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Original Research Paper

Clinical description of Fabry's disease cardiac variant in two Algerian females

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ABSTRACT:
Despite the X link, Femal with Anderson-Fabry disease can develop severe signs and symptoms of the disease, although there is considerable phenotypic heterogeneity, which correlates most closely with age. We report the case of two sisters (DN-DM) who carry a non-sense heterozygous mutation with insertion of nucleotide c. [931dupC], not known to express a cardiac variant but classical form. The extracardiac manifestations are minor. Both patients report dyspnea (more severe in DN) but no angina. On the EKG, there is a shortening of the PR interval and massive LVH: sokolow index is 60mm (DM) and 83mm (DN). On echocardiography, LVH is underestimated, especially for DM. LV diastolic function is altered in both patients : more severely in DN (E/A=2.3). LVEF remains normal. There is no dysfunction of the RV. No segmental or global kinetics problem is observed. The patients present with a thickening of the mitral valve with a slight insufficiency. Aortic insufficiency is noted in DN without dilatation of the initial aorta. DN and DM show impairment of longitudinal function with a global longitudinal strain of -9.5 (image) and -10 respectively. On cardiac MRI, DM presents myocardial hypertrophy involving the apical antrior and apical lateral, and apical inferior segments as well as the apex of the LV without an area of fibrosis or godalinium enhancement. This hypertrophy distribution exlplains the normality of echo LV mass. DN has greater and more extensive circumferential hypertrophy than DN without fibrosis or gadolinium enhancement. In fine, Our mutation, although heterozygous, has an almost exclusive and severe cardiac expression with uncommon topography of LV hypertrophy.

Keywords: Fabry Disease, Cardiac, Variant, Cardiac variant

INTRODUCTION:

Anderson-Fabry disease is an inherited lysosomal disorder with autosomal recessive X-linked transmission. Women are carriers, while men exhibit significant clinical expression. It is caused by a deficiency in alpha-galactosidase A, leading to an accumulation of undegraded glycosphingolipids in tissues and plasma. In its classic form, the disease presents with multisystemic lesions and a wide range of clinical expressions. The manifestations can be potentially severe, involving life-threatening conditions such as stroke, renal failure, and myocardial infarction. Up to 60% of men with classic Fabry disease present cardiac involvement. This primarily includes left ventricular hypertrophy (LVH), valvular dysfunction, and conduction anomalies [1-3]. The cardiac variant of the disease may manifest as isolated or predominant cardiac involvement, with left ventricular hypertrophy being the most prominent sign, potentially leading to misdiagnosis of "idiopathic" hypertrophic cardiomyopathy of sarcomeric origin. Despite being X-linked, women can develop severe signs and symptoms of the disease, although there is considerable phenotypic heterogeneity, which correlates most closely with age. This is due to the random inactivation of the healthy X chromosome (its non-expression), which can result in a mosaic pattern of tissue-level disease or expression of the "diseased" X chromosome, leading to organ dysfunction.

MATERIALS AND METHODS:

We describe an Algerian family presenting with a predominant cardiac variant of Fabry disease following a heterozygous nonsense mutation with nucleotide

insertion c. [931dupC]. In this family (Figure 1), two sisters suffer from Fabry disease. The younger sister, DM, is 46 years old, and the older sister, DN, is 50 years old. Both cases of Fabry disease underwent physical examination, electrocardiography, Holter monitoring, echocardiography, and cardiac magnetic resonance imaging with gadolinium injection, as well as evaluation of extracardiac manifestations: neurological, ophthalmological, dermatological, and renal.

