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Artículo original

Gaucher disease in Mexico. Epidemiologic overview

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RESUMEN

Introducción. La enfermedad de Gaucher (EG) es una enfermedad lisosomal autosómica recesiva genética de almacenaje, caracterizada por la actividad del déficit de glucocerebrosidasa considerada como una enfermedad "rara". Existe un tratamiento disponible pero la carencia de legislación en México limita su uso. Este informe describe las características clínicas de una muestra de sujetos afectados en México.
Material y Métodos. 63 pacientes registrados en la Asociación Mexicana de Gaucher entre 1983 y 2006 fueron estudiados por edad, sexo, origen, tipo, mutación y fueron evaluados.
Resultados. Un ejemplo de 63 pacientes confirmados fueron reclutados, 32 eran hombres (50.7%) y 31 mujeres (49.3%), la edad era de 21.8 años en promedio. El tipo 1 de EG afectó a 51 (80.9%), el tipo 3 afectó a 12 pacientes (19.1%); la edad promedio al momento del diagnóstico fue de 12.4 años. Treinta y siete pacientes fueron N370S heterocigotos y seis pacientes fueron N370S homocigotos; en L444P se encontraron 14 pacientes heterocigotos seis homocigotos. No se encontraron homocigotos de L444P en pacientes con EG tipo 1, homocigotos de N370S se observó en pacientes con EG tipo 3.
Las manifestaciones clínicas se registraron en los siguientes porcentajes: hepatomegalia 19.04%, hepatoesplenomegalia 80.9%, patología hematológica 58.07%, trastorno óseo 100%, trastorno neurológico 19.04%. Solo 40 (63.4%) estaban bajo terapia de reemplazo enzimático.
Análisis. Este es el primer informe completo de los pacientes con enfermedad de Gaucher. La enfermedad rara y los medicamentos huérfanos necesitan legislación en México.
Palabras clave: Enfermedad de Gaucher, heterocigoto, homocigoto, glucocerebrosidasa, enfermedad lisosomal por almacenaje.

ABSTRACT

Introduction: Gaucher disease (GD) is a rare genetic recessive autosomical lysosomal storage disease, characterized by deficient activity of glucocerebrosidase. Treatment is available, but a lack of legislation for it in Mexico limits its use. This report describes the clinical features of a Mexican sample of affected subjects.
Material and Methods: Sixty-three confirmed patients registered in the Mexican Gaucher Association from 1983-2006 were studied. Age, sex, type, mutation, manifestations, and treatment were evaluated. There were 32 males (50.7%) and 31 females (49.3%); mean age was 21.8 years.
Results: Type 1 GD affected 51 (80.9%) and type 3 affected 12 (19.1%) patients. Average age at diagnosis was 12.4 years. Thirty-seven patients were N370S heterozygotes and 6 patients were N370S homozygotes. L444P was found in 14 heterozygote patients and in 6 L444P homozygotes. No L444P homozygote was reported in patients with type 1 GD, and no N370S was observed in patients with type 3 GD. Clinical manifestations were reported in the following percentages of patients: hepatomegaly, 19.04%; hepatosplenomegaly, 80.9%; hematological disorder 58.7%; bone disorder, 100%; neurological disorder, 19.04%. Only 40 (63.4) were under enzyme replacement therapy.
Discussion: This is the first complete report of patients with GD in Mexico. Rare disease and orphan drug legislation is needed in Mexico.
Key words: Gaucher disease, heterocygote, homocygote, glucocerebrosidase, lysosomal storage disease.

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Gaucher disease (GD) is a rare autosomal recessive genetic lysosomal storage disease (LSD), caused by a deficiency of glucocerebrosidase enzyme, which leads to the accumulation of glucocerebroside within macrophage tissue of multiple organs. It is associated with organ failure and dysfunction. A complete decription of GD may be found in the review by Grabowski [1].

As lysosomes are present in most living cells, GD as one of the LSD variably affects the brain and cognitive function. Myopathy and skeletal abnormalities are also common as well as a range of visceral and skin disturbances.

Treatment of GD patients requires adequate diagnosis, access to effective treatment, particularly enzyme replacement treatment and involvement of a multidisciplinary team [2].

