

Hereditary muscle diseases and the heart: the cardiologist's perspective

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Introduction

Cardiac manifestations in hereditary muscle diseases include cardiomyopathies, defects of cardiac conductions with or without primary myocardial muscle involvement, and arrhythmias.^{1,2} Symptoms and signs of these diseases may exhibit in paediatric as well as in adult age,³ and in many cases only a multidisciplinary clinical approach can ensure correct diagnosis and management.^{4,5} Cardiologists might be the first to recognize an apparently lone cardiac involvement as an important clinical marker of an hereditary muscle disease or be the first in line in a multidisciplinary team when cardiac involvement represents the major clinical manifestation affecting evolution and prognosis of the disease.⁶

The actual classifications of hereditary muscle disorders are based on phenotype, aetiology, and pathology and may result complex and potentially impractical for a cardiologic clinical approach. For this reason, we are proposing the grouping of most common cardiac manifestations observed in hereditary muscle diseases on the basis of the cardiac phenotypes. A new way of describing the complexity of cardiac phenotype and genotype together with extra-cardiac clinical manifestations, as represented by MOGES nosology for cardiomyopathies,⁷ is the possible solution for nosology assignment and deep phenotype description of these

patients in a way to collect data useful in accelerating targeted treatment development.

Dilated and hypokinetic phenotypes (DCM)

The most common heritable muscle diseases affecting the heart and leading to dilated and hypokinetic cardiac phenotype include dystrophinopathies, limb girdle muscular dystrophies (LGMD), and Emery-Dreifuss Muscular Dystrophies (EDMD).

Dystrophinopathies

Mutations in the *DMD* gene encoding for dystrophin cause dystrophinopathies, a group of rare X-linked recessive (XLR) muscle diseases. Dystrophin is a large sarcolemmal protein that is essential for structural and functional integrity of the myocyte membranes. Patients affected by dystrophin defects manifest DCM as unique and often fatal cardiac phenotype. Muscle and cardiac phenotypes are clinically heterogeneous and classified according to the severity of the dystrophy [from the severe Duchenne Muscle Dystrophy (DMD) to the milder Becker Muscular Dystrophy (BMD)] or the exclusive involvement of the heart, when skeletal muscle is clinically spared (i.e. in XLR-DCM).

- *DMD* (1:4000-1:6000 live male birth)⁸ is a severe muscle dystrophy clinically and genetically diagnosed in paediatric age. In most of the cases (>70%), the

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genetic defects are large rearrangements in *DMD* gene. The pathologic hallmark is the total absence of dystrophin in the skeletal myocyte sarcolemma.⁹ Regular cardiology care is needed since initial diagnosis in all DMD patients and annual echocardiograms represent the minimum follow-up.^{4,5,8} The prevalence of DCM is age-dependent and in nearly all young-adult patients cardiac involvement is demonstrated.¹⁰⁻¹³ ECG changes like right axis deviation, Q wave in the left precordial leads, and conduction defects may exhibit an early onset.¹⁰ DCM is diagnosed through transthoracic echocardiogram and when feasible, CMR may add information on adipose and fibrous replacement of left ventricle (LV) wall structure and LV trabecular anatomy.¹¹ Patients have to be treated for cardiac manifestations according to heart failure (HF) guidelines and disease-specific recommendations^{4,5} with ACE-I and ARBs as cornerstone therapy. Multiple contributors to cardio-respiratory failure determine end-stage evolution of the disease¹³ precluding indication to heart transplantation (HTx). In recent years, life expectancy has increased from the late 20s¹² to early 40s¹⁴ thanks to steroid treatment, spinal stabilization surgery, nocturnal ventilation, and physiotherapy.

