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A new severity score index for phenotypic classification and evaluation of responses to treatment in type I Gaucher disease

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Abstract

Background Gaucher disease is the first lysosomal storage disease for which specific therapy became available. Over 4800 patients have been treated with enzyme replacement therapy. Analysis of Gaucher disease registry data has outlined the clinical heterogeneity of the disease and the different responses to treatment from patient to patient, and for different organs. This variability in clinical response justifies the development of a severity score index to assess disease activity, stage and prognosis, and to quantify the effects of treatment.

Design and Methods The new scoring system proposed here, the "Gaucher Disease Severity Score Index - Type I" (GauSSI-I), is based on the clinical experience of the authors and an extensive literature review, including data from the International Gaucher Registry. In particular for skeletal disease, all the available scoring systems have been reviewed and compared in order to provide a skeletal scoring system that allows use of any of the different methods on an equivalent basis.

Results The new scoring system, GauSSI-I, was developed. Six specific domains, in which different items were scored according to their impact on morbidity, were characterized. GauSSI-I was evaluated in 53 type I Gaucher patients treated with imiglucerase, and it was compared to the Zimran score, the only severity index score so far available.

Conclusions The GauSSI-I is a reliable method for staging the severity of adult type I Gaucher disease, and it is more sensitive than the Zimran score for monitoring the response to treatment.

Gaucher disease **severity score index**

Introduction

Gaucher disease is an autosomal recessive lysosomal storage disorder, in which a deficiency of the enzyme glucocerebrosidase leads to the accumulation of glucocerebroside in the lysosomes of monocytes and macrophages.[1-2]

The disease has traditionally been classified into three clinical phenotypes: type I - adult, non-neuronopathic; type II - infantile or acute neuronopathic form (rapidly progressive neurovisceral storage disease, with death during infancy); and type III - juvenile or chronic neuronopathic (less rapidly progressive neurovisceral storage disease).

Type I is the most prevalent form of Gaucher disease with an incidence of approximately 1/40-60,000 in the general population, and 1/450 in the Ashkenazi Jewish population. It is a chronic multiorgan disorder characterized by the presence of apparently disconnected symptoms and signs, which may encompass one or more of the following: splenomegaly, hepatomegaly,

(pan)cytopenia, various bone manifestations and pulmonary disease. Central neurological involvement is rare and different and less severe than in type II and type III Gaucher disease.

The phenotypic expression and the clinical course of the disease are extremely heterogeneous, varying in severity among individuals as well as presenting with different degrees of involvement of different organs in the same individual.

Enzyme replacement therapy (ERT), available since the early 1990s, is an effective treatment for Gaucher disease, and today imiglucerase is the acknowledged standard of care for the treatment of patients with Gaucher type I and type III disease. Substrate reduction therapy (miglustat)[3-6] has recently been approved for the treatment of symptomatic type I patients with mild to moderate disease for whom ERT is unsuitable or not a therapeutic option. Future treatments, including small molecule chaperones and gene therapy, are still under investigation.[7,8]

The availability of different therapies has increased the need for a methodology that is specific and sensitive enough to assess and monitor disease severity in individual patients, and to enable measurements of disease progression and response to treatment.

The only currently available index to estimate the severity of Gaucher disease was produced by Zimran *et al.* in 1992,[9] just at the beginning of the ERT era, and was originally designed to correlate Gaucher genotypes with phenotypes of the disease. Emerging data concerning clinical heterogeneity and different responses to treatment from different organs, as well as the availability of new imaging techniques and of new biological markers to quantify burden of disease, justify the development of a new score.[10]

Design and Methods

The new scoring system, the *Gaucher Disease Severity Score Index - Type I* (GauSSI-I), is based on the clinical experience of the authors, combined with an extensive review of the relevant literature (including data from the International Gaucher Registry, an observational database established in 1991). An adjusted Delphi technique was used to reach a consensus on the severity score. First, each participant listed all relevant disease manifestations, which were then collectively reviewed. The relative importance of the different domains, and the individual signs or symptoms included therein, was agreed upon.

