A complex unit for a complex disease: the HCM-Family Unit

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Abstract

Hypertrophic cardiomyopathy (HCM) is a group of heterogeneous disorders that are most commonly passed on in a heritable manner. It is a relatively rare disease around the globe, but due to increased rates of consanguinity within the Kingdom of Saudi Arabia, we speculate a high incidence of undiagnosed cases. The aim of this paper is to elucidate a systematic approach in dealing with HCM patients and since HCM has variable presentation, we have summarized differentials for diagnosis and how different subtypes and genes can have an impact on the clinical picture, management and prognosis. Moreover, we propose a referral multi-disciplinary team HCM-Family Unit in Saudi Arabia and an integrated role in a network between King Faisal Hospital and Inherited and Rare Cardiovascular Disease Unit-Monaldi Hospital, Italy (among the 24 excellence centers of the European Reference Network (ERN) GUARD-Heart).

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Introduction

Hypertrophic cardiomyopathy (HCM), defined as an increase in left ventricular (LV) wall thickness that cannot be solely explained by abnormal loading conditions, is associated with myocardial and electrical dysfunction [1]. The diagnosis, both in obstructive and non-obstructive form, requires the absence of other cardiovascular disease capable of producing equivalent hypertrophy [2].

The estimated prevalence of HCM is 1 in 500 coming based on echocardiographic imaging. However, with the advent of advanced imaging modalities and genetic testing, the incidence raised to 1 in 200 accounting the combined prevalence of phenotypically expressed HCM as well as genetic carriers [3,4]. Therefore, it has been estimated that HCM affects around 20 million people, making this disease the most common genetic cardiovascular disease [5]. Although HCM seems less prevalent among women, both sexes are equally affected [6].

This review presents a systematic approach to the definition, assessment, management and prognosis of patients affected by HCM and their relatives based on current scientific evidence and guidelines. Additionally, the aim is also to describe the organization and the peculiar healthcare model of our HCM-Family Unit in Saudi Arabia and the international multidisciplinary cooperation between King Faisal Specialist Hospital and Research Center and Monaldi Hospital.

HCM-Family Unit: a new healthcare model for complex and heterogeneous patients

HCM is a genetic disease with different etiologies according to age and clinical presentation. Different etiologies mean also different management, and possibly treatments. Moreover, the morpho-functional phenotype (*i.e.*, degree of hypertrophy, fibrosis, outflow tract obstruction, diastolic and/or systolic dysfunction) requires careful investigations and evaluation for possible management. It is clear that a dedicated unit needs specific characteristics, including: i) pediatric and/or adult cardiologists with a specific expertise in diagnosis and management of cardiomyopathies; ii) a multidisciplinary team, for the diagnosis and management of systemic diseases associated with cardiomyopathies; iii) a family-based approach and a transition model between pediatric and adult HCM patients. On this ground, our HCM-Family Unit, though handled by cardiologists, is a multidisciplinary team requiring different professional roles, including cardiac surgeons, cardiac pediatrics, geneticists, psychologists, neurologists and metabolism experts. A peculiarity of our Unit will be the high prevalence of rare cardiomyopathies, made possible by the high rates of consanguinity in Saudi Arabia. This also requires a Specialized link with a highly experience Cardiomyopathy team. Herein, we propose the first example of "HCM-Extended Family Unit" made possible by a collaboration network between King Faisal Hospital and Inherited and Rare Cardiovascular Disease Unit-Monaldi Hospital, Italy (among the 24 excellence centers of the European reference Network (ERN) GUARD-Heart). The *S*audi-Italian collaboration will be founded on a shared program of care (*i.e.*, teleconsultation), research (*i.e.*, registries, protocols, *etc.*), and education (*i.e.*, consultant and junior doctors exchange, meetings), (Figure 1).

The HCM-Family Unit will manage complex cases with diagnosis and treatment challenges and, by completing the "learning curve" in the near future, will be also a referral Consultation Unit/Teleconsultation for peripheral non-specialized centers, where the stratified patients will be sent back for routine follow-up [2].

Definition and etiology

In adult patients, the definition of HCM is based on left ventricular wall thickness ≥15 mm in any segment (from base to apex, ensuring thickness is recorded at mitral, mid-LV and apical levels). However genetic and non-genetic disorders can present with HCM with a wall thickness between 13-14 mm; in such cases, diagnosis is contingent upon further evaluation [2,7]. In children, diagnostic criteria of HCM have to be adjusted for body surface area [2], and a cut off of a LV wall thickness greater than 2.5 standard deviation than the predicted mean (z-score>2) at any segment of left ventricle is wildly accepted [7]. Up to 60% of adult HCM patients shows evidence of autosomal dominant transmission caused by sarcomere protein mutations. However, a subgroup of patients with non-familial HCM, defined by the absence of an overt family history of HCM (non-familial HCM) and a negative genetic testing for sarcomere causative mutations, seems to have better event-free survival and a more benign clinical course [8].

HCM can be challenging to diagnose as there are many diseases with similar presentations known as "HCM Phenocopies" or secondary causes of left ventricular hypertrophy that can have a

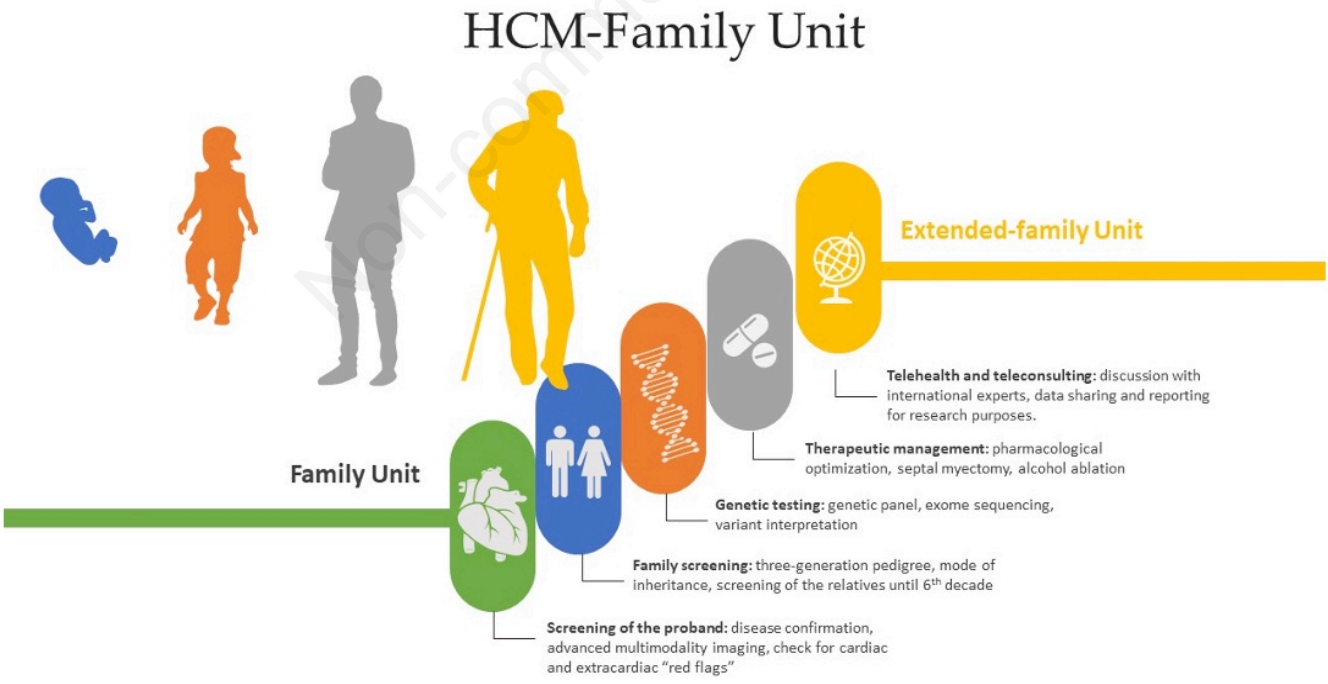


Figure 1. Graphical abstract. The HCM-Family Unit is a multidisciplinary unit, responsible for patient care from neonatal to adult-elderly age. The Unit screens the proband and family by pedigree and genetic testing, and defines risk stratification and therapeutic approach. The HCM-Family Unit is part of an international network of experts to share complex cases and knowledge and will organize a national network for local counseling. Ultimately, the HCM-Family Unit is meant to be a referral Unit for clinical, research and teaching activity.

similar presentation, yet a different etiology and *age-specific presentation* [9-12]. The identification of clinical clues ("red flags") which could raise the suspicion of non-sarcomeric variants should be systematically performed in order to orient the best therapeutic approach.

