

## Chitotriosidase genotype and plasma activity in patients with type 1 Gaucher's disease and their relatives (carriers and non-carriers)

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**Background and Objectives.** Chitinases are enzymes that hydrolyze chitin and have been found in a wide variety of non-vertebrate species; recently a human analog of chitinases, chitotriosidase (CT) has been identified. Extreme elevations of plasma CT activity are observed in patients with Gaucher's disease (GD), Gaucher cells being the source of the CT. A 24 bp duplication in the CT gene, resulting in an inactive protein, has been reported. The carrier prevalence is as high as 30 to 40% and the CT activity is half that in individuals with the wild-type gene. However no systematic evaluation of plasma CT activity has been carried out in GD patients taking into account the status of the allele defective for CT and dose in patients on enzyme replacement therapy (ERT).

**Design and Methods.** We had previously studied 210 subjects from 99 unrelated Spanish GD families (121 non-affected carriers and 89 non-carriers) in order to establish carrier prevalence of CT genotypes. Plasma CT activity and CT genotypes evaluated by polymerase chain reaction (PCR) and gel electrophoresis were measured in 109 GD patients before treatment. We also evaluated CT activity after ERT with alglucerase in 68 patients.

**Results.** Three patients had defective activities of CT. The carrier prevalence for the 24 bp duplication was 35% and the allele frequency 0.20. No correlation between CT activity and GBA genotype was detected nor between CT activity and visceral or skeletal disease in GD patients. Untreated affected patients, non-carriers for the duplication, had higher CT activity than carriers ( $p < .0001$ ). CT activity decreased dramatically during the first 12 months of ERT; even after 3 years of therapy a persistent fall

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of CT activity was observed. However, within 3 years of treatment, a significant difference in the mean decrease of CT activity was present among the group of patients receiving varying alglucerase doses ( $p < .01$ ). After 12 months of ERT the activity of plasma CT declined by the same percentage in both groups: heterozygous carriers of the 24bp duplication and wild type allele, but thereafter CT activity declined more slowly in carriers than non-carriers.

**Interpretation and Conclusions.** The present data can be used as a reference to interpret CT activity in GD patients with or without ERT, as well as to evaluate dose-response. It can also be used as a reference to interpret CT activity in carriers and non-carriers.

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Key words: chitotriosidase activity, Gaucher's disease, ERT, carriers.

Chitinases are enzymes that hydrolyze chitin and have been found in a wide variety of non-vertebrate species, including bacteria, fish, fungi, insects, nematodes and plants.<sup>1</sup> It has often been suggested that mammals do not possess a chitinase enzyme;<sup>2,3</sup> however, the human analog of chitinases, chitotriosidase (CT) has recently been identified, being secreted in large quantities by activated macrophages.<sup>4</sup>

CT is of interest for clinical reasons. CT is produced in large amounts by the lipid-laden macrophages in Gaucher's disease (GD) patients, and its activity is several hundred-fold increased in plasma of symptomatic patients.<sup>4</sup> Less important increases are found in the plasma of patients with several granulomatous immunological disorders or infectious diseases, such as sarcoidosis or leishmania-

sis.<sup>4,5</sup> The enzyme could be useful in monitoring the efficacy of therapy in GD patients. It has been reported that plasma CT levels in GD patients rapidly decrease upon enzyme supplementation therapy,<sup>4</sup> and that successful engraftment after allogeneic bone marrow transplantation in GD patients also results in correction of plasma CT activity.<sup>6</sup>

About 6% of the Caucasian population completely lack plasma CT activity.<sup>4,7</sup> This happens as result of a recessively inherited point mutation (null allele) in the CT gene, with the incidence of defective allele carriers being as high as 30-40%. Carriers for this CT defect show on average half of the plasma CT levels of individuals not carrying the mutation.<sup>8</sup>

Although increased levels of plasma CT activity in subjects with GD and in some other diseases have been pointed out previously,<sup>4,5,9</sup> no systematic evaluation of plasma CT activity, taking into account gender and carrier status of the allele defective for GD, has been reported.

