

Review Article

Anderson-Fabry Disease: A Cardiomyopathy That Can Be Cured

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Anderson-Fabry disease (AFD) is a hereditarily transmitted (with X-linked transmission and locus on chromosome Xq22) lysosomal metabolic disorder.¹ It should be noted that AFD follows X-linked dominant rather than recessive transmission, as is indicated by the fact that the prevalence of cardiac involvement in heterozygote females is high and might be as high as in males. It is a lysosomal storage disease, resulting from a deficiency of the lysosomal hydrolase α -galactosidase A (α -GalA). The total or partial failure of the activity of this enzyme inhibits the metabolism of glycosphingolipid (mainly globotriosylceramide, Gb3) to lactosylceramide, resulting in the accumulation of significant amounts of Gb3 within the lysosomes of various tissues, mainly of endothelial cells.²

This biochemical disorder and the subsequent lysosomal Gb3 accumulation in endothelial cells lead in turn to regional ischemia and infarcts, especially in the kidneys, heart muscle and brain.³ The vessels of the microcirculation of the skin are dilated and become hyperplastic, resulting in the formation of the characteristic angiokeratomas (Figure 1). These skin lesions are accumulated in groups of telangiectasias, with a blue or dark red tint that does not change with the application of pressure. They measure between the size of a pinhead and a

few mm, and are mainly seen in the periumbilical region, on the upper thighs and perinatal area, or on the palmar surface of the upper limb (Figure 2). Early and significant deposition of glycosphingolipid in the podocytes of renal glomeruli is responsible for the albuminuria.

Pathophysiology of Fabry cardiomyopathy

The classic phenotype of Fabry disease has an estimated incidence of approximately 1 in 50,000 males. But the true incidence is likely to be higher than originally thought, owing to the existence of milder, later-onset variants of the disease as identified by newborn screening. It seems that the ratio of later-onset to classic phenotypes may be as much as 11:1, raising the incidence of Fabry disease up to 1 in 3,000 or even 1 in 1,250 male births.^{4,5}

The exact mechanism by which hypertrophy and fibrosis in the heart are created is not fully understood. Lysosomal Gb3 accumulation in the myocardium is responsible for only 1-3% of mass in the hypertrophic heart,⁶⁻⁸ indicating that the left ventricular hypertrophy is not a direct result of Gb3 filtration. However it is this primary Gb3 accumulation that initiates the other pathological processes.

Several growth factors, such as the Gb3 metabolite lyso-Gb3,⁹⁻¹⁰ or mechanisms of

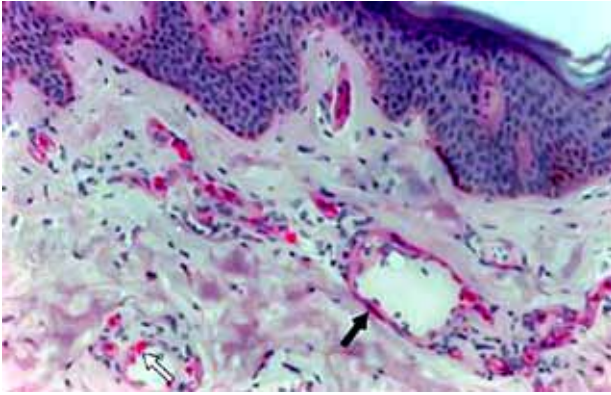


Figure 1. Tissue biopsy of skin showing the dilated blood vessels in the subcutaneous tissue. Reprinted with permission from Elsevier (The Lancet 2001; 357: 138-140).

oxidative stress¹¹ induced by excess of intracellular Gb3, resulting in deregulation of cell adhesion molecules in vascular endothelial cells, have been implicated in the development of hypertrophy and fibrosis in the myocardium. Mechanisms of oxidative stress may cause microvascular lesions in coronary vessels, leading to myocardial necrosis and reduction of cardiac reserve. Similar differences in mitochondrial metabolism that have been observed in the walls of the left ventricle of patients with hypertrophic cardiomyopathy, with a confirmed sarcomeric protein gene mutation, as well as in skin fibroblasts of patients with Anderson-Fabry disease, led to the hypothesis that the accumulation of Gb3 probably destroys the mitochondrial energy metabolism.^{12,13} Further research data will be needed for us to fully understand the pathophysiological process of the disease.



