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Phenotypic and genotypic heterogeneity in Gaucher disease type 1: A comparison between Brazil and the rest-of-the-world

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Abstract

Type 1 Gaucher disease, the most common lysosomal storage disorder, results from deficiency of glucocerebrosidase causing pathologic accumulation of glucocerebroside. The disease is characterized by marked variation in age of onset and degree of anemia, thrombocytopenia, hepatosplenomegaly, and skeletal disease. Most published data on Gaucher disease come from populations with large proportions of Ashkenazi–Jewish patients, who tend to have less severe disease. We compared selected demographic, clinical, and genetic parameters for Brazilian ($N = 221$) and rest-of-world ($N = 1477$) type 1 Gaucher disease patients entered into the ICGG Gaucher Registry since 1991. We also compared Brazilian patients to non-Ashkenazi rest-of-world patients ($N = 692$) to determine if differences were the result of fewer Brazilian Ashkenazi–Jewish patients (0.5% vs 45.0%). The Brazilian cohort differed significantly ($p < 0.05$) from the rest-of-world and rest-of-world non-Ashkenazi cohort, respectively, in the following measures: higher proportion of females (59.7% vs 50.4% and 49.7%), lower mean age at diagnosis (17.1 vs 24.1 and 18.8), and higher proportions of patients with anemia (55.5% vs 29.9% and 35.7%), bone pain (57.7% vs 33.7% and 35%), bone crises (16.1% vs 6.5% and 7.4%), and lytic lesions (17.0% vs 7.6% and 7.4%). The most common genotype in Brazil was N370S/L444P (c1448T → C/c1226A → C) (46.8% versus 16.3% and 25.7%). These data highlight the genetic and phenotypic heterogeneity among geographic populations of type 1 Gaucher patients and suggest that as a group, Brazilian patients may have a more aggressive form of the disease than rest-of-world patients. The findings also emphasize the need for caution in making generalizations about Gaucher disease across demographic groups.

Keywords: Type 1 Gaucher disease; Demographics; Brazil; Children; Bone disease; Genotype; Lysosomal storage disorder

Introduction

Type 1 or non-neuronopathic Gaucher disease is the most common of the lysosomal storage disorders. The disease results from defects in the lysosomal enzyme, glucocerebrosidase (acid β-glucosidase, EC 3.2.1.45) leading to progressive accumulation of its substrate, glucocerebroside, in cells of monocyte/macrophage origin. Clinical manifestations include hepatosplenomegaly, anemia, thrombocytopenia, and disabling skeletal disease [1–3]. The disease is panethnic, but has high frequency in the Ashkenazi–Jewish population. National incidence rates vary widely; in the United States, the estimated incidence is 1:40,000–60,000 [4], and among those of Ashkenazi–Jewish descent, 1:400 to 1:1000 [4,5].

Type 1 Gaucher disease is often referred to as the "adult type," in contrast to the more severe acute or subacute neuronopathic types 2 and 3, which manifest in infancy or childhood and always involve the central nervous system. However, the severity, age of onset, and rate of progression of patients with type 1 Gaucher disease varies widely, and the majority of type 1 Gaucher patients are diagnosed in childhood or adolescence [6]. Some type 1 Gaucher patients

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are so mildly affected that they never come to medical attention; others die of the disease in childhood [1,2]. Since the disease is progressive, earlier onset usually correlates with a more severe disease course.

To date, over 250 mutations in the glucocerebrosidase gene have been identified [2]. Genotype–phenotype correlations are limited, although the presence of an N370S (c1226A → C) allele predicts lack of central nervous system involvement, while homozygosity of L444P (c1448T → C) alleles often correlates with development of neuronopathic disease (the onset and severity of CNS involvement varies) [1,2,7]. Among symptomatic type 1 patients of Ashkenazi–Jewish ancestry, up to 60% have an N370S/N370S genotype, which is often associated with a later onset, less severe form of the disease [8].

Enzyme replacement therapy for Gaucher disease, available since 1991 in a tissue-derived form, Ceredase (alglucerase), and since 1994 in a recombinant form, Cerezyme (imiglucerase) [9], has been shown to improve or arrest hepatosplenomegaly, skeletal involvement, growth retardation, bone marrow infiltration, osteopenia, thrombocytopenia, anemia, and fatigue [10–14], and is recommended for all significantly affected patients, including children [14].