GD is included in every list of "rare diseases". These conditions are defined based on their low incidence rates, but the minimal incidence rate varies according to legislations. A limited number of countries in the world have an explicit legal framework for rare diseases and their treatment –known as orphandrugs- [3].

In Mexico as in most developing economies, a specific legislation for rare diseases and orphan drugs does not exist. The need for scientific evidence on each rare disease is necessary in order to prescribe the proper treatment.

The aim of this study was to describe the clinical manifestations of a series of Mexican patients with GD. A discussion regarding the need of a legal framework for rare diseases using GD as an example is addressed.

MATERIALS AND METHODS

Subjects were recruited from the Mexican Gaucher Association, founded in 1983. Every patient had a definitive diagnosis based on enzyme analysis of B-glucocerebrosidase activity or DNA analysis of the glucocerebrosidase gene.

Histological diagnosis was obtained through biopsy of affected organs (spleen, liver, bone, ganglia). Patients with incomplete records were excluded.

The following clinical variables were evaluated: hepatomegaly and splenomegaly, complete blood parameters, including peripheral blood smears, neurological manifestations, long bone skeletal X-rays, ultrasound based liver and spleen volumes were obtained.

Anemia was defined as a hemoglobin level below 11mg/dL, and thrombocytopenia below <150 thousand platelets.

Genotype frequency distributions for common mutations (L444P, N370S) were determined. All patients who received enzyme replacement therapy (ERT) were treated either with alglucerase (Ceredase, Genzyme Corporation, Cambridge, MA) or imiglucerase (Cerezyme, Genzyme Corporation, Cambridge, MA).

Statistical analysis

Mean and standard deviation were reported for continuous variables and proportions for discrete variables.

RESULTS

A sample of 63 patients was evaluated; 26 (41%) were under 18 years old and 37 (59%) were adults. Table 1 depicts demographic and clinical data.

At present, 40 (63.4%) of the 63 patients affiliated to the Mexican Gaucher Association are receiving enzyme therapy with imiglucerase.

Table 2 shows genotype data for the sample. No type 1 patients were L444 homozygotes. No type 3 patients had N370S alleles. The type of mutation was unknown for 51 alleles, 45 alleles for type 1 GD and 6 alleles for type 3 GD. In all patients at least one of the 2 alleles studied in each case was identified.

Table 3 shows all major clinical findings according to GD type.

Neurological manifestations were highly variable therefore only its presence or absence is reported.

DISCUSSION

This is the first complete description of a retrospective sample of Mexican GD patients. A previous report was published with a sample of 14 children, but only clinical features were described and no genetic characterization was available [4].

The absence of Ashkenazi Jewish population in Mexico, as well as, an early mortality is the main reason for the absence of type 2 GD [4]. The predominance of type 1 and a lesser proportion of type 3 are consistent with other case series in Spain and Brazil [5,6].

In this study, the ages at diagnosis of GD patients were 13.5 years for type 1 and 6.3 years for type 3 patients. The

Table 1. Gaucher Disease sample description in Mexico

Patients Enrolled	*N=63*	
Disease Type*, n (%)	**n=62**	
Type 1	51	(82%)
Type 2	0	(0%)
Type 3	11	(18%)
Sex, n (%)	**n=63**	
Males	31	(49%)
Females	32	(51%)
Average Age		
General	63 (100%) mean 21.8 ± 12.5 years	
Pediatric	26 (41%) mean 10.4 ± 7 years	
Adults	37 (59%) mean 29.8 ± 9.7 years	
Age at Diagnosis (y)	Type 1	Type 3
Mean (SD)	13.9 (12.0%)	6.5 (8.5%)
Age at Diagnosis, n (%)		
0 to 5 years	5 (8%)	
6 to 10 years	7 (11%)	
11 to 15 years	10 (16%)	
16 to 20 years	9 (14%)	
21 to 25 years	11 (17%)	
26 to 30 years	7 (11%)	
31 to 35 years	3 (5%)	
36 to 40 years	6 (9%)	
41 to 45 years	3 (5%)	
46 to 50 years	0 (0%)	
51 to 55 years	1 (1%)	
56 to 60 years	1 (1%)	
Age at First Infusion (ERT)	Type 1	Type 3
Mean (SD)	17.2 (11.1%)	4.7 (4.4%)
Length of Treatment After Diagnosis	Type 1	Type 3
Mean (SD)	3.7 (3.7%)	1.5 (0.5%)