Figure 2. Characteristic telangiectasias (angiokeratomas) on the palmar surface of the upper limbs. Reprinted with permission from Elsevier (The Lancet 2001; 357: 138-40).

Similarly, Gb3 accumulation in the valves and in the atrioventricular node causes valvular heart disease and electrical conduction disturbances. The myocardial fibrosis predisposes to ventricular arrhythmias, whereas atrial deposition of Gb3 and the consequent dilatation due to increased ventricular filling pressures lead to an increased incidence of atrial arrhythmias.

Clinical picture

Extracardiac events

Early symptoms appear on average in males at the age of 9 years and in females at the age of 13.

The neurological manifestations include intermittent episodes of severe pain in the extremities (acroparesthesias are especially common in young male patients aged <15 years),¹⁴ poor exercise heat and cold tolerance, hearing reduction or loss and tinnitus, as well as the characteristic Fabry pain crises (severe episodes of “burning” pain that are experienced in the hands and feet or even throughout the body and can last from several minutes to weeks).

Kidney involvement is a prominent feature and is the main cause of premature death in classic Fabry disease. Microalbuminuria may be apparent in adolescence and early adulthood. Progressive kidney disease is marked by the progression of proteinuria, an increase in serum creatinine levels, and the reduction of the glomerular filtration rate during the third decade of life. Long-term hemodialysis, and renal transplantation are often required.¹⁵

Central nervous system involvement includes stroke, transient ischemic attack, white matter lesions of the brain, hemiparesis, vertigo or dizziness episodes, and vascular complications such as diplopia, dysarthria, nystagmus, ataxia, memory loss and hearing impairment.¹⁶

Ocular manifestations include opacity (cloudiness) of the cornea during microscopic slit lamp examination, which does not affect vision, and opacity of the lens.

Dermal manifestations of Fabry disease include cutaneous vascular lesions (angiokeratomas) and abnormal sweating (anhidrosis or, more commonly, hypohidrosis). Gastrointestinal manifestations of Fabry disease are common (epigastric pain, nausea, diarrhea), and non-specific manifestations in the mental realm (e.g. depression) are also observed.

