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Review Article

Cardiomyopathy in a nutshell: from etiopathogenesis and diagnosis to treatment

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ABSTRACT

Cardiomyopathy is defined as a heterogeneous group of myocardial disorders wherein the cardiac muscle is functionally and structurally abnormal, without the presence of any congenital heart disease (CHD), coronary artery disease (CAD), valvular disease, and hypertension sufficient enough to lead to abnormality of the myocardium. Based on etiology, cardiomyopathies are classified into primary (acquired, mixed, or genetic) and secondary, which results in different phenotypes like hypertrophic, restrictive, dilated, etc. patterns. Hypertrophic cardiomyopathy is the most common type of primary cardiomyopathy among all cardiomyopathies usually presenting as exertional dyspnea, heart failure, atypical chest pain, syncope, and sudden cardiac death (SCD). Dilated cardiomyopathy is genetic or acquired, causing classic symptoms of heart failure with reduced ejection fraction. Restrictive cardiomyopathy is mostly associated with systemic disease and is rare. Diagnosis of cardiomyopathy includes a detailed evaluation of history, and physical examination followed by a workup including blood test, genetic testing, electrocardiography, and echocardiography testing. Treatment includes initially staging the therapy for heart failure, restriction of physical activity, evaluation of the need for implantable cardioverter-defibrillators, optimization of drugs, and consideration of heart transplantation in refractory cases. Genetic testing of families is now available as an emerging modality for early diagnosis and prevention in relatives of diagnosed cases. This review evaluates the causes, early diagnosis, and early treatment and prevention modalities for cardiomyopathies to reduce morbidity and mortality caused by it.

Keywords: Cardiomyopathies, Sudden cardiac arrest, Dilated cardiomyopathy, Hypertrophic cardiomyopathy, Restrictive cardiomyopathy

INTRODUCTION

Cardiomyopathy manifestations can range from microscopic alterations in cardiac myocytes to fulminant heart failure with fluid overload, inadequate tissue perfusion, and cardiac rhythm dysfunction. The American heart association categorizes cardiomyopathy into primary and secondary causes. The disease process is confined to the heart in cases of primary cardiomyopathy.[1]

Conditions in which cardiac involvement occurs as part of a systemic condition fall into secondary cardiomyopathies. Primary cardiomyopathy etiology is acquired, genetic, or mixed. Chromosomal abnormalities are the main cause of genetic cardiomyopathies. Acquired cardiomyopathies involve non-genetic causes and are associated with systemic diseases. Mixed types include genetic and non-genetic causes.[2,3] Wherein, a specific pathology of cardiovascular cause, like hypertension, CHD, coronary ischemia, or valvular disease is identified, such cases are not included under cardiomyopathies.

Table 1: Classification of primary and secondary cardiomyopathies.

S. no.	Classification of primary cardiomyopathies
1	**Acquired**
	Myocarditis
	Peripartum
	Tachycardia induced
	Takotsubo (stress-induced)
2	**Genetic**
	Arrhythmogenic right ventricular dysplasia
	Hypertrophic Ion channel disorders
	Left ventricular compaction
	Mitochondrial myopathies
3	**Mixed**
	Dilated
	Restrictive
	Secondary causes of cardiomyopathy
	Autoimmune/inflammatory
4	Dermatomyositis
	Systemic lupus erythematosus
	Rheumatoid arthritis
5	**Sarcoidosis**
	Polyarteritis nodosa
	Scleroderma
6	**Infectious**
	Chagas disease
	Hepatitis C
	Human immunodeficiency virus
	Mycobacteria
	Rickettsia
	Viral (adenovirus, Coxsackie, Epstein-Barr, parvovirus)
	Endocrine
	Acromegaly
	Diabetes mellitus
7	Hyperparathyroidism
	Hyperthyroidism
	Hypothyroidism
	Obesity
8	**Infiltrative disorders**
	Amyloidosis
	Gaucher disease
	Hunter syndrome and Hurler syndrome
9	**Toxic**
	Alcohol
	Anabolic steroids
	Chemotherapeutic agents (anthracyclines, cyclophosphamide, doxorubicin [Adriamycin])
	Chloroquine
	Heavy metals (arsenic, cobalt, lead, mercury)
	Iron excess (hemochromatosis)
	Radiation
	Stimulants (cocaine, methylphenidate)
10	**Nutritional deficiencies**
	Kwashiorkor
	L-carnitine, niacin, selenium, thiamine, vitamin C deficiencies
	Neuromuscular and storage disorders
11	Glycogen storage disorders
	Muscular dystrophy (Becker, Duchenne, Emery-Dreifuss, myotonic)
	Neurofibromatosis

The MOGE(S) nosology system includes characteristics and describes the morphological functional phenotype (M), organ(s) involvement (O), genetic inheritance pattern (G), etiological annotation (E), including genetic defect or underlying disease/substrate, and the functional status (S) of the disease, as described in Figure 2.[4]

The most common cause of heart failure is dilated cardiomyopathy followed by hypertrophic cardiomyopathy which is the most common inherited cardiomopathy. Restrictive cardiomyopathy is rare, caused due to stiffness of the ventricular walls due to systemic causes leading to diastolic dysfunction, raised end-diastolic pressure, and dilated atria. Arrhythmogenic cardiomyopathy (ARCV) is caused by to substitution of the myocardium with fibrofatty tissue, in young patients, presenting as a reduction in systolic function, arrhythmias, and SCD.

Takotsubo cardiomyopathy or broken-heart syndrome or stress-induced cardiomyopathy, is characterized by abrupt onset of left ventricular dysfunction due to severe emotional or physiologic stress. This chapter focuses on the most important cardiomyopathies, epidemiology, genetic aspects, early detection and diagnosis, and their ideal management.

