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Review of recent advances in the management of hypertrophic cardiomyopathy

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Abstract. – Hypertrophic cardiomyopathy (HCM) is a complex but common monogenic cardiovascular disorder characterized by unexplained non dilated left ventricular (LV) thickening in the absence of another cardiac or systemic disease. The condition is associated with sudden and unexpected death in young individuals including trained athletes. HCM represents a genetic disorder caused by mutations in genes encoding sarcomeric proteins of the cardiac myocyte. This review article discusses the genetics behind HCM, its clinical presentation, and diagnosis and the present-day pharmacological management of HCM.

Key Words:
Hypertrophic cardiomyopathy, Genetics, Diagnosis, Pharmacological management, Invasive therapy.

Introduction

Hypertrophic cardiomyopathy (HCM) is a complex, most common monogenic cardiovascular disorder that has been at the centre of intense scrutiny and investigation since it was first reported some 50 years ago. It is characterized by unexplained non dilated left ventricular (LV) thickening in the absence of another cardiac or systemic disease. It affects 1:500 of the general population. Although HCM is recognized as an important cause of disability and mortality across all ages, the most overwhelming component of its natural history is sudden and unexpected death in young individuals including trained athletes[1]. Due to complex symptomatology and heterogeneity in natural history and prognosis, proper management of this disorder poses a dilemma to the treating physician. In this review, we summarize recent changes in HCM management guidelines and novel diagnostic, and therapeutic interventions.

Molecular Genetics of HCM

Pioneering work by Seidman et al[5] in 1990 led to the discovery of the first causal missense mutation in the MYH7 gene coding for the β-myosin heavy chain (β-MyHC) in HCM[2]. Ever since more than 1400 mutations in 20 or more genes encoding sarcomeric proteins has been reported (Table I), thus, establishing the role of molecular genetics in the pathophysiology of HCM. HCM is a genetic disease caused by mutations in genes that encode sarcomeric proteins of the cardiac myocyte and is inherited as an autosomal dominant trait with every offspring having a 50% chance of developing the disease. Therefore, all family members must be screened as sudden cardiac death could often be the first presentation in apparently healthy relatives[3].

MYH7 and MYBPC3 are the two most common genes for HCM which encode β-MyHC and myosin binding protein-C (MyBP-C), respectively. Other relatively common genes are TNNT2, TNNI3, TPM1, and ACTC1, which encode cardiac troponin T, cardiac troponin I, α-tropomyosin, and cardiac α-actin, respectively. Known causal genes are responsible for about 60% of all HCM cases whereas 40% remain unknown. The presence of significant phenotypic variability in HCM reduces the prognostic value of genetic testing[4].

AHA/ACC guidelines have recognized that due to genetic and phenotypic variability clinical outcomes based on HCM related gene are often unreliable. Therefore, genetic testing is not recommended for all patient but only screening (clinical with or without genetic testing) of all first degree relatives of patients with HCM is recommended. The guidelines also recommend genetic testing for HCM and other genetic causes of unexplained cardiac hypertrophy in pa-

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Table I. Association of lncRNA DLEU7-AS1 expression with clinicopathologic characteristics of CRC.

Gene	Protein	Frequencies in patients with HCM	Associated phenotype
MYH7	B-Myosin heavy chain	25%-35%	Mild or severe HCM
MYBPC3	Myosin-binding protein C (cardiac type)	20%-30%	Expression similar to MYH7, late onset
TNNT2	Troponin T (cardiac muscle)	3%-5%	Mild hypetrophy, sudden death
TNNI3	Troponin I (cardiac muscle)	<5%	Extreme intrafamilial heterogeneity, no sudden death without severe disease
TPM1	Tropomyosin 1α	<5%	Variable prognosis, sudden death
MYL2	Regulatory myosin light chain 2 (ventricular/cardiac-muscle isoform)	<5%	Skeletal myopathy
MYL3	Essential myosin light chain 3	Rare	Skeletal myopathy
ACTC	α-Cardiac actin 1	Rare	Skeletal myopathy
TTN	Titin	Rare	Typical HCM
TNNC1	Troponin C, slow skeletal and cardiac muscles	Rare	Typical HCM
MYH6	α-Myosin heavy chain	Rare	Late onset
CSRP6	Muscle LIM protein	Rare	Late onset, variable penetrance
MYLK2	Myosin light chain kinase 2	Rare	Early onset
LDB3	LIM-binding domain 3	Rare	Mainly sigmoidal HCM
TCAP	Telethonin	Rare	Typical HCM, variable penetrance
VCL	Vinculin/metavinculin	Rare	Obstructive midventricular hypertrophy
ACTN2	α-Actinin 2	Rare	Mainly sigmoidal HCM
PLN	Phospholamban	Rare	Typical HCM, variable penetrance
MYOZ2	Myozenin 2	Rare	Typical HCM
JPH2	Junctophilin 2	Rare	Typical HCM

