Fabry Disease

Synonyms of Fabry Disease

- alpha-galactosidase A deficiency
- Anderson-Fabry disease
- angiokeratoma corporis diffusum
- angiokeratoma diffuse
- ceramide trihexosidase deficiency
- GLA deficiency

Subdivisions of Fabry Disease

- Type 1 Classic
- Type 2 Later-onset

General Discussion

Fabry disease is a rare inherited disorder of lipid (fat) metabolism resulting from the deficient activity of the enzyme, alpha-galactosidase A (α-Gal A). This disorder belongs to a group of diseases known as lysosomal storage disorders. This enzymatic deficiency is caused by mutations (or alterations) in the gene (the *GLA* gene) that instructs cells to make α-Gal A. Lysosomes function as the primary digestive units within cells. Enzymes within lysosomes break down or digest particular compounds and intracellular structures. Alpha-Gal A functions to break down specific complex sugar-lipid molecules called glycolipids, specifically, globotriaosylceramide (GL-3 or Gb3) and related compounds, by removing the terminal galactose sugarfrom the end of the glycolipid molecules. The enzyme deficiency causes a progressive build-up of GL-3 and related glycolipids in the body's cells over years, resulting in signs and symptoms that particularly affect the heart and kidneys.

The *GLA* gene is located on the X-chromosome and, therefore, Fabry disease is inherited as an X-linked disorder, affecting males and females. Males are typically more severely affected, whereas females have variable symptoms and may be asymptomatic or as severely affected as males.

There are two major disease phenotypes: the Type 1 "classic" and Type 2 "later-onset" subtypes. Both lead to renal failure, and/or cardiac disease, and early death (Desnick 2001). Type 1 males have little or no functional α-Gal A enzymatic activity (<1% of normal mean), and marked accumulation of GL-3 and related glycolipids in capillaries

and small blood vessels which cause the major symptoms in childhood or adolescence including the acroparesthesia (excruciating pain in the hands and feet); angiokeratomas (clusters of rash-like discolorations on the skin); anhidrosis or hypohidrosis (absent or markedly decreased sweating); gastrointestinal symptoms including frequent bowel movements, abdominal pain and cramping, and diarrhea; and a characteristic corneal dystrophy (star-burst pattern of the cornea seen by slit-lamp ophthalmologic examination) that does not affect vision (Desnick 2001, Desnick 2009, Germain 2010). With increasing age, the systemic GL-3 deposition, especially in the heart, and kidneys, , leads to left ventricular hypertrophy (LVH) and then hypertrophic cardiomyopathy (HCM), progressive renal insufficiency leading to renal failure, and/or cerebrovascular disease including transient ischemic attacks (TIAs) and stroke. Prior to renal replacement therapy (dialysis and transplantation) and enzyme replacement therapy, the average age of death of affected males was ~40 years (Columbo et al. 1967). The incidence of Type 1 varies with demography and race, males ranging from about ~1 in 18,000 to 1 in 95,000 based on newborn screening studies (Liao 2014, Uribe 2013, Mechtler 2012, Whittman 2012, Scott 2013, Inoue 2013, Hwu 2009, Spada 2006).

In contrast, males with the Type 2 “later-onset” phenotype (previously called cardiac or renal variants) have residual α-Gal A activity, lack GL-3 accumulation in capillaries and small blood vessels, and do not manifest the early manifestations of Type 1 males. They typically present with renal and/or cardiac disease in the third to seventh decades of life. Most Type 2 patients have been identified by enzyme screening patients in cardiac, hemodialysis, renal transplant, and stroke clinics, and recently by newborn screening (e.g., Linthorst 2010, Elliott 2011, Herrera 2013, Baptista 2014). Based on these screening studies, the incidence of Type 2 males varies by demography, ethnicity, and race, but is at least 10 times more frequent than that of Type 1 males from the same region, ethnic group, or race.

Clinical manifestations in Type 1 heterozygous females are variable due to random X-chromosomal inactivation (Dobrovolny 2011) and range from asymptomatic to as severe as Type 1 males (Desnick, 2009). Type 2 heterozygotes may be asymptomatic or develop renal or cardiac manifestations later in life; they typically lack the characteristic corneal findings or other early Type 1 manifestations (Desnick, 2009, 2014). However, the frequency of manifestations in Type 2 heterozygotes has not been systematically investigated to date.