HCM-Family Unit organization

Probands and their relatives, who are at risk of developing HCM, are evaluated at the HCM-Family Unit starting from the confirmation, risk stratification and management of therapeutic options (Table 1, Figure 2). Because of age-specific penetrance of sarcomeric mutation, childhood-onset HCM is a more heterogeneous group and, although sarcomeric mutations still represent ~60% of the cases according to recent data from the Sarcomeric Human Cardiomyopathy Registry (SHaRe) [13], other causes of non-sarcomeric HCM should be excluded. In particular, differential diagnosis should include inherited errors of metabolism (*i.e.*, glycogen storage diseases (GSDs), lysosomal storage diseases, fatty acid oxidation disorders), neuromuscular diseases, malformation syndromes (*i.e.*, RASopathies), and mitochondrial diseases [13,14]. To have information either from the proband or from the family is determinant for the final diagnosis. Since the disease is relatively rare, positive genetic studies varies between 20 to 90% depending on the disease and is frequently difficult to find a genotype-phenotype correlation. For this reason, national and international registries, particularly when shared among international HCM-comprehensive units, both with co-segregation and functional studies, may help to achieve a correct diagnosis [15].

Probands and relatives referred to the HCM-Family Unit

Most patients with HCM are asymptomatic and they are usually identified during incidental ECG screening or if 2D echocardiography is performed for other reasons.

Many pathophysiological mechanisms may contribute to cause symptoms in HCM patients. The main characteristics are left ventricular outflow tract (LVOTO) obstruction and impaired diastolic function, which may contribute to the elevation in LV filling pressures [16]. Atrial dilatation, which is a consequence of impaired diastole, predisposes HCM patients to higher risk of atrial fibrillation and supraventricular arrhythmias [17,18]. Furthermore, patients affected by HCM may show mitral valve abnormalities, and often show elongated anterior mitral leaflet or chordae tendineae or papillary muscles abnormalities. Mitral regurgitation can be frequently detected among HCM patients and represents a marker of complexity, particularly in patients who should undergo septal myectomy. The imbalance between oxygen supply and demand causes myocardial ischemia and may account for chest pain as initial presentation. Furthermore, can be involved in the pathophysiology of apical aneurysm which is characterized by the fibrotic substitution of the apical myocardium and be responsible of major arrhythmias, syncope and sudden

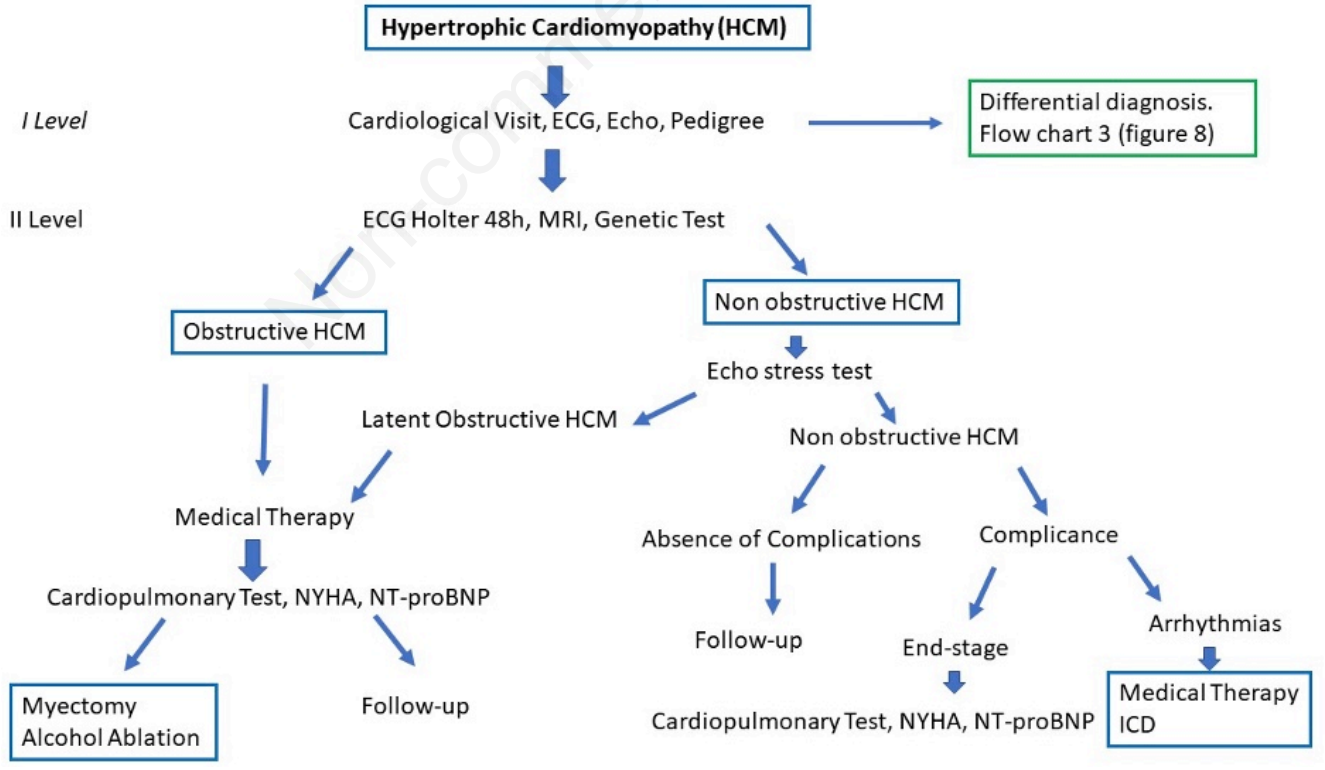


Figure 2. Flow chart for the management of patients at risk of developing HCM. ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association.

death, thrombus formation and ischemic events [19]. HCM patients with apical aneurysm have 3-fold greater adverse event than HCM without apical aneurysm [20]. Also, myocardial bridging has high prevalence in HCM and can be the cause of chest pain, arrhythmia, syncope *and* sudden death. (Table 1) [7,16,19,21-35]. First degree relative should undergo regular screening (cardiology visit, ECG, echocardiography, pedigree and genetic test, *etc*.). If a pathogenic variant is detected in the proband, first-degree relatives with positive genetic test will be followed at the HCM-Family Unit [36]. In case of pathogenic or likely pathogenic variants, the absence of the mutation in a first-degree relative excludes the patient from subsequent follow up. If the mutation is a variant of uncertain significance (VUS), as the result is not clinically actionable, regular screening has to be performed until 40-50 [7,36]. Moreover, in cases of VUS, co-segregation studies in the family should be performed and, if associated with positive phenotype, this VUS gene could be the reason of the pathology (Figure 3).

