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Review

The Diagnostic and Therapeutic Implications of Phenocopies and Mimics of Hypertrophic Cardiomyopathy

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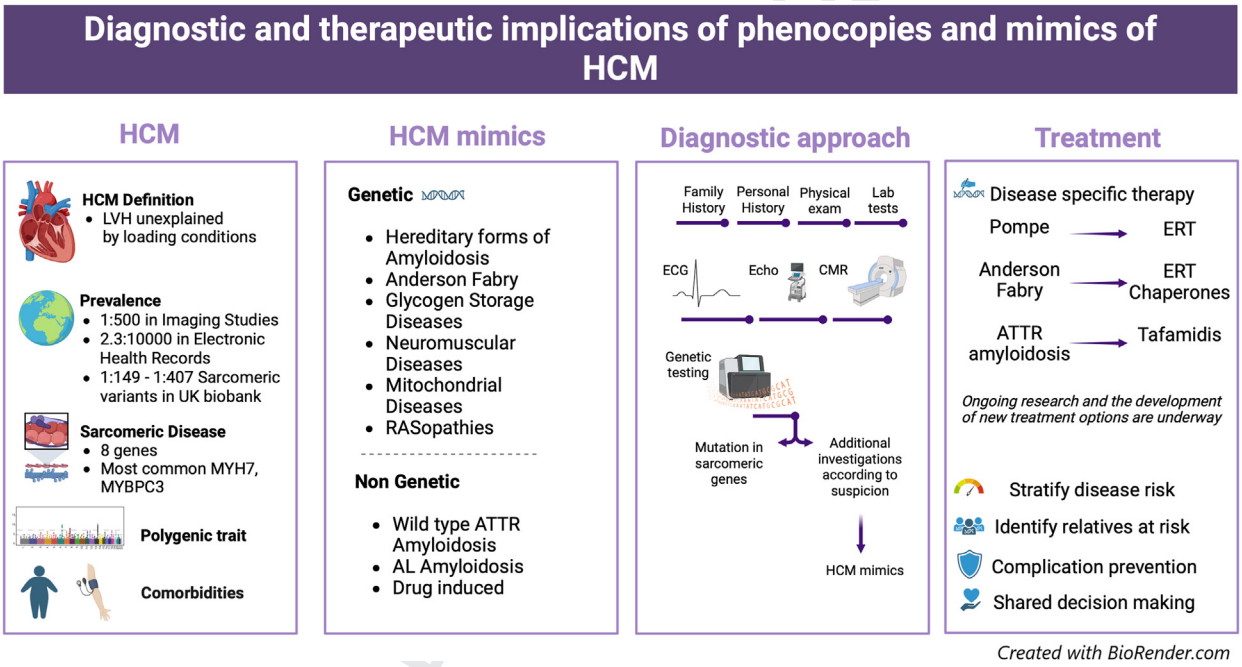

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is a common myocardial disease defined by increased left ventricular wall thickness unexplained by loading conditions. HCM frequently is caused by pathogenic variants in sarcomeric protein genes, but several other syndromic, metabolic,

RÉSUMÉ

La cardiomyopathie hypertrophique (CMH) est une maladie myocardique courante définie par une augmentation de l'épaisseur de la paroi du ventricule gauche qui ne peut être expliquée par les conditions de charge. La CMH est souvent causée par des variants patho-

Hypertrophic cardiomyopathy (HCM) is a common myocardial disease defined by increased left ventricular wall thickness unexplained by abnormal loading conditions. Most cases with an identifiable etiology present as a Mendelian autosomal dominant trait due to mutations in 1 of 8 sarcomere genes. Less than 5% of adult cases of HCM, and up to 25% of pediatric cases, are attributed to causative variants in genes associated with less-common conditions that mimic the HCM phenotype, presenting as multiorgan diseases or isolated cardiac phenotypes.[1] For cardiologists, identifying HCM mimics in patients presenting with left ventricular hypertrophy (LVH) is crucial.

Emerging evidence suggests that in some adults who fulfill the diagnostic criteria for HCM, LVH is a polygenic trait influenced by comorbidities, including hypertension and obesity.[2,3] A proportion of cases remains unexplained, even after extensive investigation.

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infiltrative, and neuromuscular diseases can result in HCM phenocopies. This review summarizes the current understanding of these HCM mimics, highlighting their importance across the life course. The central role of a comprehensive, multiparametric diagnostic approach and the potential of precision medicine in tailoring treatment strategies are emphasized.

gènes pour certains gènes des protéines sarcomériques, mais plusieurs autres maladies syndromiques, métaboliques, infiltrantes et neuromusculaires peuvent donner lieu à des phénocopies de la CMH. Cette revue de littérature résume les connaissances actuelles concernant ces conditions mimant la CMH, en soulignant leur importance tout au long de la vie. Le rôle central d'une approche diagnostique complète et multiparamétrique, et le potentiel de la médecine de précision dans l'adaptation des stratégies de traitement sont mis en évidence.

In this review, we discuss the diagnostic approach and management strategies for children and adults presenting with phenocopies or mimics of HCM. Furthermore, we provide detailed insights into the clinical presentations of the most prevalent and critical among these mimics.

Epidemiology

Estimates for the frequency of HCM depend critically on the sample population and the methods used to detect disease. The highest values derive from imaging studies using echocardiography or cardiac magnetic resonance imaging in healthy individuals, and suggest a prevalence of around 1 in 500 of the general population.[4-6] In contrast, data derived from electronic health records indicate a much lower disease prevalence (approximately 2.3 per 10,000).[7,8] By definition, estimates based on patients with overt disease are lower than those derived from asymptomatic people with preclinical phenotypes. But studies of otherwise healthy individuals may also inflate the true prevalence of disease, owing to the presence of confounding comorbidities, such as obesity and hypertension, that cause ventricular hypertrophy or extremes of normality in the general population related to body size or athleticism.