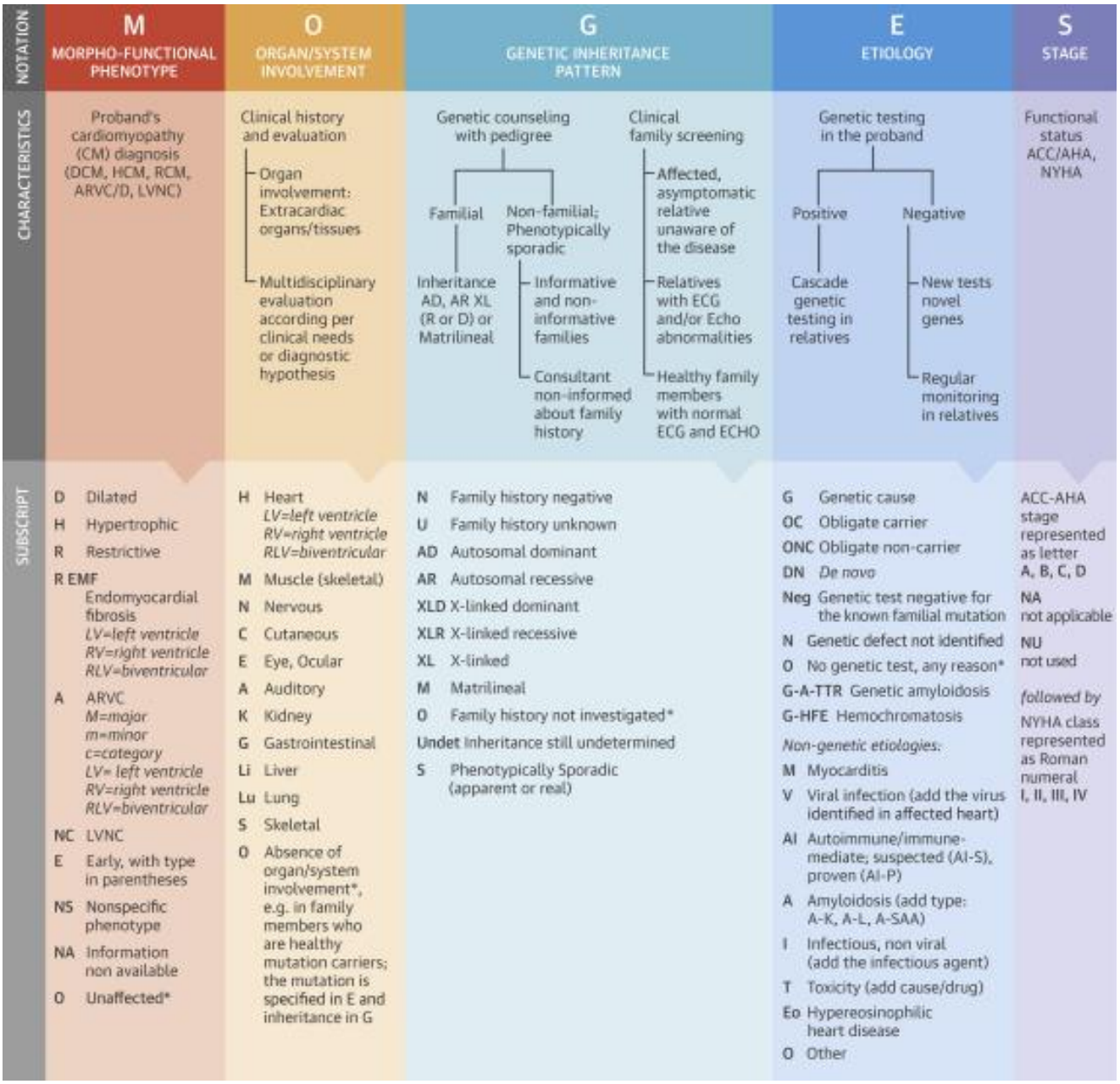

Figure 1: MOGE(S) nosology system for classifying cardiomyopathy patients.

Table 2: Classification and characteristics of cardiomyopathies.

Variables	Restrictive	Dilated	Hypertrophic
Ejection fraction (normal >55%)	25-50%	Usually <30% when symptoms severe	>60%
Left ventricular wall thickness	Normal or increased	Normal or decreased	Markedly increased
Left ventricular diastolic dimension (normal <55 mm)	<60 mm (may be decreased)	≥60 mm	Often decreased
Valvular regurgitation	Related to endocardial involvement; frequent mitral and tricuspid regurgitation, rarely severe	Related to annular dilation; mitral appears earlier during decompensation; tricuspid regurgitation with right ventricular dysfunction	Related to valve-septum interaction; mitral regurgitation
Atrial size	Increased; may be massive	Increased, may also be primarily affected	Increased; related to elevated filling pressures
Congestive symptoms*	Right often dominates	Left before right, except right prominent in young adults	Left-sided congestion at rest may develop late
Common first symptoms	Exertional intolerance, fluid retention early, may have dominant right-sided symptoms	Exertional intolerance	Exertional intolerance; may have chest pain
Arrhythmias	Ventricular tachyarrhythmia is uncommon except in sarcoidosis, conduction block in sarcoidosis, and amyloidosis. atrial fibrillation.	Ventricular tachyarrhythmia; conduction block in Chagas' disease, and some families. Atrial fibrillation.	Ventricular tachyarrhythmias; atrial fibrillation

*Right-sided symptoms of peripheral edema, systemic venous congestion, bendopnea, hepatic and abdominal distention, Left-sided symptoms of pulmonary congestion: dyspnea on exertion, paroxysmal nocturnal dyspnea, orthopnea, low blood pressure.[5]

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is characterized by dilatation and impaired function of one or both ventricles. Most cases present as heart failure, arrhythmias, atrial or ventricular, and SCD.[6,7] It is classified as primary or secondary DCM. Primary DCM is idiopathic and the diagnosis is made after excluding secondary causes which are enlisted below:

Causes of dilated cardiomyopathies[8]

Inflammatory myocarditis

Infective, viral (adenovirus, coxsackie, hepatitis C, HIV,), rickettsial (Q fever), parasitic (trypanosomiasis, T. cruzi-Chagas' disease, toxoplasmosis), spirochetal (Borrelia burgdorferi-Lyme disease), bacterial (diphtheria), systemic fungal infections, noninfective, sarcoidosis, granulomatous inflammatory disease, giant cell myocarditis, dermatomyositis and polymyositis, eosinophilic myocarditis, collagen vascular disease, transplant rejection and chemotherapy with checkpoint inhibitor

Toxic

Drugs of misuse (emetine, anabolic steroids), alcohol, catecholamines: amphetamines, cocaine, interferon, chemotherapeutic agents (anthracyclines, trastuzumab), other therapeutic agents (hydroxychloroquine, chloroquine), occupational exposure: hydrocarbons, arsenicals, heavy metals: lead, mercury

Metabolic

Nutritional deficiencies: thiamine, selenium, carnitine, endocrinopathy, thyroid disease, electrolyte deficiencies: calcium, phosphate, magnesium, obesity, pheochromocytoma, hemochromatosis and diabetes.

Inherited metabolic pathway defects

Familial

Cardiac and skeletal myopathy, hemochromatosis, dystrophin-related dystrophy (Becker's, Duchenne's), arrhythmogenic ventricular cardiomyopathy, other systemic diseases, mitochondrial myopathies (e.g.,

Kearns-Sayre syndrome) and immune-mediated myocarditis.

Overlap with nondilated cardiomyopathy

"Minimally dilated cardiomyopathy", hypertrophic cardiomyopathy("burned-out"), amyloidosis and hemochromatosis.

Idiopathic

Genetic

TTN gene, LMNA gene, Mutations in the Phospholamban (PLN) and Filamin C (FLNC) genes, other genes (Genes of dystrophin (DMD), desmin (DES), cardiac actin (ACTC), the cardiac isoforms of beta-myosin-heavy chain (MYH7), troponin I (TNNI3), troponin T (TNNT2), delta-sarcoglycan (SGCD), type V (SCN5A), sodium channel, and desmoplakin (DSP)).

Miscellaneous

Shared elements of above etiologies. Left ventricular noncompaction, peripartum cardiomyopathy, tachycardia-related cardiomyopathy, persistent nonsustained ventricular tachycardia or high premature ventricular complex burden and supraventricular arrhythmias with uncontrolled rate.

