

Gaucher Disease – Pathophysiology and Management of Adult Patients

a report by

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Gaucher disease (GD) is an inherited lysosomal storage disease caused by an autosomal recessive defect of the gene encoding glucocerebrosidase enzyme (GlcCer) responsible for the accumulation of glucosylceramide into reticulo-endothelial cells (particularly in the liver, spleen, bone marrow and lung), rendering GD a multi-organ chronic disorder. The gene is located on chromosome 1 and more than 200 different mutations have been described; however, only four of them account for almost 80% of the genotypes (N370S, L444P, IVS2⁺¹ and 84GG). The N370S mutation is the most common in the Ashkenazi Jewish population (75%), whereas it accounts for only 25% of alleles found in the Caucasian Gaucher population. In one-quarter of the cases the mutation remains undefined. The accumulation of glucosyl-ceramide into reticulo-endothelial cells is the main pathological mechanism leading to GD, which was first described in 1934 by Aghion et al. In 1965, the GlcCer deficiency was demonstrated to be the cause of this storage disease. Residual activity of GlcCer in patients with GD may vary from 5% to 25% of normal, depending on the method used for the measurement and on enzyme stability.

Lysosomes are cellular organelles that are targeted by GlcCer. Endogenous and exogenous macromolecules containing GlcCer are delivered to lysosomes by endocytosis, pinocytosis and phagocytosis. The effect of GlcCer accumulation is poorly understood. It is not yet clear whether GlcCer mediates important pathophysiological mechanisms within lysosomes or whether it escapes to other cellular organelles interacting with biochemical and cellular pathways responsible for cell damage. Recent studies support this latter hypothesis. Large macrophages (approximately 20–100µm in diameter) loaded with glucosylceramide are referred to as Gaucher cells. The macrophage origin of Gaucher cells has been demonstrated by the presence of surface macrophage markers, intense phagocytic activity and characteristic cytoplasmic inclusions. All the organs containing cells derived from the mononuclear phagocyte system (liver, bones, central nervous system (CNS), lung, spleen, lymph nodes, bone marrow, gastrointestinal (GI) and genitourinary (GU) tracts, pleura and peritoneum) may therefore be affected by GD. Recent

studies have shown that macrophageal activation, resulting in elevated serum levels of interleukin (IL)-1, IL-6, TNF- and the soluble IL-2 receptor, is one of the drivers of the GD pathogenesis. The macrophageal activation could potentially explain some clinical features of adult type-1 GD, such as osteopenia and skeletal abnormalities, anaemia, activation of the coagulation cascade or platelet activation. Moreover, chitotriosidase, a human chitinase from activated macrophages, is markedly elevated in GD and the chitotriosidase plasma level is used to determine the severity of the disease and to monitor the response to therapy.

Three major forms of GD have been clinically described. The most prevalent is the so-called non-neuronopathic form (type 1) characterised by anaemia, thrombocytopenia, enlargement of the spleen, skeletal abnormalities (osteopenia, lytic lesions, pathological fractures, chronic bone pain, bone crisis, bone infarcts, osteonecrosis and skeletal deformities) and, in a small number of patients, by lung involvement with interstitial lung disease and pulmonary hypertension. Type 1 GD patients are usually young adults. Type 2 is an acute neuronopathic form with severe prognosis and survival limited to the first two to three years of life. This disease variant is characterised by neurological symptoms (oculomotor abnormalities and brainstem involvement). Type 3 GD is also characterised by neurological involvement that usually appears later in life, compared with type 2. A tentative relationship between genotype and phenotype has been established, although a great heterogeneity of phenotype expression is observed. Homozygosity for N370S is mainly associated with 'mild' type 1 GD, while a homozygous L444P genotype is more common in type 3.

The pathological mechanism of CNS damage in the neurological forms is not fully understood. Infiltration of Gaucher cells into Virchow-Robin spaces has been demonstrated and reports have described neuronal loss and neuro-degeneration with damaged neurons in the basal ganglia, nuclei of the midbrain, pons, medulla, cerebellum, dentate nucleus and hypothalamus. Recently, an association between GD and Parkinson's disease has been discovered.