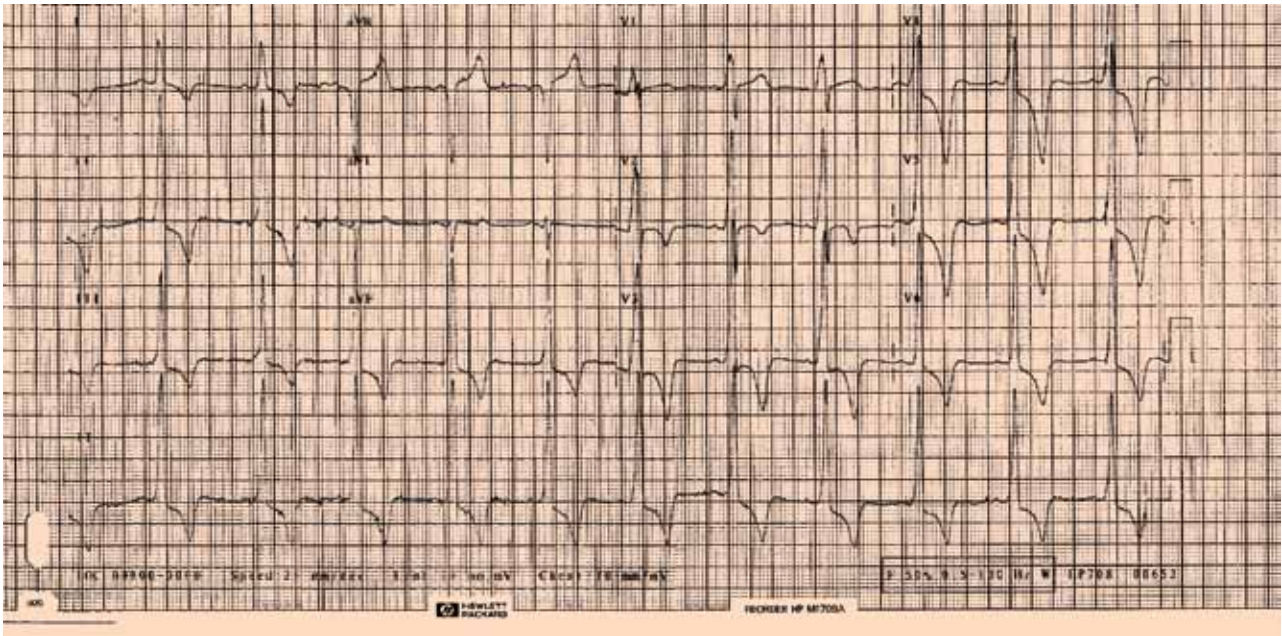


Figure 3. Resting electrocardiogram in a patient with Anderson-Fabry Disease, showing signs of electrical left ventricular hypertrophy, concomitant repolarization abnormalities (strain), and shortening of the PR interval. (Personal archive, E. Sevdalis - E.K.K.A.N).

Cardiac events

The heart is affected in almost all patients with Anderson-Fabry disease as the disease progresses.¹⁷ Although myocardial infiltration with Gb-3 starts quite early, symptoms from the cardiovascular system appear much later. In male patients the mean age of onset is 32 years and in females 40 years. The incidence of symptoms is the same in both genders. Specifically, 22% of female and 20% of male patients show dyspnea, 22% of women and 19% of men have angina,

palpitations are present in 26% of both sexes, and 2% of women and 4% of male patients have syncopal episodes.

The cardiovascular complications of the disease include myocardial hypertrophy of the left ventricle (Figures 3 and 4), thickening of the material of the valves, dilatation of the ascending aorta and conduction disturbances.^{18,19} In the end stage of Fabry cardiomyopathy, extensive areas of myocardial fibrosis are found, as well as severely impaired systolic and diastolic left ventricular function.²⁰

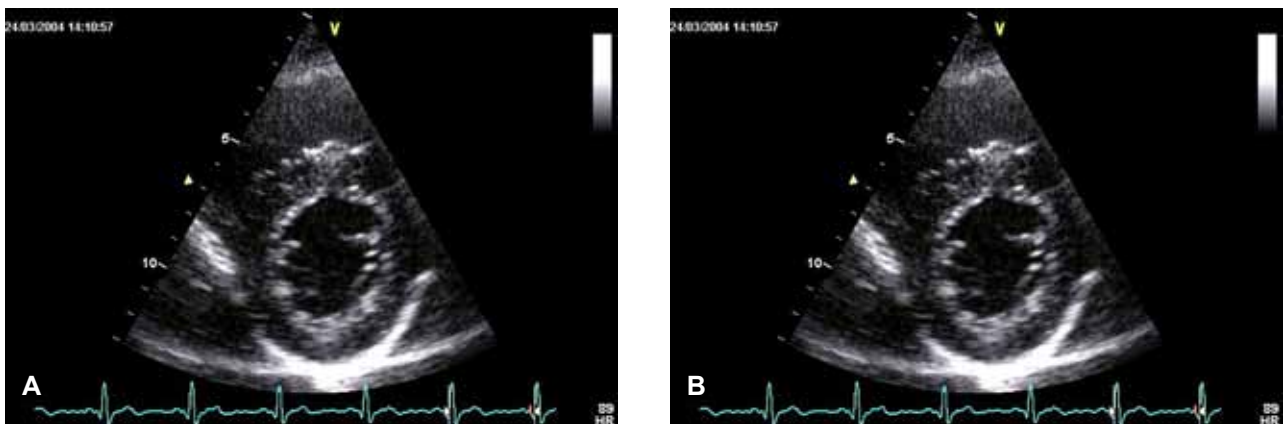


Figure 4. Two-dimensional echocardiographic imaging of a patient with Anderson-Fabry disease. A: Parasternal long-axis view; B: Parasternal short axis view. Highly diffuse echogenicity and concentric hypertrophy of the left ventricular myocardium can be distinguished, as well as the thickening of the mitral valvular tissue. (Personal archive, E. Sevdalis - E.K.K.A.N).

