The Clinical and Demographic Characteristics of Nonneuronopathic Gaucher Disease in 887 Children at Diagnosis

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Objective: To describe the clinical and demographic characteristics of nonneuronopathic Gaucher disease (GD) in children at the time of diagnosis.

Design: Longitudinal observational database of the International Collaborative Gaucher Group Gaucher Registry.

Setting: Data reported to the Registry from January 1, 1989, to June 3, 2005, were included in this report.

Patients/Participants: All 887 patients were diagnosed as having nonneuronopathic GD from birth to younger than 18 years and did not receive enzyme replacement therapy.

Main Outcome Measures: Eight measures of the clinical manifestations and demographics of nonneuronopathic GD.

Results: The most common signs and symptoms noted were splenomegaly (95%), hepatomegaly (87%), radiologic bone disease (81%), thrombocytopenia (50%), anemia (40%), growth retardation (34%), bone pain (27%), and bone crisis (9%). Anemia and more severe splenomegaly and hepatomegaly were observed more frequently in younger patients. Skeletal manifestations were found more often in older children. Only 23% were identified as Ashkenazi Jews.

Conclusions: Nonneuronopathic GD commonly manifests in childhood and affects many ethnic groups. The high prevalence of rare mutations may be associated with earlier onset and/or more severe disease. Increased awareness of the clinical and demographic characteristics of nonneuronopathic GD in children may improve early recognition of this treatable lysosomal storage disorder, decrease morbidity, and prevent irreversible sequelae.

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Gaucher Disease (GD), the most common lysosomal storage disorder, is caused by a deficiency of the lysosomal enzyme glucocerebrosidase, leading to the accumulation of glucocerebroside within tissue macrophages in multiple organs.1 Gaucher disease is almost always attributable to mutations in the glucocerebrosidase gene located on the long arm of chromosome 1 and is inherited in an autosomal recessive manner. Clinically, there are 3 subtypes of GD: nonneuronopathic (type 1), acute neuronopathic (type 2), and chronic neuronopathic (type 3).

Nonneuronopathic GD is the most prevalent form (94%) and is differentiated from the acute neuronopathic (1%) and chronic neuronopathic (5%) forms by the absence of central nervous system involvement.2,3 The manifestations of nonneuronopathic GD include splenomegaly, hepatomegaly, anemia, thrombocytopenia, bone disease (ie, bone marrow infiltration, Erlenmeyer flask deformity of the distal femur, osteopenia, osteoporosis, infarction, avascular necrosis, and pathologic fractures), and growth retardation.4,5 Bone pain is common, manifesting as mild to moderate intermittent pain or more severe acute “bone crises” accompanied by perosteal elevation, leukocytosis, and fever, which may cause debilitation for several days and require narcotic analgesics. Clinical expression of GD is highly variable among patients,6 but, particularly when manifested during childhood, the natural history of GD is that of a progressive, multisystemic, and debilitating disorder.

Because GD has typically been described as an adult disorder affecting mainly Ashkenazi Jews, many physicians do not consider this diagnosis when evaluating signs and symptoms of the disorder in children. Early recognition of GD by physicians caring for children is important because safe and effective treatment with enzyme replacement is available, and early intervention can decrease morbidity and reduce the risk of later complications.3,7 Enzyme replacement therapy has...
been shown to prevent progressive manifestations of GD and ameliorate GD-associated anemia, thrombocytopenia, organomegaly, bone pain, and bone crises. Because GD is relatively uncommon in non-Ashkenazi populations (estimated incidence, 1:57,000 live births), no large study of the pediatric manifestations of GD has been reported. Although a previous report of the International Collaborative Gaucher Group (ICGG) Gaucher Registry data noted that most affected people manifest GD in childhood, the clinical and demographic data for childhood GD were not separately analyzed.8

This study analyzes data from the ICGG Gaucher Registry to characterize the manifestations at the time of diagnosis of a large population of children and adolescents with nonneuronopathic GD. This description of pediatric nonneuronopathic GD should increase the recognition and earlier diagnosis of this condition in childhood, allowing for the initiation of treatment before the development of severe morbidity or irreversible disease complications.

