Diagnosis and Management of Cardiomyopathies – A Focus on Genetics, Cardiac Magnetic Resonance and Clinical Features

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Abstract

In recent years, outstanding progress has been made in the diagnosis and treatment of cardiomyopathies. Genetics is emerging as a primary point in the diagnosis and management of these diseases. However, molecular genetic analyses are not yet included in routine clinical practice, mainly because of their elevated costs and execution time. A patient-based and patient-oriented clinical approach, coupled with new imaging techniques such as cardiac magnetic resonance, can be of great help in selecting patients for molecular genetic analysis and is crucial for a better characterisation of these diseases. This article will specifically address clinical, magnetic resonance and genetic aspects of the diagnosis and management of cardiomyopathies.

Keywords

Cardiomyopathies, diagnosis, genetics, familial cardiomyopathies, clinical approach, cardiac magnetic resonance

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According to the latest position statement of the European Society of Cardiology (ESC), cardiomyopathies (CMP) are defined as "myocardial disorders in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality".[1]

CMP may be exclusively localised to the myocardium ('primary cardiomyopathies' according to Maron's classification) or can be part of a systemic multi-organ disorder ('secondary cardiomyopathies').[2] Moreover, we can classify CMP in familial/genetic and non-familial/non-genetic forms.[1]

In recent years, outstanding progress has been made in the knowledge of the genetic background of myocardial diseases, many of which are now considered actual genetic diseases (see *Table 1*). Moreover, cardiac imaging techniques received an incredible improvement with the acquisition, in routine clinical practice, of cardiac magnetic resonance, which is capable not only of better myocardial morphological and functional analysis but also of *in vivo* and non-invasive tissue characterisation. Consequently, many new issues are arising in this emerging field of cardiology. At the present time, the clinical cardiologist is supposed to be familiar with new diagnostic techniques for obtaining specific diagnoses, optimising pharmacological and non-pharmacological treatment and providing crucial information about the possible implications of the disease to patients and their families.

In detail, hypertrophic cardiomyopathy (HCM) is characterised by an increase in myocardial wall thickness and/or myocardial mass in the absence of pressure overload conditions, such as systemic hypertension or valvular heart diseases. HCM must be considered a relatively common genetic disease (incidence: 1/500), the most common cause of which lies in mutations of genes encoding proteins of the sarcomere.[3] The identification of a disease-causative gene mutation occurs in about 50 % of cases. While approximately 500 different mutations have been involved in the genesis of HCM,[4] in more than 75 % of cases the causative gene mutation lies in β-myosin heavy chain (*MYH7*) or myosin-binding protein C (*MYBPC3*).[3,5] Mutations of the troponin complex (*TNNT2, TNNI3, TPM1*) are quite frequent as well (10–15 % of cases).[3,5,6] The transmission of the disease is usually autosomal-dominant, with variable expressivity and incomplete penetrance; the age of onset of sarcomeric forms is usually puberty. HCM may also represent a clinical manifestation of a systemic disorder, such as Fabry disease or Danon disease (with X-linked transmission) or can be a mitochondrial disorder.[7]

Dilated cardiomyopathy (DCM) is characterised by left ventricle or biventricular dilatation and dysfunction, in the absence of known predisposing causes. In contrast to HCM, DCM aetiopathogenesis is more variable and complex and can involve infective, toxic, pharmacological or dysmetabolic causes. It is recognised that 20–50 % of cases are of genetic origin.[8] The concept that familial DCM (FDC) is a cytoskeleton disease is now obsolete; in fact, it is well known that DCM can also be caused by mutations of genes encoding proteins of the sarcomere, Z-discs, nuclear membrane, desmosomes, ion channels and transcription factors.[8–11] DCM can be defined as FDC when the disease is present in two or more relatives in the same family or in

