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REVIEW ARTICLE

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Fabry disease and its cardiac involvement

Toru Kubo MD

Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University, Kochi, Japan

Correspondence
Toru Kubo, Department of Cardiology and Geriatrics, Kochi Medical School, Kochi University, Kochi, Japan.
Email: jm-kubotoru@kochi-u.ac.jp

Abstract

Fabry disease (FD) is an X-linked lysosomal storage disorder that results from a deficiency of α-galactosidase A activity. This enzymatic defect leads to the progressive accumulation of glycosphingolipids throughout the body and causes multisystemic problems including neurological, ocular, skin, renal, and cardiac manifestations in classical type of FD. The majority of patients with this disease have cardiac involvement that is mainly manifested as left ventricular hypertrophy (LVH). A cardiac variant of FD with late-onset isolated cardiac manifestation has also been recognized. Recent studies have revealed that the prevalence of FD in patients with unexplained LVH is about 1%. Cardiac involvement of FD is associated with significant morbidity and early death due to heart failure or ventricular arrhythmias. As disease-specific enzyme replacement therapy is now available for FD, correct diagnosis is important.

KEYWORDS
cardiac hypertrophy, enzyme replacement therapy, fabry disease, hypertrophic cardiomyopathy

1 | INTRODUCTION

Fabry disease (FD), also called Anderson-Fabry disease, is an X-linked lysosomal storage disease caused by mutations in the gene encoding the lysosomal enzyme α-galactosidase A (α-Gal A).[1,2] The disease was first described as angiokeratoma corporis diffusum by dermatologist Johannes Fabry in Germany and by dermatologist William Anderson in England in 1898. Glycolipid accumulation due to deficient activity of α-Gal A occurs in several organs. Although the prevalence of FD in Japan remains unknown, the prevalence of Fabry disease in Western countries is estimated to range from 1:40 000 to 1:117 000 persons.[2,3] Involvement of the heart, kidney, and brain is particularly important for the prognosis of FD. Enzyme replacement therapy (ERT) is now available for FD, and outcomes of ERT have been shown in clinical trials and observational studies.[4,5]

2 | PATHOPHYSIOLOGY

FD is an X-linked lysosomal storage disorder that results from a deficiency of α-Gal A activity.[1,2] The disease is caused by mutations in the *GLA* gene that codes for α-Gal A enzyme, and more than 300 mutations are associated with the disease. This enzymatic defect leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide and globotriaosylsphingosine, in lysosomes in multiple cell types throughout the body and causes multisystemic problems including neurological, ocular, skin, brain, renal, and cardiac manifestations. Although FD is an X-linked disorder, most heterozygous females are now recognized to be affected.[6,7] This onset of clinical manifestations in females can be explained by a process of X chromosome inactivation, so-called lyonization. X and Y chromosomes are the sex chromosomes of mammals: Female cells contain two X chromosomes, while male cells contain one X chromosome and one Y chromosome. In females, one of the two parental X chromosomes is randomly inactivated in each cell at an early stage of development. This means that female mammals are mosaics, comprising mixtures of cell lines in which the maternal X is inactivated and cell lines where the paternally inherited X is inactivated. For example, the fur coloration of the tortoiseshell cat can be explained by this phenomenon.

3 | CLINICAL PRESENTATION

3.1 | Clinical types

Forms of FD include (i) the classic form of hemizygous males, (ii) the late-onset form of hemizygous males, and (iii) the form of heterozygous females. In male patients with the classic form of FD, symptoms are noted at a young age and there are various clinical manifestations including skin lesions and peripheral neuropathy. Renal involvement with proteinuria is often seen at a young age, and it progresses to end-stage renal function after the third decade of life. The majority of patients with this disease have cardiac involvement that is mainly manifested as left ventricular hypertrophy (LVH). Thus, adults have progressive renal, cardiac, and cerebral involvement (stroke), and these could be the major causes of death related to FD. In this classic form of hemizygous males, no α-Gal A activity is generally seen.

A cardiac variant of FD with late-onset isolated cardiac manifestation has been recognized as Nakao and colleagues reported a 3% prevalence of an atypical variant of FD in male patients with LVH.[8] Patients with this form of FD have cardiac manifestations after middle age without any other signs of FD, and there is often some residual α-Gal A activity. In the late-onset form in hemizygous males, another type, which is a renal variant, has also been reported.

