Fabry Disease, an Under-Recognized Multisystemic Disorder: Expert Recommendations for Diagnosis, Management, and Enzyme Replacement Therapy

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Fabry disease (α-galactosidase A deficiency) is an X-linked recessive lysosomal storage disorder. Although the disease presents in childhood and culminates in cardiac, cerebrovascular, and end-stage renal disease, diagnosis is often delayed or missed. This paper reviews the key signs and symptoms of Fabry disease and provides expert recommendations for diagnosis, follow-up, medical management, and the use of enzyme replacement therapy. Recommendations are based on reviews of the literature on Fabry disease, results of recent clinical trials, and expertise of the authors, all of whom have extensive clinical experience with Fabry disease and lysosomal storage disorders and represent subspecialties involved in treatment.

All males and female carriers affected with Fabry disease should be followed closely, regardless of symptoms or treatment status. Clinical trials have shown that recombinant human α-galactosidase A replacement therapy—the only disease-specific therapy currently available for Fabry disease—is safe and can reverse substrate storage in the lysosome, the pathophysiologic basis of the disease. Enzyme replacement therapy in all males with Fabry disease (including those with end-stage renal disease) and female carriers with substantial disease manifestations should be initiated as early as possible. Additional experience is needed before more specific recommendations can be made on optimal dosing regimens for reversal; maintenance; and prevention of disease manifestations in affected males, symptomatic carrier females, children, and patients with compromised renal function.

Fabry disease is an X-linked recessive lysosomal storage disorder that is caused by the deficient activity of α-galactosidase A (α-Gal A, also termed *ceramide trihexosidase*) (1, 2) and the resultant accumulation of globotriaosylceramide (also termed *ceramide trihexoside*) and related glycosphingolipids (3–5). In patients with the classic phenotype, levels of α-Gal A activity are very low or undetectable. Patients with detectable α-Gal A activity have a milder, variant phenotype (6–8). In classically affected males, the progressive glycosphingolipid accumulation, particularly in the vascular endothelium (**Figure 1**), leads to renal, cardiac, and cerebrovascular manifestations and early death. The disease is panethnic, and estimates of incidence range from about 1 in 40 000 to 60 000 males (5, 9). Fabry disease predominantly affects males, although carrier (heterozygous) females also can be affected to a mild or severe degree because of random X-chromosomal inactivation (5).

