IMAGE IN CARDIOLOGY

Hypertrophic cardiomyopathy – when the electrocardiographic findings can lead to final diagnosis

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A 62-year old female, with few cardiovascular risk factors (hypertension, dyslipidaemia), recently diagnosed with frontoparietal ischemic stroke and on the same occasion with paroxysmal atrial fibrillation and right bundle branch block (RBBB), was referred to our cardiology department for nocturnal episodes of palpitations, with variable duration, associated with anginal chest pain. Of note, the anamnestic interview documented two relatives with sudden cardiac death (SCD): mother and brother, at 65 and 62-years old, respectively (Figure 1).

Clinical examination and laboratory work-up showed no particular findings, with the exception of a mild increase in brain natriuretic peptide (BNP) of 150 pg/mL. In addition, the ECG tracing revealed a short PR interval of 110 msec, with only slight preexcitation, the known RBBB and left ventricular hypertrophy (LVH) with strain pattern and giant inverted T waves suggestive of apical hypertrophic cardiomyopathy (HCM) (Figure 2).

The 2D echocardiography (Figure 3) showed a non-dilated left ventricle (LV), with concentric hypertrophy, especially at the apical level (maximum wall thickness of 15 mm), no left ventricular outflow tract obstruction, a preserved LV ejection fraction (LVEF) and no regional wall motion abnormality; normal right ventricular free wall thickness was measured. Speckle tracking imaging showed a reduced global longitudinal strain (GLS) of -13.5%. Severe left atrial (LA) enlargement and mild functional mitral regurgitation were associated.

Given the patient's symptomatology and medical history, 24-hour Holter monitoring was performed, which revealed: severe sinus bradycardia (~30 bpm) and episodes suggestive of sinoatrial block; a few short episodes (~10 sec) of atrial tachycardia (Figure 2), as well as frequent monomorphic premature ventricular contractions. No unsustained ventricular tachycardia were observed. A DDDR cardiac pacemaker was implanted.

Due to the chest pain history of the patient, a coronary angiography was performed, showing no hemodynamically significant lesions of the epicardial coronary arteries. Therefore, angina episodes were interpreted in the context of microvascular dysfunction[3] in a patient with hypertrophic cardiomyopathy.

Gathering all data, the presence of a short PR interval without preexcitation, with several conduction disturbances (RBBB and sinoatrial block) in a patient with LVH raised the suspicion of Anderson Fabry disease. This was confirmed by low levels of alpha-galactosidase (1.8 mcmol/l/h, normal values >2.8) and high globotriaosylsphingosine (lyso-GL3) (4.9 ng/ml, normal values 0-3.5). The genetic testing identified a mutation in the α-galactosidase A (GLA) gene c.1228A>G (p. Thr410Ala), and no other mutations were found by next generation sequencing of a cardiomyopathy panel. The patient's offspring were also

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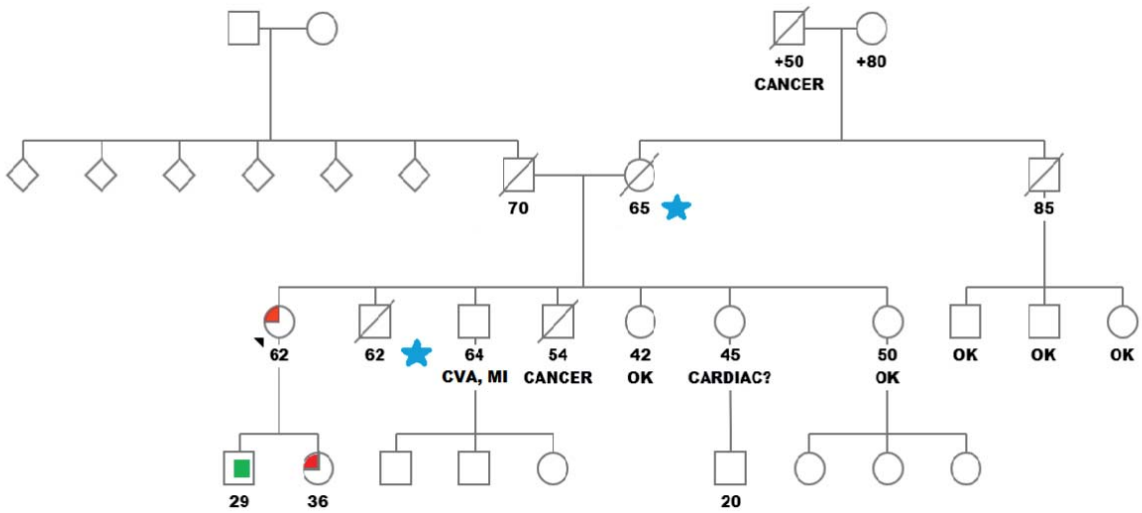

Figure 1. Pedigree. Marked with black arrowhead - the index case. Marked with red – members known as positive for GLA mutation. Green square - genetically tested, non-carrier of the GLA mutation. Blue stars - SCD in sleep.