Skeletal domain

Skeletal manifestations are a major problem in Gaucher disease. Bone pain, osteopenia and bone marrow infiltration (which are reversible following ERT), have a significant impact on the patients' wellbeing. In addition, irreversible complications such as osteonecrosis, osteolysis, permanent deformities from vertebral crush fractures or other pathological fractures, and secondary arthropathy, limit mobility, and affect quality of life substantially. As bone turnover is a slow process,[11] the full extent of manifestations, especially in the mineral bone compartment, develops over a number of years, and the skeletal response to ERT is reported to be slower than the hematologic and visceral responses.

Skeletal changes were initially diagnosed by standard planar X-ray specifically showing gross changes in the mineral component of bone. Bone mineral density (BMD), either in the whole body or at selected skeletal sites (most commonly the lumbar spine and hip), is measured by dual-energy X-ray absorptiometry (DEXA). To evaluate the degree of bone marrow infiltration by Gaucher cells, several imaging methods have been developed, including magnetic resonance imaging (MRI) and scintigraphic imaging. At least seven different (semi-)quantitative scoring systems can be employed for magnetic resonance evaluation of the bone marrow.[12-17] Among several methods proposed in the past[18] two different scintigraphic approaches are applicable routinely: ^{99m}Tc-radiocolloid bone marrow scintigraphy and scintigraphy with ^{99m}Tc-sestamibi.[19,20]

Thus, at least nine different bone marrow infiltration scores (seven MRI-based,

two scintigraphy-based) can be employed to assess severity of basically the same pathological event: bone marrow infiltration by Gaucher cells. In order to include a skeletal score in the GauSSI-I, independently of the technique used to assess bone marrow infiltration, all the bone marrow infiltration scoring systems so far available were comparatively analyzed and stratified to make them equivalent to each other (normalization process). Only one normalized score corresponding to bone marrow involvement and another one pertaining to mineral bone involvement were used to develop the final overall GauSSI-I skeletal score of any given patient. Normalization was achieved by assigning the lowest value (*0*) to the absence of skeletal abnormalities, and scores *1* to *3* for increasing severity. The original scores were thus regrouped into four new categories (*0* to *3*) based on analogy of the parameters describing the severity of the abnormalities, which were graded as initial/mild (score *1*), intermediate (score *2*), and severe (score *3*). In addition, an assessment for the presence of irreversible skeletal disease was included in the skeletal domain by adding points for the presence of osteonecrosis or pathological fractures.

Bone marrow infiltration subdomain

The categorization proposed for normalizing the various bone marrow infiltration scores for the bone marrow component is detailed in Table 1, for both MRI evaluation and scintigraphic evaluation. Preliminary validation of the approach employed for normalization of the various scores of bone marrow infiltration in a group of 44 adult patients with type I Gaucher disease was recently presented for the Vertebra Disc Ratio (VDR) score, for the Terk score, for the bone marrow burden score, for the Spanish MRI score, and for the scintigraphic ^{99m}Tc-sestamibi score.[21] Scores were blindly and independently assigned by a panel of radiologists expert in Gaucher disease. There was a strong relationship between the scores when analyzing the original data (Chrombach's α measure of agreement was between 0.82–0.85). Such a relationship was maintained, and in some cases even improved, after normalization of the scores (Chrombach's α between 0.85–0.87, p between 0.0378 and <0.0001).

Bone mineral subdomain

As for the scoring system developed for marrow infiltration, the rationale for grading bone (mineral) structural changes is based on stratification into four categories: absence of lesions (score *0*), mild abnormalities (grade *1*), abnormalities of intermediate severity (grade *2*), and severe abnormalities (grade *3*) (Table 2).

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Table 1.

Equivalence of the new categories of disease severity (*Normalized score*, first column on the left of each panel) proposed for the magnetic resonance evaluation and for scintigraphic evaluation of bone marrow involvement in patients with Gaucher disease.

