Cardiomyopathies in neuromuscular disease

C. Giordano
Inherited neuromuscular diseases are a broad spectrum of genetic disorders including dystrophic and non-dystrophic myopathies, mitochondrial myopathies, storage disease, and muscle channelopathies.

Heart is involved in many NMDs, in the form of cardiomyopathy, conduction defects, and/or arrhythmias.

Prevalence, age at onset and severity of cardiac involvement varies significantly according to the specific etiology, with phenotype/genotype correlations continuously evolving.

For many NMDs, cardiac disease represents a major cause of morbidity and mortality.
Definition and classification of cardiomyopathy

“A myocardial disorder 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”
In the clinical setting cardiac involvement:

1) May manifest after the development of skeletal myopathy, when clinical and/or genetic diagnosis of NMDs has been already established (e.g. Duchenne muscular dystrophy)

2) May occur concurrently with an undiagnosed skeletal myopathy

3) May be the first or predominant manifestation.
In the clinical setting cardiac involvement:

1) May manifest after the development of skeletal myopathy, when clinical and/or genetic diagnosis of NMDs has been already established (e.g. Duchenne muscular dystrophy)

In this circumstance diagnosis takes advantage from cardiac screening programs that are now part of the routine diagnostic workup (e.g. Duchenne muscular dystrophy, DMD)

AHA SCIENTIFIC STATEMENT

Management of Cardiac Involvement Associated With Neuromuscular Diseases
In the clinical setting cardiac involvement:

2) May occur concurrently with an undiagnosed skeletal myopathy

Cardiac phenotypes may guide diagnostic suspicion of a specific cause, muscle biopsy is often part of the diagnostic flowchart and guide rational selection of specialized tests, including, biochemical or genetic analysis.
In the clinical setting cardiac involvement:

3) **May be the first or predominant manifestation.**

When the clinical presentation is dominated by cardiac symptoms, skeletal muscle involvement may not be obvious. The systematic search for diagnostic “red flags” (pattern of inheritance, markers of muscle damage, specific cardiac phenotype), may provide clues for specific diagnosis.

**Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases**

European Heart Journal (2013) 34, 1448–1458
doi:10.1093/eurheartj/ehs397
Pathologist may be involved in the diagnostic flow chart:

• In selected cases, when endomiacardial biopsy is performed (e.g. isolated cardiomyopathy)

• After cardiac transplant and at autopsy (remarkably, cardiomyopathies may be severe enough to cause heart failure or sudden cardiac death).
Snap-freeze at least one myocardial fragment for immunostains (dhystrophin), histoenzymatic stains (i.e. cytochrome c oxidase, COX and succinic dehydrogenase, SDH).

• Fix a sample in 4% glutaraldehyde for TEM.
Dilated Cardiomyopathy (DCM)

Left ventricular dilation and left ventricular systolic dysfunction in the absence of abnormal loading conditions or coronary artery disease sufficient to cause global systolic impairment.
Dilated Cardiomyopathy (DCM) in neuromuscular disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Gene Locus</th>
<th>Gene Product</th>
<th>Heritance</th>
<th>Cardiac Features</th>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>Cardiomyopathy</td>
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<tr>
<td>X-linked recessive muscular dystrophies</td>
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<tr>
<td>Duchenne</td>
<td>Xp21</td>
<td>Dystrophin</td>
<td>XLR</td>
<td>Common (DCM)</td>
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<tr>
<td>Becker</td>
<td>Xp21</td>
<td>Dystrophin</td>
<td>XLR</td>
<td>Common</td>
</tr>
<tr>
<td>Emery-Dreifuss</td>
<td>Xq28</td>
<td>Emerin</td>
<td>XLR</td>
<td>Rare</td>
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<tr>
<td>Limb-girdle muscular dystrophies</td>
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</tr>
<tr>
<td>LGMD1B</td>
<td>1q11-q21</td>
<td>Lamin A and C</td>
<td>AD</td>
<td>Common (DCM)</td>
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<tr>
<td>LGMD1C</td>
<td>3p25</td>
<td>Caveolin-3</td>
<td>AD</td>
<td>Rare (DCM)</td>
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<tr>
<td>LGMD1E</td>
<td>7q36</td>
<td>DNAJB6 (co-chaperone)</td>
<td>AD</td>
<td>Rare</td>
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<tr>
<td>LGMD2B</td>
<td>2p13</td>
<td>Dysferlin</td>
<td>AR</td>
<td>Rare (DCM)</td>
</tr>
<tr>
<td>LGMD2C</td>
<td>13q12</td>
<td>γ-Sarcoglycan</td>
<td>AR</td>
<td>Common (DCM)</td>
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<tr>
<td>LGMD2D</td>
<td>17q12-q21</td>
<td>α-Sarcoglycan</td>
<td>AR</td>
<td>Common (DCM)</td>
</tr>
<tr>
<td>LGMD2E</td>
<td>4q12</td>
<td>β-Sarcoglycan</td>
<td>AR</td>
<td>Common (DCM)</td>
</tr>
<tr>
<td>LGMD2F</td>
<td>5q33-q34</td>
<td>δ-Sarcoglycan</td>
<td>AR</td>
<td>Rare</td>
</tr>
<tr>
<td>LGMD2I</td>
<td>19q13.3</td>
<td>Fukutin-related protein</td>
<td>AR</td>
<td>Common (DCM)</td>
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<tr>
<td>Congenital myopathies</td>
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<tr>
<td>Central core disease</td>
<td>19q13.2</td>
<td>Ryanodine receptor</td>
<td>AD/AR</td>
<td>Rare (DCM)</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td>1q21, 2q21–q22, 1q42.13, 19q13.4</td>
<td>α-Tropomyosin, nebulin, skeletal muscle α-actin, troponin T</td>
<td>AR/AD</td>
<td>DCM, HCM</td>
</tr>
</tbody>
</table>