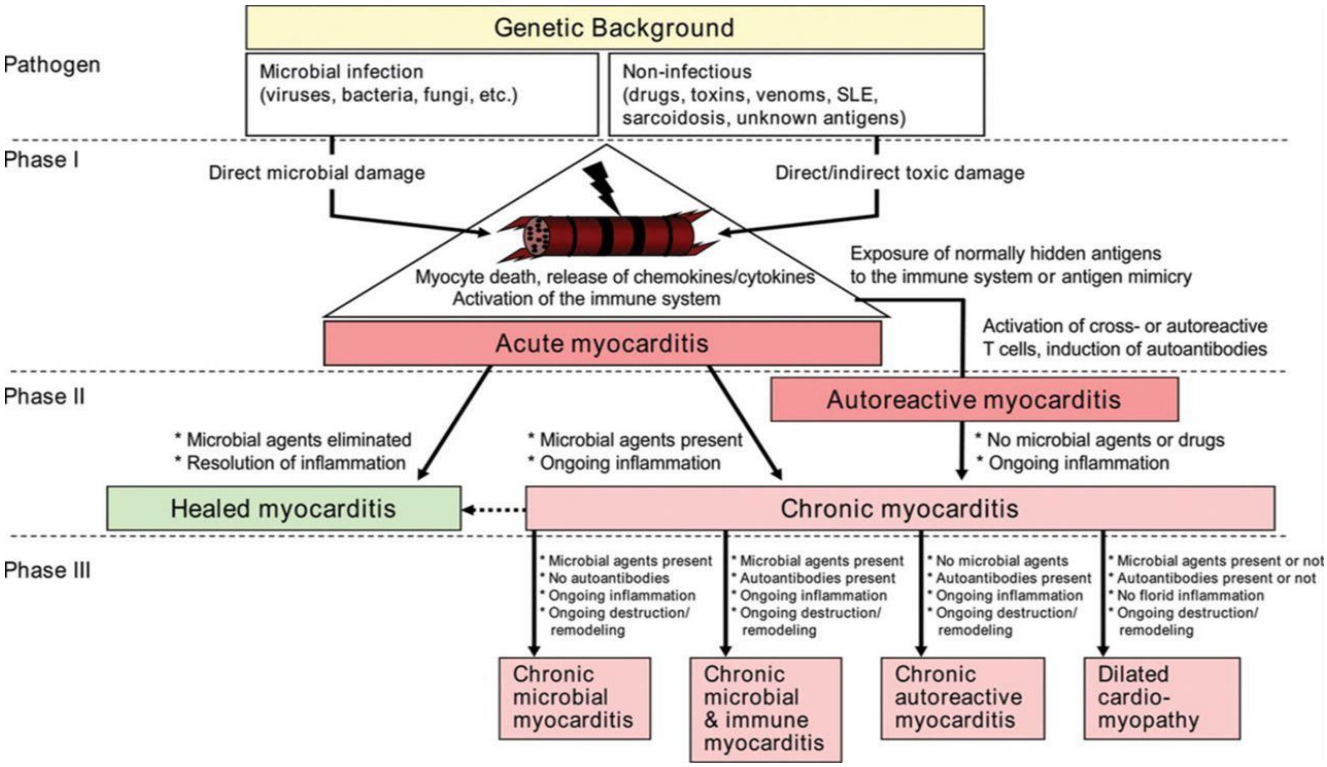

Figure 2: Pathogenetic mechanisms involved in myocarditis and progression to dilated cardiomyopathy.

Investigations

Laboratory test

First line: Calcium, ferritin, CK, liver function, full blood count, phosphate, NT-probnp, renal function, proteinuria, thyroid function, serum iron, vitamin D (children) and troponin.

Second line: Carnitine profile, lactic acid, Free fatty acids, serum autoantibodies, Thiamine, Serum angiotensin-converting enzyme, Viral serology, plasma amino acids, and Urine organic acids.[9]

EKG

The EKG is the first evaluation to be done in the case of DCMP. ECG changes seen are ventricular hypertrophy, conduction alterations such as prolongation of PR, pathological Q waves, repolarization disorders, AV blocks, left bundle branch block (LBBB), and hemiblock. LVRR development is suggested by the development of atrial fibrillation or LBBBB and is a poor prognostic marker. ECG changes in DCM due to specific diseases are mentioned below:--Atrial standstill:- Emery–Dreifuss 1 and 2, --Extremely low QRS amplitude:-PLN variant, --AV block:-Laminopathy, Desminopathy, Emery Dreifuss 1, Myotonic dystrophy, Sarcoidosis, Myocarditis

(Lyme disease, Chagas disease, diphtheria), --Low P wave amplitude:-Emery–Dreifuss 1 and 2 and --Posterolateral infarction:- Dystrophinopathy, Sarcoidosis, Limb-girdle muscular dystrophy.

Cardiac magnetic resonance imaging

MRI in DCMP is required for diagnosis and more importantly, etiology in most cases, like late enhancement of gadolinium, is seen in necrosis or a scar suggestive of inflammation, if associated with edema and hyperemia.

Coronary angiography

It is indicated in the diagnostic workup mainly to exclude an ischemic etiology.

Endomyocardial biopsy

It is indicated in cases with suspected etiologies of myocarditis, sarcoidosis, and hemochromatosis.

Genetic testing

Management

Dilated cardiomyopathy management includes diagnosing, treating, and preventing pathologies linked with higher mortality like heart failure and arrhythmias.[10]

Acute congestive heart disease is managed with diuretics (furosemide) and vasodilators (nitrates) in warm and wet form; and the use of inotropes in the cold and wet form.

Chronic heart failure is managed with diuretics and the four pillars of heart failure management i.e. ACE inhibitors and ARB (for preventing LVRR), angiotensin receptor neprilysin inhibitor (ARNI i.e. sacubitril-valsartan), beta-blockers, mineralocorticoid antagonists, SGLT-2 inhibitors, and other drugs like ivabradine, digoxin (for heart failure and atrial fibrillation).

Genetic information can be used in better management, e.g., In cases with the SCN5A gene, the treatment of choice is drugs that inhibit sodium channels, such as amiodarone and flecainide, as they respond poorly to conventional therapy.

For the prevention of ventricular arrhythmias, implantable cardioverter defibrillators (ICD) are recommended and are indicated in the following cases: -Previous ventricular tachycardia survivors, -symptomatic ventricular tachycardia, -symptomatic brady-arrhythmias cases need biventricular pacing, -in cases of post-ischemic dilated cardiomyopathy as the primary prevention.

The surgical approach involves cardiac transplantation, correction of mitral insufficiency or LVRRR, and mechanical support (ECMO). Prophylactic treatment with drugs like carvedilol or eplerenone is indicated in asymptomatic cases of DCMP but with compatible mutations (positive genotype-negative phenotype).[11]

HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy is defined as left ventricular hypertrophy that develops in the absence of causative hemodynamic factors, such as hypertension, aortic valve disease, or systemic infiltrative or storage diseases.[12,13]

Diagnostic criteria[14]

Adults: LV wall thickness ≥15 mm in any myocardial segment which cannot be explained by loading conditions is defined as HCM in adults. Evaluation of other features including family history, genetic findings, and ECG abnormalities is required in lesser degrees of wall thickening i.e.13-14 mm.

Children: LV wall thickness of >2 standard deviations greater than the predicted mean (z-score >2) is defined as HCM in children.

Relatives: In first-degree, adult relatives of patients with unequivocal disease are made based on LV wall thickness ≥13 mm, along with clinical suspicion. In first-degree, children relatives with LV wall thickness z-scores of <2, a suspicion of HCM should be made in the presence of morphological or ECG abnormalities.

Causes

The most commonly involved genes are the MYBPC3 gene (locus 11p11.2), TNNI3 gene (locus 19q13.4), MYH7 gene (locus 14q11.2), and TNNT2 gene (locus 1q32.1).

Less commonly involved genes are the MYL2 gene (locus 12q23-q24), TPM1 gene (locus 15q22.1), ACTC1 gene (locus 15q11q14), and the MYL3 gene (locus 3p21.3).

Clinical features

Most cases of HCM remain asymptomatic throughout life although few can present as supraventricular and ventricular arrhythmias, dyspnea, palpitations, and presyncope/syncope.

Few cases present with the evolution of the pathology causing remodeling of the left ventricle rarely presenting as a reduction of the ejection fraction of the left ventricle <50%, causing severe HF symptoms, and SCD.