As HCM is often a heritable trait caused by variants in genes encoding proteins of the cardiac sarcomere, genetic screening studies offer an alternative approach to determining disease prevalence[9]; but here too, prevalence varies according to the methods used to ascribe pathogenicity to genetic variants. Studies from UK Biobank, for example, report a prevalence of sarcomere variants ranging from 1:149 to 1:407 individuals.[10-12]

In adults, pathogenic variants in 1 of 8 genes encoding cardiac sarcomeric proteins account for a large proportion of HCM cases, with an identifiable etiology, the most frequent being *MYH7* and *MYBPC3,* which cause around 40%-60% of variant positive cases.[1,2] Nongenetic HCM mimics (eg, wild-type transthyretin amyloidosis) and rare genetic diseases, the most common of which are Anderson-Fabry disease (AFD) and familial forms of cardiac amyloidosis (CA). A meta-analysis of over 10,000 HCM patients revealed a 1.2% prevalence of AFD.[13] Recent meta-analysis data, which combine findings from 2 studies specifically targeting older patient cohorts with HCM, suggest a prevalence of CA ranging from 5% to 9%. An important point to note is that these figures may reflect referral bias, as the studies involve predominantly data from amyloidosis referral centres.[14-16]

HCM is one of the most common cardiomyopathies diagnosed during childhood. As with adult patients, pathogenic variants in sarcomeric genes are responsible for most cases, except in the first year of life, when RASopathies, inborn errors of metabolism, and Friedreich's ataxia (FA) are more common.[17-19] In general, pediatric-onset HCM is associated with severe phenotypic expression and a higher risk of life-threatening ventricular arrhythmias and heart failure (HF), compared to adulthood-onset HCM.[19] In a United Kingdom registry, 5-year survival in pediatric-onset HCM was 66% in inborn errors of metabolism, 90% in RASopathy, and 97% in FA.[17]

Diagnostic Approach

A comprehensive, multiparametric approach to the investigation of LVH is essential for managing symptoms, implementing disease-specific therapies, assessing risk, and preventing complications. The assessment should include pedigree analysis, full medical history, physical examination, electrocardiography (ECG), echocardiography, and laboratory evaluation[20,21]; the results of this initial screen then guide second-line investigation and the need for genetic testing.

The current role of molecular genetic testing embraces the concept of precision medicine, suggesting that genetic diagnoses might facilitate tailored treatment strategies based on genotype, supplementing phenotype-based management, and enabling effective genetic counselling.[22] The differential diagnosis is informed by age at onset, clinical presentation, and cardiac and noncardiac phenotype. Clinical features suggestive of specific etiologies are shown in Table 1, and a proposed diagnostic flowchart is presented in Figure 1. Figure 2 illustrates critical diagnostic clues.

Specific HCM Phenocopies

RASopathies

RASopathies constitute a broad spectrum of genetic disorders arising from germline pathogenic variants in genes that encode proteins involved in the Ras/Mitogen-activated protein kinase (MAPK) signal transduction pathway.[23] This critical pathway orchestrates pivotal cellular functions, such as growth, proliferation, and senescence. Among the various

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Table 1. Clinical features suggestive specific etiologies of left ventricular (LV) hypertrophy

Etiology	Extracardiac phenotype	Cardiac phenotype
RASopathy	Facial dysmorphisms: broad forehead, down slanting, palpebral fissures, hypertelorism, low-set ears, pterygium colli, epicanthal folds, short and depressed nasal root Dermatological abnormalities: lentigines, cafè-au-lait spots, pigmented nevi, keratosis pilaris of upper arm and face, sparse curly hair Other systemic features: bleeding disorders, lymphatic dysplasia, sensorineural deafness, cryptorchidism	ECG: extreme right axis deviation, left or right bundle branch block, prolonged QT, or multifocal atrial tachycardia Echocardiography: biventricular hypertrophy, abnormal papillary muscles, associated congenital heart defects (eg, pulmonary valve stenosis, mitral valve dysplasia, atrial or ventricular septal defect, or coronary artery abnormalities)
Pompe disease	Liver: hepatomegaly, increased serum transaminases Muscle involvement: hypotonia, floppy baby, frog leg position, pseudohypertrophy of gastrocnemius muscle, CK elevation, delayed motor milestones	ECG: LV pre-excitation, prominent LV voltages Echocardiography: massive LVH, concentric LVH, LV systolic dysfunction
Cori disease	Hepatic involvement: hepatomegaly, increased serum transaminases, hypoglycemia Muscle involvement: muscle weakness, CK elevation	ECG: prominent LV voltages Echocardiography: concentric LVH
Danon disease	Hepatic involvement: hepatomegaly, increased serum transaminases, hypoglycemia Muscle involvement: muscle weakness, CK elevation	ECG: ventricular pre-excitation, prominent LV voltages Echocardiography: massive LVH, concentric LVH, LV systolic dysfunction, apical sparing strain pattern CMR: extensive LGE with mid-septum sparing
PRKAG2 disease	Muscle involvement: muscle weakness, CK elevation	ECG: ventricular pre-excitation, prominent LV voltages, conduction disorders
Friedreich ataxia	Systemic features: scoliosis, foot deformity, diabetes mellitus, progressive gait ataxia, dysarthria, muscle weakness in lower limbs	Echocardiography: concentric LVH CMR: patchy and irregular LGE distribution, reduced native T1
Mitochondrial disease	Systemic features: hypotonia, lactic acidosis, cataract, bilateral sensorineural deafness, retinitis pigmentosa/ optic atrophy, leukocytopenia (in Barth syndrome), diabetes, palpebral ptosis, ophthalmoplegia	ECG: ventricular pre-excitation, prominent LV voltages, conduction disorders Echocardiography: concentric LVH, LV systolic dysfunction
Cardiac amyloidosis	Bilateral carpal tunnel syndrome, spontaneous rupture of biceps tendon, lumbar spinal stenosis Neurologic features, including autonomic dysfunction, or peripheral neuropathy	ECG: disproportion between QRS voltages and LV mass (relative low voltages despite hypertrophy), pseudo-infarct Q waves, conduction abnormalities (ie, AV block) Echocardiography: AV valve thickening, interatrial septum thickening, RV wall thickening, granular sparkling appearance, apical sparing strain pattern, increased ejection fraction-to-strain ratio CMR: diffuse subendocardial or transmural LGE in a noncoronary artery distribution, abnormal gadolinium kinetics, elevated T1 native
Anderson-Fabry disease	Systemic features: gastrointestinal symptoms, angiokeratomas, cornea verticillata, hypohidrosis, cryptogenic TIA or stroke, neurosensorial deafness, lymphedema, proteinuria, renal failure	ECG: short PR interval, bradycardia, chronotropic incompetence, AV block Echocardiography: concentric LVH, disproportionate hypertrophy of papillary muscles reduced GLS in the posterolateral basal segment, RV wall thickening CMR: mid-myocardial distribution of LGE in the posterolateral basal segment, reduced native T1