We have measured plasma CT activity in a large population in order to determine the normal range. We have also performed a systematic analysis of CT activity in GD patients, either asymptomatic or under enzymatic replacement therapy (ERT), and relatives with a defective allele of the glucocerebrosidase (GC) gene.

## Design and Methods

### Patients

We studied 109 type 1 Gaucher's disease patients from the Spanish GD Registry, 68 of whom had been receiving ERT for at least 6 months (ERT group) and 41 who were not receiving treatment (NERT group). All patients had been diagnosed by at least two of three diagnostic methods: histologic demonstration of typical Gaucher cells in a bone marrow specimen (performed prior to referral to our laboratory),<sup>10</sup> low leukocyte acid  $\beta$ -glucosidase activity<sup>11</sup> and molecular diagnosis of a defined genotype associated with GD (when both mutated alleles were identified). The gender distribution (male/female) was 31/37 and the mean age of the patients was 26.8 $\pm$ 14.1 years (range 0.5-64 years) for the ERT group and M/F 19/22, mean age 33.3 $\pm$ 16.7 years (range 0.7-68 years) for the NERT group. A severity score index (SSI) was assigned to each patient according to age at diagnosis, skeletal and hematologic complications and visceral involvement (ASSI).<sup>12</sup> We also calculated the modified severity score index without the age factor (SSI), as previously described.<sup>13</sup> In addition we studied 210 GD relatives; 121 subjects (63 men and 58 women) were non-affected carriers

(carrier group), defined by genotyping analysis of the GC locus; and 89 subjects (43 men and 46 women) were non-carriers (non-carrier group) (Table 1). In the carrier group 18 subjects were under 15 years old, as were 37 in the non-carrier group. Only subjects belonging to families in which both defective GC alleles had been identified and who did not carry any mutant allele were included in the non-carrier group.

Our experimental protocol was conducted in accordance with the Ethical Committee of the Hospital Miguel Servet of Zaragoza, Spain, and with the Helsinki declaration of 1975, as revised in 1983.

The monthly average dose of intravenous infusions of alglucerase (Ceredase) for the ERT group was 64  $\pm$  24.5 U/kg body weight (range 30-120). Ten patients received <60 U/kg, 35 received 60 U/kg and 10 >60 U/kg alglucerase per month.

### Methods

Blood samples were obtained in EDTA tubes from subjects after an overnight fast and in the patients under treatment before the alglucerase infusion. Plasma was separated by low speed centrifugation at 2,000 g for 30 min at 4°C, aliquoted and stored at -80°C until further analysis.

The  $\beta$ -glucocerebrosidase genotype for each patient was determined from DNA isolated from peripheral blood leukocytes, as described elsewhere.<sup>14</sup>

Plasma chitotriosidase activity was measured with the fluorogenic substrate 4-methylumbelliferyl- $\beta$ -D-N,N',N''-triacetylchitotrioside (4 MU-chitotrioside, Sigma Chemical Co, St Louis, MO, USA) as described by Hollak *et al.*<sup>4</sup> GD plasma samples

**Table 1. Chitotriosidase activity of Gaucher's disease subjects and their relatives.**

Status	N	Sex (M/F)	Age (years)	Chitotriosidase (nmol/mL.h) (range)
Non-carriers	89	43/46	22.7 $\pm$ 16.5 (2-73)	45 $\pm$ 35.2 (0-226)
<14 years	37	18/19	7.9 $\pm$ 4.2 (2-14)	37 $\pm$ 25.3 (0-98)
$\geq$ 15 years	52	25/27	36.8 $\pm$ 14.9 (15-77)	52 $\pm$ 39.6 (0-226)
Carriers	121	63/38	34.2 $\pm$ 17.5 (2-77)	71 $\pm$ 55.8* (0-264)
<14 years	18	11/7	9.3 $\pm$ 3.3 (2-14)	60 $\pm$ 65.5* (0-264)
$\geq$ 15 years	103	52/51	38.5 $\pm$ 15.2 (15-77)	73 $\pm$ 54.7 (0-253)
GD	109	50/59	29.3 $\pm$ 15.6 (0.5-68)	13,991 $\pm$ 12,647° (0-57,466)
<14 years	20	11/9	6.5 $\pm$ 4.4 (0.5-14)	8,456 $\pm$ 7,606° (0-26,613)
$\geq$ 15 years	89	39/50	34.2 $\pm$ 12.5 (15-68)	15,198 $\pm$ 13,606° (0-26,613)

Values are means  $\pm$  standard deviation. \* $p$ <0.01 carriers vs non-carriers.  
° $p$ <0.001 Gaucher's disease patients vs non-carriers or carriers.

were diluted 1:50 in distilled water before measurement of CT activity.