- *In patients with BMD* [1:18 000 live male birth¹⁵] DCM fully manifests in the second to fourth decade of life but it can be recognized even earlier when BMD is clinically suspected.¹⁶ Skeletal muscle involvement is milder than in DMD and variable, depending on the severity of the loss of protein expression.¹⁷ Patients usually remain ambulatory until advanced adult age.^{8,9,15} DCM may be the first clinically overt manifestation of the disease¹⁸ but *hyperCKemia* is common and by itself may represent a reason for neurological consultation. The most common cause of end-stage disease is HF.^{4,5,19} Patients with BMD-DCM have to be treated according to HF guidelines and HTx may be indicated. Post-transplant outcome is similar to that of (non-BMD) idiopathic DCM.^{4,5,19}
- *XLR-DCM* can be the unique overt manifestation in patients with dystrophin defects. The prevalence ranges from 3% to 7% in consecutive male patients with familial, non-paternally inherited DCM.^{20,21} Patients have no history or symptoms of muscular dystrophy but almost always present *hyperCKemia*. Clinical management is based on HF guidelines; transplantation is the elective treatment for patients with end-stage HF and has the same outcome as in BMD-DCM.²²

Limb girdle muscle dystrophy

The LGMD phenotype includes genetically heterogeneous group of more than 30 disorders in which skeletal, respiratory, gastrointestinal, and nervous systems may be variably involved. They are characterized by weakness and wasting of pelvic and shoulder girdle muscles. Recently, a novel gene-based nosology²³ has classified LGMDs using the clinical descriptor (LGMD) followed by a number that distinguishes autosomal dominant (AD, type 1, LGMD1) and

autosomal recessive (AR, type 2, LGMD2) diseases. Alphabetic letters indicating the mutated protein/gene complement the description.²³ Currently, eight AD LGMDs (LGMD1) and more than 25 AR LGMDs are known.

The prevalence of LGMDs is estimated to be ranging from 1:14 500 to 2.27:100 000.^{24,25} Cardiac and respiratory impairment is common. The most represented cardiac phenotype in LGMD is DCM²⁶ having a prevalence that varies between the different subgroups of patients; in sarcoglycanopathies (α -, β -, δ -, γ -) more than 30% of patients develop DCM.²⁷ The risk of sudden death (SD) is also variable, being particularly high in LGMD1B (laminopathy) where is also associated with DCM and conduction defects.²⁸ Disease-specific biomarkers exist but *hyperCKemia* represent a common finding in all LGMDs. Functional studies of cardiac (echocardiography and CMR) and skeletal muscle (electromyography, muscle ultrasound, and magnetic resonance imaging) are useful to characterize the involvement of the heart and skeletal muscles.^{29,30} Patients usually need a scheduled monitoring in multidisciplinary settings and the actual therapeutic options include steroids with variable effectiveness.³⁰ Since actionable targeted therapies currently does not exist, DCM, arrhythmias and, conduction defects have to be treated according to contemporary guidelines^{4,5,19,26}

Emery-Dreifuss muscle dystrophy

Contractures of elbows, ankles, and cervical spine associated with slowly progressive muscle weakness are the major traits in EDMD.³¹ The cardiac phenotype is characterized by LV dilation and dysfunction often preceded by conduction disease that requires PM implantation. *HyperCKemia* is common. The disease is genetically heterogeneous and is caused by mutations in genes that code for nuclear envelope protein. Half of the patients diagnosed with EDMD are carriers of mutations in genes that code for emerin, lamin A/C, nesprin-1, and nesprin-2.³¹ Depending upon the disease gene, the pattern of inheritance is either X-Linked or autosomal, both dominant (common) or recessive (rare).

In XLR emerinopathies, patients are usually referred to cardiologists for arrhythmia consultation and consideration of possible pacemaker (PM) placement; AV conduction defects and arrhythmias, mostly of atrial origin, may appear before LV systolic dysfunction.^{32,33} In AD EDMD caused by mutations in *LMNA* gene,³³ the risk of ventricular arrhythmias is high. DCM, arrhythmias and conduction disease should be treated according to HF guidelines. However, the disease-causing gene and the type of mutation should be taken into account in the stratification of arrhythmogenic risk.²

Hypertrophic phenotypes

HCM represents the cardiac phenotype in a large group of clinically and genetically heterogeneous hereditary muscle disorders caused by impaired synthesis and utilization of energy substrates with proliferation of abnormal organelles (i.e. Friedreich ataxia and mitochondrial myopathies) or by

intracellular accumulation of energy substrates (i.e. glycogen storage diseases).