Signs & Symptoms

The signs and symptoms of males with Type 1 classic Fabry disease usually begin in childhood or adolescence. Symptoms increase with age due to the progressive glycolipid accumulation in the vascular system, kidneys and heart leading to kidney failure, heart disease, and/or strokes. Early and progressive clinical symptoms include:

1. Acroparesthesia. Pain is an early symptom of the classic subtype. Affected individuals may experience episodes of severe burning pain in the hands and the feet

(acroparesthesia). Severe episodes of pain (Fabry's crises) may last for hours to days and are frequently associated with exercise, fatigue, and/or fever.

2. Anhidrosis or hypohidrosis. Type 1 males and some females have decreased or absent sweat production (hypohidrosis or anhidrosis) and discomfort in warm temperatures (heat intolerance).

3. Angiokeratomas. Early symptoms also include the appearance of a reddish to dark-blue skin rash, especially in the area between the hips and the knees. These skin lesions, which vary in color from red to blue-black, may be flat or raised. In some cases, individuals with Fabry disease, especially those with the Type 2 subtype, do not have these characteristic skin lesions.

4. Gastrointestinal problems. Abdominal cramping, frequent bowel movements, and diarrhea may also occur, particularly after a large meal.

5. Corneal dystrophy. Patients with Type 1 Fabry disease have abnormal deposits of glycolipids in their corneas resulting in a characteristic change which can only be seen by an ophthalmologic examination. the eye. These changes do not affect vision. Blood vessels in the eyes may appear twisted (cork screw-like; contorted) and/or enlarged (dilated) due to the glycosphingolipid accumulation in the vessel walls.

6. Additional symptoms. Other symptoms that may be associated with Fabry disease include chronic fatigue, dizziness, headache, generalized weakness, nausea, and/or vomiting, delayed puberty, lack of or sparse hair growth, and rarely malformation of the joints of the fingers. Some Type 1 males have abnormal accumulation of lymph in the feet and legs associated with swelling (lymphedema). In these cases, lymph, a body fluid containing certain white blood cells, fats, and proteins, accumulates outside blood vessels in spaces between cells and drains or flows back into the bloodstream via lymph vessels. Lymphedema results from disruption of lymph's normal drainage due to the glyoclipid accumulation in the lymphatic vessels and lymph nodes.

Signs of progressive organ involvement include:

7. Renal dysfunction. Progressive decrease in renal function is due to the progressive accumulation of GL-3 in the kidneys. There is histological evidence of this accumulation and ensuing cellular and vascular injury to renal tissue beginning in childhood and adolescence Tondel 2008, Najafian 2013, Wijburg 2015. In Type 1 males, decline in kidney function progresses to kidney failure and the need for dialysis or transplantation typically by 35 to 45 years of age. In Type 2 males, kidney involvement typically occurs later. Kidney involvement in female heterozygotes is more variable. Only about 10-15% of Type 1 females develop kidney failure.

8. Cardiac disease. GL-3 deposition can be found in all cardiac tissues, including myocytes, nerves, and coronary arteries. Heart disease includes heart enlargement, typically left ventricular hypertrophy (LVH) leading to hypertrophic cardiomyopathy (HCM), rhythm abnormalities, and heart failure. LVH occurs in about 20% of males and

females with an average age of diagnosis in the early 40s among males and late 40s among females.

9. Cerebrovascular complications. As a result of progressive GL-3 deposition in the small blood vessels in the brain, about 7% of males and 4% of females with Fabry disease, particularly those with the Type 1 phenotype, experience ischemic or hemorrhagic stroke, occurring in the fourth decade of life, and about 2% and 4%, respectively, reporting transient ischemic attacks (TIAs) (Wilcox 2008).

Patients with the Type 2 Later-Onset subtype typically do not have the skin lesions (angiokeratoma), they sweat normally, do not experience the Fabry pain or crises, and do not have heat intolerance or corneal involvement. These individuals develop heart or kidney disease later in adult life.

