THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

p.R220L Is a Likely Pathogenic Novel GLA Gene Mutation Responsible for Fabry Disease

INTRODUCTION

Fabry disease is a progressive and rare storage disease that occurs due to low or complete deficiency of lysosomal alpha galactosidase-A (α-GLA) enzyme activity. Low alpha galactosidase-A enzyme activity causes progressive accumulation of globotriaosylceramide in various tissues and organs including the myocardium, kidney, and nervous system. Left ventricular hypertrophy (LVH) is the most common cause of cardiac involvement in patients with Fabry disease. Over a thousand different mutations have been identified in the GLA gene up to now. We describe a case of a 54-year-old male with Fabry disease due to a novel GLA gene mutation.

CASE REPORT

A 54-year-old male patient had been followed for 16 years due to hypertrophic cardiomyopathy (HCM). He was admitted to our clinic with increased exertional dyspnea for the last 2 months. The patient's medical history was notable for long-standing, HCM. The physical examination revealed nothing remarkable; the patient's blood pressure was 126/74 mm Hg, and pulse was rhythmic with 82 beats/min. Blood testing was notable for a creatinine of 1.48 mg/dL (estimated glomerular filtration rate 48 mL/min/1.73 m^2), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitive cardiac troponin (hs-cTn) levels elevated to 1240 pg/mL (0 to 157 pg/mL) and 0.129 ng/mL (normal range <0.014). The electrocardiography demonstrated LVH (Figure 1). Transthoracic echocardiography showed normal left ventricular ejection fraction of 60%, concentric hypertrophy involving particularly the middle and apical portions of the left ventricle, as well as right ventricular free wall along with thickening of the mitral and aortic valves resulting in mild valvular regurgitation. In the apical 4-chamber view, the hyperechogenic endocardium and the hypoechogenic thin border between the myocardium and the endocardium in the interventricular septum are defined as the "binary sign" (Figure 2). Cardiac magnetic resonance imaging (MRI) and genetic testing were planned in order to elucidate the unexplained LVH. The common gene panel in patients with HCM was screened. In genetic analysis (NM_000169.2:c.659G>T (p.R220L) (p.Arg220Leu), mutation was detected in GLA gene. We made NGS but we also made Sanger sequencing of the mutation region (Figure 3). Data were evaluated by IGV 2.3 (Broad Institute) software. Variant not found in the Genome Aggregation Database (gnomAD) exomes and gnomAD genomes databases. The pathogenic computational prediction was based on 9 pathogenic predictions from BayesDel_addAF, DANN, DEOGEN2, FATHMM-MKL, LIST-S2, M-CAP, MVP, MutationAssessor, and MutationTaster vs. 2 benign predictions from PrimateAI and SIFT was detected. The gnomAD missense Z-Score is 1.88 and it is greater than 0.647. As the enzyme level is below normal and clinical picture resembles this disorder, this mutation is in the hotspot region. Missense mutations are frequent in Fabry disease cases. Due to all of these findings, this variant was evaluated as a "likely pathogenic" variant due to American College of Medical Genetics (ACMG) criteria. We found that α-GLA enzyme level of 2.50 nmol/mg/h (normal range >23.10) was significantly low and Lyso-gb3 10.40 ng/mL (normal range <1.30) levels were high. The patient had 3 boys, family screening could not

CASE REPORT

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Cite this article as: Barman HA, Atıcı A, Özyıldırım S, Ceylaner S, Dursun M, Doğan SM. p.R220L is a likely pathogenic novel GLA gene mutation responsible for Fabry disease. Anatol J Cardiol 2022;26(5):411-413.

