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Gaucher disease: from fundamental research to effective therapeutic interventions

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ABSTRACT

Gaucher disease type 1 is the most common lysosomal storage disorder, with a prevalence of 1:50,000 in most countries. It is caused by an autosomally recessive inherited deficiency of the lysosomal enzyme glucocerebrosidase, leading to the accumulation of glucocerebroside in the macrophages. The lipid-laden macrophages are called Gaucher cells and can be found in the liver, spleen and bone marrow. Gaucher disease type 1 should be considered in any patient with an unexplained splenomegaly with or without bleeding diathesis, skeletal manifestations or hepatomegaly. The diagnosis is made by showing decreased glucocerebrosidase activity in peripheral blood leucocytes or by demonstrating previously defined DNA mutations. Detailed knowledge about the molecular defect has provided a rationale for therapeutic interventions and attempts have been made to correct the defect at gene level, protein level and by manipulation of metabolism. Clinical trials of gene therapy have been conducted but so far have not resulted in successful intervention. For moderate to severely affected patients, intravenous enzyme supplementation therapy is the treatment of choice, resulting in substantial clinical improvement in the majority of patients. For individuals with mild Gaucher disease, an oral substrate inhibitor can also be considered if intravenous treatment is a less attractive option.

INTRODUCTION

Gaucher disease is the most common of the lysosomal storage disorders, a subgroup of the inherited metabolic diseases. The disease is characterised by a deficiency of the lysosomal enzyme glucocerebrosidase (glucosylceramidase), which leads to the accumulation of glucocerebroside in the macrophages.[1,2] Based on the presence or absence of neurological symptoms, Gaucher disease can be divided into three phenotypes; type 1 (non-neuronopathic), type 2 (acute neuronopathic) and type 3 (subacute neuronopathic). Type 1 Gaucher disease is by far the most common form, accounting for 99% of the Gaucher cases. Since specialists in internal medicine will rarely be confronted with the neuronopathic forms, this review will focus on type 1 Gaucher disease.

In the past two decades, Gaucher disease has received much attention for being the first of the lysosomal storage disorders for which safe and effective enzyme therapy has been developed, thereby making Gaucher disease a prototype for other intracellular protein deficiency diseases. More recent developments include the discovery of specific disease markers, the use of a new therapy based on substrate reduction and clinical trials of gene therapy.

This review provides an overview of the current knowledge and describes the recent advances concerning Gaucher type 1 disease.

EPIDEMIOLOGY AND GENETICS

Type 1 Gaucher disease can be found in all ethnic groups, but is especially prevalent in the Ashkenazi Jewish population, occurring in about 1:400 to 865 people.[3-5] The prevalence in the general population has been estimated at about 1:50,000,[6] with a carrier frequency of 1:200.

These figures could represent an underestimation, since a number of patients may well remain undiagnosed because of lack of symptoms or because physicians do not make the correct diagnosis. In the Netherlands, between 100 and 150 cases of type 1 Gaucher disease are known.[7]
Gaucher disease is transmitted in an autosomal recessive way. The 7.5 kb gene is located on chromosome 1q21 and encodes glucocerebrosidase.[8] More than 100 mutations have been described, of which the majority are point mutations.[9]
The most frequent mutations in the Ashkenazi Jews are the N370S and the 84GG mutations.[4,10] The N370S enzyme is present in normal amounts and shows considerable activity at low pH values but not at higher pH values.[11] Homozygotes for the N370S mutation often have a very mild form of the disease or are discovered as asymptomatic family members.[12] The heteroallelic presence of the N370S mutation is associated with non-neuronopathic disease only.[13,14] Alleles bearing the 84GG mutation are unable to direct synthesis of any protein at all ('null' mutation), and as such, this mutation has never been found in the homozygous state.[15] The combination of the N370S and the 84GG mutation results in relatively severe disease.[13]
The most prevalent mutations in Caucasian patients are the N370S and the L444P.[16] Homozygosity for the latter is associated with the neuronopathic forms of the disease.[16] Many of the Dutch patients have the N370S mutation in a heteroallelic form.[17]
There is a wide variability in clinical presentations of type 1 Gaucher disease and no strong correlations have been found between genotype and clinical expression.[18] A striking example of this is the description of a pair of identical twins, both carrying the N370S/N370S mutation, in which one subject has serious manifestations of the disease and the other has no symptoms at all.[19]

