Fabry Disease & Children

Identification and Diagnosis of a Silently Progressive, Increasingly Debilitating, Often Life-Threatening Genetic Disorder

A Guide for Physicians

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Would You Recognize a Child with Fabry Disease?

Pain in the hands and feet. Heat intolerance. GI problems. The early signs and symptoms of Fabry disease are often mistaken for other disorders, or dismissed as "growing pains" or attempts to stay home from school. Taken together, however, they could indicate the presence of a progressive genetic disorder that may cause life-threatening complications later in life.

Fabry disease affects an estimated 1 in every 40,000 males and 117,000 live births.[1,2] While some physicians may never see a patient with Fabry disease, others will see many—where there is one patient, there are often brothers, sisters, or other family members affected by the disorder.

Intervention by an informed physician can lead to a definitive diagnosis for children with seemingly unrelated and troubling symptoms. These symptoms may lead to premature death from renal, cardiac, or cerebrovascular complications in adulthood.

By recognizing the early signs and symptoms, physicians have the opportunity to identify Fabry disease earlier in the disease course, and to initiate appropriate intervention.

Fabry Disease Overview

Silently Progressive.
Increasingly Debilitating.
Often Life-Threatening.

- Fabry disease is a multisystemic genetic disorder that ultimately results in irreversible, potentially life-threatening disease of the kidney, heart, and brain.
- The disease is characterized by the progressive and unrelenting cellular accumulation of a lipid substrate called globotriaosylceramide (or GL-3).
- Ongoing build-up of this substance is caused by deficiency of the lysosomal enzyme alpha-galactosidase A (or α-GAL), which usually metabolizes GL-3 and keeps it from accumulating.
- Without enough of this essential enzyme, GL-3 accumulates in the lysosomes of most cell types over the course of a lifetime, often causing debilitating symptoms in childhood and adolescence and potentially irreversible tissue damage by adulthood.

Diagnosis before these signs and symptoms occur enables disease management to begin sooner.

Progressive Manifestations

In Fabry disease, GL-3 substrate builds up in the walls of blood vessels and other tissues over many years, causing progressive damage.

Early manifestations (such as pain in the extremities, hypohidrosis, and a skin rash known as angiokeratomas) can progress into more serious complications such as renal insufficiency, neurologic manifestations, cardiovascular disease, and cardiac dysfunction.

GL-3 accumulation in Fabry disease can begin before birth and continues over a lifetime.

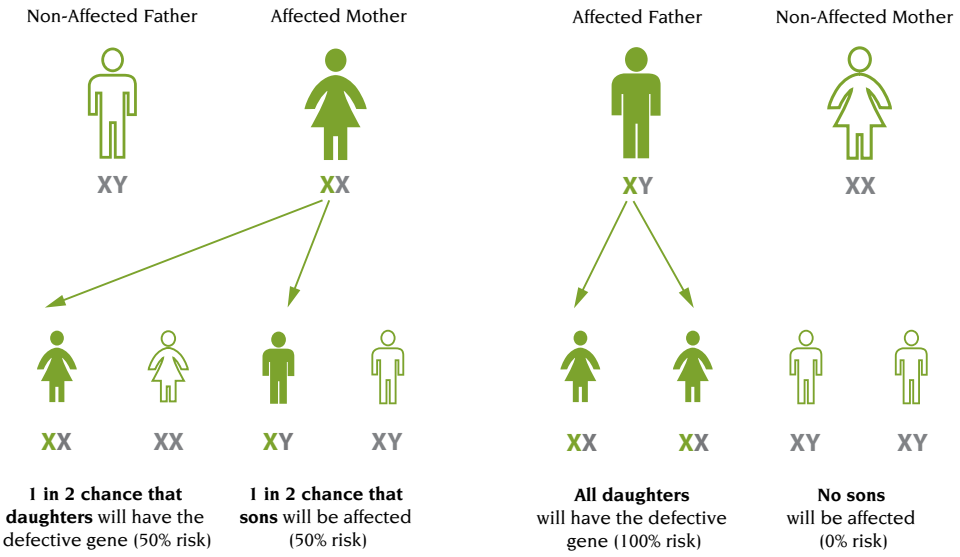
Symptoms	Childhood	Adolescence	Adulthood
Episodic pain crises	●	●	●
Neuropathic pain	●	●	●
Hypohidrosis/anhidrosis	●	●	●
Corneal and lenticular opacities	●	●	●
Recurrent fever	●	●	●
Heat and cold intolerance	●	●	●
Psychosocial manifestations	●	●	●
Gastrointestinal distress	●	●	●
Proteinuria		●	●
Angiokeratomas		●	●
Fatigue		●	●
Renal insufficiency			●
Neurological complications			●
Cerebrovascular disease			●
Cardiac dysfunction			●
Hearing loss and tinnitus			●