DOI:10.5152/AnatolJCardiol.2021.393

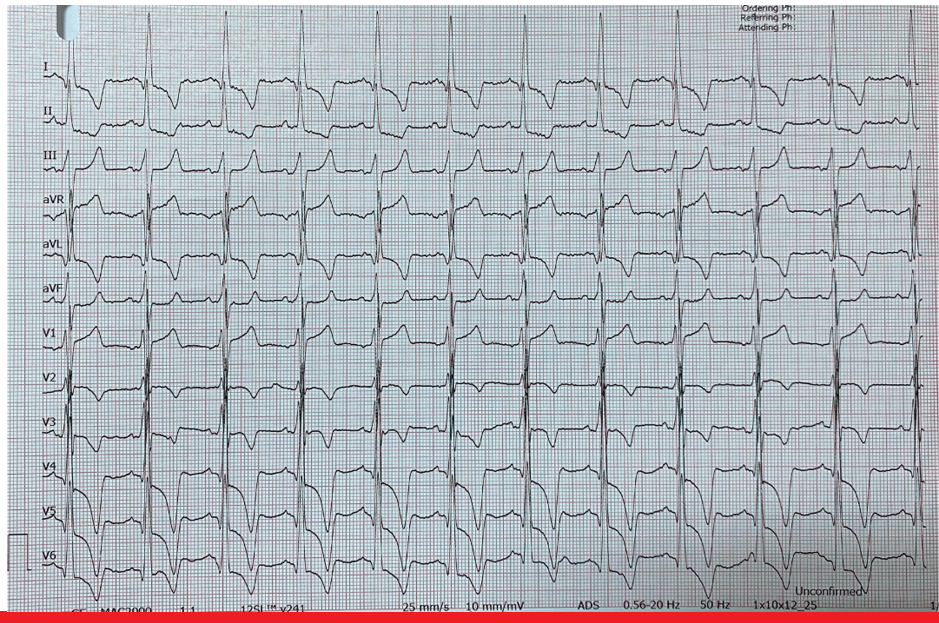

Figure 1. The electrocardiography demonstrated left ventricular hypertrophy

be done with children. Relatives and siblings of the patient did not agree to genetic screening. Cardiac MRI showed LVH; vertical long axis and midventricular short-axis late gadolinium-enhanced images demonstrated extensive anterior and inferolateral wall segment enhancement. Horizontal long axis pre-contrast T1 map shows that the ROI measured at the inferolateral wall has a reduced T1 value (959 ms) (Figure 4). Enzyme replacement therapy was initiated after being evaluated at the Fabry disease council.

DISCUSSION

Fabry disease is a progressive lysosomal storage disease characterized by the accumulation of glycosphingolipids in all tissues and especially in the heart, kidney, and neural cells due to α-GLA enzyme deficiency.[1,2] Over a thousand GLA gene mutations associated with Fabry disease have been identified.[3] Cardiac involvement is present in 69% of patients with Fabry disease, and cardiac involvement is the most common cause of death in Fabry patients.[4] Left ventricular hypertrophy is the most common cardiac involvement in Fabry patients. Fabry disease was detected in 1-4% of all HCM cases.[5] Non-obstructive type concentric HCM is frequently seen due to Fabry disease. In our case, we found non-obstructive type concentric HCM. In patients with HCM, cardiac MRI has an important role in the differential diagnosis, although it is necessary to detect segments that cannot be seen by echocardiography. The T1 mapping method, a new cardiac MRI technique, has great power in the differential diagnosis of

