Gaucher's disease: the changing paradigm of a lysosomal disorder

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ABSTRACT

Gaucher’s disease (GD) is the most common lysosomal storage disease with a frequency of approximately 1:50,000 people. It is the result of the deficiency of the lysosomal enzyme beta-glucocerebrosidase. The deficiency of the enzyme results in the accumulation of the substrate, glucosyl-ceramide, in the organs. Substitutive enzymatic treatment has been available since almost 20 years. This brief overview highlights some of the most important milestones and the treatments for this disease. The study of this rare disorder is beginning to provide information on the pathogenesis of common diseases such as Parkinson’s disease or cancer. Individuals with GD are at greater risk of developing cancer in general, especially hepatobiliary and hematologic (multiple myeloma and B-cell neoplasms). This association has been attributed to the immunologic abnormalities associated with abnormal expression of cytokines such as interleukin-6. Alternative and complementary, some recently marketed and licensed, are providing options for patients throughout Europe and the world.

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Enfermedades lisosomales. El paradigma de la enfermedad de Gaucher

RESUMEN

La enfermedad de Gaucher (EG) es la más frecuente de las enfermedades de depósito lisosomal, con una frecuencia de aproximadamente 1:50.000 habitantes. Se produce como resultado de la deficiencia de la enzima lisosomal beta-glucocerebrosidasa. El déficit de la enzima produce la acumulación del sustrato, la glucosilceramida, en los órganos. El tratamiento enzimático sustitutivo ha estado disponible desde hace casi 20 años. En esta breve reseña se destacan algunos de los hitos más importantes y los tratamientos para esta enfermedad. El estudio de esta rara enfermedad está comenzando a dar información sobre la patogénesis de enfermedades más comunes como la enfermedad de Parkinson o el cáncer. Los individuos con EG tienen mayor riesgo de desarrollar cáncer en general, sobre todo hepatobiales y hematológicos (mieloma múltiple y neoplasias de células B). Esta asociación se ha atribuido a las anomalías inmunológicas asociadas a la expresión anormal de citocinas, como la interleucina-6. Los métodos de tratamiento alternativos y complementarios en desarrollo, algunos de ellos comercializados y recientemente autorizados, están ofreciendo alternativas para los pacientes en toda Europa y el resto del mundo.

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treatments are offering choice for patients across Europe and the rest of the world.

**Clinical manifestations of Gaucher's disease**

GD is generally considered to have 3 classical forms. The commonest type of the condition is the so-called adult form or GD1. This can present at any age and typically manifests as thrombocytopenia or anaemia in a young adult. The spleen is often enlarged (sometimes markedly so, up to 30 x normal size). Substrate accumulation also occurs in other organs (eg, liver, bone marrow). Skeletal manifestations, including bone pain and pathological fracture, are the most challenging aspects of GD1. This is the commonest form encountered amongst individuals of Ashkenazi Jewish origin. A small number of mutations underlie this condition. An important feature is that central nervous system involvement is generally not found and examination of the mutant enzymes always demonstrates a significant level of residual enzyme activity. Individuals with type 2 GD have a very severe acute neuropathic form of the condition which is essentially untreatable and results in still birth or early neonatal death. Type 3 GD (GD3) is a chronic neuropathic form of the condition; nervous system abnormalities exist typically in the form of abnormal eye movements, seizures and often early intellectual deterioration. The extent of neurologic disability is extremely variable. This classical description is increasingly questioned and a continuum between GD1 and GD3 is recognised. A particular factor in this reclassification has been the finding of an association between GD and Parkinson's disease. The underlying mechanism is unknown and whereas there is some suggestion that patients with a more significant reduction in enzyme activity are particularly predisposed, an alternative suggestion is that the basic abnormality relates to an interaction between misfolded beta-glucocerebrosidase molecules and intracellular alpha-synuclein. A number of recent studies have emphasised the importance of the association of abnormalities of mutations at the GD gene locus and onset of Parkinson's disease.

A very recent large European study, however, reported that beta-glucocerebrosidase mutations were significantly more frequent (odds ratio = 7) in the Parkinson's disease patients than in controls. Furthermore, PD patients with beta-glucocerebrosidase mutations more frequently had bradykinesia as the presenting symptom and often developed levodopa induced dyskinesias. The study reported that beta-glucocerebrosidase mutations were in fact the most common genetic risk factor for PD particularly in its familial forms.

Whereas neurodegeneration is an important challenge, cancer is the other substantial burden for healthcare delivery. An association of GD and cancer has been recognised for many years. Individuals with GD have a higher risk of cancer generally but have a particular risk of developing hepatobiliary cancers and haematologic cancers. Multiple myeloma and other B-cell malignancies have been particularly reported amongst patients with GD. The underlying mechanisms are poorly understood. A range of immune abnormalities associated with abnormal expression of cytokines, particular interleukin-6, have previously been reported in patients with GD. Disturbance of p-glycoprotein expression resulting in abnormal levels of chemotherapy resistance has also been reported amongst haematologic tumours arising in GD patients. A recent study has reported an increased incidence of multiple cancers, often including multiple myeloma, amongst GD sufferers. A number of these patients had undergone splenectomy which is known to severely affect immune function. Patients with GD who have undergone splenectomy also have an increased risk of pulmonary hypertension. These recent findings emphasise the importance of detecting GD at an early stage and avoiding splenectomy. Mistry et al have demonstrated that only 20% of more than 400 haematology/oncology physicians who were surveyed in the US considered GD in the differential diagnosis when presented with a case history of its classic symptoms. Further, in over 130 patients with GD the mean time to diagnosis was 48 months. There is clearly an important need to raise awareness of this condition particularly amongst haematologists.

