



Fabry Disease

An Overview of Symptoms,
Diagnosis, and Medical Management



Deficiency of α -GAL results in cellular accumulation of the substrate GL-3 in the vascular endothelium and tissues throughout the body. Arrows indicate areas of accumulation in this light micrograph of the renal capillary endothelium in a Fabry patient.

Disease Profile

Fabry disease is a metabolic disorder caused by a defect in the gene for the lysosomal enzyme α -galactosidase A (α -GAL). The defect causes partial or complete deficiency of α -GAL activity, resulting in an inability to catabolize certain lipids, particularly globotriaosylceramide (GL-3). As a result, GL-3 progressively accumulates in visceral tissues and the vascular endothelium throughout the body.

DISEASE MANIFESTATIONS

Progressive accumulation of GL-3 starts early in life and continues for decades, and may ultimately result in vascular involvement of the kidneys, heart, and central nervous system. By the third to fifth decade, more serious renal, cardiac, and cerebrovascular complications typically occur.^{1,2}

EARLY DIAGNOSTIC FEATURES

The age of presentation of Fabry disease is variable, as are the presenting symptoms and the clinical course. The disease usually presents in childhood with pain in the hands and feet, fever, hypohidrosis, fatigue, and exercise intolerance. However, symptoms often go unrecognized until adulthood when organ system damage has occurred.¹ Earlier diagnosis may result in more effective symptom management.

HISTORICAL PERSPECTIVE

The disease – also known as angiokeratoma corporis diffusum universale, Morbus Fabry, and Anderson-Fabry disease – was first described in 1898 independently by two physicians, William Anderson in England and Johann Fabry in Germany. Today, this panethnic, X-linked, lysosomal storage disorder affects an estimated 1 in every 40,000 males and 117,000 live births.^{2,3}

Fabry Disease Progression in Males and Females

Fabry disease is an X-linked disorder that was once thought to affect only males, with females considered carriers. Recent research, however, shows that most heterozygous females are clinically affected to some extent.^{4,5}

While virtually all males with a defective α -GAL gene develop manifestations of Fabry disease, females demonstrate a wide range of disease severity, from a virtually symptom-free course to a more classical male profile, with cardiac, renal, and cerebrovascular manifestations. This variable expression is thought to be influenced by X-inactivation, a phenomenon in which one of two haploid sets of X-linked genes in each cell is inactivated, apparently at random.^{5,6}

The manifestations listed to the left include the more common signs and symptoms of Fabry disease. Both male and female patients may experience some or all of these manifestations to varying degrees, depending in part on the extent of α -GAL activity and, in females, X-inactivation.



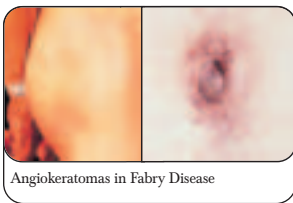
Fabry Disease Manifestations

NEUROLOGIC

- Acroparesthesia, characterized as chronic nagging, tingling, burning pain and discomfort in the palms of the hands and on the soles of the feet²
- “Fabry crises,” characterized as episodes of acute, agonizing pain, typically beginning in the extremities and radiating inward, lasting for minutes to weeks, and often induced by emotional stress, changes in temperature, exercise, or fatigue²
- Intolerance to heat, cold, and exercise
- Hearing loss and tinnitus
- According to the Genzyme Fabry Registry, neurological symptoms have been the most frequently reported symptoms. Chronic pain was reported by 27% of females and 18% of males.⁷ The Registry is an international database that included 191 reporting physicians and 2,235 Fabry disease patients (1,158 males and 1,077 females) as of December 2006

DERMATOLOGIC

- Angiokeratomas, clusters of dark red skin lesions that do not blanch with pressure, distributed primarily on the buttocks, groin, umbilicus, and upper thighs (affects approximately 63% of heterozygous females⁵)
- Hypohidrosis/anhidrosis (impaired sweating)

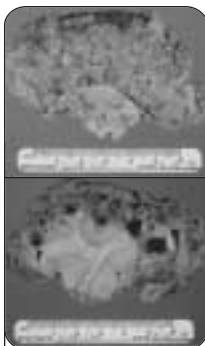


GASTROINTESTINAL

- Post-prandial abdominal pain, nausea, and watery diarrhea⁸
- Other signs of gastrointestinal distress, including bloating, early satiety and vomiting⁷

RENAL

- Renal insufficiency²
- Proteinuria, isosthenuria, azotemia²
- Alterations of tubular reabsorption, secretion, and excretion²
- In the Fabry Registry, among patients age 40 and over, 41% of males and 20% of females were in Stage 3-5 chronic kidney disease⁸



