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(CASE REPORT)

Fabry disease: A clinical case with literature review

Nadia LOUDIYI [1,*], Siham BELLOUIZE [2], Achraf ZAIMI [1], Mohamed MALKI [1], Najat MOUINE [1] and Atif BENYASS [1]

[1] *Cardiology Department, Military Instruction Hospital Mohammed V, Rabat, Morocco.*
[2] *Cardiovascular Surgery Department, Military Instruction Hospital Mohammed V Rabat, Morocco.*

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Abstract

Fabry disease is a rare genetic disorder related to lipid metabolism, caused by a deficiency in alpha-galactosidase A, a lysosomal enzyme. This deficiency leads to the accumulation of globotriaosylceramide in various tissues of the body, causing a variety of symptoms affecting several organ systems, particularly the cardiovascular system. The diagnosis is mainly clinical and should be suspected in the presence of a relevant personal and/or family history; it is confirmed by measuring enzymatic activity in leucocytes or through molecular testing. Management is multidisciplinary and involves symptomatic treatment and specific therapy, resulting in improvements in both survival and quality of life for affected individuals. We present the case of a 42-year-old patient with global heart failure as part of Fabry disease. This clinical case offers an opportunity to review the literature on cardiac involvement related to this condition and the particularities of the cardiac variant

Keywords: Left ventricular hypertrophy; Heart failure; Transthoracic echocardiography; Cardiac MRI

1. Introduction

Fabry disease is a rare genetic, hereditary disorder linked to the X chromosome, caused by mutations in the GLA gene. These mutations result in a deficiency of the enzyme alpha-galactosidase A in the lysosome. This enzyme deficiency leads to the intracellular accumulation of glycosphingolipids, which causes clinical abnormalities, particularly cardiovascular issues, that are the leading cause of death in these patients, either through heart failure, arrhythmia, or sudden death, significantly reducing life expectancy.

2. Clinical Case

We report the case of a 42-year-old male with cardiovascular risk factors including active chronic smoking (10 pack-years) and no significant medical history, admitted for worsening dyspnea associated with atypical precordial pain, tingling, and myalgia in the left upper limb for one year, which had been neglected by the patient.

On clinical examination, the patient weighed 84 kg, with a height of 1.75 m, resulting in a BMI of 27 kg/m^2. The pulse was regular at 76 bpm, and blood pressure was 120/70 mmHg. Cardiac auscultation revealed clear heart sounds with a regular rhythm and no murmurs. Pulmonary auscultation revealed basal crackles.

The ECG showed a regular sinus rhythm with a heart rate of 77 bpm, normal heart axis, PR interval of 160 ms, left ventricular hypertrophy (LVH) with secondary repolarization disturbances.

*Corresponding author: N LOUDIYI

Chest radiography revealed cardiomegaly with right border overflow and signs of pulmonary hypertension. Laboratory tests showed normal renal function (creatinine clearance at 55 ml/min) and elevated NT-ProBNP (800 ng/L), while troponin levels were normal.

Transthoracic echocardiography showed a non-dilated left ventricle with diffuse hypertrophy of the walls, the maximal thickness of 19 mm in the septal wall, without Doppler obstruction. The systolic function was good with an ejection fraction (EF) of 57%, a highly reduced strain of -9%, and a characteristic "rosette" appearance. There was right ventricular free wall hypertrophy (7 mm) with normal right ventricular systolic function. The right atrium was slightly dilated at 21 cm^2 with elevated filling pressures, an intermediate probability of pulmonary hypertension, and a 7 mm pericardial effusion in the left lateral ventricle. No valvular abnormalities or signs of endomyocardial fibrosis were noted.

