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Patients with type 1 Gaucher disease in Spain: A cross-sectional evaluation of health status

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ABSTRACT

A multicentre, cross-sectional epidemiological survey was conducted to describe the health status of patients with type 1 Gaucher disease (GD1) in Spain. Patient data were collected retrospectively from clinical records. Therapeutic goals for seven clinical parameters were chosen as primary outcome measures. 108 GD1 patients (mean age 44.8 years; 53% male) were recruited from 28 hospitals. Ninety-five patients (88%) were receiving treatment for GD1. Hemoglobin concentration was the therapeutic goal with the highest level of achievement, being met by 105 of 108 patients (97%), followed by the goals for liver volume (86/98 patients; 88%), spleen volume (67/77 patients; 87%) and platelet count (81/108 patients; 75%). The goal for bone mineral density (BMD) was met by 48 of 75 patients (64%), and the goal for quality of life was met by 65 of 103 patients (63%). Bone pain was the parameter with the lowest level of achievement (goal met by 50/94 patients; 53%). The clinical information most often missing from patient records was the BMD Z-score (missing for 31% of patients). These data suggest that most Spanish GD1 patients have good control over hematological and visceral parameters, but there is a need to improve monitoring and treatment of GD-related bone disease.

1. Introduction

Gaucher disease (GD; OMIM #230800) is an autosomal recessive disorder caused by deficient activity of the glucocerebrosidase enzyme (GBA; EC 3.2.1.45) required for the degradation of glycosphingolipids. GBA deficiency leads to accumulation of the enzyme's substrate in the lysosomes of monocyte-lineage cells which develop into pathologic "Gaucher cells" in visceral tissues [1,2]. GD has been classified into three subtypes according to the presence or absence of neurological features. Type 1 Gaucher disease (GD1) is the most common, and is characterized by the lack of central nervous system involvement. GD2 and GD3 are characterized by acute and chronic neurologic symptoms, respectively. More than 350 mutations have been described in the *GBA* gene region as the cause of GD [3]. The most common *GBA* genotype in GD1 patients is N370S/N370S, which tends to result in milder disease, followed by N370S/L444P [4–6].

The prevalence of GD in the Iberian Peninsula is estimated to be 1:149,000, similar to that of other European populations [7]. Approximately 88% of the affected population have GD1, with the most common *GBA* mutations being N370S/L444P (32%) and N370S/N370S (17%). The Spanish Foundation for the Study and Treatment of Gaucher Disease (FEETEG) reports that there are currently 342 GD1 patients in Spain [8].

Clinical manifestations of GD1 commonly include anemia, thrombocytopenia, hepatomegaly, splenomegaly and bone disease [9–12].

Abbreviations: ANOVA, one-way analysis of variance; BMD, bone mineral density; BMI, body mass index; CCL18, chemokine (C-C motif) ligand 18; EC, Enzyme commission number; ERT, enzyme replacement therapy; GBA, glucocerebrosidase; GD, Gaucher disease; DXA, dual energy X-ray absorptiometry; IQR, interquartile range; MAP Tool®, monitor, action and progress tool; MN, multiples of normal; MRI, magnetic resonance imaging; OMIM, Online Mendelian Inheritance in Man; QoL, quality of life; SD, standard deviation; SRT, substrate reduction therapy; VAS, visual analog scale.

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Pulmonary involvement and other manifestations such as coagulation abnormalities and secondary neurologic disease are also observed [13–15].

There are currently two main types of treatment for GD1: enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), which have both been shown to be effective in improving key disease parameters [16].

The clinical heterogeneity of GD1 requires an individualized approach to disease management. In 2004, an international consensus on the therapeutic goals for GD1 treatment was published to aid in therapeutic decision-making [17]. The primary objective of the present study was to describe the clinical characteristics and current health status of GD1 patients managed in Spanish hospitals, particularly with regard to the achievement of therapeutic goals. The secondary objectives of the study included describing patients according to differences in their disease management, such as by treatment and splenectomy status.

2. Materials and methods

2.1. Study design and patients

This was a multicenter observational, cross-sectional epidemiological study designed and conducted by investigators managing GD1 patients in Spanish hospitals (Study identification number: SHI-TSE-2011-01, Vall d'Hebron University Hospital). The study protocol was reviewed and approved by ethics committees of the participating hospitals, and was conducted in accordance with the Helsinki Declaration of 1975 as revised in 2008. All patients were required to sign an informed consent form. Patients younger than 18 years of age provided informed consent via a parent or legal representative.

