

FABRY DISEASE IN CHILDHOOD

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Fabry disease, also known as *Anderson-Fabry disease* or *angiokeratoma corporis diffusum universale*, is an inborn error of metabolism with profound clinical consequences. Patients with Fabry disease have a deficiency of α -galactosidase A (α -Gal A), the lysosomal enzyme responsible for the breakdown of globotriaosylceramide and related glycosphingolipids.¹ These glycosphingolipids have a terminal α -galactosyl residue and are components of most cell membranes. The deficiency of α -Gal A leads to progressive accumulation of globotriaosylceramide in the plasma and in the lysosomes of most cells in the body.

In patients with the classic disease phenotype, the accumulation of substrate in the vascular endothelium leads to ischemia and infarction (Fig 1), causing the major early manifestations of the disease, including angiokeratomas (Fig 2), hypohidrosis, and acroparesthesias. Patients also have characteristic corneal and lenticular opacities (Fig 3).² The disease culminates in life-threatening renal, cardiac, and cerebrovascular manifestations. Patients with classic Fabry disease have an average life span of approximately 50 years³; before renal dialysis and transplantation were available, it was approximately 40 years.⁴

Fabry disease is one of the more common lysosomal storage disorders, affecting approximately 1:40,000 to 1:60,000 males.^{2,5} The disease is inherited in an X-linked recessive manner (Fig 4). However, female carriers may have disease manifestations,⁶ and, rarely, full-blown classic Fabry disease, because of random X-chromosomal inactivation.⁷⁻⁹ In general, affected girls and women have an attenuated form of the disease, with later onset and milder symptoms.

Like most lysosomal storage disorders, Fabry disease encompasses a spectrum of disease severity, with the classic form representing the most severe phenotype. Less severe cardiac^{10,11} and renal¹² variants of Fabry disease have been recognized, both of which are characterized by the presence of residual α -Gal A activity, onset in adulthood, and clinical manifestations confined primarily to the myocardium or kidney.

Despite the cardinal presenting symptoms in childhood of acroparesthesias, pain crises, and angiokeratomas, Fabry disease is often misdiagnosed or overlooked; the average age at diagnosis was 29 years in two series.^{5,13} Recent clinical studies have shown that α -Gal A replacement therapy has the potential to prevent, reverse, or at least arrest disease progression.^{14,18} With this therapy now available in Europe and the United States, the need for prompt and accurate diagnosis of Fabry disease is heightened, so that therapy can be initiated before the occurrence of irreversible organ damage.

HOW FABRY DISEASE PRESENTS IN CHILDHOOD

Table I summarizes the presenting symptoms of classic Fabry disease in children. Unlike many lysosomal storage disorders, Fabry disease is not associated with mental retardation or obvious physical abnormalities. Presentation can be both subtle and varied, and lack of a particular symptom or symptoms does not rule out the diagnosis. In particular, general pediatricians and pediatric specialists, including ophthalmologists, neurologists, geneticists, cardiologists, dermatologists, and rheumatologists, should be familiar with this disease and its presentation. The signal manifestations in childhood are severe episodic pain crises and chronic acroparesthesias in the extremities, lack of or decreased sweating, and the characteristic skin lesions, the angiokeratomas.

Pain

The most striking feature of Fabry disease in young affected male patients is acute, episodic pain.^{2,19} These *Fabry crises* of agonizing neuropathic pain typically begin in the hands and feet and may radiate proximally. Pain episodes can last from minutes to weeks and are often accompanied by fever and an elevated erythrocyte sedimentation rate. Most boys with classic Fabry disease have Fabry crises^{2,3} historically beginning as early as age 4

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Supported by an unrestricted educational grant from Genzyme Corp. Dr Desnick is a consultant to Genzyme Corp, receives a research grant from Genzyme Corp, and is an inventor on patents that the Mt Sinai School of Medicine has licensed to Genzyme Corp. Dr Brady is a consultant to Genzyme Corp.

