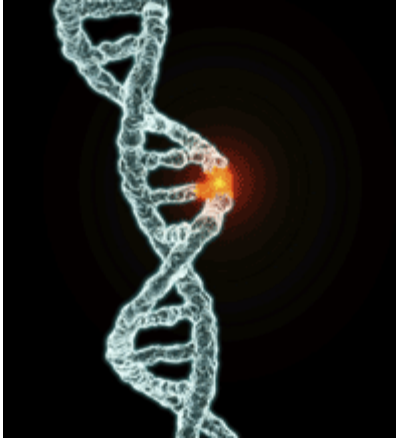


Genetics in Special Education Series

October 2010



Genetic disorders presented in this issue:

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Gaucher Disease

What is Gaucher Disease?

Gaucher disease is an autosomal recessive inherited disorder of metabolism where a type of fat (lipid) called glucocerebroside cannot be adequately degraded. Normally, the body makes an enzyme called glucocerebrosidase that breaks down and recycles glucocerebroside - a normal part of the cell membrane. People who have Gaucher disease do not make enough glucocerebrosidase. This causes the specific lipid to build up in the liver, spleen, bone marrow and nervous system interfering with normal functioning.

There are three recognized Types of Gaucher disease and each has a wide range of symptoms. Type 1 is the most common, does not affect the nervous system and may appear early in life or adulthood. Many people with Type 1 Gaucher disease have findings that are so mild that they never have any problems from the disorder. Type 2 and 3 do affect the nervous system. Type 2 causes serious medical problems beginning in infancy, while Type 3 progresses more slowly than Type 2. There are also other more unusual forms that are hard to categorize within the three Types.

Gaucher disease is caused by changes (mutations) in a single gene called GBA. Mutations in the GBA gene cause very low levels of glucocerebrosidase. A person who has Gaucher disease inherits a mutated copy of the GBA gene from each of his/her parents.

Gaucher disease occurs in about 1 in 50,000 to 1 in 100,000 individuals in the general population. Type 1 is found more frequently among individuals who are of Ashkenazi Jewish ancestry. Type 1 Gaucher disease is present 1 in 500 to 1 in 1000 people of Ashkenazi Jewish ancestry, and approximately 1 in 14 Ashkenazi Jews is a carrier. Type 2 and Type 3 Gaucher disease are not as common.

What are the symptoms of Gaucher disease?

Symptoms of Gaucher disease vary greatly among those who have the disorder. The major clinical symptoms include:

- Enlargement of the liver and spleen (hepatosplenomegaly).
- A low number of red blood cells (anemia).
- Easy bruising caused, in part, by a low level of platelets (thrombocytopenia).
- Bone disease (bone pain and fractures).

Other symptoms depending on the type of Gaucher disease include heart, lung and nervous system problems.

The symptoms of Type 1 Gaucher disease include bone disease, hepatosplenomegaly, anemia and thrombocytopenia, and lung disease.

The symptoms in Type 2 and Type 3 Gaucher disease include those of Type 1 and other problems involving the nervous system such as eye problems, seizures and brain damage. In Type 2 Gaucher disease, severe medical problems begin in infancy. These individuals usually do not live beyond age two. There are also some patients with Type 2 Gaucher disease that die in the newborn period, often with severe skin problems or excessive fluid accumulation (hydrops). Individuals with Type 3 Gaucher disease may have symptoms before they are two years old, but often have a more slowly progressive disease process and the extent of brain involvement is quite variable. They usually have slowing of their horizontal eye movements.

Recently it has been observed that both patients with Gaucher disease and Gaucher carriers have an increased risk of developing Parkinson disease and related disorders.

How is Gaucher disease diagnosed?

The diagnosis of Gaucher disease is based on clinical symptoms and laboratory testing. A diagnosis of Gaucher disease is suspected in individuals who have bone problems, enlarged liver and spleen (hepatosplenomegaly), changes in red blood cell levels, easy bleeding and bruising from low platelets or signs of nervous system problems.

Laboratory testing involves a blood test to measure the activity level of the enzyme glucocerebrosidase. Individuals who have Gaucher disease have very low levels of this enzyme activity. A second type of laboratory test involves DNA analysis of the GBA gene for the four most common GBA mutations. Both enzyme and DNA testing can be done prenatally. A bone marrow or liver biopsy is not necessary to establish the diagnosis.

When the specific gene mutation causing Gaucher disease is known in a family, DNA testing can be used to accurately identify carriers. However it is often not possible to predict the patient's clinical course based upon DNA testing.

What is the treatment for Gaucher disease?