Table 1: Modality of Transmission of Cardiomyopathies and Genetic Background

	Autosomal-dominant	Autosomal-recessive	X-linked	Mitochondrial-matrilinear

HCM	• Sarcomere and sarcomere -associated proteins
	  • Myosin complex (MYH7, MYBPC3, etc.)
	  • Troponin complex (TNNT2, TNNI3, TPM1, etc.)
	  • Titin (TTN)
	• Alpha-actin (ACTC1)
	• Noonan syndrome type 1, LEOPARD syndrome (PTPN11)
	• Heart-specific non-lysosomal glycogenosis (PRKAG2)
		• Glycogen storage diseases: Pompe disease (GAA), Cori-Forbes disease (AGL)
		• Mucopolysaccharidosis type 1H (Hurler syndrome) (IDUA)
		• Primary systemic carnitine deficiency (SLC22A5)
		• Friedreich ataxia (FRDA)
			• Danon disease (LAMP2)
			• Fabry disease (α-galactosidase A) (GLA)
				• Respiratory chain and oxidative phosphorylation disorders (Leigh syndrome)
				• MELAS and MERRF syndromes

DCM	• Sarcomere and sarcomere -associated proteins
	  • Myosin complex (MYH7, MYBPC3, etc.)
	  • Troponin complex (TNNT2, TNNI3, TPM1, etc.)
	  • Titin (TTN), titin-cap (TCAP)
	• Cytoskeletal and nuclear membrane proteins
	  • Phospholamban (PLN), Cypher/ZASP (LDB3), Desmin (DES), Alpha-actin (ACTC1), Sarcoglycan complex (SGCD/B), Lamin A/C (LMNA), Epicardin (EYA4), Alpha-B-crystallin (CRYAB), Presenilin (PS1, PS2)
	• Ion channels and associated proteins
	  • Cardiac sodium channel (SCN5A)
	  • ATP-sensitive potassium channel (ABCC9-SUR2A)
	• Myotonin protein kinase (myotonic dystrophy type 1 - Steinert disease) (DMPK)
		• Hereditary haemochromatosis (HFE)
		• Primary systemic carnitine deficiency (SLC22A5)
			• Duchenne/Becker muscular dystrophy (DMD)
			• Emery-Dreifuss muscular dystrophy type 1 (EMD)
			• Danon disease (LAMP2)
			• Barth syndrome (TAZ)
				• Respiratory chain and oxidative phosphorylation disorders (Leigh syndrome)
				• Kearns-Sayre syndrome

ARVC	• Desmosomal proteins (DSP, PKP2, DSC2, DSG2) • Ryanodine receptor 2 (RYR2) • Transforming growth factor beta-3 (TGFB3)	• Naxos syndrome (Plakoglobin) (JUP) • Carvajal syndrome (Desmoplakin) (DSP)		
RCM	• Troponin I (TNNI3) • Desmin (DES) • Transthyretin-related hereditary amyloidosis (TTR) • Noonan syndrome type 1 (PTPN11)	• Glycogen storage diseases: Pompe disease (GAA), Cori-Forbes disease (AGL) • Hereditary haemochromatosis (HFE)		
LVNC	• Myosin beta heavy chain (MYH7) • Cypher/ZASP (LDB3) • Alpha-dystrobrevin (DTNA) • Alpha-actin (ACTC1)		• Barth syndrome (TAZ)	

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LEOPARD = lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth and sensorineural deafness; LVNC = left ventricular non-compaction; MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy associated with ragged-red fibres; RCM= restrictive cardiomyopathy.
Note: causative gene acronyms (when available) are given in brackets and italics.

the presence of an unexpected sudden death in a first-degree relative before 35 years.[1,12] The clinical onset of DCM is usually in adulthood (30–50 years) but is widely variable, including infantile and elderly forms. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a myocardial disease characterised by fibro-fatty substitution of the heart muscle with dilatation and dysfunction of the right ventricle or, sometimes, of both ventricles. The diagnosis is complex and is based on morphological, histological, electrocardiographic (ECG) and family history criteria.[13] Recently Marcus et al.[14] proposed a modification of the diagnostic criteria, including cardiac magnetic resonance (CMR) among contributory examinations. ARVC is a genetic disease, usually related to mutation of genes encoding proteins responsible for intercellular junctions (desmosomes). Eight genes have been identified, most of which are related to desmosomal proteins (plakophilin, plakoglobin, desmoplakin, desmoglein and desmocollin).[15] The transmission pattern is usually autosomal-dominant with variable expressivity and low penetrance; the rarest syndromic forms, such as Carvajal and Naxos syndromes, have, conversely, an autosomal-recessive transmission.

