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Many faces of Fabry disease: Variable clinical course with typical non-cardiac symptoms and unexpected heart involvement

Short title: Many faces of Fabry disease

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Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations of the α-galactosidase A gene. Regardless of a highly variable clinical course with atypical symptoms the disease causes a progressive multiple organ dysfunctions with frequent heart involvement that determinates the long term prognosis.

We present three patients suffering from FD with similar symptoms but with different phenotypes and unexpected heart involvement.

The siblings (27-year-old male, 29-year-old female) were genetically diagnosed during their adolescence after vortex kerathopathy diagnosis (mutation: c.496C>G [p.Leu166Val] for both). They presented symptoms typical for FD, such as burning or pain in the hands or feet, heat or cold intolerance, frequent abdominal pain.

The third patient (45-year-old female) with only symptom of high and low temperature intolerance was diagnosed 2 years ago — the positive family history was indication for the diagnostic (nonsense mutation c.469 C>T [p.Gln 157 Ter]).

None of the patients complained of fatigue, dyspnea, arrhythmias and syncope as surrogates of cardiovascular system involvement.

In women the alfagalactosidaze level was in inferior limit and the marker of glicosphingolipids accumulation — deacylated derivative globotriaosylsphingosine (lyso GL3) was slightly elevated. Both α-GAL and lysoGL3 in the male were abnormal (Figure 1).
ECG scans were normal in the siblings. The ECG of older female showed typical changes for left ventricular hypertrophy (Figure 1).

The transthoracic echocardiography did not reveal abnormalities in the younger female, only minor left ventricle (LV) dilatation in her brother, moderate LV hypertrophy in the elder female (16 mm). LV ejection fraction was in normal range in all subjects. Reduced global longitudinal strain with pattern typical for FD was present in the male and the older woman [1] (Figure 1).

Cardiac magnetic resonance revealed normal LV systolic function in all subjects. The mild LV hypertrophy (12 mm) and late gadolinium enhancement in basal and medium posterior segments were observed in the older woman. Native T1 relaxation time was shortened in posterolateral segments in the younger woman's heart (typically associated with prolonged time in more advanced stages of FD); shortened in interventricular septum in the male — suggesting the typical glicosphingolipids accumulation and intramural inflammation without any fibrosis. T1 mapping acquisition in the older woman showed short native T1 relaxation time in the septal segments and long time in inferior and posterior ones — suggesting both inflammation and fibrosis [2] (Figure 1).

Based on the abovementioned tests the FD diagnosis was made and the patients were qualified for enzyme replacement or chaperone therapy [3].

To summarize, these three cases are evidence of different types of the same disease even among the firstly diagnosed as classic FD. The preclinical cardiovascular involvement was present in all patients regardless of the differences in the age, sex and symptoms. The modern imaging modalities seems to be crucial for recognition of an early and asymptomatic glicosphingolipids accumulation in the heart and should be obligatory in all FD subjects [4]. Especially the T1 mapping seemed to be of clinical value that it allows to reveal both inflammation and fibrosis in typical LV segments — pathognomonic changes for cardiological type of FD [5].

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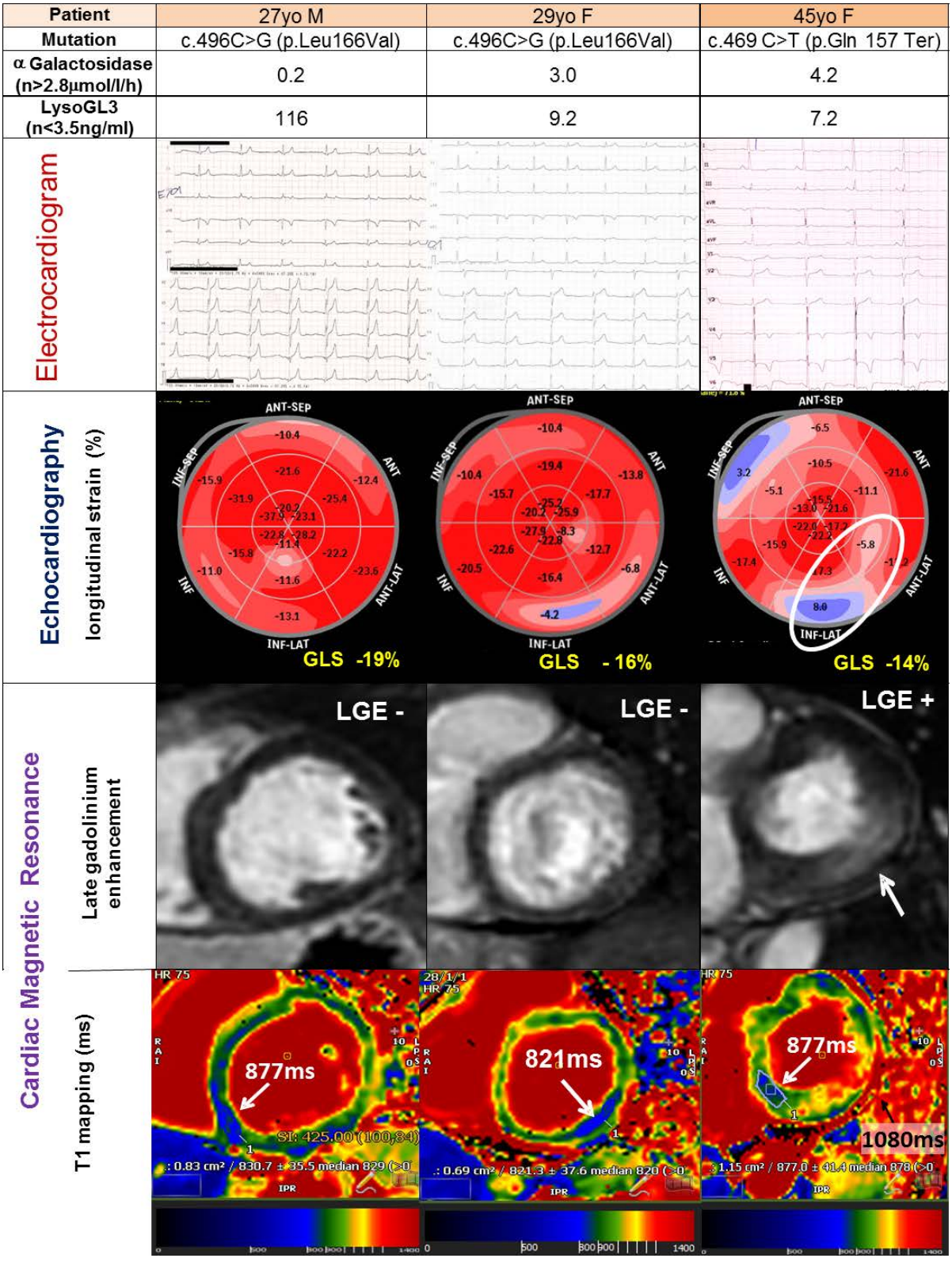

Figure 1. Characteristics of the subjects including the type of mutation, enzymatic and metabolite level, electrocardiogram recording, left ventricular longitudinal strain in echocardiography and T1 mapping in cardiac magnetic resonance

Abbreviations: GLS, global longitudinal strain; LGE, late gadolinium enhancement