In the absence of a family member who has already received a diagnosis of the disorder, many cases are not diagnosed until adulthood (average age, 29 years) (9, 10), when the pathology of the disorder may already be advanced. Although clinical onset occurs in childhood, disease presentation may be subtle, and its signs and symptoms are often discounted as malingering or are mistakenly attributed to other disorders, such as rheumatic fever, erythromelalgia, neurosis, the Raynaud syndrome, multiple sclerosis, chronic intermittent demyelinating polyneuropathy, lupus, acute appendicitis, "growing pains," or petechiae (5, 11).
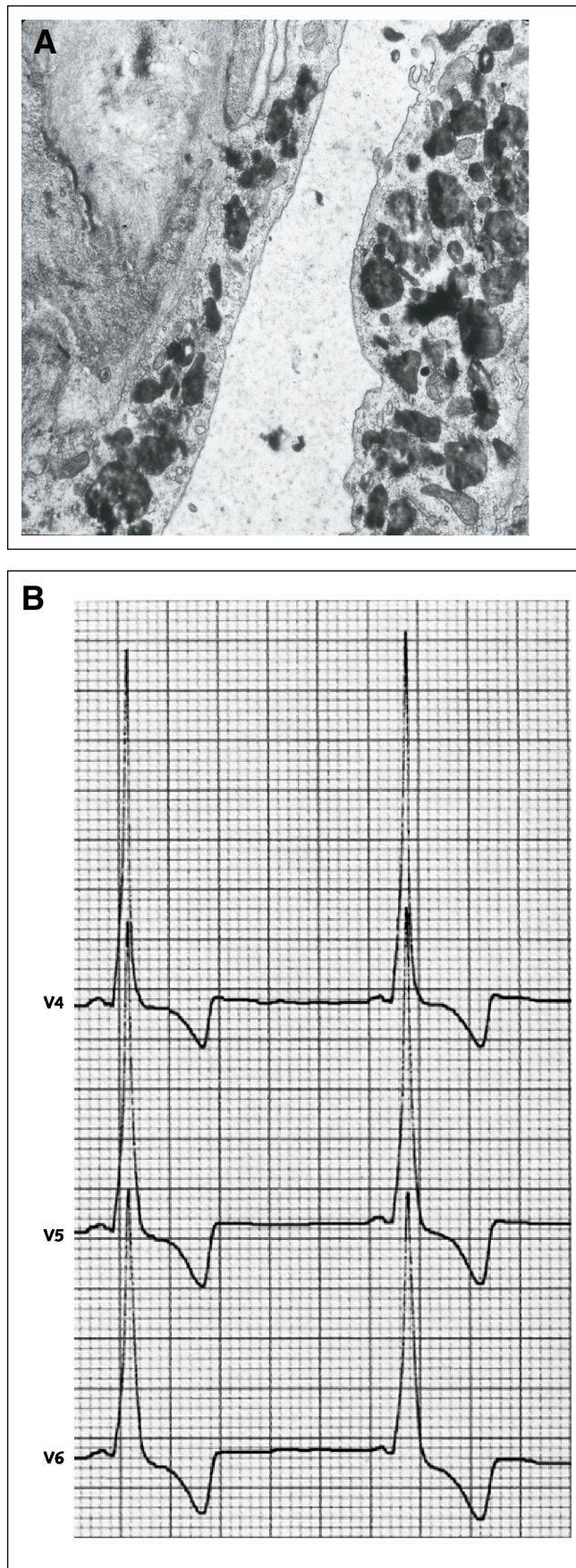
Fabry disease was first identified a century ago, but until now, no disease-specific treatment has been available. Patients have been managed with supportive, nonspecific treatment for pain management, cardiac and cerebrovascular complications, and end-stage renal disease. These interventions may prolong life, but their utility is limited because they do not address the underlying cause of the disease, that is, the lack of α-Gal A and the progressive accumulation of globotriaosylceramide. Recently, enzyme replacement with human α-Gal A has been shown to safely reverse the pathogenesis of the major clinical manifestations, to decrease pain, and to stabilize renal function in patients with Fabry disease (12, 13). The European Agency for the Evaluation of Medicinal Products has approved the treatment, and the U.S. Food and Drug Administration is currently reviewing it. Thus, recommendations for the diagnosis and treatment of Fabry disease are timely.

FORMATION OF EXPERT PANEL AND BASIS OF RECOMMENDATIONS

In June and July of 2001, two groups of investigators published randomized, placebo-controlled trials that demonstrated that enzyme replacement therapy in Fabry disease can reverse the major pathologic consequences and improve outcomes (12, 13). With a disease-specific therapy finally available, the need for prompt and accurate diagnosis of this devastating, progressive disease became paramount so that patients could be identified and treated before incurring irreversible organ damage. Recognizing the need for initial guidelines for diagnosis, management, and the use of enzyme replacement therapy, Dr. Robert Desnick and Dr. Roscoe Brady (senior authors of the enzyme replacement trials) assembled an international panel of ex-

Figure 1. **Distinctive laboratory findings in Fabry disease.**

A. 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 glycosphingolipid. The progressive lysosomal accumulation in the vascular endothelium leads to ischemia and infarction of these vessels. **B.** Electrocardiogram of a 41-year-old man with classic Fabry disease showing sinus bradycardia with short PR interval (88 msec) and left ventricular hypertrophy with QRS widening and a repolarization abnormality.

perts with extensive clinical experience and diverse subspecialty expertise in Fabry disease and lysosomal storage disorders.

Panelists met face-to-face to identify and discuss salient issues. An independent coordinator conducted numerous global and specific searches of the MEDLINE database (1991–2001), including a global search of the recent literature on Fabry disease. The coordinator then interviewed each panelist in detail and, with the first author, prepared a draft statement. In a second face-to-face session, the draft was reviewed, revised, and finalized by the panel. A teleconference was convened to revise the manuscript after journal review. Support for the expert panel process was obtained from the Genzyme Corporation (Cambridge, Massachusetts), which had no formative role in the literature review, the formulation of recommendations, or the drafting and revising of the manuscript.

