How to Perform a Diagnostic and Prognostic Analysis of Hypertrophic Cardiomyopathy in 2022: Should we Divide to Improve Treatment?

Cardiomiopatia Hipertrófica: Como Realizar uma Análise Diagnóstica e Prognóstica em 2022. Dividir para Tratar Melhor?

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Hypertrophic cardiomyopathy (HCM), the most common genetic heart disease, has an estimated prevalence in the general population of 1:500–1:200.[1] The diagnosis is based on the presence of left ventricular hypertrophy (LVH) that is not fully explained by loading conditions, and HCM occurs in the absence of other cardiac, systemic, or metabolic disease or in the context of a multiorgan syndrome associated with LVH.[2]

Despite being considered a genetic disease, the initial diagnosis of HCM does not require genetic testing. The diagnostic power of current genetic panels is modest, just 46%;[3] therefore, failure to detect a mutation does not exclude the diagnosis. Current guidelines recommend genetic testing, especially when the possibility of cascading familial genetic screening is anticipated or in cases in which the clinical presentation suggests a specific non-sarcomeric etiology potentially treatable with specific therapy, such as Anderson-Fabry disease, Danon disease, or familial amyloidosis.[4]

The diagnosis of HCM is determined using transthoracic echocardiography in most cases, the first-choice imaging modality. Although the current diagnostic criteria are based exclusively on increased wall thickness, HCM also involves structural cardiomyocyte derangement, interstitial fibrosis, microvascular remodeling, and microcirculatory dysfunction, changes that may precede increased left ventricular (LV) wall thickness.[5] Thus, cardiac magnetic resonance (CMR) imaging can play a much more precise and sensitive role in tissue characterization along with late gadolinium enhancement, T1 mapping, fractal analysis, diffusion tensor imaging, transit time, and segmental perfusion defect assessment. Some of these techniques have been implemented in clinical practice, while others are still being investigated.

HCM is a disease with great phenotypic and clinical heterogeneity ranging from long-term asymptomatic disease to being a cause of sudden death in young adults and athletes.[6] HCM can progress according to several profiles: heart failure (HF) with preserved ejection fraction due to diastolic dysfunction and/or obstruction; HF with reduced ejection fraction; atrial fibrillation (AF) and stroke; ventricular arrhythmias; and sudden cardiac death (SCD). The predictors of each of these profiles remain unclear exception made for the profile of ventricular arrhythmias and SCD. This area has been the subject of research in recent years for which quite robust sudden death risk stratification strategies have been developed.

Indeed, the European model,[6] incorporated into the 2014 European recommendations, estimates the five-year risk of sudden death of a specific patient using mathematical models and considering seven clinical and imaging variables (age, maximum LV thickness, left atrial diameter, maximum LV outflow gradient, family history of SCD, unexplained syncope, and non-sustained ventricular tachycardia [NVT]). On the other hand, the American strategy,[7] which was recently optimized, includes new risk factors in the SCD risk stratification, such as the presence of apical aneurysms with fibrosis, extensive late enhancement on CMR (usually ≥15% of LV mass), and LV systolic dysfunction (defined as an ejection fraction < 50%). The presence of a new or classic risk factor (family history of SCD in a first-degree relative, massive hypertrophy ≥ 30 mm, unexplained syncope events, NVT) may be an indication for an implantable cardioverter-defibrillator, with different strengh levels of evidence.

However, the prognostic assessment of patients with HCM goes beyond SCD risk stratification. Progression to other profiles represent a large part of the current morbidity and mortality of this disease. The international Sarcomeric Human Cardiomyopathy Registry (SHaRe),[3] which involved 4,591 HCM patients with a median follow-up of 5.4 years and >24,000 patient-years, identified two major predictors of adverse events: sarcomeric mutation status and age at diagnosis.

Survival analysis showed that groups with pathogenic mutation, probably pathogenic or variant of uncertain significance, had events at younger ages and a higher incidence of compound events — HF and AF — than the group with no identified mutation (SARC-). On the other hand, the group with a pathogenic or likely pathogenic mutation (SARC+) had a higher risk of malignant ventricular arrhythmias compared to the SARC- group.