Submitted for publication Dec 9, 2003; accepted Jan 23, 2004.

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J Pediatr 2004;144:S20-S26.

0022-3476/\$ - see front matter

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10.1016/j.jpeds.2004.01.051

α -Gal A α -Galactosidase A

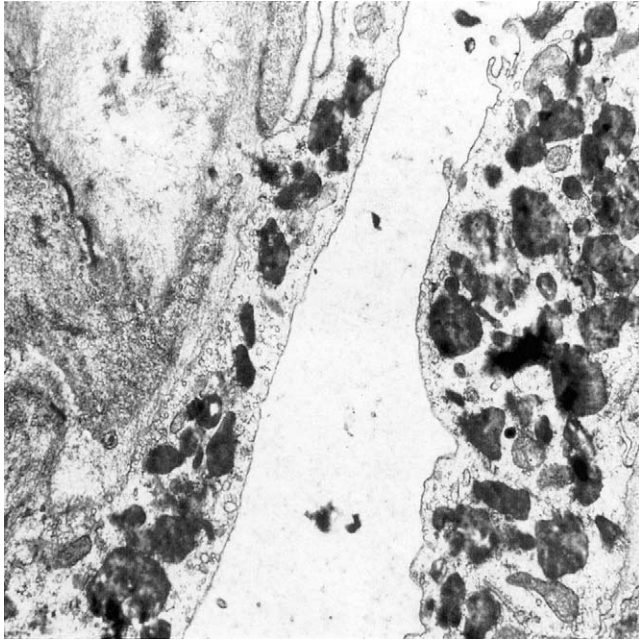


Fig 1. Electron micrograph showing the vascular endothelium of a small vessel from a patient with Fabry disease. Note the electron-dense vesicles (lysosomes) in the endothelium containing undegraded globotriaosylceramide and related glycosphingolipids. The progressive lysosomal glycosphingolipid accumulation in the vascular endothelium leads to ischemia and infarction of these vessels. Reprinted with permission.²⁶

years (mean age of onset, 10 years).³ Pain is often triggered by stress, heat, fatigue, or exercise and is related to the fact that affected male patients have hypohidrosis and cannot rid their bodies of excess heat through sweating, causing an increased core temperature that triggers the pain. Hypohidrosis also leads to heat sensitivity and exercise intolerance, both of which worsen with age. Affected male patients also have a second type of pain, *acroparesthesia*—chronic burning or tingling pain in the extremities. Female carriers may also have acroparesthesias, usually tingling in nature and beginning in adolescence.⁶

Despite their severity, the acroparesthesias in children with undiagnosed Fabry disease are often dismissed as malingering or growing pains. Physical examination may not provide clues about the diagnosis, particularly if the cutaneous involvement is subtle. Electromyography and nerve conduction studies usually fail to detect abnormalities because the neuropathology primarily involves small nerve fibers. The recurrence of the pain and the lack of a medical explanation have led to depression, even contemplation of suicide by adolescents.²⁰ Pain also has led to misdiagnoses including rheumatic fever, joint pain, carditis (misdiagnosed mitral murmur), and rash (misdiagnosed angiokeratoma). Other misdiagnoses are listed in Table II.

Gastrointestinal Disturbances

Beginning in childhood, boys with Fabry disease may have mild to severe gastrointestinal disturbances, including diarrhea, abdominal discomfort, nausea, and vomiting. Female