As would be expected for a rare, under-recognized disease, the literature on Fabry disease mostly consists of single or small case studies and reviews in addition to book chapters written by Fabry experts. The few larger studies focus on disease manifestations and mechanisms of disease rather than the effectiveness of interventions or disease management. The literature on enzyme replacement therapy is limited to the clinical trials published in the last 2 years. Thus, clinical experience and expertise played an important role in the formulation of these recommendations.

DISEASE PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

The major debilitating manifestations of Fabry disease result from the progressive accumulation of globotriaosylceramide in the vascular endothelium (**Figure 1**), leading to ischemia and infarction, especially in the kidney, heart, and brain. The ischemia and infarction of small vessels are primarily due to vascular occlusion (5); however, evidence for a prothrombotic state has recently been published (14).

In addition, early and substantial deposition of globotriaosylceramide occurs in podocytes, leading to proteinuria and, with age, in cardiomyocytes, causing cardiac hypertrophy and conduction abnormalities (**Figure 1**). Patients are generally divided into two major groups on the basis of the absence or presence of residual α-Gal A activity: classic disease and milder, later-onset, atypical variants (5). Presentation and clinical course can vary within these phenotypes, and an intermediate phenotype has also been described (15–17).

Figure 2. **Distinctive clinical features of Fabry disease.**

A and **B**. 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. **C**. Whorled corneal opacity that does not affect vision. This opacity, seen only by using slit-lamp microscopy, is found in almost all males with Fabry disease and in 70% to 90% of carrier females; it is often more distinctive in females. Note the whorl-like rays emanating from a single vertex.

The Classic Phenotype

Males with classic disease have no or very low α-Gal A activity, resulting in severe renal, cardiac, and cerebrovascular disease manifestations. Before treatment of uremia became available, the average lifespan of affected males was about 40 years (18). With the advent of renal dialysis or transplantation, the median survival was about 50 years (19). Clinical manifestations (**Figures 1** and **2**), which usually begin in childhood or adolescence, include intermittent pain in the extremities (acroparesthesias); episodic "Fabry crises" of acute pain lasting hours to days; characteristic skin lesions (angiokeratomas); a corneal opacity that does not affect vision; hypohidrosis; heat, cold, and exercise intolerance; mild proteinuria; and gastrointestinal problems. By adulthood, the renal involvement inevitably results in end-stage renal disease, which requires dialysis or transplantation (20, 21). Cardiac manifestations include left ventricular hypertrophy, valvular disease (especially mitral insufficiency), ascending aortic dilatation, coronary artery disease, and conduction abnormalities (**Figure 1**), leading to congestive heart failure, arrhythmias, and myocardial infarction (5, 22–24). Cerebrovascular manifestations include early stroke, transient ischemic attacks, white matter lesions, hemiparesis, vertigo or dizziness, and complications of vascular disease (such as diplopia, dysarthria, nystagmus, tinnitus, hemiataxia, memory loss, and hearing loss) (5, 25).

Clinical manifestations in carrier females range from asymptomatic to full-blown disease as severe as that in affected males (5, 26–28). Although many carriers will be relatively asymptomatic and have a normal lifespan, carriers may experience symptoms in childhood and adolescence (such as pain and proteinuria) and adulthood (such as cardiac or, more rarely, renal manifestations). In late adulthood, some carriers develop left ventricular hypertrophy and substantial cardiomyopathy. Data on carriers are limited. A recent study of obligate carrier females found

significant disease manifestations in 20 of 60 women, including 17 of whom who had experienced transient ischemic attacks or cerebrovascular accidents (28).

Atypical Variants

Atypical male variants have a milder, later-onset phenotype (5–7, 17, 29). Because of low residual α-Gal A levels, these patients do not have the early major clinical manifestations of classic Fabry disease. For example, cardiac variants present with cardiomegaly and mild proteinuria usually after 40 years of age, when patients with classic Fabry disease would be severely affected or would have died (6, 7, 29). Two recent studies have suggested that the cardiac variant of Fabry disease may be an important cause of idiopathic left ventricular hypertrophy (7) or late-onset hypertrophic cardiomyopathy (30). Tissue biopsies or autopsy studies of cardiac variants reveal globotriaosylceramide accumulation in the myocardium and not in the vascular endothelium throughout the body (5, 6, 29). These findings suggest that even low levels of α-Gal A can prevent globotriaosylceramide accumulation in the microvasculature and that this lack of accumulation is associated with the absence or attenuation of disease manifestations. Thus, reversal of the underlying vascular endothelial pathology by enzyme replacement therapy will probably be clinically therapeutic in patients with classic Fabry disease.