At the same time, patients with nonfamilial HCM (SARC- and no family history of HCM) had a lower risk of mortality

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and compound events than the other groups, and the age-adjusted mortality rate of this group was similar to that of the general population.

Regarding age, the age-adjusted mortality rate was four times higher in young patients (20–29 years old) and three times higher in patients 50–69 years than in the general population, with HF and non-cardiac mortality being the main causes of death. Surprisingly, SCD represented only 16% of these deaths. Regardless of age, most HCM-related complications occurred late (at 50–70 years) and involved HF and AF.

Evidence suggests the existence of two major HCM subtypes based on the identification of sarcomeric mutations.[8,9] SARC+ patients are younger at the time of diagnosis, have a higher degree of hypertrophy that is typically asymmetric, and have a more frequent family history of HCM and SCD with a worse prognosis. On the contrary, SARC- patients more often present with a sigmoid interventricular septum, less fibrosis, and more comorbidities such as hypertension and obesity; and seem to follow a more benign clinical course (Figure 1).

These findings suggest that genetic testing may play an important role in the diagnosis and prognosis of these patients, distinguishing two very different HCM subgroups that probably require different prevention, treatment, and screening strategies. Considering this new approach to HCM, genetic studies will play an even more important role in disease management, increasing our understanding of HCM from a molecular point of view and enabling the more accurate treatment of these patients. In short, we should divide cases to better treat them.

Authors' contributions

Manuscript writing: Toste A; critical review of the manuscript for important intellectual content: Cardim N.

Conflict of interest

The authors have declared that they have no conflict of interest.

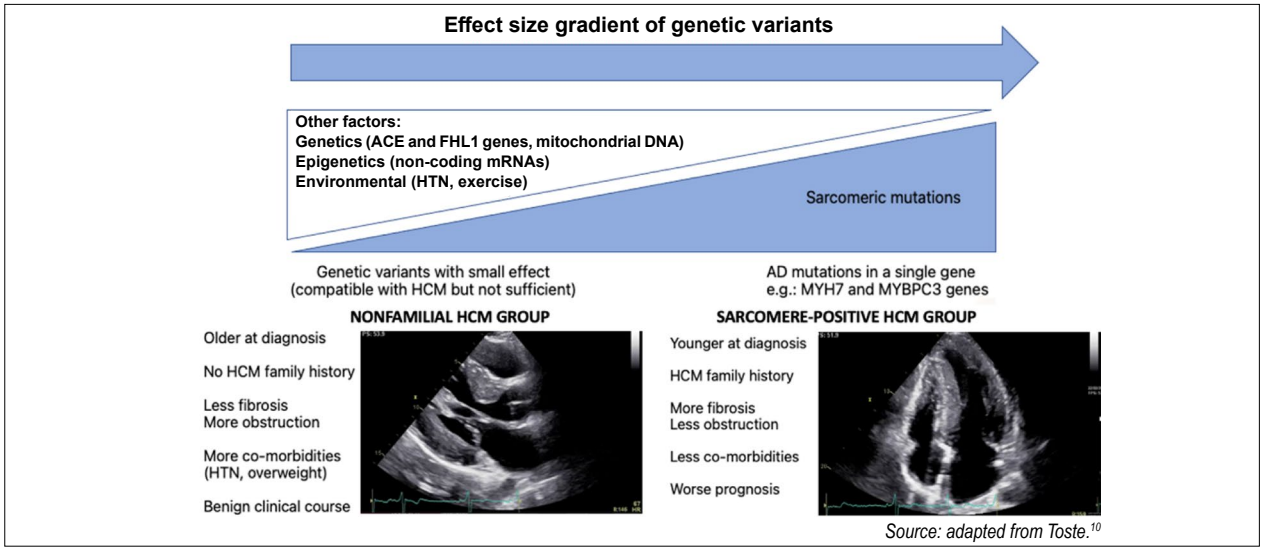

Figure 1 – *Main characteristics by HCM subgroup.*

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