Haematologica 2000; 85:792-799
original paper

Phagocytes & Lymphocytes

Report of the Spanish Gaucher's Disease Registry: clinical and genetic characteristics

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ABSTRACT

Background and Objectives. **Since 1993 the demographic, clinical, analytical, genetic and follow-up data of Spanish patients with Gaucher's disease (GD) have been collected in an anonymous national database. Some statistical analyses of these data are reported concerning the distribution, clinical and genetic characteristics of GD in Spain and the response to enzyme replacement therapy (ERT) is evaluated.**

Design and Methods. **We performed a cohort study in Spanish GD patients by national inquiry, submitted by mail to 75 Spanish hospitals (over 300 beds) directed to internal medicine, hematology and pediatric departments. The questionnaire included 30 questions (gender, height, weight, date of birth, date of diagnosis, abode and number of relatives affected, bone crises, neurologic symptoms, other symptoms, liver and spleen size, hemoglobin, leukocyte and platelet count, tartrate resistant acid phosphatase, ALT/AST, chitotrioxidase activity, total plasma cholesterol, triglycerides, high density lipoprotein cholesterol, enzymatic activity of acid β-glycosides, mutation, X-ray examination, magnetic resonance imaging-MRI-evaluation, spleen removal, and orthopedic procedures (ERT, date of first infusion). Each case with a presumed diagnosis was considered an *enrolled patient*. Written informed consent was obtained from all patients. The cases without enzymatic or genetic diagnosis were studied in a reference laboratory (the same for all the samples). Clinical status was evaluated by Zimran's severity score index. The enzymatic activity of acid β-glycosides was determined in cellular extracts of peripheral blood granulocytes by a fluorescent method using an artificial substrate (4-methyl-umbelliferyl β-D-glycoside). Polymerase chain reaction (PCR) molecular analysis was performed in DNA samples to characterize the mutations (N370S, L444P, IVS2+1, 84GG, D409H, R463C and G377S) of the glycoside genes. Two groups were created according to age at diagnosis: children under 15 years and adults, in order to evaluate clinical, genetics and follow-up. Effectiveness of ERT was evaluated using objective parameters (hemoglobin, platelets, liver and spleen size, skeletal lesions), before and after therapy. In patients under ERT, quality of life (QOL) was assessed by a SF-36 modified inquiry, including 22 questions. Statistical analysis including descriptive and frequency distribution for each variable was performed, the ANOVA test was used to identify differences between groups. Paired t-tests (before and during therapy) were carried out. The degree of linear association among measured variables was estimated by Pearson's correlation.**

Results. **By December 1999 one hundred and fifty-five patients from 117 families had been included from 66 Spanish Hospitals; the inquiry was complete for 114 patients. Mean age at diagnosis: 24.0±16.9 years, M/F: 72/83. No symptoms were present at diagnosis in 19.3%; visceral disease was present in 95.6% and bone disease in 62.4%. Hemoglobin levels, leukocyte and platelet counts were below the normal range in 62.3% of cases. Higher acid phosphatase levels were observed in 99% of cases; biochemical liver dysfunction tests were found in 42.9%. The test for acid glycosidase showed a marked decrease in enzymatic activity. Morphologic documentation (spleen or liver tissue, bone marrow biopsy or aspirate) of GD was obtained in 71% of the patients. The most frequent mutations observed were N370S (46.3% of the alleles detected), and L444P (18.5%). In 18.7% of the cases the disease was stable or progressing slightly; in 23.8% the spleen had been removed between 1-14 years after diagnosis and 60.6% were under ERT. Children showed both greater liver enlargement and higher SSI (p = 0.0001). There was a correlation between SSI and clinical or analytical data in adults patients for spleen size (Z: 3.142; CI: 0.173-0.637; p= 0.0017). In 35 patients on ERT, clinical and analytic data improved as did self-evaluated QOL (p< 0.0001).**

Interpretation and Conclusions. **In conclusion, clinical characteristics of Gaucher's disease in Spain were similar to those in other non-Jewish population. N370S allele is the most frequent mutation identified. ERT clearly contributes to improving QOL and clinical manifestations.**

Key words for index: Type I Gaucher's disease; incidence; genotype; phenotypic diversity; ERT, quality of life

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Gaucher's disease (GD) (OMIM 230800) is the most frequent sphingolipidose disorder, usually caused by a deficiency in the activity of the enzyme glucocerebrosidase (GC) (EC 3.2.1.45) and the accumulation of each undegraded substrate, glucosylceramide (GL1) in cells of monocyte/macrophage lineage.[1] Rarely, cases of patients with deficiency of the GC enzyme activating saposin 2 have been described.[2] Of the three types of the disease, type 1 or *adult chronic, non-neuronopathic* disease predominates. This type is characterized by accumulation of GL1 in the liver, spleen and bone marrow, but the central nervous system (CNS) is spared. The disease severity and its age of onset can be extremely variable. Type 2 or *acute neuronopathic* disease is characterized by hepatosplenomegaly and hypertonicity, with cranial nerve and brainstem signs; symptoms begin before the age of 6 months and follow a progressive neurodegenerative course with death usually occurring before 2 years. In type 3 *subacute neuronopathic form*, the neurologic signs appear in childhood or adolescence.[1]

