A reappraisal of Gaucher disease—Diagnosis and disease management algorithms

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Type 1 (non-neuronopathic) Gaucher disease was the first lysosomal storage disorder for which an effective enzyme replacement therapy was developed and it has become a prototype for treatments for related orphan diseases. There are currently four treatment options available to patients with Gaucher disease, nevertheless, almost 25% of Type 1 Gaucher patients do not gain timely access to therapy because of delays in diagnosis after the onset of symptoms. Diagnosis of Gaucher disease by enzyme testing is unequivocal, but the rarity of the disease and nonspecific and heterogeneous nature of Gaucher disease symptoms may impede consideration of this disease in the differential diagnosis. To help promote timely diagnosis and optimal management of the protean presentations of Gaucher disease, a consensus meeting was convened to develop algorithms for diagnosis and disease management for Gaucher disease.

The defect in Gaucher disease is an inherited deficiency of the lysosomal enzyme acid β-glucosidase (glucocerebrosidase, GBA1), which results in the accumulation of glucocerebroside within lysosomes of macrophages. Systemic accumulation of these glycolipid-lipid engorged cells (eponymously known as Gaucher cells, Fig. 1) results in variable combinations of splenomegaly with associated abdominal discomfort; anemia associated with chronic fatigue; bleeding due to thrombocytopenia and/or Gaucher disease-related coagulopathy; hepatomegaly, abnormal tests of liver function; and a diverse pattern of bone disease [1]. Increased susceptibility to infections may result from impaired neutrophil function and neutropenia [2]. Rarely, the lungs, lymphatic system, skin, eyes, kidneys, and the heart are involved and, in the rare neuronopathic forms, neurodegenerative disease results [1]. Gaucher disease is traditionally classified into three broad phenotypic categories: Type 1 (non-neuronopathic disease); Type 2, fulminant neuronopathic disease that is fatal during infancy; and Type 3, chronic neuronopathic disease, that usually results in death in childhood or early adult life [1]. Further distinct phenotypic categories may be recognized within these broad groups.

Type 1 (non-neuronopathic) Gaucher disease accounts for more than 90% all Gaucher disease patients. Its prevalence world wide is 1 in 50,000 to 100,000 but it is as high as ~1 in 850 in individuals of Ashkenazi heritage [3–6]. The broadest phenotypic spectrum in Gaucher disease with respect to age of onset, rate of progression, and organs affected occurs in Type 1 Gaucher disease [7]. Homozygosity for the N370S mutation is the most common genotype in the Ashkenazim in whom it accounts for ~70% of all disease alleles. It is associated with atypical presentation in adults or the older patient and is notable for significant skeletal disease despite inconspicuous classical manifestations (splenomegaly, hepatomegaly, anemia, and thrombocytopenia). However, severe disease with classic manifestations presenting in childhood may occur in a minority of N370S homozygous patients [8,9]. The most common disease allele of GBA1 world wide is L444P mutation, which occurs in the sequence of the closely linked pseudogene; it is believed that gene conversion events lead to L444P mutation in the active gene. It seems likely that the most frequent genotype of Type 1 Gaucher disease in populations of European descent in the world is N370S/L444P. Generally this genotype leads to more severe disease compared with N370S homozygosity [1,10,11] (Figs. 2 and 3).

Treatment with macrophage-targeted mannose-terminated glucocerebrosidase enzyme replacement therapy (imiglucerase, Cerezyme®, Genzyme Corporation, Cambridge, MA) is the standard of care for Type 1 Gaucher disease and of non-neuronopathic manifestations of Type 3 Gaucher disease. Evidence from the ICGG Gaucher Registry, indicates that enzyme replacement with imiglucerase and its predecessor alglucerase reverses hematological and visceral manifestations of the disease [12] and reduces the bone marrow burden of Gaucher cells resulting in amelioration of osteopenia, bone pain, risk of bone crises and overall improvement in quality of life [13–16]. Several aspects of bone disease, such as osteonecrosis, osteofibrosis, and lytic lesions cannot be reversed but timely initiation of enzyme therapy reduces the risk of these irreversible complications [8,17]. Other variants of macrophage-targeted enzyme replacement therapies are undergoing clinical trials: velaglucerase, a human fibroblast-derived enzyme, was recently approved for treatment of Type 1 Gaucher disease [18] and taliglucerase, a plant derived enzyme is in clinical trials [19]. Substrate reduction therapy (Zavesca® miglustat, Actelion Pharmaceuticals, Allschwil, Switzerland) is approved for patients with mild Gaucher disease who are unable to receive enzyme replacement therapy [20,21]. A more specific and potent inhibitor of glucosylceramide synthesis, eliglustat tartrate is currently in Phase 3 trials having shown impressive efficacy and safety in Phase 2 trials [22,23].

Prompt diagnosis before the occurrence of irreversible complications underpins the Gaucher disease management model [24]. The early symptoms of Type 1 Gaucher disease tend to reflect the hematological aspects of the disease (splenomegaly, anemia, thrombocytopenia, and bleeding tendency) [25]. Patients with Gaucher disease, therefore, are most likely to be referred to hematologists for diagnosis and management. However, only ~20% of hematologists/oncologists in one study considered Gaucher disease in differential diagnoses even in the presence of all classical symptoms [8]. Diagnosis may be achieved in high-risk groups, such as individuals of Ashkenazi Jewish ancestry, by opportunistic screening (i.e., those with any of the manifestations of Gaucher disease or those with surrogate indicators of disease, i.e, severe osteoporosis, hyperferritinemia, gallstones, and low HDL cholesterol) and family screening after diagnosis in a family member [26]. The aim of the consensus meeting was to develop algorithms for diagnosis and management based on current understanding of the full clinical spectrum of presentations of Gaucher disease.

Results

The authors' combined experience of 362 patients with Gaucher disease revealed a consistent pattern of previous misdiagnoses that included leukemia, immune thrombocytopenia purpura, autoimmune disease, hepatic cirrhosis, idiopathic avascular necrosis, viral disease, idiopathic splenomegaly, and anemia of chronic disease. Misdiagnosis led to complications such as avascular necrosis, osteopenia, liver disease, and bleeding complications and inappropriate procedures such as splenectomy, liver biopsy, and empirical corticosteroid therapy (see Appendix).

Malignancy is commonly the first diagnosis entertained in patients who are eventually diagnosed with Gaucher disease [8,27]. Interestingly, the first patient ever described with Gaucher disease by Dr Philippe Gaucher in 1882 was believed to harbor malignancy affecting the spleen. In one study, the diagnosis most frequently considered was hematologic malignancy (leukemia 65%, lymphoma 36%, multiple myeloma 22%, chronic granulocytic leukemia 14%) [8]. It should be noted that the risk of hematological malignancies in Gaucher disease is increased, especially of multiple myeloma [9,28–31]. The life-time risk of multiple myeloma in Gaucher disease is higher than 25-fold compared with the general population [9,29–32].

Algorithms for diagnosis

In patients of Ashkenazi ancestry, the frequency of Gaucher disease is ~1 in 800 while hematologic malignancies are much less frequent at ~1 in 2,500 [33]. Therefore, in this ethnic group, it is prudent to test for Gaucher disease as a first-line investigation, in any patient presenting with splenomegaly and cytopenia. It is important to keep in mind that the most common genotype in this ethnic group, homozygosity for N370S mutation is often characterized by mild cytopenia and splenomegaly that escape initial detec-