The study recruitment period lasted 7 months (June 2012 to January 2013) and data were gathered in a central database until April 2013. Involvement in the study was proposed to investigators by the study sponsor if they were identified as managing GD1 patients in Spanish hospitals or specialized centers. GD1 patients attending a routine clinical visit during the study recruitment period were invited to participate. Patients who agreed to participate and signed the consent form were included in the study. Patients were excluded if they were considered by the investigator to have limited cognitive abilities or impaired capacity to complete the study documentation.

The therapeutic goals MAP (Monitor, Action and Progress) Tool®, an application designed to collect and collate clinical data in one simple visual output, was used for data collection. Data were collected retrospectively from the clinical records of participating patients during a single study visit. These data included information recorded in the 6 to 12 months prior to the study visit, with the exception of the quality of life (QoL) questionnaire that was supplied at the study visit.

2.2. Outcome measures

The therapeutic goals based on a published concensus [17] for seven clinical parameters were the primary outcome measures for the study. One measurement per parameter was collected for each patient where available. The therapeutic goals for each parameter were defined as: 1) hemoglobin concentration ≥ 12 g/dL for men or ≥11 g/dL for women and children <18 years old; 2) platelet count ≥120 × 10^9/L; 3) spleen volume ≤ 8 multiples of normal (MN) as measured by magnetic resonance imaging (MRI) or ultrasound; 4) liver volume ≤ 1.5 MN as measured by ultrasound; 5) bone pain ≤1 as a patient-reported level of pain in the last 24 h according to the visual analog scale (VAS; 0–10) where 0–1 is little or no pain, 2–4 is mild, 5–7 is moderate, and 8–10 is severe or extreme pain; 6) bone mineral density (BMD) Z-score ≥ −1, measured by dual energy X-ray absorptiometry (DXA), with the ability to distinguish where the scan was performed (in the lumbar spine, femoral neck or distal forearm); 7) QoL SF-36 score ≥ 70, obtained from the physical component of the SF-36 questionnaire [18] by averaging the scores for vitality and physical function (scored from 0 to 100).

Additional information collected included sociodemographic and physical characteristics, as well as clinical data. Data collected from clinical records included details of GD1 disease history, disease features, and treatment.

2.3. Statistical analysis

Patient characteristics were summarized for the whole study population, and also analyzed according to treatment status (on treatment vs. untreated) and splenectomy status (splenectomized vs. non-splenectomized). Primary clinical parameters were analyzed in groups according to treatment status, splenectomy status, time since diagnosis (<10 years vs. 10–20 years vs. >20 years), or time since treatment initiation (<10 years vs. ≥10 years). A focused analysis of BMD was also conducted, classifying patients according to their BMD age-, sex- and race-matched DXA Z-scores (retrieved from patients' medical records).

As this was a cross-sectional study and some data were missing for the primary parameters, two independent analysis populations were defined for sensitivity analysis: the Full Analysis Set comprising all enrolled patients who met the enrolment criteria and gave informed consent (n = 108), and the Complete Data Analysis Set comprising patients in the Full Analysis Set with complete data for all seven primary parameters (n = 65). No imputation was performed for missing values and instances of missing data are indicated in the results tables.

Categorical variables were summarized by calculating the patient frequencies and percentages. Comparisons of categorical variables between two or more groups were made through Fisher's exact and Chi-square tests, respectively. Continuous variables were descriptively summarized with means, standard deviations, medians and interquartile ranges (IQRs). Comparison of continuous variables between two groups was made using the Mann–Whitney U test or Student's *t*-test, and between three or more groups using the Kruskal-Wallis test. The two-sided significance level for all statistical tests was 0.05.

All statistical analyses were performed using the SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Study population

Approximately 50 investigators at 50 hospitals were invited to be involved in the study; 35 investigators at 28 hospitals accepted, and recruited patients into the study. One hundred and eight GD1 patients geographically representing 10 of Spain's 17 autonomous communities were enrolled (Fig. 1).

3.2. Patient characteristics

Patients had a mean age of 44.8 ± 16.6 years, and nine (8%) were children (5–17 years of age). Fifty-seven patients (53%) were male (Table 1). The most frequent *GBA* mutation was N370S, seen in 95 of 105 patients (90%). The median age of onset of GD1 symptoms was 20.7 (IQR 8.2–33.0) years, with diagnosis occurring at a median age of 28.0 (IQR 14.2–38.0) years. Pre-existing bone complications were recorded for 23 patients (21%).

Ninety-five patients (88%) were receiving treatment for GD1, of whom 68 (72%) were receiving ERT (46 on imiglucerase, 22 on velaglucerase alfa) and 20 (21%) were receiving SRT (miglustat). At the study visit, the mean time on treatment for all patients was 10 years (119.0 ± 73.4 months; data not shown). Adverse events were identified in the clinical records of three patients: impotence, migraine and facial erythema, and pain during infusion. The latter was an infusion-related reaction and was the only adverse event considered