Type 1 GD is probably the most common inherited disease among the Ashkenazi Jewish population.[3] Type 2 is rare with non-ethnic predilection and type 3 is panethnic, although it is more frequently encountered in the province of Norrbottnian in Sweden.[4]

The different presentations of GD are partially explained by the broad heterogeneity in gene defects. More than 130 mutations at the GC locus associated with GD have been described and phenotype-genotype correlation has been proposed for GD.[5] Consensus exists only regarding the patients with at least one N370S allele, who are spared CNS involvement.[6] Significant phenotypic variability occurs within each variant, even among individuals of the same ancestry and there is no correlation between biochemical or genetic abnormalities and the clinical course of the disease. Genetic counseling and prediction of outcome, therefore, are difficult.

Enzyme replacement therapy (ERT) for GD, introduced in 1991, is able to reverse several clinical manifestations in symptomatic patients.[7] However, the wide variety in clinical presentation and severity of type 1 GD makes recommendations for specific therapy difficult.

The *Spanish Gaucher Disease Group* (SGDG) assesses the diagnosis, clinical evaluation and therapeutic counseling of GD patients. It also promoted the development of the Spanish Gaucher Disease Registry (SGDR) to collect data concerning GD in the Spanish population.

In this report, we present the data of the SGDR patients, between 1993 to 1999, in order to establish the incidence and geographic distribution of GD patients in Spain, as well as the clinical, genetic and follow-up features of these patients.

Design and Methods

Patients

We have evaluated clinically and /or retrospectively analyzed the medical records of all Spanish cases of GD sent to the SGDR from 66 hospitals. Currently the SGDG laboratory measures acid glucocerebrosidase (GBA), and chitotrioxidase (CT) activities as well as genotyping all Spanish GD patients.

The cohort study started in 1993 when the first fourteen patients from Aragon (Spain) were enrolled in the cohort, following a mean of 22 cases/year from different Spanish communities being incorporated in the open study. Baseline and follow-up data were entered into the Registry.

Clinical information for the SGDR was obtained from several standardized questionnaires sent to physicians who provided updated information about their patients.

The diagnosis was established by at least two of three methods: histologic demonstration of typical Gaucher cells in bone marrow tissue,[8] low leukocyte acid-β-glucosidase activity[9] and molecular characterization of a defined genotype associated with GD (when both mutated alleles were identified).

Inquiry. Demographic/anthropometric: gender, height, weight, date of birth, date of diagnosis, abode and number of relatives affected. Clinical features: date of the first symptoms, bone crises, neurologic signs, liver and spleen volume and other symptoms. Biological data: hematologic and biochemical parameters (hemoglobin levels, platelet count, tartrate resistant acid phosphatase, ALT/AST, chitotrioxidase activity, total plasma cholesterol, total plasma triglycerides, high density lipoprotein cholesterol). Skeletal findings (X-ray examination, magnetic resonance imaging-MRI-evaluation), bone marrow infiltration, infarction, lytic lesions, osteopenia, fractures, avascular necrosis and Erlenmeyer flask deformity.

Genotype. Screening for seven mutations was carried out (N370S, L444P, IVS2+1, 84GG, D409H, R463C and G377S). These mutations were identified by digestion of PCR or mismatched PCR fragments. The procedures were based on the approach used in previous reports.[10] Genotype data were correlated to clinical and biological characteristics

Therapy data. Spleen removal, orthopedic procedures, and ERT (date of first infusion, dose and treatment disruption) were recorded.

Quality of life. This was assessed in patients receiving ERT for at least 4 years. A SF-36 modified inquiry, including 22 questions (physical capability, psychological disturbances, social abilities/disabilities, constitutional symptoms, self-health perception) was used. Our clinical protocol conformed to both the directives of the Ethical Committee of the Miguel Servet University Hospital of Zaragoza, Spain, and the 1983 revision of the Helsinki declaration of 1975.

Written informed consent was obtained from all patients and from legal representatives of patients aged less than 18 years.

GD subtypes were defined by the absence of neurologic manifestations or related to the onset and severity of neurologic symptoms.

The severity of the disease was estimated by the severity score index (SSI) which includes age at presentation, degree of organomegaly, neurologic and hematologic data, severity of bone involvement and liver function parameters.[11] Patients were assigned to one of three clinical categories: mild (severity score index 0-10 points), moderate (11-25), or severe (≥26) according to Zimran *et al*.[11]

According to age at diagnosis of GD type 1, two different groups were established: children under 15 years and adults. In addition we classified the patients according to their genetic mutation and analyzed their clinical and follow-up characteristics separately.