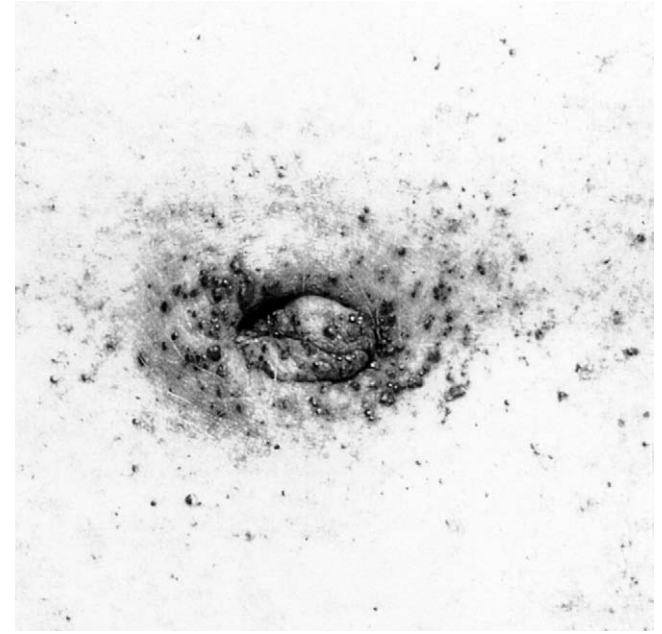


Fig 2. Angiokeratomas. These characteristic dark red to blue-black angiectases are most often found in clusters between the umbilicus and thigh. The lesions are nonblanching, become larger and more numerous with age, and range in size from pinhead to several millimeters. Reprinted with permission.²⁶

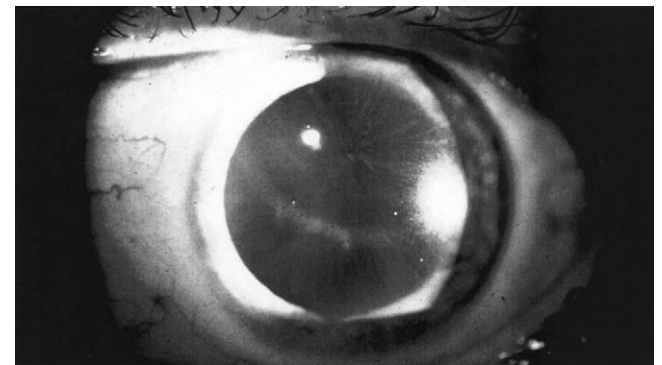


Fig 3. Whorled corneal opacity that does not affect vision. This opacity, seen only by slit-lamp microscopy, is found in virtually all male patients with Fabry disease and 70% to 80% of female carriers. It is often more distinctive in females. Note the whorl-like rays emanating from a single vertex. Reprinted with permission.²⁶

carriers may also have gastrointestinal symptoms, usually beginning in adolescence or early adulthood.^{21,22} Acute abdominal pain also occurs and can be mistaken for appendicitis.² Many affected male patients have difficulty gaining weight.²³

Dermatologic Manifestations

Virtually all male patients with classic Fabry disease develop angiokeratomas (Fig 3), usually beginning in childhood or adolescence.² These small, slightly raised, purplish-red, nonblanching telangiectases are most often found between the umbilicus and knees but can occur virtually anywhere, including the oral mucosa and conjunctiva.¹⁹ They become larger and more numerous with age. Approximately 10% to