AV, atrioventricular; CK, creatine kinase; CMR, cardiac magnetic resonance; ECG, electrocardiography; GLS, LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; RASopathy, one of a broad spectrum of genetic disorders arising from germline pathogenic variants in genes that encode proteins involved in the Ras/Mitogen-activated protein kinase (MAPK) signal transduction pathway; RV, right ventricular; TIA, transient ischemic attack.

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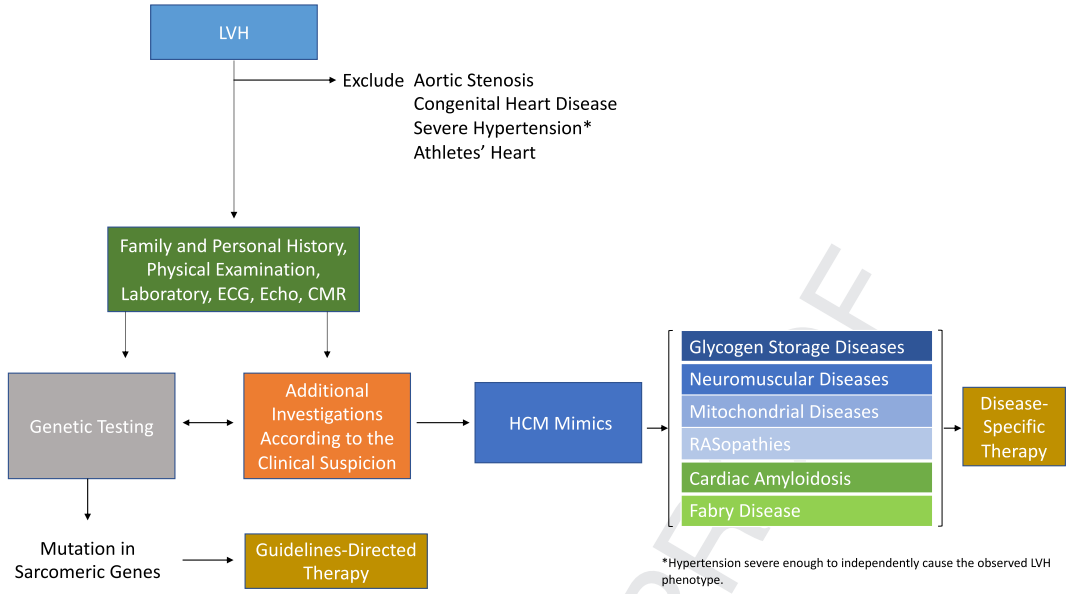

Figure 1. Diagnostic flowchart for patients with hypertrophic cardiomyopathy. Patients may present under various clinical scenarios, such as symptomatic presentation, incidental findings, or during family screening. A comprehensive and multiparametric workup is essential, beginning with the exclusion of other cardiovascular causes of left ventricular hypertrophy (LVH). This workup should incorporate personal and family history, clinical examination, electrocardiography (ECG), laboratory tests, and imaging findings. Genetic testing plays a key role in ruling out sarcomeric disease. An important point to note is that the epidemiology and causes of nonsarcomeric diseases vary between pediatric and adult populations. CMR, cardiac magnetic resonance; Echo, echocardiography; HCM, hypertrophic cardiomyopathy; RASopathies, a broad spectrum of genetic disorders arising from germline pathogenic variants in genes that encode proteins involved in the Ras/Mitogen-activated protein kinase (MAPK) signal transduction pathway. Q16

RASopathy phenotypes, Noonan syndrome (NS) is the most prevalent, followed by NS with multiple lentigines (NSML), cardiofaciocutaneous syndrome (CFCS), and Costello syndrome (CS).[23]

Variants in genes involved in the Ras/MAPK pathway are identified in up to 80% of clinically diagnosed RASopathy patients.[24] In NS, pathogenic variants in *PTPN11* are present in approximately 50% of cases, with a minority caused by variants in *SOS1*, *RAF1*, *KRAS*, *NRAS*, *BRAF*, *SHOC2*, *SPRED2*, *MAPK1*, *RIT1*, *SOS2*, *MRAS*, *RRAS2*, *LZTR1*, and *PPPC1B*.[24] NSML cases are associated predominantly with pathogenic variants in *PTPN11* and *RAF*, CFCS with variants in *BRAF*, *MAP2K1*, *MAPK2*, and *KRAS*, and CS primarily with variants in *HRAS*.[24]

The prevalence of HCM is highest in NSML (up to 85% of cases[25]), particularly within the first year of life, whereas it occurs less frequently in patients with other RASopathies (65% of patients with CS, 40% with CFCS, and 20% with NS).[26] Specific variants have been associated with earlier-onset and more-severe HCM clinical presentations. For example, pathogenic variants associated with NSML affecting *PTPN11* exon 13 are associated with more-severe hypertrophy and a worse prognosis.[25]

Clinically, RASopathies share a number of characteristics in addition to HCM, including facial dysmorphism, growth retardation, cryptorchidism, cognitive impairment, bleeding disorders, renal malformations, and susceptibility to specific cancers[23] (Table 1).