We used the StatView program (version 4.5) for statistical analysis. For each variable we estimated the significance of the differences between non-carriers, unaffected carriers and GD patients by the ANOVA test. As there were no differences between men and women for CT, we did not carry out a statistical analysis by gender. Differences between data obtained before or during alglucerase treatment were tested by paired t-tests. Pearson's correlation coefficients were calculated to evaluate the degree of linear association between measured variables. We determined the mean  $\pm$  standard deviation (SD) for all variables for each group and the level of statistical significance was set at  $p < 0.05$ .

## Results

Plasma CT activities of subjects, including non-carriers, unaffected carriers and untreated GD patients, are presented in Table 1. An absence of CT activity was observed in 19 out of the 319 subjects we studied (5.9%), these individuals were excluded from the statistical analysis concerning plasma CT activity. The highest activity, observed in GD patients, was  $13,991 \pm 12,647$  nmol/mL.h; nevertheless unaffected carriers showed higher values ( $71 \pm 55.8$  nmol/mL.h) than non-carriers ( $45 \pm 35.2$  nmol/mL.h), the differences observed being statistically significant ( $p < .01$ ).

The plasma CT activity correlated with age in both carriers and non-carriers ( $r=0.382$ ,  $p < .0001$ , and  $r=0.420$ ,  $p < .0001$ , respectively; Figure 1A and 1B), but not in GD patients ( $r=0.113$ ,  $p=.3124$ ; Figure 1C). Adult individuals (age  $\geq 15$  years) had higher plasma CT activity than children in all groups (non-carriers  $52 \pm 39.6$  vs  $37 \pm 25.3$ ; carriers  $73 \pm 54.7$  vs  $60 \pm 65.5$ ; GD  $15,198 \pm 13,606$  vs  $8,456 \pm 7,606$ ). A correlation was found between plasma CT activity and body mass index (BMI) ( $r=.434$ ;  $p=.004$ ).

Plasma CT activity was also correlated with SSI in GD patients before therapy ( $r=.351$ ,  $p=.004$ ). Similar data were recorded in patients who had been splenectomized who had higher plasma CT activity ( $25,514 \pm 14,113$  nmol/mL.h) than non-splenectomized patients ( $15,080 \pm 12,469$  nmol/mL.h), ( $p=.006$ ).

CT genetic expression was evaluated in GD patients. Individuals who were carriers of a defective allele for CT had lower CT activity  $11,873 \pm 10,458$  nmol/mL.h than non-carriers  $17,387 \pm 12,801$  nmol/mL.h ( $p=.021$ ).

