SCIENTIFIC LETTER

Hypertrophic cardiomyopathy associated with genetic variant MYBPC3:c.1119 C>G (p.Tyr373Ter)

Cardiomiopatía hipertrófica asociada a variante genética en MYBPC3:c.1119 C>G (p.Tyr373Ter)

JUAN S. HERNÁNDEZ[1], JHON J. GÓMEZ-TOVIO[1], SOFIA A. HERNÁNDEZ-MEZA[2], NICOLAS NIEDERBACHER[3]

Hypertrophic cardiomyopathy (HCM) is a genetic disease with a pathophysiological basis characterized by left ventricular hypertrophy not explained by another cardiac, systemic or metabolic condition. Although in the past it was considered a rare entity, in the United States the prevalence of asymptomatic cases is 1:500 inhabitants and 1:3000 inhabitants for symptomatic cases. (1) These data suggest that HCM is a common disease that may be under-diagnosed and of increasing importance for cardiologists in their clinical practice.

We report the case of a 65-year-old male patient who sought medical care due to palpitations which appeared two months before consultation, without chest pain, dyspnea or syncope. Among the most important antecedents, he had a 30-year-old son with a positive genetic test for hypertrophic cardiomyopathy associated with MYBPC3 mutation. The patient denied episodes of sudden cardiac death in his family. The physical examination was normal.

The initial workup included an electrocardiogram and a 24-hour Holter monitoring which showed sinus rhythm with isolated premature atrial contractions. The ambulatory blood pressure monitoring was normal and the transthoracic echocardiogram revealed a left ventricular ejection fraction of 63%, preserved wall motion, basal anteroseptal hypertrophy of 20 mm without dynamic left ventricular outflow tract obstruction (Figure 1), mild aortic regurgitation, mild mitral regurgitation with no systolic anterior motion, and absence of diastolic dysfunction. The patient underwent cardiac magnetic resonance imaging which demonstrated diastolic basal anteroseptal segment thickness of 22 mm with intramyocardial late enhancement, and diastolic inferoseptal segment thickness of 16 mm. There were no other hypertrophic segments or left ventricular outflow tract obstruction (Figure 2).

Based on these findings, we decided to perform a gene panel for HCM, which identified a nonsense variant in heterozygous state in MYBPC3 gene c.1119C>G (p.Tyr373Ter), classified as a pathogenic variant by PVS1, PM2 and PM6 criteria. (2) Medical therapy with bisoprolol 5 mg daily was initiated, reducing the symptoms. The estimated risk of sudden cardiac death using the HCM Risk-SCD score was low (2.2%), indicating that the patient was not yet a suitable candidate for devices for sudden cardiac death prevention or septal myectomy. (3)

Hypertrophic cardiomyopathy is a disease with a predominantly autosomal dominant inheritance pattern, with incomplete penetrance. It primarily affects sarcomere proteins. Left ventricular hypertrophy can have any distribution pattern; however, it is most common in the basal anterior septum, followed by the left ventricular anterior free wall. (1) It should be suspected when end-diastolic left ventricular wall thickness is ≥ 15 mm on echocardiogram or cardiac magnetic resonance imaging. In patients with a positive genetic test or family history of HCM, the diagnosis should be considered with values ≥ 13 mm. (3)

The clinical presentation varies from asymptomatic cases to patients with palpitations, chest pain, syncope and sudden cardiac death in young people and athletes. (1). Besides left ventricular outflow tract obstruction, it is important to identify other risk markers for sudden cardiac death, such as non-sustained ventricular tachycardia, ventricular wall thickness ≥ 30 mm, syncope, and left atrial diameter (also important in atrial fibrillation, the most common arrhythmia in HCM). (2) A detailed medical record, physical

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Correspondence: Juan S. Hernández. E-mail: jshernandezm74@gmail.com.

[1] Cardiology Unit, IPS Divina Misericordia, Sincelejo, Sucre, Colombia
[2] School of Medicine, Pontificia Universidad Javeriana, Bogotá, Colombia
[3] Institute of Human Genetics, Pontificia Universidad Javeriana, Bogotá, Colombia

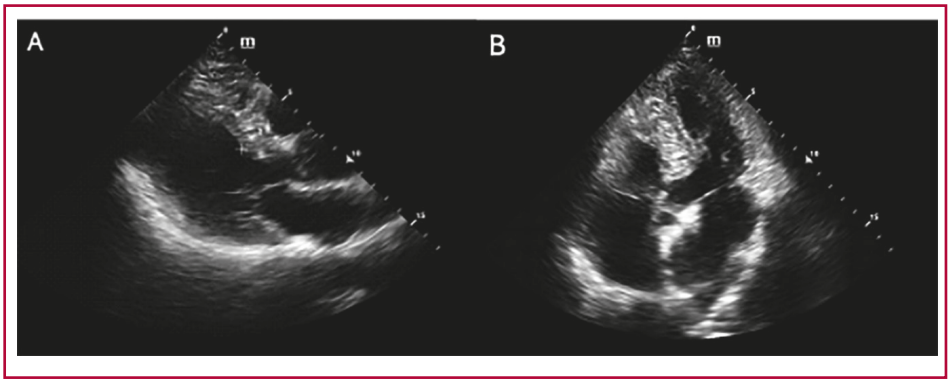

Fig. 1. Transthoracic echocardiogram. **A**) long axis view and **B**) 4-chamber-view, showing increased interventricular septum thickness.