PATHOPHYSIOLOGY

The enzyme glucocerebrosidase catalyses the cleavage of glucose and ceramide from glucocerebroside, an intermediate in the degradation of complex glycosphingolipids, which are mainly present in cell membranes. Since macrophages degrade apoptotic and senescent blood cells and their precursors that are rich in this glycosphingolipid, it is not surprising that the lysosomes of these cells accumulate glucocerebroside when there is a deficiency in glucocerebrosidase activity. The lipid-laden macrophages are called Gaucher cells and are characterised by eccentric nuclei and a typical striated 'crumpled silk' cytoplasm (see *figure 1*).[20] Macrophages are especially found in the liver, spleen, bone marrow and, to a lesser extent, in the lung, and therefore these organs are predilection sites for excessive storage of undegraded glycolipid.

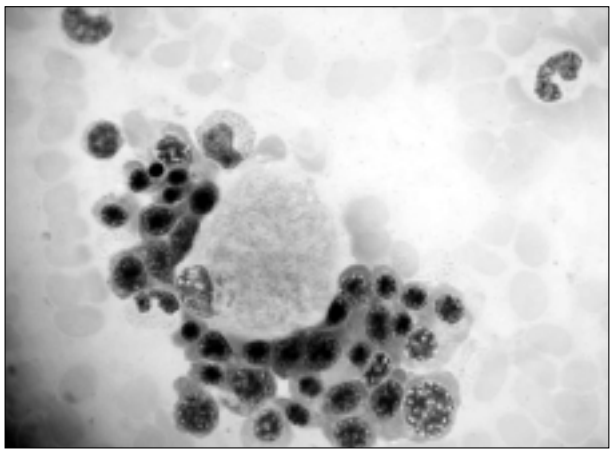

Figure 1
A microscopic view of a typical Gaucher cell, with a 'crumpled silk' cytoplasm and an eccentrically located nucleus, in the bone marrow aspirate of a patient with Gaucher disease

The glucocerebroside concentration in spleens can be increased 10- to 1000-fold, but high levels can also be detected in liver and bone marrow.[21] The increase in plasma concentration of glucocerebroside is far less spectacular, with an average of about twofold.[22,23] Other substances than glycolipid have also been found to be elevated in plasma and tissue of Gaucher patients. For example, tartrate resistant acid phosphatase 5B (TRAP), ferritin, angiotensin-converting enzyme (ACE), hexosaminidase and the lysosomal hydrolase chitotriosidase.[24] The last mentioned is by far the most elevated in symptomatic patients, with levels increased at least 100-fold and ranging to more than 4000 times the median normal value, while asymptomatic Gaucher patients show no or only slight increases.[25] Extensive studies have shown that chitotriosidase originates from the Gaucher cell and that plasma levels are closely associated with the total body burden of Gaucher cells. It is therefore a good marker to monitor disease progression and response to therapy.[24]
Since the presence of large numbers of storage cells in itself cannot explain all the phenomena observed in Gaucher patients, it has been suggested that the accumulated glucocerebroside activates macrophages, which induce inflammatory responses by releasing cytokines. Indeed, elevated levels of IL-1β, IL-6, IL-10 and M-CSF in sera from patients with Gaucher disease have been found,[26-29] as well as a trend towards elevated TNF-α mRNA.[30] In addition, glucocerebrosidase deficient mice showed a multisystem inflammatory reaction with inflammatory cell infiltration in several organs, lymphadenopathy, and elevated TNF-α and IL-1β expression. Evidence of B-cell proliferation was also found, as well as elevated serum IgG levels.[31] These findings also support the hypothesis that chronic stimulation of B cells occurs, which may be

the cause of the increased incidence of autoantibodies and the high frequency of gammopathies and multiple myeloma that have been found in patients with Gaucher disease.[32]

CLINICAL PRESENTATION

Type 1 Gaucher disease is a highly variable non-neuronopathic disease with a clinical picture that is dominated by a slowly to rapidly progressive hepatomegaly and splenomegaly, bone involvement, and a cytopenia. The mean age at diagnosis is 21 years,[13] but the age of onset can range from early childhood to the eighth decade. In general, early onset may be associated with a poor prognosis, but variability is the rule.