Moreover, CMP include less common myocardial diseases, such as restrictive cardiomyopathy (RCM), characterised by myocardial stiffness and diastolic dysfunction[16] and left ventricular non-compaction (LVNC), characterised by prominent left ventricular trabeculae and deep intertrabecular recesses.[17]

Role of Cardiac Magnetic Resonance

CMR offers additional insight in the diagnosis and clinical management of CMP. Through steady-state free precession (SSFP) imaging, which allows an accurate assessment of regional and global ventricular function and myocardial mass, CMR has become the gold standard for the assessment of ventricular volumes, mass, regional and global function.[18] In addition, the possibility of performing sequences that assess various aspects of disease is helpful for tissue characterisation (T1 imaging for fat infiltration, T2 imaging for oedema, T2* for iron overload, early gadolinium enhancement for thrombosis and late gadolinium enhancement (LGE) for necrosis, scarring, oedema or protein infiltration). The role of CMR in specific CMP is discussed below.

Dilated Cardiomyopathy

The most important role of CMR in the work-up of ventricular dysfunction is the differentiation between ischaemic and non-ischaemic forms through LGE patterns (see *Table 1*). In a study by McCrohon et al.,[19] subendocardial LGE, suggestive of ischaemic cardiomyopathy, was found in 13 % of DCM patients, whereas mid-wall or subepicardial LGE, characteristic of non-ischaemic cardiomyopathy, was found in 28 % of DCM patients; LGE was absent in nearly 60 % of patients with DCM. Conversely, subendocardial LGE was found in most patients with ischaemic cardiomyopathy.[19–21] The presence and extent of LGE correlates with the severity of disease[20] and predicts response to beta-blocker therapy in terms of remodelling and improvement in systolic function.[21] Furthermore, LGE correlates with mortality, re-hospitalisation, ventricular dissynchrony, spontaneous and inducible ventricular arrhythmias and sudden cardiac death.[22–25]

Hypertrophic Cardiomyopathy

Owing to elevated spatial and contrast resolution, CMR has a higher diagnostic accuracy compared with transthoracic echocardiography in identifying hypertrophic segments, especially for apical and lateral wall localisations and severe forms of hypertrophy (see *Figure 2*).[26,27] LGE indicating fibrosis may be found in most patients with HCM (see *Figure 2*). It occurs in hypertrophic regions, usually in a multifocal pattern in the middle third of the ventricular wall. LGE has an inverse correlation with systolic function[28] and a positive correlation with the extent of hypertrophy, disease progression, inducible ventricular tachycardia and sudden cardiac death.[29–32] More extensive case series show that LGE is a strong risk factor for adverse long-term prognosis.[33,34] Increased aortic stiffness, a marker of unfavourable prognosis in ischaemic cardiomyopathy, was also found in HCM, its degree correlating with the extent of fibrosis.[35]

Arrhythmogenic Right Ventricular Cardiomyopathy

The importance of CMR in the diagnosis of ARVC lies in its ability to detect regional right ventricular wall motion abnormalities and an increased end-diastolic volume or reduced ejection fraction, which are among the revised task force diagnostic criteria for ARVC.[14] Despite showing initial promise in evaluating right ventricular free wall fatty replacement, T1-weighted imaging has been removed from ARVC diagnostic criteria, due to its low sensitivity and reproducibility.[36,37] Conversely, LGE provides better sensitivity in detecting fibro-fatty replacement in advanced stages of the disease. LGE presence and extent also correlates with sustained ventricular tachycardia and ventricular dysfunction.[38] However, CMR alone must not be relied on for the diagnosis of ARVC.[39]