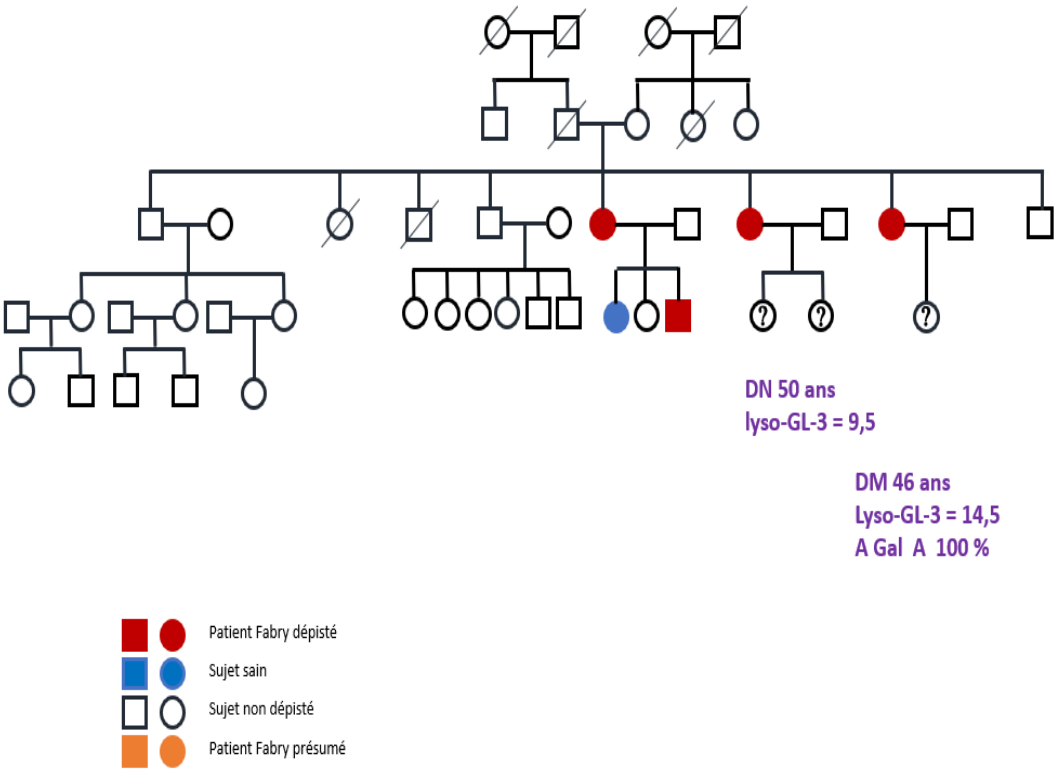

Figure 1 : Family tree

RESULTS:

Extracardiac Manifestations:

Angiokeratomas are not observed in the patients. Ophthalmological examination reveals whorled corneas in both DM and DN, and flake-like cataracts in DM. Retinal tortuosity is observed in DN. Neuropathic pain and acroparesthesia are described by the patients; however, no Fabry crises are reported. Audiograms are performed and return strictly normal for both sisters. On cerebral magnetic resonance imaging, a few punctate rounded demyelinating lesions are found above the tentorium in DM (Figure 2). Neither patient presents with renal insufficiency, but microalbuminuria is detected in the younger DM. Casts are observed in the urinary sediment of the older DN. Bone densitometry of both patients shows no abnormalities.

	Case 1 DM	Case 2 DN
Year of age	46	50
Lyso GL-3 (ng/ml) normal = 3.5.	14,5	9,5
Alpha-galactosidase (mol/L/h) normal > 1.2	1,4	-
Angio-kératome	No	No
Ocular manifestations	yes	No
Anterior capsular opacities	yes	No
Whorled cornea	yes	yes

Conjunctival vascular tortuosities	No	No
Retinal vascular tortuosities	No	yes
Neurological manifestations	yes	yes
Fabry crisis	No	No
Pain	yes	yes
Acroparesthesia	yes	yes
Hypohidrosis	No	No
Exercise intolerance	yes	yes
Stroke	No	No
Orthostatic hypotension	No	No
Deafness	No	No
Glomerular filtration rate cockroft (ml/min)	99	130
Proteinuria (mg/24h)	130	50
Bone densitometry	Normal	Normal

Table 1: Extracardiac Manifestations of Fabry Disease

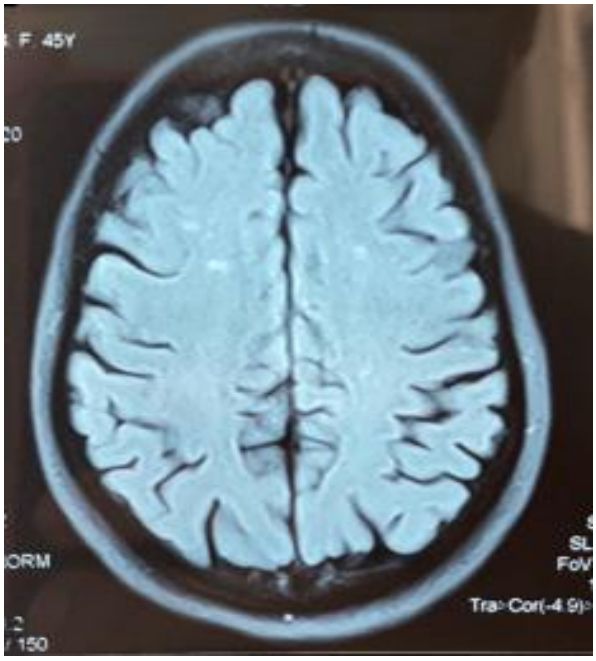

Figure 2: Supratentorial demyelinating lesions

Cardiac Manifestations:

Cardiac manifestations and electrocardiogram data are presented in Table 2. Both patients report dyspnea, which is more severe in DN, who also complains of palpitations. Neither patient reports anginal pain. Cardiac auscultation reveals a mitral regurgitation murmur in DN. Blood pressure is normal for all patients. On electrocardiography, there is a shortening of the PR interval and left ventricular hypertrophy with secondary repolarization abnormalities in both patients. The Sokolow index is 60 mm in DM and 83 mm in DN. Chest X-rays are normal for both cases.

	Case 1 DM	Case 2 DN
Age (years)	46	50
Lyso GL-3	14,5	9,5
Dyspnea	yes	yes
NYHA (New York heart association)	II	III
Angina/Myocardial infarction	No	No

SBP/DBP (mmHg) (Systolic blood pressure/Diastolic blood pressure)	100/50	105/56
Heart rate	52	67
ECG abnormalities	**yes**	**yes**
PR Interval (msec)	118	114
LVH/Sokolow index	yes/60	yes/83
Atrioventricular block	No	No
ST Segment deviation	yes	yes
QT Interval (msec)	440	400

Table 2: Clinical and electrical cardiac manifestations of Fabry disease

The echocardiography and cardiac magnetic resonance imaging data are well described (Table 3). In echocardiography, left ventricular hypertrophy appears to be underestimated by the measured LV mass index, due to the heterogeneous distribution, especially in DM. There is an abnormality in left ventricular diastolic function in both patients, but more severely in DN, who suffers from significant compliance issues with an E/A ratio of 2.3. Left ventricular ejection fraction remains normal. There is no dysfunction of the right ventricle. No segmental or global kinetic problems are observed. However, the patients present with thickening of the mitral valve with mild insufficiency: grade 1-2. The aortic cusps are also remodeled. Aortic insufficiency is noted in DN without initial aortic dilation. DN also shows impairment of longitudinal function with a disrupted global longitudinal strain of -9.5 as shown in Image 3.

	Case 1 DM	Case 2 DN
Echocardiographic data		
Left ventricular end-diastolic diameter (mm)	42	45
Left ventricular end-systolic diameter (mm)	23	30
Interventricular septum thickness (mm)	7	9
Posterior wall thickness (mm)	10	11
Left ventricular mass index (g/m^2)	95	107,9
Left ventricular ejection fraction by simpson (%)	60	63
Fractional shortening (%)	46	34
E/A ratio	1,5	2,3
Segmental and global kinetic disorders	No	No
Global longitudinal strain		-9,5
Mitral insufficiency	yes/grade1	yes/grade2
Mitral valve thickening	yes	yes
Aortic insufficiency	yes	yes
Aortic cusp thickening	yes	yes
Cardiac mri data	29	20
Right ventricle minor axis diameter (mm)	63	56
Right ventricle major axis diameter (mm)	43	44
Left ventricular end-diastolic diameter (mm)	14	23
Left ventricular end-systolic diameter (mm)	18	22
Right atrium surface area (cm^2)	16	22
Left atrium surface area (cm^2)	11	10
Basal anteroseptal wall thickness (mm)	11	8
Basal posterolateral wall thickness (mm)	11	11
Mid anteroseptal wall thickness (mm)	9	11
Mid posterolateral wall thickness (mm)	13	14
Apical anteroseptal wall thickness (mm)	9	18
Apical septal wall thickness (mm)	13	16
Apical lateral wall thickness (mm)	12	14
Apical posterior wall thickness (mm)	14	15
Apex thickness (mm)	71	68
Ejection fraction (%)	131	150
Left ventricular Mass (g)	No	No
Pathological enhancement with gadolinium	No	No

