Cardiac Involvement of Neuromuscular Disorders in Children

Rik De Decker
Cardiology
Red Cross Children’s Hospital
A first emergency...

- 12 yr old boy in ward B2, RXH
- known DMD
- sudden deterioration with ?pneumonia
- cardiomegaly on CXR
- in severe CCF
- died 1 week later of severe cardiomyopathy
...and listed by their implicated gene(s)

<table>
<thead>
<tr>
<th>Table 1 Genetic forms of muscular dystrophy grouped by molecular pathogenesis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene product (gene)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Dystrophin and associated proteins</strong></td>
</tr>
<tr>
<td>Dystrophin (DMD)</td>
</tr>
<tr>
<td>α-sarcoglycan (SGCA)</td>
</tr>
<tr>
<td>β-sarcoglycan (SGCB)</td>
</tr>
<tr>
<td>γ-sarcoglycan (SGCG)</td>
</tr>
<tr>
<td>δ-sarcoglycan (SGCD)</td>
</tr>
<tr>
<td><strong>Proteins that affect sarcomere integrity</strong></td>
</tr>
<tr>
<td>Telethonin (TCAP)</td>
</tr>
<tr>
<td>Titin (TTN)</td>
</tr>
<tr>
<td>Myotilin (TTID)</td>
</tr>
<tr>
<td><strong>Membrane and extracellular proteins and associated putative enzymes</strong></td>
</tr>
<tr>
<td>Laminin α2 (LAMA2)</td>
</tr>
<tr>
<td>Integrin α7 (ITGA7)</td>
</tr>
<tr>
<td>Fukutin (FCMD)</td>
</tr>
<tr>
<td>Protein O-linked mannose β 1,2-N-acetyl-glucosaminyltransferase (POMGnT1)</td>
</tr>
<tr>
<td>Protein-O-mannosyltransferase 1 (POMT1)</td>
</tr>
<tr>
<td>Fukutin related protein (FKRP)</td>
</tr>
<tr>
<td>Like-acetyl-glycosyltransferase (LARGE)</td>
</tr>
<tr>
<td><strong>Proteins of the nuclear membrane</strong></td>
</tr>
<tr>
<td>Lamin A/C (LMNA)</td>
</tr>
<tr>
<td>Emerin (EMD)</td>
</tr>
<tr>
<td><strong>Proteins associated with muscle repair or protein turnover</strong></td>
</tr>
<tr>
<td>Dysferlin (DYSF)</td>
</tr>
<tr>
<td>Calpain-3 (CAPN3)</td>
</tr>
<tr>
<td>Caveolin-3 (CAV3)</td>
</tr>
<tr>
<td>Tripartite motif containing protein 32 (TRIM32)</td>
</tr>
</tbody>
</table>

*These genetic defects typically have not been associated with cardiomyopathy, BMD, Becker muscular dystrophy; CMD, congenital muscular dystrophy; DMD, Duchenne muscular dystrophy; EDMD, Emery–Dreifuss muscular dystrophy; LGMD, limb-girdle muscular dystrophy; NA, not available; WWS, Walker-Warburg syndrome.

The commoner NMDs

- Duchenne and Becker Types
- Emery-Dreifuss Type
- Limb Girdle Type
- Facioscapulo-humeral Type
- Oculopharyngeal Type

Main areas of muscle weakness in different types of dystrophy
Research indicates that disruption of the dystrophin glycoprotein complex … may be the final common pathway leading to myocardial dysfunction and end-stage ventricular failure.
A common pathway: the **DGC**

a macromolecular complex essential to membrane stability and extracellular interaction
The DGC and the loci for NMDs