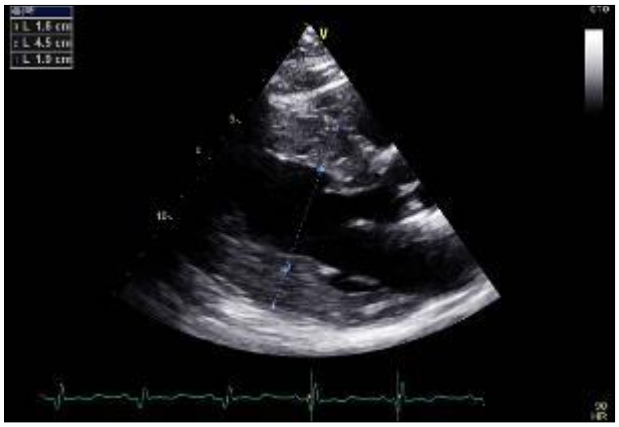

Figure 1 Concentric left ventricular hypertrophy

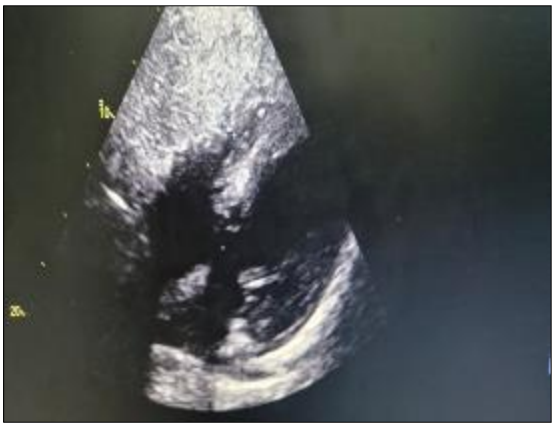

Figure 2 Right ventricular hypertrophy

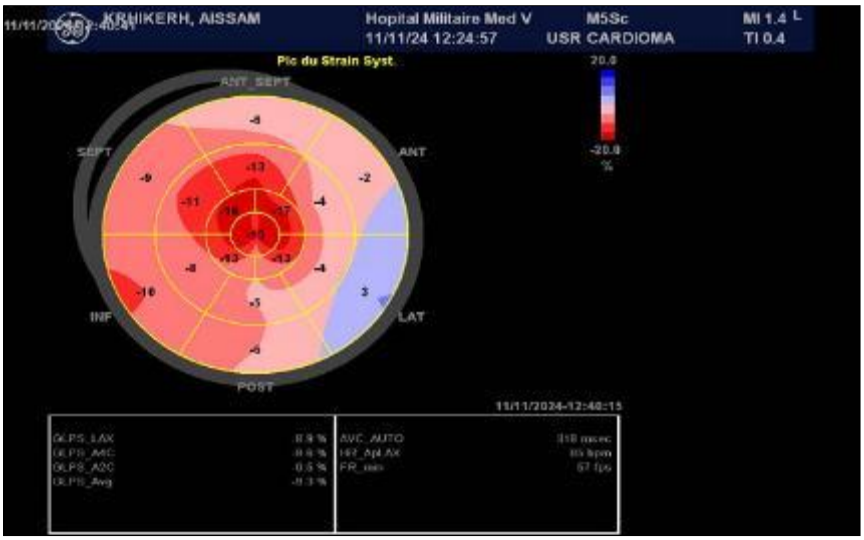

Figure 3 Longitudinal strain anomalies, significantly reduced in the lateral wall typical of Fabry disease

Cardiac MRI showed diffuse, non-obstructive left ventricular hypertrophy with a maximal septal thickness of 20 mm. T1 mapping showed low values in the inferolateral basal area (902 ms), and late gadolinium enhancement showed mid-myocardial enhancement at the basal inferolateral segment and replacement fibrosis at the septobasal area with an EF of 58%.

