Essentials of Hypertrophic Cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is an uncommon disease with significant consequences. Since the 1950s, major strides in understanding its etiology and pathogenesis have led to improved management and patient survival. Hypertrophic cardiomyopathy is associated with various mutations in several cardiac sarcomeric genes. Due to the complications of HCM, such as left ventricular outflow tract obstruction, diastolic dysfunction, arrhythmias, increased risk of stroke, infective endocarditis, and, most importantly, sudden cardiac death, appropriate and timely diagnosis is critical. This review summarizes current knowledge about HCM and the most appropriate investigations for persons suspected of having HCM. Treatment strategies for the disease and its complications are presented briefly.

Key words: hypertrophic cardiomyopathy, cardiomyopathy, sudden cardiac death, older adults

Introduction

Cardiomyopathies (CMs) are diseases with a primary abnormality of the myocardium, often classified as dilated, restrictive, or hypertrophic (Figure 1).1 Dilated cardiomyopathy is characterized by ongoing cardiac dilatation and systolic dysfunction, while restrictive cardiomyopathy manifests as impaired ventricular filling during diastole and normal or near-normal systolic function.1 Hypertrophic cardiomyopathy (HCM) is distinguished from the other CM by the presence of myocardial hypertrophy and in approximately 25% of individuals, left ventricular outflow tract obstruction (LVOTO).1,2

This CM was initially described as a septal hypertrophy but is now a distinct entity called HCM.3-5 Defined by its now characteristic lesion—the presence of asymmetric septal hypertrophy. It is a complex, multifaceted disease, related primarily to a genetic defect of the cardiac sarcomeric/contractile apparatus.5,6

Affecting approximately 1 in 500 individuals,6-8 HCM is perhaps the most commonly inherited cardiovascular disorder,6,9-11 with many complications, including LVOTO, atrial and ventricular arrhythmias, diastolic dysfunction, myocardial infarction (MI), stroke, infective endocarditis (IE), and sudden cardiac death (SCD). Early identification of individuals with this condition, and screening of their families, is essential if these complications are to be avoided. The risk of death from HCM has been reported to be 1-6%.2,6,12 A majority of these individuals today will live to older age and some will undergo septal myectomy in their late 60s. The incidence of new diagnosed cases of HCM in the older individual is not certain. However HCM appears to carry a better prognosis in the older individual, although the prognosis is altered by the higher prevalence of comorbidities.

Etiology – Genetics

Several genes have been implicated in HCM, and these account for 60-70% of all cases of HCM.5 These genes encode proteins of the cardiac sarcomeric apparatus and exhibit an autosomal dominant pattern of inheritance.6,13 The most commonly mutated sarcomeric genes that cause HCM are the genes for the β-myosin heavy chain (MYH7) and the cardiac myosin-binding protein C (MYBPC3), which are thought to be responsible for over 50% of all cases of HCM.6 Genetic diversity is compounded by intragenic heterogeneity, with over 400 different mutations identified within these 11 genes.6,13

Clinical Presentation

The common presenting symptoms among individuals with HCM include dyspnea, angina, and presyncope or syncope. Chest pain may occur at rest or be precipitated by exertion or, among those with LVOTO, a heavy meal.

Persons with obstructive HCM may be identified on physical examination: the jugular venous waveform may demonstrate a prominent ‘a’ wave; the carotid upstroke may be brisk or double
(traditionally called the spike and dome carotid upstroke); palpation of the precordial may reveal a palpable fourth heart sound, a sustained apical impulse, or a triple apical impulse (the latter being seen only among individuals with LVOTO); auscultatory findings include reversed splitting of the second heart sound and a dynamic systolic ejection murmur. Bedside maneuvers that accentuate the murmur include assuming the standing position after squatting and performing the Valsalva maneuver, there may also be an associated systolic murmur of mitral regurgitation.

Pathology
In HCM, the heart usually shows modest

![Figure 1: Hypertrophic cardiomyopathy](image)

Hypertrophic cardiomyopathy, or HCM, is a disease of the myocardium in which a portion of the myocardium is hypertrophied without any obvious cause.
cardiomegaly with left ventricular hypertrophy (LVH). Sixty-seven percent of patients with cardiomegaly show asymmetric hypertrophy, usually affecting the subaortic portion of the interventricular septum. Hypertrophy may also involve other regions of the heart, such as the midventricular septum, the free walls of the left ventricle (LV) and the apex. Symmetrical hypertrophy is seen in up to 10% of patients. Young patients show significant deformation of the LV cavity, while older patients relatively show little change.

Microscopic
The typical histological finding in HCM is myocyte hypertrophy and disarray (see Figure 2). Myocytes, normally arranged in parallel bundles, are found at oblique and perpendicular angles to each other, often in an interlacing or basket weave pattern, with interstitial fibrosis. Myocyte disarray is not unique to HCM and may also be seen in some areas of normal myocardium. Caution must therefore be exercised in the interpretation of this finding.

Investigations
The diagnosis of HCM is most frequently made using echocardiography. Hypertrophic cardiomyopathy must be distinguished, most commonly, from hypertensive heart disease and infiltrative processes such as amyloidosis.

Electrocardiogram
About 75–90% of persons with HCM have an abnormal electrocardiogram (ECG). Some abnormalities seen are due to LVH and include voltage abnormalities, ST segment and T wave abnormalities, prominent Q waves, and signs of LA enlargement. An ECG finding of giant negative T waves in the precordial leads is characteristic of apical HCM.