Causes

Fabry disease is caused by mutations (alterations) in the alpha-galactosidase A (*GLA*) gene located on the X chromosome and is inherited as an X-linked disorder. Chromosomes are found in the nucleus of all body cells. They carry the genetic characteristics of each individual in thousands of specific segments, called “genes”, that span the length of the chromosomes. Each of these genes has a specific function in the body. Human chromosomes are organized in pairs, numbered from 1 through 22, with an unequal 23rd pair of X and Y chromosomes for males and two X chromosomes for females. Individuals inherit one chromosome in each pair from each parent. Females have two X chromosomes, while males have one X chromosome and one Y chromosome. Therefore, in X-linked disorders including Fabry disease, in females disease traits on the X chromosome can be masked by the normal gene on the other X chromosome. More specifically, because only one functioning X chromosome is required in males and females, one of the X chromosomes in each cell of a female is essentially “turned off”, usually in a random pattern (random X chromosome inactivation). This means that in X-linked disorders some cells will have the X chromosome with the mutated gene activated and some will have the X chromosome with the functioning gene activated. Therefore, in Fabry disease the symptoms and severity of organ involvement are dependent on what tissues/organs have the X chromosome with the *GLA* gene mutation activated, and females with Fabry disease may manifest certain, typically more variable features of the disorder. Since males have only one X chromosome, if a male has the X chromosome with the *GLA* gene mutation, he will be affected with the disorder. Therefore, males with Fabry disease are more uniformly affected, whereas females, due to random X-inactivation, may be asymptomatic or as severely affected as males.

Males with X-linked Fabry disease transmit the *GLA* gene mutation to all their daughters, who are heterozygotes, but never to their sons. Females with a mutation causing Fabry disease on X chromosome are referred to as “heterozygotes” and have a 50 percent risk of transmitting the disease to each of their children, both daughters and sons, with each pregnancy.

The *GLA* gene normally instructs the body's cells to make a specific enzyme, alpha-galactosidase A (α-Gal A), which breaks down globotriaocylceramide (GL-3) in the cell's lysosomes. Fabry disease is caused by mutations in the *GLA* gene.There are over 750 mutations in the *GLA* gene that are responsible for Fabry disease, thus, the severity and range of symptoms may vary among individuals depending on the *GLA* mutation in their family. Some mutations cause no or deficient enzyme activity and result in the Type 1 Classic subtype, while other mutations result in a small amount of residual enzyme activity and the Type 2 Later-Onset subtype.. The signs and symptoms of Fabry disease develop due to deficient or low activity of the lysosomal enzyme alpha-galactosidase A (α-Gal A). Patients with the Type 1 Classic subtype, who have no or very low activity levels (less than 1% of normal) of this enzyme, accumulate the sugary-fat glycolipid substances (GL-3 or Gb-3 and related glycolipids) in various tissues of the body, especially small blood vessels, as well as other cells in the heart and kidneys. Patients with the Type 2 Later-Onset subtype have residual enzyme activity (1-10% of normal), and also accumulate GL-3, but to a lesser degree and at a slower rate. They tend to have a somewhat less severe form of the disease, but males with the Type 2 subtype ultimately develop severe cardiac disease and/or renal failure.

Affected Populations

Fabry disease is a rare pan ethnic disorder, meaning that it occurs in all racial and ethnic populations, affecting males and females. It is estimated that Type 1 Classic Fabry disease affects approximately one in 25,000 to 40,000 males. Type 2 Later-onset Fabry disease is more frequent with about 1 in 1,500 to 4,000 males, depending on the demographic, racial, or ethnic population.

Related Disorders

Symptoms of the following disorders can be similar to those of Fabry disease. Comparisons may be useful for a differential diagnosis:

Schindler disease is a rare inherited metabolic disorder characterized by a deficiency of the lysosomal enzyme alpha-N-acetylgalactosaminidase (alpha-NAGA), which leads to an abnormal accumulation of certain complex compounds (glycosphingolipids and oligosaccharides) in many tissues of the body. Schindler disease is inherited as an autosomal recessive disorder. There are three types of Schindler disease. The classical form of the disorder, known as Schindler disease, type I, has an infantile onset. Affected individuals appear to develop normally until approximately one year of age, when they begin to lose previously acquired skills that require the coordination of physical and mental activities (developmental regression). Additional neurological and neuromuscular symptoms may become apparent, including diminished muscle tone (hypotonia) and weakness; involuntary, rapid eye movements (nystagmus); visual impairment; and episodes of uncontrolled electrical activity in the brain (seizures). With continuing disease progression, affected children typically develop restricted movements of certain muscles due to progressively increased muscle rigidity, severe intellectual disability,

hearing and visual impairment, and a lack of response to stimuli in the environment. Type 2 Schindler disease also known as Kanzaki Disease, is the adult-onset form with symptoms presenting in the second or third decade of life. The disorder is characterized by angiokeratoma, a skin lesion and distribution similar to that seen in Type 1 classic Fabry disease. Presentation may also include lymphedema, intellectual impairment, and distinct facial features including mildly coarse features, thick lips, a depressed nasal bridge and an enlarged tip of the nose. Type III Schindler disease is an intermediate form the disorder. Symptoms can range from more serious intellectual impairment, neurological dysfunction and seizures to milder neurological and psychiatric issues such as speech and language delays and mild autism-like symptoms. (For more information on this disorder, choose “Schindler” as your search term in the Rare Disease Database.)

Gaucher disease is one of the most common of the lipid storage diseases and is characterized by the abnormal accumulation of certain fatty substances in various parts of the body. Symptoms develop due to a deficiency in the enzyme glucocerebrosidase and may include enlargement of the liver (hepatomegaly) and spleen (splenomegaly), a general feeling of ill health (malaise), visual difficulties, abdominal swelling, severe bone pain and bone disease. Gaucher disease is inherited as an autosomal recessive trait. (For more information on this disorder, choose “Gaucher” as your search term in the Rare Disease Database.)

Fucosidosis is an extremely rare inherited lysosomal storage disease characterized by a deficiency of the enzyme alpha-L-fucosidase. There are at least two types of fucosidosis (i.e., type 1 and type 2), determined mainly by the severity of the enzyme deficiency and resulting symptoms. The symptoms of fucosidosis Type 1, the most severe form of the disease, may become apparent as early as six months of age. Symptoms may include a skin lesion similar to Fabry disease (angiokeratoma), progressive deterioration of the brain and spinal cord (central nervous system), intellectual disability, loss of previously acquired intellectual skills, and growth retardation leading to short stature. Other physical findings and features become apparent over time, including multiple deformities of the bones (dysostosis multiplex), coarse facial features, enlargement of the heart (cardiomegaly), enlargement of the liver and spleen (hepatosplenomegaly), and/or episodes of uncontrolled electrical activity in the brain (seizures). Additional symptoms may include increased or decreased perspiration and/or malfunction of the gallbladder and/or salivary glands. Fucosidosis is inherited as an autosomal recessive trait. (For more information on this disorder, choose “fucosidosis” as your search term in the Rare Disease Database.)

Erythromelalgia is a rare condition that primarily affects the feet and, less commonly, the hands. It is characterized by intense burning pain of affected extremities, severe redness, and increased skin temperature that may be episodic or almost continuous in nature.

Diagnosis

The diagnosis of Fabry disease is frequently made by physicians who recognize the pain in the extremities, absent or decreased sweating (anhidrosis or hypohidrosis),

typical skin lesions (angiokeratoma), gastrointestinal abnormalities, corneal involvement, renal insufficiency, and heart symptoms present in childhood, adolescence or adulthood. The diagnosis is confirmed by demonstrating the enzyme deficiency in males and by identifying the specific alpha-galactosidase A gene mutation in males and females.

Prenatal diagnosis of Fabry disease is made by measuring alpha-galactosidase A activity and demonstrating the family-specific alpha-galactosidase A mutation in cells that are removed from the amniotic fluid surrounding the developing fetus at about 15 weeks of pregnancy. Early prenatal diagnosis at about 10 weeks of pregnancy can be made by alpha-galactosidase A enzyme and gene analyses of villi obtained by chronic villus sampling.