Dystrophinopathy

- Duchenne muscular dystrophy (DMD)
- Becker muscular dystrophy (BMD),
- X-linked dilated cardiomyopathy,
- DMD and BMD female carriers
Dystrophinopathy

- **DMD**: weakness in the early childhood progressing to loss of the ability to walk and respiratory insufficiency by the 2°-3° decade.
- **BMD**: milder and more variable phenotype

Elevated CK level is a diagnostic sign that should prompt to perform muscle biopsy or genetic testing.
Dystrophinopathy

- Immunostain with antibodies against the N- and C- domains and rod domains of dystrophin demonstrate the absence of protein in DMD or reduction in BMD.
Dystrophinopathy

Cardiac involvement in DMD always becomes clinically evident after the onset of muscular symptoms with incidence increasing with age:

- 25% at 6 years of age
- 59% by 10 years of age
- more than 90% over 18 years of age

In BMD over 70% of patients develop cardiomyopathy

The onset of cardiomyopathy is variable in BMD and is not correlated to skeletal muscle involvement. Cardiomyopathy, often associated with cardiac arrhythmias, may be the predominant manifestation.

Hyper-CK is common and should be considered a sufficient reason for consultation with a neurologist.

M, 33 years old, DMB
The majority of female carriers of DMD and BMD are asymptomatic; however, female carriers can become symptomatic.

Prevalence of manifesting carriers 20%

Manifesting carriers can present mild muscle weakness, elevated serum creatinine kinase, and cardiomyopathy.

X-inactivation is the mechanism where 1 of the 2 X chromosomes in female cells randomly becomes transcriptionally inactive. It is postulated that carriers can become symptomatic on the basis of the extent of random X-inactivation of the normal X chromosome versus the dystrophic X chromosome.
Laminopathy

- ECG abnormalities, conduction system defects and arrhythmias with or without LV enlargement and systolic dysfunction may manifest in subject bearing mutations in lamin A and C proteins.
- Immunohistochemical staining for lamin A/C may shows discontinuity or loss in perinuclear staining, however data on the use of immunohistochemistry for diagnostic purpose are not available.
Hypertrophic cardiomyopathy (HCM)

Myocardial hypertrophy in the absence of haemodynamic stresses sufficient to account for the degree of hypertrophy

*Circ Res. 2017;121:722-730*
Hypertrophic cardiomyopathy is the most frequent cardiac phenotype in metabolic/storage disorders. Epidemiology and clinical presentation are strictly age-related.

- In the **pediatric population** metabolic/storage disorders account for the vast majority of cardiomyopathy with hypertrophic phenotype.
- In this setting, cardiomyopathy rapidly progresses to heart failure and is often associated with neuromuscular abnormalities.
Hypertrophic cardiomyopathy (HCM) in neuromuscular disorders

Hypertrophic cardiomyopathy is the most frequent cardiac phenotype in metabolic/storage disorders.