EDMD
LGMD 1B
DMD
BMD

LGMD
LGMD 21

Gene mutations and cardiac manifestations of the neuromuscular disorders

<table>
<thead>
<tr>
<th>NMD</th>
<th>Gene Mutation</th>
<th>Cardiomyopathy</th>
<th>ECG</th>
<th>Arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Dystrophin</td>
<td>Dilated</td>
<td>Short PR interval, prolonged QT interval, increased QT:PT ratio, Right ventricular hypertrophy, deep Q waves II, III, aVF, %, v6</td>
<td>Increased baseline HR, decreased rate variability, premature ventricular beats (58% of patients by 24 years of age)</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy-female carrier</td>
<td>Dystrophin</td>
<td>Dilated</td>
<td>None</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Becker's muscular dystrophy</td>
<td>Dystrophin</td>
<td>Dilated</td>
<td>Conduction system disease</td>
<td>Similar to DMD</td>
</tr>
<tr>
<td>Emery Dreifuss autosomal dominant or proximal dominant limb-girdle muscular dystrophy IB</td>
<td>Lamin A/C</td>
<td>Dilated</td>
<td>Conduction abnormalities: prolonged PR interval and sinus bradycardia</td>
<td>Atrial fibrillation or flutter and atrial standstill.</td>
</tr>
<tr>
<td>Limb Girdle muscular dystrophy</td>
<td>α, β, γ, δ sarcoglycans</td>
<td>Dilated</td>
<td>Incomplete right bundle-branch block, tall R waves in V1 and V2 or left anterior hemiblock</td>
<td>Ventricular dysrhythmias Uncommon</td>
</tr>
<tr>
<td>Congenital Muscular Dystrophy</td>
<td>Laminin alpha 2</td>
<td>Dilated</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Limb Girdle muscular dystrophy 21</td>
<td>Fukutin</td>
<td>Dilated</td>
<td>AV node and bundle branch block, age at onset late teens and early 2Qs, Conduction abnormalities: prolonged PR interval and sinus bradycardia</td>
<td>Atrial arrhythmias and/or ventricular arrhythmias</td>
</tr>
<tr>
<td>Emery Dreifuss X-linked</td>
<td>Emerin</td>
<td>Rare</td>
<td>Atrial fibrillation or flutter and atrial standstill.</td>
<td></td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>Frataxin gene</td>
<td>Hypertrophic</td>
<td>T wave inversion, left axis deviation and repolarization abnormalities</td>
<td>Ventricular arrhythmias</td>
</tr>
<tr>
<td>Myotonic dystrophy type 1, infantile</td>
<td>Myotonic dystrophy protein kinase gene</td>
<td>Hypertrophic</td>
<td>Conduction disease, Prolonged PR interval, widening of the QRS complex</td>
<td>Atrial fibrillation and flutter, complete heart block</td>
</tr>
<tr>
<td>Myotonic dystrophy type 1</td>
<td>Myotonic dystrophy protein kinase gene</td>
<td>LV noncompaction</td>
<td>Conduction disease, Prolonged PR interval, widening of the QRS complex</td>
<td>Atrial fibrillation and flutter, complete heart block</td>
</tr>
</tbody>
</table>
Duchenne muscular dystrophy
Guillaume-Benjamin-Amand Duchenne (de Boulogne)
1806 - 1875
Cardiomyopathy!

- Shoulders and arms are held back awkwardly when walking
- Sway back
- Weak butt muscles (hip straighteners)
- Knees may bend back to take weight
- Thick lower leg muscles (the muscle is mostly fat, and not strong)
- Tight heel cord (contracture) child may walk toes
- Belly sticks out due to weak belly muscles (child is poor at sit-ups)
- Thin, weak thighs (especially front part)
- Poor balance; falls often
- Awkward clumsy if walking
- Weak muscles in front of leg cause “foot drop” and tip toe contractures
The presence of clinical heart failure can be difficult to ascertain in patients with generalized neuromuscular weakness, because respiratory and peripheral myopathic findings can mimic heart failure symptoms.
By 20 yrs of age

• 80-90% of patients with Duchenne MD and
• 50% of patients with Becker MD
  will have *echocardiographic* evidence of a dilated cardiomyopathy
• 50% of DMD patients will have *clinical* signs of heart failure.
• BMD patients by 40yrs
LV dysfunction shortens life significantly

Echo of DMD cardiomyopathy
Echo of DMD cardiomyopathy
The electrocardiogram

“a curious question”
The electrocardiographic abnormalities in Duchenne dystrophy have been regarded as a manifestation of the dystrophic process in the myocardium.

This view, however, fails to explain two fundamental facts in this form of muscular dystrophy:

1. the absence of the symptoms of heart failure and
2. the uniform, typical electrocardiographic pattern.

The predominant view is that the depressed motor activity of the patients protects them against the onset of heart failure.

Slucka C Circulation 1968;38:933-940
Early interpretations of the ECG changes of DMD

106pts, 3-29yr old

“seen no relation between the type of electrocardiographic abnormalities and the duration of the disease or severity of the condition ... and immobilization.”

