

Cardiac manifestations in a two-generation family with Fabry disease (RCD code: III-2B.2a)

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Abstract

Fabry disease (FD), which is also called angiokeratoma corporis difusum, ceramide trihexosidosis, and Anderson-Fabry disease, is an X-linked inborn error of metabolism of glycosphingolipid pathway. It is caused by the deficiency of the the lysosomal enzyme – hydrolase α -galactosidase A, which results in the accumulation and subsequent tissue deposition of globotriaosylceramide, the glycolipid substrate for α -galactosidase A. The incidence of the disease varies between 1:17,000 to 1:117,000 males in the Caucasian populations. The disease is less common among women, and if present the symptoms are milder. Enzyme replacement therapy of the agalsidase- α or agalsidase- β offers a specific treatment for patients with FD. Since 2001 the ERT, using recombinant human α -galactosidase A, has become the most efficient and specific therapy, which address the underlying defect of FD. The guidelines on the ERT greatly vary among countries, the main reason being the high cost of this treatment. Pediatric patients firstly suffer from neurological involvement, manifesting as a persistent, neuropathic pain of the extremities, often misdiagnosed as a “growing pain”, as well as gastrointestinal disorders (diarrhea, nausea, vomiting). In the later stages other organs are becoming involved causing multi-organ failure renal insufficiency, cardiovascular impairment, cerebrovascular incidences, cutaneous changes (teleangiectasias, angiokeratomas and lymphoedema), malfunction of sensations organs (cornea verticillata, retinal vascular tortuosity) and other symptom like anhidrosis, sweating problems, heat collapse or depression.

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Key words: angiokeratoma, glycosphingolipid, alpha-galactosidase A, hypertrophic cardiomyopathy

Background

Fabry disease (FD), also called angiokeratoma corporis difusum, ceramide trihexosidosis, and Anderson–Fabry disease, is an X-linked inborn error of metabolism of the glycosphingolipid pathway. It is caused by the deficiency of the lysosomal enzyme, hydrolase α -galactosidase A, which results in the accumulation and subsequent tissue deposition of globotriaosylceramide, the glycolipid substrate for α -galactosidase A. The incidence of the disease varies between 1:17 000 to 1:117 000 men in the Caucasian population. The disease is less common among women and, if present, the symptoms are milder. Enzyme replacement therapy of the agalsidase- α or agalsidase- β offers a specific treatment for patients with FD.

Clinical manifestation frequently begins in childhood but because it resembles more common diseases, the diagnosis of FD

based on symptoms only is challenging. Pediatric patients first show neurological involvement, manifesting as persistent, neuropathic pain of the extremities, (often misdiagnosed as growing pains) and gastrointestinal disorders (diarrhea, nausea, vomiting). In the later stages, other organs are becoming involved causing multiorgan failure, renal insufficiency, cardiovascular impairment, cerebrovascular incidents, cutaneous changes (telangiectasias, angiokeratomas, and lymphedema), malfunction of the sensory organs (cornea verticillata, retinal vascular tortuosity), and other symptom such as anhidrosis, sweating problems, heat collapse, or depression.

Case presentation

We report a case of a two-generation family with FD; a 53-year-old man and his 22-year-old daughter who were referred to our de-

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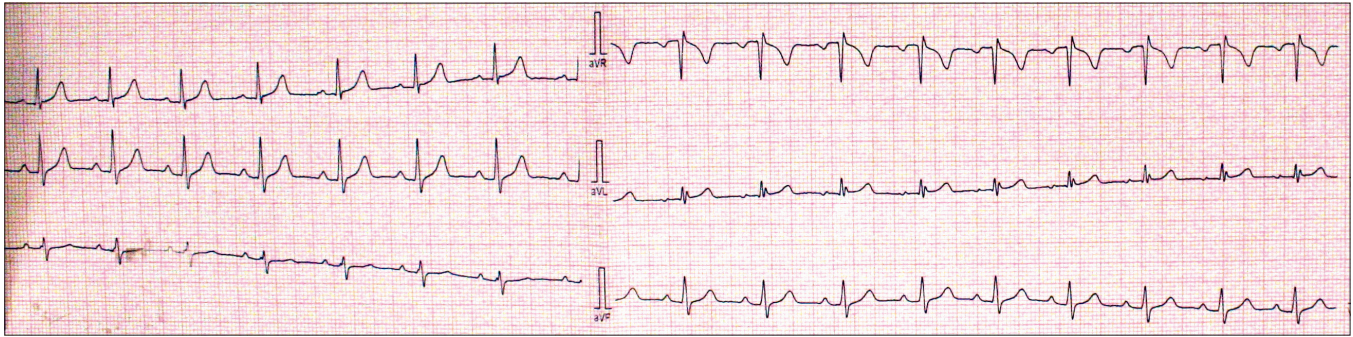