Inheritance

Fabry disease is an X-linked disorder. Males with the defective gene are always affected. Females with the defective gene are affected to varying degrees due to random X inactivation (lyonization), which will be discussed in more detail, since it is critical to understanding Fabry disease in women.

- Males who inherit a mutated α-GAL gene on their X chromosome will be affected by Fabry disease (because they only have one X chromosome).
- Females who inherit a mutated α-GAL gene on one of their two X chromosomes may have disease manifestations to varying degrees.
- Females with Fabry disease are heterozygotes because they have two X chromosomes, only one of which in each cell has the mutated α-GAL gene.

Because Fabry disease is X-linked, there is no male-to-male transmission. Males with a defective gene pass it on to none of their sons and all of their daughters. These heterozygous females have a fifty percent chance with each pregnancy of passing on the defective gene to each of their offspring.



A medical genetic counselor can assist in developing a medical family pedigree to identify other family members at risk of Fabry disease, and in directing families to diagnostic, medical, and support services.

Signs and Symptoms of Fabry Disease

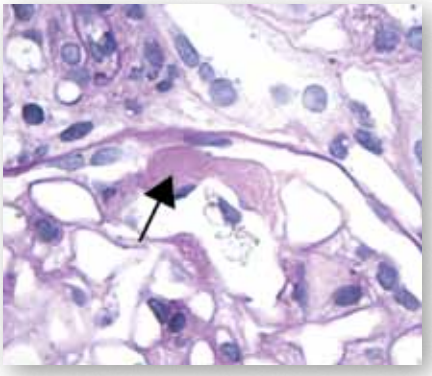
The early signs and symptoms of Fabry disease can make everyday childhood activities difficult, uncomfortable, or even impossible for some children. Since Fabry disease is progressive, GL-3 accumulation can lead to serious organ involvement in late adolescence and adulthood.

Presentation	Description
Chronic and/or acute pain	Children with Fabry disease may experience chronic tingling, burning pain and discomfort in the palms of the hands and soles of the feet (acroparesthesia) as well as episodes of acute pain, typically beginning in the extremities and radiating inward, lasting for minutes to several days.[1]
Temperature sensitivity	Intolerance to heat and cold.
Hearing issues	Hearing loss and tinnitus (ringing in the ears) may occur in older children with Fabry disease.
Skin lesions	Angiokeratomas, clusters of dark red skin lesions that do not blanch with pressure, may be distributed primarily on the buttocks, groin, umbilicus, and upper thighs of children with Fabry disease.
Lack of sweating	Many children with Fabry disease may experience hypohidrosis (diminished sweating) or anhidrosis (lack of sweating).
GI complaints	Pain after eating, abdominal cramping, nausea, and diarrhea.[3]
Ocular signs	Children with Fabry disease may have whorl-like corneal opacities (visible through slit-lamp) that typically do not impair vision,[1,3] vascular lesions of the conjunctiva and retina, and lens opacities.
Excessive protein in the urine	Protein may appear in the urine during childhood and adolescence. Proteinuria and other signs of renal impairment may increase with age.[1]
Psychosocial issues	Children with Fabry disease often demonstrate psychosocial trends common to other chronic illnesses, including clinical depression, denial of clinical symptoms, and feelings of alienation and loneliness.

