Gaucher Disease  
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Gaucher disease is an autosomal recessive lysosomal storage disorder characterized by a deficiency of glucocerebrosidase. This lysosomal enzyme normally breaks down the glycolipid glucocerebroside, a cell membrane constituent of red and white blood cells. When glucocerebrosidase is impaired, its substrate accumulates in the lysosomal compartment of macrophages throughout the body. The glucocerebroside filled cells take on a characteristic morphology with a wrinkled appearance of their cytoplasm and are referred to as Gaucher cells. The impaired function of glucocerebrosidase is due to mutations in the glucocerebrosidase gene. The disease ranges from a perinatal-lethal form to an asymptomatic form. Due to the broad variability in presentation, Gaucher disease is sub-divided into three clinical subtypes, which aids in determining prognosis and management.

**CLINICAL SUBTYPES**

Type 1 Gaucher disease is the most prevalent form and differs from the other two subtypes in that it does not involve the primary central nervous system. However, neurological complications may occur as a result of bone disease, which is the most debilitating aspect of Type 1 Gaucher disease. It occurs in 70-100% of individuals and can range from asymptomatic osteopenia to focal lytic or sclerotic lesions and osteonecrosis. Other common symptoms include hepatomegaly and splenomegaly with anemia and thrombocytopenia. Anemia may also contribute to chronic fatigue. Pulmonary involvement such as interstitial lung disease, alveolar/lobar consolidation and pulmonary hypertension has also been noted.

Type 2 and Type 3 Gaucher disease are often classified based on the age of onset of neurological symptoms and the rate of progression with Type 2 representing the infantile, acute type and Type 3 representing the juvenile sub-acute type. Individuals affected with Type 2 Gaucher disease often have onset of the disease prior to two years of age and a rapid progressive course with death by two to four years of age. Those affected with Type 3 Gaucher disease may have onset as early as two years of age, but have a slower progressive course and may live into thirty or even forty years of age. More recently, neuropathic Gaucher disease has been viewed as a phenotypic continuum. The most prevalent neurological finding Type 3 Gaucher disease is a horizontal supranuclear palsy. Occulomotor apraxia, generalized seizures, progressive myoclonic epilepsy and dementia may also be present. Type 2 Gaucher disease often presents with cognitive impairment and bulbar and pyramidal signs (squint, difficulty swallowing, opisthotonos, head retroflexion, etc). Individuals with Type 2 or Type 3 Gaucher disease may also exhibit hepatomegaly, splenomegaly, cytopenia, pulmonary disease and dermatologic changes. Additional subtypes of Gaucher disease also exist such as the perinatal lethal and cardiovascular forms.

**GENETICS**

More than 180 Gaucher disease causing mutations in the glucocerebrosidase gene (chromosome1q21) are known including point mutations, splice site mutations, deletions and recombinant alleles. These mutations are caused by recombination between the
glucocerebrosidase gene and a related pseudogene that is on the same locus. They generally result in mRNA instability, severely truncated proteins, or an enzyme with an altered activity and or confirmation. There are four common mutations: N370S, 84GG, IVS2+1G>A, and L444P. They account for 50-60% of mutant alleles in Type 1 Gaucher disease in non-Jewish individuals and about 90% of alleles in the Ashkenazi Jewish populations.

The N370S missense mutation has been exclusively associated with type 1 Gaucher disease. Individuals who are homozygous for N370S have a milder form of the disease than those who are compound heterozygous. The most prevalent mutation among the non-Jewish population is the L444P mutation, which can be associated with all three types of Gaucher disease. It occurs as either a single base substitution or part of a recombinant allele. An individual homozygous for the L444P mutation typically develops Type 3 Gaucher disease, while compound heterozygotes will more likely develop Type 1 or Type 2 Gaucher disease. However, in a large Gaucher disease registry, 25% of patients with the homozygous L444P mutation were categorized as Type 1. No live-borns homozygous for the 84GG or the IVS2+1 mutations have been identified. Compound heterozygotes (84GG/IVS2+1) show a subacute disease course that includes progressive pulmonary involvement. These individuals do not survive past the first or second decade of life.

Siblings with identical genotypes can present with different disease severities, illustrating the diversity of phenotypic expression in GD. In addition, a study on children homozygous for the L444P mutation showed a wide spectrum of phenotypes. This study also found that residual enzyme activity was highly variable and did not correlate with the clinical presentation of the disease. Although mutations in the glucocerebrosidase gene are required to cause GD, other factors probably play an important role. It has been suggested that modifier genes have an effect on the disease pathway or protein-protein interactions at the cellular level. Different genetic backgrounds have demonstrated differences in clinical presentation. It has been observed that African-American patients have more severe neurologic involvement, while those of Hispanic origin have a less favorable developmental outcome. However, no specific modifier genes have been identified to date.

**FAMILIAL RISK**

Gaucher disease is an autosomal recessive disease that is passed on and inherited through the genes a person acquires from his or her parents. Specifically, the gene affected is a gene which is responsible for creating the enzyme glucocerebrosidase. Patients who have inherited at least one normal copy of this gene have no signs or symptoms of disease, but are carriers of the disease. A patient is only affected with Gaucher if they inherit two mutated or abnormal copies of this gene, one from each parent. Although carriers do not manifest disease they have a 50% chance of passing on the mutated gene to their offspring. According to autosomal recessive heritability, when two carriers mate there is a 25% chance that the offspring will have both mutated genes and develop Gaucher disease.

