Left Ventricular Hypertrophy in Fabry's Disease in an Old Male Patient

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Abstract

Fabry disease is an X-linked disorder due to deficiency of the lysosomal hydrolasea-galactosidase A and the resultant accumulation of glycosphingolipids throughout the body, such as in the heart. Cardiac manifestations in Fabry disease are due to glycosphingolipid deposition in the myocardium, valves, and conduction system. Fabry cardiomyopathy, characterized by progressive severe concentric left ventricular hypertrophy. We, as a result of this, have reported a case of Fabry disease with left ventricular hypertrophy. He was admitted with dyspnea and also dizziness, general weakness, and acroparesthesias. Physical examination showed Angiokeratoma on the skin. The electrocardiography revealed ST-segment depression in leads V3–V6, and changes related to left ventricular hypertrophy. Echocardiography showed concentric left ventricular hypertrophy.

INTRODUCTION

Fabry disease (FD) is a devastating, progressive, hereditary, and rare X-linked recessive genetic disorder of sphingolipid storage disorder characterized by the deficiency of the lysosomal enzyme α-galactosidase A [1, 2]. This enzymatic defect leads to progressive pathologic intracellular deposition of globotriaosylceramide (Gb3) and galactosylceramide, the major glycosphingolipid substrates of α-galactosidase A, in the whole body, especially the skin, nervous system and solid organs such as kidney, eye, and heart [3]. A common manifestation of FD includes angiokeratomas of skin, asymptomatic corneal dystrophy (cornea verticillata and posterior lenticular cataract), severe and early cerebrovascular disease, strokes, infrequent attacks of neuropathic pains and renal failure have been documented [4]. Precipitates of glycosphingolipid in the different parts of the heart, such as myocardium, valves, and conduction system, affect the function and structure of the heart. This change is the cause of various cardiac manifestations in FD [5]. The most crucial feature of Fabry cardiomyopathy is the thickening of the left ventricular wall, without significant dilatation and enlargement of the cavity, which Fabry cardiomyopathy classified by the severity of the wall thickening. In fact, the most common abnormal structural pattern of Fabry cardiomyopathy is left ventricular hypertrophy. (LVH), which may mimic the morphologic and clinical features of hypertrophic cardiomyopathy [6]. LVH in FD is the most important cause of death in affected patients [7]. Electrocardiographic abnormalities also occur in FD. These changes include varying degrees of atrial conduction block, tachyarrhythmia, and ST / T wave abnormalities. [8]. Other cardiovascular complications of FD can be Mitral valve prolapse, thromboembolic events, various cardiac arrhythmias, and sudden death at any time of cardiovascular involvement [6]. Rarely the heart can be the only organ involved called "cardiac variant." This condition has been shown in 3% and 6% of male and female patients with LVH, respectively [9]. We have now reported a case of FD with LVH.

CASE PRESENTATION

History and Physical Findings

A 59-year-old male patient confirmed the case of FD based on documents, and also, His medical history shows hypertension, renal transplantation due to renal failure, 11 years later, Two times and transient ischemic attacks. He was admitted with exertional dyspnea. He also complained of dizziness, general weakness, and acroparesthesias. The patient had no personal or family history of heart disease based on before electrocardiography (ECG), echocardiographic examination, and other documents. On review at first hospitalization, his body temperature, heart rate, and blood pressure were 37.1°C, 94 bit/Min, 145/90 mmHg, respectively. On physical examination of the skin showed small, raised, and dark-red spots which suggestive of Angiokeratoma (Fig 1). Eye fundoscopy and physical examination of other organs were normal.

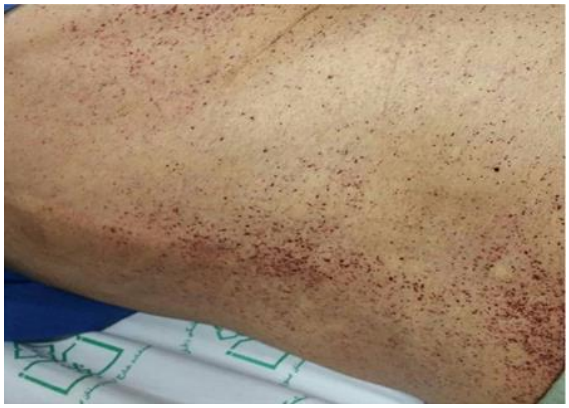

Figure 1. Small, raised, dark-red spots in the all over the body witch suggesting Angiokeratoma

ECG

The ECG changes at admission revealed sinus tachycardia relatively with ST-segment depression in leads V3–V6, I and V1, and modifications related to voltage criteria of LVH.