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Table 1: Type 1 GD Highest Risk Patients – One or More of the Following Symptoms

Symptomatic skeletal disease	
Moderate to severe osteopenia	Avascular necrosis
Chronic bone pain	Pathological fractures
Bone crises	Joint replacement(s)
Impaired quality of life due to GD	
Cardiopulmonary disease, including pulmonary hypertension	
Platelet count <60,000mm ³ or documents abnormal bleeding episode(s)	
Symptomatic anaemia or haemoglobin <8g/dl	
Transfusion dependency	
Significant liver disease	
severe hepatomegaly (>2.5 x normal)	infarcts
varices	portal hypertension
hepatitis	
Significant splenic disease	
severe splenomegaly (>1.5 x normal)	infarcts
Significant renal disease	

Table 2: Lower Risk Adult GD Patients

Normal liver, cardiac, lung and renal function
Minimal impairment of quality of life
No obvious and recently rapid progression of disease manifestations
Skeletal disease limited to mild osteopenia and Erlenmeyer flask deformity
Haemoglobin >10.5g/dl for females and >11.5g/dl for males (or not more than 2g/dl below lower limit of normal for age and sex)
Platelet count >60,000mm ³ on three determinations
Liver volume <2.5 x normal
Spleen volume <1.5 x normal

Management of Adult GD

GD is a multiorgan, chronic, heterogeneous disorder, requiring an individualised approach towards treatment. Many variables such as severity and rate of disease progression, concomitant pathological conditions, the impact of disease manifestations on quality of life and the phenotype/genotype relationship should be considered prior to the initiation of treatment in a patient with GD. At present, the therapeutic options for adult GD patients are enzyme replacement therapy (ERT) and substrate reduction therapy (SRT). Bone marrow transplantation and gene therapy have been applied in rare cases. It is generally accepted that a GD patient must be treated in the presence of complications such as anaemia, thrombocytopenia, bleeding tendency, skeletal disease, liver or lung involvement or organomegaly. Type 1 adult GD patients are, at present, the best candidates for ERT. In order to establish the severity of disease and to individualise the initial and maintenance ERT dose, a classification in high- and low-risk type 1 GD patients has been suggested by Anderson et al. as shown in Tables 1 and 2. Alglucerase, a first-generation placental GlcCerCase, was introduced in 1991. The drug was extracted from a large pool of

human placental tissue and remained the standard therapy for symptomatic GD patients for many years. More recently, imiglucerase – a recombinant enzyme (Cerezyme®) with high catalytic activity – became available and gradually replaced human placental-derived alglucerase in the treatment of GD patients. ERT GlcCerCase is targeted to the mannose receptors (MRs) localised on the macrophageal surface. Sequential enzymatic modifications led to GlcCerCase uptake. The modified enzyme is endocytosed and is subsequently delivered to the lysosomes where it supplements the defective enzyme.

There is clear evidence that ERT ameliorates systemic involvement in adult non-neuronopathic patients, whereas limited data is available on neuronopathic patients in whom ERT could stabilise or slow the progression of neurological involvement. Given the fact that children with GD are at a high risk from developing irreversible complications, early initiation of ERT with appropriate doses is advisable to attain their peak skeletal mass by early adulthood. For the physician prescribing ERT, the clinical challenge is to find the dosing regimen that will achieve the optimal clinical benefit for each individual patient. This challenge is best met if the risk classification is taken into account. In low-risk adult patients, ERT should be administered at least every two weeks, at a dose not exceeding 30U/Kg/two weeks, whereas high-risk patients and children should receive 60U/Kg/two weeks as a starting dose. In neuronopathic GD patients, it has been suggested to initiate a dose of 120U/Kg/two weeks as soon as the patient is diagnosed, and to maintain this dose if neurological disease manifestations remain stable. Doses up to 240U/Kg/two weeks for no more than six months may be considered in case of neurological disease progression. Therapeutic goals for the ERT treatment of the various complications, which reflect the published guidelines (ICGG), are summarised in Table 3. These therapeutic goals should be evaluated by regular monitoring, taking into account the fact that the timeframe for achieving these goals varies from organ to organ.

Generally, at least 12 to 36 months of sustained treatment is required. Dose adjustments have to be considered according to the achievement of therapeutic goals or worsening of the disease after the exclusion of confounding intercurrent illness.

Chitotriosidase, a protein secreted from activated macrophages, is markedly increased in patients with GD and will decrease in response to ERT, in conjunction with improvements in haematological and visceral parameters. Chitotriosidase is therefore suggested as a parameter for the monitoring of ERT responses.

Recently, an oral alternative therapeutic strategy became available for type 1 GD, namely substrate reduction therapy (SRT), using N-butyldeoxynojirimycin (OGT 918, miglustat, Zavesca®). Miglustat is an inhibitor of glucosylceramide synthase (the first committed step in the biosynthesis of glycosphingolipids). This approach reduces the formation of glycosphingolipids. Miglustat is a small molecule with broad tissue distribution throughout the body and its access to the CNS crossing the blood-brain barrier is documented both in animals models and in humans. Miglustat is licensed in Europe, in the US and in Israel for the oral treatment of mild to moderate type 1 GD where ERT is not suitable.

