide a valuable source of information on the characteristics of patients with GD, registries have a number of inherent limitations. Owing to the voluntary nature of participation in GOS (at the discretion of patients and their treating physicians), data may be incomplete, missing, with some level of inconsistency, or subject to selection bias, particularly in the reporting of treated patients over untreated patients. Although physicians are encouraged to enter information for all their GD patients, regardless of treatment status, other disease- and treatment-specific registries for GD exist, and some sites may not be able to enroll all patients into all registries for which they are eligible. Furthermore, conclusions drawn from these data are limited by the relatively small number of patients in this evaluation.

The GD3 population included in this analysis originates from Brazil, the United Kingdom, Israel, and the United States, none of which have been previously noted for having a particularly high prevalence of GD3 [14,29,30]. In this analysis, 3 of 33 (9.1%) patients enrolled in GOS in Brazil had GD3, compared with a previous report of 5% [29], although absolute numbers were small. Given the low patient numbers involved, the percentage of patients reported as having GD3 in GOS (2.7%) is similar to that reported by other registry studies (5%), which typically include countries known to have higher prevalence rates of GD3, such as Sweden, Egypt, China, India, Korea, and Japan [4–9]. Further work would be needed to establish whether the *GBA1* genotype, disease course, and clinical characteristics of patients with GD3 in GOS differ from those in countries with a higher prevalence of GD3.

5. Conclusions

In this analysis of data from the GOS disease registry, patients with GD3 first experienced GD symptoms at a young age, and most had *GBA1* genotype L444P/L444P, consistent with previous reports. Most patients with GD3 had hemoglobin concentrations within the normal range at GOS entry, regardless of treatment status (any GD-specific treatment) or splenectomy status, and there were no reports of severe hepatomegaly or splenomegaly. Nearly all patients with treatment history information had received GD-specific treatment prior to enrollment into GOS, which may explain the mild hematological and visceral findings observed in this cohort. This analysis indicates that ERT is being used in real-world clinical practice to treat non-neurological manifestations of GD3, and suggests that current treatment recommendations for patients with GD3 are appropriate for the management of non-neurological symptoms of the disease. Longitudinal follow-up of these patients will provide further information on treatment outcomes and the natural history of the disease. Furthermore, data from Asian and Middle Eastern countries (with the exception of Israel), where neuronopathic GD is more prevalent than in the countries represented in this analysis, will provide a more global view of the demographics, disease characteristics, and management of patients with GD3.

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Authorship contributions

I.V.D.S., O.G-A., P.S.K., A.Z, and P.D are investigators involved in GOS. L.R. is the GOS registry lead. Z.P. is the GOS medical monitor. All authors contributed to the development of the manuscript, critically reviewed the manuscript during development, and approved the final draft prior to submission.

Competing interests

I.V.D.S. has membership on advisory boards or similar committees for Shire.

O.G-A. receives research support from Genzyme, Pfizer, and Shire; receives consulting fees from Actelion, Genzyme, Pfizer, and Shire; and has current or recent involvement in clinical trials sponsored by Alexion, Amicus, Genzyme, Protalix, and Shire.

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L.R. is an employee of Shire.

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