Patients carrying sarcomere variants may have different phenotypes within the same family. In other words, a broad phenotypic spectrum could be associated to the same sarcomere mutation (*i.e.*, restrictive cardiomyopathy or dilated cardiomyopathy, non-compaction cardiomyopathy and HCM) and recurrent patterns of disease progression have been studied (Figure 4) [37,38]. Moreover phenotype overlap can coexist and "restrictive phenotype" could be part of the continuum spectrum of HCM [39]. Variant in genes MYH7, TNNI3, MYL2 associated with HCM can show the restrictive phenotype [40].

Pedigree/genetics

A pedigree represents the distribution of a specific disease in a family and in the case of HCM at least three generations should be included during the evaluation to identify the possible inheritance pattern [41]. Family screening should occur regardless of age. After the first evaluation, first-degree family members should undergo regular follow-up, depending on disease severity. A family study should be conducted to look for the pathogenic mutation that was found in the proband and the relatives should be screened as soon as possible. An autosomal dominant mode of transmission, as the case of HCM, each offspring of an affected family has 50% chance to be affected and the age at which the disease become manifest within each individual is quite variable. In the case of consanguinity, quite frequent in Saudi Arabia, auto-

Table 1. Diagnostic approach and most common findings in hypertrophic cardiomyopathy patients.

Clinical criteria	
Cardiac symptoms	Patient symptoms: abnormal growth, impaired vision, hearing deficits, previous seizures, neuromuscular abnormalities Dyspnea, postprandial breathlessness (common), orthopnea and paroxysmal nocturnal dyspnea (rare) [23] Chest pain [24] History of syncope, palpitation, arrhythmias related to LVOTO exercise intolerance, dizziness Family history of SCD, cardiomyopathies, exercise intolerance, implantable cardioverter-defibrillators, multisystem diseases, and recurrent syncope [25]
Physical examination	Musculoskeletal involvement, dysmorphic features, and other organ system involvement Split S2 sound due to delayed closure of the aortic valve [16]
Diagnostic criteria	
Lab tests	Hemoglobin, renal function, liver transaminases, creatinine phosphokinase, plasma/leukocyte alpha galactosidase A, serum immunoglobulin light chain, fating glucose, NT-proBNP, thyroid function, plasma lactate [7]
ECG	Normal in less severe HCM phenotype Signs of LVH and repolarization abnormalities are the most common findings, pathological Q-waves, left-axis deviation, left atrial dilation [26,27]
48-hour Holter ECG	Atrial and ventricular arrythmias (AF up to 50%, NSVT, PVCs, conduction abnormalities) [7,28,29]
Transthoracic echocardiography	All LV segments from apex to base have to be measured [30,31] Two-thirds of patients have LVOTO induced by physical effort or Valsalva maneuver [17,21,22] Apical aneurysm LVEF is usually preserved, GLS is an accurate parameter of systolic function [32]
Genetic test	Proband and family
Pedigree	History of at least three generations
Exercise stress echocardiography	In symptomatic patients if bedside maneuvers fail to induce LVOTO >50 mmHg
MRI	Particular useful for apical and antero-lateral wall involvement. Myocardial fibrosis in 65% of patients [23-25] Diffuse and extensive late gadolinium enhancement quantified or estimated by visual inspection, comprising 15% of LV mass is now considered an established risk factor for sudden death [2,19]
CT	CT with contrast provides accurate measurements of ventricular thickness, volume, ejection fraction and mass [26,27]. CT detects anomalous coronary arteries, which is the second most common cause of SCD at 17%, right behind HCM at 36% [22,33-35]
Endomyocardial biopsy	Not part of the routine diagnostic workup. Performed when myocardial infiltration or storage disease is suspected Myocyte hypertrophy, myocardial disarray, interstitial fibrosis

MRI, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiogram; GLS, global longitudinal strain; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; NT-proBNP, N-terminal pro brain natriuretic peptide; AF, atrial fibrillation; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular complex; SCD, cardiac sudden death.

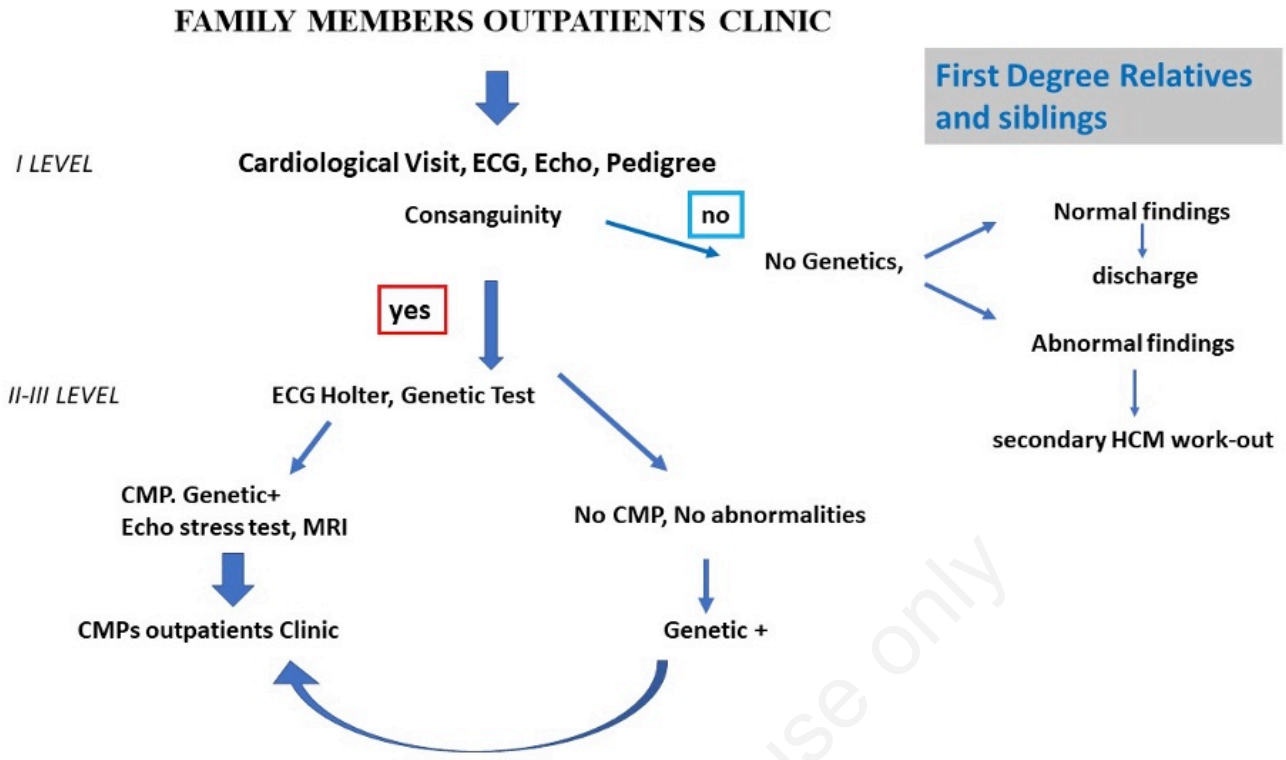


Figure 3. Flow chart for the management of family members. CMP, cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; MRI, magnetic resonance imaging.