Effectiveness of ERT was evaluated by comparison of different clinical and biological data before and after ERT: hemoglobin levels, platelet count, liver and spleen size.

Statistical evaluation was performed using a SPSS-8.0 application database. We determined mean ± standard deviation (SD) for all variables for each group. The frequency of distribution of qualitative variables was analyzed. The ANOVA test was used to determine differences between groups for each variable. Data concerning ERT were evaluated by a paired t-test (before and during therapy). The degree of linear association between measured variables was estimated by Pearson's correlation. The probability of statistically significant differences was set at a *p* value of <0.05 and CI 95%.

Results

Demographics.

This series include 155 patients with GD, 72 males and 83 females from 117 apparently unrelated GD families with a mean of 1.36 patient/family. The cohort comprised 47 children (<14 years old) and 108 adults. The mean age of SGDR patients was 31.5 ±16.6 years and the mean age at diagnosis was 24.0±16.9 years (Figure 1).

The distribution of the GD patients in Spanish autonomic communities is given in Figure 2. The prevalence of GD was 1/300,000 inhabitants for some regions and in accordance with the population data (data not shown).

Diagnosis

Patients tend to be diagnosed at a younger age. Twenty-two cases were detected after previous diagnosis of a sibling. According to GD type, 149 were classified as having type 1, 2 type 2 and 4 type 3.

Clinical data

For the analysis we only considered the 114 patients for whom we had full information (Table 1). The most prevalent clinical feature in this series was organomegaly (95.6%). Thirty-two patients had had a splenectomy, and the remaining 92 showed varying sizes of spleen enlargement. The liver was enlarged in 85.9% of the patients, and bone disease (ranging from painful crises to fractures) was present in 62.4%. Our series contained only six patients (3.8%) with neurologic disease: two patients affected by the acute neuronopathic form of GD, type 2, were diagnosed within the first 5 months of life, and died before reaching 2 years old; 4 patients were classified as having type 3 disease because of myoclonic seizures, mental retardation, and motor disturbances which developed during the childhood.

Among 149 patients with GD type 1 non-neuronopathic form, 5 died, 2 of them of multiorgan failure, 2 from liver cirrhosis and 1 from acute bleeding; the mean age at death was 53 years (range 37-70).

Biological data were available for 114 patients. Hemoglobin level, leukocyte and platelet count, expressed as mean ± SD are detailed in Table 2. The values were frequently below the normal range. Cytopenias were present in 72 patients (62.3%). Liver enzyme function markers, AST and ALT, were raised as were plasma chitotrioxidase activity and tartrate acid resistant phosphatase. High acid phosphatase levels were observed in 99% of cases and biochemical liver dysfunction in 42.9%. By contrast, total cholesterol and HDL-c were below the 10 percentile in 92% and 96% of cases, respectively. In 71% of the patients mor-

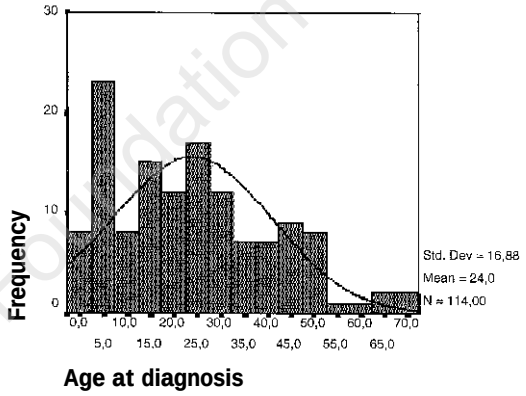


Figure 1. Age distribution at diagnosis of SGDR patients.

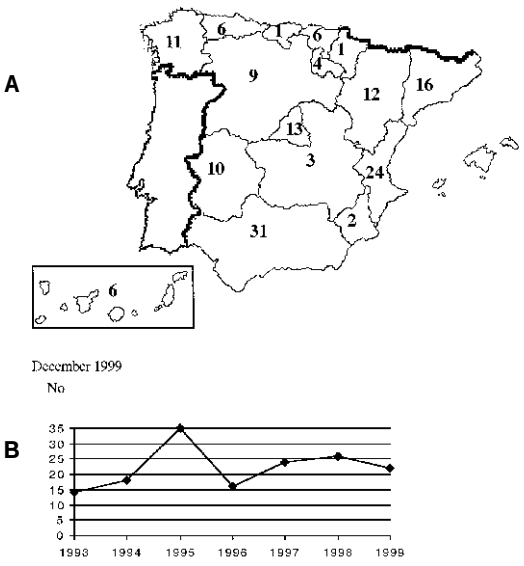


Figure 2. Spanish Gaucher's Disease Registry. Geographic distribution (A), and number of cases / year (B).