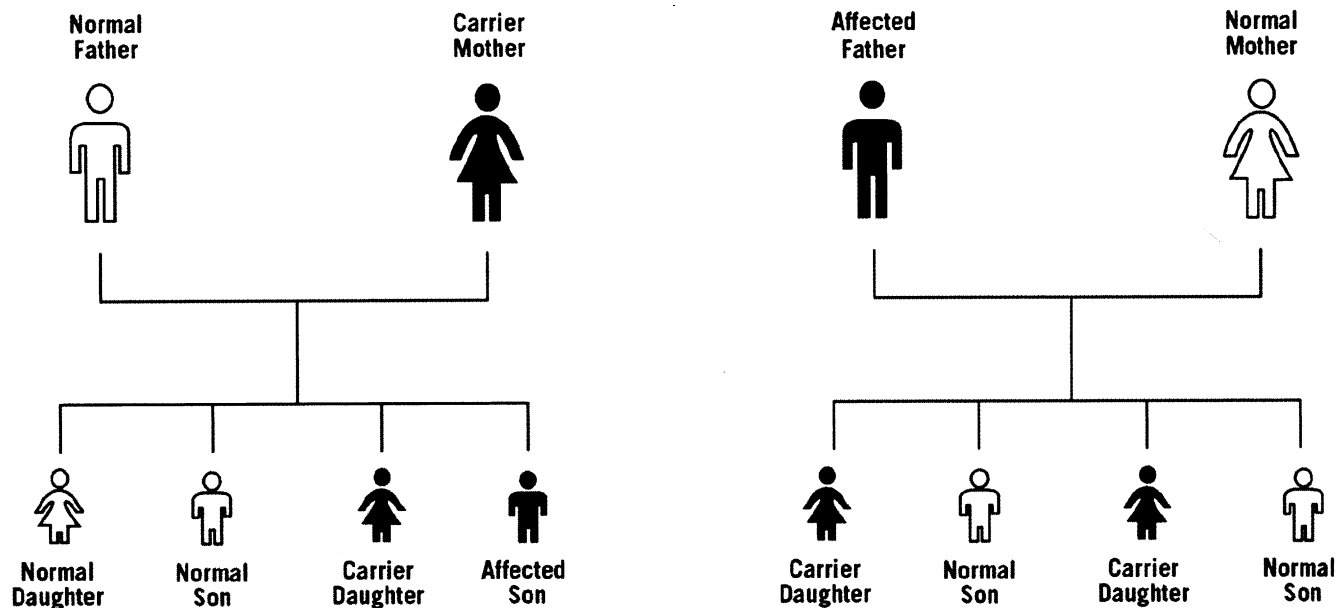


Fig 4. Inheritance of Fabry disease. Fabry disease is an X-linked recessive disorder. Statistically, 50% of the sons of a female carrier will have the disorder, and 50% of her daughters will be carriers. None of the sons of an affected father will inherit the disease, but all of his daughters will be carriers. Carriers may also have clinical manifestations.

Table I. Clinical manifestations of classic Fabry disease*

Age 4–16 years

- Intermittent paresthesia and acroparesthesia consisting of chronic, burning, tingling pain in the hands and/or feet, usually beginning in early childhood. Can occur daily and can last minutes to days.
- Episodic Fabry crises of severe, incapacitating pain, lasting from days to weeks. Often precipitated by stress, illness, physical exertion, or temperature changes and accompanied by fever and an elevated erythrocyte sedimentation rate. Very rare in carriers.
- Angiokeratomas that appear in adolescence and worsen in adulthood (Fig 2).
- Whorled corneal opacity (Fig 2; also frequently observed in female carriers with or without disease manifestations).
- Gastrointestinal problems, including diarrhea, abdominal discomfort, vomiting, nausea.
- Hypohidrosis or anhidrosis.
- Heat, cold, and/or exercise intolerance.
- Mild proteinuria and urinary sediment containing globotriaosylceramide.

Late adolescence to adulthood

- Renal dysfunction that leads to uremia and hypertension and progresses to end-stage renal disease.
- Cardiovascular dysfunction, including myocardial infarction, valvular abnormalities, arrhythmias, left ventricular hypertrophy.
- Cerebrovascular complications, such as risk of early stroke, hemiplegia, hemianesthesia, transient ischemic attacks.
- Pulmonary complications, such as airflow obstruction, dyspnea.

*Most patients with classic Fabry disease are male; however, female carriers can also have disease manifestations.

35% of female carriers also develop angiokeratomas, generally beginning in adolescence. In female patients, the lesions are usually isolated, small macules on the breasts, groin, or flanks.

Ocular Abnormalities

Most boys with Fabry disease and >70% of carrier girls have a characteristic corneal opacity, observed by slit-lamp microscopy, that does not affect vision (Fig 4).