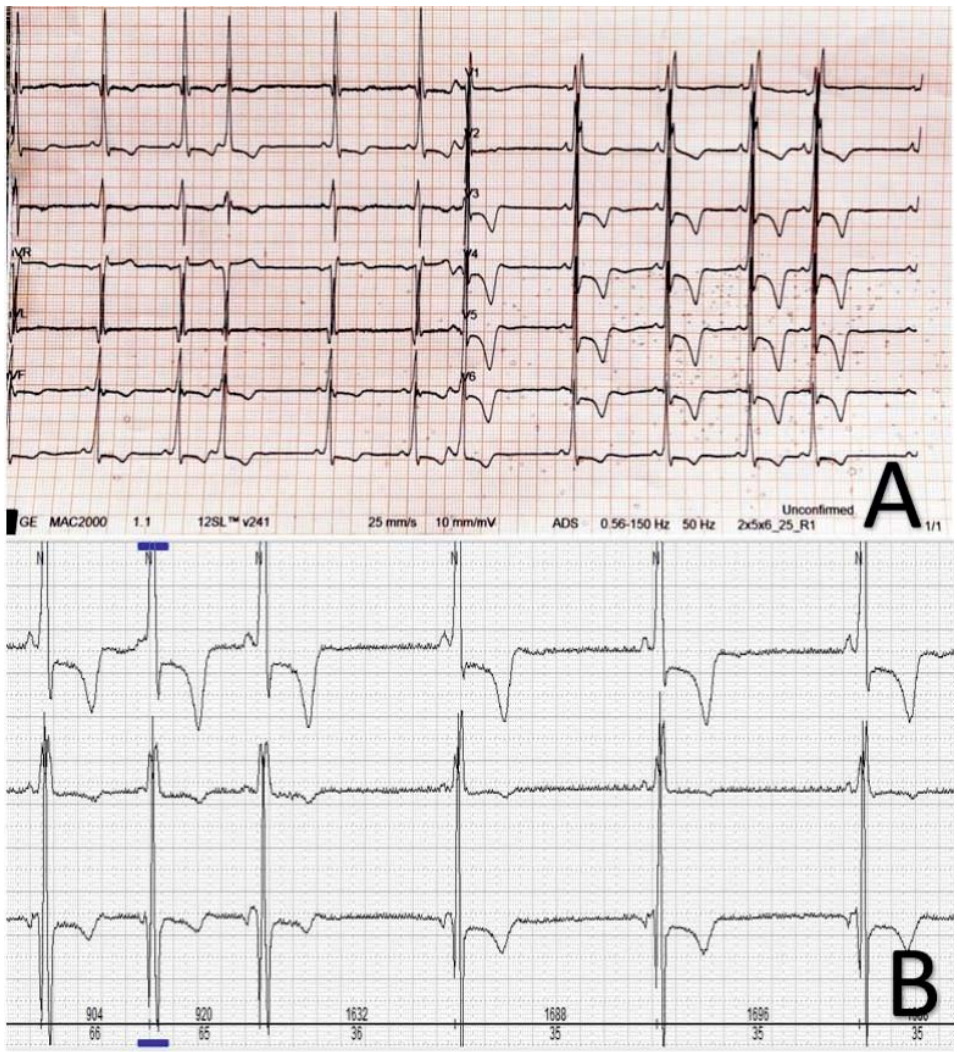

Figure 2. Panel A. Electrocardiogram: short PR interval with slight septal preexcitation appereance, right bundle branch block (more obvious when premature atrial beat occurs – 4th QRS complex), left ventricular hypertrophy voltage criteria with deep inverted T waves in the precordial leads suggestive of apical HCM. **Panel B.** ECG Holter: 2nd QRS complex is a junctional escape beat (often seen in Fabry disease) followed by marked sinus bradycardia.