Left ventricular hypertrophy

In male patients, it seems that hypertrophy occurs quite frequently (43% versus 26% in women). Hypertrophy progressively worsens with age (in women less than in male patients) and is accompanied by a progressive partial reduction of left ventricular function.^{21,22} The functional changes occur most frequently in the lateral wall of the left ventricle.²⁰ The presence of left ventricular hypertrophy is associated with a higher incidence of cardiac symptoms, arrhythmias and valve disease.¹⁷ In the majority of patients, hypertrophy is concentric, while at the same time an asymmetrical pattern of hypertrophy and left ventricular outflow tract gradient are rare.

Coronary heart disease

Despite the reported high incidence of angina in both men and women, the incidence of acute myocardial infarction is very low (4% in female patients, 1% in male patients).¹⁷ The myocardial ischemia is caused by increased myocardial oxygen requirements and microvascular lesions and not by coronary thrombosis.^{23,24}

Arrhythmias

There is a high incidence of both ventricular and atrial arrhythmias. A wide range of events can be found, such as a small PR interval, various degrees of atrioventricular block, and complex ventricular arrhythmias.²⁵⁻²⁸ Pacemaker implantation will be required in 2-4% of patients.

Valve disease

It seems that the valve lesion that is caused by deposition of Gb3, and secondarily by fibrosis and calcino-

sis, is rarely of particular hemodynamic significance. Abnormalities of the mitral valve are noted more frequently. Valvular abnormalities are not associated with a significant degree of regurgitation.^{17,19}

The serious cardiovascular complications cause significant morbidity and contribute to the reduced life expectancy of male patients, in whom end-stage chronic renal failure is the primary cause of death. In female patients it appears that cardiac complications are the leading cause of death. The main cardiac cause of death is heart failure and more rarely ventricular arrhythmias.²⁵

Cardiac variant of the disease

The heart may be the only affected organ in patients with specific gene mutations,⁷ as well as in female carriers who have reduced a-GalA enzymatic activity (cardiac variant of the disease).^{6-7,29-32} Tissue biopsies and necrotomy studies of patients with the atypical form of the disease have confirmed the accumulation of substantial amounts of Gb3 in myocardial cells, but not in the rest of the body.⁶

Diagnosis

A high average delay has been reported between the onset of symptoms and diagnosis (13-19 years), and many patients remain undiagnosed until adulthood.^{14,33} The disease is most commonly diagnosed in patients who exhibit renal complications.

Early symptoms

The ability to recognize the early signs and symptoms of the disease (Table 1) is extremely critical for early diagnosis. From the family history, the existence of

Table 1. Early symptoms of Anderson-Fabry disease.

Symptom	Description
Neuropathic pain	Numbness, burning in the extremities. Intermittent episodes of severe pain in the extremities lasting from minutes to days
Neurological	Tinnitus, hearing loss
Gastrointestinal	Flatulence, abdominal pain, diarrhea, nausea
Hypohidrosis	Heat intolerance, frequent fevers
Dermal	Telangiectasias with dark red or blue tint, mainly seen in the periumbilical area, on the upper thighs and perinatal area, or on the palmar surface of the upper limb
Central nervous system	White matter lesions of the brain, transient ischemic attacks, early strokes
Cornea	Opacity, with a characteristic star-shaped cornea that does not affect vision.
Renal	Mild albuminuria, proteinuria, decreased glomerular filtration rate, leading to progressively end-stage renal disease

deaths from chronic renal failure or stroke at a young age should be noted. The absence of extracardiac events, however, should not exclude the disease, as it is known that cardiac symptoms predominate in the cardiac variant of the disease.