Skeletal and Growth Abnormalities

Children with Fabry disease do not have the skeletal abnormalities characteristic of other lysosomal disorders such

as Gaucher disease and several of the mucopolysaccharidoses (eg, Hurler [severe mucopolysaccharidosis type I], Hunter, Maroteaux-Lamy, Morquio diseases), but many children have subtle evidence of musculoskeletal involvement. Retarded growth, delayed puberty, and sparse, fine facial and body hair are common.² A characteristic facial dysmorphism is found in about half of male patients and may be recognizable in early adolescence.³

Family History

A history of family members with similar symptoms; male relatives with early kidney disease, stroke, or cardiac

Table II. Misdiagnoses of Fabry disease

Disease	Misleading symptom
Acute appendicitis	Severe right lower quadrant abdominal pain
Carditis	Mitral value murmur
Chronic intermittent demyelinating polyneuropathy	Pain, tingling in feet and hands
Growing pains	Unexplained pain in extremities
Erythromelalgia	Acute pain in the extremities
Lupus	Angiokeratomas
Multiple sclerosis	Stroke-like findings on brain magnetic resonance images
Neurosis	Acute pain with no apparent cause
Petechiae	Angiokeratomas
Raynaud syndrome	Pain and temperature sensitivity in the extremities
Rheumatic fever	Pain accompanied by fever and an elevated erythrocyte sedimentation rate
Rheumatoid or juvenile arthritis	Pain in the joints, elevated erythrocyte sedimentation rate

problems; or both is suggestive of Fabry disease and warrants investigation. However, because the disease gene can be passed through the maternal line for one or several generations by asymptomatic or mildly affected female carriers, the absence of a family history does not rule out the diagnosis. In addition, de novo mutations in the α -Gal A gene do occur, although rarely.

CLINICAL LABORATORY FINDINGS

Routine serum and urine chemistries, hematologic indices, and pulmonary function tests typically are normal in affected boys. Older boys with Fabry disease may have an elevated erythrocyte sedimentation rate, mild proteinuria, or isosthenuria. Urinary sediment examination reveals casts, erythrocytes, and cells containing the accumulated glycosphingolipid, which appears as Maltese crosses under polarization microscopy.

DIAGNOSIS

Fabry disease can be diagnosed in male patients by markedly deficient or absent α -Gal A activity in plasma or peripheral leukocytes by using commercially available 4-methylumbelliferyl- α -D-galactoside as substrate.²⁴ Normal enzyme values vary depending on the enzyme source, substrate concentrations, and assay variables.

In female patients, a very low α -Gal A level is also diagnostic of the carrier state for Fabry disease. However, normal or near-normal α -Gal A activity does not rule out the possibility that a female is a carrier. Obligate heterozygotes can have normal α -Gal A activities because of random X-chromosomal inactivation. Thus, all girls and women at risk for carrying the disease gene should have their status determined by molecular studies to detect the family's mutation.

Fabry disease can be diagnosed prenatally by demonstration of an XY karyotype and deficient α -Gal A activity in direct or cultured chorionic villi or in cultured amniocytes.²⁵ If the family's α -Gal A mutation is known, molecular studies can replace or confirm the enzymatic diagnosis.

GENETIC COUNSELING

Genetic counseling is essential after diagnosis, both to provide patients and families with information about the natural history of the disease and treatment options and to advise parents of the likelihood that siblings, relatives, and future children will inherit the disease or carry the disease-causing gene (Fig 1). Parents should encourage other family members to have diagnostic testing and genetic counseling.

TREATMENT

Fabry disease was first identified a century ago, but until now, no disease-specific treatment has been available. Patients have been treated with supportive, nonspecific treatment for pain management, cardiac and cerebrovascular complications, and end-stage renal disease. These interventions may prolong life, but their utility is limited because they do not address the underlying cause of the disease—the deficient activity of α -Gal A and the progressive accumulation of globotriaosylceramide.