Figure 1. Electrocardiogram in the patient's daughter. Sinus rhythm with a heart rate of 87/min. No axis deviation

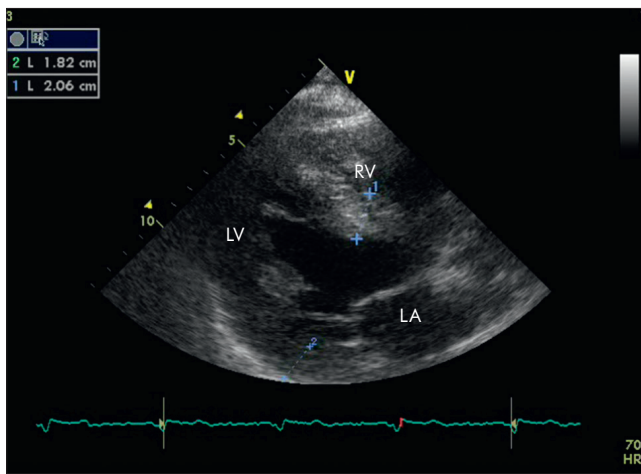


Figure 2. Transthoracic echocardiography of the father. Parasternal long-axis view. Symmetric left ventricular hypertrophy. LV – left ventricle; LA – left atrium; RV – right ventricle

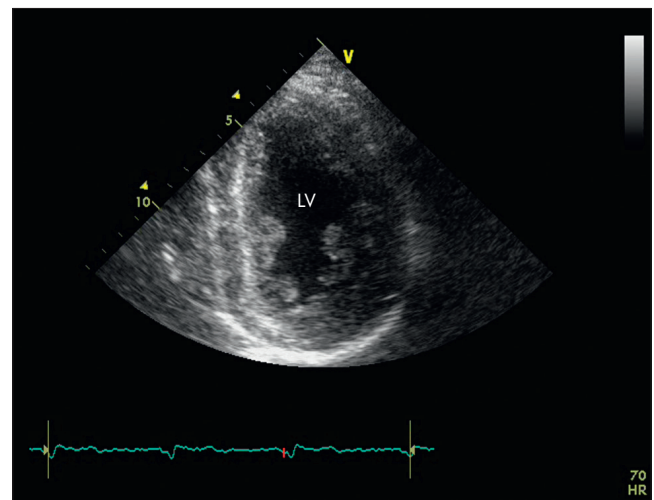


Figure 3. Transthoracic echocardiography of the father. Parasternal short-axis view. Left ventricle with two-layered structure consisting of the thickened hyperechogenic layer of intracellular glycolipid. LV – left ventricle

partment for evaluation and treatment. The father has suffered from severe neuropathic limb pains (precipitated by heat) since childhood. He also had cutaneous changes (angiokeratomas), mostly on the lower back and buttocks, sweating problems (anhidrosis), and visual disturbances. At the age of 28 years, he was diagnosed with hypertrophic cardiomyopathy and, 2 years later, a pacemaker was implanted because of bradycardia. At the age of 47 years, he underwent a cerebrovascular stroke but there were no major neurological consequences and he almost completely recovered. In 2008, he was diagnosed with severe renal insufficiency (proteinuria, hematuria, significantly decreased estimated glomerular filtration rate [eGFR]). Because of suspected amyloidosis, the patient underwent kidney biopsy, which unexpectedly revealed the abnormal deposition of globotriaosylceramide in the glomerular cells. Based on his general symptoms and very low activity of lysosomal α -galactosidase in leukocytes (0.5 nmol/mg/h), he was diagnosed with FD. In the years 2008–2010, specific treatment with agalsidase- α enzyme was introduced.

The patient's daughter has also suffered from various unspecific symptoms including severe neuropathic limb pain, paresthesia, chronic diarrhea, hearing impairment, and visual disturbances since childhood. She was diagnosed with FD at the age of 19 years when a lower activity of lysosomal α -galactosidase in leuko-

cytes (2 nmol/mg/h) was confirmed. The genetic tests were performed, which revealed that she was a carrier of c.1118G>A mutation in the *GLA* gene on chromosome Xq22 (reference sequence NM_000169.2). She has never been on specific enzyme replacement therapy (ERT).

