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Gaucher Disease (Glucocerebrosidase Deficiency)

Background

Gaucher Disease is a lysosomal storage disorder defined by glucocerebrosidase deficiency, also known as glucosylceramidase or acid beta-glucosidase (ABG) deficiency. It is a sphingolipid degradation disease. This deficiency leads to the accumulation of glucocerebroside (a lipid) within the lysosomes of the monocyte-macrophage system. Cells become enlarged and have irregular nuclei due to the excess glucocerebroside. These Gaucher Cells are found in organs and tissues and create multi-system dysfunction by displacing healthy cells. There is a wide range in severity and age of onset, but splenomegaly is the common symptom among all types of Gaucher Disease.

Clinical

There are three clinical types of Gaucher Disease, based on the presence or absence of central nervous system (CNS) involvement. Type 1 is the most common form of Gaucher Disease, with a variable age of onset and severity of symptoms. Mild forms may not be diagnosed until adulthood. Type 1 is clinically distinct from the other forms in that there is no neurological involvement. Gaucher Cells infiltrate bone marrow and visceral organs (commonly the liver and spleen) causing blockages within organ tissues. This leads to hepatosplenomegaly along with anemia, thrombocytopenia, and immunologic abnormalities. Children tend to be short-statured and have delayed puberty due to the energy needed to maintain massively enlarged organs. Patients experience bruising, fatigue, and bone crises; skeletal deformations include Erlenmeyer Flask-shaped femurs and thoracic kyphosis. Lung disease can occur when Gaucher Cells infiltrate pulmonary tract and hypoxia is often found. Cardiovascular and dermatologic symptoms have also been reported. Gaucher Cells are not found in the brain or nervous system. There is a normal life expectancy with this phenotype. The incidence of Type 1 is 1 in 40,000 across all ethnicities. There is a higher frequency among the Ashkenazi Jewish population (1 in 1,000 incidence, 1 in 15 are carriers).

Type 2 is marked by neurological involvement. Symptoms appear within the first few months of life; they are generally severe and progress rapidly. Though the first clinical sign may be asymptomatic hepatosplenomegaly, neurological complications (strabismus, hypertonia, cognitive impairment, ataxia, seizures, pyramidal tract involvement, and bulbar dysfunction) will appear soon after. Babies exhibit failure to thrive, have swallowing difficulties and stridor due to laryngospasm. Icthyosiform is commonly found in Type 2 patients. The classic symptom triad is: trismus, strabismus, opisthotonus. Death can occur from aspiration pneumonia or apnea due to psychomotor degeneration and brainstem involvement. Survival is usually less than 2 years of age. The incidence of Type 2 is 1 in 100,000 across all ethnicities.

Type 3 is a combination of Type 1 and Type 2 symptoms, and typically presents in childhood. It has similar organ involvement as Type 1 but can progress more rapidly and be more clinically severe. Like Type 2, there are neurological manifestations with Type 3, but they present at an older age than Type 2 and progress more slowly (developmental delay, ataxia, dementia, oculomotor abnormalities, seizures, progressive spasticity). Since the CNS is involved, patients' lifespan is significantly decreased. The incidence of Type 3 is 1 in 50-100,000 across all ethnicities. Type 3 occurs most often in the Norbottnian region of Sweden, possibly due to founder effect. They have an incidence of 1 in 50,000.

Testing

The pathological hallmark is the presence of Gaucher Cells in the macrophage-monocyte system, particularly within bone marrow. Gaucher Cells have a wrinkled tissue paper appearance. Confirmation of Gaucher Disease includes an enzyme assay that measures the activity level of glucocerebrosidase in peripheral blood leukocytes. Less than 15% activity is considered positive for Gaucher Disease. The amount of residual enzymatic activity does not accurately predict disease subtype or severity. Carriers have approximately 50% normal activity but there is a 20% overlap with the range for normal activity for non-carriers. Therefore, enzymatic testing is not reliable for carrier testing.

Patients with abnormal screening results for Gaucher Disease should initially be evaluated for hepatosplenomegaly and neurological involvement. Evaluation for neurological involvement is essential to diagnosis Gaucher Type 2 and 3. The lack of CNS involvement diagnoses Gaucher Type 1. Certain mutations are useful in predicting the potential for neurological involvement, but DNA analysis should not be the only confirmatory method. Bone marrow aspiration is no longer a recommended method to confirm Gaucher Disease. Niemann-Pick Disease and Parkinson Disease should be ruled out when diagnosing Gaucher Disease.

Treatment

Enzyme Replacement Therapy (ERT) is shown to be a promising treatment for Gaucher Types 1 and 3. It is typically administered on an out-patient basis. Significant reversal of visceral and hematological manifestations has been observed. Improvements in physical growth and puberty have been seen as well. However, skeletal abnormalities are slow to respond; progress is usually not detectable for at least a year after ERT has been started. Pulmonary symptoms are essentially resistant to ERT.

Due to the unpredictability of the disease course and the patient's response to ERT, the administration of this and any treatment should be closely supervised by a metabolic geneticist specializing in Gaucher Disease. ERT should be started once clinical symptoms appear; presymptomatic ERT is controversial due to cost and unproven efficacy. Also, patients should be evaluated for allergic reactions to the therapy. Allergies can be alleviated with pre-treatment medications.

ERT has not been found to be an effective treatment for the neurological manifestations of Type 2 or Type 3. There is no disease-specific treatment available at this time for Type 2. Dietary changes do not affect the disease course, but children may need high-caloric diets to maintain energy levels in the presence of organomegaly. The FDA has recently approved an alternate form of ERT (recombinant ERT) but its use should be determined by a metabolic/genetic specialist.

Inheritance

More than 200 mutations have been identified for Gaucher Disease (chromosome 1q22), however, there is not a reliable genotype-phenotype correlation. The six most common mutations (N370S, L444P, V394L, c.84insG, IVS2+1G>A, R496H) in the Ashkenazi Jewish population account for 90-95% of the alleles in this population. It is estimated that 60% of people of Ashkenazi Jewish descent are homozygous for the mild N370S mutation for Type 1. Many patients with this genotype do not seek medical attention and may not be formally diagnosed; therefore it is believed that the disease frequency is underestimated. This allele accounts for 75%of the disease alleles in the Ashkenazi population. A rare subgroup of Type 3 is homozygous for D409H mutation. They have corneal clouding and cardiac calcifications. The Norbottnian region of Sweden has another rare subgroup of Type 3 patients who are homozygous for L444P mutation. These patients present in early childhood.

This disorder follows an autosomal recessive inheritance pattern; affected patients have two copies of a disease gene (or mutation). People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

As with all genetic diseases, genetic counseling is appropriate to help families understand recurrence risks and ensure that they receive proper evaluation and care.

References

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