Additional cardiovascular abnormalities, including pulmonary valve stenosis, mitral valve dysplasia, and atrial and ventricular septal defects, may be observed.[27] Approximately 5%-10% of patients experience severe clinical presentations in infancy, culminating in a 1-year mortality rate of 70%.[17]

The pathophysiology of HCM in RASopathies varies between genotypes. For example, variants related to NS are often gain-of-function alleles, displaying increased upregulation of MAPK signaling. In contrast, variants associated with NSML are characterized by catalytic impairment and heightened signal transmission through the PI3K-AKT-mTOR pathway.[28]

A better understanding of the molecular pathophysiology has led to the development of novel therapies targeting the underlying substrate.[22] Studies suggest that MEK1 inhibitors may effectively address cardiovascular and lymphatic abnormalities associated with RASopathies, stabilizing or regressing clinical phenotypes and enhancing outcomes when the pathogenic variant is responsible for an upregulation of the Ras/MAPK pathway.[29] Conversely, mTOR inhibitors appear to ameliorate the cardiac phenotype in patients carrying variants associated with an upregulation of the PI3K-AKT-mTOR pathway.[30] In some cases, a variable degree of overactivation of both pathways has been observed, suggesting the need for further studies to explore the benefit of specific disease-modifying treatments. Important to note is that the use of MEK1 and mTOR inhibitors in these contexts is off-label for infants and remains investigational, with data derived exclusively from case reports, with no cohort studies or trials.

Glycogen Storage Disorders

Glycogen storage disorders (GSDs) are a broad group of disorders caused by pathogenic variants in genes encoding proteins involved in glycogenesis, glycogenolysis, or

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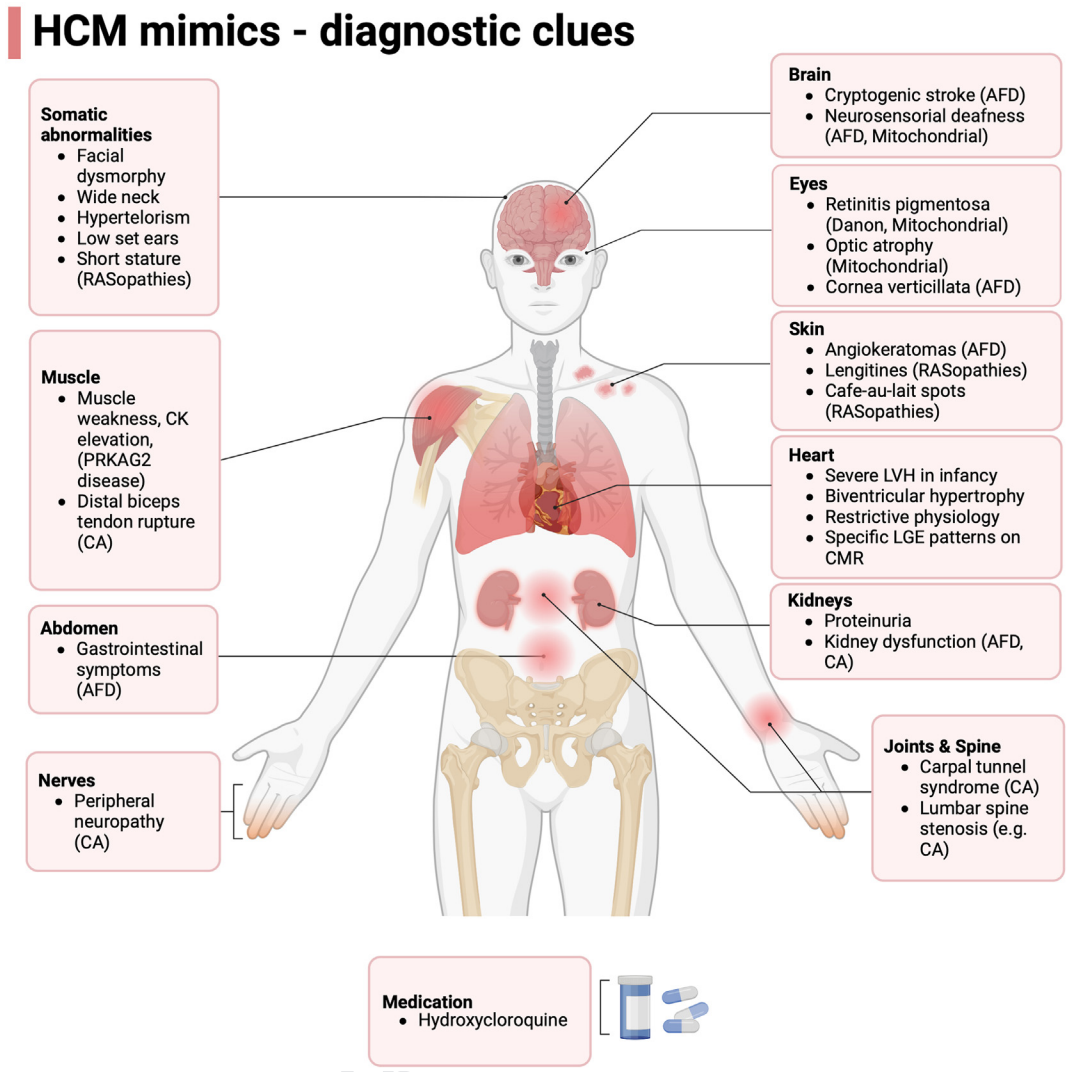

Figure 2. Diagnostic clues in hypertrophic cardiomyopathy (HCM) mimics. AFD, Anderson Fabry disease; CA, cardiac amyloidosis; CK; creatine kinase; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; RASopathies, a broad spectrum of genetic disorders arising from germline pathogenic variants in genes that encode proteins involved in the Ras/Mitogen-activated protein kinase (MAPK) signal transduction pathway. Created with BioRender.com. Q17

glycolysis[31] that results in increased glycogen content in several organs, primarily the liver, skeletal muscle, and myocardium.[31] Pompe disease (GSD type IIa), Danon disease (GSD type IIb), Cori disease (GSD type III), and PRKAG2 disease are typically associated with HCM presenting during childhood.

The pattern of inheritance and the clinical presentation of individual GSDs vary. Pompe disease is inherited as an autosomal recessive trait caused by biallelic variants in *GAA*, which encodes the acid α-glucosidase enzyme.[32] Clinical presentation varies according to the degree of residual enzyme activity. In patients with absent or severely reduced enzyme activity, disease onset usually occurs during infancy, with marked cardiac hypertrophy and skeletal muscle weakness associated with a poor outcome, if left untreated.[33] In contrast, variants associated with residual enzyme activity are associated with skeletal myopathy during childhood or adulthood, usually without cardiomyopathy.

