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Review

Hypertrophic cardiomyopathy☆

Juan José Santos Mateo[a], María Sabater Molina[b,c], Juan Ramón Gimeno Blanes[a,c,*]

[a] Unidad de Cardiopatías Familiares, Servicio de Cardiología, Hospital Clínico Universitario Virgen de la Arrixaca, El Palmar, Murcia, Spain
[b] Laboratorio de Cardiogenética, Instituto Murciano de Investigación Biosanitaria, Murcia, Spain
[c] Universidad de Murcia, Murcia, Spain

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ABSTRACT

Hypertrophic cardiomyopathy is the most common inherited cardiovascular disease. It is characterized by increased ventricular wall thickness and is highly complex due to its heterogeneous clinical presentation, several phenotypes, large number of associated causal mutations and broad spectrum of complications. It is caused by mutations in sarcomeric proteins, which are identified in up to 60% of cases of the disease.

Clinical manifestations of hypertrophic cardiomyopathy include shortness of breath, chest pain, palpitations and syncope, which are related to the onset of diastolic dysfunction, left ventricular outflow tract obstruction, ischemia, atrial fibrillation and abnormal vascular responses. It is associated with an increased risk of sudden cardiac death, heart failure and thromboembolic events. In this article, we discuss the diagnostic and therapeutic aspects of this disease.

Miocardiopatía hipertrófica

Palabras clave:
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RESUMEN

La miocardiopatía hipertrófica es la enfermedad hereditaria cardiovascular más frecuente. Se caracteriza por un aumento del grosor de las paredes ventriculares y se trata de una entidad con un manejo clínico complejo como lo demuestra la gran heterogeneidad en su presentación clínica, las diferentes manifestaciones fenotípicas, el gran número de mutaciones causales y el amplio espectro de complicaciones asociadas. Es causada por mutaciones en las proteínas sarcoméricas, pudiendo identificarse hasta en un 60% de los casos la mutación patogénica.

Las manifestaciones clínicas de la enfermedad son disnea, dolor torácico, palpitaciones y síncope, y están relacionadas con la aparición de disfunción diastólica, obstrucción al tracto de salida del ventrículo izquierdo, isquemia, fibrilación auricular y respuesta vascular inadecuada. Conlleva un aumento del riesgo de muerte súbita, de insuficiencia cardiaca y de eventos tromboembólicos. En el presente artículo, se revisan los aspectos diagnósticos y terapéuticos de la enfermedad.

Cardiomyopathies are a heterogeneous group of diseases that have the involvement of the cardiac muscle in common, characterized by alterations in size, ventricular thickness or contraction in the absence of hypertension, valvular or congenital heart disease. The group of myocardiopathies of the European Society of Cardiology (ESC) has classified them according to both morphological and functional criteria in 5 types, the most prevalent being hypertrophic cardiomyopathy (HCM), dilated and arrhythmogenic.[1]

HCM is defined by the presence of an increase in ventricular thickness in the absence of abnormalities determining an abnormal increase of overload.[2]

HCM was described by D. Teare, who in 1958 analysed the clinical and histological characteristics of a series of 7 sudden deaths.[3] In the following decades, the concepts of HCM continued to evolve in line with the development of new technologies, such as the use of catheterization and echocardiography, which helped to understand the hemodynamic alterations derived from the obstruction, and to define the different involvement patterns of hypertrophy.

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* Corresponding author.
E-mail address: jgimeno@secardiologia.es (J.R. Gimeno Blanes).

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In 1990, the first mutation causing the disease was identified in the gene encoding the β-myosin heavy chain. HCM became the first hereditary cardiovascular disorder in which the genotype had been determined.[4] Subsequently, mutations in other sarcomeric proteins were identified, which led to the concept of sarcomere disease and the analysis of correlations between genotype and phenotype.[5,6]

In conclusion, HCM is a complex, heterogeneous, dynamic disease, with differentiated pathophysiological mechanisms and a great diversity of morphological, functional and clinical aspects.

Pathogenesis, genetics and pathological anatomy

It is a common monogenic disease that affects 1:500 subjects. Penetrance is incomplete and varies according to age and sex. It usually follows an autosomal dominant inheritance pattern.