Two murmurs are common in HCM[16-] # A systolic murmur, best heard at the lower left sternal border and apex, due to LVOTO obstruction. #A holosystolic murmur that is best heard at the apex, radiating to the axilla, caused by mitral regurgitation.

Table 3: Cause of SCD in HCM.

Major risk factor		Screening technique
Family history of spontaneous sustained ventriculartachycardia/ cardiac arrest*		History
Family history of SCD		Family history
Syncope	Non vagal, often with or after exertion	History
LV thickness >30 mm	Present in <10% of patients	Echocardiography
Spontaneous non sustained ventricular tachycardia**	>3 beats at rate >120	Exercise or 24- to 48-h ambulatory recording
Abnormal blood pressure response to exercise**	Systolic blood pressure fall or failure to increase at peak exercise	Maximal upright exercise testing

*Implantable cardioverter-defibrillator is advised for patients with prior arrest or sustained ventricular tachycardia regardless of other risk factors. **Prognostic value most applicable to patients <40 years old.[15]

Diagnosis

The most evident point in the diagnosis of HCM is family history. The EKG, echocardiogram, and cardiac MRI identify structural anomalies like the thickness of the left ventricular wall, when >15 mm, constitutes a diagnosis of HCM, in the absence of overload conditions (e.g., hypertension, valvular disease, etc.).

EKG

ECG findings in HCM in specific diseases are following:--short PR interval/pre-excitation:-Danon disease; Glycogeosis; Anderson-Fabry disease PRKAG2 cardiomyopathy; mitochondrial disease, -extreme LVH:-Danon disease; PRKAG2 cardiomyopathy glycogenosis (e.g. Pompe disease), -AV block:-amyloidosis; PRKAG2 cardiomyopathy Anderson-Fabry disease (late stage); sarcoidosis; Danon disease, -Q waves/ pseudoinfarction:-amyloidosis, -low QRS voltage:- Friedreich ataxia; amyloidosis and -superior QRS ('northwest axis'):-Noonan syndrome.

ECG findings of HCM are left axial deviation, left or bilateral atrial dilation as seen by P wave abnormalities, repolarization anomalies, Q waves prominence in the lower (II, III, aVF) and lateral (I, aVL, V4-V6) leads, deep and inverted T waves in the precordial ones (V2-V4).

Holter monitoring

Holter monitoring in HCM is needed to diagnose arrhythmias like non-sustained ventricular tachycardia (NSVT), which correlates with SCD.

Laboratory investigations

CK, liver function, proteinuria, NT-proBNP, renal function, alpha-galactosidase A levels (males) and lyso-Gb3, troponin, free fatty acids, carnitine profile, lactic acid, immunofixation and free light chains, urine organic acids, myoglobinuria, pyruvate, PTH, urine and plasma protein, and plasma amino acids.

Echocardiography

Diagnosis of HCM on transthoracic echocardiography (TTE) can be made if the left ventricular wall thickness is>15 mm. Other findings suggestive of HCM are: # Left atrium enlargement, with risk of atrial fibrillation. # Diastolic dysfunction; # global longitudinal strain (GLS) causing systolic dysfunction with normal LV ejection fraction presenting with heart failure. # Systolic anterior motion (SAM) of the mitral valve causing LVOTO obstruction defined as maximal left ventricular gradient >30 mmHg at rest or during provocative maneuvers (such as Valsalva) or exercise. # Exercise stress testing is needed in cases with no gradient at rest, provocable ventricular arrhythmias, coexistent CAD, abnormal blood pressure response, and a high tendency for SCD.[17]

Echocardiographic features that suggest specific aetiologies in hypertrophic cardiomyopathy are the following:[5]-Interatrial septum thickness increase:-amyloidosis, -RV-free wall thickness increase:-amyloidosis, Anderson-Fabry disease, myocarditis, Noonan syndrome, and related disorders, -AV valve thickness increase:-Anderson-Fabry disease, amyloidosis, -mild-to-moderate pericardial effusion:-myocarditis/myopericarditis, amyloidosis, -extreme concentric LVH (wall thickness ≥30 mm):- Pompe disease, Danon disease, -concentric LVH:- Glycogen storage disease, Friedreich ataxia, PRKAG2 cardiomyopathy variants, Anderson–Fabry disease, -RVOTO:- Noonan syndrome and associated disorders, -Global LV hypokinesia:-mitochondrial disease, myocarditis, Friedreich ataxia, TTR-related amyloidosis, Anderson–Fabry disease, PRKAG2 variants, advanced sarcomeric HCM and Danon disease.

Cardiovascular magnetic resonance (CMR)

CMR is of utmost diagnosis of HCM. It is the investigation of choice for identifying anatomy showing

details of the septum, papillary muscles, and the mitral valve, especially needed in ventricular septal myectomy. In late gadolinium enhancement (LGE), it detects typical patterns of hyperenhancement that can differentiate HCM from its mimics like Anderson-Fabry disease. Myocardial fibrosis, detected with LGE, increases the risk of ventricular arrhythmias and SCD in patients with HMC.

Table 4: Imaging evaluation in hypertrophic cardiomyopathy.[5]

Item to assess	Primary imaging modality	
LV wall thickness	ECHO/CMR	Examine all LV segments from base to apex, in end-diastole, measuring wall thickness at mitral, apical levels, and mid-LV. CMR investigation of choice for LV apical and anterolateral hypertrophy, thrombi, and aneurysms.
Systolic function (global and regional)	ECHO/CMR	In cases of HCM, ejection fraction is a suboptimal measure of LV systolic performance.
Diastolic function	ECHO	Mitral inflow assessment, pulmonary vein flow velocities, tissue Doppler imaging, LA size/volume, and pulmonary artery systolic pressure are necessary routine examinations.
Mitral valve	ECHO	For assessing the presence and severity of SAM and mitral regurgitation.
LVOT	ECHO	
LA dimensions	ECHO/CMR	LA enlargement is most commonly caused by SAM-related mitral regurgitation and increased LV filling pressures. Gives prognostic information.
Myocardial fibrosis/LGE	CMR	The severity and distribution of interstitial expansion suggest specific diagnoses.

Genetic testing

Management

A conservative approach is to be followed for asymptomatic patients with regular follow-up for disease evolution evaluation. Left ventricular outflow tract (LVOTO) is defined as LV outflow tract gradient >30 mmHg either provocated or at rest. LVOTO causes 90% of symptoms of progressive HF (fatigue, dyspnea) or chest pain in HCM. Treatment includes beta-blockers, disopyramide, or calcium channel blockers (verapamil and diltiazem). Maintaining an ideal body weight should be encouraged. Vasodilators and diuretics are not indicated as they can cause hypovolemia, which should be avoided. If pharmacological therapy is ineffective or the LV outflow gradient is >50 mmHg, invasive treatment like ventricular septal myectomy (Morrow procedure) or septal alcohol ablation should be performed. In HCM patients without LVOTO, symptoms are caused due to diastolic dysfunction and reduced ventricular filling. In cases with no obstruction and LVEF is >50%, treatment includes diltiazem or verapamil, ß-blockers, low-dose thiazide, or loop diuretics. ACE-i, mineralocorticoid receptor antagonist (MRA), ß-blockers, low dose loop, or thiazide diuretics should be used if LVEF <50%. The most common supraventricular arrhythmia in HCM is atrial fibrillation, and high heart rates are not tolerated well with greater thromboembolic risk thus, requiring aggressive rhythm control and early prophylactic anticoagulant therapy. Implantable cardioverter defibrillator (ICDs) therapy should be done in patients with NSVT, VT as secondary prophylaxis along with treatment with amiodarone or ß-blockers. Mavacamten improved LVOT obstruction, exercise capacity, and NYHA functional class in obstructive hypertrophic cardiomyopathy.[18,19]

ARRHYTHMOGENIC CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) occurs in the second to fourth decade and is characterized structurally by progressive myocardial atrophy with fibro-fatty replacement of the RV myocardium and rarely LV myocardium; however, predominant LV disease exists in families.[4] In adolescents or young adults with palpitations, syncope, or aborted sudden death ARVC should be suspected. The most common clinical presentations are frequent VEs or VT of LBBB morphology.[20]

ARCV is an arrhythmogenic disorder of the myocardium not caused by ischemic, valvular heart disease, or hypertension. The term "arrhythmogenic cardiomyopathy" includes structural myocardial abnormalities identified by macro and microscopic pathological examination along with cardiac imaging and ventricular arrhythmia.[21] ARCV includes a broad spectrum of systemic, genetic, inflammatory, and infectious disorders like sarcoidosis, cardiac amyloidosis, Chagas disease, and left ventricular noncompaction.