Clinical presentation in female patients is generally milder and occurs later than that in male patients, although heterozygous manifestations vary widely. The most commonly reported clinical features in females are neurological and cardiac disorders.[7]

TABLE 1 Clinical manifestations

Neurologic manifestations
acroparesthesias (constant discomfort, paroxysmal burning pains of the palms and soles)
hypohidrosis
cerebrovascular complications
Skin manifestations
angiokeratomas and telangiectasias
hypohidrosis
Ocular manifestations
cornea verticillata
cataract
tortuous retinal vessels
Ear manifestations
tinnitus
hearing loss (Sensorineural)
Gastrointestinal manifestations
abdominal pain
diarrhea
Cardiac complications
left ventricular hypertrophy, heart failure, arrhythmia and conduction abnormalities
Renal complications
proteinuria, polyuria, end-stage renal disease
Cerebrovascular complications
transient ischemic attack, ischemic stroke

3.2 | Clinical manifestations

Clinical manifestations of classic FD first appear in childhood or adolescence and include intermittent pain in the hands and feet (acroparesthesias), hypohidrosis, and mild proteinuria. The general symptoms are shown in Table 1. Clinical manifestations are variable. Severe limb pain and hypohidrosis are often regarded as feigned disorders and are often misdiagnosed as other diseases. Organ dysfunctions that affect the prognosis include cardiac, renal, and cardiovascular dysfunctions. Cardiac involvement begins with hypertrophy, which leads to the development of heart failure. Renal involvement begins with microalbuminuria, followed in the third decade of life by a decline in glomerular filtration rate and obvious proteinuria, which lead to end-stage renal failure. In the brain, narrowing of vascular lumens that accompanies deposition of sphingoglycolipids causes progressive blockage of intracranial arterioles, leading to cerebral infarction. On the other hand, patients with a cardiac variant of FD show LVH after middle age without any other signs of FD.

In both types of FD, LVH is an early cardiac abnormality shown by echocardiography. It has also been reported that a decrease in mitral annulus velocity determined by tissue Doppler imaging occurs before cardiac hypertrophy and that this index is useful for early detection of cardiac abnormality.[9] The LVH pattern is diffuse concentric in most cases, although cases with asymmetric septal hypertrophy have also been reported.[10] Echocardiographic findings in our male patients are shown in Figure 1. A pressure gradient sometimes arises in the LV mid-ventricle depending on the degree of hypertrophy. In early manifestations of the heart, hypertrophy resembling hypertrophic cardiomyopathy (HCM) occurs, but progression of the hypertrophy causes a decrease in ventricular wall motion, particularly at the base of the posterior wall of the left ventricle, leading to intractable heart failure.[11] Takenaka et al.[12] reported that patients with terminal stage cardiac manifestations of FD showed hypokinesis with thinning of the base of the LV posterior wall. Their histologic studies revealed that the thinned region showed marked fibrosis with almost no myocardial cells.

High voltage of R wave reflecting LVH is often observed on an electrocardiogram (Figure 2). There are various electrocardiographic findings including abnormal Q waves and ST-T changes, and sick sinus syndrome or atrioventricular block sometimes occurs due to accumulation of glycosphingolipids in not only myocardial cells but also in conduction system cells.[13] Shortening of the PQ interval and WPW syndrome-like waves have also been reported as electrocardiographic findings. Some early reports on FD showed a shortened PR interval and its usefulness for detecting cardiac involvement in FD.[13,14] On the other hand, Niemann et al.[15] reported that a short PR interval (<120 ms) was not relevant (16%) in their large cohort of patients with untreated FD in all stages of cardiomyopathy. Attention should be given to the occurrence of lethal arrhythmias such as ventricular tachycardia with the progression of cardiomyopathy. Cardiac

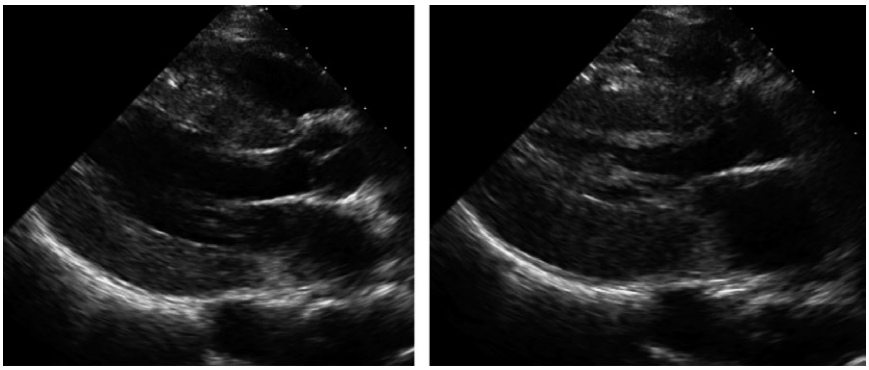

FIGURE 1 Echocardiography in male patient (parasternal long axis view. Left: at end-diastole, right: at end-systole) showing concentric left ventricular hypertrophy with wall thickness of 18 mm