Friedreich ataxia

Friedreich ataxia is a rare (1:50 000) AR neuromuscular disease characterized by HCM as cardiac phenotype. In most of the cases, it is caused by homozygous GAA triplet expansions in the first intron of the *FXN* gene³⁴ that encodes for frataxin, a mitochondrial protein involved in iron homeostasis. The GAA triplet expansion (60-1500 vs. <12 in normal individuals^{34,35}) leads to transcriptional gene silencing and loss of frataxin expression³⁶ impairing and dysregulating mitochondrial iron trafficking. The clinical onset is usually in the first or second decade of life^{35,36} and presentation is characterized by cerebellar ataxia, dysarthria, HCM, diabetes, neurosensory hearing loss, and visual impairment. The HCM is usually symmetrical and non-obstructive with diastolic dysfunction and progression to systolic dysfunction.^{37,38} Cardiac involvement is demonstrated in more than 90% of patients with about 40% suffering from supraventricular tachycardia.³⁹ Therapy is based on the use of antioxidants and iron chelators but their efficacy is still debated.⁴⁰ In end-stage cardiomyopathy HTx may be a potential option but it has to be considered feasible when neurologic dysfunction is mild or absent.⁴¹

Mitochondrial myopathies and cardiomyopathies

Deficiencies in the mitochondrial oxidative phosphorylation system are at the basis of mitochondrial diseases. The estimated prevalence is 1:4000⁴² and both heart (mitochondrial cardiomyopathies) and skeletal muscle (mitochondrial myopathy) are involved. The clinical traits however can include hearing loss, ocular disorders, cryptogenic stroke, gastrointestinal diseases, renal failure, and diabetes. They are caused by defects in mitochondrial DNA (mtDNA) or in nuclear genes, with matrilinear or Mendelian inheritance, respectively.^{42,43} *mtDNA defects* most commonly lead to concentric, non-obstructive LV hypertrophy characterized by potential evolution to LV dilation and dysfunction.^{44,45} ECG may show short PR interval and pre-excitation, a sign that may constitute a useful marker for clinical hypothesis.⁴⁶ The severity of clinical manifestations depends on the degree of somatic heteroplasmy.⁴³ Mutations in mtDNA genes coding transfer RNAs are the most common cause of MELAS, one of the more malignant mitochondrial disorders.⁴⁷ Death in MtDNA-related diseases mostly occurs for recurrent stroke-like episodes, HF, and renal failure.⁴⁸

Mitochondrial nuclear genes encode for over 1500 mitochondrial proteins and the number of novel diseases caused by nDNA defects is progressively increasing.⁴⁸ They are inherited mostly with AR pattern, with clinical onset in paediatric/juvenile age. The current classification of nuclear mitochondrial myopathies is based on phenotype and genetic cause.^{42,43} The most common cardiac phenotype is HCM, followed by DCM, RCM, and arrhythmogenic cardiomyopathy.⁴⁸

Glycogen storage disorders

Both heart and skeletal muscle are involved in glycogen storage disorders (GSD). Each glycogenesis is a rare disease but when considered collectively, they are relatively common. Screening studies and the extensive application of next generation sequencing have modified knowledge on GSDs prevalence favouring the discovery of late-onset phenotypes that were previously undiagnosed.⁴⁹ Most frequent GSDs forms involving heart muscle are Pompe disease and McArdle disease (about 1:40 000 people).^{50,51}

Pompe disease (GSD type II) is an AR disease caused by mutations in *GAA* gene leading to deficiency of alpha1,4 glucosidase activity.^{51,52} The enzyme deficiency leads to glycogen accumulation in heart, skeletal muscle, and liver. Myocytes and myocardial walls are thickened by progressive lysosomal glycogen gathering (diastolic dysfunction) and are irreversibly damaged. This leads to systolic dysfunction and HF.⁵² In infantile forms, characterized by enlarged tongue, severe skeletal muscle hypotonia (floppy babies) and normal liver size, HCM is the main cause of death. The ECG shows large QRS complexes and short PR intervals.⁵² The disease is rapidly fatal in absence of the specific enzyme replacement treatment (ERT). Heart is less commonly involved in juvenile forms, which are characterized by delayed motor milestones and gradually worsening myopathy, especially in the limb girdle and truncal muscles. Death occurs for respiratory failure before adulthood in absence of ERT.^{51,52} In adult-onset or late-onset Pompe disease, the most common form of the disease, mild and non-specific cardiac abnormalities are detectable by CMR only in a small proportion of patients.⁵³ The diagnosis can be achieved non-invasively through the dosage of enzyme activity and genetic testing even if skeletal muscle or endomyocardial biopsy can be useful.⁵³