Causes

Causes of arrhythmogenic right ventricular cardiomyopathy:[22]

Infiltrative disorders

Amyloidosis, Gaucher disease, sarcoidosis, fatty infiltration and hurler syndrome were included.

Storage diseases

Glycogen storage disease, hemochromatosis and Fabry disease were mentioned.

Familial

Familial cardiomyopathy with unknown gene, Familial cardiomyopathy with known gene (JUP, DSP, PKP2, DSG2, DSC2, LMNA, TMEM43, DES, PLN, TGFB3, TTN, SCN5A). Naxos disease is characterized by palmoplantar keratoderma, woolly hair, and arrhythmogenic cardiomyopathy with a recessive pattern with the JUP gene. Familial amyloidosis, Fabry disease, sarcomeric protein mutations (essential light chain of myosin, troponin I), pseudoxanthoma elasticum and desminopathy, glycogen storage disease and hemochromatosis

Other disorders

Diabetic cardiomyopathy, scleroderma, endomyocardial fibrosis (caused by drugs, hyper eosinophilic syndrome, idiopathic), carcinoid heart disease, radiation, chemotherapy and metastatic cancers,

Idiopathic RCM

Secondary causes

Ischemic heart disease, dilated cardiomyopathy and hypertension were secondary causes.

Clinical features

ARVC can be asymptomatic to presenting as fatal ventricular arrhythmias leading to SCD. The most common presentation is associated with arrhythmias causing palpitations, syncope (often during exercise) to cardiac arrest. It can also present as myocarditis with changes in EKG repolarization and chest pain.

ARCV has the following four stages.[23]

With no or subtle structural changes in the right ventricle, and with or without minor ventricular arrhythmias are seen in the concealed phase of ARVC. At this early stage, most young patients are asymptomatic, however SCD can still occur.

Functional and structural abnormalities in the right ventricle are characteristic of the second phase. Syncope, palpitations, or cardiac arrest are symptoms occurring due to arrhythmia.

The third phase is characterized by right ventricular (RV) failure with a relatively preserved LV function.

Significant parallel left ventricular (LV) involvement with systolic dysfunction is characteristic of the end stage of ARVC. ARVC mimics dilated cardiomyopathy with its related complications at this stage, such as atrial fibrillation and thromboembolic events. Fatal ventricular arrhythmias, due to the development of reentry circuits in the areas where fibro-fatty scar can cause SCD.

Palpitations, syncope, and ventricular arrhythmias are the usual presenting symptoms in young adults and children. Common presentation with chest pain associated with dynamic ST-T wave changes in ECG and increased myocardial enzyme with normal coronary arteries is seen in ARVC.

DIAGNOSIS

The key elements of the diagnostic work-up in ARVC are defined by the diagnostic criteria used for the identification of affected individuals. The revised Task Force criteria for the diagnosis of ARVC published by Marcus et al have been used for the diagnosis of ARVC for more than a decade.[24,25] Key elements of the diagnostic work-up are ECG, cardiac imaging, Holter monitoring, in specific circumstances genetic testing.

Laboratory test

C-reactive protein, liver function, NT-proBNP, renal function and troponin were lab tests.

Echocardiography and cardiac magnetic resonance

All suspected cases of ARVC should undergo echocardiography and CMR to assess structural and functional alterations required for a diagnosis like a wall motional abnormality such as RV dyskinesia, akinesia, or bulging, and RV dilatation or dysfunction (major and minor criteria) determine the diagnostic performance. Cardiac magnetic resonance is an investigation of choice for RV functional structural abnormalities. Tissue characterization by CMR or indirectly by electroanatomical voltage mapping helps detect fibro-fatty replacement that can be present in either ventricle.

EKG and Holter monitoring

The characteristic diagnostic element is the presence of fragmented QRS, inverted T waves in the anterior leads, right branch bundle block, epsilon wave (reproducible low-amplitude signals between the end of the QRS complex and onset of the T wave), late potentials on signal-averaged electrocardiogram (SAECG) and ventricular arrhythmias.

Biopsy

Residual myocardial cells with a fibrous replacement which accounts for less than 60% of cells, in the free wall of the right ventricle on more than one sample is pathognomic of ARVC. In cases with negative CMR, electroanatomic voltage mapping-guided endomyocardial biopsy can be used.

Family history

Features suggestive of ARVC are the presence of a history of premature death in a first-degree family member or confirmed ablation in arrhythmogenic right ventricular cardiomyopathy (ARVC) in a first-degree family member. Presence of RV systolic global or regional dysfunction, electrocardiographic abnormalities (e.g. prolonged terminal activation duration, repolarization abnormalities, low QRS voltages, NSVT in a first-degree relative of an individual with ARVC, frequent ventricular extrasystoles [>500 per 24 h], or a first-degree relative with autopsy-proven ARVC) is highly suggestive of ARVC needing close follow-up.

Nuclear medicine

Cardiac sarcoidosis shows focal or focal-on-diffuse FDG uptake patterns on PET.

MANAGEMENT

Preventing SCD in cases of ARVC is the main aim of management. Adapting to lifestyle change is of utmost importance. Exercises increase the risk of ventricular arrhythmias in ARVC and hence should be strictly prohibited. Beta-blockers are the first line of management as they reduce adrenergic activity and risk of developing arrhythmias. Amiodarone and sotalol with beta-blockers, in cases with premature ventricular beats or non-sustained ventricular tachycardia, are beneficial. Monomorphic ventricular tachycardia needs to be treated with catheter ablation.[26] Indication of ICD implantation is as follows:

High-risk category: i.e. estimated event rate >10% per year, includes cases with a sustained VT, history of cardiac arrest, severe dysfunction of the RV, LV, or both.

Intermediate-risk category: i.e. estimated event rate of 1-10% per year, includes cases with ≥1 risk factor and no previous malignant arrhythmic events. In such cases, for primary prevention of SCD, ICD should be implanted in the following cases: Syncope, non-sustained VT, or moderate ventricular dysfunction which are high-risk factors an ICD is recommended. In cases with ≥1 minor risk factor, where the risk of arrhythmia is not high or defined, ICD therapy could be considered. In asymptomatic patients with no risk factors and in healthy gene carriers with an event rate is <10% per year, prophylactic ICD implantation is not recommended

Newer therapeutic approaches that activate Wnt signaling, blocking GSK3β, have shown to be beneficial in animal models, however, it warrants more research. PPARγ and PPARα are possible treatment targets for arrhythmogenic cardiomyopathy. Stem cell therapy is also being developed.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy (RCM) is a disease of the heart muscle characterized by stiffness of the ventricular walls leading to raised end-diastolic pressure, diastolic dysfunction, and dilated atria. Ventricles have physiological wall thickening and are not dilated, hence systolic function is usually preserved.[27,28] Advanced stages of secondary RCM present with impaired ventricular structure and systolic function.