According to the Genzyme Fabry Registry, an international database of information on Fabry disease patients, boys with Fabry disease first experience symptom onset at a median age of 6.0 years (n=123), compared to 8.1 years for girls (n=127).[4] The median age at diagnosis was 7.2 years for boys and 7.8 years for girls.[4]

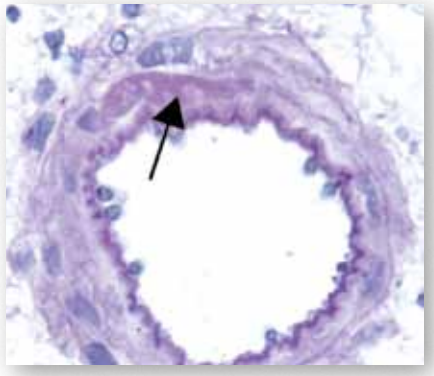
We are beginning to understand how early renal and cardiac abnormalities, in particular, can occur.

A small study of symptomatic patients aged 7 to 18 years demonstrated that glomerular and vascular changes were present even before progression to overt proteinuria and decreased glomerular filtration rate.[5]



Glomerular changes in 7-year-old patient with Fabry disease.[5]

Renal biopsy specimen — arrow points to glomerular hyaline.

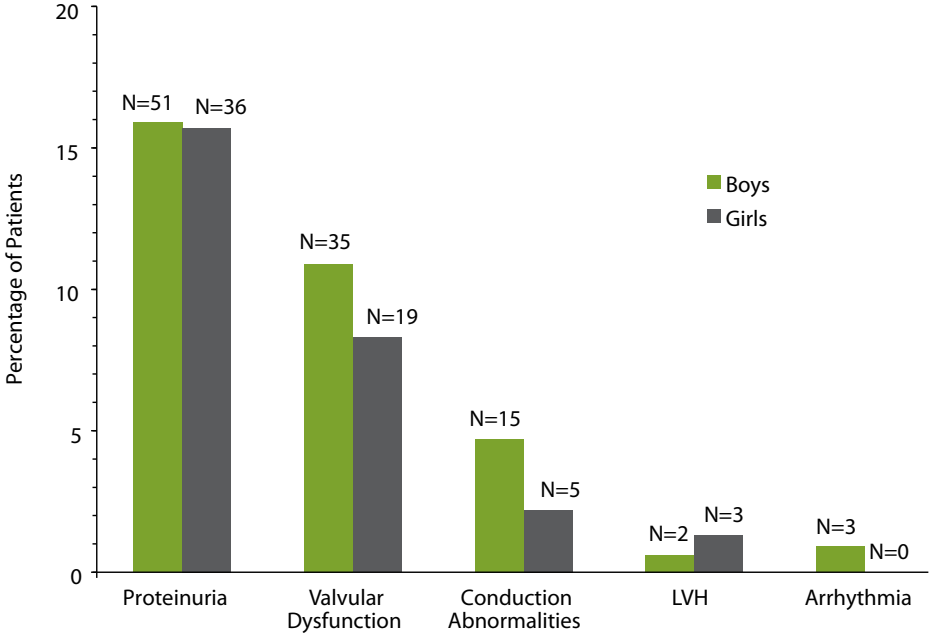


Arteriopathy in an 11-year-old patient with Fabry disease.[5]

Renal biopsy specimen — arrow points to hyaline-like material in the media of a small artery.

Data from the Fabry Registry indicate children with Fabry disease can experience renal and cardiac manifestations.[6] In the figure to the right, data are for patients who were <18 years old at the time they enrolled in the Fabry Registry. Percentages were calculated based on the number of pediatric patients for whom urinary protein or cardiac examination data were available. Proteinuria was defined as a urinary protein:urinary creatinine ratio ≥0.3 or urinary protein levels ≥0.3g/day. The number of patients in each group is indicated above each bar.

Children with Fabry Disease Experience Renal and Cardiac Manifestations[6]



Additionally, the 2011 Fabry Registry Annual Report documented that 13 of 83 males (16%) and 2 of 54 females (4%) experienced a cardiovascular event before age 35.[7]

These findings underscore the concern that Fabry disease be accurately identified and effectively managed as early as possible in a patient's life – before potentially irreversible damage occurs. Unfortunately, diagnosis often occurs years after symptom onset.