Danon disease is an X-linked disorder caused by pathogenic variants in *LAMP2*, which encodes the lysosomal-associated membrane protein 2 (LAMP2).[34] The absence or reduction in LAMP2 results in the accumulation of autophagosomes and glycogen in the skeletal and cardiac muscles, associated with progressive HF and premature death during adolescence or early adulthood, especially in male patients.[34]

Cori disease is an autosomal recessive trait caused by biallelic pathogenic variants in *AGL*, which encodes the glycogen debranching enzyme.[35] Two different forms have been described, with GSD type IIIa affecting the liver, cardiac, and skeletal muscles, and GSD type IIIb showing isolated hepatic involvement.[35] PRKAG2 disease is inherited, with an autosomal dominant pattern, and is caused by pathogenic variants in PRKAG2, which encodes for the γ2 regulatory subunit of AMP-activated protein kinase, leading to impairment in glucose metabolism and glycogen storage in the myocardium.[36]

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These conditions are characterized by prominent LVH, often accompanied by typical electrophysiological abnormalities, including a short PR interval or ventricular pre-excitation and prominent electrocardiographic voltages.[37] Family history, although informative for PRKAG2 disease, is typically absent in patients with Pompe disease or Danon disease, owing to the recessive inheritance patterns of these conditions. Pompe disease should be considered in infants presenting with multiorgan involvement, characterized by severe biventricular hypertrophy, hepatomegaly, increased serum transaminases and creatine kinase levels, hypotonia, and motor delay.[8] In contrast, Danon disease and PRKAG2 usually present after the first year of life, and in the case of Danon disease, male patients exhibit an earlier-onset clinical presentation, with muscle involvement and cognitive impairment.[38]

Enzyme replacement therapy (ERT) is available for both patients with early-onset and those with late-onset Pompe disease and results in significant improvements in cardiac and muscle function, and an overall increase in survival.[39] For other GSDs, clinical surveillance should be tailored to the known manifestations of disease. For instance, patients with PRKAG2 disease are at a heightened risk of atrioventricular block and ventricular arrhythmias.[36]

Friedreich's Ataxia

FA is an autosomal recessive neuromuscular disorder caused by a pathologic variant in *FXN* encoding the protein frataxin. Of affected individuals, 90% are homozygous for an expanded GAA trinucleotide repeat in intron 1 of *FXN*, with the remainder being compound heterozygous.[40] The number of repeats correlates with an earlier onset and increased disease severity.[41] Frataxin, a highly conserved protein, acts as an iron chaperone[42] that plays a vital role in the synthesis of iron-sulfur cluster proteins that regulate mitochondrial iron content. Complete frataxin deficiency in cardiac and skeletal muscle leads to increased mitochondrial iron levels, and in turn, to mitochondrial dysfunction and severe oxidative stress.[42] This condition is associated partially with an impairment of the transcriptional factor nuclear factor erythroid 2-related factor 2 (NRF2) signaling pathway, which is crucial in protecting against several conditions associated with inflammation and oxidative stress.[43]

Typically, FA manifests during the second decade of life with progressive neuromuscular symptoms, HCM, and diabetes.[44] Cardiac disease in FA is characterized by ventricular hypertrophy and mitochondrial proliferation within cardiomyocytes and a later hypokinetic phase due to oxidative stress, progressive iron accumulation, and fibrosis.[45] Patients who develop the hypokinetic phase have a poor prognosis due to progressive HF. Nearly one-third of patients manifest conduction abnormalities, atrial tachyarrhythmias, and atrial fibrillation.[46]

Several treatments aiming at reducing oxidative stress have been evaluated. Idebenone, a coenzyme Q10 analog with antioxidant activity, has been evaluated in different randomized clinical trials but has failed to demonstrate beneficial effects on neurologic and cardiac function.[22] Omaveloxolone, an NRF2 agonist has been shown to improve neurologic function in a phase II randomized clinical trial and has received US Food and Drug Administration (FDA) approval for the treatment of FA. However, its effect on cardiac function is unknown.[47]

Mitochondrial Diseases (MDs)

Mitochondrial diseases (MDs) are a diverse group of disorders stemming from mutations in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) that encode mitochondrial respiratory chain units. These mutations disrupt the oxidative phosphorylation system, leading to decreased adenosine triphosphate production, which is crucial for energy generation in cells. MDs affect predominantly high-energy-demand tissues, causing multisystemic defects, especially in the neurologic, ophthalmologic, auditory, endocrinologic, and cardiovascular systems.[48,49] The most prevalent genetic variant is the m.3243A > G variant, followed by single, large-scale mtDNA deletions.[50]

Clinically, MDs present a spectrum from mild to severe multisystemic involvement, but isolated cardiac phenotypes are not uncommon. Common manifestations include increased creatine kinase levels, skeletal myopathy, endocrine disorders, and central nervous system symptoms, such as encephalopathy and stroke-like episodes.[48] A maternal inheritance pattern and extracardiac features are important for diagnosis.[20]

Various mtDNA mutations result in distinct cardiovascular phenotypes.[51] About 30% of patients exhibit cardiac involvement, and up to 23% have LVH. Another 8% of patients exhibit symptoms of HF and a reduced left ventricular ejection fraction (LVEF).[50] Conduction disease is another important finding at baseline, with a short PR interval and Wolff-Parkinson-White syndrome being common findings.