CAUSES

The following are the causes of restrictive cardiomyopathy:[29]

Infiltrative (Between myocytes)

Amyloidosis (acquired/ inherited), familial (abnormal transthyretin). Genes: TTR gene variants (V122I; I68L; L111M; T60A; S23N; P24S; W41L; V30M; V20I), APOA1. Primary (light chain amyloid), Inherited metabolic defects, Primary hyperoxaluria (inherited) and Senile (normal transthyretin or atrial peptides)

Storage (Within myocytes)

Glycogen storage disease (II, III), Fabry's disease, Gaucher disease (inherited). Gene: GBA, Inherited metabolic defects, hereditary hemochromatosis (inherited). Genes: HAMP, HFE, HFE2, HJV, PNPLA3, SLC40A1, TfR2;, Niemann–Pick disease (inherited). Genes: NPC1, SMPD1, NPC2. Mucopolysaccharidosis type I (Hurler syndrome), mucopolysaccharidosis type II (Hunter syndrome).

Endomyocardial

Possibly related fibrotic diseases, carcinoid syndrome, carcinoid heart disease (acquired), tropical endomyocardial fibrosis, endomyocardial fibrosis idiopathic (acquired), hypereosinophilic syndrome (Löffler's endocarditis), Radiation Drugs: e.g., serotonin, ergotamine, Chronic eosinophilic leukemia (Acquired), Drugs (serotonin, methysergide, ergotamine, busulfan, mercurial agents,) (acquired); Consequence of cancer/cancer therapy: metastatic cancer, radiation, drugs (anthracyclines), Endocardial fibroelastosis (inherited). Genes: BMP5, BMP7, TAZ.

Fibrotic

Scleroderma and radiation were mentioned.

Overlap with other cardiomyopathies

Hypertrophic cardiomyopathy/ pseudohypertrophica, minimally dilated cardiomyopathy, Early-stage dilated cardiomyopathy, Partial recovery from dilated cardiomyopathy and sarcoidosis

Non-infiltrative

Diabetic cardiomyopathy (acquired); Myofibrillar myopathies (inherited). Genes: BAG3, DES, CRYAB, FHL1, DNAJB6, LDB3, FLNC, MYOT. Idiopathic (acquired); Sarcomeric protein disorders (inherited). Genes: ACTC, TNNT2, β-MHC, TNNI3, DES, TNNC1, MYL3, MYH, CRYAB. Scleroderma (acquired); Pseudoxanthoma elasticum (inherited). Gene: ABCC6; Werner's syndrome (inherited). Gene: WRN.

CLINICAL FEATURES

In idiopathic RCM, both the left and right ventricles are affected by diastolic dysfunction. RCM presents with systemic and pulmonary congestion, like dyspnea, pulmonary edema, fatigue, palpitations, orthopnea, and chest pain. On clinical examination, the following can be found: pulmonary rales, jugular venous distension (Jugular venous pressures often show rapid Y descents and may increase during inspiration (positive Kussmaul's sign)), third heart sound, systolic murmur, and peripheral edema. Advanced stages of the disease present with hepatosplenomegaly, ascites, and anasarca.[30] Peripheral autonomic dysfunction in RCM causes reduced baroreflex sensitivity, causing clinical deterioration and arrhythmias. RCM cannot be distinguished from constrictive pericarditis (CP) clinically, however, trauma history, cardiac surgery, malignancy, tuberculosis, etc. are suggestive of constrictive pericarditis, while RCM has a high BNP level. Pericardial calcifications on chest radiograph and/or low QRS voltages on EKG are diagnostic of CP. Echocardiography and cardiac magnetic resonance (CMR) can further help distinguish RCM and CP.[31]

DIAGNOSIS

EKG

In RCM atrial enlargement most commonly causes atrial fibrillation. Other EKG findings in RCM are premature ventricular and atrial beats, AV blocks, elevated ST segment with notched or biphasic late peaking T waves, significant ST depression with T inversion mimicking subendocardial ischemia, and are associated with increased risk of SCD.

Chest radiography

Cardiomegaly, due to bilateral atrial enlargement, pleural effusion, pulmonary venous congestion, and interstitial edema can be seen on chest X-ray in RCM.

Laboratory test

CK, ferritin, full blood count, iron studies, NT-proBNP, liver function, proteinuria, serum angiotensin-converting enzyme, renal function, troponin, free light chains, urine and plasma protein immunofixation, autoantibodies.

Echocardiography

Absent ventricular hypertrophy or dilatation, bilateral atrial enlargement, preserved systolic LV ejection fraction, and diastolic dysfunction are seen in RCM in echocardiography. Diastolic dysfunction can be identified by the following according to the American society of echocardiography: # Atrial left (LA) maximum volume index >34 ml/m; # Tricuspid regurgitation peak velocity (TRV) >2.8 m/s; # Average E/e' ratio >14; # Annular e' velocity (septal es).

Increased LV filling pressures are suggested by the ratio of pulmonary vein peak systolic to peak diastolic velocity and changes in E/A ratio with the Valsalva maneuver. Some echocardiographic findings help distinguish RCM from CP, as well as idiopathic and secondary RCM.[32]

Cardiac magnetic resonance

CMR helps identify specific patterns characteristic of diseases causing RCM as well as is a valuable prognostic factor, for example, diffuse subendocardial late gadolinium enhancement (LGE) in cardiac amyloidosis (CA) and cardiac sarcoidosis.

Endomyocardial biopsy

Endomyocardial biopsy is a precision diagnostic tool where other diagnostic modalities are inconclusive like in restrictive cardio-desminopathies; intramyocyte in hemochromatosis, iron myocardial overload, and mitochondrial cardiomyopathy in Friedreich ataxia; cystinosis; generalized arterial calcification of infancy; and lysosomal storage diseases (LSDs). LGE-CMR-guided biopsy is more precise and decreases the likelihood of a false negative.

Genetic testing

Management

Secondary RCMs are treated depending on particular etiopathogenesis e.g. therapeutic phlebotomy for hemochromatosis; ERT for Anderson–Fabry disease, glycogenosis such as Pompe disease; immunosuppressive therapeutics for sarcoidosis; new biological drugs for systemic autoimmune diseases and removal of the toxic causes. Limiting the symptoms of HF is the main aim of treatment in idiopathic RCM. Non-dihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) and beta-blockers are used to improve ventricular filling, reduce diastolic dysfunction, reduce heart rate, and have a

positive effect on ventricular relaxation. Venous congestion in the pulmonary and systemic circulation can be reduced by using loop diuretics, however at low doses to avoid excessive drop of preload, reducing the cardiac output and causing hypotension. Reverting arrhythmias is vital and sinus rhythm is preferred but if arrhythmias persist oral anticoagulation needs to be added. Implantable defibrillators to reduce the risk of SCD can be considered.[33] Heart transplantation is the only definitive treatment for RCM and is reserved for cases of untreatable HF.[34]

PERIPARTUM CARDIOMYOPATHY

Heart failure during pregnancy and the peripartum period is most commonly caused by peripartum cardiomyopathy.[35] The ESC Working Group defines peripartum cardiomyopathy as: # When heart failure (HF) develops toward the end of pregnancy or within five months following delivery. # Absence of another identifiable cause for the HF. # Left ventricular (LV) systolic dysfunction with an LV ejection fraction (LVEF) of less than 45 percent with or without LV dilatation.[36]