Noninvasive methods

The most significant electrocardiographic findings are electrical signs of left ventricular hypertrophy, a long QRS interval and a short PR interval in younger patients (Figure 3). As the disease progresses, the ECG records progressive prolongation of the PR interval, all degrees of atrioventricular block and complex ventricular arrhythmias.³⁴ Twenty-four-hour ambulatory electrocardiographic monitoring records non-sustained ventricular tachycardia, and disturbances in heart rate variability.

Ultrasound

On two-dimensional echocardiography, unlike the majority of patients with a family history of hypertrophic cardiomyopathy, who frequently show asymmetrical hypertrophy of the interventricular septum,³⁵ most patients with Anderson-Fabry disease show concentric-type ventricular hypertrophy with no left ventricular outflow tract LVOT gradient,^{19,20} diffused distinct echogenicity of myocardial tissue with regional myocardial wall motion abnormalities, and thickening of almost all cardiac valves, especially the mitral valve (Figure 4).

Diastolic dysfunction is recognized from tissue Doppler measurements (tissue Doppler imaging, TDI), while using strain rate imaging displays a characteristic pattern of “double-peak point”, indicating the development of regional fibrosis.³⁶⁻³⁹ These findings are detectable before the manifest development of left ventricular hypertrophy and the characteristic expression of the classical parameters of echocardiographic diastolic dysfunction, while they are more exacerbated in patients with the disease who have left ventricular hypertrophy. Therefore, TDI and strain rate imaging can be used as sensitive and specific indicators for the early detection of myocardial infiltration of the disease.⁴⁰

Diagnostic laboratory assays

Measuring enzyme activity

The diagnosis of the disease in men is documented by the determination of a-GalA enzyme activity in

plasma, peripheral leukocytes or in cultured fibroblasts. The most reliable method is the measurement of GalA in peripheral leukocytes.³⁰ Levels of the a-GalA enzyme $<1.2 \text{ nmol.h}^{-1}.\text{mL}^{-1}$ are diagnostic of the disease.²⁹ Residual enzyme activity occurs in male patients with atypical forms of the disease who develop late symptoms; it is related to specific mutations, and includes the cardiac variant of the disease.^{1,29} Reduced levels of a-GalA activity, though, do not automatically lead to the diagnosis of Anderson-Fabry disease, since they may be caused by pseudo-deficiency alleles.⁴¹ Female carriers, in contrast, may have slightly reduced or even normal values in the enzyme assay.

Endomyocardial biopsy

Endomyocardial biopsy has been used for the diagnosis of Anderson-Fabry disease, especially in female heterozygote carriers who have no significant clinical findings.^{42,43} The disease has a characteristic appearance in electron microscopy, with the presence of lysosomal inclusions consisting of tightly packed, concentric lamellae (lamellar bodies). The biopsy material should also be carefully examined for iron accumulation in cardiac myocytes or interstitial amyloid deposition, because hemochromatosis and amyloidosis should be taken seriously into consideration in the differential diagnosis of diseases causing systolic and/or diastolic dysfunction of the myocardium.

Genetic testing

In both genders, the diagnosis is confirmed by the discovery of the gene mutation. It is worth noting that so far more than 300 gene mutations of the enzyme responsible for the disease have been reported.^{41,44,45}

The disease can be diagnosed even by prenatal testing of the XY-karyotype in combination with the enzymic determination of a-GalA in amniotic cells or chorionic villi.

Family screening

Family screening of patients with laboratory and genetically confirmed Anderson-Fabry disease is very crucial. On average, 3-10 affected members are found per proband.⁴⁶⁻⁴⁹ Early diagnosis, and the consequent early initiation of medication, have a strong effect on the patient's prognosis. The X-linked type of transmission excludes disease transmission from father to son.

Differential diagnosis

Anderson-Fabry disease should be considered likely in the differential diagnosis of patients (mostly men) with unexplained myocardial hypertrophy of the left ventricle, or hypertrophic⁵⁰ or restrictive⁵¹ cardiomyopathy (there are cases that gradually develop dilated cardiomyopathy).