At presentation, the father complained of paroxysmal atrial fibrillation, had gradually increasing dyspnea on exertion, and peripheral edema, while the daughter complained of gradually increasing dyspnea on exertion and palpitations. Apart from mild edema and angiokeratomas on the lower back and buttocks, a physical examination did not reveal any significant abnormalities in the father. There were no pathological findings on a physical examination in the daughter.

A 12-lead electrocardiogram showed a pacemaker rhythm of 60 ppm (the VVIR mode) in the father and no abnormalities in the daughter (Figure 1). Biochemical serum and urine test results were normal in the daughter, while they revealed mild anemia and severe renal insufficiency in the father (creatinine level, 204 μ mol/L; eGFR, 29.9 mL/min). Transthoracic echocardiography in the father revealed significant/severe symmetric left ventricular (LV) hypertrophy (LVH), moderately impaired LV systolic function, as well

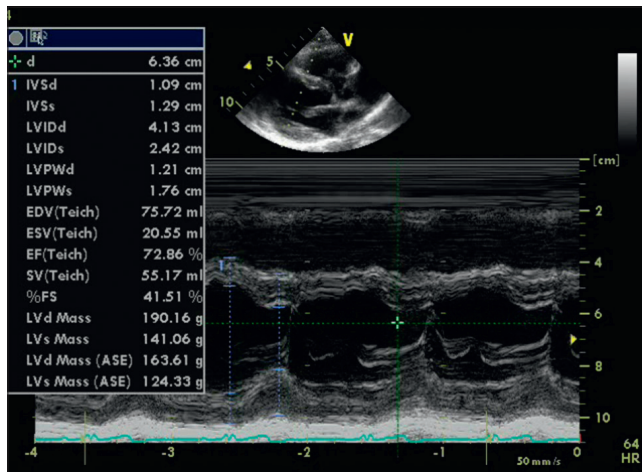


Figure 4. Transthoracic echocardiography of the father. Parasternal long-axis view. Mild projection of the left ventricle in the parasternal long axis. Mild hypertrophy of the posterior wall; preserved ejection fraction of the myocardium

as characteristic thickened hyperechogenic layer (which may represent intracellular glycolipid deposition in the endocardium and the subendocardial myocardium) and hypoechogenic layer that paralleled the hyperechogenic layer (which may represent either the mildly affected mid-wall myocardium or, possibly, a shadowing artifact due to the intracellular lipid-rich layer) (Figure 2, 3). Transthoracic echocardiography in the daughter revealed mild enlargement of the left atrium, proper LV size with preserved systolic function, and mild thickening of the walls (Figure 4). Cardiac magnetic resonance imaging showed a small area of nonischemic damage of the myocardium on the inferior wall of the heart.

Spirometry revealed mild obstruction in the father. On a neurological examination, the father had normal mental status; he was alert, attentive, and oriented; there was no focal neurological deficit. The ankle reflexes were bilaterally decreased; there were no signs of paresis; sensation was reduced in all 4 extremities (right upper extremity up to two-thirds of the forearm; left upper extremity up to half of the forearm; lower extremities up to half of the thighs). His deep sensation was intact; there were no signs of meningeal irritation.

Therapy with valproic acid (300 mg twice daily) was recommended by a neurologist.

A neurological examination in the daughter revealed that she was aware, alert, and oriented. She complained of the lower back pain. The cranial nerves II through XII and the deep tendon reflexes on the upper extremities were intact. Reflexes in the ankles were absent and sensation was reduced in the right lower extremity (nerve roots, L3–L4). Deep sensation was intact; there were no signs of meningeal irritation. Therapy with carbamazepine (200 mg twice daily) was recommended by a neurologist. An ophthalmology examination revealed the characteristic finding of cornea verticillata (corneal deposits). Visual field deficits were also observed (white and red color). Both the father and daughter presented signs of mild depression.

Discussion

Epidemiology

FD belongs to a group of lysosomal storage disorders, which comprises at least 50 genetically distinct diseases. The exact prevalence of FD is unknown and is estimated to range from 1:17 000 to 1:117 000 in Caucasian men.

Genetics

The basis of FD is the deficiency of the lysosomal enzyme, hydrolase α -galactosidase A, which is responsible for the cleavage of the galactose from globotriaosylceramide (Gb3). The lack of this enzyme is a consequence of the mutation in the *GLA* gene, mapped to the long arm (Xq22.1) of the X chromosome. More than 500 mutations in this gene have been identified so far, most of which are private mutations. The progressive accumulation of Gb3 in various cells and tissues, especially endothelium, vascular smooth muscles, autonomic ganglia, dorsal root ganglia, renal glomerular, tubular and interstitial cells, and cardiomyocytes, is probably the main cause of the disease's manifestations. However, it is postulated that Gb3 deposition may be only partially responsible for clinical manifestations, and yet unexplained mechanisms likely contribute to the pathology.