The classic form of occurrence in the adult is produced by mutations in the sarcomeric genes MYBPC3 and MYH7 (70% of the mutations).[7] Other genes identified are TNNT2, TNNI3, TPM1, MYL2, MYL3, and ACTC1[8] (Table 1). A genetic alteration can be identified in up to 60% of cases in one of the genes described.[7]

Some genotype–phenotype correlations have been established in terms of age of presentation, severity of hypertrophy, tendency to develop systolic dysfunction or an increased risk of sudden death (SD).[5,7,9–12]

In recent years, the development of mass sequencing technologies has allowed to reduce the cost and increase diagnostic performance. More than 1000 mutations have been described, and new ones in non-sarcomeric proteins that could act as phenotypic and prognostic modifiers.[8,13] However, it has also led to the identification of a large number of variants of uncertain significance that require pathogenicity studies to determine their functional relevance.[8,14]

Penetrance and expressivity are variable because of the participation of genetic and environmental modulating factors. Among those that have been described include some variants involved in the regulation of the renin–angiotensin–aldosterone system (RAAS), sex, obesity or physical exercise.[10,15–17] Males and athletes seem to develop the disease a decade earlier than women and sedentary people. HBP has been considered a trigger for the development of hypertrophy in genetic carriers. The impact of these factors on the severity of the hypertrophy and on the prognosis is not fully defined.

The defining anatomopathological finding is the presence of myocardial *disarray*. In addition, we can find interstitial fibrosis, myocyte hypertrophy and hypertrophy of the middle layer of the intramural coronary arteries that can condition the occurrence of ischemia.[18]

Diagnosis

When hypertrophy is detected, a systematic study should be carried out to rule out secondary causes that may justify it, which will include a careful personal and family clinical history, physical examination, laboratory, imaging and genetic studies.

In case of identifying an affected family member, the study should be extended; this is called cascade strategy. It is recommended to perform an ECG and an echocardiogram to all first-degree relatives.[19,20]

Diagnostic criteria

The diagnostic criterion continues being the increase in ventricular thickness of unexplained cause.[2] In adults, the cut-off point is located at ≥15 mm in one or more segments regardless of the imaging technique used. In children, a *z*-score ≥ 2SD[2] is used. The diagnostic criteria in family members is less demanding, establishing the cut-off point in ≥13 mm[2].[21] The presence of certain echocardiographic or electrocardiographic abnormalities may be sufficient for diagnosis in a family member in the absence of ventricular hypertrophy. However, the presence of a causal mutation is not enough to establish the diagnosis.

A regular follow-up program should be carried out in family members in the absence of a genetic study. It is recommended to perform the first study at 10–12 years, repeat annually until 20 years and from 20 to 60 every 3 years. This type of studies requires the development of an important infrastructure, usually assumed by the cardiology services.[22]

In those affected, ECG and echocardiogram follow-up would be performed annually, including Holter monitoring and exercise tests on a regular basis (every 2–3 years).[22]

Clinical history and physical examination

Currently, with the active family study strategy, most of those affected are in an asymptomatic phase.[19] The symptomatology is variable and more frequent in the obstructive forms, which involve at least 30%.[23,24]

The most frequent symptoms are exertional dyspnoea, palpitations, chest pain and syncope.[25,26] Dyspnoea affects more than 50% of patients at some point during their progression. Palpitations may be related to atrial arrhythmias and, less frequently, ventricular arrhythmias. Atrial fibrillation (AF) affects 20% of cases and usually involves a poor tolerance.[27]

The only symptom that has been shown to be a predictor of SD in adults with HCM is syncope. SD is the leading cause of death among affected patients.[24,26] A smaller percentage of patients (10–20%) develop ventricular dysfunction and dilation.[28]

Electrocardiogram

The ECG is abnormal in 90% of cases and often suggests the diagnosis.[25,29] The electrocardiographic changes are usually quite significant and precede the development of hypertrophy.[11] The most frequent anomalies are alterations in repolarization and occurrence of Q waves. The isolated presence of high voltage QRS complexes should not be considered as diagnostic since it is frequent in young, athletic and hypertensive subjects. The occurrence of negative giant T waves on the anterior face is characteristic of apical hypertrophy. A decreased ST-segment is more common, but there are also elevations in cases with apical aneurysms (Figs. 1 and 2).

Echocardiogram

Echocardiography allows to locate and define the severity and extent of hypertrophy, confirming or ruling out the diagnosis.[2,29] The most frequent distribution is classically described as septal asymmetric (70%), concentric (15%) or apical (10%). More recently, and considering the morphology of the septum, it has been classified as reverse, neutral and sigmoid. The reverse septum is characteristic of young patients with more severe hypertrophies in which family affectation and the genetic study's usefulness is higher, whereas the sigmoid septum is more frequent in older women, with less significant thicknesses and in which genetic studies are less useful.[30]

In addition, it allows to know the symptom-triggering mechanisms and to monitor the changes during follow-up to prevent complications. The presence and severity of dynamic obstruction in the left ventricle (LV) outflow tract should be assessed, establish the hypertrophy's participation, mitral valve, subvalvular apparatus and the papillary muscles in its mechanism; and evaluate the