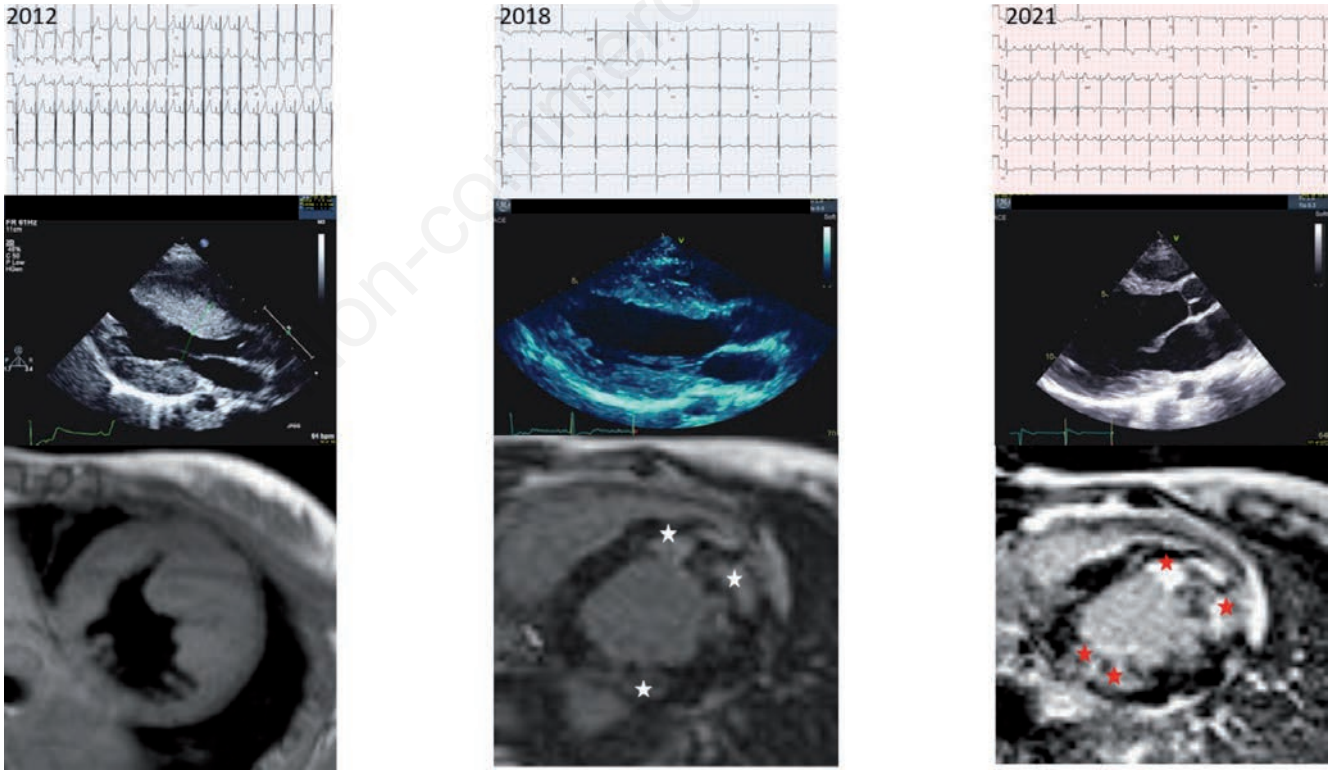


Figure 4. Evolution from HCM to dilated cardiomyopathy. Patients with hypertrophic cardiomyopathy evolved to dilated cardiomyopathy after 10 years. 2012: Severe asymmetric hypertrophy. 2018: Diffuse patchy fibrosis, non-ischemic pattern, consistent with non-obstructive hypertrophic cardiomyopathy. 2021: Abnormal dyskinetic ventricular wall motion abnormalities. Eccentric hypertrophy with abnormal trabeculations on the apical and lateral wall segments. Fibrosis at the ventricular septum at right ventricular insertion sites. Stars indicate fibrosis at MRI.

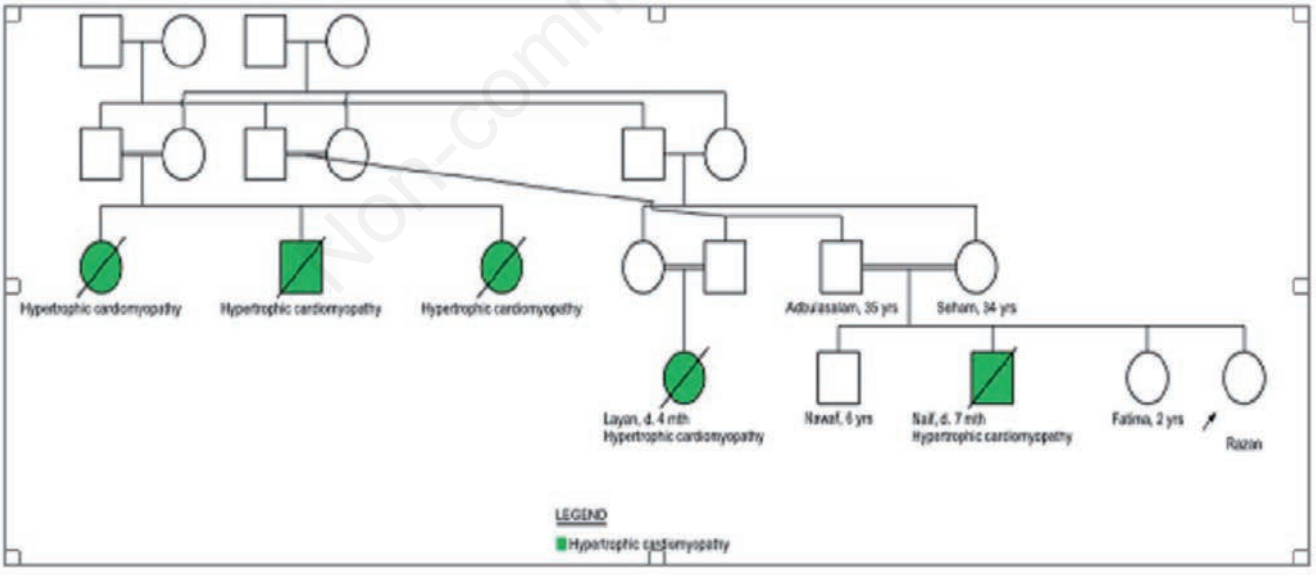
somal recessive inheritance is more likely and each descendent has a 25% chance of inheriting two mutated alleles (Figure 5). A mutation can sometimes appear de novo in the proband with no involvement of the family but could still be transmitted to any descendent [42].

Moreover, HCM presents with variable expressivity with incomplete penetrance [43,44] and may coexist with other forms of cardiomyopathy. Extensive molecular screening of sarcomere genes has been conducted in the past 25 years, discovering more than 1400 mutations associated with HCM [45]. The majority of the disease-causing variants occur in myosin heavy chain (MYH2) and myosin binding protein C (MYBPC3) [44]. On aggregate, 60% of patients with positive family history of HCM and 40% of sporadic cases of HCM tend to have mutations in the sarcomere proteins. Furthermore, clinical and genetic studies have uncovered the relatively uncommon role of pathogenic variants in other sarcomere protein genes [46]. In a small minority of cases, HCM is caused by mutations in non-sarcomere genes [44]. For example, recently a research group described in Saudi Arabia a cluster of 16 families with homozygous c450T>C (p.Phe154Leu) in ELAC2 gene, characterized by poor outcome in pediatric age and presenting with either form of HCM or dilated cardiomyopathy (Table 2) [14,47-92]. The genetic approach is a stepwise genetic testing. Blood samples are sent to a core lab with patient information, phenotype and pedigree. The panel includes the 36 genes most commonly associated with familial forms of HCM with a probability to detect the disease close to 60%. If mutation is not identified, analysis is extended to exome/whole genome to cover genes that are either implicated in an overlapping phenotype or could be involved in a similar pathway but not strongly clinically implicated. Sometimes the genetic study cannot identify the genetic mutation responsible of the disease because not all the genes involved in the phenotype can be studied and/or there are some cases (5%, identified in members of small families) that exhibit two (digenic) or more (oligogenic) causal mutations in the same gene or causal mutations in different genes [93-95]. The severity of ventricular hypertrophy in these patients is more pronounced. It is important to underline that not to find the mutation, does not mean that there is no disease.