When measuring BMD with DEXA, for the T-score (expressing the relationship with healthy individuals at the peak of BMD) we considered the acknowledged levels of -1 and -2.5, while for the Z-score (expressing the relationship with healthy individuals of the same age) we introduced the -1.5 threshold level in addition to the conventional -1 level, to indicate increasing severity in BMD reduction (Table 2).

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Table 2.

Equivalence of the new categories of disease severity.

The presence of osteonecrosis and/or of pathological fractures was also considered in the new score since they contribute to the severity of the disease. The term osteonecrosis includes lesions occurring in the metaphysis/diaphysis of the bone (bone or medullary infarct) and lesions in the epiphysis (*avascular necrosis*). Although MRI cannot evaluate bone changes *per se* (as the mineral

content is virtually unresponsive to magnetic field stimulation), it is nevertheless highly sensitive for demonstrating early osteonecrosis. If unrecognized and untreated, osteonecrosis can progress to cortical collapse and degenerative joint disease, with consequent increase in pain and disability and need for joint replacement. Avascular necrosis, probably the most clinically significant and disabling skeletal manifestation of Gaucher disease, affects predominantly the femoral head and the proximal humerus and frequently follows one or more bone crises. Both osteopenia and osteonecrosis appear to predispose patients to pathological fractures, and the most affected sites are the vertebral bodies (causing vertebral collapse) and the long bones. The GauSSI-I takes into account the presence of medullary infarcts (score *1*), avascular necrosis (score *3*) and disabling necrosis requiring arthroplasty (score *4*) as damage indicators and prognostic factors with a profound impact on the quality of life of patients with Gaucher disease. The GauSSI-I assigns additional points (score *2*) when bone fractures are present (Table 3).

Hematologic domain

Abnormal hematologic parameters are common in Gaucher disease[9] and are used to monitor the natural history of the disease and response to therapy.[22] Hematologic involvement can be quantitative and/or qualitative, affecting the function of blood elements, causing pancytopenia, a bleeding tendency, or immunological disturbances. Pancytopenia in Gaucher disease is a multifactorial event, in particular with regard to anemia and thrombocytopenia. The increased hemorrhagic risk in subjects with moderate thrombocytopenia is often associated with altered platelet function[23] and/or decreased levels of coagulation factors, with a shortening of the prothrombin time and/or a prolonged activated partial thromboplastin time. Gaucher disease patients have an increased risk of infection, presumably because of reduced specific and non-specific chemotactic activity of neutrophil granulocytes.[24] Moreover, chronic stimulation of the immune system from the accumulated glucocerebroside might cause persistent activation of B lymphocytes with consequent hyper-gammaglobulinemia, which affects about 20% of subjects with Gaucher disease, with an increased risk of developing multiple myeloma.[25] In the GauSSI-I, the hematologic domain scores anemia (score *0-3*), thrombocytopenia (score *0-3*), leukopenia (score *0-3*) and abnormalities of hemostasis (score *0-1*) separately. For both leukocyte and platelet counts, *a* indicates non-splenectomized patients and *b* denotes prior splenectomy. Although cytopenia in a splenectomized patient indicates more severe disease (being the result of reduced production solely), it was agreed that a notation *b* does not translate into an actual increase of the numerical score. Measurement of the bleeding time, using the standardized Ivy technique, allows a combined evaluation of vascular hemostasis and thrombocytic hemostasis and, therefore, of the risk of early bleeding.[26] The normal bleeding time is between 3-8 minutes; therefore, score *0* is assigned to a bleeding time shorter than 8 minutes, and score *1* to any bleeding time longer than 8 minutes (Table 3).

Biomarker domain

Although serum levels of several biological markers have been used to evaluate the severity and progression of Gaucher disease, as well as the efficacy of therapy, chitotriosidase and CCL18/PARC (pulmonary activated-related chemokine) are currently the two most widely acknowledged reliable biomarkers.[27]

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Table 3.

GauSSI-I.