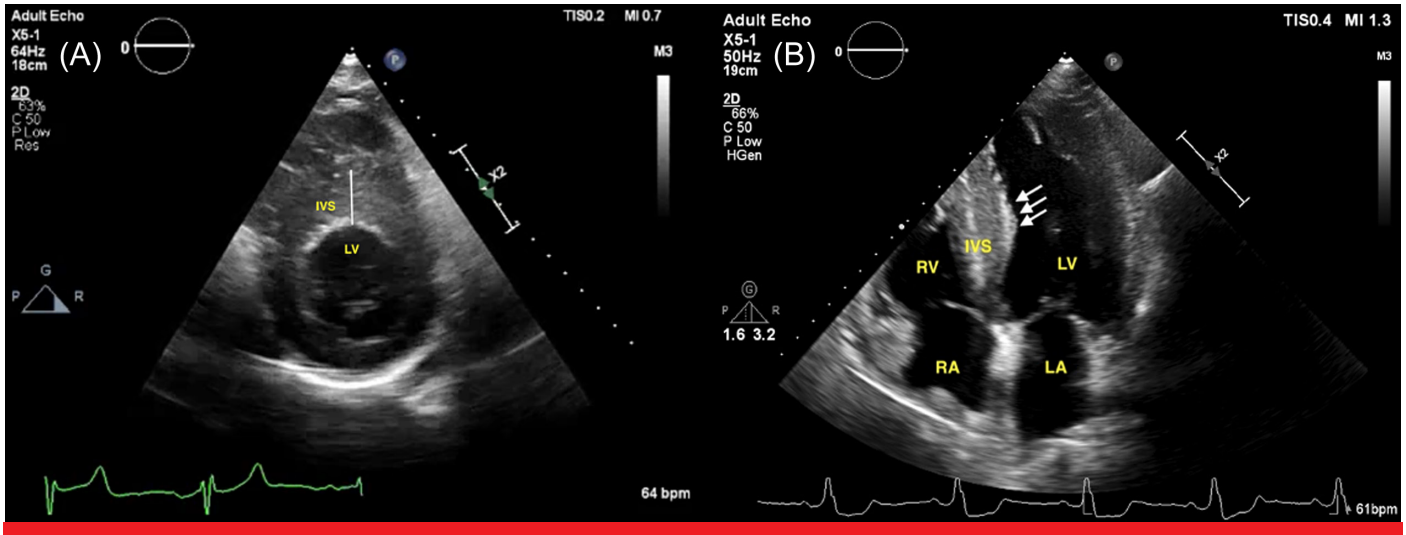

Figure 2. Two-dimensional echocardiography 4-chamber view showing binary sign in interventricular septum (IVS), including hypertrophied left and right ventricles (LV and RV) and enlarged left atria (LA).

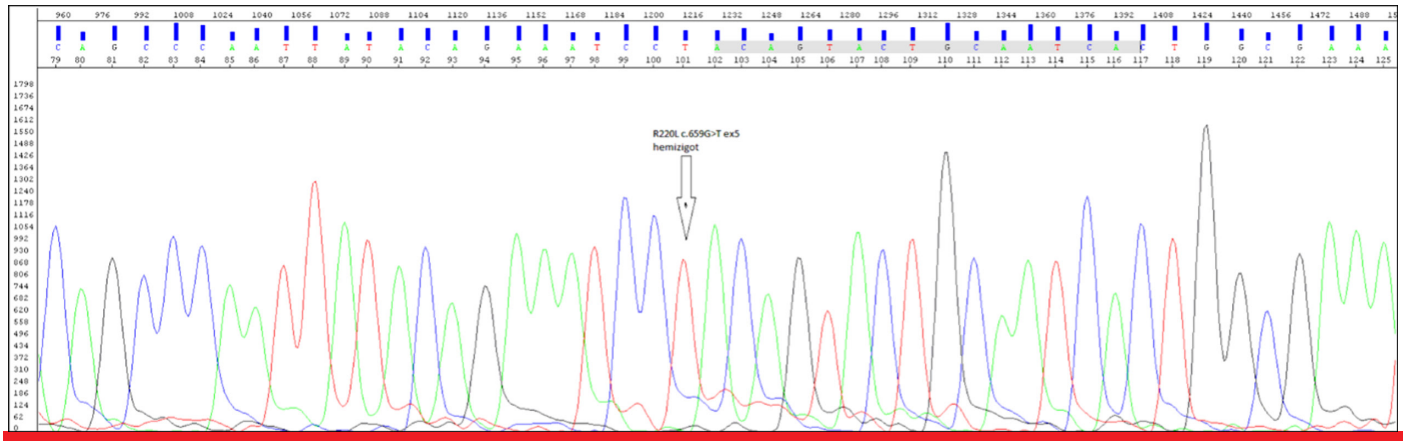

Figure 3. In genetic analysis, c.659G>T (p.R220L) (p.Arg220Leu) mutation diagnostic of Fabry disease was detected.