The European Society of Human Genetics recommend not to perform genetic testing in children before the age of 10. In Middle East and in particular in Saudi Arabia, the high incidence of consanguinity makes genetic as first line in the diagnostic protocol of HCM, *particularly in children* [96].

Phenocopies

Some infiltrative and storage diseases may present as phenocopies of HCM according to morphology, ventricular function and maximum interventricular wall thickness is >15 mm [7]. Unmasking the underlying disease and looking beyond the ventricular morphology and function, is of paramount importance in order to define prognosis, guide reproductive choices, and specific therapy to the patient. Age of onset is among the factors to consider for differential diagnosis given that glycogen storage diseases are more common in infants, whereas wild-type transthyretin amyloidosis (ATTRwt) is common in advanced age (predominantly men over the age of 65 years) or Fabry disease in adult patients [9-11,97,98] (Table 3; Figures 6 and 7).



Parents are 2nd degree relatives
History of death for HCM

Mutation: ELAC2 c.460T>C:p.Phe154Leu

Figure 5. Example of a pedigree.

Table 2. Most common genes involved and phenotype expression.

Sarcomeric genes	Clinical features	Prognosis
Myosin heavy chain (MYH7) [32]	Presents at younger age [48], HCM, weakness of distal muscles, and foot deformities [49]	Poor prognosis [50]
Myosin binding protein C (MYBPC3) [32]	HCM, syncope, dyspnea, chest pain, and elevated blood pressure [48]	Good prognosis before age 40 years/favorable prognosis [48]
Troponin T (TNNT2)	HCM, high incidence of SCD, slow disease progression of HCM, low incidence of SCD without hypertrophy [51]	Poor outcome [51]
Troponin I (TNNI3)	HCM, severe and early onset [52], high incidence of SCD despite mild hypertrophy often in children [53] (low incidence of restrictive cardiomyopathy)	Poor prognosis [52]
α-tropomyosin (TPM1)	HCM, left ventricular dysfunction and SCD	Poor prognosis [54]
Myosin regulatory light chain 2 (MYL2)	HCM, SCD usually in the early age [55]	Good prognosis [56]
Myosin essential light chain (MYL3)	Mainly adult onset HCM, SCD at a young age [57], mid-left ventricular chamber type hypertrophy [58]	
Actin (ACTC1)	HCM, increased likelihood of advanced left ventricular dysfunction and heart failure [53], ASD [59]	Good prognosis [60]
Non-sarcomeric genes		
Titin (TTN)	Increases risk for cardiovascular death [61]	
α-actinin (ACTN1, ACTN2)	HCM, syncope, heart failure and premature sudden death [62] asymmetrical hypertrophy, early onset SVT and AV bock [63]	Mild cardiac hypertrophy but poor outcome in affected individuals [62]
α-myosin heavy chain (MYH6)	Late onset HCM [64], ASD [65], dilated cardiomyopathy [66], susceptibility to sick sinus syndrome [67]	
Glycine-rich protein 3 (CSRP3)	Pronounced HCM, onset of symptoms in young adulthood, SCD can be seen, and dilated cardiomyopathy [68]	Good prognosis in heterozygous carriers [69]
Telethonin (TCAP)	TCAP-HCM phenotypically resembles other myofilament-HCM and is more severe than patients who still remain without a disease-causing mutation, dilated cardiomyopathy, age of onset around 38.8±9, dyspnea, angina [70] AD, alleles can cause limb girdle myodystrophy [71]	
Vinculin (VCL)	Cytoskeletal	
RASopathies or syndromic cardiomyopathies		
PTPN11	50% cases of Noonan syndrome, facial features include widely spaced eyes, light-colored eyes, low-set ears, a short neck, and a small lower jaw [14,72-74]	
BRAF, KRAS, HRAS, RAF1, SOS1, SPRED1	Noonan/Costello/cardio-cutaneous syndrome	[75-80]
PTPN11	Leopard syndrome	[81]
Metabolic disorders		
GAA	Pompe disease	Alpha-glucosidase deficiency (GSD). Levels of alpha-glucosidase determine the type of GSD II an individual may have [82,83]
GLA	Anderson-Fabry disease, acroparesthesia, kidney dysfunction, skin manifestations (angiokeratoma, anhidrosis) and neuropathy	Lysosomal storage disorder Deficient alfa-galactosidase A enzyme X-linked disorder [84–86]
LAMP2	Danon disease, X-linked lysosomal and glycogen storage disorder associated with HCM, skeletal muscle weakness, and intellectual disability	Lysosome-associated membrane protein 2[87,88]
ELAC2 gene (mitochondrial tRNA)	HCM, psychomotor retardation/delay, muscular hypotonia, intrauterine growth retardation, microcephaly, dysphagia, hearing impairment [47]	Poor outcome
Systemic disorders		
TTR	Transthyretin amyloidosis [89-92]	Extracellular deposition of transthyretin
Neuromuscular disorders		
FRDA1	Friedreich ataxia	

ASD, atrial septal defect; AV, atrio-ventricular; GSD, glycogen storage disease; HCM, hypertrophic cardiomyopathy; SCD, sudden cardiac death; SVT, supraventricular tachycardia.

Counselling

HCM is an inherited disease most frequently transmitted as autosomal dominant trait, followed by autosomal recessive, X-linked transmission have been described and this has important reproductive implications [47]. This is particularly important in Saudi Arabia due to high rates of consanguinity. Counseling helps patients to be aware about the consequence of a genetic positive test for the proband and relative, the possibility to transmit the disease, eventual reproductive alternatives and ways to avoid transmission. In this context all cultural, social, ethical, legal aspects should be considered (Figure 8).

Therapy

Treatment in asymptomatic patients *i.e.*, without LVOTO mainly focuses on the management of arrhythmias, reducing LV filling pressures, and the treatment of chest pain. Various therapies have been suggested for the treatment of symptomatic HCM. In patients with symptomatic LVOTO pharmacological agents such as non-vasodilating beta blockers are considered first line followed by non- dihydropyridine calcium channel blockers (verapamil) and lastly disopyramide or septal reduction is recommended for symptomatic relief. Just as important is to avoid the medications that may promote LVOTO such as dihydropyridine class calcium chan-

Table 3. Presentation of different disease etiology with preference age groups.