METHODS

The ICGG Gaucher Registry is an observational database of clinical, biochemical, and therapeutic characteristics of patients with GD (hereafter referred to as GD patients), regardless of disease status.9 The ICGG Gaucher Registry, initiated in 1991 and supported by Genzyme Corporation, Cambridge, Mass, is governed by a collaborative group of international physician experts in GD (the ICGG). With appropriate institutional review board or ethics committee approvals, more than 700 physicians from 52 countries have voluntarily submitted data on their patients to the ICGG Gaucher Registry. All nonneuronopathic GD patients included in this report were diagnosed from January 1, 1989, to June 3, 2005, ranged in age from birth to younger than 18 years at diagnosis, and had not received enzyme replacement therapy. A definitive diagnosis was based on results of enzyme analysis of glucocerebrosidase activity and/or DNA analysis of the glucocerebrosidase gene. To avoid inclusion of children who did not manifest signs or symptoms of GD, patients with a prenatal diagnosis of GD, patients with a diagnosis before 1 year of age and before initiation of enzyme replacement therapy, patients with nonneuronopathic GD who had not received enzyme replacement therapy, and patients with a diagnosis of neuronopathic GD were excluded from this study. Patients were categorized into the following 3 groups according to age at diagnosis: birth to younger than 6 years, 6 to younger than 12 years, and 12 to younger than 18 years. For each clinical variable studied, the data closest to the diagnosis date were analyzed within an interval of ±2 years from diagnosis and before initiation of enzyme replacement therapy. Genotype frequency distributions for common, rare, and unknown mutations were determined. Hemoglobin level was analyzed as a binary variable, with anemia defined as below the reference age- and sex-adjusted value as follows: less than 10.1 g/dL for infants younger than 6 months; less than 9.5 g/dL for children 6 months to younger than 2 years; less than 10.5 g/dL for children 2 to younger than 12 years; less than 12 g/dL for boys 12 years and older; and less than 11 g/dL for girls 12 years and older. Platelet counts were analyzed in patients with intact spleens. Patients with partial or total splenectomy underwent separate analysis. Platelet counts were used to classify thrombocytopenia into the following groups: severe (<60 x 10^9/L), moderate (60 x 10^9/L to 120 x 10^9/L), and mild/normal (>120 x 10^9/L). Liver and spleen volumes were measured by means of magnetic resonance imaging, computed tomography, or ultrasonography and reported as multiples of normal size predicted for body weight (MN).9 Ultrasound measurements were converted to volumetric equivalents using the formula developed by Elstein et al.10

RESULTS

On June 21, 2005, the ICGG Gaucher Registry contained data for 887 nonneuronopathic GD patients who had been diagnosed between birth and age younger than 18 years. Hemoglobin and platelet data from the time of diagnosis were reported for 68% and 64% of the patients, respectively; 27% of patients had data for spleen and liver volumes; and 34% had radiologic examination data. Genotype data were available for 72% of the patients. Of the 887 total study patients, the 2 largest ethnic groups were non-Jewish white subjects (30%) and Ashkenazi Jews (23%) (Table 1). The largest groups of pediatric patients participating in the ICGG Gaucher Registry were from the United States (29%) and Latin America (25%). Europe and Israel contributed 19% and 15% of participating patients, respectively.

Genotype data for this population indicate that 4 common mutations constitute 72% of all GD alleles: N370S, L444P, IVS2-1, and 84GG (Table 2). (The mutations are notated according to standard nomenclature.)14 Two hundred twenty-five (18%) of all 1270 reported alleles were rare, and 132 (10%) were unknown. Forty-seven percent of patients had at least 1 rare or unknown allele. Patients with the N370S/N370S genotype had a median age of diagnosis of 10 years. Patients with the L444PL444P genotype had a median age at diagnosis of 1 year. All other allele groupings had a median diagnosis age ranging from 3 to 7 years.