Mitochondrial cardiomyopathies have a different natural history and progression compared to sarcomeric HCM.[52] Approximately 10% of patients experience life-threatening cardiac complications over 10 years. Patients who carry single, large-scale mtDNA deletions exhibit worse cardiac outcomes.[50] Conduction disease, LVEF below 50%, and large-scale mtDNA deletions are independently associated with the development of arrhythmic endpoints, including sudden cardiac death, high-degree conduction disease, and sustained ventricular arrhythmias. In contrast, conduction disease, LVH, LVEF < 50%, the m.3243A > G variant, and premature ventricular beats are independent predictors of HF outcomes, including death, HF hospitalization, and heart transplant.[50]

Diagnosing MDs involves a comprehensive evaluation, owing to its clinical and genetic heterogeneity. Molecular testing and skeletal muscle biopsies are essential.[53] The presence of red ragged fibers in biopsies and biochemical analyses of tissue samples are key diagnostic indicators.[48,53]

Currently, no specific pharmacologic treatments are available for managing MDs.[54] However, innovative therapeutic approaches, such as using mitochondrially targeted enzymes to selectively degrade mutant mtDNA while allowing the proliferation and restoration of wild-type molecules, show promise.[55] Patients are advised to avoid certain medications and fasting.[56] Standard guidance should be followed for the management of arrhythmias, HF symptoms, and left ventricular dysfunction. However, approaches to prevention of sudden death in the context of mitochondrial disease are not

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well-defined. Prophylactic permanent pacing may be considered for individuals with large-scale mtDNA deletions, especially those with multiple risk factors.[50,57] Implantable cardioverter-defibrillators may be appropriate for patients with severe LVH and fibrosis.[50]

Anderson-Fabry Disease

AFD is a progressive, multisystem X-linked lysosomal storage disorder resulting from pathogenic variants in the *GLA* gene. These variants result in deficiency of the lysosomal enzyme alpha-galactosidase A (α-Gal A), leading to the systemic deposition of globotriaosylceramide (Gb3) and its deacylated derivative, globotriaosylsphingosine (lyso-Gb3). Accumulation occurs in various cell types and affects multiple organs and tissues, including the renal, cardiac, and nervous systems.[58]

The severity and age of onset of AFD correlate with the level of α-Gal A activity and are influenced by the specific *GLA* variant and patient sex. The classical phenotype of AFD, generally associated with little to no α-Gal A activity, often results from nonsense and frameshift variants. Conversely, some missense and less-common cryptic splicing variants may allow for residual enzyme activity, leading to milder or late-onset forms of the disease.[59,60] In heterozygous female patients, random X-chromosome inactivation results in a range of clinical features, from asymptomatic to severe phenotypes.[61]

Classical AFD is characterized by an array of symptoms in childhood, including neuropathic pain, angiokeratomas, hypohidrosis, and gastrointestinal manifestations. Early renal involvement results in albuminuria, and later in progressive renal impairment. Cerebrovascular manifestations, in the form of transient ischemic attacks and stroke, typically emerge by the third or fourth decade of life.[62,63] Cardiac involvement in AFD is a major determinant of patient prognosis. Patients with AFD develop cardiomyopathy characterized by progressive LVH, often presenting initially as concentric remodelling and later as hypertrophy.[64] Asymmetric septal hypertrophy is also observed, mimicking sarcomeric HCM.[65,66]

Cardiac magnetic resonance goes beyond structural assessment by detecting sphingolipid accumulation, edema, and interstitial fibrosis. Native T1 measurements are particularly relevant in AFD, as they can reflect the presence of glycosphingolipid accumulation, even before the development of LVH. This makes native T1 mapping a potential screening tool for AFD in patients with unexplained LVH. Posterolateral left ventricular late gadolinium enhancement and a low native T1 are characteristic of AFD. [63,67,68] However, sarcomeric HCM and AFD may be indistinguishable on cardiac magnetic resonance.

Diastolic dysfunction is a common early feature, but it only rarely progresses to a restrictive cardiomyopathy.[69] Microvascular ischemia caused by impaired coronary flow reserve may explain exertional chest pain and dyspnea in some patients.[70] In a minority of patients with advanced disease, systolic LV dysfunction and valvular disease may occur.

Late-onset AFD may be confined to a single organ system that is often unrecognized until later in adult life. The p.Asn215Ser *GLA* variant is the most common variant associated with this late-onset presentation and usually presents with isolated cardiac involvement without significant renal or cerebrovascular manifestations.[71,72] Other variants previously described as being associated with late-onset presentations, such as p.Asp313Tyr and p.Glu66Gln, are now considered to be benign polymorphisms, as they are common in the general population and are not associated with elevated plasma levels of lyso-Gb3 or tissue deposits of Gb3.

The diagnosis of AFD requires a high index of suspicion and should be considered in patients with unexplained LVH, proteinuria, and stroke. For male patients, diagnosis of AFD can be made by measuring α-Gal A activity in plasma or leukocytes. However, due to the variability in enzyme activity, female heterozygotes may have normal α-Gal A levels, and thus diagnosis often requires genetic analysis. The identification of a pathogenic *GLA* gene variant provides definitive evidence for AFD, but when genetic tests yield variants of unknown significance (VUS)[62], histologic examination of affected tissues, including light and electron microscopy showing characteristic "zebra bodies," can be helpful.

Two enzyme replacement formulations, agalsidase alfa and agalsidase beta, are currently available. Studies have demonstrated that ERT is associated with stabilization of renal function and myocardial hypertrophy. In addition, ERT has been associated with a reduction in cerebrovascular events and an enhancement in overall quality of life.[73,74] A second-generation ERT, pegunigalsidase-α, characterized by reduced immunogenicity and an extended half-life, has proven to be safe and effective in AFD patients. Migalastat, a chaperone therapy approved for the treatment of AFD, provides an alternative to ERT activity in patients with amenable *GLA* pathogenic variants, and it may stabilize renal function and cardiac mass. Unlike ERT, migalastat has the potential to cross the blood-brain barrier.[75,76] Research is ongoing into new treatment options for AFD, including substrate reduction and gene therapies.