Anderson-Fabry disease as a cause of “hypertrophic cardiomyopathy” – or better, “idiopathic hypertrophy” – is uncommon. Its prevalence has been calculated as 0-12%,^{42,46,52-53} according to the selection of the population in each study. In the study that included the largest number of patients with hypertrophic cardiomyopathy the prevalence of Anderson-Fabry disease was 1%.⁴⁶ It is crucial for the cardiologist who is treating a patient with hypertrophic cardiomyopathy to include Anderson-Fabry disease in the differential diagnosis algorithm, since this is a disease for which there is currently an effective treatment (Figure 5).

The “usual suspects” in the patient population with hypertrophic cardiomyopathy are male patients with concentric hypertrophy, usually aged over 40 years, without a family history of disease or with an X-linked type of transmission.⁴⁶

Treatment

Enzyme replacement therapy

Enzyme replacement therapy (ERT) is nowadays the treatment of choice for this disease. The treatment stabilizes the levels of Gb3 in the endothelial cells of the myocardium, acting effectively on the main pathophysiological mechanism of fibrosis development in the myocardium and precluding irreversible functional damage. There are two alpha-galactosidase preparations: human protein α -galactosidase A, produced in a human cell line by genetic engineering technology (ga-haGalA, agalsidase alfa, Replagal); and the man-made form of the naturally-occurring enzyme α -galactosidase A (r-haGalA, agalsidase beta, Fabrazyme). There only limited data comparing these approved ERT drugs with each other.⁵⁴

Many studies have shown that enzyme replacement therapy reduces myocardial mass and Gb3 histological score, and improves left ventricular function.^{40,54-61} In addition, all indices of heart rate variability improved significantly in boys after treatment with agalsidase alfa. Agalsidase beta treatment was associated with an improvement in regional myocardial function, as measured by radial peak systolic strain rate and longitudinal systolic strain.^{40,54}

However, recent studies show that if treatment is not started early enough, the results in terms of reducing symptoms and improving heart function and morphology are minimal.^{60,62} In particular, there is no evidence that enzyme replacement therapy improves the impairment of micro-circulation of the coronary vessels or that it increases cardiac reserve. The key to success seems to be a low degree of myocardial fibrosis at the start of treatment.^{54,60,63-66} The diagnosis of subclinical forms of the disease using newer techniques – TDI, strain rate and cardiac magnetic resonance imaging – is therefore particularly critical.

Regarding other systems, treatment reduces neuropathic pain, stabilizes renal function and contributes to the regression of the major pathological complications as well as to an improvement in prognosis.^{55,67-69}

As for the cost of the treatment, it should be noted that in Europe one year's treatment for a patient weighing 70 kg costs approximately €70,000 (Replagal 0.2 mg/kg or Fabrazyme 1 mg/kg, iv infusion every second week). The therapy should continue throughout the patient's lifetime.

The ideal dosage for the prevention and reversal of Gb3 accumulation in target organs of the disease is unknown. But it seems that recurrent (every 2 weeks) infusions of the enzyme derivative in doses of 1 mg/kg results in regression of the pathophysiological process in the vascular endothelium of the kidney, myocardium and skin, while at the same time renal interstitial tissue normalizes after a treatment course of 6 to 12 months. It is possible that higher doses and longer treatment may be required for the pathological depositions in myocardial cells and in the renal glomeruli podocytes to be reversed.⁷⁰⁻⁷¹

Because of the theoretical risk of inhibition of intracellular activity of α -GalA, human α -GalA should not be administered along with chloroquine, amiodarone, benoquin or gentamycin.⁷²

Gene therapy

Studies of the blood-forming cells in bone marrow have led to gene therapies using retroviruses as vehicles to carry and insert working genes into abnormal or diseased cells. Genetic modification of tissues other than bone marrow may also be a suitable approach. Gene replacement therapy has been investigated in the mouse model of Fabry disease; no human trials have been undertaken to date. These trials demonstrate that, in glycolipid storage diseases without central nervous system involvement, various virally modi-