Chitotriosidase activity in serum can increase 100-4,000-fold over the normal values in Gaucher disease, and is reduced by therapy. However, 5-6% of the general population are homozygous for a chitotriosidase gene mutation causing complete deficiency of the enzyme activity, while approximately 35% of the general population are heterozygous for the mutation.[28] Chitotriosidase measurements are unreliable in these situations. The serum levels of chemokine CCL18/PARC, which are not affected by any known genetic abnormality, are

increased 10-40 fold over the normal levels in Gaucher disease and decrease during therapy with a pattern similar to that of chitotriosidase.[29] The normal serum activity of chitotriosidase is 4-76 nmol/mL/hour, while in the Gaucher population levels in the 300-65,000 nmol/mL/hour range have been described. The normal serum levels of CCL18 are between 10-72 ng/mL, and in the Gaucher population a range of 237-2285 ng/mL (with a median of 948 ng/mL) has been reported. Only one biomarker (either chitotriosidase or CCL18/PARC) is employed in the GauSSI-I and chitotriosidase is used only after exclusion of homozygous or heterozygous mutations (Table 3).

Visceral domain

According to the Gaucher Registry, hepatosplenomegaly at diagnosis is very common.[30] Organ volumes should be measured by quantitative imaging (preferably MRI, otherwise computed tomography [CT] or ultrasound when MRI is not available), not merely by physical examination. Volumetric CT and MRI are both more accurate than conventional two-dimensional ultrasound, particularly when applied to irregularly shaped or large organs.[31-33] MRI has greater sensitivity and specificity than CT or ultrasound for the study of parenchyma, especially for detecting focal lesions in the liver and spleen. Abdominal thin-slice axial images are used to calculate visceral volumes with great accuracy.

Splenomegaly is defined as a splenic mass greater than the normal 0.2% of total body weight in kilograms. In untreated Gaucher disease spleen size can reach 100-times the normal volume. The most reliable methods to assess spleen enlargement are CT and MRI, which allow evaluation of the volume in milliliters (the normal volume being about 150 mL in an adult subject of standard body weight). A description of the spleen morphology is also important in the assessment of Gaucher patients, since fibrotic scarring, infarcts and hematologic malignancies can be present (Table 3).

Hepatomegaly is defined as a liver mass greater than 1.25 times the normal 2.5% of total body weight in kilograms, and hepatomegaly >2.5 times normal is a severe risk factor for an untoward outcome of Gaucher disease. Abnormal biochemical tests of liver function require a further diagnostic survey for other concomitant hepatic disease, i.e., viral or toxic hepatitis, autoimmune hepatitis or other metabolic liver disease. GauSSI-I takes into account the degree of hepatomegaly and possible liver pathology related to Gaucher disease, such as hepatic fibrosis and portal hypertension (Table 3).

Lung domain

Pulmonary disease is a possible complication of type I Gaucher disease, although its incidence and pattern of progression are not yet well established.[34] Signs consist of airway obstruction with reduced expiratory flow; reduced lung volume and reduced alveolar-capillary diffusion.[35] Lung involvement can be investigated through chest X-ray, pulmonary function tests, high-resolution CT of the chest and oxygen saturation in arterial blood. Pulmonary hypertension is the most severe lung complication in Gaucher patients. Its exact pathophysiology is still debated, but seems mostly linked to prior splenectomy in type 1 Gaucher patients. The GauSSI-I score considers pulmonary involvement only when pulmonary hypertension is present. Accepted criteria are employed, which define pulmonary arterial hypertension in other underlying conditions as well, assuming that the cardiac ejection fraction is normal.

An additional score used in the lung domain is assigned to respiratory failure documented by pulmonary function tests; this score ranges from *0* to *2* and is employed after excluding possible concomitant causes of respiratory failure other than Gaucher disease (Table 3).