Mutations in the *LAMP2* gene, encoding the lysosomal-associated membrane protein 2, cause a rare multi-systemic disorder, the *XLD Danon Disease* (or GSD II type 2b). The phenotype is early onset in male patients and characterized by cognitive impairment, severe biventricular HCM with evolution to LV thinning with systolic dysfunction, and skeletal muscle disease with *hyperCKemia*. HCM is later-onset but severe even in female patients. Common ECG findings are tall QRS voltages, short PR, and pre-excitation. In end-stage hearts, extensive fibrosis is demonstrated by CMR. No specific treatment for Danon disease exist and patients are cared for as per phenotype⁵⁴ with HTx as therapeutic option in end-stage disease. Post-transplant outcome is similar to other cardiomyopathies.⁵⁴

The AR McArdle Disease (GSD type V) is caused by homozygous or double heterozygous mutations in *PYGM* that reduce or abolish myophosphorylase enzyme activity in the muscle. The enzyme initiates glycogen breakdown in the skeletal muscle fibres.⁵⁵ The disease clinically manifests in late childhood or in early teens with cramps, myalgias, and skeletal muscle weakness worsened by physical activity and relieved by rest. Episodes of rhabdomyolysis and prolonged pain may be elicited by strenuous exercise.⁵⁵ Exercise-associated symptoms are characterized by a partial relieve of the muscles pain which presents after the first minutes of activity ('second wind' phenomenon). This

is due to the mobilization of other forms of energy (fatty acids). Exercise-related symptoms, baseline *hyperCKemia*, myoglobinuria (>50%) help in suspecting the diagnosis which can be confirmed with the dosage of myophosphorylase and with genetic testing. In a minority of cases, cardiomyopathy may be present as a mild HCM with possible evolution through LV dilatation.

Fatty acid oxidation disorders

Fatty acid oxidation disorders may variably involve both heart and skeletal muscle. They are classified depending on whether the enzymatic defect involves the plasma membrane function or transport or the long-, medium-, and short-chain fatty acid β -oxidation. In the severe early-onset cardiac and multiorgan failure form of VLCADD (Deficiency of very long-chain acyl-CoA dehydrogenase), diagnosis is confirmed on the basis of abnormal acylcarnitine biochemical analysis and/or biallelic mutations in the *ACADVL* gene.⁵⁶ HCM or HCM with DCM-like evolution characterize the cardiac phenotype. Low-fat diet supplemented by medium-chain triglycerides and triheptanoin and early supportive care can improve both cardiomyopathy and myopathy.

Restrictive phenotypes

Diastolic dysfunction, presence of normal or reduced diastolic volumes of one or both ventricles, normal or reduced systolic volumes, normal ventricular wall thickness, and enlarged atrial chambers characterize restrictive physiology.⁵⁷ The latter recurs most of all in patients with myofibrillar myopathies (MFM).

Myofibrillar myopathies with RCM

This group of myopathies is characterized pathologically by the abnormal accumulation of intrasarcoplasmic proteins with disorganization of the myofibrillar network at the level of the Z-disks. In about one-third of patients, they usually manifest at the cardiac level with a restrictive pattern and conduction defects in association with *hyperCKemia*.⁵⁸ Slowly progressive weakness of both the proximal and distal skeletal muscles (80%), sensory defects, skeletal muscle stiffness, cramps, and aching complete the clinical presentation.

AVB and intramyocyte accumulation of osmiophilic granulophilic and desmin-immunoreactive material is the clinico-pathologic phenotype of the highly malignant, restrictive cardiodesminopathy. The clinical exordium is in young age and rapidly evolving to end-stage HF. These patients usually require HTx at a relatively young age.⁵⁹ Even in the absence of clinically overt myopathy the skeletal muscle is always structurally affected.⁵⁹⁻⁶¹ When the skeletal muscle involvement is minimal, HTx has to be considered and has the same outcome of non-*DES* patients.