Like all lysosomal storage disorders, Fabry disease is best managed by a team of specialists headed by a physician with Fabry expertise. Treatment should consist of both symptom management and enzyme replacement therapy. In addition, pediatricians should be sensitive to the effect of a chronic, progressive disease on children and their families. Genetic, family, and individual counseling are important resources to offer Fabry families and patients.

How Children Should Be Followed

After the clinical diagnosis of Fabry disease is confirmed by enzyme assay or mutation analysis, all children should have a detailed medical and family history taken. ABO blood type and secretor status should also be determined, because the presence of B blood group antigen (a glycosphingolipid catabolized by α -Gal A) may be associated with a more severe prognosis. Pain; gastrointestinal complications; size, density, and distribution of angiokeratomas; hypohidrosis; eye findings; and all other signs and symptoms should be carefully

Table III. Follow-up of children with Fabry disease

Evaluation at diagnosis

- Detailed medical history
- Detailed family history
- Detailed physical examination
- Documentation of pain (frequency, character, intensity, and so forth), gastrointestinal symptoms, and angiokeratomas
- Laboratory tests
 - ABO blood type and secretor status (B blood group may be associated with a more severe prognosis)
 - Routine hematology, chemistries, and urinalysis

Routine follow-up (additional follow-up as indicated by symptoms or abnormal findings)

- Annual detailed physical examination, documentation of level of pain, hypohidrosis, gastrointestinal symptoms, and angiokeratomas
- Annual laboratory tests
 - Routine hematology, chemistries, and urinalysis
 - For adolescents: urinary protein (including creatinine to albumin ratio), and creatinine clearance tests to monitor renal function
- Every other year for adolescents: echocardiography and electrocardiography to detect and monitor cardiac abnormalities
- Early adulthood and/or before initiation of enzyme replacement therapy: baseline kidney, heart, and brain magnetic resonance imaging to monitor disease progression and effect of therapy

documented at baseline and then at least annually (Table III). Monitoring and treating pain is especially important in children and may require additional follow-up. Annual evaluations should include a detailed physical examination and routine hematology, chemistry, and urinalysis. In addition, because renal disease begins silently and patients with Fabry disease as young as 16 years have developed renal failure,²³ adolescent patients should have yearly serum creatinine, urinary protein (including a creatinine/albumin ratio), and creatinine clearance tests to determine renal function. Similarly, adolescents should have an echocardiogram and electrocardiogram at least every 2 years to detect and monitor cardiac abnormalities. In early adulthood or before initiation of enzyme replacement therapy, baseline magnetic resonance images of kidney, heart, and brain are useful to document disease progression and assess the effect of therapy.²⁶

Girls who are Fabry carriers should have a complete baseline examination as described here by a physician with expertise in Fabry disease. In female patients, disease manifestations vary widely. Girls with no signs or symptoms of disease can be re-evaluated every 3 to 5 years. Symptomatic carriers should be followed annually with tests focused on their disease manifestations.²⁶

Symptom Management

Affected male patients should be encouraged to identify and avoid stimuli that trigger pain crises, such as extreme heat or cold, stress, or physical exertion. Patients with frequent and severe pain can benefit from prophylaxis with diphenylhydantoin,²⁷ carbamazepine,²⁸ or gabapentin.²⁹ Narcotic analgesics should be avoided. Nonsteroidal antiinflammatory drugs are generally ineffective for pain relief. Pancrelipase or metoclopramide can ameliorate gastrointestinal symptoms.²¹

Enzyme Replacement Therapy

Despite its often subtle presentation, the pathology in Fabry disease begins at birth, or even before birth.³⁰ Enzyme

replacement therapy supplies the patient with the biologically deficient protein and reverses metabolic and pathologic abnormalities.¹⁴⁻¹⁸