**Pathogenesis of Gaucher's disease**

An important impediment to the study of the pathogenesis of GD has been the lack of reproducible animal models. Currently available models do not accurately reflect human disease, characterised as it is by a spectrum of conditions with bone manifestations as a central abnormality. A recent publication from Mistry et al describes an animal model which faithfully recapitulates human GD, in particular the visceral and bony manifestations. The model emphasises the importance of cell types other than macrophages (eg, osteoblasts, dendritic cells and other cells within the immune system) which are of critical importance in GD.

**Treatment of Gaucher's disease**

The initial treatment of GD was with a placental derived enzyme. This impure preparation was shown to be effective but soon became replaced by the use of a preparation made by recombinant DNA technology and translated using a Chinese hamster ovary cell line. This preparation (imiglucerase) has a well established safety and efficacy record. Goals of therapy have been established and it has recently been demonstrated that a large percentage of patients will achieve these goals. Treatment goals reflect improvements in the baseline abnormalities observed in GD patients (anaemia, thrombocytopenia, liver and spleen volume, bone pain, abnormal results of imaging and biomarker assessment). There has been debate about the required dose of treatment to achieve these goals. It is apparent that using higher doses of enzyme replacement therapy will lead to more rapid achievement of goals, however, these rapid achievements are particularly marked in terms of achieving improvements in biomarkers (eg, chitotriosidase). The true clinical relevance of a more rapid achievement of treatment goals has been questioned. Enzyme replacement therapy requires intravenous access. Oral substrates are licensed and clearly have a role in the management of GD. They have become increasingly important because of recent shortages in the availability of imiglucerase. The shortages arose because of production difficulties due to viral contamination in the manufacturing plants. It must be emphasised that these contaminations do not pose a threat of any description to patients. However, they have resulted in a substantial reduction in the output of available imiglucerase. This has led to increased interest in alternatives to imiglucerase. Although the licensed oral alternative is effective, its use is associated with side effects. Whilst many of these side effects are trivial and subside rapidly (eg, tremor, diarrhoea) other side effects are more persistent and some (eg, peripheral neuropathy) can be disturbing for patients. A new form of substrate reduction therapy is currently undergoing phase 3 trials. Phase 2 trials with eliglustat tartrate are very encouraging and demonstrate an extremely high level of safety and tolerability.

Small molecules have a number of important advantages when used as therapeutic materials for the treatment of lysosomal storage disorders. They are orally available and widely distributed including to the central nervous system. This wide distribution is likely to lead to better penetration of these molecules to bone which is a major reservoir of disease in GD sufferers. The use of pharmacologic chaperones offers a different approach to substrate reduction therapy. Pharmacologic chaperones will aid folding of misfolded protein molecules and allow easier transport through the cell with reduced proteosomal degradation of misfolded proteins. This approach is being intensively investigated in phase 2 and 3 trials for Fabry disease. A phase 3 trial in GD has recently been terminated because of failure to demonstrate clinical activity. However, the challenges in appro-
priate dosing of the agent will undoubtedly be overcome in future studies. Other small molecule approaches include attempts to refine the activities of aminoglycoside derivatives so that stop codon mutations will no longer cause premature termination of messenger RNA molecules at the ribosomal level. Future trials of such agents are eagerly anticipated.

**Newer enzyme replacement therapies for Gaucher’s disease**

At least 2 new formulations of enzyme replacement therapy for GD are in phase 3 studies and beyond. Taliglucerase\(^2\) is a plant cell derived product which has been developed with an expressed determination to reduce the costs of enzyme replacement therapy. Preliminary studies demonstrate that this compound is efficacious and well tolerated. The recent shortage of imiglucerase has led to the development of an early access programme and there is much positive experience of this product throughout the world. Velaglucerase\(^2\) has already been licensed. In contrast to imiglucerase, velaglucerase is the human gene translated within a human cell line. The product is not made by recombinant DNA technologies; rather the technology involves increasing the expression of the human gene within a human derived fibroblast cell line. The advantage is that the post translational modification of the protein is exactly in accord with endogenously derived human enzyme. Furthermore, the single amino acid mismatch which characterises imiglucerase with respect to wild type beta-glucocerebrosidase has been corrected. A recent publication\(^2\) has reported the long term experience in phase 1 and 2 trials of velaglucerase. Patients in Israel have been receiving the enzyme for more than five years and the treatment clearly has an impressive long term safety and efficacy record. Results of phase 3 trials are eagerly awaited; they have been presented in abstract form at a number of meetings and long term safety, efficacy and safety of switching patients from Cerezyme\(^2\) to velaglucerase has been demonstrated.

These developments in the understanding of the basic pathogenesis of GD have laid the foundation for evolution in the existing paradigm. Newer measures of visualising beta-glucocerebrosidase enzyme within cells promise further important advances in our understanding of basic pathophysiology.\(^2\) At a clinical level, these advances are already being translated into a greater choice of better tolerated treatments for patients with Gaucher’s disease.

**Conflicts of interest**

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**References**