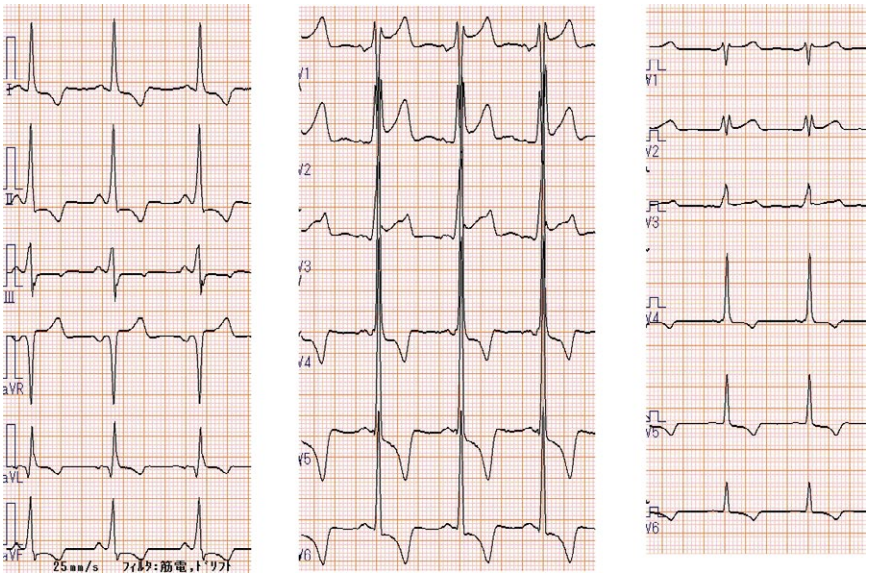

FIGURE 2 Electrocardiography in male patient showing left ventricular hypertrophy with ST-T change

involvement of FD, either the classic form or a cardiac variant, is associated with significant morbidity and early death due to heart failure or ventricular arrhythmias.[1,12]

Cardiac dysfunctions generally occur about 10 years later in women than in men. As for the relationship between female carriers and cardiomyopathy, it was reported that all of the 25 patients over 45 years of age among 55 female patients diagnosed with FD had LVH.[6]

4 | DIAGNOSIS

How can FD be diagnosed? First, it is important to suspect FD whether there are symptoms suggestive of FD. Symptoms seen in the classic type of FD such as acroparesthesias and hypohidrosis provide important clues for diagnosis. In our institute, we in fact experienced two families for which painful extremities related to peripheral neuropathy in adolescence led to a diagnosis of FD. If FD is suspected, a detailed interview with the patient should be conducted to determine whether there is a family history of factors related to FD such as limb pain and dialysis treatment. FD must be included in differential diagnosis for patients with LVH of unknown etiology.

In diagnostic approaches of FD, α-Gal activity is first measured if FD is suspected from characteristic symptoms of classic FD or unexplained LVH. Biopsies should be performed from the involved organs to detect characteristic findings of FD, and to check for *GLA* gene abnormality, as necessary. In male patients, a definite diagnosis is made if marked reduction is found in α-Gal activity in plasma or leukocytes (FD can be ruled out if α-Gal activity is normal.). On the other hand, as female carriers (heterozygotes), as described above, have two X chromosomes in each cell with one of the X chromosomes having been randomly inactivated, enzyme activity in each cell will be either normal or defective. Thus, α-Gal activity varies in plasma and organs. Even if enzyme activity in plasma is normal, the activity in organs might be reduced, that might cause organ dysfunction in results. Diagnosis for female carriers is therefore difficult. The combination of α-Gal activity measurement, histological diagnosis, genetic diagnosis, and family survey is needed for diagnosis in female carriers. Genetic diagnosis is particularly important for female patients. For women who are suspected of having FD from their family history, the following can be assumed: (i) I the father has FD (hemizygote), the daughter will be a heterozygote; (ii) if the mother has FD (heterozygote), there is a 50% probability of the daughter being a heterozygote (genetic diagnosis being necessary); and (iii) if the daughter has FD and the

father does not have FD, the mother is likely to be a heterozygote, although not all mothers will be heterozygotes because there are some de novo mutations.[16,17]