Table 3: Cardiac imaging data

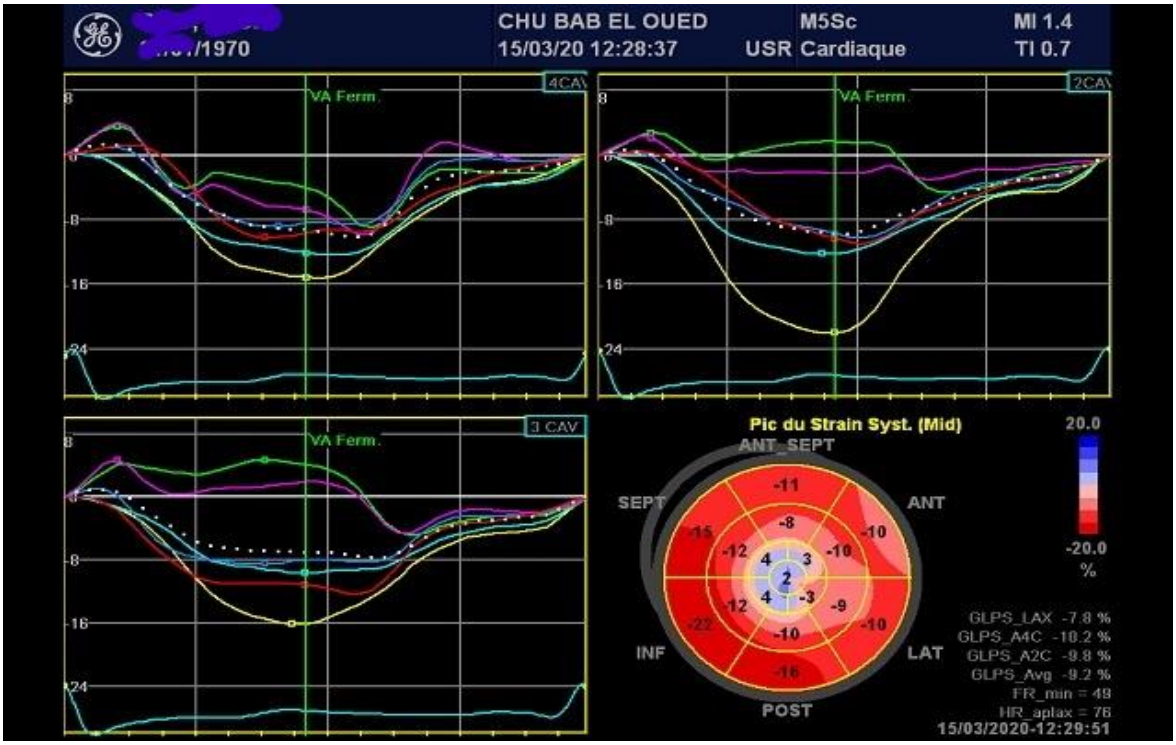

Image 3: DN, 50 years old. Global longitudinal strain: -9.2

On cardiac magnetic resonance imaging, DM presents myocardial hypertrophy involving the antero-apical, lateral-apical, and infero-apical segments as well as the apex of the left ventricle without any area of fibrosis or gadolinium enhancement (Image 2). DN exhibits more extensive and significant circumferential hypertrophy than DM without fibrosis or gadolinium enhancement (Image 4).