Echocardiography

Parasternal long-axis echocardiography showed concentric LVH. The systolic septum width was 25 mm, diastolic 23 mm. Global ejection fraction decreased to 40% (Fig 2).

Laboratory Investigations

The initial complete blood count revealed a hemoglobin count of 9.2 g/dL with Mean corpuscular volume 82.1, which suggests chronic disease anemia. A complementary laboratory workup showed that cholesterol, triglyceride, and low-density lipoprotein levels were a high level of normal limits. Also, high-density lipoprotein was low at 34 mg/dl (normal: >50 mg/dl). Arterial blood gases showed metabolic acidosis. Both blood urea nitrogen and creatinine were elevated to 94 mg/dl and 9.4 mg/dl, respectively. Serum levels of albumin were low.

His serum electrolytes levels, the erythrocyte sedimentation rate and C-reactive protein, coagulation screening tests, and other laboratory investigations were within normal limits (or negative).

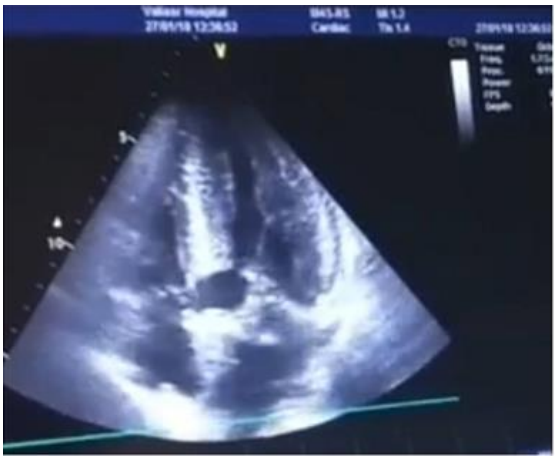

Figure 2. Apical 4 chamber view of echocardiography revealing diffuse left ventricular hypertrophy with increases septal thickness

Treatment and Follow up

Although enzyme replacement therapy (ERT) is a specific treatment for FD; however, we have not accessed to those. Thus, in addition to the particular management for each organ, according to cardiac findings, captopril and carvedilol were begun. He is being followed up now.

DISCUSSION

Epidemiological Aspects

Different literature reports the incidence of FD, ranging from 1 in 476,000 in some studies to 117,000 in other studies [10]. And even in some other studies are high, as high as 1 in 3,100 [11]. Although our review was male, the prevalence of FD in women is four times (3% vs. 12%) for men. There is also a higher prevalence of FD complications in women, but these complications are rare and usually mild and progress slowly [12]. The early step of FD starts in the fetal stage of infancy. However, most patients are clinically asymptomatic during infancy, against too many other lysosomal storage diseases [13]. The first clinical symptoms start in childhood and between the ages of 3 to10 years, a few years later in girls than in boys. Advanced organ systems damage extend to organ failure in both genders, over timing [14]. LVH most commonly occurs in the fourth or fifth decade, at an average age of 32 years and 40 years in men and in women, respectively [15]; however, our case was diagnosed at 59 years old.

Etiology

FD is caused by a deficit in the lysosomal enzyme α-galactosidase A (α-Gal A), the resulting gene mutation,

which is located in the X chromosome region Xq22 (3). Lysosomal enzyme α-Gal A deficiency makes to deposition of Gb3 and galactosylceramide in many cells of the whole body, such as capillary endothelial cells, renal (podocytes, tubular cells, glomerular endothelial, mesangial and interstitial cells), cardiac (cardiomyocytes and fibroblasts) and nerve cells [16].
Cardiac involvement in FD due to deposition of glycosphingolipid in the different parts of the heart, such as myocardium, valves, and conduction system that caused structural and functional changes. These depositions in the heart is like to deposition in other organs. Although deposition of glycosphingolipid may be seen in all cardiac tissues; however, the major concentrations of depositions happen in the left ventricular myocardium, the mitral valve and the left atrium [17, 18].

Histopathology

The histopathology of FD is that Gb3 and digalactosylamide deposition occur in the cells of the body that causing cellular dysfunction and resulting in histopathologic events. These events include cell death, compromised energy metabolism, small vessel injury, impaired K channel function in endothelial cells, oxidative stress, autophagosome maturation, tissue ischemia, and most importantly, Irreversible cardiac and kidney tissue fibrosis [19-21].
The pattern of cardiac hypertrophy in FD differs from hypertensive cardiomyopathy or other infiltrative cardiomyopathies. The literature reports that the Lysosomal deposits, increased contractile proteins, myocyte volume, and consequently left ventricular muscle mass may contribute to left ventricular hypertrophy [17, 22].