For further reading, refer to the expert consensus document on the management of cardiovascular manifestations of Fabry disease.[63]

Cardiac Amyloidosis

The term amyloidosis refers to the extracellular deposition of insoluble fibrils that are derived from various precursor proteins but share a common fibrillar structure.[77] Identification of the precursor protein is crucial for determining prognosis and directing treatment options. Immunoglobulin light chain amyloidosis (AL) and transthyretin (TTR)- related amyloidosis (ATTR) account for the majority of cardiac forms, with the latter further classified into wild-type (wtATTR) and familial subtypes caused by variants in the *TTR* gene.[78]

AL amyloidosis

AL amyloidosis is a rare condition, with an incidence ranging from 3 to 12 affected individuals per million person-years.[79-81] The mean age at diagnosis is 63 years, and approximately 55% of patients are male.[82] AL amyloidosis is caused predominantly by an expansion of a B-cell clone, resulting in the excess production of immunoglobulin light chains. This condition typically occurs in individuals with clonal plasma cell disorders, such as multiple myeloma and monoclonal gammopathy of unknown significance

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(MGUS).[83] The heart and kidneys are the main organs affected by AL amyloidosis, but virtually all organs, excluding the brain, can be impacted. Cardiac involvement is evident in 50% to 75% of AL amyloidosis cases and results from amyloid infiltration of the myocardium and a direct cytotoxic effect of immunoglobulin light chains.[84] An abnormal increase in either lambda or kappa free light chains, and the presence of a monoclonal band on immunofixation, suggests a plasma cell dyscrasia. Diagnosis can be challenging in chronic kidney disease due to elevated kappa and lambda light chains, and also with aging, with which the prevalence of MGUS increases.[85]

TTR amyloidosis

TTR is a tetrameric protein synthesized primarily in the liver that binds and transports thyroxine and retinol-binding protein in the plasma. Pathogenic variants in the *TTR* gene lead to the destabilization of the TTR tetramer and its dissociation into monomers and oligomeric structures that subsequently deposit as amyloid fibrils. More than 120 pathogenic variants in the *TTR* gene are described and are inherited as an autosomal dominant trait with incomplete penetrance. Some variants occur in geographic clusters. For instance, p.Val30Met is endemic in Portugal, northern Sweden, Japan, and Brazil, whereas the p.Val122Ile mutation, which causes primarily cardiac disease, has a high prevalence (3%-4%) among individuals of Black West-African ancestry.[86-89] Wild-type ATTR occurs as an acquired, sporadic form. The underlying mechanism that drives protein instability and aggregation is not fully understood, but the disease occurs exclusively in older adults.

Clinical presentation

ATTR exhibits a significant male predominance, although recent studies have shown a higher proportion of female patients than previously was recognized.[90] ATTR also can cause various systemic symptoms involving the peripheral and autonomic nervous systems, such as bilateral carpal tunnel syndrome, lumbar spinal stenosis, and peripheral sensorineuropathy. Other systemic signs, such as dysautonomia, presenting as orthostatic hypotension, gastrointestinal disturbances, and erectile dysfunction, may also be present, especially in variants of the *TTR* gene. Neurologic symptoms can precede cardiac symptoms and are often overlooked or attributed to other causes.[91] Other extracardiac manifestations include bicep tendon rupture and vitreous opacities.

Individuals with AL or ATTR-CA may experience symptoms of HF while maintaining a normal ejection fraction (HFpEF) and moderate to significant wall thickening. LVEF tends to be preserved or only slightly decreased, but the stroke volume is notably below the standard reference range, and the left ventricle is small. The combination of diastolic dysfunction and the low stroke volume, which only slightly increases during physical activity, results in reduced exercise capacity and symptoms of HF.

Cardiac amyloidosis can cause atrioventricular block and other conduction abnormalities, especially in wild-type ATTR, which shows the highest need for pacemakers.[90] First-degree atrioventricular block is particularly prevalent, occurring in nearly half of the ATTR population. Atrial fibrillation is a major complication in ATTR-CA, occurring in up to 70% of wild-type ATTR patients.[92-94] The loss of atrial contribution to ventricular filling in atrial fibrillation can be poorly tolerated, and the risk of intracardiac thrombus systemic embolization is increased in all CA patients.[95]

Diagnosis

Echocardiography is the primary screening tool for CA; key findings include increased left ventricular wall thickness, dilated atria, thickening of the interatrial septum and cardiac valves, right ventricular thickening, and pericardial effusion. The pattern of left ventricular thickening is typically concentric, but about 25% of patients may exhibit an asymmetric hypertrophy pattern, and a normal wall thickness does not exclude CA. Global longitudinal strain is often reduced, particularly in basal segments, leading to the distinctive "apical sparing" pattern. Contrast-enhanced cardiac magnetic resonance imaging often shows diffuse subendocardial or transmural late gadolinium enhancement with markedly elevated native T1 mapping and increased extracellular volume.

Nuclear imaging with bone-avid tracers (technetium-99m-labelled [99mTc]-pyrophosphate, 99mTc 3,3-diphosphono-1,2-propanodicarboxylic acid [99mTc-DPD], and 99mTc hydroxymethylene diphosphonate [99mTc-HMDP]) provides a sensitive noninvasive method for detecting wtATTR in the absence of monoclonal gammopathy and free light chains in serum and urine.[77,96] In the presence of monoclonal gammopathy, tissue biopsy (including endomyocardial biopsy) is essential to identify light-chain amyloid deposits. Immunohistochemistry, immunofluorescence, and laser microdissection with mass spectrometry help in subtype diagnosis.[77,97] Genetic testing is essential in the diagnosis and management of ATTR cardiomyopathy. In CA cases with a normal *TTR* gene but a strong family history, non-TTR variants such as gelsolin, AApoA1, A2, and fibrinogen should also be considered (Fig. 3).

Treatment

The general management of CA includes maintenance of euvolemia and careful use of diuretics and aldosterone antagonists for HF symptoms. Angiotensin-converting enzyme inhibitors and beta-blockers are often less well tolerated in advanced CA, owing to the fixed stroke volume and hypotension. Arrhythmia management includes anticoagulation for stroke risk in atrial fibrillation, irrespective of **C**ongestive Heart Failure, **H**ypertension, **A**ge $\geq$ 75 Years, **D**iabetes Mellitus, **S**troke, **V**ascular Disease, **A**ge 65 to 74 Years, **S**ex **C**ategory (CHA_2DS_2Vasc) or other stroke risk calculators. Pacemakers may be necessary for conduction disease.