As far as concerns the effect of ERT (Table 2),

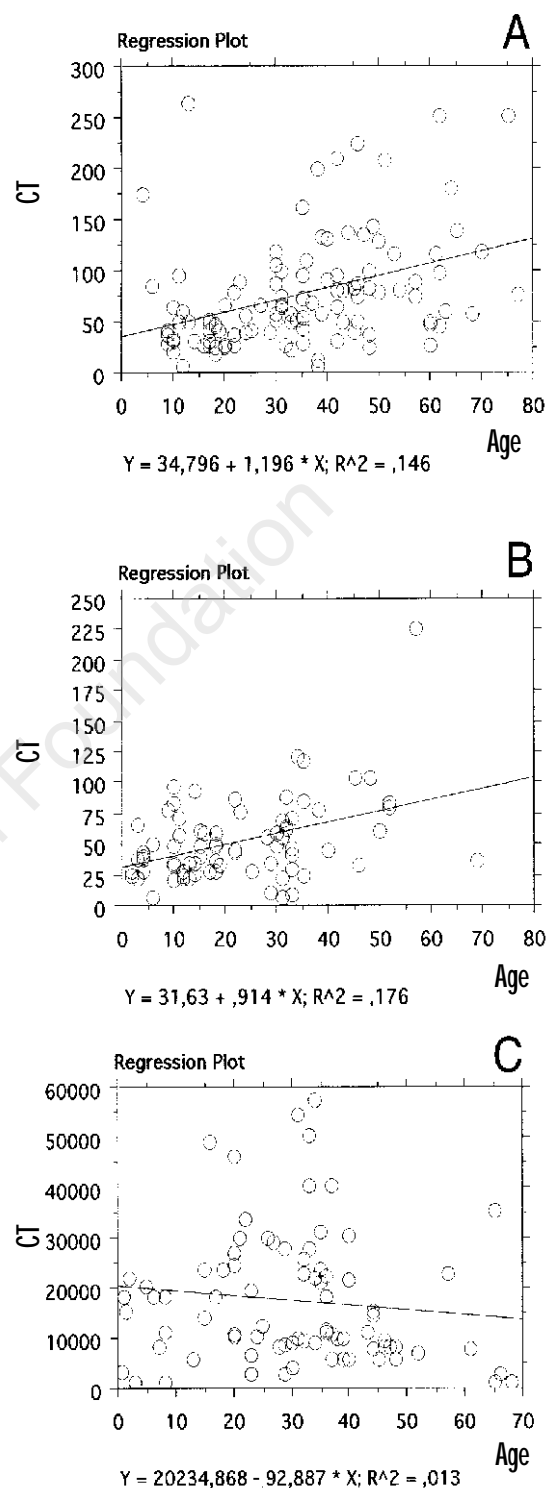


Figure 1. Regression plots for plasma CT activity (nmol/mL.h) and age (years). A: carriers; B: non carriers; C: Gaucher's disease patients.

**Table 2. Description of Gaucher's disease patients in our study.**

	<i>N</i>	<i>Age (years)</i>	<i>Sex M/F</i>	<i>ASSI</i>	<i>SSI</i>	<i>Splenectomy*</i>	<i>Hepatomegaly*</i>	<i>Bone involvement*</i>	<i>CT activity nmol/mL.h</i>
All	109	29.3± 15.6	50/59	10.5±4.9	8.3±4.5	16	51	35	13,991±12,647
ERT	68	26.3± 14.1	31/37	11.4±4.2	9.3±4.0	12	35	25	16,490±14,220
NERT	41	33.4± 16.8	19/22	9.0±5.7	6.4±4.9	4	16	10	10,676±9,114

Values are means ± standard deviation. ERT: enzyme replacement therapy group; NERT: non-enzyme replacement therapy group; CT: chitotriosidase; \*number of patients; ASSI: severity score index adjusted by age; SSI: severity score index.

patients under ERT (n=68) showed higher activity 16,490±14,220 nmol/mL.h than untreated patients (n=41) 10,676±9,114 nmol/mL.h ( $p=.048$ ).

Alglucerase doses ranged from 30 to 120 U/kg per month. Response to enzyme treatment is shown in Figure 2A, 2E and 2F. During the first six months of therapy the mean percentage decrease in plasma CT activity was 50% for the group on higher doses (HD) ranging from 60-120 U/kg, (Figure 2F) and 35% for patients on lower doses (LD) 30-40 IU/kg (Figure 2E). Two years after ERT, the mean CT activity for HD subjects whose plasma samples were available was 70% of the initial value. However, 2 years post-treatment, the mean level of the LD-treated patients was 11,754 nmol/mL per h (40% of the initial value). The mean differences between both groups, HD vs LD, were statistically significant ( $p < .01$ ). Therefore, the relative rate of decrease of CT in patients treated with HD alglucerase was greater than in LD recipients.

A comparison of decrease of CT activity in splenectomized vs non-splenectomized patients showed no difference ( $p=.08$ ) during ERT (Figure 2C and 2D). For comparison with ERT patients, a group of 10 untreated GD patients was followed up over 3 years; their CT activity increased slightly during this period, although this did not reach statistical significance (Figure 2 B).