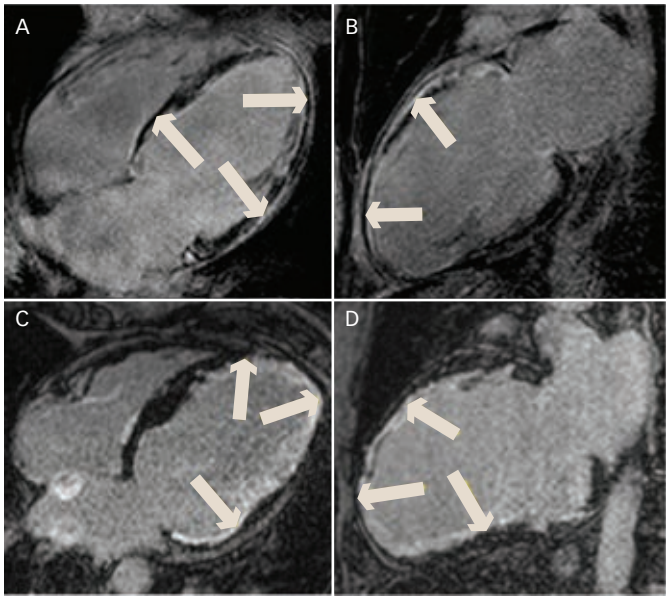
Infiltrative Forms

CMR is a powerful tool in the differential diagnosis of infiltrative diseases of the heart due to specific findings which are unique to these diseases. Amyloidosis is characterised by subendocardial circumferential LGE,[40] reflecting interstitial expansion by amyloid fibrils. Cardiac sarcoidosis is characterised by areas of inflammation visible on T2-weighted imaging, patchy areas of scarring in basal and lateral segments on LGE and mediastinal lymph node enlargement.[41] Anderson–Fabry disease shows homogeneous LGE involving the mid-subepicardial region of the basal inferolateral wall.[42]

Roles of Clinical Approach and Molecular Genetics

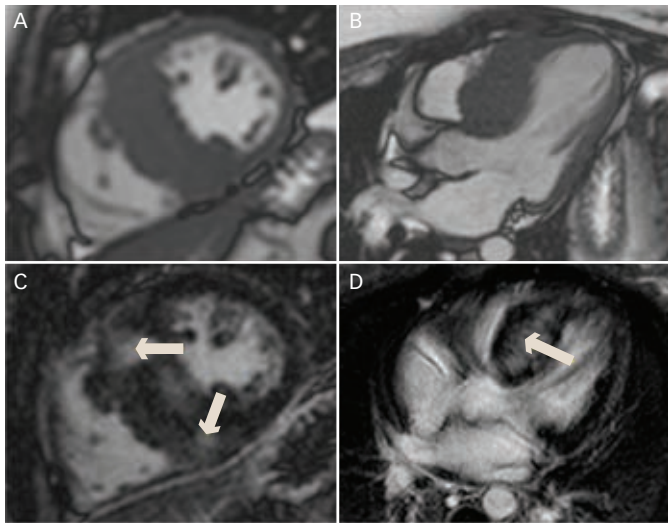
Many authors[1,10] have already underlined the importance of a clinical, patient-based approach to CMP. Moreover, familial screening, genetic counselling and aetiological diagnosis with genetic testing have gained importance in recent years and could play a significant role in the management of patients with CMP.[43–45] A recent position statement of the ESC[43] indicates the correct timing of familial screening in first-degree relatives of patients with CMP. The genetic testing is a non-invasive analysis which can be performed at any time during the patient's life, but involves elevated costs and execution time. Moreover, at the present time, the clinical implications of genetic analysis in CMP lie mainly in the possibility

Figure 1: Cardiac Magnetic Resonance – Late Gadolinium Enhancement Patterns in Dilated Cardiomyopathy



Inversion recovery after contrast administration images showing patchy subepicardial and subendocardial late gadolinium enhancement in a patient with post-myocarditis dilated cardiomyopathy in four-chamber (A) and two-chamber (B) views. Inversion recovery after contrast administration images showing late gadolinium enhancement (arrows) in the apex, lateral, anterior and inferior walls of a patient with ischaemic dilated cardiomyopathy following multiple myocardial infarctions in four-chamber (C) and two-chamber (D) views.