Patients with
Fabry disease
as young as
age 16
can experience
renal failure.[8]

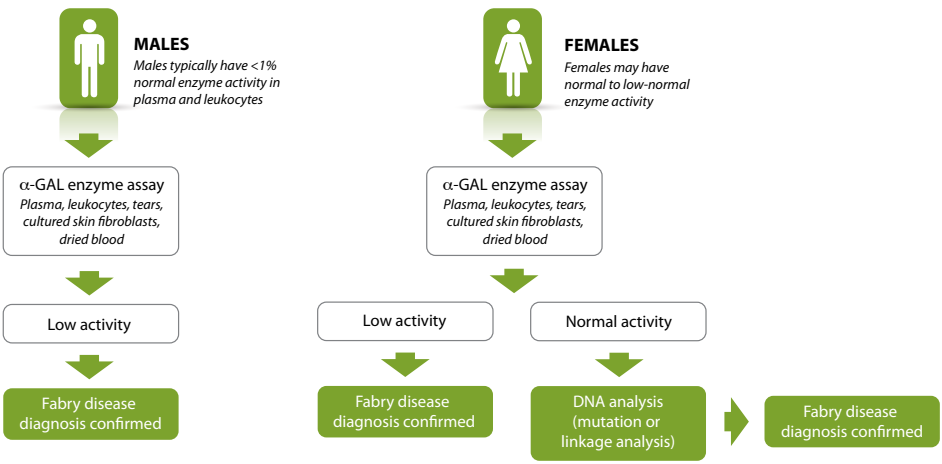
Diagnosing Fabry Disease

Making a Clinical Diagnosis

Fabry disease may be suspected in children based on the signs and symptoms discussed on the previous pages, including the characteristic angiokeratomas and corneal whorling (visible through slit-lamp ophthalmoscopy).

Confirming the Diagnosis

- In males, definitive diagnosis can be made by assaying for deficient α-GAL enzyme activity in plasma, leukocytes, tears, biopsied tissue or dried blood.
- Females, on the other hand, may have enzyme activity in the normal to low-normal range. If a female is suspected to have Fabry, and enzyme assay reveals normal activity, Fabry disease cannot be ruled out. She should also receive DNA analysis (either mutation analysis or linkage analysis, depending on whether the family mutation is known).
- A number of laboratories across the United States and worldwide perform diagnostic testing for Fabry disease.



Children with a known familial history of Fabry disease should be tested regardless of whether symptoms are present.

Managing the Symptoms of Fabry Disease

Because Fabry disease affects multiple organ systems, a multidisciplinary team (pediatrician, geneticist, genetic counselor, gastroenterologist, nephrologist, neurologist, dermatologist, ophthalmologist, cardiologist) may be needed to manage it effectively.

The subsections below outline some common practices in addressing the symptoms of Fabry disease.

It is especially important that kidney complications be managed as early as possible, as they may result in irreversible damage.

Pain

Patients with frequent and severe pain may benefit from prophylactic therapy with medication. Lifestyle changes that may help in symptom management include avoiding stimuli that precipitate pain and increasing consumption of liquids.[3,9]

Renal Manifestations

Mild reduction in renal function may be managed in part by a low-sodium, low-protein diet.

Gastrointestinal Manifestations

Gastrointestinal symptoms may improve with a low-fat diet.

Psychosocial Manifestations

Emotional support and family counseling can be an integral part of patient care.[9] Guilt, denial, and depression are some of the emotions family members may struggle with. Contact with other patients and families who are coping with similar issues may be beneficial. (See the Fabry Disease Resources section on page 12 for a list of patient organizations.)

Facing the Future: Living with Fabry

The Challenges Children with Fabry Disease May Face

Missing gym class because of heat/exercise intolerance, embarrassing and frequent trips to the restroom due to gastrointestinal issues, and missing school are just some of the many challenges children living with Fabry disease may face.