Table 1. Clinical data at diagnosis (no. 114).

Features	*No.*	*Percentage*
Asymptomatic	22	19.3
Organomegaly	109	95.6
Hepatomegaly	98	85.9
Splenomegaly	100	87.7
Skeletal involvement	71	62.4
CNS involvement	6	3.8*
Others (lung, kidney, hearth)	2	1.7
Splenectomy	32°	28.1
Orthopedic procedures	20	17.5
Enzymatic replacement therapy (ERT)	94	60.6*

**Percentage calculated from 155 registered patients; °one case partial splenectomy.*

Table 2. Biological data at diagnosis (No. 114).

Parameters	*mean± SD*	*range*	*NV*
Hemoglobin (g/dL)	11.4±2.0	6-15.7	
M/F	11.8±2.3/ 11.4±1.7	6.8-15.7/ 6.0-14.6	13.5±1.0/ 12±1.0
Leukocytes (x10^9/L)	6.3±3.7	1.6-18.1	4.5-11.0
Platelets (x10^9/L)	110.5±88.2	4-410	140-450
AST (U/L)	37.7±17.8	13-100	10-35
ALT (U/L)	29.3±20.0	4-142	10-31
GBA activity (nM/mg P.h)	0.91±0.334	0.1-1.6	> 10
Acid phosphatase (U/L)	22.6±13.7	5.7-66	<6.0
Chitotriosidase (nM/mL.h)	13,991±12,647	0-57,466	0-100
Cholesterol (mg/dL)	133.2±35.5	58-269	120-220
Triglycerides (mg/dL)	126±92.3	32-770	<175
HDL-cholesterol (mg/dL)	24.9±7.9	10-57	>45

NV: normal values.

phologic documentation of the diagnosis was obtained (spleen or hepatic tissue, bone marrow biopsy or aspirates).

Genotyping. The frequencies of GBA mutations in the 108 unrelated patients in the SGDR are shown in Table 3. The most common mutation was N370S, occurring in 46.3% of the total number of alleles, followed by the L444P in 18.5%. The most frequent genotype was N370S/L444P; other genotypes represent 64.0% of total (Table 4). The genotype N370S/N370S is not reported very often in SGDR patients. Eleven of the genotypes included in the group *all others* are unique to Spain, and include N370S/T134P N370S/G195W, N370S/G202R, N370S/1451delAC, N370S/Y313H, N370S/P391L, G377S/G195W, G377S/G377S, G377S/R436C, and L444P/E326K.

Clinical and biological features were correlated with

Table 3. Frequency of GBA mutations in 108 unrelated Gaucher's disease patients.

Mutation	*No. of alleles*	*Percent*
N370S	100	46.3
L444P	40	18.5
Delec/Rec	8	3.7
G377S	6	2.7
D409H	3	1.3
G195W	2	0.8
T134P	2	1.3
R436C	2	0.8
G202R	1	
Y313H	1	
E326K	1	
1451delAC	1	
P391L	1	
Unknown	48	22.2

Table 4. Clinical features of type 1 GD according to genotype (no. 114).

	Genotypes			
Variable	*N370S/N370S*	*N370S/L444P*	*N370S/?*	*Others*
No. of patients (%)	11 (9.6)	42 (36.8)	33 (28.9)	28 (24.6)
Gender (M/F)	4/7	21/21	15/18	14/14
Age at diagnosis (yr)* mean ± SD	38.7±18.4	25.0±14.8	24.0±15.7	18.6±14.9
Hepatomegaly (%)	3.0	25.4	22.4	20.5
Splenomegaly (%)	4.4	32.6	27.7	28.8
Skeletal involvement (%)	3.7	23.2	15.7	21.3
Abnormal liver function tests (%)	7.5	11.9	11.5	13.4
Cytopenias (%)	3.5	21.2	17.6	23.5
Splenectomy (%)	0	8.3	6.5	9.2
Severity score index° mean ± SD	5.5±3.7	7.6±3.2	9.1±4.2	12.3±5.1

**N370S/N370S vs others p<0.0002; °N370S/N370S vs others p<0.0455.*

genotype (Table 4); patients with N370S/N370S genotype showed fewer clinical manifestations than other genotypes. Age at diagnosis was higher in N370S/N370S cases, being statistically significant compared to the other phenotypes ($p<0.0002$). In spite of the absence of statistical significance for several clinical manifestations such as organomegaly, cytopenia or skeletal involvement, the severity score index showed statistical significance for the N370S/N370S genotype compared to the other genotypes ($p<0.0455$). The relationship between the mutation and the severity of the disease is shown in Figure 3. The lowest SSI was observed in patients with N370S/N370S and the highest in the group of patients with uncommon genotypes.