The etiology remains uncertain; some mechanisms have been considered, such as angiogenic imbalance. Possible risk factors are: Age greater than 30 years; Cocaine abuse; long-term use (>4 weeks) of tocolytics (terbutaline); Pregnancy with multiple fetuses; African descent; Preeclampsia, eclampsia;

The most common presentation is symptoms of congestive heart failure like cough, dyspnea, nocturnal dyspnea, orthopnea, peripheral edema, and fatigue. Peripartum cardiomyopathy is very commonly complicated by arrhythmias and thromboembolism, already being a hypercoagulable state. Apart from clinical diagnosis, the following can aid in the same: EKG showing sinus tachycardia, repolarization anomalies, Q waves; High BNP; Chest X-ray may show enlargement of the cardiac silhouette, signs of pulmonary congestion like redistribution of flow and pleural effusion echocardiography shows reduced left ventricular ejection fraction.[37]

Managing heart failure is main mainstay of treatment with oxygen, inotropes, and pre-load optimization. ICD implantation and anticoagulation in arrhythmias. Bromocriptine, intravenous immune globulin, antisense therapy against micronRNA-146a, and apheresis are under trial treatment for peripartum cardiomyopathy. A hemodynamically stable patient can undergo vaginal delivery with epidural whereas, in case of hemodynamic instability, an emergency cesarean delivery should be done. As regards breastfeeding, recommendations are controversial. The mortality of peripartum cardiomyopathy is 10% in two years, and 6% in five years. Left ventricular function recovers completely in up to six months of diagnosis in about 20-70% of cases.[38,39]

TAKOTSUBO CARDIOMYOPATHY

Takotsubo cardiomyopathy broken-heart syndrome or stress-induced cardiomyopathy is defined as a sudden onset of left ventricular dysfunction in response to severe emotional or physiologic stress. It most commonly affects post-menopausal women. Typical ischemic changes are seen on EKG, with elevated cardiac enzymes, and account for about 1-2% of admissions of acute coronary syndrome.[40] A typical apical ballooning of the left ventricle is seen on echocardiography with normal coronary angiography. Initial treatment is like that of myocardial infarction and acute complications like shock or heart failure, are managed accordingly. Stable patients are treated with diuretics, beta-blockers, and ACE inhibitors or ARBs. In case of loss of wall motion in the left ventricular apex, anticoagulation should be added. Symptoms and abnormalities typically reverse within one month, with full recovery in most cases and treatments may be withdrawn accordingly.

CARDIOTOXICITY AND CHEMOTHERAPY DRUGS

Cancer patients undergoing chemotherapy may develop cardiomyopathies. Anthracyclines and trastuzumab most commonly cause cardiotoxicity. Anthracyclines cause myocardial damage by forming oxygen free radicals, increasing oxidative stress and causing myocardial damage. Presenting as arrhythmias, pericarditis myocarditis, EKG abnormalities, atrioventricular block, presenting with symptoms of heart failure.[41]

Doxorubicin forms a ternary complex by binding topoisomerase 2 and DNA causing myocyte death. Risk factors associated with doxorubicin-induced cardiotoxicity are: #Old age (>65 year) or young (<4 years), obesity, hyperlipidemia, female gender, smoking, diabetes, pre-existing heart disease, hypertension, high cumulative anthracycline exposure.

A monoclonal antibody trastuzumab targeting human epidermal growth factor receptor 2, does not cause myocardial damage, instead alters contractility, is not linked to drug accumulation, and is usually reversible. Risk factors include: # Over 50 years of age, previous or concomitant use of anthracyclines, obesity, preexisting cardiac dysfunction, hypertension.

Other chemotherapy agents that can cause cardiomyopathies are: # Paclitaxel: cardiotoxicity like

doxorubicin, causing heart failure in 20% of cases, # Cyclophosphamide: dose associated with cardiotoxicity and heart failure; negative prognostic factors being pre-existing cardiac abnormalities, lymphoma, advanced age, and preceding mediastinal irradiation. # Cisplatin: caused due to electrolyte abnormalities secondary to cisplatin-induced nephrotoxicity. Cardiotoxicity presents with

myocardial infarction, supraventricular tachycardia, the acute ischemic events, bradycardia, ST-T wave changes, left bundle branch block, and the ischemic cardiomyopathy.[42]

Table 5: Clinical features and management of syndromic and metabolic cardiomyopathies.[43]

Clinical red flags	Specific cause	Diagnosis	Management
Abnormal facial features **Sensorineural deafness** **Cryptorchidism** **Pulmonary valve stenosis** **Growth retardation** **Café au lait spots** **CHD** **Lentigines** **Extreme right-axis deviation at ECG** **Lymphangiectasia** **Bleeding diathesis**	Noonan syndrome Noonan syndrome with multiple lentigines Costello syndrome Cardio-faciocutaneous syndrome	NGS panel testing for RASopathy	Beta-blockers/CCBs Selective management of RVOTO/ pulmonary valvuloplasty, SCD risk stratification
Short PR interval End-stage, Hypokinetic HCM AV block (Kearns-Sayre syndrome) **Lactic acidosis** **Sensorineural deafness** **Neutropenia (Barth syndrome)** **Diabetes Stroke-like lesions at brain MRI**	MELAS syndrome MERRF syndrome Leigh syndrome Other mitochondrial disease Beta-oxidation disorders	NGS panel for mtDNA and nuclear DNA Skeletal muscle biopsy/ endomyocardial biopsy	Avoiding drugs/situational /stressors β-oxidation disorders: avoidance of fasting, aggressive treatment during increased metabolic stress, nutritional management, carnitine supplementation
Short PR interval **Skeletal myopathy Massive LVH** **Intellectual disability X-linked inheritance,** **Increased serum CK enzym**	Danon disease	NGS or target testing for LAMP-2 variants	No treatment
Hepatomegaly **Increased aminotransferase enzymes** **Hypotonia** **Delayed motor milestones** **Short PR interval** **Extreme LVH**	Type II glycogen storage disease (Pompe disease)	Screening: GAA activity in DBS or leucocytes/Glc4 dosing diagnostic confirmation-acid alpha-glucosidase assay performed on skin fibroblasts/muscle biopsy	Enzyme replacement therapy
Progressive limb ataxia **Pes cavus** **Diabetes mellitus, Reduced native T1 at CMR imaging**	Friedreich ataxia	NGS testing for bi-allelic expansion of GAA repeats in the FXN gene	No specific treatment
Short PR interval **Early-onset atrial fibrillation** **AV block autosomal dominant inheritance pattern Increased serum CK enzyme**	PRKAG2 syndrome	NGS or target testing for PRKAG2	No treatment
X-linked inheritance pattern **Gastrointestinal symptoms** **Sensorineural hypoacusia** **Angiokeratoma** **Cornea verticillata** **Chronic kidney disease** **Proteinuria** **Stroke/TIA** **Neuropathic pain** **Short PR interval** **Low native T1 at cardiac CMR**	Anderson–Fabry disease	Screening in males: lyso-Gb3 dosing Screening in females/diagnostic confirmation: genetic testing for *GLA* variants	Enzyme replacement therapy (agalsidase alfa/beta) Migalastat

Continued.