Slucka C Circulation 1968;38:933-940
LAD, rSR’s’, RBBB
RAD, rSR’ pattern, dom R wave in V1, poor R wave progression, upright T in V1...
Spectrum of ECG changes in DMD

Not correlated to dystrophin gene mutations

Deep Q waves in anterolateral leads (I, aVL, V4-6) in inferior leads (II, III, aVF)
Abnormal R/S ratio in V1
Tall R wave in V1
Shortened PR interval
High frequency notches on QRS
Low RV5+SV1
Sinus tachycardia
High RV5+SV1
Tall P wave in II
Right axis deviation
Left axis deviation
PSVT
Prolonged QTc interval

ECG abnormalities per age groups

No significant difference between age groups

ECG and DCM

ECG abnormalities correlated well with the presence of existing DCM, with 94% of patients with DCM having an abnormal ECG vs. 44% of those without DCM.

Interestingly in many patients, ECG abnormalities preceded the development of DCM by an average of 3.7 years before overt echocardiographic evidence of cardiomyopathy.

Can an ECG predict DCM?

<table>
<thead>
<tr>
<th>ECG abnormality</th>
<th>Number (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left axis deviation</td>
<td>30 (8)</td>
<td>18</td>
<td>97</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td>8 (2)</td>
<td>4</td>
<td>98</td>
<td>.12</td>
</tr>
<tr>
<td>Intraventricular conduction delay</td>
<td>31 (8)</td>
<td>22</td>
<td>98</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Right ventricular hypertrophy</td>
<td>78 (21)</td>
<td>34</td>
<td>86</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td>76 (20)</td>
<td>32</td>
<td>90</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Biventricular hypertrophy</td>
<td>26 (7)</td>
<td>19</td>
<td>90</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Abnormal Q wave infero lateral</td>
<td>21 (5)</td>
<td>15</td>
<td>96</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ST-segment depression</td>
<td>37 (10)</td>
<td>20</td>
<td>97</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>T-wave inversion infero laterally</td>
<td>2 (1)</td>
<td>98</td>
<td>100</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Nonspecific T-wave abnormalities</td>
<td>106 (28)</td>
<td>79</td>
<td>94</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Any repolarization abnormality</td>
<td>131 (35)</td>
<td>69</td>
<td>90</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Borderline prolonged QT interval</td>
<td>4 (1)</td>
<td>98</td>
<td>100</td>
<td>.59</td>
</tr>
<tr>
<td>Prolonged QT interval</td>
<td>4 (1)</td>
<td>98</td>
<td>100</td>
<td>.31</td>
</tr>
<tr>
<td><strong>Any ECG abnormality</strong></td>
<td><strong>269 (71)</strong></td>
<td><strong>96</strong></td>
<td><strong>40</strong></td>
<td><strong>&lt;.01</strong></td>
</tr>
</tbody>
</table>

96% sensitivity
Survival from DCM based on ECG abnormalities at presentation

ECG abnormalities at presentation correlate strongly with the risk of having or developing DCM in the ensuing years.

What’s so curious...?
78 DMD pts younger than 6yo, none on steroids

- 78% had ECG changes, only 1 patient had echo changes
- early ECG changes occur in the absence of myocardial inflammation or fibrosis
- the early ECG phenotype is not a manifestation of dystrophin deficient cardiomyocytes but rather dystrophin deficient Purkinje fibers
- ECG may be a more sensitive diagnostic test than echocardiography for detecting early manifestations of DMD associated cardiac disease
- An abnormal ECG in a young boy with skeletal muscle weakness or gross motor delay should prompt testing for a dystrophinopathy
- Earlier diagnosis may improve clinical outcomes in an era where corticosteroid treatment is being initiated at a young age

The effect of steroids on the heart

• The natural history of the disease has been altered by the use of corticosteroids, which have demonstrated preservation and improvement of cardiac, pulmonary, and motor functions.

• Prolonged lifespan of these patients puts more stress on the heart, with a larger number dying of cardiac causes.

• The most important finding in this study is that there is no difference between ECG findings in patients with CMO and those without CMO.

Thrush PT Am J Cardiol 2009;103:262–265
But remember...