Figure 2: Cardiac magnetic resonance in Hypertrophic Cardiomyopathy



A and B: Short-axis images (A) and three-chamber view (B) of an asymmetric septal hypertrophy in a patient with hypertrophic cardiomyopathy, acquired by steady-state free precession imaging at end-diastole; C and D: Inversion recovery after contrast administration images showing late gadolinium enhancement (arrows) in the hypertrophied septum in short-axis (C) and three-chamber (D) views.

Table 2: 'Red Flags' – Possible Phenotypic Characteristics and Diseases Associated with Cardiomyopathies

	Skeletal Muscle Disorders	Arrhythmias and Conduction Defects
HCM	• Glycogenosis-related myopathies • Glycogenosis type 2 (Pompe disease) (GAA) • Glycogenosis type 2b (Danon disease) (LAMP2) • Glycogenosis type 3 (Cori-Forbes disease) (AGL) • Primary systemic carnitine deficiency-related myopathy (SLC22A5)	• Ventricular pre-excitation, WPW • HCM related to glycogenosis and other storage diseases (LAMP2, PRKAG2, GSD2, GSD3, GLA)
DCM	• Duchenne/Becker muscular dystrophy (DMD) • Emery-Dreifuss muscular dystrophy • Type 1 (EMD) • Type 2 (LMNA) • Limb-girdle muscular dystrophy • Lamin A/C (LMNA) • Sarcoglycan complex (SGCD/B) • Lamin-related congenital muscular dystrophy (LMNA) • Myofibrillar myopathy (DES, LDB3, CRYAB) • Myotonic dystrophy type 1 (Steinert disease) (DMPK) • Titin-related myopathy (TTN)	• SSS, sinus block, AF, SD • Lamin A/C (LMNA) • Supraventricular arrhythmias, AV and IV conduction defects, 'pseudo-necrosis' • DCM associated with dystrophinopathies and other myopathies (DMD, EMD, DES, DMPK) • Lenegre syndrome, SSS, AV block, AF, LQTs, Brugada syndrome, idiopathic familial VF • Ion channel disorders (SCN5A, SUR2A)
ARVC		• Epsilon waves, inverted T waves in right precordial leads (withou RBBB),frequent VEBs, NSVT with LBBB morphology
RCM	• Myofibrillar myopathy (DES) • Noonan syndrome type 1 (PTPN11)	• AV and IV conduction defects (DES)
LVNC	• Myofibrillar myopathy (LDB3) • Barth syndrome-related skeletal myopathy (TAZ)	

AF = atrial fibrillation; ARVC = arrhythmogenic right ventricular cardiomyopathy; AV = atrioventricular; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; IV = intraventricular; LBBB = left bundle branch block; LQTs = long-QT syndrome; LVNC = left ventricular non-compaction; NSVT = non-sustained ventricular tachycardia; RBBB = right bundle branch block; RCM = restrictive cardiomyopathy; SD = sudden death; SSS = sick sinus syndrome; VEBs = ventricular ectopic beats; VF = ventricular fibrillation; WPW = Wolff-Parkinson-White syndrome.
Note: causative gene acronyms (when available) are given in brackets and italics.

of early diagnosis in relatives[44] and related aspects (exclusion from follow-up in the absence of mutation, 'cascade screening', genetic counselling, risk stratification and the possibility of preclinical pharmacological treatment). Thus, since no gene therapies are currently available, the real impact of molecular genetics on the clinical management of CMP patients is still limited. Nevertheless, there are some important exceptions, such as mutations of the lamin gene (LMNA), in which the elevated arrhythmic risk should lead the clinician to consider an implantable cardioverter-defibrillator (ICD) implantation for primary prevention of sudden death,[46] or HCM related to Fabry disease in which enzyme replacement therapy provided significant clinical benefits, mainly in patients at an early phase of the disease.[47,48] Moreover, the negative prognostic role of multiple sarcomeric mutations in HCM recently emerged through genetic analysis.[49] In fact, the identification of several mutations in sarcomeric genes in the same individual is related to particularly poor outcomes.[49] For this reason, genetic analysis in HCM can be considered as one of the useful tests for prognostic stratification of the patient.