For hemoglobin levels and spleen and liver volumes, younger patients tended to have significantly...
more severe abnormalities at the time of diagnosis (Table 3). Across all age groups, 40% of patients had anemia; 50% had platelet counts less than 120 × 10^9/µL; 93% had spleen volumes greater than 3 MN; and 87% had liver volumes greater than 1.25 MN. Twenty-seven (5%) of the 370 patients submitting platelet count information reported partial or total splenectomy at the time of diagnosis, with 93% and 7% of these patients presenting with mild/normal and moderate thrombocytopenia, respectively; none had platelet counts less than 60 × 10^9/µL.

Overall, most children (81%) had at least 1 radiologic skeletal abnormality at the time of diagnosis (Table 4). The 2 most common radiologic manifestations were Erlenmeyer flask deformity (49%) and bone marrow infiltration (38%). Bone pain was reported in 27% and a history of bone crisis, in 9%. Older children had significantly (P < .001) more severe skeletal disease (Table 4). Growth was less than the 5th percentile of height for sex and age at diagnosis (Figure 1) in 34% of children (Table 4); in 28%, from the 5th to 25th percentiles; and 39%, greater than the 25th percentile.

Without definitive and uninterrupted treatment, nonneuronopathic (type 1) GD, particularly when diagnosed in childhood, is a progressive multisystemic disorder with substantial morbidity, potential for disability, reduced quality of life, and even reduced life expectancy. Fortunately, the underlying enzyme deficiency and resulting pathology can be treated effectively with enzyme replacement therapy (with recombinant glucocerebrosidase or imiglucerase for injection [Cerezyme]). However, there is reason to believe that there are children with GD that is unrecognized and undiagnosed and who may experience unnecessary morbidity and irreversible disease sequelae if treatment is not initiated at the earliest signs and symptoms. In part, this may be because nonneuronopathic GD is often thought to be an adult disorder primarily affecting or even restricted to Ashkenazi Jews.

The data described in this report clearly indicate that many patients with nonneuronopathic GD are symptomatic when they are children. Furthermore, in this international population, 77% of children who manifested nonneuronopathic GD were not Ashkenazi Jews. In fact, nonneuronopathic GD is prevalent across all ethnic groups, and many physicians caring for children can expect to encounter 1 or more children with nonneuronopathic GD in their practice.

The hematologic and organ volume factors indicate that symptoms and signs that manifest at a younger age may indicate more severe disease. Statistically significant differences in disease severity were noted among the 3 age groups. Anemia and hepatosplenomegaly at the time of diagnosis were greatest in the youngest group (birth to <1 year). Thrombocytopenia was prevalent in all age groups. Differences in disease severity were noted among the 3 age groups. Anemia and hepatosplenomegaly at the time of diagnosis were greatest in the youngest group (birth to <1 year). Thrombocytopenia was prevalent in all age groups. This finding supports our clinical experience that the hematologic and visceral manifestations tend to appear first in the natural history of GD.

The skeletal manifestations of GD may progress slowly and only become apparent in the teenage years, although growth failure is often obvious much earlier. Exemplifying the progressive nature of skeletal pathology in GD, bone pain and bone crisis increased with the age at diagnosis. Children with GD who manifest evidence of bone pain are often incorrectly characterized as having normal growing pains. In this study, 27% of children diagnosed as having GD presented with bone pain...
at the time of diagnosis. Older children were more likely to have more severe radiologic manifestations of GD, with evidence of bone disease in 72% of the group diagnosed between birth and age younger than 6 years; 84%, between ages 6 and younger than 12 years; and 92%, between ages 12 and younger than 18 years. The high prevalence of bone disease (81%) reported in children with nonneuronopathic GD at the time of diagnosis has several implications. First, evidence of early and potentially reversible bone disease is rarely evident on physical examination and may not correlate with the degree of visceral and hematologic involvement. Appropriate radio-