BAG3-opathies with MFM are also characterized by early RCM phenotype with typical intrasarcoplasmic inclusion bodies.⁶² In end-stage myocardial disease, HTx is the only

treatment option, although it has to be considered in the context of the severity of systemic involvement.

Left ventricular non-compaction

Left ventricular non-compaction (LVNC) describes a left ventricular wall anatomy with prominent trabeculae, a thin compacted layer, and deep inter-trabecular recesses.⁶³ The definition does not imply functional effects, which are manifest only when LVNC is associated with dilated, hypertrophic or restrictive cardiomyopathy. Left ventricular non-compaction has been described as part of the cardiac phenotype in many different heritable muscle diseases as well as in congenital heart defects, genetic syndromes, and cardiomyopathies.^{64,65} Even if its possible prognostic role is still debated in the general population,⁶⁶ in DMD/BMD, the presence of LVNC has been significantly associated with a faster deterioration in LV function and higher mortality.⁶⁷

Left ventricular non-compaction is part of the dilated, hypokinetic cardiomyopathy that occurs in more than 90% of XLR Barth syndrome (BTHS) patients together with early non-progressive, hypotonic skeletal myopathy involving proximal muscles with developmental motor delay.⁶⁸ Oral aphtae, dysmorphic facial traits, and selective learning difficulties may also be part of the phenotype. The disease gene (*TAZ*) encodes Tafazzin, a protein that is located on the inner mitochondrial membrane. Tafazzin is essential for high energy-consuming tissue. The severity of the cardiac phenotype is variable with HTx as a possible treatment option.⁶⁹

Rhythm disorders and myopathies

Conduction diseases and arrhythmias are common in skeletal muscle diseases even in absence of primary myocardial muscle involvement with cardiomyopathic phenotypes. Myotonic dystrophies and skeletal muscle channelopathies may have life-threatening ventricular arrhythmias and SD as their first clinical manifestations.

Myotonic dystrophies (DM)

Type 1 (DM1) and type 2 (DM2) AD myotonic dystrophies are clinically characterized by myotonia, progressive skeletal muscle weakness, conduction defects, and CNS involvement. The DM1 patients are referred to cardiologists mostly for AVB and need for PM implantation. Genetic testing is usually available as it has been feasible for decades with nearly 100% diagnostic yield. SD risk has not to be under-evaluated because about 30% of these patients die suddenly.⁷⁰

The unstable CTG repeat expansion in *DMPK* gene is the cause of DM1; the extent of the expansion is associated with the severity of the muscular phenotype.⁷¹ DM1 has been recently classified in five groups according to the most recent criteria of the International Myotonic Dystrophy Consortium.⁷² The most common and well-recognized cardiac traits of the disease are conduction defects;⁷³ cardiomyopathy is uncommon. Conversely, the

