Gaucher Disease
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Gaucher disease is an inherited metabolic disorder that affects multiple organs systems. It is the most common lysosomal storage disorder, which results from a deficiency of the enzyme glucocerebrosidase, also known as glucosylceramidase (GlcCerase). This enzyme works in macrophage lysomes and is necessary for the breakdown of glucocerebroside, a compound that is found in the cell membranes of red and white blood cells. In patients with Gaucher disease, macrophages engulf the short lived red and white blood cells, but are unable to eliminate the waste product which accumulates in the lysosome. This accumulation leads to organ damage, predominately in the liver and spleen and also to the skeletal system (Michelin 2006). Affected cells include those of the spleen, liver, kidneys, lungs, brain and bone marrow; the accumulation of lysosome waste products eventually leads to organ damage and many clinical problems. In particular, skeletal accumulation of the glucocerebroside leads to skeletal (bone) disease and splenomegaly can lead increased destruction of red and white blood cells and platelets causing anemia, neutropenia, and thrombocytopenia (Mehta 2006).

A recent study by Sinclair et. al, demonstrated progressive splenomegaly with Gaucher cell infiltration using mice with biochemically induced Gaucher disease. This experiment was important in demonstrating the overall progression of visceral symptoms seen in type I Gaucher disease, with splenomegaly having the earliest onset, followed by hepatomegaly and then bone marrow storage which did not occur until the later stages. The authors of this paper believe they have found a useful model for studying the complex pathophysiology of Gaucher disease (Sinclair 2006).

Clinical Manifestations

In the past Gaucher disease was described as having discrete phenotypes, however today it has been established as a disease with a wide spectrum of clinical findings. These range from a perinatal-lethal form to an asymptomatic form, however three main clinical subtypes, type I, II and III, are used for determining prognosis and management (Pastores 2006).

Type I (nonneuropathic) is the adult form of Gaucher disease, which may first present early in life or as late as 60 or 70 years of age. The disease onset and severity ranges significantly, with the principal symptoms being bone disease and organ enlargement in the absence of primary central nervous system involvement. These patients may also develop, anemia, neutropenia, thrombocytopenia, lung disease and immune system abnormalities. Skeletal problems, which include osteopenia, focal lytic or sclerotic lesions and osteonecrosis are often the most disabling feature of type I disease, causing pain, immobility, impairment of bone marrow function, fracture, infection and osteomyelitis (Pastores 2006).

Types II and III Gaucher disease both involve primary neurologic disease. Type II, also known as acute infantile neuropathic Gaucher disease, has a rapidly progressive course usually beginning within the first 6 months of life. Children with type II disease do not normally live past age 3 or 4, and often have extensive brain damage. In addition, they have bulbar signs which include difficulting breathing, sucking and swallowing.
Pyramidal signs, which include severe hyperextension of the head, neck and spinal column as well as spasticity and trismus, are frequently present. Many of these children experience cognitive impairment and limited psychomotor development (Pastores 2006).

Type III is also called chronic neuropathic Gaucher disease, and has similar symptoms to type II with a slower progressive course and a life span extending to age 30 or 40. These patients also have bone disease, and primary CNS involvement including oculomotor apraxia (difficulty controlling horizontal eye movements), seizures, and progressive myoclonic epilepsy. It is understood that the distinction between types II and III Gaucher disease are not absolute, and there is a phenotypic continuum (Mehta 2006).

Epidemiology

Gaucher disease is relatively rare, with an incidence of about 1:40,000 individuals. Type II and III, which lack neurological symptoms, occur even less frequently (about 1:100,000). Type I Gaucher disease occurs primarily in adults and is one of the most common lysosomal storage disorders, occurring once in every 40,000 people. However, the incidence of the disorder is disproportionately high within the Ashkenazi Jewish population, where the prevalence is 1:1000, and the carrier frequency is 1:14, as a result of the founder effect (Mehta 2006).

Genetic Testing and Counseling

There are a relatively limited number of mutant alleles that result in Gaucher disease, rendering this abnormality particularly amenable to genetic testing. In the Ashkenazi Jewish population the four mutations N370S, L444P, 84GG, and ICS2+1 make up over 90% of the Gaucher causing alleles. In non-Jewish populations affected individuals are typically compound heterozygotes and present with one of the more prevalent mutations and one rare or unique mutation. Diagnosis of the disease is confirmed via an enzymatic assay of glucosylceramidase (Pastores 2006).

There is significant heterogeneity in the phenotype of affected individuals. Mutations are categorized into three categories, which are mild, severe, and null mutations. Different combinations of these disease alleles result in a varying age of onset and severity of Gaucher disease. An individual’s prognosis can be predicted by phenotype-genotype correlation studies or by the phenotype of a sibling (Levy-Lahad 1997).

There are no clinical consequences for carriers of a mutant Gaucher allele as one wild type copy is sufficient to carry out normal cellular functions. Thus carrier screening is carried out solely for reproductive purposes, and is primarily done by genetic testing as enzymatic assays are unreliable for Gaucher heterozygotes (Levy-Lahad 1997).