## Discussion

In several clinical investigations in GD, plasma chitotriosidase activity has been shown to be a good marker for monitoring patients who have been treated either by ERT or bone marrow transplantation;<sup>4,6,15</sup> however only scarce data have been published regarding plasma CT activity levels in non-carriers, non-affected carriers and GD patients not receiving ERT. This report presents the plasma levels of CT activity in 109 untreated GD patients, showing that an important reduction of CT activity occurs in a large subgroup of patients under ERT

for 6 months to 3 years. Our data provide information about CT activity in response to enzyme therapy, as well as the influence of total amount of alglucerase administered. Unexpectedly, our investigation shows a higher increase of plasma CT activity in non-affected carriers than in non-carrier relatives.

The reliability of the results in samples stored at -80°C up to 4 years, as is the case of the early pre-treatment patient samples, could be questioned. Nevertheless human CT is a very stable enzyme, so the possibility that the values obtained in the pre- and early post-ERT samples might have been higher can be ruled out.<sup>5,16</sup>

Our results show an increase in plasma CT activity with age in carriers and non-carriers. A similar effect of age on CT activity has been previously reported by Guo *et al.* in the general population,<sup>5</sup> but no correlation between CT activity and age was observed in untreated GD patients; in our series, children showed lower plasma CT activity than adults. Several explanations could be argued for this fact; the first is the number of children included (23.5%). The second could be related to the fact of a higher correlation between BMI and plasma CT activity, and finally is possible that the variability of the clinical spectrum of the disease interferes with the effect of age in GD patients.

We assessed the effect of carrier and non-carrier status on CT activity in available subjects selected for having an affected relative. Obligate carriers or presence of any of the mutations at the GC locus was associated with higher CT activity than that in non-carrier relatives. This effect was observed in both children and adult subjects. This finding disagrees with the results of Dodelson de Kremer *et al.* who did not find an increase of CT activity in 3 obligate heterozygotes of GD.<sup>15</sup> This discrepancy might be explained by the small number of subjects studied by these authors in comparison with our study. Recently we have reported that heterozygous