Neurological domain

Although type I Gaucher disease has classically been defined as *chronic non-neuronopathic*, there is growing evidence of a correlation between carriership of one or two mutations for Gaucher disease and parkinsonism or Parkinson's disease.[36,37] Initial oversight of subtle supra-nuclear gaze palsy in mild type III disease and/or the possible association being linked mainly in Ashkenazi Jewish

populations, but not in other populations,[38] may be alternative explanations for the recent epidemiological observations. Reports suggest that peripheral neuropathy may be a late manifestation in Gaucher disease; this has led to a suggestion to assess motor conduction velocity in patients with type I Gaucher disease when peripheral neuropathy is suspected on clinical grounds.[39] The GauSSI-I score value proposed for central and peripheral neurological involvement ranges from *0* to *3* (Table 3).

Comparative evauation of GauSSI-I and Zimran SSI

Study procedures conformed to our institutions' guidelines for human studies and all patients provided informed written consent. We retrospectively examined a total of 53 adult patients with type I Gaucher disease for whom all clinical, biochemical and imaging data were available for about 2 years apart, computing the two scores at two different time-points. Data sets on 30 women and 23 men, with a mean age of 39±15 years (range, 18-85), were available. The average age of the patients when the first symptoms of Gaucher disease appeared and were reason to consult a physician was 14±10 years (range, 2-50), while the average age at the time of diagnosis of Gaucher disease was 23±16 years (range, 2-69). The most common mutation was *N370S* (total of 56/106 alleles), followed by *L444P* (13 alleles).

Twenty-two patients had never received ERT at inclusion for the baseline assessment for this validation, whereas the other 31 patients had already been receiving imiglucerase for a mean of 21±12 months (median 21; range, 3-78), with a mean dose of 41±14 U/kg body weight per month (median 37; range, 21-60), at the baseline assessment. After the baseline evaluation, all ERT-naive patients also started enzyme treatment. Thus, at the follow-up validation assessment (performed after a mean of 30±17 months, median 24, range 12-86), all 53 patients had been treated with imiglucerase (mean dose 44±16 U/kg body weight per month, median 42, range 20-90).

The first step in the comparative evaluation of the Zimran severity score index (SSI) score and the GauSSI-I, estimating the ability to reflect changes in disease severity induced by ERT, was to normalize each set of data to the maximum possible values of the two scores (51 for the Zimran SSI and 42 for the GauSSI-I). Such normalization was performed in order to avoid possible biases in the evaluation of follow-up versus baseline differences in severity scores due to the different scales of the two scoring systems. A new set of data was, therefore, generated, in which each patient's score (both at baseline and at follow-up evaluation) was expressed as a fraction of the possible maximum score (51 in the case of the Zimran SSI and 42 in the case of GauSSI-I). After this normalization, the two scores remained non-parametric, as were the original Zimran score and GauSSI-I values.

Results

The GauSSI-I described in this paper has a maximum of 42 points, distributed over six different domains with unequally weighted parameters:

- - skeletal domain (bone marrow infiltration and bone mineral component subdomains) (maximum combined score: *11*);
- - hematologic domain (maximum score: *10*);
- - biomarker domain (maximum score: *3*);
- - visceral domain (maximum score: *11*);
- - lung domain (maximum score: *4*);
- - neurological domain (maximum score: *3*) (Table 3).

This score can only be used in adults since the measurement of bone marrow infiltration is not validated in children.

In comparison with the Zimran score, the weight of hematologic domain involvement was increased by our consensus group whereas the influence of visceral involvement was reduced. The weight of bone involvement, which is one

of the most important and debilitating complications of type I Gaucher disease, having a greater impact on quality of life than hematologic and visceral manifestations, was increased from 17% to 27%. The percent weight of neurological involvement was reduced from 39% to 7% because in type I Gaucher disease neurological involvement is rare, still contentious, and less severe than in type II and III disease. A domain for biological markers, reflecting total burden of Gaucher cells or substrate storage, was introduced *de novo*; these parameters were not available when the Zimran score was originally published.

As a general proof of concept, the GauSSI-I was compared with the Zimran SSI score, under the hypothesis that the new score would reflect variations in disease severity induced by treatment more readily than the SSI score.

