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GAUCHER DISEASE

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INTRODUCTION

Gaucher disease is an inherited disorder that affects many of the body's organs and tissues. The signs and symptoms of this condition vary widely among affected individuals. GD was first described by Phillippe Gaucher in 1882, two decades prior to the dictum of «Inborn errors of metabolism" given by Sir Archibald Garrod. Gaucher observed large cells in a splenic aspirate during the evaluation of a large spleen and he thought that it was evidence of a primary neoplasm of the spleen. In 1924, Epstein first recognized the storage of glucocerebroside, while Brandy *et al*. delineated that the metabolic defect was due to the deficiency of the enzyme β-glucosidase (GBA) (Bohra 2011). Researchers have described several types of Gaucher disease based on their characteristic features. Type 1 Gaucher disease is the most common form of this condition, also known as non-neuronopathic Gaucher disease because the central nervous system is usually not affected. Types 2 and 3, on the other hand, are known as neuronopathic forms of the disorder because they are characterized by problems that affect the central nervous system. The most severe type of Gaucher disease is called the perinatal lethal form. This condition causes severe or life-threatening complications starting before birth or during infancy. Another form of Gaucher disease is known as the cardiovascular type because it primarily affects the heart, causing the heart valves to calcify. Gaucher disease occurs in 1 in 50,000 to 100,000 people in the general population. Type 1 is the most common form of the disorder; it occurs more frequently in people of Ashkenazi Jewish heritage than in those with other backgrounds (Beutler 2006). There is a paucity of reported cases in the literature with reference to the Indian subcontinent, possibly due to the rarity of this disease in this part of the world. A series of seven cases from Malabar region in Kerala showing increased incidence in the tribal population of Mappila Muslims has been published (Feroze 1994).

MOLECULAR BASIS

Gaucher disease (GD) type I is an autosomal recessive disease caused by a genetic deficiency of lysosomal β-glucosidase (GBA) that leads to accumulation of undergraded substrate glucocerebroside and other glycolipids, thus causing damage in different organs. The protein saposin C presents glucocerebroside to GBA and directly activates the enzyme. Deficiency of saposin C, which is rare, results in a severe disorder similar to GD (Scnabel 1991). The *GBA* gene is located on chromosome 1q21 (Cormand 1997). More than 300 distinct mutations of the *GBA* gene have been described in which 80% are single nucleotide substitutions while rare or unknown alleles account for the remaining 20%. Molecular genetic testing is used to identify carriers among at-risk family members once the disease-causing mutations have been identified in the family. Other alternatives include testing for the four common GBA alleles designed for screening in the Ashkenai Jewish population. Also, pre-conception testing of the partner of a known carrier or affected individual may be requested in ethnic groups of high prevalence. GBA is the only gene in which mutations are known to cause Gaucher disease. Nearly 300 mutations have been identified in GD patients, including frame-shift mutations, point mutations, deletions, insertions and splice site mutations. Four mutations N370S (c. 1226A>G), L444P (c. 1448T>C), 84GG (-c.84dupG), and IVS2+1 (c.27+1G>A) account for approximately 90% of the disease causing alleles in the Ashkenazi Jewish population. In non-Jewish populations, the same four alleles account for approximately 50-60% of disease causing alleles. Individuals who are homozygous for the N370S mutation are said to have milder disease than those who are compound heterozygous. However, patients with the N370S/N370S genotype exhibit a high degree of phenotypic heterogeneity. Individuals who are homozygous for the L444P mutation tend to have severe disease, often showing neurologic complications. Mutations of GBA are considered a well-

established susceptibility factor for Parkinson's disease and other Lewy body disorders (DiRocco 2013).

VARIANT FORMS OF GAUCHER DISEASE AND CLINICAL FEATURES

Clinically, Gaucher disease is characterized by vast phenotypic heterogeneity, with manifestations ranging from death in utero to asymptomatic octogenarians. The disorder classically has been divided into three types, based upon the presence or absence and rate of progression of neurologic manifestations. Type 1, non-neuronopathic Gaucher disease, is by far the most frequent type. Even among type 1 patients, there is variability both in presentation and disease progression. Among Ashkenazi Jews, based upon the known carrier frequency, it is clear that many, if not most, affected individuals go undiagnosed. However, in some patients the disease manifestations are significant, and commonly include organomegaly, anemia, and thrombocytopenia and bone involvement. In contrast, type 2, or acute neuronopathic Gaucher disease, is more stereotypic, with an onset by a few months of age and rapidly progressive and devastating neurologic deterioration. Most affected children succumb to the disease within the first year or two of life. Type 3, chronic neuronopathic Gaucher disease, encompasses multiple different phenotypes. Patients can have primarily visceral involvement with slowed horizontal saccadic eye movements, or can develop myoclonus, ataxia, seizures, or dementia (Sidransky 2004).