Diagnosis

Considering the effective ERT, although not widely available, the early diagnosis can favorably alter the natural course of the disease. However, the initial clinical manifestation is highly variable, especially in the pediatric setting, which makes early identification of FD difficult. To confirm the clinical suspicion of FD, the measurement of the activity of α -galactosidase in plasma or leukocytes is regarded as a laboratory reference method. The measurement of plasma Gb3 has also been performed but it is considered inferior owing to difficult and long laboratory procedures. A definitive diagnosis is established on the basis of molecular analysis and sequencing of the *GLA* gene. Considering the small size of the *GLA* gene, a direct molecular analysis is relatively simple and provides information on the type of *GLA* gene mutation.

Clinical manifestations

As deposition of Gb3 can occur in virtually all cells and tissues, FD is characterized by a wide array of clinical symptoms. This clinical spectrum ranges from highly symptomatic homozygous men, who have no residual α -galactosidase A activity, to the seemingly asymptomatic heterozygous women.

Kidney involvement is one of the major features of FD and is observed in at least 50% of the men and 20% of the women. The severity of renal pathology usually increases with age. Kidney impairment typically begins in the second or third decade of life and is probably the result of the accumulation of Gb3 in renal cells, including glomerular endothelial, mesangial, and interstitial cells, in podocytes, and in the epithelium of the Henle's loop or in the distal tubules. This leads to the destruction of functional nephrons and, eventually, to progressive chronic kidney disease (CKD). In

untreated patients, CKD may progress to end-stage renal failure, which is the main cause of death in patients with FD.

One of the first and most frequent symptoms is an unspecific pain in various areas, particularly in the limbs, which is a consequence of nerve fiber damage of both the systemic and autonomic systems. It is estimated that 60% to 80% of young boys experience various degrees of pain in their first years of life. Most patients are affected by two different types of pain. The first one is called “Fabry crises”; it is described as episodic and is characterized by burning pain of the extremities, frequently radiating to the other parts of the body. The second type is chronic pain with concomitant paresthesia.

Unspecific gastrointestinal disorders, such as abdominal pain, diarrhea, nausea, vomiting, or irritable bowel syndrome, also occur early in childhood and persist during adolescence. They are probably related to the deposition of Gb3 in the autonomic ganglia of the bowel and mesenteric blood vessels.

The typical skin manifestations are angiokeratomas – small reddish skin lesions commonly found on the buttocks, lower back, umbilicus, and upper thighs or groins. Additionally, telangiectasia and subcutaneous edema can also be observed.

The sensory organs such as the eyes and ears can be affected with the corneal and lenticular changes – “cornea verticillata” (dystrophy of cornea) – causing visual impairment as well as symptoms of tinnitus, vertigo, and even loss of hearing.

Cerebrovascular involvement is characterized by a wide variety of signs and symptoms, including headache, vertigo, dizziness, transient ischemic attack, ischemic stroke, and dementia.

Patients with FD also suffer from respiratory disorders due to airway obstruction and they can present with dyspnea on exertion, chronic cough, and wheezing. The majority of patients have some degree of osteopenia or osteoporosis, which may lead to spontaneous bone fractures. Finally, patients with FD complain about abnormal sweating or overheating during exercise as well as chronic fatigue and difficulty in weight gaining.

Cardiac involvement

The frequency of cardiac involvement increases with age, and approximately half of the adults with FD have some degree of cardiovascular abnormalities. The hallmark is LVH, followed by conduction disturbances, coronary artery disease, aortic and mitral valve insufficiency, and aortic root dilatation. The degree of LVH correlates with the severity of the disease. Importantly, LVH is usually concentric (symmetric) in contrast to asymmetric LVH, typically observed in hypertrophic cardiomyopathy. However, both systolic and diastolic functions are relatively preserved and overt heart failure symptoms are rarely observed. Although not always present, the echocardiograms typically reveal two-layered LV structure, comprising of a thickened hyperechogenic layer of intracellular glycolipid deposition in the endocardium and epicardium and an inner hypoechogenic layer of deposition-spared myocardium. Moreover, LVH may also result from progressive myocardial fibrosis, which almost always starts in the mid-myocardium of the posterior lateral wall. The intensity of fibrotic process determines the development of diastolic and, at later stages, systolic dysfunction. Arrhythmias and conduction disturbances are the consequence of lipid deposits in virtually all components

