Cardiac involvement in patients with myotonic dystrophy type 1

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Purpose

• Background for investigating cardiac involvement in patients with DM1
• Method
• Results
• Clinical relevance
Case

- 11-year-old girl
- Previously healthy
- Cardiac arrest
Case

Autopsy
- Heart: normal weight and chamber dimensions

Microscopy
- Pronounced fat-infiltration and fibrosis
Case

Family interview
- Vague muscular symptoms and cataract surgery
- Cousin: severe myotonic dystrophy type 1 (DM1)

Genetic examination
- Positive for DM1
Case

Cardiac investigations
- Incomplete right bundle branch block

Prophylactic procedure
- Implantable cardioverter defibrillator

Follow-up
- Brother and father: several shocks due to ventricular tachycardia
Aims

- Describe the degree and progression of cardiac involvement in patients with:
  - Myotonic dystrophy type 1 (DM1)
- Propose recommendations for cardiac management
Cardiac involvement

Conduction abnormalities (ECG and Holter)
- Atrio-ventricular block
- Bundle branch block
- Fascicular block

Arrhythmias (ECG and Holter)
- Ventricular premature contractions
- Supraventricular arrhythmias
- Ventricular arrhythmias

Structural changes (Echocardiography and Magnetic resonance)
- Abnormal wall thickness and/or chamber dimensions
- Reduced pump function (left ventricular ejection fraction (LVEF))
Myotonic dystrophy type 1

Cardiac manifestations of myotonic dystrophy type 1

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Dystrophia myotonica type 1
Arrhythmia
Left ventricular systolic dysfunction
Sudden cardiac death

A B S T R A C T

Aims: To estimate the degree of cardiac involvement regarding left ventricular ejection fraction, conduction abnormalities, arrhythmia, risk of sudden cardiac death (SCD) and the associations between cardiac involvement and cytosine–thymine–guanine (CTG)-repeat, neuromuscular involvement, age and gender in patients with myotonic dystrophy type 1 (MD1).

Methods and results: A Pub-Med search for the period 1980 to 2010 was performed according to specified criteria. Cardiac parameters including left ventricular ejection fraction (LVEF), conduction abnormalities and arrhythmia were compiled and only studies without ascertainment bias were included. Eighteen studies, 1828 MD1-patients, were included. The prevalence of atrioventricular block grade 1 (AVB1) was 28.2%, QTe>440 ms 22%, QRS>120 ms 19.9%, frequent ventricular premature contractions (VPC) 14.6%, atrial fibrillation/flutter (AF/AFL) 5%, right/left bundle branch block (RBBB/LBBB) 4.4/5.7% and non-sustained ventricular tachycardia (NSVT) 4.1%. Left ventricular systolic dysfunction (LVSD) was reported in 7.2% of the patients.

There was an overall positive association between CTG-repeat size and cardiac involvement and between the degree of neuromuscular and cardiac involvement. Male gender and age were positively associated with arrhythmia and conduction abnormalities.

The prevalence of pacemaker- (PM) and implantable cardioverter defibrillator- (ICD) implantations were 4.1% and 1.1%, respectively.

The risk of SCD in this MD1-population was 0.56% per year.

Conclusion: MD1-patients have a high level of cardiac morbidity and mortality, strongly emphasizing the need of pre-symptomatic screening for arrhythmia and heart failure, as effective and well-documented preventive means are available.

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Myotonic dystrophy type 1

Patients
• 18 studies
• 1828 patients with DM1
• Mean age 40 years

Cardiac involvement
• Conduction disturbances: AVB grade 1 (28%)
• Arrhythmias: Atrial fibrillation/flutter (5%)
• Reduced pump function: LVEF ≤ 50% (7.2%)

Sudden cardiac death: 3-fold increased incidence rate
Aims

• To investigate the prevalence of cardiac involvement in patients with DM1 assessed by ECG, Holter-monitoring and echocardiography

• To assess the association between abnormal findings on each of the used modalities

• Secondly, to assess whether specific intervals between cardiac follow-up could be recommended
Study population
• DM1-patients > 18 years followed at the Neuromuscular Clinic, RH (n=129)

Cardiac investigations
• ECG, Echocardiography (incl. GLS) and Holter-monitoring

Muscle strength
• Handgrip and ankle dorsal flexion

Blood samples
• NT-proBNP, creatinine kinase and myoglobin
• Screening for liver, renal and thyroid diseases
Conduction abnormalities and reduced pump function