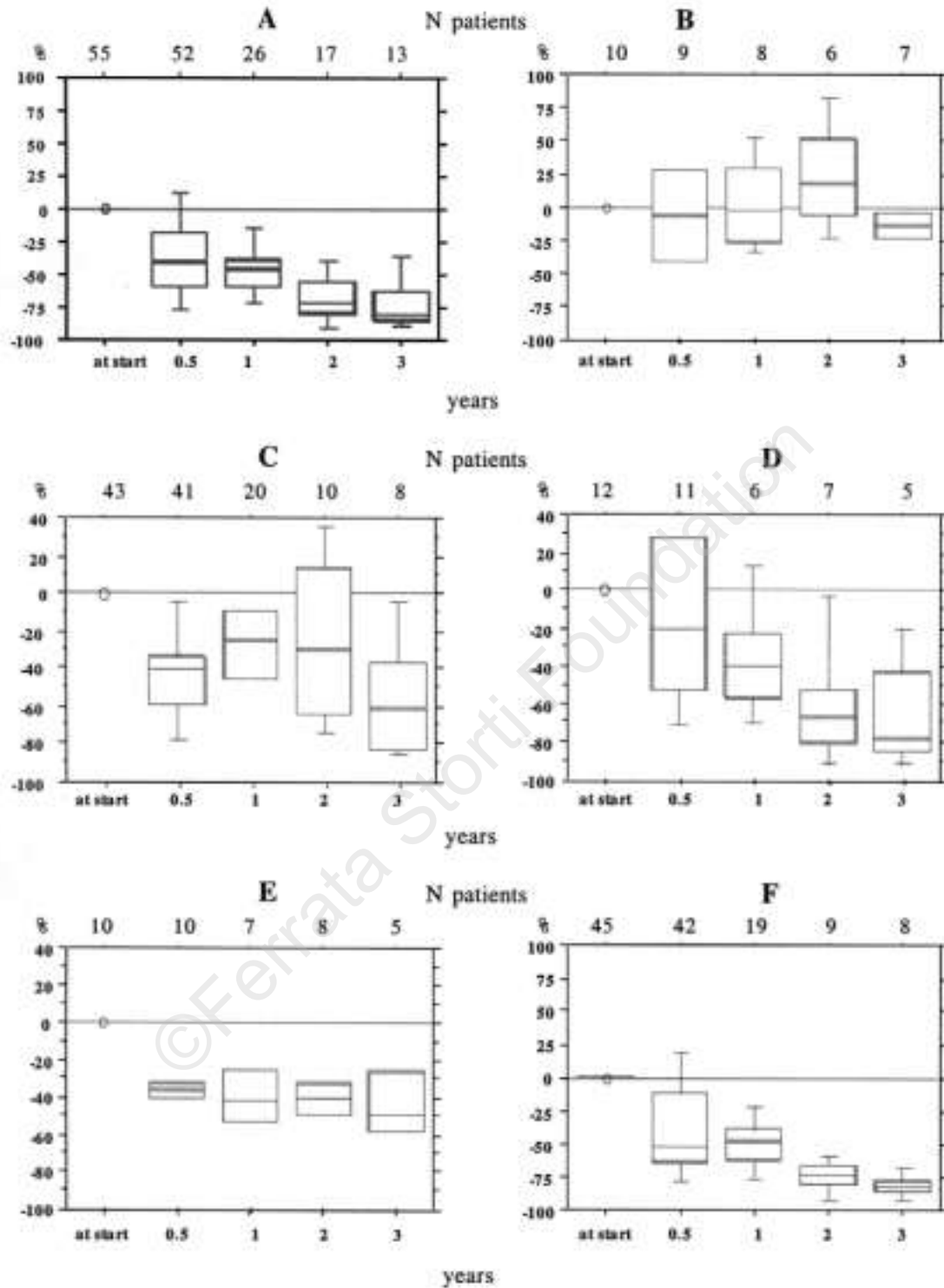


Figure 2. Percent of initial plasma chitotriosidase activity over time. Data are presented as box whisker plots. The horizontal line within each box represents the median value for the data set. The box itself depicts the inner quartile of values surrounding the mean. The vertical bars expand the range of the data. A) All patients treated with alglucerase. B) Alglucerase untreated patients. C) Non-splenectomized patients under alglucerase treatment. D) Splenectomized patients under alglucerase treatment. E) Patients treated with alglucerase doses <50U/kg per month. F) Patients treated with alglucerase doses >60U/kg per month.

subjects for any of several different loss-of-function mutations at the glucocerebrosidase gene locus have a decreased concentration of plasma HDL cholesterol and apolipoprotein A-I.<sup>14</sup> On the assumption that hypoalphalipoproteinemia is due to enhanced activation of macrophages,<sup>17</sup> it is tempting to speculate that in carrier subjects there is a small activation of macrophages with enhanced production of CT; however further *in vitro* studies will be required in order to assess this *activation hypothesis*. Similar biochemical abnormalities have been described in carrier subjects for other recessive lysosomal storage diseases. Intermediate activity of lysosomal acid lipase in lymphocytes from obligate heterozygotes with Wolman disease was reported;<sup>18</sup> moreover a patient's father and mother had an increased activity of other lysosomal hydrolases in their leukocytes.<sup>18</sup> In addition, in Fabry disease, heterozygous females may have an attenuated, usually asymptomatic, form of the disease; the most frequent clinical finding in carrier females is the characteristic whorl-like corneal epithelial dystrophy, only observed by slit-lamp microscopy, increasing some minor symptoms of the disease increasing with the age.<sup>19</sup>

It is widely accepted that GD subjects receiving ERT show improvements in clinical symptoms and regression of signs of disease, such as disappearance or reduction of visceral enlargement, skeletal improvement or improvement of blood cytopenias.<sup>20-31</sup> Our findings show that plasma CT activity decreases during ERT, the greatest rate of decrease occurring during the first 6 months of therapy. These observations are similar to those reported by Hollak *et al.*<sup>4</sup> On the other hand, we also observed a more important reduction of plasma CT in patients treated with HD-ERT than in patients scheduled on LD-ERT. From these results it would appear that LD-ERT is less effective than HD-ERT in reducing the total body activated macrophages that produce CT. However, we do not know whether such CT activity reduction is necessary to achieve a good clinical improvement.