Enzymatic and Molecular Diagnosis

In affected males with the classic or variant phenotype, the disease is readily diagnosed by determining the α-Gal A activity in plasma or peripheral leukocytes. In contrast, female carriers can have normal to very low α-Gal A activity; therefore, their specific family mutation in the α-Gal A gene must be demonstrated. Most kindreds have family-specific or private mutations; to date, more than 300 mutations have been identified, of which most are missense (amino acid substitutions) or nonsense (causing premature truncation of the amino acid sequence) mutations. Splicing

defects, small deletions and insertions, complex insertions and deletions, and other rearrangements also have been found. De novo mutations are rare.

CLINICAL TRIALS OF ENZYME REPLACEMENT THERAPY

Extensive preclinical evaluations of enzyme replacement therapy were performed in α-Gal A–deficient mice (31). To date, 109 patients with classic Fabry disease have been evaluated in recent clinical trials of enzyme replacement therapy (12, 13, 32, 33). Human α-Gal A, produced by two companies, has been used in these trials. Recent independent studies comparing specific activity, biochemical composition, and cell uptake of the two preparations—gene-activated human α-Gal A (ga-hαGalA, agalsidase alfa [Replagal, Transkaryotic Therapies, Inc., Cambridge, Massachusetts]) and recombinant human α-Gal A (r-hαGalA, agalsidase beta [Fabrazyme, Genzyme Corp., Cambridge, Massachusetts])—found that the proteins were structurally and functionally very similar, with comparable specific activities and glycosylation (34, 35).

Phase I and I/II Clinical Trials

A phase I trial involving 10 affected males demonstrated that a single dose of ga-hαGalA could reduce the accumulated globotriaosylceramide in the liver and urinary sediment (32). Five single doses were administered (0.007, 0.014, 0.028, 0.056, and 0.1 mg/kg of body weight), each to 2 patients, and no dose effect was observed. A phase I/II open-label, dose-escalation trial involving 15 males with classic disease evaluated five doses of r-hαGalA in dose regimens of 0.3, 1.0, or 3.0 mg/kg every 14 days or 1.0 or 3.0 mg/kg every 48 hours (33). The enzyme was well tolerated, and plasma and tissue levels of globotriaosylceramide decreased rapidly and markedly, as shown biochemically, histologically, and ultrastructurally. The decrease in plasma globotriaosylceramide was dose dependent. Mean globotriaosylceramide content decreased 84% in liver ($n = 13$) and was markedly reduced in kidney in 4 of 5 patients who had pretreatment and post-treatment biopsies. Globotriaosylceramide deposits also were reduced in the vascular endothelium of the kidney, heart, skin, and liver, as demonstrated by light and electron microscopic evaluation. In addition, patients reported decreased pain and increased ability to perspire.

Phase II and III Clinical Trials

A single-center, double-blind, placebo-controlled phase II trial of ga-hαGalA involved 26 male patients with neuropathic pain who received 0.2 mg/kg every 2 weeks for 22 weeks (12 doses) (12). The primary efficacy end point was pain at its worst. Pain medication was withdrawn before evaluations. The severity of neuropathic pain improved in 14 patients treated with ga-hαGalA and changed little in the 12 patients assigned to receive placebo ($P = 0.02$ for the comparison between groups). Mean creatinine clearance did not change substantially for patients

receiving ga-hαGalA but decreased by 16.1 mL/min for patients receiving placebo ($P = 0.02$). Renal biopsies were reported to show decreased mesangial widening ($P = 0.01$), increased normal glomeruli ($P = 0.01$), and decreased glycolipid inclusions in the renal vascular endothelium ($P = 0.002$) in patients receiving ga-hαGalA. However, 1 patient in the placebo group advanced to renal failure. Plasma globotriaosylceramide levels decreased approximately 50% in patients receiving ga-hαGalA. In related studies of the same patients, the elevated regional cerebral blood flow and abnormal cerebrovascular responses, as measured by [^{15}O] H$_2$O and positron emission tomography and transcranial Doppler studies, were significantly reduced or improved after 22 weeks (36, 37) or 18 to 24 months (38) of treatment.