Haematology

Thrombocytopenia is the most common peripheral blood abnormality in patients with Gaucher disease, often leading to spontaneous bruising and bleeding.[33] Initially, this is the result of enhanced clearance of blood cells by the enlarged spleen. In a later stage of the disease or in patients who have undergone a splenectomy, replacement of the bone marrow by Gaucher cells adds to the development of cytopenia. Low levels of several clotting factors have also been found in patients with Gaucher disease, but the clinical expression of this derangement seems to be modest.[34] Anaemia and neutropenia are usually mild, but may result in pallor and palpitations or recurrent bacterial infection.[35]

Spleen

Splenomegaly is present in all but the very mildest cases of Gaucher disease and is often a presenting symptom.[36] In severely affected patients the spleen may be huge, sometimes weighing more than 10 kilogram, and interfering with normal food intake. Fibrotic areas and regions of extramedullary haematopoiesis sometimes present as nodules.[37,38] Splenic infarctions sporadically occur, presenting with local pain and tenderness, fever and abdominal guarding.[36]

Liver

The liver is increased in size in most patients, but gross enlargement, in which the liver may fill the entire abdomen, is typically found in splenectomised patients. The bulk of the liver may cause distress and episodes of pain occur. On physical examination the liver is usually hard and smooth. Between 30 and 50% of patients have elevated liver enzymes. However, hepatocytes appear not to be involved in the storage process and liver function is usually preserved.[38] Frank hepatic failure and cirrhosis with portal hypertension and ascites are uncommon but occur sporadically.[37,39]

Bones

The skeletal involvement probably leads to the most debilitating symptoms.[40] Bone disease in Gaucher is characterised by bone marrow infiltration of Gaucher cells as well as defective bone remodelling, leading to osteopenia, osteonecrosis and avascular infarction. Nearly all patients have signs of bone involvement, but the clinical presentation varies widely. Some patients experience chronic, ill-defined bone pain that can be debilitating and poorly correlated with radiographic findings. Pathological fractures, avascular necrosis of the femoral head, as well as instability of the spine with consequent vertebral compression and spinal cord involvement can result in severe mobility impairment.[40] Deformities of the distal femora can lead to the classical Erlenmeyer configuration. A number of patients experience one or more bone crises, which can occur spontaneously or follow a febrile syndrome and begin with a deep, dull, aching pain in the involved bone. These crises are usually very painful, requiring high doses of analgesics, and can last for weeks to months. Bacterial osteomyelitis should be excluded by appropriate cultures.

Lungs

Although relatively uncommon, pulmonary failure is one of the most serious consequences of Gaucher disease. It may result from infiltration of the lung by Gaucher cells or from left-to-right shunting, probably secondary to liver disease.[41] Massive visceromegalia or kyphoscoliosis following vertebral collapse can cause compression of the lung, which is probably a more frequent cause of respiratory disease.

DIAGNOSIS

Histological

The classical method for diagnosis of Gaucher disease was the detection of lipid-laden Gaucher cells in bone marrow, in a biopsy of the liver, or in a surgically removed spleen. However, the finding of Gaucher cells is not pathognomonic for Gaucher disease of as a diagnostic tool. So-called 'pseudo-Gaucher' cells can be found in several haematological diseases, including chronic granulocytic leukaemia,[42,43] lymphomas,[44,45] and multiple myeloma.[46] Since the development of the glucocerebrosidase assay and DNA mutation analysis, histological examinations are no longer necessary for diagnosing Gaucher disease.

Enzymatic

Glucocerebrosidase activity can be measured in peripheral blood leucocytes,[47,48] urine samples,[49] or cultured skin fibroblasts.[10] The typical adult Gaucher patient will have

enzyme activity that is 10 to 30% of normal values. The usefulness of this assay in the detection of heterozygotes is limited, since there is a considerable overlap of glucocerebrosidase activity between normal and heterozygous individuals.[50] The main advantage of this method is that it can establish the diagnosis regardless which disease mutations are present. A disadvantage is that glucocerebrosidase is relatively labile, and therefore, rapid transportation of refrigerated samples to a reference laboratory is required to obtain valid results.

DNA-mutation analysis

A major advantage of DNA-based diagnosis is that, since DNA is very stable, blood samples can be transported at ambient temperature without haste. The DNA can then be extracted from the leucocytes and stored for years. A second advantage is its potential to give some prognostic information, taking into consideration the limitations mentioned previously.

