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GENOMICS

Pompe Disease (Glycogen Storage Disease II)

Background

Pompe Disease is a lysosomal storage disorder that is the result of a defect in acid alpha-glucosidase (GAA) production, the enzyme needed to metabolize glycogen within lysosomes. This defect leads to an accumulation of glycogen in lysosomes, with a profound effect on cardiac and skeletal muscle. The cellular pathway for glycogen degradation is intact, therefore hypoglycemia and metabolic acidosis are not found, unlike other glycogen storage disorders. Pompe, also known as Acid Maltase Deficiency (AMD), Glycogen Storage Disease II, or Type II Glucogenosis, has an incidence of 1 in 40,000 across all ethnicities.

Clinical

There are two forms of Pompe: infantile-onset and late-onset. There is a wide spectrum of clinical severity. Over time, all forms of Pompe will progress to a severe clinical phenotype, including progressive muscle weakness and respiratory insufficiency. Infantile-onset is defined by the presence of clinical symptoms beginning at birth up to 12 months of age. There is a rapid progression of these symptoms, which include: severe hypotonia (floppy baby) which leads to progressive muscle weakness, feeding difficulties (failure to thrive), cardiomyopathy, moderate hepatomegaly, macroglossia, delayed developmental milestones, and respiratory insufficiency with frequent infections. Cardiomyopathy is seen almost exclusively in the infantile form. Death occurs from cardiorespiratory failure by 12 months of age.

The late-onset form can occur during childhood through late adulthood. The first sign is usually progressive muscle weakness, especially in the trunk, lower limbs and diaphragm, which results in exercise intolerance, gait abnormalities, and scoliosis, lordosis or kyphosis. Other symptoms include respiratory insufficiency with frequent infections, sleep apnea, hepatomegaly, and decreased deep tendon reflexes. Children can exhibit delayed motor milestones. Symptoms develop more slowly than the infantile form, but they will still become clinically severe. Death occurs from respiratory failure. It is extremely rare to have cardiac involvement in the late-onset form.

Testing

Enzyme analysis results will show a decreased or absent alpha-glucosidase activity level, typically <1% (in infants) to 40% of normal levels. This is usually measured in skin fibroblasts or lymphocytes, but can also be done through muscle biopsy. Blood-based assays cannot distinguish between the infantile-onset and late-onset forms, therefore, multiple testing methods are used to confirm the diagnosis. Patients should also be assessed for cardiomyopathy. Gene analysis can be performed but should not be the only method of confirming the diagnosis.

Treatment

Enzyme replacement therapy (ERT) is available to treat the symptoms of Pompe Disease, but there is no known cure at this time. Early intervention has been shown to provide the best chance for a positive outcome. ERT should be started as soon as possible after diagnosis of the infantile form; it should be started at the first sign of muscle weakness for the late-onset form. ERT has been found to decrease the severity and delay onset of symptoms but mortality is not changed. Bone marrow transplant has not been shown to be effective for Pompe Disease. Additional treatment includes management of symptoms.

Because the diagnosis and treatment of Pompe Disease is complex, the pediatrician is advised to manage the patient in close collaboration with a metabolic geneticist who specializes in lysosomal storage disorders.

Inheritance

Pompe Disease (chromosome 17q25.3) 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

Hirschhorn R, Reuser AJJ. Glycogen Storage Disease Type II: Acid α-Glucosidase (Acid Maltase) Deficiency. In: Scriver, C.R. and Kaufman, S. The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al. McGraw-Hill. Chapter 135.