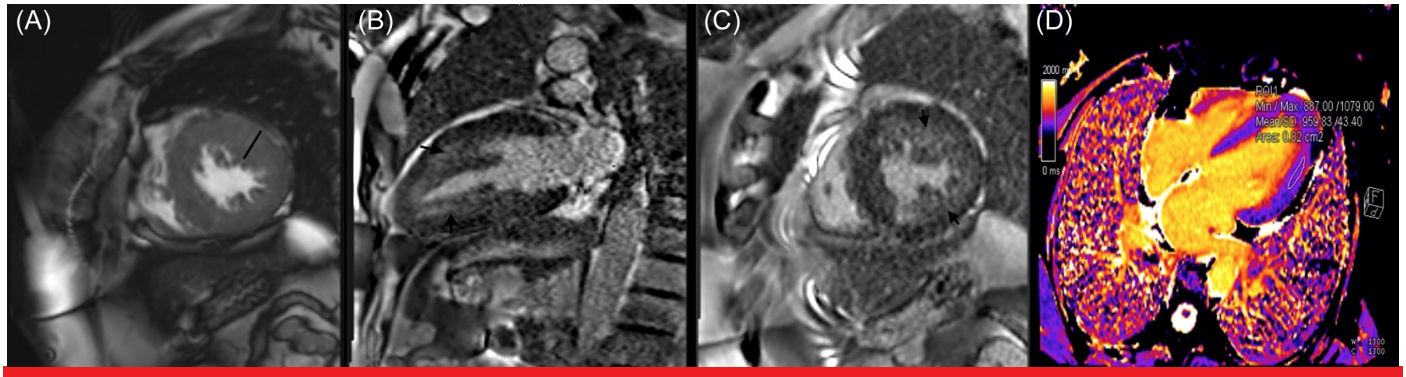

Figure 4. Cardiac Magnetic Resonance Imaging. (A) Short-axis cine SSFP image shows left ventricular hypertrophy (black line indicates increased wall thickness). (B and C) Vertical long axis and midventricular short-axis late gadolinium-enhanced image demonstrates extensive anterior and inferolateral wall segment enhancement (arrows). (D) Horizontal long axis pre-contrast T1 map shows that the ROI is measured at the inferolateral wall has reduced T1 value (959 ms).

HCM from infiltrative cardiomyopathies. In Anderson–Fabry cardiomyopathy, a low T1 occurs associated with an increase in extracellular volume due to sphingolipid accumulation.[6] Similarly, T1 value was found to be low in our case. While some of the gene mutations detected by genetic analysis are true pathogenic, some are polymorphisms. The challenge is to determine which GLA variants may cause clinical signs of Fabry disease.[7] Therefore, α-GLA enzyme and Lyso-gb3 levels should be measured. In this case, we found that the α-GLA enzyme level was significantly lower and the Lyso-gb3 levels were high. In patients with late-onset cardiac variant Fabry, signs and symptoms generally begin to appear at the age of 30 years in men and 40 years in women. Unlike the classical form, late-onset Fabry disease usually progresses with heart and kidney involvement. This new mutation appears to cause the late phenotype of the Fabry disease.

CONCLUSIONS

Fabry's cardiomyopathy commonly manifests in the third to fourth decade of life, predominantly presenting with unexplained LVH or HCM in the absence of other proven etiologies. Early diagnosis is important in preventing cardiovascular complications. It should be kept in mind that patients with unexplained LVH may have Fabry disease.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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