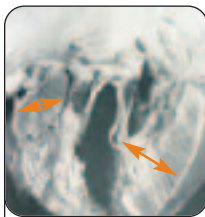
End-Stage
Fabry Disease Kidney
(Reproduced with permission
from E. Gilbert-Barness and
L. Barness. 2000. *Metabolic
Diseases: Foundations of
Clinical Management,
Genetics, and Pathology.*
Eaton Publishing, Natick, MA)

CEREBROVASCULAR

- Early ischemic stroke^{2,9,10}
- Thromboses^{2,10}
- Transient ischemic attacks^{2,10}
- Hemiparesis^{2,9,10}
- Vertigo/dizziness^{2,10}
- A study of white matter lesion severity in 13 males and 14 females with Fabry disease found a comparable incidence (36% of females and 31% of males) and level of severity in both groups⁴

CARDIAC

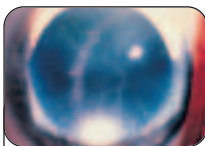
- Left ventricular hypertrophy^{2,11,12}
- Myocardial failure^{2,11}
- Valvular disease (especially mitral insufficiency)^{2,11,12}
- Coronary artery disease^{2,11}
- Conduction abnormalities^{2,11}
- Arrhythmias^{2,11}
- Of 475 males and 354 females for whom cardiac manifestations were reported in the Fabry Registry, 12% of males and 10% of females experienced first cardiac events at mean ages of 39 years and 46 years, respectively⁷



Left Ventricular Hypertrophy
in a 50-Year-Old Patient with
Fabry Disease

OCULAR

- Whorl-like corneal opacities, which typically do not impair vision^{2,8} (affects approximately 82% of heterozygous females⁵)
- Vascular lesions of the conjunctiva and retina, and lens opacities






Distinctive Corneal Opacity
in Fabry Disease

PSYCHOSOCIAL

- Patients 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
- In the Fabry Registry, 204 males who completed an SF-36® Health Survey had an average social function score of about 70 on a scale of 1 to 100. The scores were relatively stable across age groups. Of 389 females who completed the same survey, those in the 14-20 age bracket had an average score of 84, while those in the >40 age bracket had an average score of 72⁷

Potential Clinical Progression of Fabry Disease Manifestations

Symptoms of Fabry disease may progressively worsen over time as GL-3 continues to accumulate in tissues throughout the body.

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

Fabry Disease Diagnosis

Fabry disease can be diagnosed histologically, biochemically, and genetically. Clinical heterogeneity and the rarity of the disease (1:40,000 males and 1:117,000 live births^{2,3}) can make reaching a diagnosis of Fabry disease challenging. In order to provide the most appropriate, supportive care after a diagnosis is made, patients should be carefully assessed for evidence of renal, cardiac, or neurologic involvement.

A genetic counselor should be enlisted to assist in developing a family pedigree to identify other family members with Fabry disease, and in directing families to diagnostic, medical, and support services.



PRESUMPTIVE CLINICAL DIAGNOSIS

Made on the basis of the symptoms and laboratory findings discussed on the previous pages, including the characteristic angiokeratomas and corneal whorling (visible through slit lamp ophthalmoscopy).

DEFINITIVE 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.^{2,13} Because females with Fabry disease can have α -GAL activity in the low-normal range, mutation or linkage analysis should be used.¹⁴ More than 400 gene mutations for Fabry disease have been identified; none of them, however, are common.^{15,16}

PRENATAL DIAGNOSIS

Available via cultured amniotic fluid cells and by chorionic villus sampling (at 12 weeks) and amniocentesis (at 16 weeks).²

DIFFERENTIAL DIAGNOSIS

Fabry disease should be considered in the differential diagnosis of fever, pain, and skin lesions of unknown origin, or in stroke or renal disease of unknown etiology. Additionally, symptoms in Fabry disease are similar to those of other disorders, including:

- Rheumatoid or juvenile arthritis
- Rheumatic fever
- Erythromelalgia
- Lupus
- “Growing pains”
- Petechiae
- Raynaud’s syndrome
- Multiple sclerosis

Patients with a known familial history of Fabry disease should be tested by a confirmatory method regardless of symptomatology.