	Infants (0-12 months) and toddlers	Early childhood	School age and adolescence	Adulthood
Systemic features	Metabolic acidosis, failure to thrive, and dysmorphic features	Abnormal or delayed cognitive development, hearing/visual deficits	Skeletal muscle weakness or movement disorder	Kidney failure, peripheral neuritis, movement disorder
Differential diagnosis	RASopathies, glycogen storage disease, other metabolic or mitochondrial diseases, infant of a diabetic woman	RASopathies, mitochondrial diseases	Mitochondrial disease, Friedrich ataxia, or Danon disease	Glycogen storage diseases, amyloidosis, or Anderson-Fabry disease
Diagnostic approach	Genetics assessment (geneticist assessment), newborn metabolic screening, and specific metabolic assays	Biochemical screening, and genetic testing	Genetic testing, neuromuscular assessment, and biochemical screening	Biochemical screening, neuromuscular assessment, and genetic testing

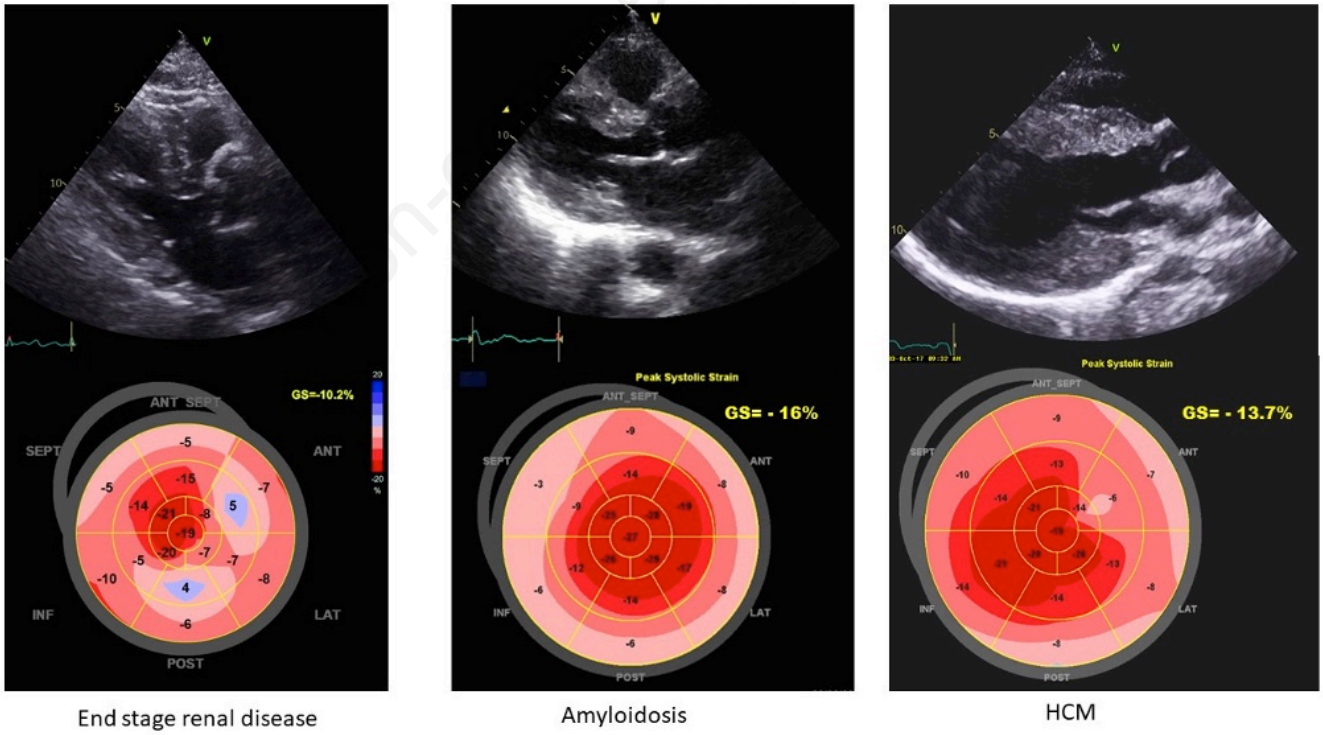


Figure 6. Echocardiographic phenocopies. Phenotype in an 88-year-old patient with amyloidosis [interventricular septum (IVS) 18 mm, posterior wall thickness (PWT) 16 mm], a 35-year-old patient with end-stage renal disease (IVS 16 mm, PWT 12 mm), and a 24-year-old patient with hypertrophic cardiomyopathy (IVS 18 mm, PWT 17 mm).

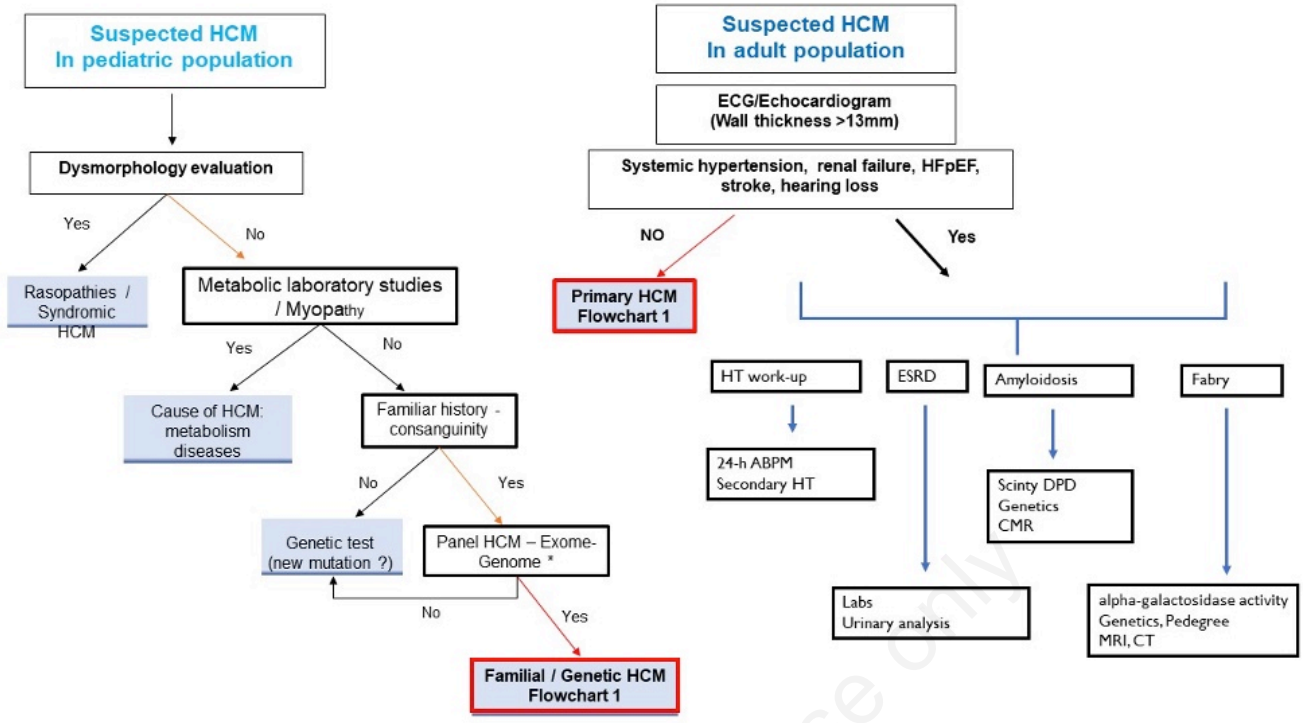


Figure 7. Flow chart for the management of suspected HCM. 24-h ABPM, 24-hour ambulatory blood pressure monitoring; CMR, cardiac magnetic resonance; CT, computed tomography; DPD, diphosphonates; ECG, electrocardiogram; ESRD, end-stage renal disease; HCM, hypertrophic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; HT, hypertension; MRI, magnetic resonance imaging.