'Red Flags'

The clinical approach to the CMP patient can lead to the discovery of some peculiar phenotypic characteristics which can eventually help focus subsequent molecular genetics analysis (see *Table 2*). Some CMP may occur in association with skeletal muscle disorders with variable degrees of severity, from a frank progressive muscular dystrophy (Duchenne or Becker) to an isolated increase in creatine phosphokinase (CK).[50–53] Therefore, an accurate neuromuscular physical examination should always be part of the first clinical approach to the CMP patient.

Arrhythmias and conduction defects are quite common in many forms of acquired or familial CMP. Arrhythmias can be the first sign of disease or may represent a complication of the clinical course and an indicator of worse prognosis. Some 'familial arrhythmias', such as Lenegre, long QT and Brugada syndromes, are related to mutations of genes encoding ion channel proteins (*SCN5A, SUR2A*).[54] However, the line between 'channelopathies' and CMP is blurred because channelopathies are often characterised by an absence of signs of organic involvement, but the same mutations are able, in some cases, to determine definite DCM.[55] In HCM patients, the presence of ventricular pre-excitation may suggest the presence of a (rare) storage disease, such as Fabry disease, glycogenosis (Pompe and Cori–Forbes diseases) or Danon disease.[56–58] This finding is probably related to the disruption of the annulus fibrosus by 'pseudo-hypertrophic' myocytes with the formation of anomalous conduction pathways.[59]

Many genetic diseases are characterised by a multi-organ involvement, in which the heart muscle disease is only part of a more complex syndrome. The description of all these diseases is beyond the scope of this article. However, the early recognition of some peculiar syndromic forms may have crucial therapeutic and prognostic consequences. An HCM related to an extra-cardiac involvement characterised by progressive renal failure with proteinuria, cerebrovascular disease (stroke), small-fibre peripheral neuropathy (pain) and/or skin lesions (angiokeratoma) should lead the clinician to suspect Fabry disease. This genetic disease is characterised by an α-galactosidase A enzyme deficiency, with systemic accumulation of globotriaosylceramide and can be susceptible of treatment with enzyme replacement therapy.[47,48,60]

Mutations of the lamin A/C gene (*LMNA*)[61–64] are characterised by an elevated phenotypic heterogeneity. Indeed 'laminopathies' include DCM, related or not to skeletal muscle disease, lipodystrophy, Charcot–Marie–Tooth type 2 disease, Hutchinson–Gilford progeria

syndrome and other rare diseases. In lamin-related DCM, skeletal muscle involvement may be variable, from a frank muscular dystrophy (Emery–Dreifuss type 2 muscular dystrophy or limb-girdle muscular dystrophy) to an isolated increase in serum CK. Lamin-related DCM is usually characterised by mild or sometimes absent left ventricle dilatation and dysfunction, with frequent supraventricular arrhythmias (sick sinus syndrome, sinus block, supraventricular tachycardia or atrial fibrillation) and conduction defects, leading to an early need for pacemaker implantation and an increased risk of sudden death.[64] Some authors suggest treating these patients, who frequently require permanent endocardial pacing for conduction disorders, with a prophylactic ICD implant, even in the absence of significant left ventricular dysfunction.[46]

Conclusions

In the very broad and complex set of CMP, molecular genetics is emerging as an important point to improve the diagnosis and the management of these diseases. Despite the undoubted benefits, the techniques of molecular genetics are not yet commonly used in clinical practice, especially in consideration of the elevated costs and long execution time. The clinical approach to the patient and CMR imaging are crucial steps in the characterisation of the patient with a heart muscle disease and can help considerably to focus molecular genetic testing. An improvement in knowledge of the correlations between genotype and phenotype will be very useful in correctly aiming the more advanced diagnostic and therapeutic strategies and hence in improving quality of care in CMP patients and their families. ■

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