Spearman's correlation test revealed that in the overall group of 53 patients the two scores were highly correlated with each other both at baseline (R=0.729, $p<0.00001$) and at follow-up (R=0.806, $p<0.00001$). Using Wilcoxon's test, it was demonstrated that both scores measure reductions induced by ERT in the follow-up versus the baseline values very well: the mean normalized SSI score at follow-up (0.135±0.013 SEM) was significantly lower than the corresponding baseline value (0.189±0.012 SEM, $p<0.00001$), and similarly the mean follow-up normalized GauSSI-I value was significantly lower than the corresponding baseline value (0.150±0.013 SEM versus 0.257±0.015 SEM, $p<0.00001$) (Figure 1).

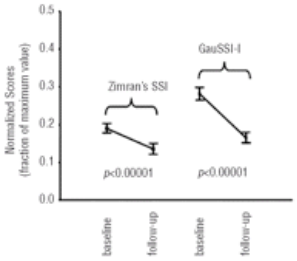

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Figure 1.

Plot of the changes in the mean Zimran's severity score index (SSI) and in the new index proposed here (GauSSI-I) versus baseline observed in 53 patients following ERT administered for an average period of 30 months (± SEM bars are also indicated). For the purposes of statistical comparison and analysis, both sets of data (SSI and GauSSI-I) were normalized to the maximun possible score for each index (51 for SSI and 42 for GauSSI-I). While both scores demonstrate highly significant improvement induced by ERT ($p<0.00001$ in both instance), the fractional reduction of the GauSSI-I is significantly greater (almost 2-fold) than that of the SSI (0.117 ± 0.011 SEM versus 0.054 ± 0.006 SEM, $p<0.00001$). This translates graphically into the slope of the GauSSI-I line being obviously steeper than that of the SSI line.

The final step in the comparison was to test the hypothesis that the GauSSI-I would reflect changes in disease severity induced by ERT more readily than the Zimran SSI score. To this purpose, the distribution of the changes observed in each patient between follow-up and baseline scores was analyzed for each set of data (Zimran score and GauSSI-I), and these distributions were found to be of a Gaussian-type pattern. The one-tail paired *t* test, employed to compare the reductions in normalized scores induced by ERT between the scores, showed that the mean change from baseline to follow-up observed with the GauSSI-I (0.107 ±0.010 SEM) was significantly greater (by a factor of almost 2) than the equivalent change observed using the SSI (0.054±0.006 SEM, $p<0.00001$). This result confirms that the GauSSI-I is a more sensitive method than the Zimran score for measuring changes in disease severity caused by therapy.

Discussion

The superiority of GauSSI-I is presumably due to the SSI assigning more weight (almost 55% of maximum total score) to complications of the disease (e.g., splenectomy, fractures, and central nervous system involvement) that will not change with cause-specific therapy. Instead, GauSSI-I assigns only about 19% of the total score to such abnormalities, while the majority of the total index points

are assigned to manifestations that are amenable to treatment. Since a validation of the GauSSI-I was beyond the scope of the current study, a limitation of this instrument remains that it is not validated. However a validated Gaucher disease severity scoring tool is not currently available. In future studies GauSSI-I will be validated against established standards for measuring clinical changes, such as the Short Form-36.

If the applicability of GauSSI-I is confirmed by further testing in larger groups of patients, then the accuracy and sensitivity of GauSSI-I may allow its use in the determination of individualized therapeutic regimens. This proposed score may also become a crucial parameter for assessing the efficacy of new therapies for Gaucher disease, such as substrate reduction or molecular chaperones, during clinical trials. The GauSSI-I could also be used as a model for developing similar scores in other lysosomal storage diseases for which effective treatments have or will soon become available.

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Authorship and Disclosures

All authors participated in the production of this paper. MDR worked in particular on the skeletal, biomarker and neurological domains; FC on the visceral domain, SL on the hematologic domain, GM on the skeletal domain, MDCi on the hematologic domain and FM on statistical analysis.

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