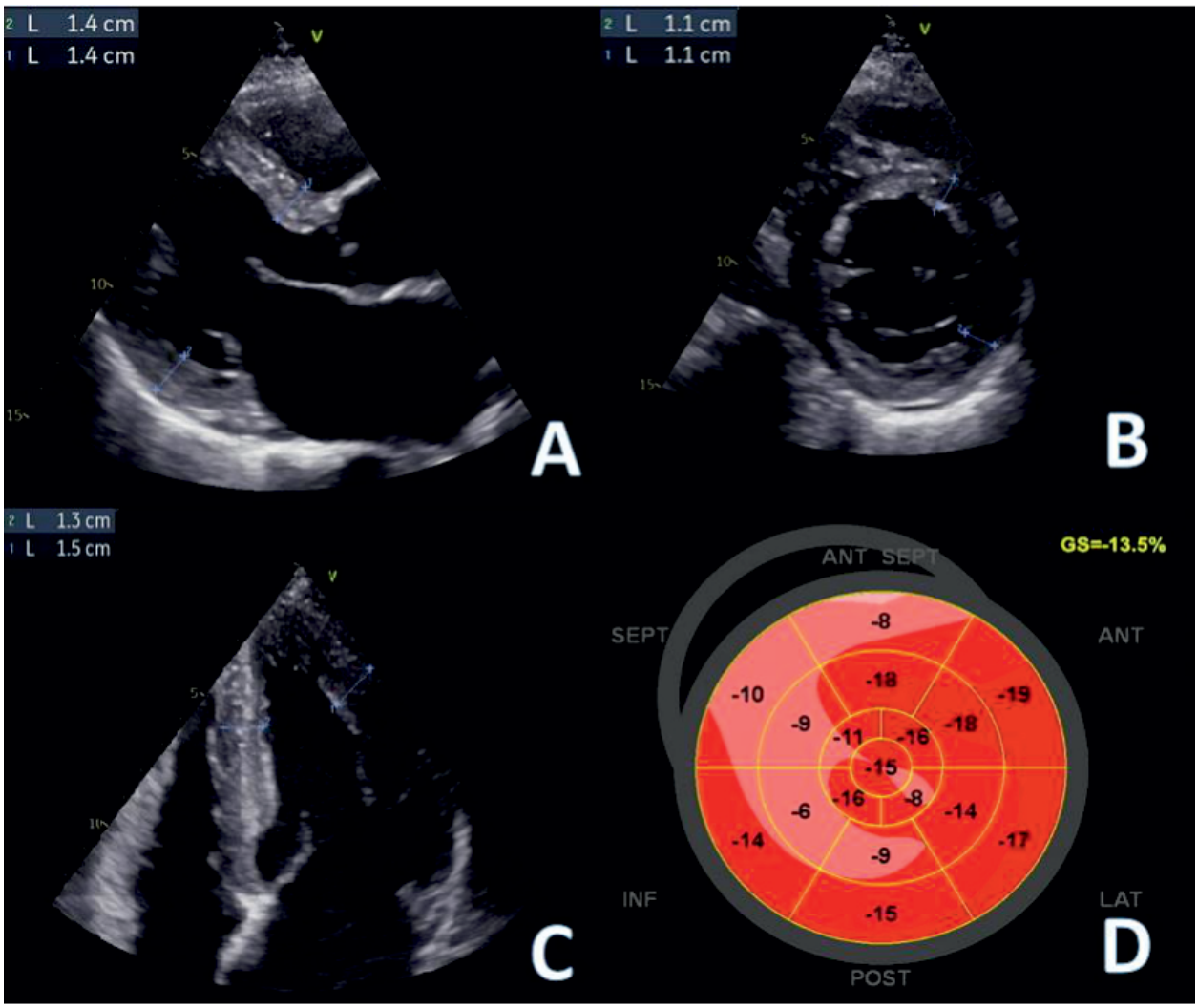

Figure 1. Transthoracic echocardiography. Basal anterior septum and posterior wall measurements in panels **A.** Parasternal long axis view (PLAX) and **B.** Parasternal short axis at mitral valve level (PSAX- MV). **C.** Apical four chamber view (A4C) measurements of apical inferior septum and anterolateral wall (maximum thickness 15 mm). **D.** Myocardial deformation imaging. Longitudinal strain bull's eye plot showing a reduced global longitudinal strain (-13.5%) with lowest segmental values in septal and inferior segments.

tested, the daughter sharing the same GLA mutation, but the son proved to be negative. Other siblings will also be tested.

The case is an illustration of bringing together red flags leading to the diagnosis of Fabry disease, an X-linked genetic disease, characterized by a deficiency of the lysosomal enzyme GLA and the pathological accumulation of globotriaosylceramides in the body's cells, determining various cardiac, neurological, renal and cutaneous manifestations[4]. Women have long been considered healthy carriers of the GLA mutation, but studies have shown that women can develop phenotypes comparable to those of men, yet with a later onset of cardiovascular manifestations than men[5]. In addition, in most patients with Fabry disease (76.9%), ischemic stroke occurred before cardiac or renal manifestations[6]. A short PR interval, commonly found in patients with Fabry disease, is probably caused by accelerated intraatrial conduction[7]. However, with disease progression, patients may develop atrioventricular or bundle branch blocks, as well as sinus node dysfunction[8], features also observed in our case. Although reduction of LV GLS, quantified by two-dimensional speckle tracking is typically found in the basal postero-lateral segments[9] of Fabry hearts, in our case the bull's eye of segmental longitudinal peak strain values assessed by two-dimensional speckle tracking showed lower values in the anteroseptal region.

The main implication of a precise diagnosis in this patient is the specific therapy that can be recommended, enzyme replacement therapy or chaperone therapy being available[10]. The identified mutation in the

present case is amenable for migalastat treatment, an oral pharmacological chaperone which attaches to specific mutant forms of alpha-galactosidase, increasing its activity[11]. Cascade family screening allows timely diagnosis in the family members.

To conclude, we emphasize on the importance of corroborating all clinical and paraclinical data in patients with hypertrophic cardiomyopathy, given the diverse umbrella of underlying diagnoses, especially since women with Fabry disease are diagnosed with a delay of about 19 years from the first symptoms[4] and targeted therapies are wide available nowadays.

Keywords: hypertrophic cardiomyopathy, short PR interval, sinoatrial block, Fabry disease.

Conflict of interest: none declared.

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