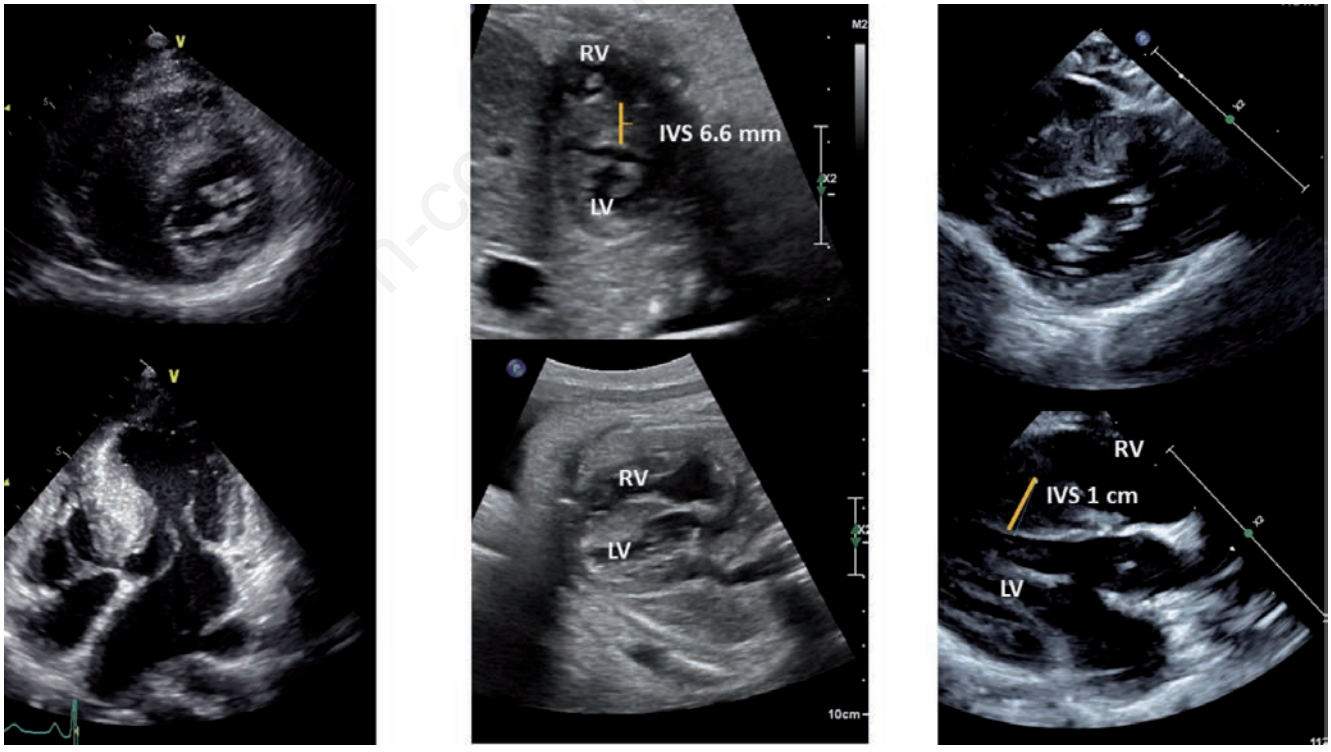


Figure 8. Mother and child with hypertrophic cardiomyopathy. A) Mother with S/P myomectomy in left ventricular outflow tract obstruction; first pregnancy ended with spontaneous abortion; genetic testing result of the fetus was Turner syndrome; second pregnancy: prenatal diagnosis of hypertrophic cardiomyopathy of the fetus. B) Fetus: moderate to severe hypertrophic myocardium mainly in the interventricular septum (IVS); echo at 34 weeks. C) Baby boy with hypertrophic cardiomyopathy at 5 months; gene expression of TPTN11 variant (Leopard); counseling could have helped planning the second pregnancy. LV, left ventricle; RV, right ventricle.

nel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and high-dose diuretics.

Mavacamten is a first-in-class cardiac myosin inhibitor indicated in symptomatic obstructive hypertrophic cardiomyopathy with LVOT gradient ³50 mmHg. Mavacamten is an allosteric modulator of cardiac myosin and acts reducing cardiac muscle contractility by inhibiting excessive myosin-actin cross bridge formation. The EXPLORER-HCM phase 3 trial, showed a reduction in LVOT gradient after exercise (-36 mmHg), greater increase in pVO2 (+ 1.4 ml/Kg/min), improved symptoms score, NYHA functional class, and the overall quality of life [99].

Patients with LVOT, who remain unresponsive to medical therapy can opt for septal reduction therapy in the form of surgical ventricular septal myectomy (Morrow procedure) or alcohol septal ablation, particularly among patients with NYHA functional class III or class IV. Transaortic extended septal myectomy is appropriate covering a broad range of patients with symptomatic, obstructive HCM [100,101].

The most effective strategy for lengthening life and preventing fatal, life threatening tachyarrhythmias is an implantable cardioverter-defibrillator (ICD), especially in high risk population [102]. This therapy proved to be equally as beneficial in children and adolescent with extreme left ventricular hypertrophy being the most common risk factor associated with future ICD interventions [103]. Adult and pediatric that have progressive left ventricular diastolic or systolic dysfunction that is refractory to pharmacological therapy may be candidates for cardiac transplantation or mechanical circulatory support [104]. All patients are also advised to stop excessive alcohol consumption, avoid dehydration, and are motivated to lose weight (Table 4) [7,99,105-125].

Prognosis

The majority of individuals with HCM are able to enjoy an active lifestyle and tend to live the average lifespan. This is particularly true for patients with HCM without significant LVOTO, however special considerations must be discussed thoroughly with patients regarding pregnancy, and physical exercise [7]. The most common HCM related death is due to sudden cardiac death (SCD), but with the evolution of contemporary medicine and treatment modalities, the overall mortality can effectively be reduced to <1% per year [126]. In Table 5 subtypes of HCM are reported [127-145].

Sudden death

Sudden cardiac death is an unpredictable and devastating complication of HCM [146]. The pathophysiology is complex and not completely understood but genetic and molecular substrate, myofibrillar disarray, ventricular hypertrophy, microvascular

Table 4. Treatment options for patients with hypertrophic cardiomyopathy.

Pharmacological drug	Uses	Adverse events
Beta-blockers (non-vasodilating)	Abolish and reduce resting provocable LVOTO; Provide symptomatic relief; Suppress arrhythmia [105-107]	Hypotension [7]
Disopyramide (Class IA anti-arrhythmic)	Abolish basal LV outflow pressure gradients; Improves exercise tolerance [108,109]	Dry eyes and mouth, urinary hesitancy or retention, and constipation; Prolonged QT [109]
Verapamil or diltiazem (non-dihydropyridine)	Increase exercise capacity; Improve symptoms; Normalize or improve LV diastolic filling [110-113]	Pulmonary edema in patients with elevated pulmonary artery systolic pressure [114]
Low dose loop or thiazide diuretics	Improve dyspnea associated with LVOTO [7]	Hypovolemia worsening LVOTO [7]
Mavacamten	Improves exercise capacity and LVOTO; Improves overall quality of life [99]	Atrial fibrillation and decreased LV ejection fraction at high concentrations [99]
Invasive therapy	**Uses**	**Adverse events**
Ventricular septal myectomy	Reduces LVOT gradient; Reduces systolic anterior motion MR; Improves exercise intolerance [115,116]	AV nodal block; Ventricular septal defect; Aortic regurgitation [117]
Septal alcohol ablation	Reduces LVOT gradient; Symptom improvement; Increased exercise tolerance; Larger residual LV outflow tract gradients [118]	AV block [119]
Dual chamber pacing	Reduces LVOT gradient; Improves symptoms and quality of life [120,121]	Spontaneous backup reversion, unexpected battery depletion, total loss of telemetry without change in pacing mode [122]
Mitral clip	Used to target SAM causing dynamic LVOTO; Improves symptoms and quality of life	Recurrency of MR [123,124]
Cardiac transplant	Improves survival; Only treatment option for drug refractory cases without LVOTO [125]	Rejection, cardiac allograft vasculopathy, immunosuppressants effects

AV, atrio-ventricular; LV, left ventricular; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MR, mitral regurgitation; SAM, systolic anterior motion.

ischemia and fibrosis predispose patients with HCM to re-entrant ventricular arrhythmias [147,148]. While it seems that there is no difference in SCD based on gender, age is an important factor. Patients younger than 35 years of age are particularly affected although 20% of SCD occurs in patients older than 65 years [149,150]. The European Society of Cardiology developed a risk-SCD calculator where are included age, maximum LV wall thickness, left atrium, max LVOT gradient, family history of SCD, non-sustained VT, unexplained syncope (AHA HCM SCD calculator) [7].