Several therapeutic options of dosage and frequency are available for the treatment of GD patients. There is not currently an agreement regarding the best dose and the optimal frequency of treatment; if CT levels could be correlated with regression of cytopenias and visceral enlargement, then CT activity could be a key marker in monitoring the evolution of GD patients receiving ERT. In our study improvement in clinical manifestations was not related with ERT dosage in the first six months on therapy. Nevertheless after this peri-

od high doses seemed to be more efficient than low doses in maintaining a stable response.

The data presented in this paper can be used as a reference to interpret CT activity in carriers, non-carriers, as well as GD patients with or without ERT. In our experience several guidelines could be obtained in order to appreciate the real value of this marker. The main conclusion is that variations in plasma CT activity must be evaluated individually in each case because the activity is widely influenced by several factors such as age, body mass, CT genotype expression and clinical severity of disease or previous splenectomy. For this reason reductions in plasma CT activity must be reported as a percentage from the baseline activity in order to be used to monitor alglucerase dosage in GD patients receiving ERT. Nevertheless more detailed studies directed at evaluating this aspect will be required.

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*PG and AC contributed equally to this study. The authors would like to thank to The Spanish Gaucher Disease Group (SGDG) for providing clinical data and plasma samples. The whole list of physicians of the SGDG who have contributed is available at the web site: [www.unizar.es/gaucher/](http://www.unizar.es/gaucher/). The authors are also extremely grateful to the families whose participation made this work possible.*

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#### *Disclosures*

*Conflict of interest: none.*

*Redundant publications: < 50%; some aspects of this study were submitted at the 40<sup>th</sup> Annual Meeting of American Society of Hematology, Miami Beach, 1998 and published as an abstract form (Blood, 1998, Suppl) and at the 6<sup>th</sup> Meeting of the European Hematology Association, Frankfurt 2001 and published as an abstract form (The Hematology Journal, 2001, Suppl).*

#### *Manuscript processing*

*This manuscript was peer-reviewed by two external referees and by Professor Mario Cazzola, who took the final decision to accept this paper for publication. Manuscript received July 10, 2001; accepted August 21, 2001.*

*Potential implications for clinical practice*

Evaluation of plasma chitotriosidase activity may be helpful in the management of patients with Gaucher's disease.<sup>32,33</sup>

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### 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. Martínez 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. Hernandez. Hospital Clínico San Carlos (Madrid), Dr. Díaz-Mediavilla. Hospital Clínico Universitario Lozano Blesa (Zaragoza), Dr. Perez Calvo/Dr. Torralba. Hospital Costa del Sol (Málaga). Dra. Medina/Dra. Queipo de Llano. Hospital de Galdakao (Bilbao), Dr. Atutxa. Hospital del Rio Hortega (Valladolid), Dra. Romero Gomez. Hospital Dr. Peset (Valencia), Dr. Gracia Antequera/Dra. León. Hospital Francisc de Borja (Gandía), Dra. Ruiz Guinaldo. Hospital General (Valencia), Dra. Tomás. Hospital 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 Doce de Octubre (Madrid), Dr. de la Serna, 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/Dra. Martínez Pardos/Dr. Villarubia. Hospital S. Juan de Dios (Barcelona), Dra. Toll. Hospital Sagunto (Sagunto), Dr. García Díaz. Hospital San Pedro Alcántara (Cáceres), Dr. Gómez-Arteta. Hospital Sta. M<sup>a</sup> 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. Hospital Vega Baja (Orihuela), Dr. Acedo. Hospital Universitario Puerto Real (Cádiz), Dr. Mendoza. Hospital Universitario Reina Sofía (Córdoba), Dra. Adarraga/Dr. Jiménez Pérezperez.