It can be extremely important for patients and their families to feel empowered with information about Fabry disease, as they may find themselves in the position of needing to educate school nurses, gym teachers, or camp counselors about the disease.

Understandably, children living with this chronic, progressive, lifelong disease may experience a range of psychosocial issues, including anger, resentment, depression, fear, and feelings of isolation. A genetic counselor or hospital social worker can help direct patients and their families to support services, advocacy groups, and other resources. Children and their families may take comfort in knowing that although the disease is rare, there are others out there in similar situations. The Fabry Disease Resources section in the back of this booklet lists several patient and information groups, as well as other resources available to those living with Fabry disease.

After Diagnosis: the Opportunities Ahead

While hearing a diagnosis of Fabry disease can be frightening for children and parents, it sometimes serves as validation and explanation of many of the symptoms they have been experiencing—sometimes for years. Many patients say they were told prior to diagnosis that their signs and symptoms were just growing pains, malingering, or psychosomatic.

By recognizing the signs and symptoms of Fabry disease, physicians have the opportunity to identify Fabry disease earlier in the disease course, and to initiate the appropriate interventions. Perhaps as important, the diagnosis of one patient makes earlier diagnosis possible for affected family members.

Early recognition of the disease can enable appropriate intervention to help avoid potentially irreversible damage.

Fabry Disease Resources

Physician Resources

Diagnostic Testing

For a listing of laboratories that offer testing for Fabry disease, visit www.genetests.org or contact Genzyme Medical Information at 800-745-4447 or 617-768-9000, option 2.

Genzyme Medical Information

Genzyme Medical Information can provide additional information on Fabry disease. Please call 800-745-4447 or 617-768-9000, option 2.

Fabry Registry

The Fabry Registry is open to all physicians treating patients with Fabry disease, and can serve as a resource in patient care. This international, longitudinal database, sponsored by Genzyme, is dedicated to improving the understanding of Fabry disease. Patients should be encouraged to participate through their physician and advised that their participation is voluntary and may involve long-term follow-up. Visit www.fabryregistry.com to learn more.

Patient Resources

The listings below are provided by Genzyme as additional information for people living with Fabry disease, their families, and their healthcare providers. The web pages and their content are maintained by the organizations listed below. With the exception of its own websites, Genzyme does not endorse any particular organizations or the content contained on their websites.

Fabry Community (Genzyme)

www.fabrycommunity.com

Genzyme Case Managers

http://support.genzyme.com
1-800-745-4447, option 3

Fabry Support and Information Group (FSIG)

www.fabry.org

National Fabry Disease Foundation (NFDF)

www.thenfdf.org

National Organization for Rare Disorders (NORD)

www.rarediseases.org

References

1. Desnick RJ, Ioannou YA, Eng CM. Alpha-galactosidase A deficiency: Fabry disease. In: Scriver C, Beaudet A, Sly W, et al., eds. Metabolic and Molecular Bases of Inherited Disease. New York: McGraw Hill 2001;3733-3774.

2. Meikle PJ, Hopwood JJ, Clague AE, Carey WF. Prevalence of lysosomal storage disorders. JAMA 1999;281:249-254.

3. Kolodny EH. Fabry disease. In: Bogousslavsky J, Caplan L, eds. Stroke Syndromes. New York: Cambridge University Press 1995;453-459.

4. Genzyme Fabry Registry 2007. Data on file.

5. Tøndel C, Bostad L, Hirth A, Svarstad E. Renal biopsy findings in children and adolescents with fabry disease and minimal Albuminuria. Am J Kidney Dis 2008; 51:767-76.

6. Fabry Registry Annual Report 2010. Genzyme Corporation.

7. Fabry Registry Annual Report 2011. Genzyme Corporation.

8. Sheth KJ, Roth DA, Adams MB. Early renal failure in Fabry's disease. Am J Kidney Dis 1983;II:651-654.

9. Stryker VL, Kreps C. Fabry disease. Am J Nurs 2001;101:39-44.

Contact Genzyme Medical Information at 800-745-4447, option 2 for more information on diagnostic testing or for additional information on Fabry disease.

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