EDITORIAL COMMENTARY

The electrocardiogram: A useful screening test for cardiac involvement in some but not all of the muscular dystrophies

William J. Groh, MD, MPH

From the Department of Medicine, Division of Cardiology, Krannert Institute, Indiana University, Indianapolis, Indiana.
Cardiac screening recommendations for neuromuscular disorders

<table>
<thead>
<tr>
<th>Neuromuscular Disorder</th>
<th>Echocardiogram</th>
<th>ECG</th>
<th>24 hour Holter Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>Initial at 6 years of age, biannually until 10 years of age, then annually</td>
<td>Initial at 6 years of age, biannually until 10 years of age, then annually</td>
<td>As indicated</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy female carrier</td>
<td>Initial at 16 years then every 5 years</td>
<td>Initial at 16 years then every 5 years</td>
<td>As indicated</td>
</tr>
<tr>
<td>Becker’s muscular dystrophy</td>
<td>Initial at 10 years, then biannually</td>
<td>Initial at 10 years, then biannually</td>
<td>As indicated</td>
</tr>
<tr>
<td>Emery-Dreifuss autosomal dominant</td>
<td>At diagnosis and annually</td>
<td>At diagnosis and annually</td>
<td>As indicated</td>
</tr>
<tr>
<td>Limb Girdle muscular dystrophy, sarcoglycans</td>
<td>At diagnosis and annually</td>
<td>At diagnosis and annually</td>
<td>As indicated</td>
</tr>
<tr>
<td>Limb Girdle muscular dystrophy 21, Iukutin</td>
<td>At diagnosis</td>
<td>At diagnosis</td>
<td>As indicated</td>
</tr>
<tr>
<td>Congenital Myopathy</td>
<td>At diagnosis and annually</td>
<td>At diagnosis and annually</td>
<td>As indicated</td>
</tr>
<tr>
<td>Emery-Dreifuss x-linked</td>
<td>At diagnosis, then every five years</td>
<td>At diagnosis and annually</td>
<td>As indicated</td>
</tr>
<tr>
<td>Myotonic dystrophy type 1, infantile</td>
<td>At diagnosis</td>
<td>At diagnosis and annually</td>
<td>As indicated</td>
</tr>
<tr>
<td>Myotonic dystrophy type 1</td>
<td>At diagnosis</td>
<td>At diagnosis and annually</td>
<td>As indicated</td>
</tr>
</tbody>
</table>

Hsu DT. Paediatric Respiratory Reviews 11 (2010) 35–38
Cardiac screening:

All with the potential to have NMD

- ECG
- 24hr Holter ECG
- Echo (inc myocardial tissue Doppler echo)
- CMR

- [cardiac biomarkers: BNP, Troponin, CPK]
Treatment
Perindopril effect on LVEF

Survival of patients on perindopril

Group 1 (initially allocated to perindopril)
26 of 28 pts alive

Group 2 (initially allocated to placebo)
19 of 29 pts alive

$P = .0125$ (log-rank test)

Treatment recommendations

107th ENMC International Workshop: the management of cardiac involvement in muscular dystrophy and myotonic dystrophy

- **Echo** and **ECG**
  - every 2 years to age 10
  - annually after age 10
- **respiratory function**
- **ACE inhibitors** and **beta blockers**
- **steroid treatment**
- rarely fit for cardiac transplantation

Bushby K et al. Neuromuscular Disorders 13 (2003) 166–172
There is an urgent need ... to determine whether treatment of patients with cardiomyopathy, prior to the onset of symptoms, improves prognosis.

There is also unpublished evidence to suggest that treatment even before any impairment of ventricular function is detectable on echocardiogram, may delay the onset and progression of cardiomyopathy.
Anaesthesia
Anaesthetic complications of NMDs

- intraoperative heart failure
- rhabdomyolysis and hyperkalaemic cardiac arrest
  - with or without succinylcholine administration
- malignant hyperthermia
- post-operative respiratory failure

Gurnaney H et al suggest:

“All children presenting for administration of general anesthesia or sedation should be screened for motor milestones.

...signs of motor loss or delay should prompt suspicion of a subclinical myopathy and should warrant neurological evaluation and genetic testing before elective surgery.”

In conclusion

ALL boys with undiagnosed motor delay deserve an ECG

ANY abnormality on that ECG is suspicious

ALL boys with motor delay and a suspicious ECG deserve full screening for a cardiomyopathy and an NMD
Thank you for your attention!
See you at the World Congress next week!
Epigenetics to the rescue?

Figure 2. Schematic illustration of the epigenetic status of HDACi-responsive genes in muscle progenitors exposed to differentiation cues.