<table>
<thead>
<tr>
<th>Cardiomyopathies with hypertrophic phenotype sorted by age at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
</tr>
<tr>
<td><strong>Infancy</strong></td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
</tr>
<tr>
<td>Disorders of fatty-acid beta-oxidation</td>
</tr>
<tr>
<td>Pompe disease</td>
</tr>
<tr>
<td>Noonan/LEOPARD syndromes</td>
</tr>
</tbody>
</table>

Hypertrophic Cardiomyopathy (HCM) in neuromuscular disorders

Hypertrophic cardiomyopathy is the most frequent cardiac phenotype in metabolic/storage disorders.

Diagnosis is based on the demonstration of a specific biochemical defect and skeletal muscle biopsy is often part of the diagnostic flow-chart.
Hypertrophic Cardiomyopathy (HCM) in neuromuscular disorders

- In **adult patients**, unexplained cardiac hypertrophy is mostly related to mutations in genes encoding sarcomere-associated proteins.
- Massive hypertrophy may be the only manifestation of a metabolic disorder (phenocopy of sarcomeric HCM).
- Clue for differential diagnosis with sarcomeric HCM are:
  - Pattern of inheritance
  - Symmetric pattern of hypertrophy
  - Conduction abnormalities (WPW)
  - Subclinical myopathy (CK)

Endomyocardial biopsy may help in diagnosis.
Hypertrophic Cardiomyopathy (HCM) in neuromuscular disorders

Endomiocardial biopsy may help in diagnosis.
Phenocopy of sarcomeric HCM

Storage disease
PRKAG2 mutations
Danon disease
Glycogenosis
Fabry disease

Mitochondrial cardiomyopathies
Female, 21-years old, mild mental retardation. Dyspnea, mild muscular weakness.
Pre-excitation pattern
Mild LV dilation

Family history positive for DCM
Female, 21-years old, mild mental retardation. Dyspnea, mild muscular weakness.
Pre-excitation pattern
Mild LV dilation

Family history positive for DCM
Female, 21-years old, mild mental retardation. Dyspnea, mild muscular weakness. Pre-excition pattern. Mild LV dilation.

Family history positive for DCM

**Danon disease**

X-linked disorder caused by the primary deficiency of lysosome-associated membrane protein 2 (LAMP2), which coats the inner surface of the lysosomal membrane and is supposed to act as a receptor for proteins to be imported and degraded within lysosomes.
Rare LAMP2 negative fibers at immunofluorescence consistent with a status of manifesting carrier of Danon disease.
Rare LAMP2 negative fibers at immunofluorescence consistent with a status of manifesting carrier of Danon disease.

One year later the patient experienced severe heart failure and underwent cardiac transplantation.
Paternal allele (WT) of the X chromosomes was inactivated in the left ventricle (56% of methylation) and in the septum (61% of methylation).

Next generation sequence analysis with a panel including LAMP+ 91 genes involved in CM disclose a truncating mutation in LAMP2 (chrX::c.453delT, p. F151fs)

A novel LAMP2 mutation associated with severe cardiac hypertrophy and microvascular remodeling in a female with Danon disease: a case report and literature review

Danon disease

• Heart disease is the dominant clinical feature in both males and females, and it is often associated with conduction disease. Remarkably, the ECG pattern of WPW is observed in about 68% of men and 27% of women.

• The onset of cardiac symptoms is usually 10 years later in affected women as compared to males and life expectancy is about 25 years longer.

Early onset cardiomyopathy in females with Danon disease

Carola Hedberg Oldfors a,*, Gyöngyvér Máthé b, Kate Thomson c, Mar Tulinius d, Kristjan Karason e, Ingegerd Östman-Smith f, Anders Oldfors a
Male, 16 years old,
Symmetric LV hypertrophy
Sensorineural hearing loss from
the age of 2
CK (324 IU/L)
Male, 16 years old,
Symmetric LV hypertrophy
Sensorineural hearing loss from
the age of 2
CK (324 IU/L)
Male, 16 years old,
Symmetric LV hypertrophy
Sensorineural hearing loss from the age of 2
CK (324 IU/L)

4277T>C, mt-tRNA $^{1le}$
Restrictive cardiomyopathy (RCM)

Reduced diastolic relaxation of either the left or both ventricles, with impeded diastolic filling, increased ventricular filling pressure, and normal (or near normal) systolic function.
Myofibrillar myopathies