Specific treatment for AL amyloidosis is focused mainly on treating the underlying plasma cell disorder. This treatment involves targeting the suppression of abnormal free light chain production by means of chemotherapy, with or without autologous stem cell transplantation. On the other hand, therapies for ATTR amyloidosis aim to disrupt the pathologic cascade from TTR production to amyloid fibril formation.[22] Tafamidis, the only licensed therapy for the treatment of ATTR cardiomyopathy binds to TTR, stabilizing its tetrameric form and inhibiting dissociation into monomers that aggregate into amyloid deposits. Tafamidis slows functional deterioration, decreases mortality, and reduces cardiac-related hospitalizations in patients with ATTR cardiomyopathy.[98]

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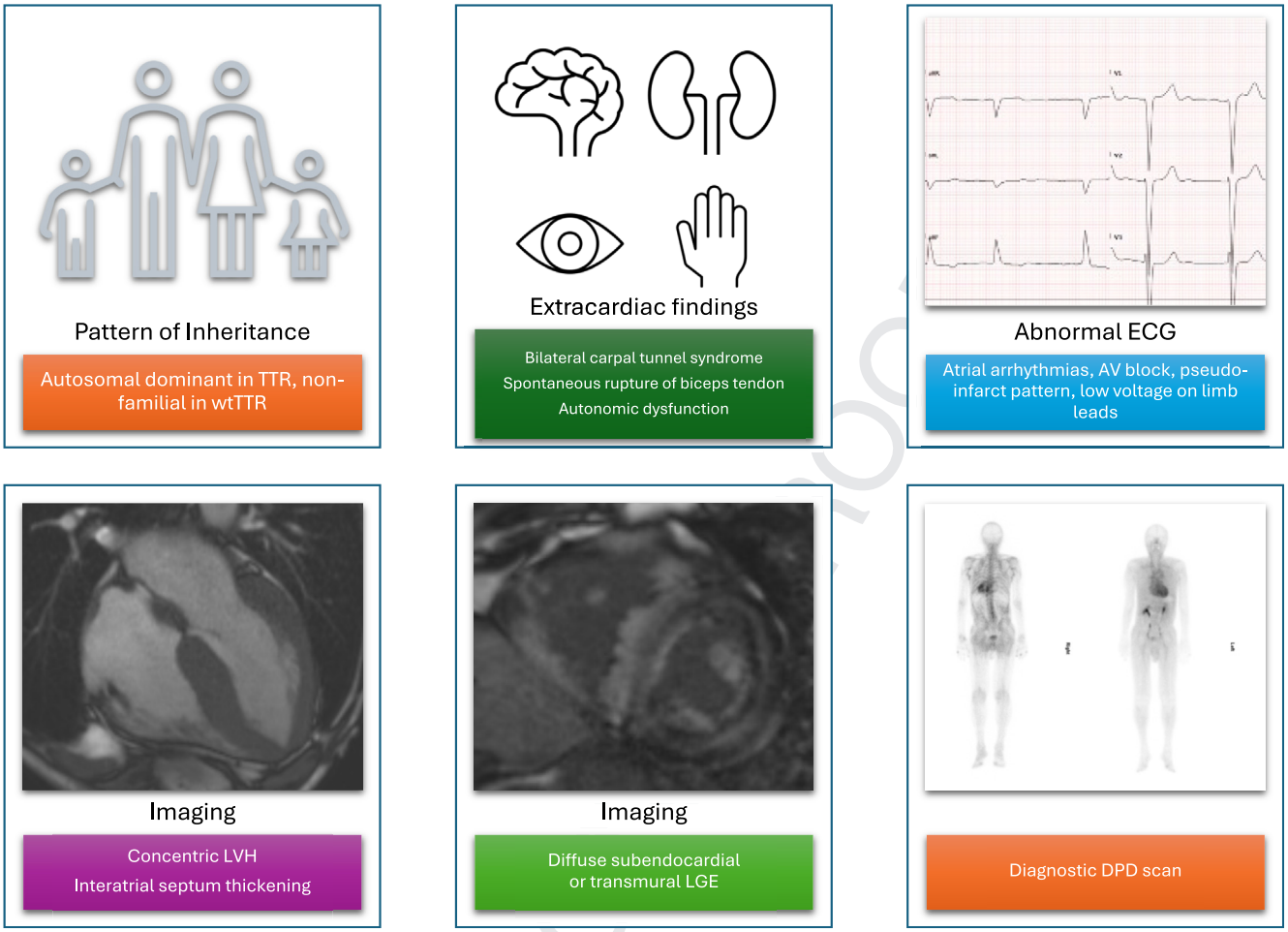

Figure 3. Diagnostic red flags in cardiac amyloidosis. AV, atrioventricular; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; ECG, electrocardiography; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; TTR, transthyretin; wtTTR, wild-type transthyretin. . Created with BioRender.com.

Orthotopic liver transplantation previously was the only disease-modifying treatment option to halt TTR production, particularly in early-onset ATTRv amyloidosis. Novel approaches include antisense oligonucleotides (ASOs), which are single-stranded molecules that bind to TTR mRNA, leading to its degradation.[22] Gene editing with clustered regularly interspaced palindromic repeats (CRISPR) Cas9 technology is under investigation in ongoing clinical trials.[99] Monoclonal antibodies, such as NI006, target amyloid deposits, facilitating phagocytosis and clearance of amyloid deposits from tissues. Clinical trials have shown that NI006 can effectively remove amyloid without significant adverse events, thereby providing a promising therapeutic strategy.[100]

For further reading, see the position statement of the European Society of Cardiology (ESC) Working Group on Myocardial and Pericardial Diseases on the diagnosis and treatment of CA.[78]

Summary

HCM is an umbrella term that encompasses autosomal dominant disease caused by sarcomeric gene mutations and other conditions such as metabolic, infiltrative, and neuromuscular diseases. These mimics have distinct pathophysiology and treatment approaches. Recent advances have led to novel therapies, marking a new era in personalized treatment for hypertrophic heart disease. Early diagnosis and treatment are vital for preventing disease progression and complications, with a growing emphasis on tailored treatments for the various causes of HCM.

Ethics Statement

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Patient Consent

The authors confirm that patient consent is not applicable to this review article, as it does not analyze individual identifiable data.

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Disclosures

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