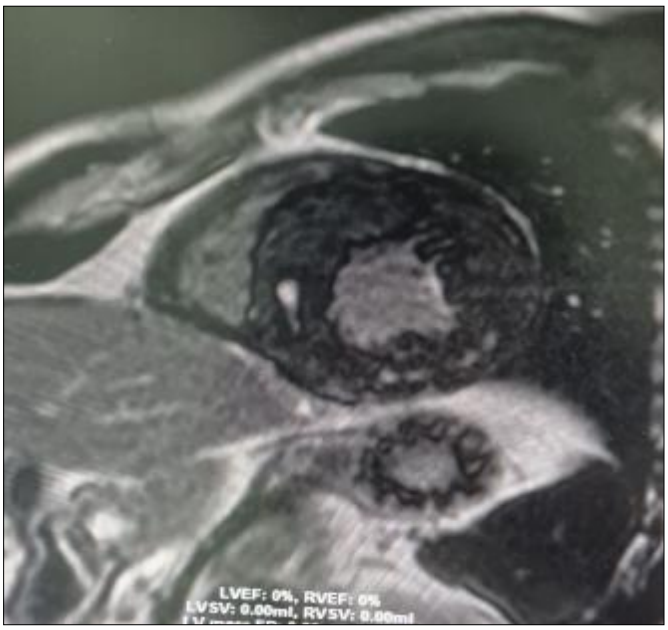

Figure 4 Late gadolinium enhancement in a short-axis view showing diffuse left ventricular hypertrophy with mid-myocardial enhancement at the basal inferolateral segment and replacement fibrosis in the septobasal area

Fabry disease was diagnosed and confirmed by a low alpha-galactosidase level of 1.1 umol/L/H. The patient improved with symptomatic heart failure management, and enzyme replacement therapy was initiated with good progress. The patient remains under surveillance.

3. Discussion

Fabry disease is a lysosomal storage disorder caused by abnormalities in glycosphingolipid metabolism linked to the X chromosome due to mutations in the gene encoding alpha-galactosidase A (Xq22.1, with over 700 known mutations). These mutations lead to the accumulation of globotriaosylceramide (GL-3 or Gb3) in all cells of the body, including skin,

kidneys, nerves, and the heart, resulting in fibrosis and organ dysfunction, symptoms, and premature death [1]. Men are generally more severely affected than women and at a younger age. Cardiovascular complications are the leading cause of death (>40%) with an average age of 55 for men and 66 for women, primarily from sudden death and/or heart failure [2].

The global incidence of Fabry disease is estimated at 1 in 40,000 in the general population, but it is underdiagnosed due to an average diagnostic delay of about 15 years [3]. From a pathophysiological standpoint, the enzymatic deficiency in Fabry disease leads to the accumulation of lipid substances (GL-3) in all cardiac cells: cardiomyocytes, valvular fibroblasts, conduction tissue, and endothelial cells. This triggers various growth factors leading to increased ventricular mass, inflammatory and ischemic phenomena, apoptosis, necrosis, fibrosis, and smooth muscle cell proliferation. These processes are responsible for heart failure (often with preserved ejection fraction), myocardial ischemia, conduction abnormalities (particularly PR interval shortening due to lipid infiltration of conduction pathways), arrhythmias, syncope, or sudden death. Chronotropic incompetence is also common, with functional exercise intolerance.

Cardiac and endothelial dysfunction precede clinical manifestations by several years, which makes early specific treatments more effective before irreversible tissue fibrosis occurs.

There are classic forms presenting in childhood/adolescence with multisystem involvement (skin, eyes, nerves, kidneys, cerebrovascular, cardiovascular...) and the cardiac variant, which accounts for 0.7-1% of hypertrophic cardiomyopathies (HCM) seen in cardiology, with isolated left ventricular hypertrophy or associated conduction disorders (high-degree AV block) or arrhythmias, which can mimic HCM caused by mutations in genes coding for cardiac sarcomeric proteins (prevalence of sarcomeric forms = 1/200 to 1/500 in adults). At least 10% of adult HCM cases have a non-sarcomeric origin (amyloidosis, Fabry disease, mitochondrial diseases...) requiring specific treatments [2, 3].

4. Conclusion

Fabry disease is an important condition to recognize as it has a specific treatment. It is caused by an inherited metabolic defect linked to the X chromosome and the lysosomal enzyme alpha-Gal A, leading to abnormal lysosomal storage. Patients with the late-onset variant of Fabry disease present with heart failure, arrhythmias, and valvular disease. Therefore, it is crucial to consider the diagnosis in the presence of hypertrophic cardiomyopathy (HCM) and to search for signs that point to the cardiac variant of Fabry disease. Although the measurement of plasma alpha-galactosidase has prognostic value, genetic analysis provides diagnostic confirmation. Enzyme replacement therapy remains the cornerstone of management, provided it is started early.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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