Prenatal Screening

Pre-Natal screening is done by enzymatic assay of glucosylceramidase activity and genetic testing via chorionic villus sampling or amniocentesis. If a fetus is found to be affected then the severity of the disease can be predicted by genotype-phenotype correlation studies or from the phenotype of diseased siblings. Whether or not the particular form of the disease is neuropathic or non-neuropathic and the overall ability of the disease type to be treated are major factors in couples decisions to selectively abort affected fetuses (Levy-Lahad 1997).
Familial Risk

Type I Gaucher disease often goes undiagnosed or is asymptomatic. Thus when an affected individual is discovered in a family, additional affected family members may be discovered along with carriers (Levy-Lahad 1997). Gaucher disease is inherited in an autosomal recessive manner and therefore parents of diseased individuals are obligate carriers. Siblings of affected progeny have a 25% chance of being affected, a 50% chance of being carriers, and a 25% of having two normal copies of the Gaucher allele. Extended family members are also at a greater risk of developing Gaucher or being carriers (Pastores 2006).

Management

The most commonly used treatments for Gaucher disease involves reducing glucosylceramide (GlcCer) storage by either enzyme replacement therapy (ERT), using recombinant GlcCerase (Cerezyme®), or substrate reduction therapy (SRT), using a glycolipid synthesis inhibitor (Zavesca®). ERT achieves this by supplementing defective enzyme with active enzyme, while SRT lowers the rates of synthesis of all GlcCer-based glycolipids, effectively reducing glycolipid accumulation. ERT is currently used by roughly 3000 patients worldwide, and has been proven safe and effective for a period of over 14 years, by reducing clinical symptoms such as liver and spleen volumes, anemia, and bone pain. Despite the success of ERT therapy, there are several aspects that have limited its effectiveness among patients. Treatment with Cerezyme® requires life-long, intravenous infusions at least once every two weeks, making treatment impractical. As a result of its poor delivery to bone and lungs, and its inability to cross the blood-brain barrier, Cerezyme® is not effective in treating patients with severe or pre-existing bone and lung lesions, as well as patients with neuropathic involvement (Type II & III) (Futerman 2004).

For patients for whom ERT is unsuitable, SRT therapy is the preferred choice. While liver and spleen volumes also decrease with SRT treatment, the hematological responses were less impressive than those of patients who received ERT. As a result of SRT’s relatively recent suitability for Gaucher disease in comparison to ERT, many clinical trials are still being performed. By contrast to the intravenous infusions given to patients participating in ERT, Zavesca® is given orally and crosses the blood-brain barrier. However, it does cause several side effects such as diarrhea, abdominal pains, weight loss, and peripheral neuropathy. Additionally, the adverse effects of long-term glycolipid reductions achieved by SRT are still under question, and as a result Zavesca® has been approved in Europe and the USA only for patients for whom ERT is unsuitable. Moreover, patients who receive Zavesca® must undergo follow-up neurological monitoring. Both drugs, Cerezyme® and Zavesca®, are extremely expensive, and therefore unavailable to patients in poor countries. Despite the increase in quality of life achieved by these two drugs, it is apparent that there is still ample room for improvement between these two classes of drugs (Futerman 2004).

One recent alternative therapeutic approach involves an active-site directed inhibitor, which not only stabilizes the GlcCerase enzyme, but serves as a chaperone protein as well. Because certain Gaucher disease mutations involve an improperly folded GlcCerase, these chaperones may aid in its movement through the secretory pathway and
its level in lysosomes. While this novel approach demonstrates promise, its efficacy in the human population is still in the distant future (Futerman 2004).

Improving already prominent treatments such as ERT have also proved promising. Activators could be designed to enhance the activity of common mutant enzymes, such as the prevalent N370S mutation found predominantly within the Ashkenazi Jewish population, or enzymes administered in ERT to enhance its activity and stability. Another approach would involve engineering a more stable GlcCerase with a higher catalytic activity. This approach could have several implications involving reduced number of infusions and reduced costs to the patients (Futerman 2004).

There are several other symptomatic treatments used in the management of Gaucher disease for patients whom ERT and SRT are unsuitable or unavailable. These may include total or partial splenectomy for patients with splenomegaly who have a high risk of bleeding. For patients with severe anemia and bleeding, a transfusion may be necessary. Analgesics may be prescribed for bone pain, or joint replacement surgery may be an option for the relief of chronic pain. Additionally, oral bisphophonates and calcium supplements may be beneficial to patients with Gaucher disease and low bone density. For patients with severe Gaucher disease (Type III), bone marrow transplantation can correct the metabolic defect, hematological symptoms, and decrease liver volume. However, the morbidity rates of bone marrow transplantation limit this type of treatment (Pastores 2006).

Conclusion
While Gaucher disease is relatively rare, it is the most common lysosomal disorder that doctors encounter. Because Gaucher disease is caused by mutations in a single gene, many of which are known, presymptomatic testing, pre-natal testing, and carrier screening has the potential to be effective in improving the treatment of patients. While treatment is available, further research into the complex pathophysiology of Gaucher disease and pharmacological therapies will better improve the lives of these individuals.

References