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Anderson-Fabry Disease: A Disease with Polymorphic Cardiac Involvement

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Abstract **Case Report**

Fabry disease (FD) is an under-recognized X-linked recessive lysosomal storage disorder resulting from the deficient activity of the enzyme α-galactosidase A (α-Gal A). This 65 year-old male was follow-up in dermatology department since 1972 for angiokeratoma corporis. He was being explored for cardiac symptoms : dyspnea and atypical chest pain. His echocardiography revealed hypertrophic cardiomyopathy initially, and his coronarography was normal. The diagnosis of Fabry disease was evoked clinically and then confirmed by deficiency of alpha-galactosidase α-Gal A activity. The evolution was marked by aggravtion of cardiac symptoms, frequent hospitalisations for heart failure related to dilated cardiomyopathy with severe left ventricular dysfunction, arrythmias, a renal failure, and cerebrovascular events. This case illustrates the rich manifestations of this disease and the polymorphism of cardiac involvement that can lead to fatal complications and poor prognosis. FD is treatable with specific treatment. Therefore, the early diagnosis of this disease is important for amelioration of the morbidity and mortality.

Keywords: Fabry disease, a genetic disorder, deficiency of alpha-galactosidase A activity, cardiovascular dysfunction, specific therapy.

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INTRODUCTION

Fabry disease is an X-linked lysosomal storage disorder, characterized by decreased or absent activity of lysosomal alpha-galactosidase A. As a result of this enzyme deficiency, globotriaosylceramide (GL-3) and other glycosphingolipids accumulate within various tissues, including kidney, skin and heart (cardiomyocyte, conduction tissue, valve fibroblasts, endothelial cells…) [1]. The prevalence of FD has been estimated between 1/40 000 and 1/117 000 individuals [2]. However, this prevalence is underestimated because of underdiagnosis. Women are less affected than men due to the phenomen of inactivation of X. Recently, cardiac variant have been described, found in 88% of men and in 52% of women with FD and usually appears at the quarantine [2]. It correspond to around 2% of patients initially diagnosed as having familial CMH [1]. Cardiac manifestations are the most leading cause of morbidity and mortality in patients with FD.

This clinical case provides an review on diagnosis of cardiac manifestations and events in patients with and specially the cardiac variant because of their impact in morbidity and mortality.

CASE REPORT

In this article we report an interesting case of 60 years old men, black race, with negative family history, without cardiovascular risk factors, suffering from a skin tropism of Fabry disease diagnosed since 1972 (by measuring the α-Galactosidase A activity that was very deficient). Initially, he was asymptomatic, and the systematic exploration of this disease revealed hypertrophic cardiomyopathy at first, but unfortunately he was lost sight of He accused chest pain and dyspnea class II of NYHA, that he neglected for several years, then a dilated non ischaemic cardiomyopathy has been diagnosed in 2019; (his coronary angiography was normal). He has also an unilateral hearing loss. He was admitted in january 2020 for aggravation of his dyspnea, palpitations, edema of the ankles and asthenia. He was hemodynamically stable, he has a clinical presentation of global heart failure. He had diffuse angiokeratomas and telangiectasias in the gluteal, lower abdominal, lumber and inguinal regions, and on the scrotum, very specific of the Fabry disease (Figure 1).

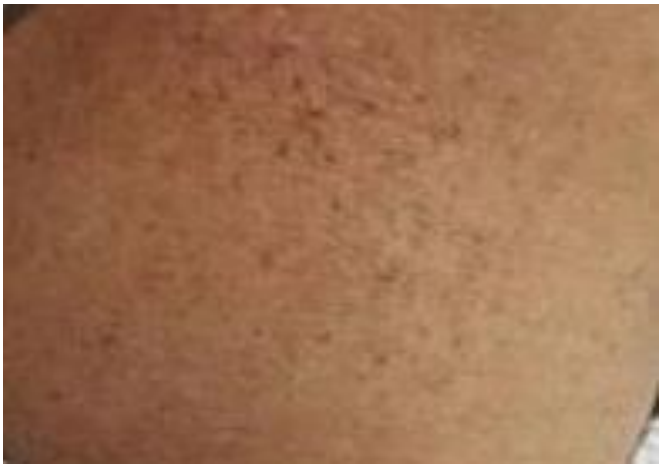

Figure 1: Angiokeratomas very specific of FD in lumber region

His electrocardiogram (ECG) showed regular sinus rhythm with a normal PR interval (200 ms) and a complete left bundle block (with duration of the complexes QRS= 150ms) (Figure 2).