A multicentre phase 2/3 open-label study in 28 adult type-1 GD patients was conducted in three European centres and in Israel in 2000. The drug was given in dosages of 100mg once to three times daily. At 12 months, a significant mean decrease in liver (12%) and spleen (19%) volume and modest increases in haemoglobin (0.26 g/dl) and platelets (8.3 x 10⁹/l) were observed in those who persisted with the study. A decrease in plasma chitotriosidase activity (16.4%) was reported. Further improvement and/or absence of clinical GD deterioration was observed in 18 patients at 18 months and 36 months of extension treatment. However, miglustat causes a number of side-effects such as diarrhoea, loss of weight, peripheral neuropathy or tremor. These also caused drop-out from the clinical trials. The proportion of patients experiencing diarrhoea ranged from 86% during the first six months of treatment to 36% by month 36. Flatulence and diarrhoea ameliorated with loperamide and simethicone and with a sucrase- and maltase-deficient diet. Approximately 60% of patients reported clinically significant transient loss of weight. Approximately 20% of patients showed tremor during treatment that resolved spontaneously or following the reduction or discontinuation of therapy in some. Only one patient presented cognitive impairment. Although miglustat represents an alternative to ERT in adults with GD who have, for example, an allergy to one of the excipients of Cerezyme® or a venous excess problem, further investigations and a surveillance programme are needed and have been requested by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

Treatment of Skeletal Complications

Skeletal involvement in GD may lead to avascular necrosis and osteoporosis with fractures. Once these severe complications have been established, ERT as a stand-alone therapy is not likely to have an impact. Bisphosphonates acting directly on osteoclasts are used to reduce the bone resorption, increase calcium absorption, improve calcium balance and maintain or improve bone density

Table 3: Therapeutic Goals for ERT in GD Patients

<i>Therapeutic goals for anaemia</i>
<i>Increase haemoglobin levels within 12 to 24 months to</i> <i>≥ 11 g/dl for women and children</i> <i>12 g/dl for men</i>
<i>Eliminate blood transfusion dependency and reduce fatigue, dyspnoea and angina</i>
<i>Maintain improved haemoglobin values achieved after 12 to 24 months of therapy</i>
<i>Therapeutic goals for thrombocytopenia</i>
<i>Increase platelet count during the first year of therapy sufficiently, to prevent surgical, obstetrical and spontaneous bleeding</i>
<i>Patients with splenectomy – normalisation of platelet count by one year of treatment</i>
<i>Moderate baseline thrombocytopenia – the platelet count should increase by 1.5- to 2-fold by year one and approach low normal levels by year two.</i>
<i>Severe baseline thrombocytopenia – the platelet count should increase by 1.5-fold by year one and continue to increase slightly during years two to five, but normalisation is not expected</i>
<i>Avoid splenectomy</i>
<i>Maintain stable platelet counts to eliminate risks of bleeding</i>
<i>Therapeutic goals for hepatomegaly and splenomegaly</i>
<i>Reduce and maintain the liver volume to 1.0 to 1.5 times normal</i>
<i>Reduce the liver volume by 20% to 30% within years one to two by 30% to 40% by years three to five</i>
<i>Reduce and maintain spleen volume to less than two to eight times normal</i>
<i>Reduce the spleen volume by 30% to 50% by year one and by 50% to 60% by years two to five.</i>
<i>Alleviate symptoms due to splenomegaly</i>
<i>Eliminate hypersplenism</i>
<i>Therapeutic goals for skeletal pathology</i>
<i>Lessen or eliminate pain within one to two years</i>
<i>Prevent bone crisis</i>
<i>Prevent osteonecrosis and subchondral joint collapse</i>
<i>Improve bone mineral density</i>
<i>Increase trabecular bone mineral density by three to five years</i>
<i>Paediatric patients:</i>
<i>Attain normal or ideal peak skeletal mass</i>
<i>Increase cortical and bone mineral density (BMD) by year two</i>
<i>Therapeutic goals for growth in paediatric patients</i>
<i>Normalise growth and achieve normal onset of puberty</i>
<i>Therapeutic goals for pulmonary involvement</i>
<i>Reverse hepatopulmonary syndrome and dependency on oxygen</i>
<i>Ameliorate pulmonary hypertension (ERT+ adjuvant therapies)</i>
<i>Improve functional status and quality of life</i>
<i>Prevent sudden death</i>
<i>Prevent pulmonary disease by timely initiation of ERT and avoidance of splenectomy</i>

indices, preventing complications. In the presence of avascular necrosis or fractures, orthopaedic intervention may be necessary. Lebel et al. described total hip arthroplasties in 23 patients with GD with enhancement of the quality of life, improvement of function and restoration of normal activities. ■

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