A phase III multinational, multicenter, randomized, double-blind, placebo-controlled study evaluated the safety and effectiveness of r-hαGalA in 58 patients who received 1 mg/kg of r-hαGalA or placebo every 2 weeks for 20 weeks (11 doses) (13). The primary efficacy end point was the percentage of patients whose renal capillary endothelial globotriaosylceramide deposits cleared to normal or near normal. The histologic clearance of microvascular endothelial globotriaosylceramide deposits in the heart and skin and changes in pain (Short-Form McGill Pain Questionnaire) and in quality of life (Medical Outcomes Study Short Form-36 General Health Survey) were also evaluated. In 20 of 29 patients (69%) treated with r-hαGalA compared with 0 of 29 patients receiving placebo, the accumulated globotriaosylceramide cleared from the renal capillary endothelium ($P < 0.001$). Compared with the placebo group, patients treated with r-hαGalA also had markedly decreased microvascular endothelial globotriaosylceramide in the skin ($P < 0.001$) and heart ($P < 0.001$). Patients receiving r-hαGalA cleared the accumulated globotriaosylceramide in plasma to nondetectable levels. Compared with baseline assessments, both treatment groups had improvements in pain and quality-of-life assessments, which were indistinguishable from a placebo effect. In contrast to the phase II study, patients in this study were not selected for pain and therapy with pain medications was not discontinued during treatment.

All 58 patients who completed the phase III trial received r-hαGalA in an extension study. After 6 months of the open-label therapy, all 22 patients formerly in the placebo group and 20 of 21 patients formerly receiving r-hαGalA (42 of 43; 98%) who had biopsies achieved or maintained normal or near-normal renal capillary endothelial histology. Similar results were observed for skin capillary endothelium; 96% of both former placebo recipients (22 of 23) and of r-hαGalA recipients (23 of 24) who had biopsies achieved normal or near-normal histology. In the capillary endothelium of the heart, histology scores improved with duration of treatment. Among patients who had heart biopsies, 67% (10 of 15) attained normal or near-normal histology after 6 months of r-hαGalA treat-

ment and 82% (14 of 17) attained normal or near-normal histology after 12 months.

RECOMMENDATIONS FOR DIAGNOSIS AND TREATMENT
When Should the Diagnosis of Fabry Disease Be Considered?

In children, pediatricians and family practitioners should be alert to acute, unexplained episodes of pain often accompanied by fever and unresponsive to conventional analgesics; chronic pain or discomfort in the extremities; heat, cold, and exercise intolerance; unexplained gastrointestinal disturbances (diarrhea, vomiting, nausea, and abdominal pain); angiokeratomas (**Figure 2**); hypohidrosis; or mild proteinuria. In most patients, these symptoms persist or worsen with adulthood (19). In adults, other hallmarks of the disease include unexplained renal dysfunction progressing to end-stage renal disease; unexplained cardiomyopathy, especially left ventricular hypertrophy; arrhythmias; valvular abnormalities; stroke; unexplained fatigue or heat intolerance; hearing loss; obstructive pulmonary disease (39); and the characteristic corneal opacity (**Figure 2**). Even in classic Fabry disease, presentation can vary and the absence of certain signs or symptoms should not rule out the diagnosis. If Fabry disease is a possibility, an α-Gal A enzyme level should be obtained before invasive evaluations or treatments are initiated.

What Are the Optimal Methods for Diagnosing Fabry Disease in Affected Males and Carrier Females?

Fabry disease can be diagnosed reliably in males 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 (40). To inhibit cross-reactivity with α-galactosidase B, the α-Gal A assay mixture must include 500 mmol of N-acetylgalactosamine per L (41). Normal enzyme values differ depending on the enzyme source, substrate concentrations, and assay variables.

Carrier detection with the α-Gal A assay is not reliable because some obligate heterozygotes have normal α-Gal A activity. Thus, all women at risk for carrying the disease gene should have molecular studies to detect the family's mutation.

When a diagnosis is made, genetic counseling should be provided to inform the patient of the natural history of the disease; its inheritance; and the options for treatment, including enzyme replacement therapy. Patients should be advised to inform other family members of the availability of diagnostic testing and genetic counseling.