of the heart conduction system. Moreover, an imbalance between sympathetic and parasympathetic nervous systems may also increase arrhythmic problems. Apart from the signs of LVH, typical findings on an ECG include a short PR interval and prolonged QRS complex often associated with the right bundle branch block pattern. Although almost half of the patients complain about angina-type chest pain, the results of coronary angiography are normal or near-normal in the majority of the cases. The possible explanation of those symptoms is endothelial dysfunction, which leads to the impairment of coronary micro-circulation. The valvular insufficiency is only modest in most of the cases and results from the accumulation of globotriaosylceramide in the valve tissues. Progressive dilatation of the aortic root may potentially have life-threatening consequences. Furthermore, approximately two-thirds of the patients also have associated changes in right ventricular morphology and function, such as hypertrophy and diastolic dysfunction. The ERT may have a beneficial effect on the heart just as it has on the kidneys and other affected organs. It was observed to reduce LVH, improve cardiac function, and clear endothelial lipid deposits.

Management

The optimal management of FD involves conventional treatment, ERT, and adjunctive therapies. The cornerstone of the contemporary therapy is a multidisciplinary approach. One of the most bothersome symptoms in FD is pain, which can be managed in several ways. The neuropathic pain is best avoided by eliminating frequent triggers such as physical exertion or temperature shocks. From the wide array of painkillers, nonsteroidal anti-inflammatory drugs should be avoided because they are ineffective and potentially harmful for the kidneys. The widely used drugs in FD are carbamazepine, oxcarbazepine, gabapentin, pregabalin, and phenytoin. Gastrointestinal symptoms are addressed with metoclopramide and histamine receptor type 2 antagonists. Angiotensin-converting-enzyme inhibitors (ACEIs) or, if not tolerated, angiotensin receptor blockers are used in proteinuria and more advanced stages of CKD. Because CKD progresses during the course of FD, many patients require dialysis or even renal transplantation. Use of aspirin or, if not tolerated, clopidogrel is recommended for stroke prevention. In the case of stroke despite antiplatelet therapy, oral vitamin K antagonists are the treatment of choice. B-group vitamins, particularly B₆, B₉, and B₁₂ are also recommended for patients with cerebrovascular involvement. In the case of exertional angina, the first-line therapy is calcium channel blockers, followed by β -blockers. Device cardiac therapy with permanent pacemaker and cardioverter-defibrillator is increasingly popular in patients with severe conduction disturbances to prevent sudden cardiac death in the case of malignant ventricular arrhythmias. Amiodarone should be avoided because it may interfere with lysosomal metabolism. Although overt heart failure is rare in FD, if present, it should be managed according to the current guidelines with ACEIs and β -blockers as the backbone of therapy.

Enzyme replacement therapy

Since 2001, specific ERT, using recombinant human α -galactosidase A, has become the most efficient therapy, which addresses the underlying defect of FD. The guidelines on the ERT vary greatly between individual countries, mainly because of the high cost of treatment. It is generally accepted that patients with renal manifestations of FD should be started with ERT as soon as the diagnosis is confirmed. Moreover, ERT is also recommended in male and female carriers with substantial nonrenal manifestations, particularly cardiac involvement. At present, there are two enzyme preparations available: agalsidase- α (Replagal[®]), registered for use at a dose of 0.2 mg/kg twice a week and agalsidase- β (Fabrazyme[®]) with a dose of 1.0 mg/kg twice a week. According to the meta-analyses, treatment with agalsidase- α remarkably slows down the progression of renal insufficiency in patients with mild-to-moderate nephropathy and proteinuria. However, this treatment did not show any significant benefit in patients with more advanced nephropathy. As for cardiac involvement, numerous studies have shown a significant reduction in the LV mass, measured by magnetic resonance imaging after 6 months of therapy with agalsidase- α . Moreover, patients with the highest degree of LVH at baseline had the largest decrease in the LV mass. Similarly, treatment with agalsidase- β also improved the regional LV structure and function. However, the effectiveness of ERT on other organs, including the central nervous system, has not yet been established and is still under research.

Prognosis

Male patients, who are more severely affected, have significantly reduced survival. The life expectancy of FD patients is reduced by approximately 20 years for men and 10 years for women compared with the general population. The median survival is less than 50 years. The main contributors of death in untreated patients are renal failure, cerebrovascular and cardiovascular incidents, including myocardial infarctions, cardiomyopathy, and pulmonary embolism.

Screening

Screening for FD can be performed by the measurement of plasma α -galactosidase A levels in patients with unexplained LVH, particularly in those with binary appearance of the LV endocardial border and in those who are diagnosed with hypertrophic cardiomyopathy or have a family history consistent with X-linked disease.

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