DIAGNOSTIC WORKUP

Adult onset (non-neuronopathic type) GD Type1 is characterized by variability in signs, symptoms, severity, and progression even among siblings with the same genotype. The most common visceral involvement is a splenomegaly, which may vary from moderate to massive in volume. Most of the common symptoms of Nonneuronopathic Type 1 also include: hepatomegaly, bone disease, thrombocytopenia, anemia, growth retardation, bruising/ bleeding, fatigue, bone pain/crisis and abdominal pain. The degree of anemia and thrombocytopenia in patients with GD is often related to whether or not they have had splenectomy. Associations have also been shown with Parkinsonism, particularly of the akinetic rigid type. The clinical course and life expectancy of GD1 is variable. Phenotypic expression cannot be reliably predicted by genotype since severity may vary among siblings, even identical twins (Bohra 2011).

Infantile cerebral GD also known as acute neuronopathic Type 2 is the rare form with an estimated incidence of 1 in 150,000 (Sidransky 1997). It is characterized by early onset, typically in infancy, and by a rapidly progressive neurologic deterioration. Visceral involvement is also extensive and severe. Oculomotor dysfunction, strabismus, saccade initiation abnormalities and bulbar palsy or paresis are common. Death occurs before the child reaches 2 years of age, with a median age of 9 months (Bohra 2011). Other symptoms include retroflexion of the neck, cortical thumbs, visceromegaly, failure to thrive and cachexia.

Subacute or chronic neuronopathic form consists of three different subtypes. Type 3A or Norrbottnian Gaucher was first described in the Norrbottnian region of Northern Sweden. It is characterized by progressive dementia, ataxia, and myoclonus. Patients with type 3B have a panethnic distribution and have extensive visceral and bone involvement with central nervous system involvement limited to supranuclear gaze palsy. Type 3C is rare and characterized by supranuclear gaze palsy, corneal opacity, and cardiovascular calcification, with little visceral disease. Neurologic involvement may begin late, with a variable progression (Bohra 2011).

TREATMENT

The advent of the ERT in the early 1990s changed the outlook of management of a patient with GD. In addition to this, development of substrate reduction, pharmacological chaperone, and gene therapies has broadened the horizon for this rare disease. ERT consists of infusions of mannose-terminated glucocerebrosidase which have helped in the regression of many visceral manifestations of the disease. Imiglucerase (Cerezyme) and velaglucerase alfa (VPRIV) are produced by recombinant DNA technology and are currently marketed for use in ERT for GD. The usual starting dose is 30–60 U/kg administered intravenously over 2 hours every 2 weeks.

Indications for ERT developed by consensus of international experts, using data from the Gaucher registry, are: 1) symptomatic children (including those with malnutrition, growth retardation, impaired psychomotor development, and/or fatigue) and 2) patients with severe disease (i.e. platelet count <60,000/μL, liver >2.5 times normal size, spleen >15 times normal size, radiologic evidence of skeletal disease).

In a double-center study done in Amsterdam (The Netherlands) and Dusseldorf (Germany), low-dose enzyme therapy was compared to high-dose therapy. The high-dose group had a better response of the bone marrow burden scores and reductions in bone marrow and the biomarker chitotriosidase than did the low-dose group. Other studies have

focused on different doses (15, 30, and 60 U/kg/fortnight) and found incremental differences in responses to enzyme therapy. An initial response was more rapid in the higher-dose group (60 U/kg) than in the other groups; other markers of response, such as the hemoglobin concentration, platelet count, and decrease in hepatic and splenic volumes, were greater in the group given 60 U/kg during follow-up at 60 months (deFost 2006).