Fabry disease can be diagnosed prenatally by demonstration of an XY karyotype and deficient α-Gal A activity in cultured amniocytes or chorionic villi (42). If the family's α-Gal A mutation is known, molecular studies can replace or confirm the enzymatic diagnosis.

How Should Disease Progression Be Followed?

All patients with Fabry disease should be followed regularly, regardless of disease status or treatment protocols. The course of the disease varies, even among family members with the same mutation. Although signs and symptoms will dictate the frequency and extent of follow-up, lack of overt symptoms does not preclude the need for an annual comprehensive medical evaluation because kidney, cardiac, or cerebrovascular function can decline so insidiously.

Clinical evaluations should involve a multidisciplinary team of subspecialists, which should be coordinated by a physician experienced in the care of patients with Fabry disease. Annual evaluations ensure that patients receive optimal interventions and support and also provide data on the natural history of the disease and the effectiveness of various interventions.

All health professionals who treat patients with Fabry disease should be sensitive to the psychosocial burden of a chronic, rare, progressive disease. Clinical depression and denial among affected males can lead to suicidal tendencies or substance abuse. Guilt among carriers is associated with passing the abnormal gene on to their male offspring. Therefore, emotional support and family counseling should be an integral part of patient care. In addition, providing patients with the resources to learn about their disease and to contact other patients and families struggling with similar issues may help ameliorate feelings of isolation, loneliness, and despair (See Appendix, available at www.annals.org).

The recommendations for following patients with Fabry disease and carriers are based on the clinical experience of the authors and the current understanding of Fabry disease pathophysiology. Because the manifestations and disease progression can vary greatly, recommendations are necessarily general, with additional monitoring dictated by each patient's individual clinical course.

Baseline Evaluation and Follow-up for Patients with Classic Fabry Disease

After a diagnosis of Fabry disease is confirmed, all affected persons should have a detailed medical and family history taken. ABO blood type (43) and secretor status (44) should also be determined because the B blood group antigen is a glycosphingolipid that accumulates in Fabry disease and may be associated with a more severe prognosis.

Pain, gastrointestinal complications, intensity of angiokeratomas, and all other signs and symptoms should be carefully documented at baseline and then at least annually. Monitoring and treating pain is especially important in children and may require additional follow-up. Annual evaluations should include a detailed physical examination, routine hematology and chemistry tests, and urinalysis. In addition, because renal and cardiac disease are all but inevitable and usually begin "silently," adolescent and adult patients should have yearly urinary protein (including a

creatinine-to-albumin ratio) and creatinine clearance tests to determine renal function; at least every 2 years, patients should also have echocardiography and electrocardiography to detect and monitor cardiac abnormalities. Abnormal findings should be monitored more frequently, as indicated. In early adulthood or before initiation of enzyme replacement therapy, baseline magnetic resonance imaging of kidney, heart, and brain is useful to document disease progression and assess effect of therapy.

Follow-up for Carriers in Classic Fabry Families

Even in the absence of symptoms, all female carriers should have a complete baseline examination (as described earlier) performed by a physician with expertise in Fabry disease. Asymptomatic females can be reevaluated every 3 to 5 years, with increasing frequency with age. Symptomatic carriers should be followed annually with tests focused on their disease manifestations.

Follow-up for Atypical Patients with Fabry Disease

Atypical males with Fabry disease usually receive a diagnosis when disease manifestations become evident. They should undergo complete baseline and annual evaluations similar to those described for patients with classic Fabry disease in order to monitor disease progression, especially cardiac and renal symptoms.

What Therapies Are Available?

Fabry disease traditionally has been managed with various supportive, palliative, and nonspecific measures, most of which are standard interventions for the presenting symptom—for example, valve replacement for valvular disease or dialysis and transplantation for renal failure. In the clinical experience of the authors, the following interventions have provided benefit.

Pain, the earliest and most debilitating symptom in childhood and adolescence, can be controlled prophylactically with diphenylhydantoin (45), carbamazepine (46), or gabapentin (47). Narcotic analgesics should be avoided, if possible, because patients may become vulnerable to drug abuse as a result of the depression and psychosocial aspects of Fabry disease. Nonsteroidal anti-inflammatory drugs are generally ineffective for pain relief and may have effects on renal function. Lifestyle modifications to avoid stimuli that precipitate pain can also be important.