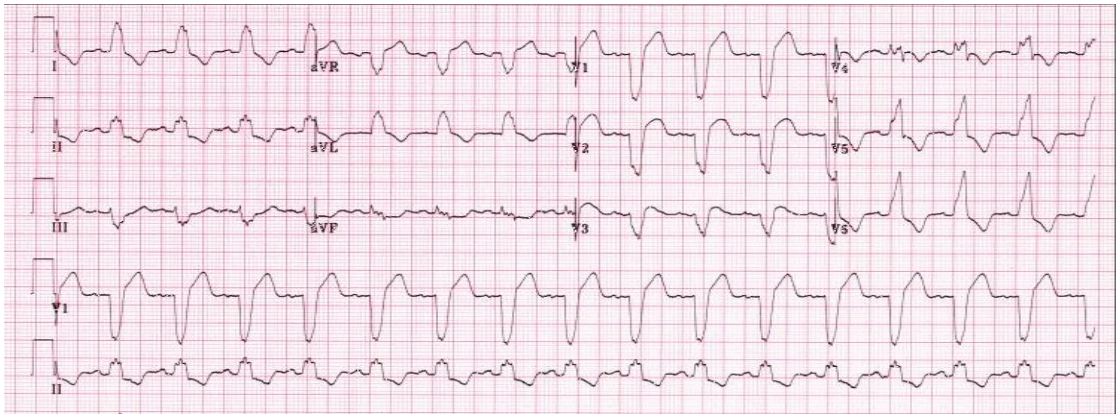

Figure 2: ECG showing a complete left bundle block

His echocardiography revealed a dilated cardiomyopathy with a severe left ventricular dysfonction (ejection fraction =15% with the Simpson's Biplane methode for measurement), and a global hypokinesia. The mitral and aortic valves were thickened with infiltrated appearance. Doppler analysis: Trans mitral profile was restrictive; moderate mitral regurgitation and mild tricuspide regurgitation allowing to estimate systolic pulmonary arterial pression at 58 mmgh. The study of asynchronous parameters showed presence of intra-ventricular and enter-ventricular asynchronism and absence of atrio-ventricular asynchronism.

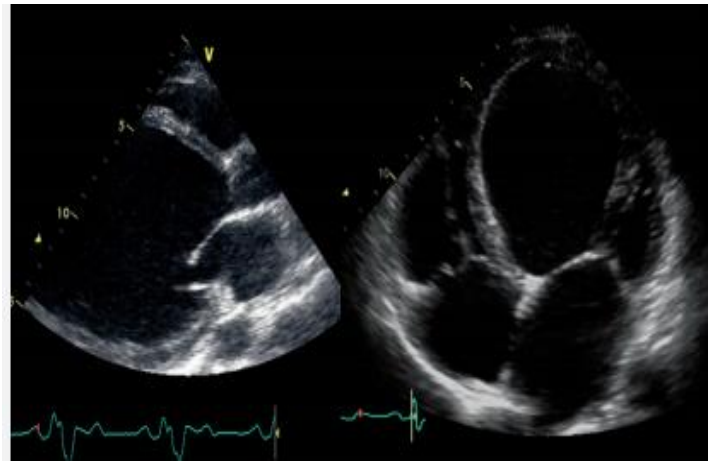

Figure 3: Echocardiography revealing a dilated cardiomyopathy

Routine hematological tests were normal including the coagulation profile. Renal function was normal except for mild proteinuria. High sensitive cardiac troponin (hs-cTn) was normal. NT-pro-brain natriuretic peptide (NT-proB-NP) was at 5000 ng/L (N < 300 ngL).

During his hospitalisation, a 24 hours holter monitoring EKG revealed the apparition of many supraventricular premature beats with some episodes of atrial fibrillation (>30 seconds), frequent and monomorphic premature ventricular contractions (PVC) were recorded without ventricular tachycardia. His endocavitary electrophysiological exploration was negative.

The cardiac CMR (cardiac magnetic resonance) was done to explore his cardiomyopathy ; accurate the characteristics and measures of this dilated cardiomyopathy, the left ventricle was very dilated with severe systolic dysfunction, the LVEF was of 20%, the right ventricle had good size and good systolic function. The MRI revealed the presence of fibrosis with localisation infero-latero-basal of the left ventricle which is specific of the Fabry disease.

The patient was treated with conventional treatment for heart failure : furosemide intravenously then orally, valsartan 40 mg, spironolactone 25mg, carvedilol 6,25 mg and acenocoumarol 4mg then he was switched to sacubitril-valsartan 50mg but he was stopped because it wasn't hemodinamically tolerated and because of the renal failure that it caused.

After few months of monitoring and good therapeutic compliance, the medical staff decided a cardiac resynchronisation therapy : the patient was implanted with an RCT-D and had a well clinical evolution. He was a good responder to resynchronisation.

The enzyme replacement therapy for Fabry disease was never administrated to our patient because of his high cost.

DISCUSSION

Anderson-Fabry disease is a genetically transmitted lysosomal sphingolipidosis disease. The initial signs and symptoms of Fabry disease are typically extra-cardiac, heterogeneous, and appear during childhood, including angiokeratomas, neuropathic pain in the extremities, cochleo-vestibular impairement, glomerular and tubular nephropathy and left ventricular hypertrophy. Vital organ function progressively declines over time, putting patients with FD at risk of developing renal failure, cardiovascular dysfunction, and stroke. This clinical case is important, because the patient has both, extra-cardiac and cardiac manifestations of FD, that are very evocative. The cardiac involvment is responsable of cardiac manifestations (dyspnea, chest pain, palpitations), and cardiovascular complications are the most common cause of death at an average of 55 for men an 66 of women with FD [3]. Cardiovascular events and complications occur in 40% of the patients according to the Fabry registry [4]. The cardiac variant has been recently discribed, the physiopathology is the accumulation of the GL-3 in cardiomyocytes, endothelial cells, valvular tissue, fibroblasts, and the conduction pathway with clinical consequences and electric abnormalities [1]. This is why cardiac involvement in FD is polymorphic and variable.