### Table 3. Patient Hematologic and Organ Volume Characteristics at Diagnosis

<table>
<thead>
<tr>
<th>Skeletal Manifestations</th>
<th>0 to &lt;6</th>
<th>6 to &lt;12</th>
<th>12 to &lt;18</th>
<th>All Ages</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain, patient population</td>
<td>n = 287</td>
<td>n = 164</td>
<td>n = 131</td>
<td>n = 602</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Patients reporting</td>
<td>128 (45)</td>
<td>62 (34)</td>
<td>49 (37)</td>
<td>239 (40)</td>
<td></td>
</tr>
<tr>
<td>Bone crisis, patient population</td>
<td>n = 277</td>
<td>n = 176</td>
<td>n = 117</td>
<td>n = 570</td>
<td>.003</td>
</tr>
<tr>
<td>Patients reporting</td>
<td>24 (9)</td>
<td>12 (7)</td>
<td>15 (13)</td>
<td>51 (9)</td>
<td></td>
</tr>
<tr>
<td>Radiologic evidence of bone disease, patient population</td>
<td>n = 115</td>
<td>n = 72</td>
<td>n = 54</td>
<td>n = 241</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any evidence of radiologic bone disease‡</td>
<td>111 (11)</td>
<td>n = 68</td>
<td>n = 58</td>
<td>n = 237</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Erlenmeyer flask deformity</td>
<td>59 (44)</td>
<td>48 (51)</td>
<td>43 (57)</td>
<td>150 (49)</td>
<td>.009</td>
</tr>
<tr>
<td>Marrow infiltration</td>
<td>40 (30)</td>
<td>41 (43)</td>
<td>35 (47)</td>
<td>116 (38)</td>
<td>.04</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>21 (16)</td>
<td>20 (21)</td>
<td>21 (28)</td>
<td>62 (20)</td>
<td>.16</td>
</tr>
<tr>
<td>Avascular necrosis</td>
<td>8 (6)</td>
<td>6 (6)</td>
<td>9 (12)</td>
<td>23 (8)</td>
<td>.11</td>
</tr>
<tr>
<td>Infarction</td>
<td>6 (5)</td>
<td>11 (12)</td>
<td>7 (9)</td>
<td>24 (8)</td>
<td>.50</td>
</tr>
<tr>
<td>Lytic lesions</td>
<td>7 (5)</td>
<td>9 (9)</td>
<td>5 (7)</td>
<td>21 (7)</td>
<td>.87</td>
</tr>
<tr>
<td>New fractures</td>
<td>2 (1)</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>6 (2)</td>
<td></td>
</tr>
<tr>
<td>Height, percentile, patient population</td>
<td>n = 245</td>
<td>n = 150</td>
<td>n = 101</td>
<td>n = 496</td>
<td>.50</td>
</tr>
<tr>
<td>&lt;5th</td>
<td>79 (32)</td>
<td>62 (41)</td>
<td>26 (26)</td>
<td>167 (34)</td>
<td></td>
</tr>
<tr>
<td>5th-25th</td>
<td>77 (31)</td>
<td>34 (23)</td>
<td>27 (27)</td>
<td>138 (28)</td>
<td></td>
</tr>
<tr>
<td>&gt;25th</td>
<td>89 (36)</td>
<td>54 (36)</td>
<td>48 (48)</td>
<td>191 (39)</td>
<td></td>
</tr>
</tbody>
</table>