tients with an atypical clinical presentation of HCM[5].

HCM proband genetic testing which has been available since 2003 has various drawbacks. It can only identify 50%-60% of clinically affected probands, as all genes causing HCM have not yet been identified, and are missing from testing panels[3].

A new genotype positive phenotype negative population is growing as more families undergo screening for HCM. These individuals carry the HCM causing gene but do not show proof of hypertrophy. The AHA/ACC guidelines recommend electrocardiogram (ECG), transthoracic echocardiogram (TTE), and clinical assessment at periodic intervals of 12 to 18 months in children and adolescents and about every 5 years in adults in these patients[5].

Moreover, in 5-10% of patients often other conditions known as phenocopies such as metabolic diseases and genetic cardiomyopathies (e.g., Fabry's disease, Danon's disease) present with left ventricular hypertrophy and mimic HCM. It is important to differentiate between sarcomere HCM and phenocopies as the natural history and management approach often differ[4].

Relevant Clinical Aspects of Hypertrophic Cardiomyopathy

A primary disease of cardiac myocytes, it is diagnosed by the presence of unexplained cardiac hypertrophy and by a preserved or increased LV systolic function. Light microscopy efficiently shows the hypertrophied cardiac myocytes, myocyte disarray, interstitial fibrosis, hypertrophy or hyperplasia of the media of the intramural coronary arteries, and mitral valve leaflet abnormalities. Cardiac myocyte disarray is atelltalesign of HCM[6].

HCM is a relatively benign disease with most patients being asymptomatic or mildly symptomatic. Sudden cardiac death (SCD) is often the first presentation of the disease. The commonest presenting symptom is dyspnea particularly during exercise due to diastolic dysfunction. Myocardial hypoperfusion and increased oxygen demand may cause chest pain. Palpitations are common and often associated with lightheadedness and dizziness, and rarely with syncope. Atrial fibrillation and supraventricular arrhythmias may occur and are associated with poor clinical outcomes[3].

The most feared and devastating event in HCM is SCD, often seen as the first manifestation in

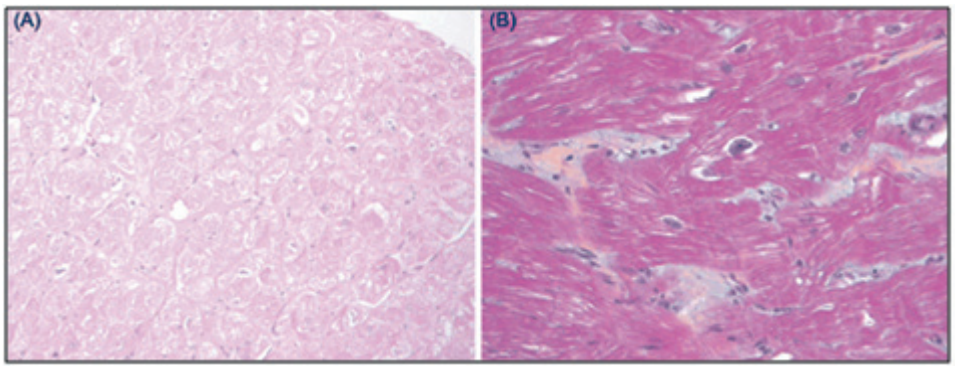

Figure 1. Photomicrograph showing ***(A)*** normal myocardium versus (10 x). ***(B)*** muscle fibre hypertrophy, disarray and interstitial fibrosis of HCM (40 x).

young, healthy individuals even in young athletes. Few recognized major risk factors of SCD in HCM include history of cardiac arrest, syncope due to cardiac arrhythmias, a strong family history of SCD, repetitive nonsustained or sustained ventricular tachycardia, and severe cardiac hypertrophy[4].