Clinical trials have demonstrated the safety and effectiveness of enzyme replacement therapy.¹⁴⁻¹⁷ Two different preparations of human α -Gal A—agalsidase alfa (Replagal; Transkaryotic Therapies, Cambridge, Mass) and agalsidase beta (Fabrazyme; Genzyme Corp, Cambridge, Mass)—have been used at doses of 0.2 and 1 mg/kg, respectively. Biochemical comparison studies have shown that the α -Gal A preparations are structurally and functionally very similar^{31,32}; therefore, the trial data can be taken together as a body of evidence supporting the use of enzyme replacement therapy in Fabry disease.¹⁴⁻¹⁸ In summary, human α -Gal A replacement has been shown to decrease pain,¹⁶ to reverse abnormal cerebrovascular responses,¹⁸ and to deplete storage significantly of globotriaosylceramide in the plasma and the capillary endothelium of the heart, kidney, and skin, major organs of pathology in Fabry disease.¹⁷ In addition, globotriaosylceramide was depleted in renal endothelial, mesangial, and interstitial cells and reduced in renal epithelial cells in response to human α -Gal A replacement.³³

Therefore, experts recommend that enzyme replacement therapy be initiated in all affected male patients with Fabry disease as soon as clinical signs and symptoms (such as pain or isosthenuria) are observed.²⁶ Carriers with substantial disease manifestations also should be treated with enzyme replacement therapy. It is important to recognize that globotriaosylceramide accumulation is progressive, and experience with enzyme replacement therapy in Gaucher disease and many other inherited metabolic diseases has emphasized the importance of early intervention to prevent and avoid irreversible damage.

Both α -Gal A products were approved in Europe and elsewhere in 2001, and experience has been gained in more than 500 patients, most of whom are age 16 years or older. In the United States, only agalsidase beta, which obtained accelerated approval from the Food and Drug Administration in April 2003, is available.

Although results are not yet available, enzyme replacement therapy is now being evaluated in children with Fabry disease in the United States and Europe. However, enzyme replacement therapy has been used safely by hundreds of children with Gaucher disease,³⁴ including children as young as 1 year of age.

As with any rare disease, collecting and sharing of information is essential. Disease registries provide an invaluable repository of clinical information that can be used as a decision-making resource for clinicians to determine the natural course of the disease, to assess the effectiveness of various interventions, and to track individual patients regardless of treatment choice or status. Therefore, we urge all physicians treating patients with Fabry disease to enroll them in a disease registry.

CONCLUSIONS

Fabry disease has significant, although subtle, manifestations in childhood. The benefits of early diagnosis are particularly compelling with the advent of enzyme replacement therapy, which may prevent or even reverse life-threatening disease manifestations. Pediatricians should be alerted to the possible significance of unexplained pain, gastrointestinal disturbances, lack of or decrease in sweating, angiokeratomas, and corneal whorls or lens opacities, as well as unexplained left ventricular hypertrophy or mitral murmurs and proteinuria, isosthenuria, or abnormal urinary sediment analysis in children and adolescents.

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APPENDIX: FABRY DISEASE RESOURCES

Resources and Support Groups for Patients and Families

Fabry Community

E-mail: fabry@genzyme.com

<http://www.fabrycommunity.com>

Tel: 617-768-9000, 800-745-4447

Fax: 617-591-7178, 800-737-3642

Fabry Support and Information Group

E-mail: JJohnson@fabry.org

<http://www.fabry.org>

Tel: 660-463-1355

Fax: 660-463-1356

Resources for Physicians

Genetic Leadership Collaborative

<http://www.geneticleadership.com>

The International Center for Fabry Disease

Department of Human Genetics

Mount Sinai School of Medicine

Fifth Avenue and 100th Street

New York, New York 10029

E-mail: fabry.disease@mssm.edu

<http://www.mssm.edu/genetics/fabry/fabry.html>

Tel: 1-866-MD FABRY, 866-322-7963 (toll-free)

Fax: 212-360-1809

Lysosomal Storage Disease Network

<http://www.lsdn.com>

Fabry Disease Registries

Fabry Registry

<http://www.fabryregistry.com>

Fabry International Research Exchange (FIRE)

<http://spitfire.emmes.com/study/fire>