Manifestation

The early clinical symptoms of FD begin in childhood [14]. Whole-body cells are affected in FD, including renal epithelial cells, myocardial cells, and neuronal cells, endothelial cells, pericytes, and vascular smooth muscle cells [18]. The common manifestation of FD in male patients with the classic form is acroparesthesias, hypohidrosis, corneal opacities, and kidney, brain, and heart dysfunction [23]. As the complaint of our case in this study, angina and dyspnea are common in cardiac involvement, and these symptoms reported in almost 40-60% of patients with FD [24, 25]. As seen in the case of this study, Left ventricular structural abnormalities are a vital feature of cardiac involvement in echocardiographic studies. As observed in our study, in most cases, LVH is concentric [26]. Also, electrocardiographic changes in patients with FD are generally related to LVH similar to us cases in this study. Other abnormalities of FD in ECG include ST-segment depression and T-wave inversions, a short PR interval due to a short P wave, widening QRS complex and prolonged QTC intervals, supraventricular tachycardia, atrioventricular node blocks, bundle branch blocks, and others arrhythmias [27].
Other cardiac manifestations in FD and symptom/sign of other organs involvement shown in Table 1.

Table 1. Symptoms and Signs of Fabry disease

Organ	Symptoms/Signs
Heart	Impaired heart rate variability, ECG abnormalities (shortened PR interval), Arrhythmias, Mild valvular insufficiency, Aortic root dilatation
Nervous system	Acroparesthesias, headache, vertigo/dizziness, transient ischemic attacks, ischemic strokes, Heat intolerance, tinnitus, vascular dementia
Skin	Angiokeratomas, Absence or ability of sweating, heat and exercise intolerance
Gastrointestinal tract	Nausea, vomiting, diarrhea, abdominal pain after eating, early satiety, Difficulty gaining weight
Kidneys	Microalbuminuria, proteinuria, Increased GFR, Renal failure
Eyes	Corneal and lenticular opacities, tortuosity of the conjunctival and retinal vessels
Auditory and vestibular	hearing loss, tinnitus and vertigo
Respiratory	Exertional dyspnea, chronic cough and wheezing, airway obstruction,
Skeletal	Osteopenia or osteoporosis
Miscellaneous	Chronic fatigue, weight loss, Impaired concentration ability, anemia, depression, azoospermia, hypothyroidism, lymphedema, priapism

Differential Diagnosis and Diagnosis

Differentiate of FD from other causes of LVH, such as other myocardial storage diseases such as amyloidosis, hypertrophic cardiomyopathy, or hypertensive heart disease, is difficult. Using symptom, echocardiographic findings, and ECG may help to differentiate FD from another differential diagnosis in unexplained LVH [28].
Other differential diagnoses of FD include rheumatic fever, systemic lupus erythematosus, Reynold's disease, celiac disease, and sclerosis, and growing disease (in children with FD) should be ruled out in unexplained LVH [29].
In male patients with FD Evaluation of the α-gal, A enzymatic activity in plasma is a useful method for the diagnosis of FD [30]. Autopsy shows cardiac storage of ceramide trihexoside in classical cases of FD [31]. Prenatal diagnosis determines by α-gal A activity in chorionic villi at ten weeks of pregnancy or in cultured

amniotic cells at about 14 weeks of pregnancy [32]. The differential diagnosis of FD from hypertrophic cardiomyopathy is essential because effective enzyme enhancement therapy and ERT for FD has recently been made available [33].

Treatment

Treatment and management of FD are supportive, including comprehensive treatment by ERT [34], conventional medical treatment [35], and adjunctive therapies [36]. In cardiac involvement, the differential diagnosis of FD from hypertrophic cardiomyopathy is critical clinically and outcome because β-blockers, Ca-blockers, and disopyramide generally used in hypertrophic cardiomyopathy, may be contraindicated in Fabry cardiomyopathy patients [12]. In addition; although, there are few data on the effectiveness of enzyme therapy on cardiac involvement in FD [7], enzyme replacement therapy help to resolve of glycolipid accumulation in myocytes, and returns some aspects of the cardiac relationship such as LVH and mass and help improvement in cardiac function [12].

Conflicts of Interest

None

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