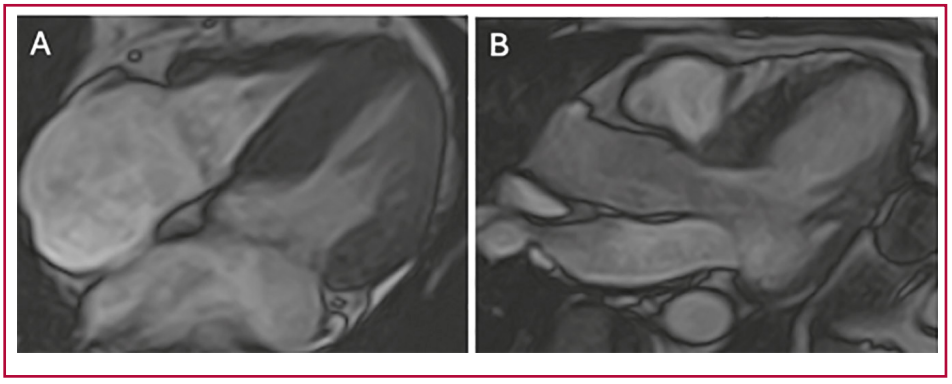

Fig. 2. Cardiac magnetic resonance imaging. **A**) Four chamber view with significant thickening of the interventricular septum. **B**) Left ventricular outflow tract, with absence of obstruction.

examination and complementary tests are essential to rule out diseases that may mimic HCM, such as RASopathies, lysosomal or glycogen storage diseases, Fabry disease and amyloidosis.

While echocardiography and cardiac magnetic resonance imaging are essential for diagnosing this condition, other diagnostic tests, such as electrocardiogram, 24-hour Holter monitoring, ambulatory blood pressure monitoring and genetic testing are also crucial for a comprehensive evaluation, prognosis and tailored management plan. The toolkit for this entity includes cardioselective beta-blockers, non-dihydropyridine calcium channel blockers, disopyramide, septal reduction therapy and, more recently, mavacamten.

The most common variants occur in the MYH7 (β-myosin heavy chain) and MYBPC3 (myosin-binding protein C) genes with penetrance of 65% and 55%, respectively, according to the meta-analysis by Topriceanu et al. which evaluated the penetrance of sarcomeric gene variants in HCM. (4) Most cases of MYBPC3 mutations are characterized by a late onset and a favorable clinical course; (5) however, Herrera et al. have described MYBPC3 variants linked to sudden cardiac death. (6) Even so, the European Society of Cardiology states that the role of sarcomeric variants as a predictor of sudden cardiac death independent of existing risk-prediction models remains to be demonstrated. (3) The mechanisms underlying the development of HCM in the context of sarcomeric variants include haploinsufficiency (when one copy of a gene is inactivated or deleted and the remaining functional copy of the gene is not adequate to produce the needed gene product to preserve normal function), increased calcium sensitivity, and direct toxicity of the defective protein. (5) In particular, the MYBPC3:c.1119 C>G (p.Tyr373Ter) variant causes a premature termination codon, forming a truncated protein that is explained by the haploinsufficiency phenomenon. Although this variant has a record in ClinVar, it is not present in population databases, and its allele frequency in gnomAD (Genome Aggregation Database) is not documented. In our case, this variant was associated with a favorable clinical course and low risk of sudden death. Nevertheless, further case studies and prospective research are required to validate this information.

In conclusion, the phenotype of the clinical presentation is variable in patients with MYBPC3 variants. Therefore, it is important to characterize genetic variants and their clinical outcomes in order to individualize the optimal medical therapy and to establish a reliable clinical prognosis. To the best of our knowledge, this would be the first case report of the MYBPC3:c.1119 C>G (p.Tyr373Ter) variant and its potential favorable phenotypic correlation.

Ethical considerations

The patient signed an informed consent form for the development of this study. Approval from the institutional review

board was not required, since, according to the 2016 International Ethical Guidelines for Health-related Research Involving Humans (CIOMS), this research is safe. We declare that this article does not contain any personal information that could be used to identify the patient.

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Conflicts of interest
None declared.
(See conflicts of interest forms on the website).

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