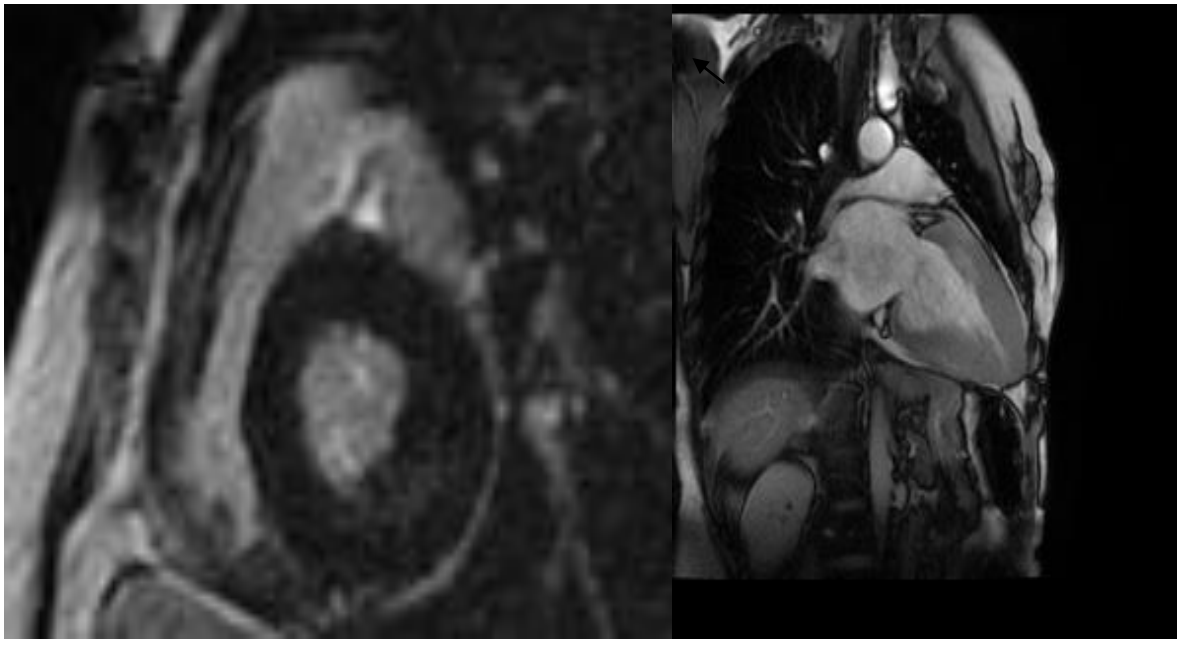

Image 4: Cardiac MRI of DN, 50 years old

DISCUSSION:

Our patients are relatively young. This explains the presence of ocular manifestations, neuropathic pain, acroparesthesia, and microalbuminuria without renal insufficiency. These manifestations of the disease are often present at a very young age, unlike left ventricular hypertrophy, which appears a little later. Heterozygous women develop cardiac disease but generally later than men. Women start developing hypertrophy at the age of 45 [4]: and this is the case with our two patients. There is a strong correlation between age and the severity of left ventricular hypertrophy, and all untreated patients over 45 years of age have left ventricular hypertrophy [5]. Our patients are symptomatic. The presence of left ventricular hypertrophy conditions clinical relevance. Myocardial

infarction is rare in Fabry disease. It is most often myocardial ischemia with chest pain on healthy coronary arteries. This ischemia is multifactorial: left ventricular hypertrophy, decreased capillary density, increased filling pressures, and accumulation of Gb3 in endothelial cells [6]. There is no noted conduction slowing in our patients. In Fabry's disease, conduction system involvement initially presents with shortening of the PR interval, which subsequently evolves into atrioventricular block [5]. Additionally, various forms of supraventricular and ventricular arrhythmias are described [5]. According to the literature, valvular abnormalities are frequently noted. Our patients also have involvement of the mitral and aortic valves. In Fabry's disease, slight thickening of the aortic and mitral valves is observed in 25.5% of patients. It is due to the accumulation of sphingolipids in fibroblasts of valvular tissue. Mild mitral valve prolapse is documented in only 10.9% of patients [5], which is not the case with our patients.

The cardiac Doppler ultrasound of our patients confirms the existence of left ventricular hypertrophy, but the data underestimate this hypertrophy compared to magnetic resonance imaging. However, cardiac Doppler ultrasound shows compliance disorders with a type 4 mitral profile that raises suspicions. Cardiac magnetic resonance imaging confirms the existence or absence of myocardial fibrosis. Doppler tissue imaging echocardiography can be contributory in this case, but its sensitivity depends on the experience of the observer and anatomical conditions [7]. Cardiac magnetic resonance imaging appears as a key examination for diagnosing cardiac involvement. It evaluates both cardiac morphology and function with high spatial resolution and low inter-observer variability [8]. This imaging allows visualization and localization of myocardial fibrosis in the form of late gadolinium enhancement [9,10]. Studies using cardiac magnetic resonance imaging in patients with Fabry disease have identified a specific mapping of gadolinium-enhanced myocardial enhancement [11-13]. This specific enhancement is not found in our patients.

CONCLUSION:

Serious complications of Fabry disease can lead to premature death in the absence of diagnosis and treatment. Early identification of individuals affected by Fabry disease, even females, allows for the assessment of target organ involvement. Severe cardiac involvement is not exclusive to male Fabry patients.

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