†Indicates P value test for trend and severity across age groups (Jonckheere-Terpstra 2-sided tests).12,13
‡Some patients demonstrated more than 1 indicator of bone disease.
graphic studies are required and must be evaluated by a radiologist familiar with the bone changes of GD. Second, the presence of severe manifestations, particularly avascular necrosis, fractures, and lytic lesions, indicates a clinically aggressive form of GD, a fact that is often unrecognized by physicians whose focus is restricted to the hematologic and visceral manifestations of GD. For many nonneuronopathic GD patients, the morbidity of bone disease has the greatest long-term impact on quality of life. Untreated bone disease can lead to severe acute and chronic pain sometimes requiring even opioid analgesia; decreased bone mass, density, and strength; and increased risk of pathologic fractures. Avascular necrosis and joint collapse may affect linear growth and require joint replacement, ambulation with crutches, and/or the use of a wheelchair. Finally, the increasing prevalence of bone disease at diagnosis among older children with GD may indicate a need for earlier diagnosis and initiation of enzyme replacement therapy to prevent or reduce the risk of irreversible bone complications.6,16

Linear growth retardation is common in the pediatric nonneuronopathic GD population, with more than 30% of all children below the fifth percentile for height at the time of diagnosis. For all 3 age groups, the median height was below the expected height based on population standards. Because most patients (66%) in our population were American, Canadian, European, or Israeli, the National Center for Health Statistics 2000 growth data11 were used for comparison. One possible explanation for the poorer growth seen in the group younger than 6 years may be more severe and earlier disease manifestations. Previous literature suggests that enzyme replacement therapy significantly improves growth in children with GD.4 The goal of treatment is to normalize growth and achieve normal peak skeletal mass within 3 years of initiating enzyme replacement therapy.17

Nonneuronopathic GD in children can be caused by a wide range of glucocerebrosidase mutations. The 4 most common mutations (N370S, L444P, 84GG, and IVS2+1) accounted for 72% of all mutated alleles in our nonneuronopathic GD population, and the remaining 28% of alleles were rare, unique, or unknown. The method of genotyping is not recorded in the ICGG Gaucher Registry, and it is possible that only common mutations were analyzed. The manifestation of GD in childhood may indicate more severe disease than GD found in patients who present in adulthood. Childhood presentation represents an earlier accumulation of pathologic amounts of undegraded substrate in viscera and bone, which results in clinical signs and symptoms and indicates more severe disease.16 This finding agrees with our clinical experience. We believe that all children should undergo regular evaluation.

The GD in patients with the L444P/L444P genotype in this study was classified as nonneuronopathic. However, these patients are at risk for development of neuronopathic disease (type 3) in later childhood and should undergo regular evaluation for central nervous system manifestations of GD.

Although the ICGG Gaucher Registry is the largest longitudinal database of the GD population, registry data are
voluntarily reported by physicians caring for GD patients and are not subject to independent verification. Therefore, the data may have limitations. First, the subjects may not represent the full spectrum of disease severity. Second, the prevalence of signs and symptoms could be biased by the identification of siblings of index cases. Third, differing testing modalities may have been used (as occurs for organ volume measurements and genotyping). Fourth, there may be variable quantities of data submitted by different physicians.

Nevertheless, the ICGG Gaucher Registry offers the largest cohort available with longitudinal data, making statistical analysis of clinical characteristics possible for a disorder in which its rarity essentially obviates the ability to conduct large-scale clinical trials.

In summary, nonneuronopathic GD is a treatable lysosomal storage disorder that most commonly manifests during childhood. A definitive diagnosis requires an enzyme assay demonstrating deficient or absent activity of glucocerebrosidase supplemented by mutational analysis of the glucocerebrosidase gene. Common disease manifestations in children include splenomegaly, hepatomegaly, anemia, thrombocytopenia, easy bruising, and significant growth retardation (Figure 2). Most patients have evidence of significant skeletal manifestations of disease, which may not be evident on physical examination and require radiologic examination for detection.16 Pediatric GD, when left untreated, is most often associated with progressive morbidity and even shortened life expectancy. All providers of health care for children should be aware of the presenting signs and symptoms of nonneuronopathic GD because the timely initiation of appropriate treatment with enzyme replacement therapy will prevent or decrease morbidity and reduce the risk of later irreversible complications of this disease.

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