Table 5. Abnormal ECG- and echocardiographic findings in patients with DM1

<table>
<thead>
<tr>
<th>ECG*</th>
<th>n (%)</th>
<th>Men (n)</th>
<th>Women (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVB grade I</td>
<td>30 (23.6)</td>
<td>14</td>
<td>16</td>
<td>0.68</td>
</tr>
<tr>
<td>IRBBB</td>
<td>11 (8.8)</td>
<td>7</td>
<td>4</td>
<td>0.53</td>
</tr>
<tr>
<td>RBBB</td>
<td>7 (5.5)</td>
<td>1</td>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>LBBB</td>
<td>4 (3.2)</td>
<td>1</td>
<td>3</td>
<td>0.37</td>
</tr>
<tr>
<td>Prolonged QTc</td>
<td>9 (7.2)</td>
<td>5</td>
<td>4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Echocardiography†</th>
<th>n (%)</th>
<th>Median (range)</th>
<th>Men (n)</th>
<th>Women (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤ 50%</td>
<td>26 (20.6)</td>
<td>48 (33-50)</td>
<td>18</td>
<td>8</td>
<td>0.05</td>
</tr>
<tr>
<td>IVSD &gt; 11 mm</td>
<td>14 (11.4)</td>
<td>13 (11-17)</td>
<td>9</td>
<td>5</td>
<td>0.27</td>
</tr>
<tr>
<td>LVIDD &gt; 55 mm</td>
<td>6 (4.9)</td>
<td>57 (56-60)</td>
<td>6</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>LAEDVi &gt; 34 ml/m²</td>
<td>9 (8.3)</td>
<td>36 (35-40)</td>
<td>7</td>
<td>2</td>
<td>0.09</td>
</tr>
<tr>
<td>GLS &gt; -15.9%</td>
<td>20 (21.7)</td>
<td>-14 (-15 to -10)</td>
<td>13</td>
<td>7</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*ECG was available in 127 patients
†Echocardiography was performed in 125 patients. Parameters were not available in all patients; percent is calculated from the actual number of observations.

Petri et al, Int J Cardiol 2014
# Arrhythmias

Table 6: Holter-findings in patients with DM1 and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>DM1 (n= 122)</th>
<th>Controls (n= 285)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD) (yrs)</strong></td>
<td>44 (14.7)</td>
<td>58 (2.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>AVB grade II, n (%)</strong></td>
<td>7 (5.6)</td>
<td>4 (1.4)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>AF/AFL, n (%)</strong></td>
<td>5 (4.1)</td>
<td>4 (1.4)</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>SVT, n (%)</strong></td>
<td>9 (7.3)</td>
<td>24 (8.4)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>VPC &gt;30/h, n (%)</strong></td>
<td>7 (5.8)</td>
<td>17 (6.0)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>NSVT, n (%)</strong></td>
<td>5 (4.1)</td>
<td>21 (7.3)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

AF/AFL: atrial fibrillation/flutter  
AVB grade I/II: atrio-ventricular block grade I/II  
NSVT: non-sustained ventricular tachycardia  
SVT: supraventricular tachycardia  
VPC: ventricular premature contractions  

*Petri et al, Int J Cardiol 2014*
**ECG as a predictor of cardiac involvement??**

<table>
<thead>
<tr>
<th>Holter</th>
<th>ECG</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>67</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

P value = 0.08

<table>
<thead>
<tr>
<th>Echocardiography</th>
<th>ECG</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EF&gt;50</td>
<td>Normal</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>EF≤50</td>
<td>Normal</td>
<td>14</td>
<td>12</td>
</tr>
</tbody>
</table>

P value = 0.37

*Petri et al, Int J Cardiol 2014*
Cardiac involvement and muscle strength

Petri et al, Int J Cardiol 2014
Electrocardiographic Abnormalities and Sudden Death in Myotonic Dystrophy Type 1

METHODS
We assessed whether the electrocardiogram (ECG) was useful in predicting sudden death in 406 adult patients with genetically confirmed myotonic dystrophy type 1. A patient was characterized as having a severe abnormality if the ECG had at least one of the following features: rhythm other than sinus, PR interval of 240 msec or more, QRS duration of 120 msec or more, or second-degree or third-degree atrioventricular block.

RESULTS
A severe ECG abnormality (relative risk, 3.30; 95% confidence interval [CI], 1.24 to 8.78) and a clinical diagnosis of atrial tachyarrhythmia (relative risk, 5.18; 95% CI, 2.28 to 11.77) were independent risk factors for sudden death.
Reduced pump function

- Left ventricular systolic dysfunction (LVEF ≤ 50%) was non-existing before the age of 40 years.

Bhakta et al, Am Heart J 2010
Cardiac involvement in myotonic dystrophy: a nationwide cohort study

Marie Lund, Lars Jorge Diaz, Mattis Flyholm Ranthe, Helle Petri, Morten Duno, Inger Juncker, Hans Eiberg, John Visser, Henning Bundgaard, Jan Wohlfahrt, and Mads Melbye

Aims
To quantify the association between myotonic dystrophy (DM) and cardiac disease in a nationwide cohort.