We compared clinical and biological data from children (aged under 14 years) and adults (Table 5). For children, the most relevant clinical findings were organomegaly (90.4%) and skeletal involvement (76.6%). Significant statistical differences were found for liver enlargement ($p=0.0001$) and SSI ($p=0.0001$).

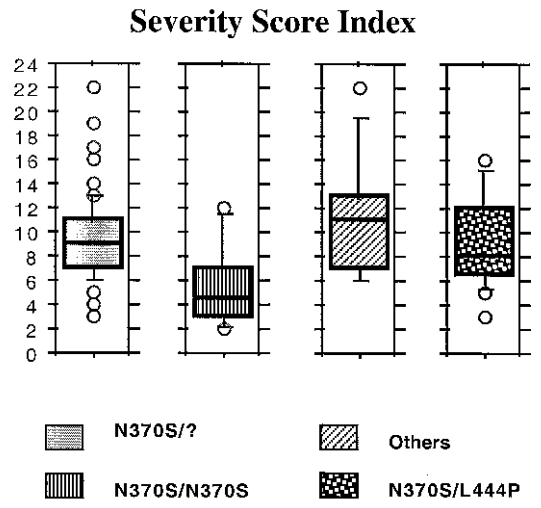


Figure 3. Genotype and severity score index.

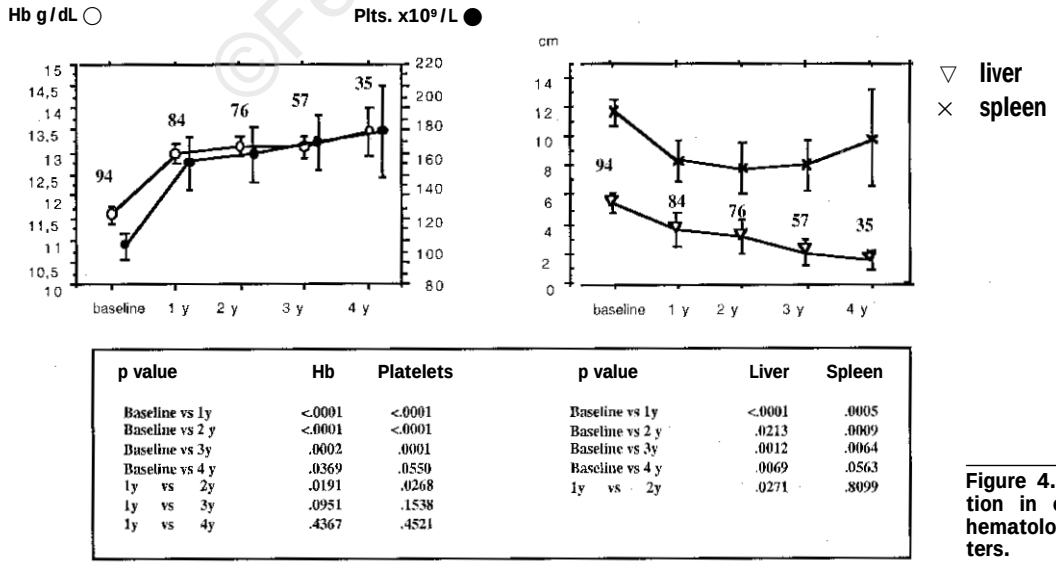
SSI was taken as the dependent variable and analyzed by correlation tests against liver and spleen size, hemoglobin levels and platelet count. No correlation between SSI and the other parameters was observed in children, although in adults there was a significant correlation for spleen size (Z-value: 3.142; p= 0.0017; CI: 0.173-0.637).

In 1993 four patients in Spain started ERT with alglucerase. In 1999, 94 patients were on ERT (60.6%), 10 receiving a low dose, high frequency schedule and the remaining 84 receiving doses above 30 U/Kg/every two weeks. Baseline clinical characteristics of patients receiving ERT, compared to patients without ERT, are shown in Table 6; skeletal involvement and chitotrioxidase activity were the factors that differed most between groups, followed by spleen enlargement and cytopenia. Age at diagnosis was lower in patients receiving ERT (p=0.0007). The response to ERT was evaluated yearly (Figure 4). The

Table 5. Clinical features at baseline (children vs adults with GD).