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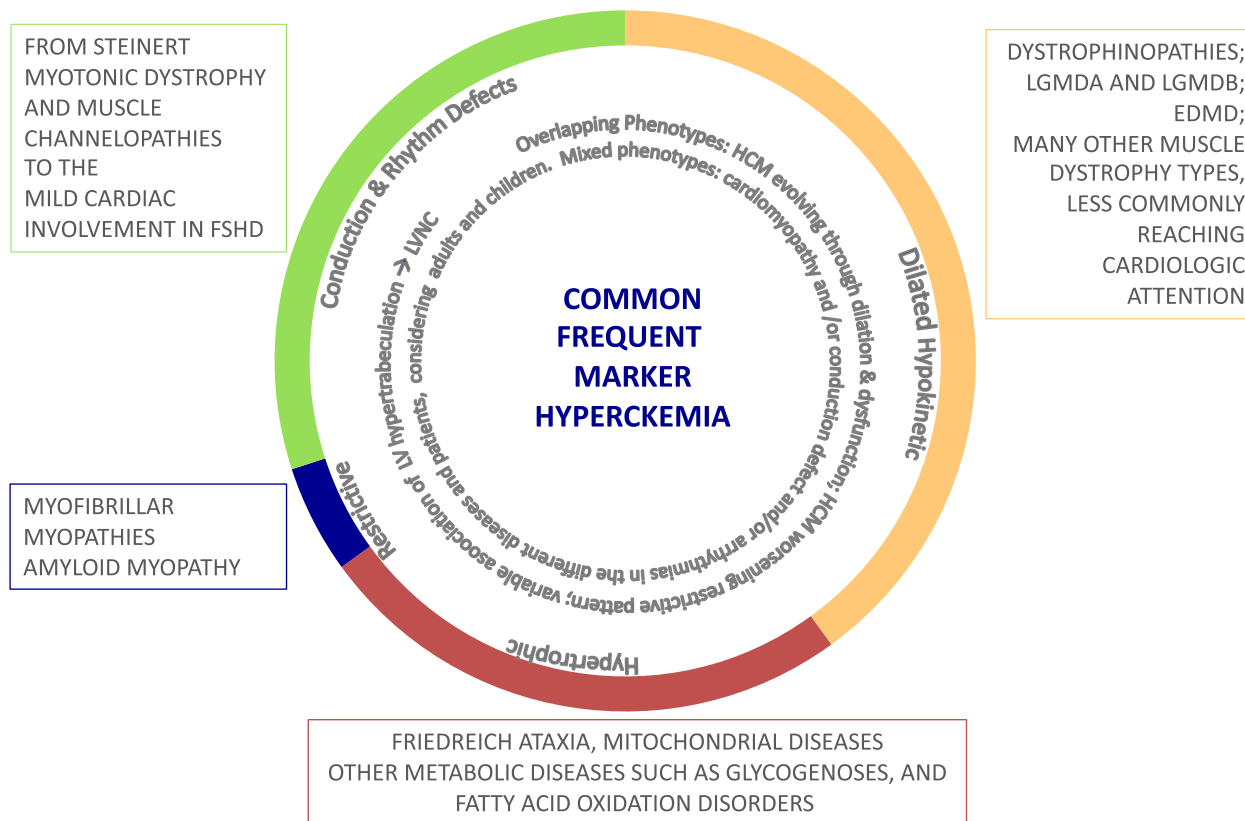


Figure 1.

risk of SD is high and ventricular arrhythmias or complete heart block can occur in the early stages of disease.⁷⁴ The risk of cardiac events has been demonstrated not to be correlated with the extent of CTG expansions. Patients with small and large triplet expansions have a similar increase in the risk of cardiac events and the follow-up should not differ in the two groups.⁷⁵

A CCTG-repeat expansion in intron-1 of the *CNBP/ZNF9* gene represents the molecular basis of DM2 (or proximal myotonic myopathy, PROMM). Skeletal muscle pain and weakness, myotonia (from 60%⁷⁶ to 85%⁷⁷) hypogonadism (male patients), cardiac rhythm disorders, diabetes, and early cataracts characterize the phenotype. About 20-36% of patients show cardiac conduction defects.⁷⁸ In 10-20% of cases atrial fibrillation, LV systolic dysfunction, and HF have been demonstrated.⁷⁹ A minority of patients may manifest DCM, but it may be characterized by a severe phenotype.⁸⁰ SD have been reported in rare cases in DM2.⁸¹

Heritable skeletal muscle channelopathies

Skeletal muscle channelopathies are very rare genetic neuromuscular disorders having a prevalence in the general population of 1:100 000. They are of cardiac interest because they are a possible cause of malignant ventricular arrhythmias and SD. They include the non-dystrophic myotonias⁸² and the primary periodic paralysis.⁸³

Conclusions

The heart is frequently involved in Inherited Muscle Disorders. Cardiomyopathies (i.e. dilated, hypertrophic, or restrictive, with potential overlap) together with rhythm disorders can be the first or predominant manifestations (Figure 1). They can present as an apparently lone cardiac involvement or be part of a complex 'cardio-skeletal-muscular' disease. Serum CKemia and lactic acidemia represents 'red flags' providing preliminary clues for exploring skeletal muscle disease in patients with cardiomyopathies or rhythm disorders. Cardiovascular care is necessary in a large proportion of patients with skeletal muscle disorders and cardiac involvement. Cardiologist may be key figures in complex diagnostic pathways or in clinical emergencies.

Conflict of interest: none declared.

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