*Disease type as reported by physicians belonging to the Mexican Association
ERT: Enzyme research therapy

Table 3. Hematologic and Visceral Manifestations of Mexican Patients* with Gaucher Disease

	Number of Patients, n (%)	
	N=63	
Total Number of Patients Enrolled	Type 1Ü 51 (81%)	Type 3Ü 12 (9%)
	37 (59%)	
Hematological disorder Ü (anemia and thrombocytopenia)	Type 1 30 (47.6%)	Type 3 7 (11.13%)
	51 (81%)	
Splenomegaly	Type 1 40 (63.4%)	Type 3 11 (17.4%)
	12 (19%)	
Hepatomegaly	Type 1 11 (17.4%)	Type 3 1 (1.5%)
Splenectomized	N=33 (52%)	
	Type 1 28 (54.9%)	Type 3 5 (58.3%)
	N=63	
Bone disorder	Type 1 51 (81%)	Type 3 12 (19%)
	N=12(19%)	
Neurological disorder ß	Type 1 0 (0%)	Type 3 12 (100%)

* Each patient may present with more than one clinical manifestation. The percentages for each disease type were calculated using the total number of patients as denominator.
ßNeurological disorders were predominantly oculomotor apraxia and delayed psychomotor development.
Ü The number of patients with total or partial splenectomy was classified by subtype of Gaucher disease as: 28 (54.9) type 1 and 7 (58.3) type 3.

Table 2. Frequency of Genotype Groups of Patients with Gaucher disease in Mexico. Mutations found in 63 Mexican patients with Gaucher Disease

Mutation	*Homozygote*		*Heterozygote*		*Totals*	
	No.	*Percentage*	*No.*	*Percentage*	*No.*	*Percentage*
N370S	6	9.5%	37	58.7%	43	68.2%
L444P	6	9.5%	14	22.2%	20	31.7%
Total	12	19%	51	81%	63	100%

* Heterozygote is defined as any known allele including N370S, L444P, IVS2+1, D409H or 84GG.

diagnosis of type 3 patients at a younger age may be related to the visceral and neurological manifestations which prompted these patients to seek for medical care sooner. In contrast, some type 1 patients remain asymptomatic until adulthood [7].

In this report, the average age of the sample was 21.8 years; which is consistent with published reports from the International Collaborative Gaucher Group (ICGG).

Gaucher Registry indicates that the average age of patients with GD was under 30 years [8].

Genotype data showed two common mutations comprising all GD alleles: N370S (68.2%) is predictive of a non-neuronopathic course and is in accordance with other case series while L444P (31.7%) is associated with type 3 GD [1].

Viceromegalies are salient clinical features. In this study splenomegaly was found in 81% subjects and hepatomegaly in 9% of the patients. It is important to highlight the fact that patients receiving enzyme replacement therapy develop less size hepatomegaly [9].

The percentage of splenectomized patients is similar to other reports [7]. Other studies report bone damage as the second most common manifestation for patients with GD [10]; in our series, every patient had at least one bone manifestation. It is also known that ERT is not as effective in bone manifestations as in viceromegalies [9].

Enzyme replacement therapy availability for GD is limited in Mexico. In this series, 63% of the patients affiliated to the Mexican Gaucher Association received ERT with imiglucerase. The ICGG Gaucher Registry reports that 81.7% of patients worldwide are receiving ERT with imiglucerase [9].

ERT is considered an orphan drug. The concept emerged because there are more than 7600 rare diseases and it is as costly to develop a treatment for a rare disease as for a common disease. On ethical grounds, in 1983 the orphan disease act passed in the US, and the emergence of effective solutions for rare diseases began to appear [11]. GD was one of the first benefitted.

Orphan drugs are expensive for the health system, but different solutions have been proposed to increase the number of patients treated.

In Mexico, the use of ERT is approved, but 40% of the population that has no affiliation to the social security remains untreated.

The evidence of this report shows that GD patients behave as other populations when treated. It is the first Mexican research, that might give scientific support for an orphan disease legislation in Mexico.

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