The Gaucher Registry (www.gaucherregistry.com) is the largest cooperative, observational database on Gaucher disease in the world [1]. It was founded in 1991, with scientific oversight by the International collaborative gaucher group (ICGG), and support from Genzyme Corporation. This longitudinal database tracks outcomes of routine clinical practice with the goal of enhancing understanding of the natural history of Gaucher disease and evaluating the effectiveness of therapy. Data collected include demography, gender, age, genotype, ethnicity, disease type, spleen status, date of symptom onset, date and method of diagnosis, date of first enzyme infusion, physical assessments (height, weight, bone pain, and bone crises), hematology (hemoglobin, platelets), enzyme therapy (status, dosage), organ involvement (assessment dates, methods, spleen and liver volumes), and skeletal involvement (assessment dates, methods, radiologic evidence of bone disease). The data can be stratified by numerous variables, allowing clinicians to study trends, evaluate the effects of interventions, and compare populations. In 2001, Brazil began to participate regularly in the ICGG Gaucher Registry [15].

Availability of safe and effective enzyme replacement therapy with alglucerase and imiglucerase has intensified efforts to understand the natural history of the disease and to determine optimal therapeutic regimens. These efforts have been complicated by the wide phenotypic heterogeneity of Gaucher disease. Anecdotally, patients with type 1 Gaucher disease vary in severity in different geographic regions of the world. However, much of the published literature on type 1 Gaucher disease comes from the United States, Europe, and Israel where a higher proportion of patients are of Ashkenazi–Jewish ethnicity who may manifest a more restricted disease phenotype. Whether or not the clinical characterization of type 1 Gaucher disease based on data primarily from the United States, Europe, and Israel can be generalized to other geographic regions of the world has not been previously studied.

This report from the ICGG Gaucher Registry compares data collected from Brazilian type 1 Gaucher disease patients diagnosed in 1991 or later (Brazilian cohort) to data from type 1 patients in the rest-of-the-world diagnosed in 1991 or later (rest-of-world cohort) and to data from the subset of these rest-of-world patients reported to be of non-Ashkenazi–Jewish heritage (rest-of-world non-Ashkenazi cohort). The post-1991 inclusion date was chosen to minimize selection bias since enrollment in the ICGG Gaucher Registry was not possible until that date. Furthermore, patients diagnosed before 1991 have very limited baseline clinical data from the time of their diagnosis.

Methods

All physicians caring for patients with Gaucher disease throughout the world are eligible to participate in the ICGG Gaucher Registry and join the

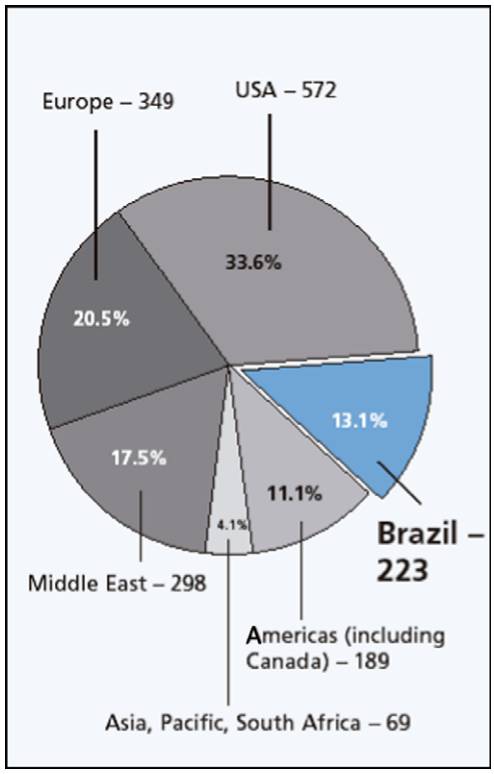

Fig. 1. Geographic distribution of all patients with gaucher disease Type 1 in the ICGG Gaucher Registry diagnosed in 1991 or later. In addition to Brazil and the United States, the following countries are represented in the ICGG Gaucher Registry: In Europe: Albania, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia and Montenegro, Slovenia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom; in the Middle East: Egypt, Israel; in Asia, Pacific and South Africa: Australia, Japan, Korea, Philippines, South Africa, Taiwan, Thailand; in the Americas: Argentina, Bolivia, Canada, Chile, Colombia, Ecuador, Mexico, Paraguay, Peru, Uruguay, Venezuela.