Pancrelipase or metoclopramide can ameliorate gastrointestinal symptoms (48). Control of hypertension is essential to minimize renal, cardiovascular, and cerebrovascular disease. Prophylaxis with antiplatelet or anticoagulant medication can be important for patients who have had transient ischemic attacks or a stroke. For patients with proteinuria, use of angiotensin-converting enzyme inhibitors and decreasing dietary sodium and protein intake are recommended (47). Hearing loss can be treated with hearing aids, and noise trauma should be avoided to preserve hearing. Patients should be encouraged not to smoke.

For advanced renal disease, dialysis or transplantation can prolong life because renal failure is the most frequent cause of death in classic Fabry disease. Engrafted kidneys remain free of disease, but other organ system damage continues unabated, particularly the vascular disease of the heart and brain (49, 50).

Who Should Be Treated with Replacement Therapy?

Fabry disease is an inborn error of metabolism with profound clinical consequences and a pathology that begins at birth. Enzyme replacement therapy supplies the patient with the biologically deficient protein and reverses metabolic and various pathologic abnormalities. Therefore, we recommend that enzyme replacement therapy be initiated in all patients with Fabry disease even though important questions regarding dosing and long-term benefits still must be addressed with additional research. Treatment should ideally begin as soon as clinical signs and symptoms, such as pain or isosthenuria, are observed. Although enzyme replacement therapy has not yet been evaluated in affected children, experience in type 1 Gaucher disease indicates that enzyme replacement infusions are well tolerated by young children. Carriers with substantial disease manifestations should also be treated with enzyme replacement therapy. This is an active area of research. There are no published studies of enzyme replacement therapy in patients with Fabry disease who are undergoing dialysis or have received a kidney transplant. However, because these patients are at high risk for cardiac and cerebrovascular complications, including transient ischemic attacks and stroke, enzyme replacement therapy is recommended for these patients.

What Are the Risks and Safety Concerns of α-Gal A Replacement Therapy?

Because of a theoretical risk for inhibited intracellular α-Gal A activity, human α-Gal A should not be co-administered with chloroquine, amiodarone, benoquin, or gentamicin. To date, no patient has experienced an anaphylactic reaction to either α-Gal A product. Use during pregnancy and lactation is cautioned because clinical data are not available.

Treatment with both α-Gal products has been well tolerated, except for mild to moderate infusion-associated reactions, which have been managed conservatively. Although both products are administered at different doses, the initial rates of infusion-associated reactions in the clinical trials were essentially the same: 57% for ga-hαGalA (dose, 0.2 mg/kg) and 59% for r-hαGalA (dose, 1 mg/kg). However, when the infusion time was increased from 20 to 40 minutes for ga-hαGalA, the rate of infusion reactions decreased to about 10%. These reactions were associated with the formation of non-neutralizing IgG antibodies. Renal biopsies did not show evidence of immune complex deposition. The reactions can be managed conservatively with preadministration of ibuprofen and nonsedating antihistamines and by decreasing the infusion rate. More se-

vere reactions can be managed with prednisone. After tolerance is established, the reactions cease and the infusion rate can be increased accordingly. For at least the first 6 months of therapy, all infusions should be performed at a medical facility or under close physician supervision. If infusions are well tolerated thereafter, patients can move to a home-care setting.

Seroconversion rates in the placebo-controlled trials were 64% for ga-hαGalA and 88% for r-hαGalA (88%). These differences presumably reflect the fivefold difference in dose and sensitivity of the immunoprecipitation assay. Because patients with the classic phenotype have little, if any, enzyme protein, the antibody response elicited by infusion of human α-Gal A in the clinical trials was expected. However, in contrast to the clinical experience with protein replacement therapy in hemophilia (51, 52), there is no evidence that antibody formation alters efficacy (12, 13).

What Does Therapy Cost?

As with other recombinant protein therapies, human α-Gal A treatment, including the cost for infusions, is expensive. In Europe, 1 year of treatment for a 70-kg patient costs approximately $160 000 for either Replagal (0.2 mg/kg biweekly) or Fabrazyme (1 mg/kg biweekly). Costs in the United States are currently unknown.

What Are the Goals of Enzyme Replacement Therapy, and How Can Therapeutic Effectiveness Be Assessed?