Variable	Adults (no. 72) No.	%	p	Children (no. 42) No.	%
Gender (M/F)	31/41	42.7/57.3	–	21/21	50.0/50.0
Subtype 1	72	100	.179	36	86.4
Age at diagnosis (year)°	32.3±13.0 (15–68)	–	–	7.0±4.5 (0–14)	–
Hepatomegaly	41	60.3	.0001	36	90.4
Splenomegaly	61	89.7	.885	36	90.4
Skeletal involvement	39	57.4	.068	30	76.6
Abnormal liver function tests	29	42.6	.445	20	50.0
Cytopenias	46	67.6	.575	25	62.5
CNS involvement	–	–	–	6	15.0
Other organs involved lung, kidney, heart	2	2.9	–	1	2.5
Splenectomy	22	30.5	.439	10	23.8
Severity score index°	7.7±3.4 (2–17)	–	.0001	13.9±6.2 (8–36)	–
ERT*	58	80.5	.484	36	85.7

**Enzymatic replacement therapy; °mean ± SD (range).*



p value	Hb	Platelets	p value	Liver	Spleen
Baseline vs 1y	<.0001	<.0001	Baseline vs 1y	<.0001	.0005
Baseline vs 2 y	<.0001	<.0001	Baseline vs 2 y	.0213	.0009
Baseline vs 3y	.0002	.0001	Baseline vs 3y	.0012	.0064
Baseline vs 4 y	.0369	.0550	Baseline vs 4 y	.0069	.0563
1y vs 2y	.0191	.0268	1y vs 2y	.0271	.8099
1y vs 3y	.0951	.1538			
1y vs 4y	.4367	.4521			

Figure 4. ERT, variation in clinical and hematologic parameters.

Table 6. Clinical differences at baseline between patients receiving ERT and not.

Variable	*ERT*	*No ERT*	*p*
Age*	28.3±14.4	39.2±16.8	.0162
Age at diagnosis*	20.2±13.7	35.8±19.2	.0007
Hepatomegaly (%)	61.2	20.8	.0045
Splenomegaly (%)	71.7	20.8	.0009
Cytopenia (%)	63.5	16.6	.0009
Skeletal involvment (%)	52.9	4.1	<.0001
SSI*	8.8±3.6	6.6±3.2	.075
Chitotriosidase nM/mL.h	19,965±15,733	14,161±10,870	<.0001

**Mean±SD.*

Table 7. Quality of life assessement (no. 35).

	No.	*%*
Physical activities		
self-care (good/bad)	28/7	80/20
walking (normal/abnormal)	27/8	77.2/22.8
vigorous activities (yes/no)	10/25	28.6/71.4
Psychologic disturbances		
familial (yes/no)	16/19	45.7/54.3
working activities (yes/no)	27/8	77.1/22.9
global (yes/no)	32/3	91.4/8.6
Social abilities		
satisfactory /mild/unsatisfactory)	29/2/4	82.8/5.7/11.5
constitutional symptoms (yes/no) *intense/mild	10*/257/3	28.6/71.4

Table 8. ERT* and self-evaluation of health.

	Before		*After*	
	No.	*%*	*No.*	*%*
Acceptable	8	22.8	6	17.1
Satisfactory	2	5.7	15	42.8
Good	2	5.7	11	31.5
	12	34.3	32	91.4

*p<0.0001; *mean time on therapy: 45.4 months (range: 6-70).*

majority of patients showed a positive response to therapy with a significant increase in hemoglobin mean value and platelet counts mainly after the 1st and 2nd years under ERT; hematologic values tended to stabilize or increase slightly in the following years. Simultaneously, following a similar pattern, a significant decrease in liver and spleen sizes was detected; a clear improvement was observed in this parameter, comparing baseline and follow-up data. Statistical significance was achieved between baseline data and yearly data, but no differences between data at one year and data from the following years.

Quality of life assessment. This was performed in 35 patients receiving ERT, with 4 years of follow-up. Results concerning the evaluated aspects are given in Tables 7 and 8. There was substantial restriction of vigorous activities (71.4%). Psychologic disturbances were present in 91.4% of cases, especially related to working activities (77.1%). Social abilities were usually satisfactory and constitutional symptoms were present in 10 cases. Self-evaluation of health showed a large improvement, from 34.3% to 91.4%, in patients receiving ERT. This improvement was statistically significant ($p< 0.0001$).

Discussion

Gaucher's disease has a wide range of clinical presentations, from the severely affected child to the asymptomatic elderly person. Indeed the features of the disease raise some questions concerning the specific criteria necessary to define diagnosis and therapy.[1]

From a clinical point of view GD is a rare disease with both heterogeneous clinical and genetic variability and consequently an imperfect genotype/phenotype correlation.[6,12] Experience is scarce and focused on families or isolated cases; different specialities (hematology, internal medicine, pediatrics and gastroenterology) are involved in the diagnosis and therapy. ERT is only considered for symptomatic patients and each case requires careful evaluation. The co-operation between different specialists and physicians sometimes far apart is particularly important in order to provide evaluable parameters to give a general overview of the disease.

The usefulness of registries to improve knowledge about rare diseases has been established; Gaucher's disease is a good model in this setting, allowing advantageous information about different aspects of the disease such as diagnosis, follow-up and therapy to be collected. Data from the registries are also useful for developing homogeneous guidelines for specialists and general practitioners.