Enzyme replacement therapy is now available as an effective treatment for individuals who have symptoms from Gaucher disease. The treatment involves giving a modified form of the enzyme, glucocerebrosidase, by intravenous infusion every two weeks. Enzyme replacement therapy helps to stop progression and often reverse many of the symptoms of Gaucher disease, but does not affect the nervous system involvement.

Several other therapies including oral treatments are in various stages of development.

Other treatments that have been required include: removal of the spleen (splenectomy); blood transfusions; pain medications; and joint replacement surgery.

Is Gaucher disease inherited?

Gaucher disease is inherited in families in an autosomal recessive manner. Normally, a person has two copies of the genes that provide instructions for making the enzyme, glucocerebrosidase. For most individuals, both genes work properly. When one of the two genes is not functioning properly, the person is a carrier. Carriers do not have Gaucher disease because they have one normally functioning gene that makes enough of the enzyme to carry out normal body functions. When an individual inherits an altered gene from each carrier parent, he or she has Gaucher disease.

Carrier parents have, with each pregnancy, a 1 in 4 (25 percent) chance to have a baby born with Gaucher disease; a 1 in 2 (50 percent) chance to have a child who is a carrier like themselves; and a 1 in 4 (25 percent) chance to have a child who is neither affected nor a carrier.

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Progeria

What is Progeria?

What do we know about heredity and progeria?

Progeria is an extremely rare genetic disease of childhood characterized by dramatic, premature aging. The condition, which derives its name from "geras," the Greek word for old age, is estimated to affect one in 4 million newborns worldwide.

The most severe form of the disease is Hutchinson-Gilford progeria syndrome, recognizing the efforts of Dr. Jonathan Hutchinson, who first described the disease in 1886, and Dr. Hastings Gilford who did the same in 1904.

As newborns, children with progeria usually appear normal. However, within a year, their growth rate slows and they soon are much shorter and weigh much less than others their age. While possessing normal intelligence, affected children develop a distinctive appearance characterized by baldness, aged-looking skin, a pinched nose, and a small face and jaw relative to head size. They also often suffer from symptoms typically seen in much older people:

- stiffness of joints
- hip dislocations
- severe, progressive cardiovascular disease

However, various other features associated with the normal aging process, such as cataracts and osteoarthritis, are not seen in children with progeria

Some children with progeria have undergone coronary artery bypass surgery and/or angioplasty in attempts to ease the life-threatening cardiovascular complications caused by progressive atherosclerosis. However, there currently is no treatment or cure for the underlying condition. Death occurs on average at age 13, usually from heart attack or stroke.

In 2003, NHGRI researchers, together with colleagues at the Progeria Research Foundation, the New York State Institute for Basic Research in Developmental Disabilities, and the University of Michigan, discovered that Hutchinson-Gilford progeria is caused by a tiny, point mutation in a single gene, known as lamin A (LMNA). Parents and siblings of children with progeria are virtually never affected by the disease. In accordance with this clinical observation, the genetic mutation appears in nearly all instances to occur in the sperm prior to conception. It is remarkable that nearly all cases are found to arise from the substitution of just one base pair among the approximately 25,000 DNA base pairs that make up the LMNA gene.

The LMNA gene codes for two proteins, lamin A and lamin C, that are known to play a key role in stabilizing the inner membrane of the cell's nucleus. In laboratory tests involving cells taken from progeria patients, researchers have found that the mutation responsible for Hutchinson-Gilford progeria causes the LMNA gene to produce an abnormal form of the lamin A protein. That abnormal protein appears to destabilize the cell's nuclear membrane in a way that may be particularly harmful to tissues routinely subjected to intense physical force, such as the cardiovascular and musculoskeletal systems.

Interestingly, different mutations in the same LMNA gene have been shown to be responsible for at least a half-dozen other genetic disorders, including two rare forms of muscular dystrophy.

In addition to its implications for diagnosis and possible treatment of progeria, the discovery of the underlying genetics of this model of premature aging may help to shed new light on humans' normal aging process.

Is there a test for progeria?

A genetic test for Hutchinson-Gilford progeria syndrome, also called HGPS, is currently available. In the past, doctors had to base a diagnosis of progeria solely on physical symptoms, such as skin changes and a failure to gain weight, that were not fully apparent until a child's first or second year of life. This genetic test now enables doctors to diagnose a child at a younger age and initiate treatment early in the disease process.

This genetic test for Hutchinson-Gilford progeria syndrome also serves to reassure parents of affected children that their disorder stems from a sporadic genetic mutation and that therefore it is unlikely that any future offspring would have the condition.

To learn more about the genetic test for progeria, go to The Progeria Research Foundation Diagnostic Testing Program

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