To avoid this tragic event and in other patients is important to have the correct diagnosis. For this reason a complete autopsy must be performed according to well defined protocols; in case of death a molecular "autopsy" can diagnose the cause of death in 35% of patients [151]. In Saudi Arabia it is rarely performed but tissue samples from patients who underwent myomectomy and heart transplantation should be collected and preserved also for future pathologically revised using different techniques.

Long term outcome

The clinical course of HCM is less favorable in patients with the obstructive form of the disease and in the young compared to adult patients. Moreover, a small subgroup may progress to LV systolic dysfunction (ejection fraction less than 50%), wall thinning, apical aneurysm, chamber enlargement, and progressive symptoms of heart failure. These patients are also at high risk of sudden death [19,132,133,142,144]. Surgical relief of LVOT obstruction, ICD implantation and medical therapy changed the natural history of the disease, nevertheless heart failure and AF, especially in patients diagnosed at younger age and with sarcomere mutations, are still determinant factors of morbidity and mortality [117-120,125]. Heart failure is the clinical picture of the advanced stage of the disease, congestive heart failure therapy is recommended and later on heart transplantation can be the only definitive option to extend HCM patient life [152,153] (Table 6).

Table 5. Different phenotypes of hypertrophic cardiomyopathy and correlated prognosis.

Subtype	Percentage of subtype	Prognosis	Age of development	Genetics	Complications
Isolated basal septal hypertrophy [128-130]	46%	15-year survival similar to the general population	Elderly	Less than 10% of those having positive findings with the same genetic test	Angina and dizziness. Hypertension and coronary artery disease. Systolic anterior motion
Reverse septal curvature [128,131]	40%	Unfavorable prognosis with increased septal thickness at end diastole/left ventricular end-diastolic diameter ratio	Young population	Genetic test for myofilament HCM (in 80%), MYH7	Often associated with a family history of SCD, hypertension, and increased LVOT pressure, syncope
Apical HCM [132-134]	25% in Japan to 2% in western countries	Good	Middle aged men	Most common mutations: MYBPC3 and MYH7	Rarely associated with SCD, associated with hypertension
Mid-cavity hypertrophy (midventricular). Could be complicated by apical aneurysm [135-138]	2-5%	Midventricular obstruction is strongly associated with adverse effects	Middle aged men	44% of patients with midventricular obstruction was associated with some form of cardiomyopathy associated genetic variant. 21% had a mutation in sarcomere protein (5.9% MYH7, 12% MYBC3)	Higher incidence of clinical events. Risk of SCD of 5% per year, ventricular arrhythmia, myocardial necrosis, systemic embolism, obstruction and increased gradient at midventricular level
Symmetrical HCM [138,139]	42%	Variable	Middle aged		LVOTO is common
Asymmetric (septal) HCM [140-142]	60-70%	Good	Middle aged men		Resting systolic pressure gradient of the LVOT caused by SAM of the mitral valve leaflets, mitral regurgitation
Mass-like HCM [138,143]	Rare				DD with neoplastic masses Diagnosis by MRI LVOTO seen if thickening is at basal region
Non-contiguous HCM [144,145]	Found in 42 (13%) of 333 patients		35-73		Dyspnea, sleep apnea

DD, differential diagnosis; HCM, hypertrophic cardiomyopathy; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MRI, magnetic resonance imaging; SAM, systolic anterior motion; SCD, sudden cardiac death.

Table 6. Therapy in associated condition that complicate hypertrophic cardiomyopathy.

Clinical conditions associated with HCM		
Dyspnea and angina in non-LVOTO	Beta-blockers (propranolol, atenolol, nadolol, metoprolol, bisoprolol)	Bisoprolol in end-stage HF and usually not useful in LVOT
	Oral diuretics	Despite the use of beta-blockers or calcium channel blockers
	ACEi or ARB	(EF <50%)
	MRA	(EF <50%)
AFVentricular rate control	Bisoprolol or carvedilol	LV systolic dysfunction
	Verapamil or diltiazem	Only with preserved LVEF
	Digoxin	Only if LVEF <50% and no LVOTO
Prevention of cardioembolic events	NOAC	Independently of CHA2DS2-VASc score
Prevention of AF recurrences	Amiodarone, sotalol (Class III antiarrhythmic drug)	
	Disopyramide	In LVOTO associated with beta-blockers and verapamil
HF	ACEi or ARB	HF with reduced EF
	Sacubitril/valsartan	
Ventricular arrhythmias		
Reduction of NSVT	Amiodarone	
	Sotalol	
Reduction of symptomatic tachycardia or recurrent shock (ICD)	Amiodarone	
	Beta-blockers	

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blocker; CHA2DS2-VASc, Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke, Vascular disease, Age 65-74 years, Sex category (female); EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; LVOTO, left ventricular outflow tract obstruction; MRA, mineralocorticoid receptor antagonist; NOAC, new oral anticoagulant; NSVT, non-sustained ventricular tachycardia.

Telemedicine and teleconsulting

The experience of the SHaRe registry has shed new light on the importance of telemedicine and teleconsulting for the diagnosis and management of HCM, allowing a better understanding of the factors contributing to the heterogeneous outcomes in this complex disease [154,155]. The European Reference Network for Rare and Low prevalence Complex Diseases of the Heart (ERN-GUARD Heart) has been conceived as a virtual network involving healthcare providers across Europe aiming to give patients affected by rare and complex heart disease access to highly-specialized centers and best standards of care [96]. In addition, the spread of COVID-19 pandemic and the restrictions imposed by local Governments significantly limited patients and healthcare professionals' international exchanges. Consequently, telehealth networks have assumed pivotal importance during COVID-19 pandemics, particularly for rare and complex diseases requiring highly specialized multidisciplinary teams.

To our knowledge, we proposed the first teleconsulting network between Saudi Arabia and Italy for the management and diagnosis of HCM and complex heart diseases. The HCM-Extended Family Unit consists in a virtual network involving different specialists including cardiologists, cardiac surgeons, geneticists, neurologists, pediatric cardiologists and metabolisms experts aiming to discuss the best management for complex and rare disease of the heart, both in adults and pediatric patients. In addition, the cooperation between Saudi Arabia and Italy aims to provide new scientific perspectives in the understanding of rare cardiovascular diseases, with the creation of shared datasets and digital platforms and multicenter research protocols.

Conclusions

HCM is a relatively rare disease, most of the patients can have a good quality of life but accurate diagnosis starting with the family screening and the identification of phenocopies. The HCM-Family Unit is a "way of working" where health care professionals such as cardiologists, internists, cardiovascular surgeons, geneticists, pediatric cardiologists, nurses, psychologists are involved. Moreover, international cooperation is mandatory given the relatively uncommon/rare disease in order to share knowledge, create a research platform that will undoubtedly improve the quality of health care.

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