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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