Fabry Disease Management

Fabry disease management requires a multidisciplinary approach. Symptom management may help to reduce the burden of disease. A geneticist, genetic counselor, nephrologist, neurologist, pediatrician, dermatologist, cardiologist, ophthalmologist, and gastroenterologist can each play a role.¹⁷

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.^{2,9}

CEREBROVASCULAR COMPLICATIONS

Prophylaxis with anticoagulant medication may be considered for patients vulnerable to stroke.²

CARDIAC COMPLICATIONS

Coronary artery disease may be treated with coronary bypass, medications, or angioplasty, as appropriate. Arrhythmias and conduction abnormalities may be treated with antiarrhythmic medications or pacemaker insertion, as appropriate.²

RENAL COMPLICATIONS

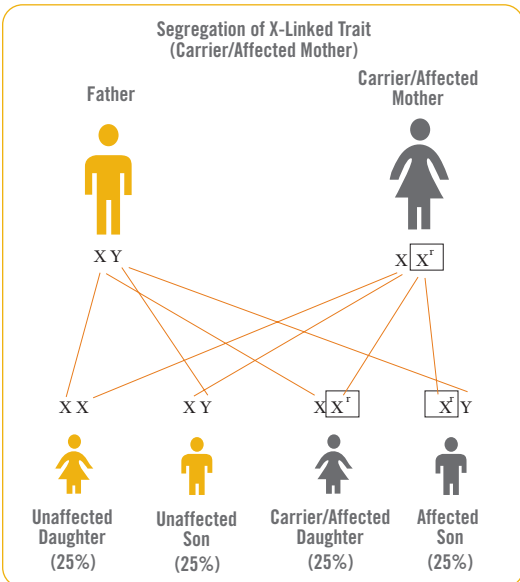
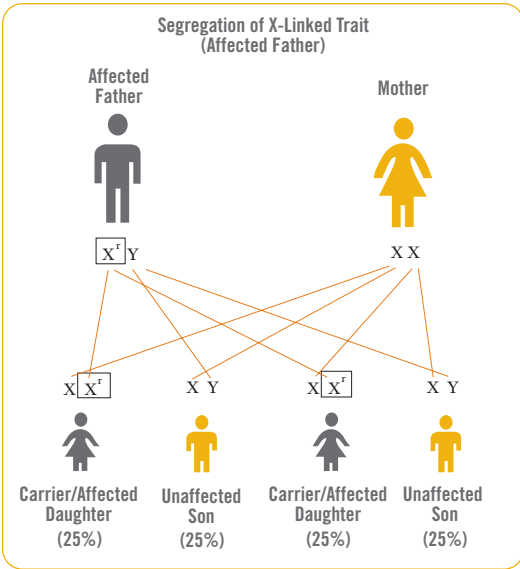
Mild reduction in renal function can be managed in part by a low-sodium, low-protein diet. Renal dialysis and/or renal transplantation, as well as certain medications, may be appropriate for advanced chronic kidney disease.

GASTROINTESTINAL SYMPTOMS

Gastrointestinal symptoms may improve with a low-fat diet.

Inheritance Pattern

Fabry disease is an X-linked disorder (the location of the defective gene is on the X chromosome). Males with the defective gene pass it to all of their daughters and none of their sons. Females have a 50% risk with each conception of transmitting the defective gene to each of their offspring.



Fabry Resources

Genzyme is committed to helping medical professionals get the information and resources they need to provide comprehensive care for their patients with Fabry disease.

MEDICAL INFORMATION

Genzyme offers access to a network of medical specialists that connects patients to health care professionals with expertise in lysosomal storage disorders such as Fabry disease. In addition, providers can request Fabry disease-related scientific papers, educational materials, and information on diagnostic testing and genetic counseling. Call **800-745-4447** or **617-768-9000** (option 2).

FABRY REGISTRY

The Genzyme Fabry Registry is an international, longitudinal database dedicated to improving the understanding of Fabry disease. To learn more call **617-768-9000, ext. 17024** or visit **www.fabryregistry.com**.

FABRY COMMUNITY

Genzyme offers patient resources and advocacy to help connect patients and their families to others living with similar diseases. It also provides patient and physician resources at www.fabrycommunity.com or call **800-745-4447** or **617-768-9000** (option 2).

FABRY RESEARCH

Genzyme's research and development programs serve as vehicles for investigating new and innovative treatments for Fabry disease and other lysosomal storage disorders. Patients and practitioners can request information on current clinical trial programs for lysosomal storage disorders at **800-745-4447** or **617-768-9000** (option 2).

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Learn more about Fabry disease online.

www.fabrycommunity.com

www.fabryregistry.com

An Ongoing Commitment

For more than 25 years, Genzyme has been committed to researching and developing products for people living with lysosomal storage disorders such as Fabry disease. Providing comprehensive and confidential support services that address the unique needs of those living with Fabry disease is part of this ongoing commitment.

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