The present series includes most Spanish patients diagnosed as having GD. The overall incidence of GD in Spain in our study is 0.4 cases per 100,000 inhabitants, lower than expected. A possible reason for this could be the clinical variability of the disease, specially type 1, with a large number of asymptomatic or mildly symptomatic patients. Probably this value will increase in the future as a consequence of the Spanish Gaucher Group's activities, particularly those of providing guidelines for clinical diagnosis and genetic characterization of the patients. Previously reported data about the frequency of GD in non-Jewish populations from EU countries give similar results.[13,14]

The analysis of the mutations in GD is a very interesting way of providing knowledge about the geographic and ethnic origin of the disease, as has recently been reported.[15] In accordance with previous reports in Spain,[16-19] we found a similar overall prevalence of N370S (45.4%) and L444P (17%) mutation among GD patients in the SGDR. GD recombinant alleles harboring pseudogene sequences are frequent in SGDR patients (4%), this prevalence being similar to that reported in a non-Jewish population.[20] In this study the G377S mutation is the third most frequent mutation as we have previously reported[19] in contrast with results from other Spanish studies of fewer patients.[16] Furthermore this mutation has also been observed frequently in Portuguese GD patients.[21] Among our registered cases, D409H

mutation was observed in 1.3% of alleles, one case being homozygous. Nevertheless, the real incidence of the D409H mutation must be higher, because in our data we did not consider cases without full clinical data.[22,23] Eighty percent of GD alleles observed in the SGDR patients were N370S, L444P, Rec/Del and G377S mutations.

In our series, clinical manifestations of type 1 Spanish GD were similar to those reported in other European countries;[13] the high frequency of N370S allele in Spain[16-19] could explain the mild degree of disease. In this sense, homozygous N370S cases were diagnosed in adult age more frequently than the other genotypes.[24] Patients with other genotypes have more severe disease with regards to hepatic and bone involvement, and SSI, and earlier onset of disease.

Children had more aggressive clinical manifestations than adults, especially for liver and skeletal involvement, and a higher SSI. These data have also been reported previously.[25,26]

ERT was started in more than 60% of diagnosed patients. In Spain there is no National Committee Decision for therapy, and the indications for ERT were usually established individually by the physician caring for the patient. The main indications for ERT in this series were skeletal involvement and higher chitotrioxidase activity followed by spleen enlargement, usually associated with cytopenias.

Only 10.6% of patients under ERT received a low dose/high frequency schedule in contrast to 89.4% who received the high dose/low frequency schedule. In both groups the response to ERT was positive with a significant increase of hemoglobin and platelet levels after 1 and 2 years of therapy and significant reductions of both spleen and liver size at the same time. In patients receiving ERT for more than two years, clinical and analytical variations were not statistically different; this fact could indicate that ERT is effective in the early period of therapy in reversing GD-related manifestations and remains effective over the follow-up without, however, producing additional improvement. For this reason, in our opinion a progressive and gradual reduction in the dose of ERT, supported by clinical data and monitoring, should be considered.[27]

The self-assessment of quality of life (QOL) in patients under ERT showed a marked improvement. Some questions concerning ERT remain to be analyzed. Is earlier therapy better than later in terms of cost-effectiveness analysis and how much should QOL be taken into consideration when making therapeutic decisions?

Prospective studies are necessary to identify the best strategy.

In conclusion, the clinical characteristics of Gaucher's disease in Spain were similar to those in other non-Jewish populations. The N370S allele was the most frequent mutation identified. ERT clearly contributes to improving QOL and clinical manifestations.

Appendix

Spanish Gaucher's Disease Registry participants.