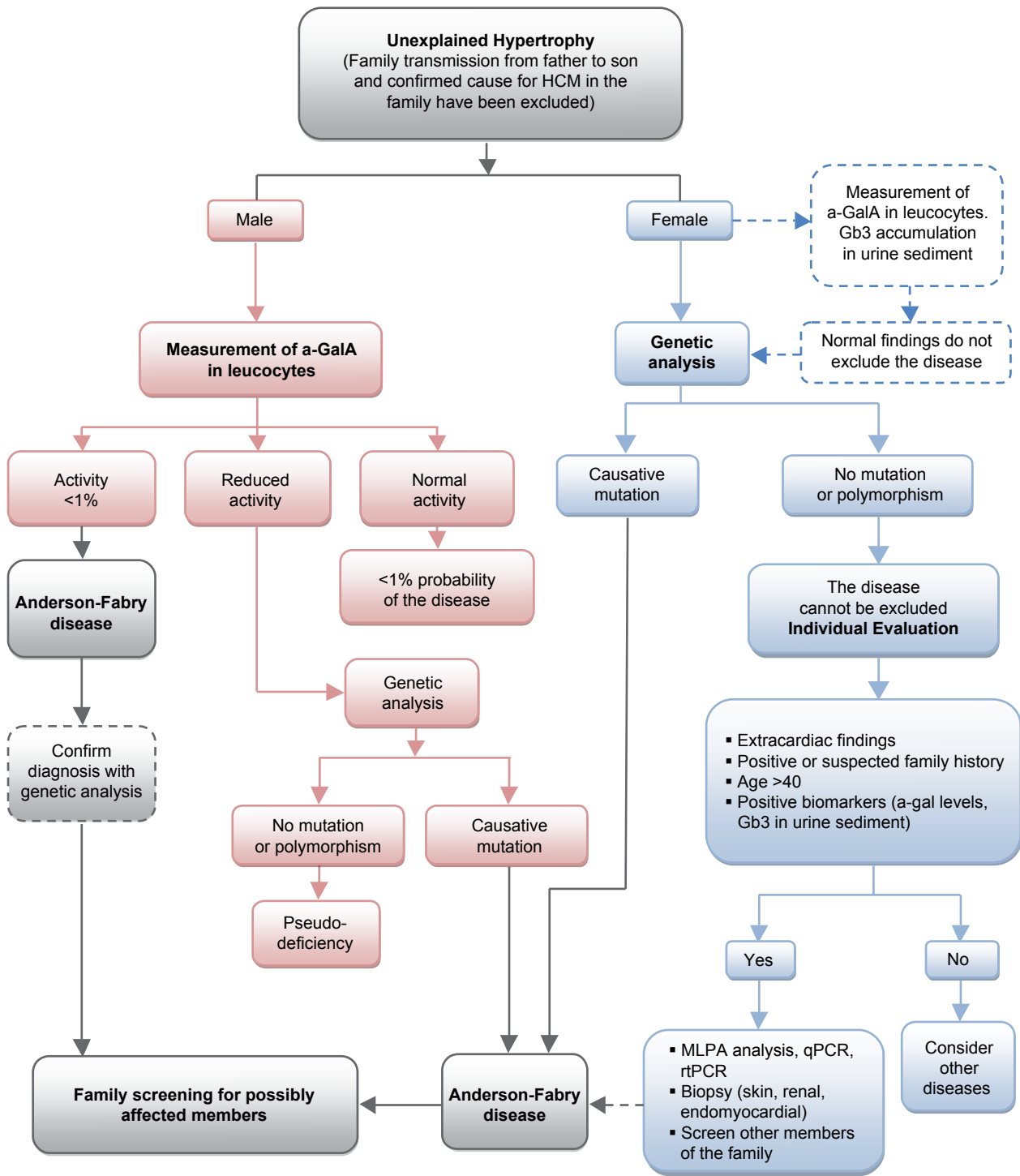


Figure 5. Diagnosis of Anderson-Fabry disease. a-GalA – a-galactosidase A; Gb3 – globotriosylceramide; MLPA – multiplex ligation-dependent probe amplification; qPCR – quantitative real time polymerase chain reaction; rtPCR – reverse transcription polymerase chain reaction.