However, a major difficulty is that current technology permits routine examination only for previously defined mutations, but not for the entire sequence of the gene. As a consequence, it is important to realise that the presence of two apparently normal alleles does not rule out the diagnosis, and finding only one abnormal allele does not automatically mean that the patient is simply a carrier.[51]

THERAPY

Symptomatic treatment

Before enzyme supplementation therapy became available, treatment of Gaucher disease was only symptomatic. Splenectomy was the customary treatment in cases in which massive splenomegaly caused severe cytopenia or mechanical discomfort.[52,53] After removal of the spleen, a reversal of the cytopenia occurs almost invariably and the well-being of the patient usually improves considerably.[52,54] Splenectomy is now only indicated in the very severe cases in which life-threatening complications, such as bleeding, make rapid intervention necessary. For treatment of bone crisis, analgesics and bed rest are usually needed. Bacterial osteomyelitis may occur and requires extensive treatment with intravenous antibiotics. Orthopaedic procedures, such as hip and knee joint replacement or stabilisation of the spine, are often performed.

Bone marrow transplantation

Since macrophages are derived from haematopoietic stem cells, bone marrow transplantation is expected to cure Gaucher disease. Indeed, allogenic bone marrow transplantation in a number of patients with type 1 and 3 Gaucher disease showed good haematological and visceral responses.[55,56] However, bone marrow transplantation is a high-risk procedure with severe complications and this treatment is therefore not usually recommended for patients with type 1 disease.

Gene therapy

The idea that Gaucher disease will also benefit from gene therapy is based on the positive results of bone marrow transplantation, the lack of need for strict regulation of glucocerebrosidase secretion and the fact that Gaucher disease is a monogenic disorder. However, clinical trials of retroviral transfer of the normal glucocerebrosidase gene into CD34+ cells from patients with Gaucher disease showed gene-containing cells in peripheral blood only transiently and at very low levels.[57,58] Methods of more efficient gene transfer need to be developed to improve these results.

Enzyme supplementation therapy

Gaucher disease was the first of the lysosomal storage disorders that could be treated using enzyme supplementation therapy, which has been available in the Netherlands since 1991.[59] Clinical trials using modified enzyme from placental tissue (Ceredase, alglucerase,) and later enzyme produced by recombinant techniques (Cerezyme, imiglucerase, both manufactured by Genzyme Corp., Mass., USA) showed a dramatic clinical response to regular intravenous administration.[60-63] In general, patients report striking improvements in well-being, energy level and quality of life.[64,65] Improvement in cytopenia and decreases in splenic and hepatic size are apparent after 3 to 12 months of treatment. Splenic size decreases by approximately 20% and liver size by approximately 10% after six months of treatment.[60,62,63] Liver volume usually normalises while the spleen continues to show some enlargement, even after a long period of treatment. Bone marrow and mineral skeleton usually respond slower and a maximal response may take years to achieve. The most sensitive method for measuring bone marrow infiltration is quantitative chemical shift imaging (QCSI). QCSI determines the ratio between triglyceride and water content of the bone marrow, which is greatly reduced in type 1 Gaucher disease,[66,67] probably due to displacement of normal triglyceride-rich adipocytes by Gaucher cells.[68] There are no serious side effects associated with enzyme supplementation therapy. About 13% of patients develop IgG antibodies to enzyme replacement therapy with alglucerase, but anaphylactic reactions are very rare.[69] There is still controversy about the most effective dosing regimen, one that results in an optimal therapeutic effect, while decreasing the infusion rate and the cost of care (€ 100,000 to 300,000 per patient per year in the Netherlands). In the Netherlands an individualised dosage regimen is used, starting with a low dose which is adjusted according to the response to treatment.[63]

Substrate reduction

The orally administered compound OGT 918 (Zavesca™, Oxford Glycosciences, UK) is an inhibitor of glucosylceramide synthase, the enzyme which catalyses the first step in the synthesis of most glycosphingolipids. Studies in untreated patients showed improvements in all key clinical features and biochemical markers, although less impressive compared with enzyme supplementation therapy. The most common adverse effect was diarrhoea.[70,71] In practice, enzyme replacement therapy remains the first choice for patients with moderate to severe disease. For patients with a mild or minimal residual disease, the disadvantages of the side effects should be balanced against the advantages of oral administration. Further studies will be needed to identify those patients that will benefit most from OGT 918.

Gaucher disease provides a good example of how fundamental research can contribute to the development of effective therapeutic strategies. Current research in the pathogenesis of Gaucher disease is likely to clarify unsolved aspects, aiding in the better understanding and management of this disease, as well as in other lysosomal storage disorders.

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