Magnetic Resonance Imaging
Magnetic resonance imaging (MRI) is useful when hypertrophy is confined to unusual areas, such as the apex, which may be difficult to image adequately with echocardiography in some patients. Contrast agents such as gadolinium may be used with MRI to identify regions of interstitial fibrosis and/or scarring.

Cardiac Catheterization
Cardiac catheterization helps exclude coronary disease as the cause of angina in patients with risk factors for coronary atherosclerosis. It can also be used to measure LV outflow tract gradients, both at rest and with provocation, among persons with LVOTO.

Other tests, including radionuclide studies, cardiopulmonary exercise testing, genetic testing and family screening, are helpful in the diagnosis and management of HCM.
Clinical Implications

Differential Diagnosis

Differentiating HCM from hypertensive heart disease may be difficult; however, several characteristics can be used. First, HCM tends to result in more severe hypertrophy as compared to hypertensive heart disease. Unless the patient has a long history of poorly controlled hypertension, a wall thickness of greater than 20 mm is more likely to be due to HCM than hypertension. Secondly, asymmetric septal hypertrophy is frequent in HCM, while a concentric pattern is more common in hypertensive heart disease. Lastly, although SAM can occur in both diseases, the combination of SAM with a substantial LVOT gradient and asymmetric septal hypertrophy is highly suggestive of HCM.

Athlete’s Heart

It may be difficult to differentiate between normal myocardial adaptations to athletic activity and the morphologic changes associated with HCM. The diagnosis of HCM is more likely than the diagnosis of athlete’s heart in the presence of a family history of HCM, bizarre electrocardiographic patterns, asymmetric hypertrophy (or other unusual pattern of left ventricular hypertrophy), a small left ventricular cavity size (<45mm), left atrial (LA) enlargement, and an abnormal left ventricular filling pattern.

Hypertrophic Cardiomyopathy among Older Adults

Older adults with HCM have a more favourable prognosis and a lower risk of SCD. The LV cavity of younger persons tends to be more crescent shaped compared to the somewhat more ovoid cavity among older adults. An additional age-related feature seen in older adults is a decrease in the angle between the ascending aorta and the long axis of the LV. This morphological feature, along with age-related shrinkage of the heart, is believed to result in an upper-septal bulge and consequent obstruction of the outflow tract. This should not be mistaken for the septal hypertrophy of HCM. There is evidence now to suggest that sarcomeric gene mutations associated with HCM in older adults are not the same as those seen in younger persons with HCM.

Treatment Counselling

Prior to any treatment strategy, patients should be counselled on family screening and activity levels. Since HCM has an autosomal dominant pattern of inheritance, informing patients of screening protocols for first-degree relatives may help identify asymptomatic affected individuals. Further, patients should be counselled to avoid extreme exertion. Individuals with no symptoms and no evidence of obstruction should not be given any treatment. Instead, disease progression should be monitored using ECG and echocardiography, as outlined above.

Left Ventricular Outflow Tract Obstruction

The treatment strategies for the management of LVOTO in HCM include pharmacotherapy, surgical myectomy, septal ethanol ablation (SEA), and dual-chamber (DDD) permanent pacing (Table 1).

Arrhythmias

Persons with HCM usually become symptomatic with the onset of atrial fibrillation. Physicians should attempt to control patients’ heart rate medically using calcium channel and β-blockers, and patients should receive anti-coagulant therapy. Amiodarone may be effective in the long-term management of atrial fibrillation.

Sudden Cardiac Death

Patients with sustained ventricular arrhythmias are at increased risk of SCD. Recent studies have demon-

Table 2: Comparison of Different Treatments for Varying Clinical Manifestations of Hypertrophic Cardiomyopathy.

<table>
<thead>
<tr>
<th>Clinical Scenario</th>
<th>Pharmacologic Treatment</th>
<th>Surgical/Interventional Treatment</th>
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<tr>
<td>Asymmetric Non-Obstructive HCM*</td>
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<tr>
<td>Symptomatic Non-Obstructive HCM**</td>
<td>Beta blockers</td>
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<tr>
<td>Atrial Fibrillation</td>
<td>Anti-coagulants ± Amiodarone</td>
<td>Cardioversion</td>
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<td>End-stage HCM (LV systolic dysfunction)</td>
<td>ACE Inhibitors</td>
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<td>Diuretics</td>
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<tr>
<td>Obstructive HCM**</td>
<td>Beta blockers ± Disopyramide</td>
<td>Septal myectomy</td>
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<td>Septal ethanol ablation</td>
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<td>Dual chamber pacemaker</td>
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ACE: Angiotensin converting enzyme; LV: left ventricle
*Pharmacotherapy is not recommended; care of this group involves serial screening of all first-degree relatives
**Surgical/interventional treatment is used in patients refractory to pharmacotherapy

Table 2: Comparison of Different Treatments for Varying Clinical Manifestations of Hypertrophic Cardiomyopathy.
strated the efficacy of automatic implantable cardioverter defibrillators (AICDs) in the primary and secondary prevention of SCD. These devices have been shown to be highly effective in treating arrhythmias, and their benefits are believed to be superior to those of amiodarone. However, AICDs are associated with an incidence of inappropriate ICD discharges.

For a summary of treatments, please see Table 2.

**Conclusion**

The understanding of HCM has changed dramatically over the last two decades. It is now recognized as a genetically inherited, autosomal dominant, sarcomeric protein-associated disease. Its genetic heterogeneity is matched by its variable clinical and morphological presentations. Screening and early identification of cases and asymptomatic family members is essential for improved survival of patients. A lot of progress has been made in unraveling the mysteries of this disease; however, much more progress is still essential. More registries, analyses, and publications about all aspects of the disease are clearly needed.

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**References**