- Foci of myofibril disruption that begins at the sarcomeric Z-disk associated with abnormal accumulation of myofibrillar degradation products.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Muscle weakness</th>
<th>Heart</th>
<th>Respiratory system</th>
<th>CK levels</th>
<th>Extramuscular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desminopathy</td>
<td>Distal &gt; proximal, SPS</td>
<td>DCM, CB</td>
<td>Insufficiency</td>
<td>n – 5x</td>
<td>Cataracts</td>
</tr>
<tr>
<td>aBCopathy</td>
<td>Proximal &gt; distal</td>
<td>DCM, CB</td>
<td>Insufficiency</td>
<td>n – 7x</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Filaminopathy</td>
<td>Proximal &gt; distal</td>
<td>DCM, CB</td>
<td>Insufficiency</td>
<td>n – 8x</td>
<td>Neuropathy, contractures</td>
</tr>
<tr>
<td>Myotilinopathy</td>
<td>Distal &gt; proximal</td>
<td>DCM</td>
<td>Insufficiency</td>
<td>n – 5x</td>
<td>RSS, scoliosis, contractures, neuropathy</td>
</tr>
<tr>
<td>BAG3opathy</td>
<td>Proximal</td>
<td>DCM</td>
<td>Insufficiency</td>
<td>n – 15x</td>
<td>RSS, scoliosis contractures</td>
</tr>
<tr>
<td>FHL1opathy</td>
<td>Distal = proximal, hypertrophy, SPS</td>
<td>CB</td>
<td>Insufficiency</td>
<td>n – 10x</td>
<td>RSS, scoliosis contractures</td>
</tr>
<tr>
<td>ZASPopathy</td>
<td>Distal &gt; proximal hand muscle atrophy</td>
<td>DCM, CB</td>
<td>Insufficiency</td>
<td>n – 6x</td>
<td>Neuropathy</td>
</tr>
<tr>
<td>Plectinopathy</td>
<td>Distal &gt; proximal</td>
<td></td>
<td></td>
<td>n – 5x</td>
<td>EBS, nail dystrophy</td>
</tr>
</tbody>
</table>

Myofibrillar Myopathies: A Clinical and Myopathological Guide
Rolf Schröder, MD¹; Benedikt Schoser, MD²

Brain Pathology 19 (2009) 483–492
• Clinically, develops later in life (7-77 years of age) with slowly progressive muscle weakness, from distal to proximal lower extremities.

• Peripheral neuropathy and cardiomyopathy are associated features in 15% to 30% of patients.

• Cardiac involvement is more prevalent in mutations that cause childhood-onset MFM.

• Although the RCM can be the first clinical manifestation of the disease, the skeletal muscle is always structurally affected, even in the absence of clinically overt myopathy.

Associated features include sinus node dysfunction, atrioventricular block, supraventricular and ventricular tachycardias, heart failure, and sudden death.
Male, 22 years-old, family history negative for myopathy or cardiomyopathy, CMP with restrictive pattern and AVB
Arrhythmogenic Cardiomyopathy

Family of diseases that feature structural myocardial abnormalities identified by macro- and microscopic pathological examination besides cardiac imaging and ventricular arrhythmia.

Definition and treatment of arrhythmogenic cardiomyopathy: an updated expert panel report
Explanted heart, 23 years old female

- ECG: sinus rhythm in absence of repolarization and depolarization abnormalities.
- **Mild form of ataxia** diagnosed in childhood. Genetic screening for Friedreich and spinocerebellar ataxia (SCA) genes had been done with negative results.
- **Serum lactate level slightly increased** (3.70 mM; control < 2.2 mM).
Whole exome sequencing detected two heterozygous variants (one truncating and one missense mutation) in the gene for mitochondrial translation factor EF-TS
Marked decrease of the mutant EF-Ts protein in cardiac tissue from the proband confirm the pathogenicity of the mutation.

Novel compound mutations in the mitochondrial translation elongation factor (TSFM) gene cause severe cardiomyopathy with myocardial fibro-adipose replacement
Conclusions

• The heart is commonly involved in most cases of NMDs with a wide spectrum of phenotypes

• Cardiomyopathies can be the first or predominant manifestations of NMDs.

• Simple biomarkers (e.g., serum creatine kinase, lactic acidemia) should be systematically tested because they can provide preliminary clues for exploring skeletal muscle disease

• Pathologists play a major role in unraveling the specific etiology, provided that a detailed diagnostic flowchart, including both morphologic and molecular analysis of heart muscle, is followed.
Department of Radiological, Oncological and Pathological Sciences, Sapienza University of Rome

Collaborations:

Department of cardiac Surgery and Transplantation, San Camillo-Forlanini Hospital, Rome

Wellcome centre for Mitochondrial Research, institute of Neuroscience, Newcastle University