In young patients, the goal of enzyme replacement therapy is to prevent disease. For older patients with more advanced disease, the goal is to both halt disease progression and reverse the underlying pathologic abnormalities and the resultant organ dysfunction. Clinical experience with Gaucher disease supports these goals (53–56).

Patients receiving enzyme replacement therapy should be followed at least once annually, as we have described earlier. If plasma globotriaosylceramide levels prove to be a useful marker of disease burden and treatment efficacy (13, 31, 33), a goal of therapy may be to normalize plasma levels. For children, monitoring the frequency and severity of peripheral pain and gastrointestinal symptoms also will indicate clinical effectiveness.

What Dose Should Be Used?

The optimal doses for the reversal, maintenance, and prevention of globotriaosylceramide accumulation in the kidney, heart, and vasculature are unknown. Doses of 0.2 mg/kg (12) and 1 mg/kg (13) have been studied in separate randomized clinical trials but trial end points differed. Experience with 1 mg/kg showed clearance of globotriaosylceramide in the vascular endothelium of the kidney, heart, and skin. In addition, renal interstitial and mesangial cells were cleared after 6 to 12 months of treatment (57). However, a higher dose or longer treatment may be required to clear the massive, lifelong accumulation of globotriaosylceramide in podocytes and cardiomyocytes. Thus, long-term experience is required to determine optimal dosing protocols, including frequency of infusions, especially for children, symptomatic carriers, and males treated for end-stage renal disease. Experience with Gaucher disease shows that enzyme delivery and substrate clearance in certain tissues may require higher doses. Preclinical studies in mice with Fabry disease and clinical trials of enzyme replacement therapy support this concept (13, 31, 33).

CONCLUSIONS AND DIRECTIONS FOR FUTURE RESEARCH

With the availability of enzyme replacement therapy, prompt diagnosis and treatment of Fabry disease have assumed new importance. There is no comparable alternative to enzyme replacement therapy for this devastating, progressive disease. Future research should address the development of protocols for early diagnosis as well as optimal enzyme protocols for reversal, maintenance, and prevention of the underlying pathology of Fabry disease, especially for children, patients with compromised renal function, and those with cardiac disease. Enrollment of all patients in a Fabry disease registry is encouraged (See Appendix, available at www.annals.org) to increase knowledge of the natural history and complications of the disease and the efficacy of treatment regimens.

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Appendix. Organizations and Web Sites for Patients with Fabry Disease and Their Families

Organizations that Provide Information and Support for Patients with Fabry disease and Their Families

Fabry Community
e-mail: fabry@genzyme.com
Web site: www.fabrycommunity.com
Phone: 617-768-9000, 800-745-4447
Fax: 617-591-7178, 800-737-3642

Fabry Support and Information Group
e-mail: JJohnson@fabry.org
Web site: www.fabry.org
Phone: 660-463-1355
Fax: 660-463-1356

Genetic Leadership Collaborative
Web site: 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, NY 10029
e-mail: fabry.disease@mssm.edu
Web site: www.mssm.edu/genetics/fabry/fabry.html
Phone: 866-MD-FABRY (322-7963)
Fax: 212-360-1809

Lysosomal Storage Disease Network
Web site: www.lsdn.com

National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, MD 20892
Web site: www.ninds.nih.gov

National Organization for Rare Disorders (NORD)
PO Box 8923
100 Route 37
Fairfield, CT 06812-8923
e-mail: orphan@rarediseases.org
Web site: www.rarediseases.org
Phone: 203-746-6518, 800-999-NORD (6673)
Fax: 203-746-6481

Web sites with Medical, Technical, and Bibliographic Information about Fabry Disease and Its Mutations

www.uwcm.ac.uk/uwcm/mg/search/119272.html
Web site of The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff, from the University of Wales College of Medicine

www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispmim?301500
OMIM Web site (Online Mendelian Inheritance in Man). A catalog of human genes and genetic disorders. The data base contains textual information, pictures, reference information, and copious links to NCBI's Entrez database of MEDLINE articles and sequence information.

http://bioinfo.weizmann.ac.il/cards
Weizmann Institute of Science GeneCards Web site. A data base of human genes, their products, and their involvement in disease

Fabry Disease Registries

Fabry International Research Exchange (FIRE)
Web site: http://spitfire.emmes.com/study/fire

Fabry Registry
Web site: www.fabryregistry.com

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