Complejo Hospitalario de Leon (León) Dr López González/Dr Muñoz Rodríguez. Complejo Hospitalario de Albacete (Albacete) Dr Ibañez. Complejo Hospitalario San Millán (La Rioja) Dr Campo/Fernández Villamayor. Hospital 12 de Octubre (Madrid) Dr Castellano Tartajada/ Dr de la Serna/ Dr Prieto. Hospital Basurto (Bilbao) Dr Martinez Odriozola. Hospital Bellvitge (Barcelona) Dr Vidaller Palacín. Hospital Cabueñes (Gijón) Dr Fernández García. Hospital Carlos Haya (Málaga)Dra Heiniger. Hospital Central Asturias (Oviedo) Dra Luño/ Dr García de Jalón. Hospital Clínico Universitario (Salamanca) Dr Rios. Hospital Clínico San Carlos (Madrid) Dr Díaz-Mediavilla.Hospital Clinico Universitario Lozano Blesa (Zaragoza)Dr Perez Calvo/Dr Torralba. Hospital Costa del Sol (Málaga)Dra Medina/DraQueipo de LLano. Hospital de Galdakao (Bilbao) Dr Atutxa. Hospital del Rio Hortega (Valladolid) Dra Romero Gomez. Hospital Dr Peset (Valencia) Dr Gracía Antequera/ Dra León. Hospital Francesc de Borja (Gandía) Dra Ruiz Guinaldo. Hospital General (Valencia) Dra Tomás. Hospita General Manresa (Manresa) Dr Salinas. Hospital General Yague (Burgos) Dr Lorenzo González. Hospital General Alicante (Alicante) Dr Mut Barberá. Hospital General Universitario(Elche) Dr Conesa. Hospital General(Valencia) Dr Ferriols. Hospital Jativa (Jativa) Dr Pastor. Hospital Jerez de la Frontera (Jerez) Dra Romero Gallardo/Dr Campo. Hospital Juan Canalejo/Hospital Virxe da Junqueira (A Coruña) Dra Vale. Hospital La Paz (Madrid) Dra Aguado. Hospital Marina Baixa (Villajoyosa) Dr García Pérez. Hospital Meixoeiro (Vigo) Dr Lite. Hospital Miguel Servet (Zaragoza) Dra Giraldo/Dr Baldellou. Hospital Montecelo (Pontevedra) Dra Loyola/Dr Lamberti. Hospital Motril (Motril) Dra Gómez Morales. Hospital Ntra.Sra. del Pino (Las Palmas) Dr Aguiar. Hospital Ntra Sra Candelaria (Sta Cruz de Tenerife) Dra Amerigó. Hospital Ntra Sra Sonsoles(Avila) Dr Barez García. Hospital Puerta del Mar (Cádiz) Dra Fornell Forcadas. Hospital Punta Europa (Algeciras), Dr Zarate/Dr Franco. Hospital Ramón y Cajal (Madrid) Dr Martín Çapa/Dr Martinez Pardos. Hospital S Juan de Dios (Barcelona) Dra Toll. Hospital Sagunto (Sagunto) Dr García Díaz. Hospital San Pedro Alcántara (Cáceres) Dr Santos. Hospital Sta Mª del Rosell (Murcia) Dr Albaladejo. Hospital Torrecárdenas (Almería) Dr López Muñoz. Hospital Universitario Cruces (Bilbao) Dr Sanjurjo. Hospital Universitario Josep Trueta (Gerona) Dra Fernández Fidalgo. Hospital Universitario La Fé (Valencia) Dr Calabuig/Dr Dalmau/Dr García. Hospital Universitario Marques de Valdecilla (Santander)Dr Garijo. Hospital Vall d'Hebrón (Barcelona) Dr Castelló Girona/Dra Domínguez. Hospital Virgen de la Luz (Cuenca) Dr Morillas/Dr Nieto. Hospital Virgen del Puerto (Plasencia) Dr Martín Nuñez/ Dr García Nazario/Dra Fernández Galán. Hospital Virgen del Rocío (Sevilla) Dra Alonso/Dr Plaza Delgado. Hospital Virgen Macarena (Sevilla) Dr Figueredo/Dr Fabiani/Dra Reyes Santos. Hospital Virgen Nieves (Granada) Dr Aporta/Dr Cabrera/Dr Salvatierra. Hospital Xeral de Galicia (Santiago de Compostela) Dr Rodriguez Lopez/Dr López Guerra. Hematoclin Médico SL (Madrid) Dr Fernández Rañada/Dr Gil Fernández. Hospital General de Elda (Valencia) Dr García Garay. HospitalVega Baja (Orihuela) Dr Acedo. Hospital Universitario Puerto Real (Cádiz) Dr Mendoza. Hospital Universitario Reina Sofía (Córdoba) Dra Adarraga/Dr Jiménez Pérezperez.

Contributions and Acknowledgments

GP, PM, P-CJ collected the data and designed this paper. GP performed the statistical analysis and R-FD and GM contributed to revising and reviewing the final version.

Funding

This work was carried out with funds provided by FIS grant number 00/0546, DGA: PCM-1094 and Fundación Española Estudio y Terapéutica de la Enfermedad de Gaucher.

Disclosures

Conflict of interest: none.

Redundant publications: there is a less than 50% overlap with a previous paper,[17] which however included fewer cases, and did not analyze evolutive data; in the present paper clinical, genetic and evolutive data are statistically analyzed in order to establish correlations between them.

Manuscript processing

Manuscript received December 29, 1999; accepted May 25, 2000.

Potential implications for clinical practice

- The establishment of a National Registry has contributed to the development of homogeneous guidelines for diagnosis and follow-up of Spanish Gaucher patients.
- The clinical picture in pediatric patients is more aggressive than in adults, with a higher SSI.
- ERT improves clinical and analytical data as well as QOL. This improvement occurs quickly.
- ERT must be continued indefinitely; for this reasons monitoring systems and dose adjustments must be defined.

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