Effect of enzyme therapy on the lung (pulmonary hypertension or interstitial or alveolar disease) has not been demonstrated. The CNS and lymph nodes also are inaccessible to intravenously administered enzyme that is mannose terminated. The commonest adverse effect of the ERT is immune mediated hypersensitivity. The shortcoming of the ERT is its high cost (US$ 100,000–US$ 200,000 per year). The rarity of the disease has inhibited large-scale randomized trial for the optimum dose, and therefore controversies have developed about the appropriate dose and dosing schedules. Large numbers of randomized control trials (RCTs) have begun to evaluate these issues.

During a 24-month trial of miglustat, the first randomized, controlled study of a drug treatment in patients with GD3, did not show significant differences on the chosen neurological endpoints over that period. Their conclusion suggested that miglustat may have positive effects on systemic disease (pulmonary function and chitotriosidase activity) in addition to ERT in patients with GD3 (Schiffmann 2008).

Substrate reduction therapy (SRT) may be offered to patients who are either unwilling or unable to afford the cost of ERT. It reduces glycolipid accumulation by decreasing the synthesis of glucocerebroside, the substrate of the deficient enzyme. Miglustat, an FDA approved therapy, is an oral agent (*N*-butyldeoxynojirimycin) which has shown decreases in hepatic and splenic volumes, and increases in platelet counts during 1–3 years in affected adults. Another oral formulation, eliglustat tartrate, is under phase III trials. Ceramide analogues were developed as alternatives to the deoxynojirimycin derivatives by Shukla *et al*. Short-chain ceramide analogues are being tested preclinically in mouse models of GD.

An alternative approach called the pharmacological chaperone has been devised to modify *in situ* the endogenous mutant enzyme with the use of specific agents that interact with these dysfunctional enzymes. This counterintuitive approach used competitive inhibitors of the enzyme to improve lysosomal activity. The range of mutations that might be responsive to one chaperone needs further investigation. In the era when ERT was not available, splenectomy was considered a treatment option in the face of life-threatening anemia and thrombocytopenia. Bone marrow transplantation (BMT) has the potential and has been demonstrated to provide a definitive cure for GD. However, this procedure is associated with substantial morbidity and mortality and thus has been effectively replaced by ERT in clinical practice. Progress in gene therapy has slowed because of issues of gene delivery and expression, especially in stem cells derived from bone marrow. Concerns about toxic effects are related to insertional mutagenesis and malignant cell transformation (Bohra 2011).

CONCLUSION AND RECENT ADVANCES

While significant advances have occurred in diagnosis and therapy, there is an ongoing need to expand the knowledge of the more basic features of the disease. A paper published not a few weeks ago about recent advances and future challenges in Gaucher Disease shows the clinical manifestations. The paper states that although hepatomegaly is listed among the four key disease features, the majority of the patients today do not have the massive hepatomegaly which was particularly common among splenectomized patients in the pre-ERT era and their liver function tests (LFTs) are usually within the normal range, or slightly abnormal. Two papers deal with children with Gaucher's Disease. A major concern of children and their parents is the issue of height. In this issue, Mendelsohn report a 15 year follow up of the growth parameters in 41 children both treated and untreated, where the key findings were of a lower final height of the patients, but without short stature. The impact of ERT on final height was not as significant as previously assumed. A second paper from the same group describes the changing phenotype of pediatric patients with GD in the era of ERT, highlighting the huge impact of this therapeutic modality. Children no longer undergo splenectomy and do not suffer from severe bone involvement. Many have been diagnosed prenatally and those who required ERT because of symptomatic disease started before the development and awareness, and hinting to a future when neonatal screening becomes widely available. It is hoped that prudent medical judgment will still be exercised in those children diagnosed so many years before the onset of signs or symptoms.

In the last 15 years, we have learned that the underlying pathology in GD is not only due to the lysosomal accumulation of glucosylceramide in the tissue macrophages and that the diverse phenotypic heterogeneity is not just a reflection of the many different mutations which can develop within glucosylceramidase beta (GBA) gene. It is hoped that in coming years, some of the currently studied drugs, such the pharmacological chaperones or new

SRTs, as well as new modalities that would address different metabolic pathways, will lead to even better means of treating patients with GD, including neuronopathic forms, before our futuristic dreams of cure become a reality (Zimran 2017).

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