Methods and results
We identified a nationwide cohort of 1,146 DM patients (period 1977–2011) using the National Patient Registry (NPR) and a subcohort of 485 patients who had undergone genetic testing for DM1. Information on incident cardiac diseases was obtained from the NPR. We estimated standardized incidence ratios (SIRs) of cardiac disease compared with the background population, overall and according to selected diagnostic subgroups (cardiomyopathy, heart failure, conduction disorders, arrhythmias, and device implantation). In the DM cohort, SIR for any cardiac disease was 3.42 (95% confidence interval CI 3.01–3.86); for a cardiac disease belonging to the selected subgroups 6.91 (95% CI 5.93–8.01) and for other cardiac disease 2.59 (95% CI 2.03–3.25). For a cardiac disease belonging to the selected subgroups, the risk was particularly high in the first year after DM1 diagnosis [SIR 15.4 (95% CI: 10.9–21.3)] but remained significantly elevated in subsequent years [SIR 6.07 (95% CI 5.11–7.16)]. The risk was higher in young cohort members (e.g., 20–39 years: SIR 18.1 (95% CI: 12.3–25.8)) compared with older age groups (e.g., 60–79 years: SIR 3.99 (95% CI: 2.98–5.23)) but remained significantly increased in all age categories. Results were similar in separate analyses of the genetically confirmed DM1 patients.

Conclusion
Myotonic dystrophy is strongly associated with cardiac disease. The risk is pronounced in the young and remains elevated throughout life, stressing the importance of lifelong cardiac follow-up from time of DM diagnosis.

Keywords
Myotonic dystrophy • Cardiac disease • Epidemiology
Heart muscle involvement

*Aims*

- To describe the prevalence and localisation of myocardial fibrosis on magnetic resonance in patients with DM1

- To assess the association between myocardial fibrosis and abnormal findings on ECG, Holter-monitoring and echocardiography
Study population
• 30 patients with DM1
  Group I: patients with abnormal findings on ECG or Holter-monitoring
  Group II: patients without abnormal findings on ECG or Holter-monitoring

Cardiac investigations
• Cardiac magnetic resonance (CMR)
12 patients (40%, 9 men) had myocardial fibrosis
Associations between MF and other cardiac abnormalities

CMR
- Patients with myocardial fibrosis:
  - Trend toward reduced pump function
  - Higher left ventricular mass
  - Larger left atrium

ECG
- No association with myocardial fibrosis except IRBBB

Holter-monitoring and echocardiography
- No association with myocardial fibrosis
DM1 and myocardial fibrosis

- Prevalence ranging from 10 - 40%
  - De al, Eur Heart J 1995
  - Nazarian et al, Magn Reson Med 2010
  - Verhaert et al, Circ Cardiovasc Imaging 2011
  - Turkbey et al, Heart Rhythm 2012

- Correlation between myocardial fibrosis and QRS-interval
  - Nazarian et al, Magn Reson Med 2010

Histology verified fibrosis

- Autopsy/biopsi findings in DM1 patients
- Pathology studies with animal models of DM1
  - Nguyen et al, J Am Coll Cardiol 1988
  - Bharati et al, Chest 1984
  - Wang et al, J Clin Invest 2007
Prognostic importance of myocardial fibrosis

- Non-ischaemic cardiomyopathies:
  - Heart failure and cardiac death
  - Sudden cardiac death and ventricular arrhythmias

  Assomull et al, JACC 2006
  Segawa, Heart Vessels Suppl 1990
  Nazarian, Circulation 2005

- Hypertrophic cardiomyopathy: arrhythmia and sudden cardiac death

  Chan et al, Circulation 2014
  Rubinshtein et al, Circ Heart Fail 2010
  Kwon et al, JACC 2009

- Fabry Disease: malignant arrhythmias

  Krämer, Am J Cardiol, 2014

- Myocardial infarction: predictor of ventricular tachycardia

  Bello, J Am Coll Cardiol 2005
Conclusion

- Conduction abnormalities, arrhythmias and/or reduced pump function was observed in more than 50% of the patients

- Reduced pump function was prevalent and not age-dependent

- ECG is not sufficient to detect cardiac involvement

- Global longitudinal strain: marker of subclinical myocardial dysfunction

- Myocardial fibrosis had a high prevalence in patients with DM1 (40%)

- Myocardial fibrosis was not detectable on ECG, Holter-monitoring and echocardiography

- CMR might prove to be a valuable tool for early detection of cardiac involvement and for risk stratification in DM1
DM1 - Clinical implications

- Conduction abnormalities and arrhythmias were predominant findings
- Reduced pump function was not associated with age
- A normal ECG could not exclude cardiac involvement
- The risk of cardiac involvement remains increased throughout life

Proposals for cardiac management in asymptomatic DM1 patients

<table>
<thead>
<tr>
<th>Time</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| At diagnosis | ECG  
             Holter  
             Echocardiography |
| 2 years | ECG  
             Holter |
| 4 years | ECG  
             Holter  
             Echocardiography |
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Patients

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http://nbv.cardio.dk/arvelige-hjertesygdomme
Muscular dystrophies

- Rare inherited muscle diseases
- Progressive weakness and atrophy of the skeletal muscles
- Replacement of skeletal and myocardial muscle tissue by fat and fibrosis
- Degree and type of skeletal muscle involvement varies
- Increased risk of cardiac involvement