FD is one of the important of cardiac desease and specially hypertrophic cardiomyopathy with left ventricular hypertrophy and restrictive mitral profil in echocardiography. Involvement of differents heart structures has as a consequence different alterations of the cardiovascular system. Patients develop at first hypertrophic cardiomyopathy, arrhytmias, conduction abnormalities, coronary artery disease and/or valvular abnormalities wich occur in different ways (isolated or associated). At advanced stages of the disease ; the evolution is towards dilated cardiomyopathy with severe systolic and diastolic dysfunction, wich is responsable of the worsening of symptoms, deterioration of quality of life but above all the high incidence of cardiovascular complications ; all impacting patient prognosis with FD. Arrhythmias have a prevalence of 27% in the same registry [4].

Severe ventricular arrythmias and also sudden death have been reported: 8% of the of patients according to a cohorte of 78 patients have presented unsustained ventricular tachycardia (NSVT) ; supra tachyarrythmias such atrial fibrillation has been observed in 17% according to the same study [5, 6]. The high incidence of severe ventricular arrhythmias led to implantation of the automatic defibrillator (ICD) to prevent sudden death [7].

Chronotropic incompetence has also been reported in patients with FD such as sinusal bradycardia and conductive disorders including short PR and high degree atrioventricular block that led to pacemaker therapy [2, 3].

The importance of this clinical case is to remember that FD exist and more that the cardiac variant is frequent and polymorphic. Our patient had initially hypertrophic cardiomyopathy, with preserved systolic function, that was neglected for many reasons, he was at first totally asymptomatic but after few years he presented dyspnea, chest pain and many clinical episodes of heart failure that required hospitalisations. Evolution was marked by the aggravation of the symptomatology, limitation of physical activities related to the transformation into dilated cardiomyopathy ; but especially the occurrence of cardiovascular complications. This patient has

presented some episodes of atrial fibrillation that required anticoagulation but he unfortunately presented a partially reversible cervebral vascular accident (even if he was under anticoagulation with acenocoumarol with INRs in the therapeutic target between 2 and 3). He also presented frequent PVC in his monitoring ECG without ventricular tachycardia probably related to the myocardial fibrosis confirmed by cardiac MRI.

Cardiovascular therapeutic management in FD must be aggressive and potentialy combine risk factors control, optimal medical treatment of heart failure when established using new drugs and even cardiac resynchronisation if necessary. Anticoagulation for atrial fibrillation or flutter (the CHA2DS2-VASc score does not apply in this case because of the thromboembolic risk is always high) [8]. Implantable cardioverter defibrillator or pacemaker can be indicated referring to current guidelines of the ESC concerning the management of arrythmias and conduction disorders [9].

Specific treatments should be initiated early, upon detection of the first structural or functional cardiac abnormalitities and include also enzyme replacement therapy that should be started precociously, as soon as the diagnosis of Fabry disease is confirmed [10].

The enzyme replacement therapy has revolutionized our knowledge of this disease, and has beneficial effects for patients. This therapy has slowed the progression of the cardiopathy and nephropathy and improved neuropatic pain in patients with FD. This specific therapy aims to arrest the progression of target organs dammage, including cardiac manifestation and to improve the clinical symptoms of FD [10]. It is when treatment is instituted at an early stage of the disease that the benefits of enzyme replacement therapy are greatest but this is rarely because of the delay in diagnosis and management (more than 10 years, for example, for cardiac variants) [10]. This is what unfortunately happened with our patient.

CONCLUSION

This case reminds us of the existence of the Anderson-Fabry disease. Have to think about it in front of any unexplained hypertrophic cardiomyopathy especially in young adult, before reaching the advanced stages of dilated cardiomyopathy with severe systolic dysfunction and the appearance of cardiovascular complications with poor prognosis. The therapeutic arsenal is varied combining symptomatic medical treatment, defibrillator or pacemaker; also the specific treatment of the Fabry disease wich is the enzyme substitutive therapy that revolutionized the therapeutic and improved the prognosis of the patients with Fabry disease.

What is kown about this topic

- The cardiac variant of Fabry disease can involve the patient's vital or functional prognosis.
- Heart failure caused by the evolution of the cardiac FD is a real public health problem.
- Not all the patient are early diagnosted for this pathology and the screening of the cardiac involvement is often done late at the stage of heart damages.

What this study adds?

- The cardiac variant can be polymorphic with different manifestations of varying severity.
- The cardiac complications in FD affect the prognosis and have to be screened systematically
- The enzyme replacement therapy of FD is very beneficial and should be started as early as possible to amliore the prognosis of patients.

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Authors' Contributions

Authors contributed to the conception or design of the work; the acquisition, analysis, or interpretation of data for the work, and drafting the work or revising it critically for important intellectual content.

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