Clinical red flags	Specific cause	Diagnosis	Management
Bilateral carpal tunnel syndrome **Autonomic dysfunction** **Positive serum or urine monoclonal chain at immunofixation** **Lumbar spinal stenosis** **Peripheral neuropathy** **Pseudonecrosis Q waves** **Relative apical sparing pattern** **Ejection fraction/ strain ratio >5** **Low ECG voltages**	Cardiac amyloidosis (AL or ATTR)	DPD/HMDP Tc99 scintigraphy Free light chain/serum and urine immunofixation Endomyocardial biopsy	Tafamidis Inotersena (ATTR-CA) Patisirana Specific chemotherapy (AL amyloidosis)
Skeletal myopathy **AV block** **Premature atrial fibrillation** **Malignant ventricular arrhythmias**	*LMNA* cardiomyopathy Emery–Dreifuss muscular dystrophy	NGS testing	SCD risk prevention Pacing if indicated
Skeletal myopathy **Posterolateral or inferolateral akinesia** **Posterolateral pseudo necrosis pattern**	DMD	Genetic testing for dystrophinopathies	Steroids (prednisone or deflazacort)
Previous transfusions **Elevated ferritin** **Chronic liver disease** **Hypogonadotropic hypogonadism** **Skin pigmentation** **Diabetes** **AV block**	Iron overload cardiomyopathy	Iron status Complete blood count Peripheral blood smear Increased T2* values at CMR imaging Genetic test for HFE, HJV, ferroportin, hepcidin receptor, HAMP gene Haemoglobin electrophoresis Genetic testing for hereditary hemoglobinopathies	Iron-chelating drugs phlebotomy
Bilateral hilar lymphadenopathy **Pulmonary infiltrates** **Uveitis** **Gastrointestinal involvement** **High-degree AV block** **Frequent VEs** **Thinned basal interventricular septum** **Extended LGE at CMR imaging**	Sarcoidosis	18F-FDG-PET Lung biopsy Endomyocardial biopsy	Steroids Steroid-sparing Immunosuppressant

AMYLOIDOSIS

Extracellular deposition of misfolded proteins in the ventricular myocardium with the pathognomonic histological property of green birefringence when viewed under cross-polarized light after staining with Congo Red is characteristic of cardiac amyloidosis. Monoclonal immunoglobulin light chain amyloidosis (AL) or transthyretin amyloidosis (ATTR) is most commonly seen in cardiac amyloidosis, either in its hereditary (ATTRv) or acquired (ATTRwt) form. ATTRwt form is the most frequent form of cardiac amyloidosis worldwide and is associated with aging.[44]

CLINICAL FEATURES

If LV wall thickness is increased with cardiac or extracardiac red flags and/or in specific clinical

situations, especially in patients >65 years of age, then cardiac amyloidosis should be suspected.

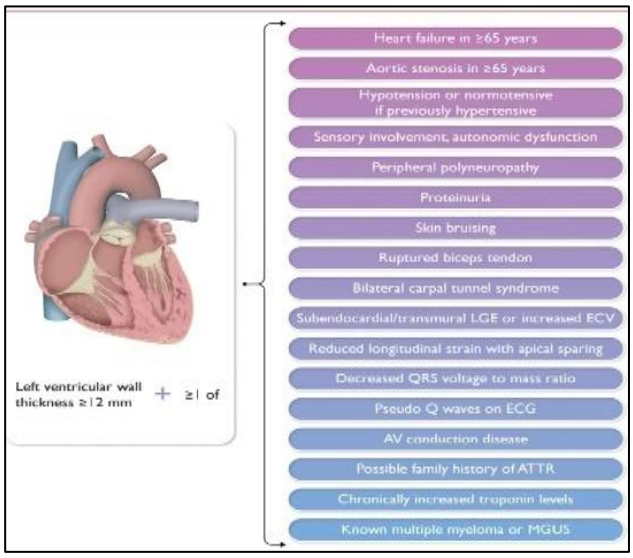

Figure 3: Signs and symptoms, investigation findings in cardiac amyloidosis.

AV, atrioventricular; ECV, extracellular volume; MGUS, monoclonal gammopathy of undetermined significance; LGE, late gadolinium enhancement.[5]

DIAGNOSIS

Cardiac amyloidosis can be diagnosed using both invasive and non-invasive diagnostic criteria. All cases of cardiac amyloidosis need invasive diagnostic criteria, except ATTR where non-invasive criteria is accepted for diagnosis. Amyloid fibrils within cardiac tissue if demonstrated in cardiac tissue or, amyloid deposits demonstrated on an extracardiac biopsy with echocardiography or CMR features suggestive of cardiac amyloidosis are included in the invasive criteria. Typical echocardiographic/CMR findings along with planar and single-photon emission computed tomography (SPECT) features are included in the noninvasive criteria. Clonal dyscrasia is ruled out by serum free light chain assay, and serum and urine protein electrophoresis with immunofixation. Tomographic scintigraphy can be done.

TREATMENT

Regular heart failure seems to have a sub-optimal effect in cases of amyloid cardiomyopathy. Cardiac amyloidosis hampers the electrical conduction disease causing advanced AV block and symptomatic bradycardia, which should be managed with medical therapy, and the threshold for implantable pacemakers should be low.

AL cardiac amyloidosis treatment is based on specific therapies for underlying hematological problems with chemotherapy or autologous stem-cell transplant. TTR cardiac amyloidosis treatment aims at transthyretin reduction of its production and its stabilization. The mainstay of treatment in ATTR is tafamidis, which significantly reduces cardiac morbidity and mortality.

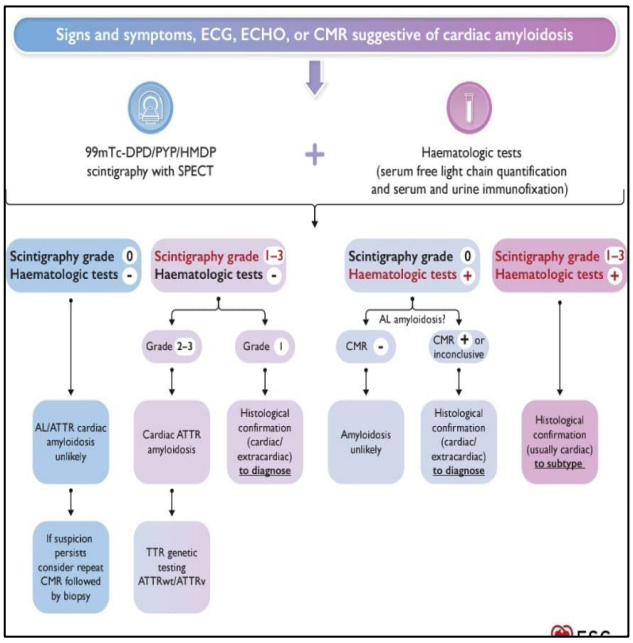

Figure 4: Diagnostic approach for cardiac amyloidosis.

CMR, cardiac magnetic resonance; DPD, 3,3-diphosphono-1,2-propanodicarboxylic acid; PYP, pyrophosphate. HMDP, hydroxy methylene diphosphonate.[5]

CONCLUSION

Cardiomyopathies are the most common cause of SCDs especially in the young, heart failure, and hospitalizations causing significant mortality and morbidity. The American heart association categorizes cardiomyopathy as primary or secondary. Hence, it is very crucial to achieve pharmacological and invasive procedures in time to manage cardiomyopathies, preventing sudden death or cardiac transplantation. Future treatments of cardiomyopathy include siRNA-based gene silencing, repurposed molecularly directed drugs, and genome editing. Shortly, understanding the molecular genetics of cardiomyopathies could well lead to clinical advances in early diagnosis and treatment.

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