Regarding the incidence of FD in cases of LVH of unknown etiology, Nakao et al.[8] measured plasma α-Gal activity in 230 male patients in whom echocardiography showed LVH (wall thickness ≥13 mm) and found reduced enzyme activity in 7 (3%) of the male patients, for whom a diagnosis of FD with late-onset isolated cardiac manifestation was made. A study conducted in the UK also showed reduced enzyme activity in 4% of male patients who were diagnosed with HCM (in 6% of the patients when the cases were limited to late-onset cases with age at the time of diagnosis of HCM being over 40 years).[18] In our hospital, we performed clinical evaluation including measurements of plasma α-Gal A activity in 177 consecutive unrelated male patients with a clinical diagnosis of HCM (maximum LV wall thickness ≥15 mm) and found that the prevalence of FD in our Japanese cohort was 1.1%.[19] Our data are consistent with results of recent studies with larger numbers of patients by means of screening based on low plasma enzymatic activity.[20,21] Monserrat et al.[20] reported that they screened plasma α-Gal A activity in 328 unrelated male patients with HCM and found a prevalence of FD of 0.9%. Hagege et al.[21] performed systematic screening for FD in patients with a diagnosis of HCM by an α-Gal A assay on dried blood spots using a filter paper test and they identified four FD patients of 278 men (1.4%). Based on the results of studies conducted so far, it can be concluded that FD does exist in patients with cardiac hypertrophy.

5 | TREATMENT

Before the establishment of enzyme replacement therapy, only symptomatic treatment was used for FD. Commonly used anti-inflammatory analgesic drugs have little effect on pain in the extremities, but carbamazepine or phenytoin administered alone or in combination is effective for reducing pain. Ocular manifestations are usually asymptomatic. Cork screw-like corneal opacity is sometimes seen, but treatment is not needed. Treatment for acute sensorineural hearing loss is the same as that for sudden deafness. Treatments for cardiac dysfunction, renal dysfunction, and cerebrovascular dysfunction include administration of antiheart failure drugs (such as angiotensin-converting enzyme inhibitors and beta-blockers), administration of a diuretic and arrhythmia treatment, protein-restricted diet, hemodialysis, and administration of an antiplatelet drug.

Enzyme replacement therapy has recently been developed as a therapy to improve the deficiency or reduced level of α-Gal activity in patients with FD, and the therapy has been covered by insurance in Japan since 2004. Enzyme replacement therapy has been shown to be effective for eliminating globotriaosylceramide that has accumulated in plasma or tissues.[4,5] It has been reported that initiation of this therapy before irreversible changes occur in organs can improve organ dysfunction and symptoms. As for its effects on the heart, it has been reported that in patients without myocardial fibrosis assessed by the magnetic resonance imaging late-enhancement technique, enzyme replacement therapy resulted in a significant reduction in left ventricular mass, an improvement in myocardial function as shown by systolic radial strain rate, and a higher exercise capacity obtained by bicycle stress exercise.[22] In contrast, patients with myocardial fibrosis showed a minor reduction in LVH and no improvement in myocardial function or exercise capacity. Despite drawbacks of the therapy including the need for intravenous administration every 2 weeks, the possibility of hypersensitivity reaction, and high cost of the drug (although the cost burden for the patient is greatly reduced using a system of subsidies for specified patients), enzyme replacement therapy is at present the only effective therapy for FD. However, the effectiveness of the therapy for patients with advanced cardiomyopathy has not been confirmed, and further investigation is needed to determine the effectiveness of enzyme replacement therapy for suppressing disease progression. Studies on chaperone therapy and gene therapy for FD are also currently being conducted.

6 | SUMMARY

It is thought that many cases of FD have been left undiagnosed. As effective therapy has now been established for this progressive disease that has a poor prognosis, attention must be given to the possibility of FD in patients who have symptoms of FD in childhood such as pain in the extremities and patients who have LVH of unknown etiology. Early diagnosis and treatment are important for patients with FD.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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