fied peripheral organs can serve equally successfully as enzyme sources. Even 10-30% of normal enzyme activity can result in at least partial clearance of the storage compound in models of Fabry disease.⁷³⁻⁷⁵

In one recent study, systemic delivery of a cationic lipid-pDNA complex partially corrected the enzyme deficiency and reduced glycolipid storage in a mouse model of Fabry disease. The results are one of the few demonstrations of long-term efficacy in a genetic disease model using non-viral vectors. However, substantial improvements in expression, especially in critical organs such as the kidney, are required before these vectors can become a viable approach to the treatment of Fabry disease and other lysosomal storage disorders.⁷⁶

Adjunctive therapy

Apart from enzyme replacement therapy, in patients with extensive heart disease and symptoms additional treatment is necessary. Blood pressure control using beta-blockers is of particular importance in limiting renal, cardiovascular and cerebrovascular complications of the disease. Before administration, the existence of atrioventricular block or marked bradycardia, which may require pacemaker implantation, should be excluded. Recording of non-sustained tachycardia should indicate implantation of an implantable cardioverter defibrillator (ICD).

In order to reduce the preload, especially in patients with albuminuria, administration of angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists is recommended, in combination with a reduction of dietary sodium intake and proteins. In patients with a prior history of transient ischemic attack or stroke, prophylactic administration of anticoagulants or antiplatelet agents is recommended.

In all patients, systematic efforts should be made to change coronary heart disease risk factors (smoking cessation, control of disturbance of glucose tolerance, dyslipidemia treatment and control of body weight).

Recommendations for patient follow up

The characteristic signs and symptoms of the disease should be carefully recorded in the original study and reassessed at least annually, as renal, cardiac and brain function may deteriorate without warning signs. Blood group is particularly important, because the antigen of B and AB groups is a glycosphingolipid that accumulates in Anderson-Fabry disease and may

be associated with a worse prognosis. The course of the disease varies considerably, even among members of the same family.

All adolescents and adult patients should be tested annually for possible albuminuria, creatinine/albumin ratio and creatinine clearance, and at least every 2 years the ECG and echocardiographic study should be repeated. From the moment even mild damage is detected, retesting should be done more frequently. The reassessment of asymptomatic carriers should be done every 3 to 5 years, with smaller intervals as they get older. Immediately after adulthood, or before starting enzyme replacement therapy, magnetic resonance of the kidney, heart and brain should be performed in order to document the evolutionary stage of the disease and thus to assess the effectiveness of treatment.^{72,77}

Particular sensitivity is required concerning the psychological impact of the disease. Depression caused by the disease may lead to suicide attempts or substance abuse. Carriers of the disease may also be emotionally affected to a significant degree, because of the possibility of transmitting the mutation to their offspring. Therefore, emotional, psychological and family support of both patients and carriers of the disease is essential.

Conclusions

Anderson-Fabry disease is an inherited metabolic lysosomal disorder with a wide phenotypic spectrum, latent and silent course, serious cardiovascular, renal and cerebrovascular complications, and usually a poor prognosis. Given the truly revolutionary enzyme replacement therapy and its striking future perspectives, there is now an urgent need for more sensitive and specific indicators that can facilitate the earlier detection of patients and carriers of the disease. In this way, by taking advantage of the therapeutic possibilities that are offered by modern biotechnology, we could achieve prevention in the young and regression of the very serious and life-threatening complications of the disease in adult patients.

In cardiological terms, Anderson-Fabry disease is a variant of idiopathic hypertrophy and consequently of hypertrophic cardiomyopathy.⁵⁰ Male patients who have hypertrophic cardiomyopathy, without a family history of disease or with an X-linked transmission type, should now routinely be tested for levels of agalactosidase. Potentially diseased women should be referred for genetic testing, the cost of which is now more accessible.

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