Gaucher disease

Gaucher disease is the most common of the lysosomal storage diseases It is a form of sphingolipidosis (a subgroup of lysosomal storage diseases), as it involves dysfunctional metabolism of sphingolipids.

The disease is named after the French physician Philippe Gaucher, who originally described it in 1882.

Gaucher disease (GD) is a genetic disorder is caused by low levels of glucocerebrosidase (GCase), an enzyme that breaks down a fatty chemical in the body called glucocerebroside. Gaucher cells are normal scavenger cells called macrophages that become full of unprocessed glucocerebroside. Gaucher cells accumulate primarily in the spleen, liver and bone marrow, causing organ inflammation and dysfunction.

The disease is caused by a recessive mutation in the GBA gene located on chromosome 1 and affects both males and females.

Types of Gaucher disease

GD type I (non-neuropathic) is the most common and least severe form of the disease (occurrence in the general population 1:40.000 με 1:60.000 -among Ashkenazi Jews, the occurrence is 1:500). Symptoms may begin early in life or in adulthood and mainly affect the liver, spleen, and bone. Depending on disease onset and severity, type I patients may live well into adulthood. The range and severity of symptoms can vary dramatically between patients.

GD type II (acute infantile neuropathic) typically begins within 6 months of birth and has an incidence rate around one 1 in 100,000 live births. Symptoms include an enlarged liver and spleen, extensive and progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow. Affected children usually die by age two.

GD type III (chronic neuropathic) can begin at any time in childhood or even in adulthood, and occurs in about one in 100,000 live births. It is characterized by slowly progressive, but milder neurologic symptoms compared to the acute or type II version. Major symptoms include an enlarged spleen and/or liver, seizures, poor coordination, skeletal irregularities, eye movement disorders, blood disorders, and respiratory problems.

Diagnosis

Gaucher disease is suggested based on the overall clinical picture. Initial laboratory testing may include enzyme testing. Decreased enzyme levels will often be confirmed by genetic testing.

Prenatal diagnosis is available and is useful when a known genetic risk factor is present.

Clinical Manifestations

- enlarged spleen and liver
- pancytopenia (anemia, neutropenia, leukopenia, and thrombocytopenia),with an increased risk of infection and bleeding
- skeletal disorders (bone pain and bone crisis,bone infarction or avascular necrosis (AVN),osteopenia and osteoporosis,joint pain and joint damage
- neurological complications (Type II and III)

Treatment

Enzyme replacement therapy

The first drug for Gaucher's was alglucerase (Ceredase), which was a version of glucocerebrosidase.It was approved by the FDA in 1991.

Available recombinant glucocerebrosidases are:

Imiglucerase (approved in 1995)

Velaglucerase (approved in 2010)

Taliglucerase alfa (approved in 2012)

Substrate reduction therapy

Miglustat (Zavesca) (approved in 2002) orally available drug that was first approved for Gaucher's Disease in Europe.

Eliglustat (Cerdelga) (approved in 2014) alsoorally available.

For those with type-I and most type-III, treatment, can decrease liver and spleen size, reduce skeletal abnormalities and reverse other manifestations.

Other Specific Treatments

Gene Therapy

Lentiviral vector gene transfer techniques have been used in mouse models of GD with promising results, but this approach is still at the basic research stage

Molecular Chaperones

Molecular chaperones can therefore help the production of functional enzymes.The development of this type of treatment for GD is still in the early stages.