Standard Therapies

Treatment

The U.S. Food and Drug Administration (FDA) approved an enzyme replacement therapy called agalsidase beta (Fabrazyme®) as a treatment for patients with Fabry disease in 2003. Fabrazyme®, which is administered intravenously, is a form of the human enzyme produced by recombinant DNA technology. This replacement of the missing enzyme reduces the accumulation of the accumulated glycolipids in cells, including the cells of the kidney and other organs. Double-blind, placebo-controlled Phase 3 and 4 clinical trials have demonstrated the safety and effectiveness of Fabrazyme® enzyme replacement therapy for Fabry disease.

Fabrazyme® had been designated an orphan drug and was approved by the FDA under an accelerated or early approval mechanism. One of the requirements of the accelerated approval is that the sponsor complete a post-market study verifying that patients will benefit from the product, which was accomplished and reported in 2007.

For additional information on Fabrazyme®, contact the manufacturer:

Genzyme Corporation

One Kendall Square

Cambridge, MA, 02139

Tel: (617) 252-7500

Fax: (617) 252-7600

Low doses of diphenylhydantoin, carbamazepine, or neurontin, may help to prevent the acroparesthesias- the discomfort in the hands and feet. Other later complications (e.g., kidney failure or heart problems) should be treated symptomatically after consultation with a physician who is experienced in the care of people with Fabry disease. Hemodialysis and kidney (renal) transplantation may be necessary in cases that have progressed to kidney failure.

Genetic counseling will be of benefit for affected individuals and their families. Other treatment is supportive.

Investigational Therapies

The FDA has granted orphan drug status to AT1001, manufactured by Amicus Therapeutics, Inc., for the treatment of Fabry disease. This oral therapy was designed to enhance an individual's residual alpha-galactosidase A activity. Studies are being conducted to determine its safety and effectiveness. For information, contact:

Amicus Therapeutics, Inc.
6 Cedar Brook Drive
Cranbury, NJ 08512
Phone: (609) 662-2000
Fax: (609) 662-2001
Website: www.Amicustherapeutics.com
Email: info@amicustherapeutics.com

Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials sponsored by private sources, contact:

www.centerwatch.com

Contact for additional information about Fabry disease:

International Center for Fabry Disease
Icahn School of Medicine at Mount Sinai
Fifth Avenue at 100th Street
New York, NY 10029
(212) 659-6700
Toll-free: 1-866-FABRY-MD

NORD Member Organizations

- CLIMB (Children Living with Inherited Metabolic Diseases)
  - Climb Building
  - 176 Nantwich Road
  - Crewe, CW2 6BG United Kingdom
  - Phone: 4408452412173
  - Email: enquiries@climb.org.uk
  - Website: http://www.CLIMB.org.uk
- Proyecto Pide un Deseo México, i.a.p.
  - Altadena #59-501
  - Nápoles

- Benito Juárez, 03810 México, D.F.
- Phone: 525555432447
- Email: info@pideundeseo.org
- Website: http://www.pideundeseo.org

Other Organizations Specifically Focused on Fabry Disease

- Fabry Support & Information Group
  - 108 NE 2nd Street
  - Suite C
  - Concordia, MO 64020-0510 USA
  - Phone: (660) 463-1355
  - Email: info@fabry.org
  - Website: http://www.fabry.org
- Instituto de Errores Innatos del Metabolismo
  - Carrera 7 No 40 - 62
  - Bogota, Colombia
  - Phone: (571) 320-8320
  - Email: abarrera@javeriana.edu.co
  - Website: http://www.javeriana.edu.co/ieim/programas_ieim.htm
- International Center for Fabry Disease
  - Mount Sinai School of Medicine
  - Fifth Avenue at 100th Street
  - New York, NY 10029 USA
  - Phone: (212) 659-6700
  - Toll-free: (866) 322-7963
  - Email: fabry.disease@mssm.edu
  - Website: http://www.mssm.edu/research/programs/international-center-for-fabry-disease
- National Fabry Disease Foundation
  - 4301 Connecticut Ave. N.W., Suite 404
  - Washington, DC 20008-2369
  - Toll-free: (800) 651-9131
  - Email: info@fabrydisease.org
  - Website: http://www.fabrydisease.org/

References

TEXTBOOKS

Desnick R, Ioannou Y, Eng C. Alpha-Galactosidase A deficiency: Fabry disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease.8th ed. New York, NY: McGraw-Hill; 2001:3733-3774.