Diagnostic Evaluation of HCM Patients

AHA/ ACC guidelines recommend a 12-lead ECG in the initial evaluation of patients with HCM and as part of screening for first degree relatives of patients with HCM. Holter monitoring is recommended in initial evaluation of HCM patients to detect ventricular tachycardia and identify patients for ICD treatment and in patients who develop lightheadedness or palpitation. Annual ECGs are recommended in asymptomatic HCM patients to assess asymptomatic changes in conduction or rythm[5].

Echocardiography is particularly important to demonstrate dynamic outflow tract obstruction and to evaluate clinically relevant abnormalities in cardiac as well as valvular structure and function. A transesophageal echocardiogram (TEE) is recommended in all patients with suspected HCM, for screening first degree relatives of HCM patients and every 12-18 months for children of patients with HCM. Repeat TTE should be done in case of change in clinical status or new cardiovascular event in HCM patients. Cardiac magnetic resonance (CMR) yieldshigh-grade resolution and complete visualization of the left ventricular myocardium. This helps in establishing the diagnosis and phenotype of HCM.Additionally, it helps with identifying the distribution of LVH and the mechanism of LVOT obstruction. CMR is indicated in patients who are suspected of having HCM but echocardiography has failed to establish the diagnosis[5].

Contemporary Pharmacological Management of HCM

The presence of 2 or more major risk factors as discussed earlier in an asymptomatic individual makes the individual a candidate for internal cardioverter-defibrillators (ICD implantation) to prevent SCD. Current pharmacologic treatment of patients who have HCM includes the use of β-blockers (without intrinsic sympathetic activity), calcium-channel blockers (without vasodilating activity), and disopyramide. Patients with exercise-induced symptoms, left ventricular outflow tract (LVOT) obstruction, and chest pain are candidates for β-blocker therapy. Calcium-channel blockers such as verapamil and diltiazem are also beneficial in HCM and should be used in β-blocker intolerant individuals or in combination with β-blockers in patients with angina or dyspnea. They should be avoided in patients with LVOT obstruction. Disopyramide, a class I antiarrhythmic drug, in combination with β-blockers attenuates LVOT obstruction and improves symptoms in patients with HCM. Diuretics should only be used in low doses in patients with volume overload to avoid volume depletion and hypotension. RAAS inhibitors, HMG-CoA reductase inhibitors, and N-acetylcysteine are the potential new pharmacological therapies in the management of HCM[3,4].

Invasive Therapies

Surgical myectomy involves resection of a small portion of the interventricular septum at its base. It is recommended in patients with severe drug-refractory symptoms and LVOT obstruction. It is the procedure of choice in patients with co-morbid conditions such as coronary artery disease and valvular disorders. The proce-

dure is associated with the regression of cardiac hypertrophy and with favourable LV remodeling and long-term survival is excellent[3,4].

Transcatheter septal ablation is a procedure wherein a small amount of alcohol is infused into the major septal perforator branch of the left anterior descending coronary artery that leads to localized myocardial necrosis in the septum[7]. This helps in minimizing LVOT obstruction. This procedure should be used in symptomatic patients who do not respond to medical therapy. Additionally, these patients should have an interventricular septal thickness of 15 mm or more and a substantial resting or provoked LVOT gradient to be subjected to transcatheter septal ablation. The adverse effect of transcatheter septal ablation includes complete or advanced atrioventricular (AV) block that may require the implantation of a permanent pacemaker. Dual-chamber pacing may be useful in patients who do not respond to medical therapy and are not candidates for surgical myectomy or transcatheter septal ablation[3,4].

Conclusions

Advances in molecular genetics, cardiac imaging and potential new pharmacological therapies developed in recent years have had a substantial impact on management of HCM patients. However, as no treatment has yet been proved to prevent, attenuate, or reverse the cardiac phenotype in HCM, the disease merits further evaluation in clinical studies.

Conflict of interest

The authors declare no conflicts of interest.

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