It is significant to note that there are certain populations with a high risk of carriage. These populations have an increased disease occurrence due to the population’s high carriage rate of the mutant allele. One such population is the Ashkenazi Jewish
Among these individuals, the incidence of Type 1 Gaucher disease is significantly higher (1 in 450 people) compared to the general population (1 in 40,000-60,000). It has been estimated that approximately 1 in every 12-15 Ashkenazi people are carriers of the mutated gene. Consequently, an individual’s risk of inheriting Gaucher disease is increased in these populations because of the increased chance that they will inherit two mutated genes from the population. As a result, it is important to test people of mating age in these populations to determine if they have the carrier status. In addition, it is essential to educate known carriers of the risks of the disease in order to allow for appropriate family planning. Testing for the four common mutations is available on a clinical basis and sequence of analysis of the coding region may be used if affected individuals are only found to have a single mutation after preliminary target mutation analysis.

In the case where two individuals at risk of being carriers have decided to mate, prenatal testing for the disease is available via a direct DNA analysis of the fetus to detect for mutations in the glucocerebrosidase gene, or biochemical testing to determine the levels of the affected enzymes in the fetus. Both of these tests are done with samples obtained via amniocentesis or chorionic villus sampling. The uncertain prognosis of patients with Gaucher disease makes it increasingly difficult for parents who undergo prenatal testing to make decisions about how they will handle the information obtained through test results. As such, prenatal testing is often offered in conjunction with genetic counseling so that parents can be educated on their options and make informed decisions.

**DIAGNOSIS**

A preliminary diagnosis of Gaucher disease includes an extensive family history. When the history reveals that the patient has had family members with the disease, the physician can make a preliminary diagnosis based on an evaluation of the most common signs and symptoms of the disease. These signs and symptoms are discussed here. Accumulated Gaucher cells can cause an enlarged liver and/or spleen which can push against the stomach to give a feeling of fullness and decrease a patient’s appetite. The enlarged spleen will result in over reactivity and an increased breakdown of red blood cells, white blood cells, and platelets which may result in signs of anemia, low white blood cell count and an increase in bruising and bleeding respectively. Anemia may explain feelings of fatigue in patients and a low white blood cell count may increase patient’s frequency of infection and sickness. Frequent nosebleeds and long, heavy periods may be indication of the decreased platelet count. Patients may also be bedridden from skeletal complications such as severe bone pain, bone tissue death, and bone thinning with fevers that last up to weeks. These are caused by insufficient blood flow to bone as a result of interfering Gaucher cells and make patients more susceptible to bone fractures from normal activities. Remodeling of damage bones is often irregular in shape due to the poor circulation, and may interfere with the normal timeline of growth and development for a child of pubescent age.

These symptoms, however, overlap with similar symptoms in more common diseases and thus, a physician will want to further evaluate a patient with familial risk by performing a blood sample analysis. Specifically, the level of glucocerebrosidase enzyme activity should be measured in the patient’s blood sample. Determination of the
enzyme activity level will allow for a definitive diagnosis. Affected individuals will show a markedly decreased (0-30%) level of activity for the enzyme glucocerebrosidase. However, enzyme assay is not definitive for carrier detection since enzyme activity levels overlap between carriers and non-carriers.

In addition, blood tests can confirm low RBC or platelet counts and X-rays, MR imaging and CT modalities can be used to confirm skeletal abnormalities as a consequence of disease.

TREATMENT/PROGNOSIS

Gaucher disease may require several different treatments to affect its various conditions caused secondarily to the problematic enzyme deficiency. Historically, these have included medications for pain, interventions such as joint replacements for bone and joint abnormalities and in certain cases surgery to remove the spleen or liver. Blood transfusions are common for anemic patients and antibiotics are used for infections. To treat the central problem of a deficiency of the glucocerebrosidase enzyme, however, targeted enzyme replacement therapy is now used by convention to treat Type 1 patients. There is currently no treatment shown to be effective in stopping the progression of Type 2 or Type 3 Gaucher disease and the neurological deficits caused by these subtypes are permanent.

Patients with Gaucher disease lack the enzyme glucocerebrosidase which breaks down the fatty waste that causes the swelling of Gaucher cells. Cerezyme is the current existing enzyme replacement therapy and consists of a recombinant β-glucosidase. The enzyme replacements taken intravenously enter the patient’s bloodstream and target the Gaucher cells, thereafter acting as the natural enzyme to break down accumulated waste. Dosage varies from less frequent high dose regimens to more frequent low dose regimens. Both regimens have been described as having good responses to disease progression. However, a correlation has not been shown between the responsiveness and age, disease severity or genotype at the beta-glucosidase locus. There is an ongoing debate to determine the most suitable initial dose and maintenance doses. It should be noted that Cerezyme does not offer a cure of the disease because it does not correct the underlying enzyme deficiency. In order to continue the reversal of symptoms which have been shown, Cerezyme needs to be taken for life. Needless to say, at costs of up to $750,000 annually per patient, the financial burden on many families is overwhelming.

References
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