Myotonic Muscular Dystrophy: Global Impact - Cardiac Involvement

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Topic: Myotonic Muscular Dystrophy: Global Impact - Cardiac

Disclosure

Speakers Bureau: None

Unlabeled / Unapproved Uses Disclosure: The use of primary prevention ICDs in myotonic patients without LV dysfunction is investigational only.
Myotonic Muscular Dystrophy: Global Impact – Cardiac Involvement

Learning Objectives

1. Overview the cardiac manifestations that occur in patients with the myotonic muscular dystrophies
2. Know the genetic basis of myotonic dystrophy and the relationship between the genetic abnormalities and the cardiac phenotype
3. Evaluate the data looking at predictors of sudden death in patients with myotonic dystrophy
4. Appreciate the role and the continued uncertainties of arrhythmia treatment in patients with myotonic dystrophy
# Muscular Dystrophies associated with cardiac abnormalities

## Table 8. Frequency of Events in Neuromuscular Disorders Associated With Heart Disease

<table>
<thead>
<tr>
<th>Muscle Disorder</th>
<th>Inheritance</th>
<th>HB</th>
<th>VA</th>
<th>CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne</td>
<td>X-linked</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Becker</td>
<td>X-linked</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>X-linked dilated CM</td>
<td>X-linked</td>
<td>—</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Limb-girdle 1B</td>
<td>AD</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Limb-girdle 2C-2F</td>
<td>AR</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Myotonic MD</td>
<td>AD</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Emery-Dreifuss MD and associated disorders</td>
<td>X-linked, AD, AR</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>
Myotonic Dystrophy

- Dystrophia myotonica (DM), Steinert’s disease
- Autosomal dominant neuromuscular disease (anticipation)
  - Reflex and percussion myotonia
  - Weakness and progressive atrophy of skeletal muscle
- Systemic manifestations
  - Early balding
  - Gonadal atrophy
  - Cataracts
  - Cognitive abnormalities (severely affected)
  - Cardiac involvement
- Most common of the adult MD (prevalence 1 / 7500)
- Subcategorized into DM1 (90%+) and DM2 by genetic findings

Steinert HGW: Deutsche Zeitschrift für Nervenheilkunde 1909
Cardiac Involvement in Myotonic Dystrophy

Griffith, 1911:
a 48-year-old man with an abnormal pulse described as:

“Usually infrequent…. often below 50 and on some occasions fell to 40…. and sometimes as low as 36.”

Griffith TW: Quart J Med 1911
Cardiac Involvement in Myotonic Dystrophy

Maas and Zondek, 1920:
a 45-year-old man with dystrophia myotonica and:

Changes of the cardiovascular system manifested by hypotension, bradycardia, distant heart sounds, generalized cardiac enlargement, and prolongation of the P-R interval.

Maas O, Zondek H: Ztschr f d ges neurol u psychiat 1920
Cardiac Involvement in Myotonic Dystrophy

Table I. Summary of Electrocardiographic Changes

<table>
<thead>
<tr>
<th></th>
<th>CASES</th>
<th>PER CENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>27</td>
<td>31.7</td>
</tr>
<tr>
<td>Altered P-R interval</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-R of 0.20 second</td>
<td>7</td>
<td>48.3</td>
</tr>
<tr>
<td>With inverted T wave</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>P-R over 0.20 second</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>With prolonged QRS and intermittent 2nd block</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>With prolonged QRS</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>With prolonged QRS and transient flutter</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>With transient flutter</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>With low T wave</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Prolonged QRS</td>
<td>10</td>
<td>11.7</td>
</tr>
<tr>
<td>Transient auricular flutter</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Transient auricular fibrillation</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Left ventricular preponderance</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Nonspecific S-T changes</td>
<td>1</td>
<td>1.2</td>
</tr>
<tr>
<td>Low T waves</td>
<td>3*</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>85†</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table II. Distribution of Abnormal Electrocardiograms According to Age

<table>
<thead>
<tr>
<th>AGE (YEARS)</th>
<th>-20</th>
<th>21-25</th>
<th>26-30</th>
<th>31-35</th>
<th>36-40</th>
<th>41-45</th>
<th>46-50</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of electrocardiograms</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>15</td>
<td>12</td>
<td>20</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Per cent of abnormality</td>
<td>20</td>
<td>60</td>
<td>77.7</td>
<td>80</td>
<td>50</td>
<td>75</td>
<td>66.6</td>
<td>75</td>
</tr>
</tbody>
</table>
Cardiac Involvement in Myotonic Dystrophy

However, the high incidence of electrocardiographic abnormalities, the type of alteration, their uniform distribution among the various age groups, coupled with other, but less common cardiac abnormalities and a conspicuous lack of antecedent history of one of the more common etiological agents, suggest strongly that the alterations of the cardiovascular system are an integral part of dystrophia myotonica rather than a coincidental finding.

Charles Fisch (1920-2002)

THE HEART IN DYSTROPHIA MYOTONICA

Charles Fisch, M.D.*
Indianapolis, Ind.

Fisch C: Am Heart J 1951
Cardiac Involvement in DM (1996)

Cardiac Involvement
- Cardiac muscle fibrosis especially targeting the conduction system => manifests primarily as arrhythmias
- Dilated cardiomyopathy – rare?
- Arrhythmias: Heart block, atrial and ventricular arrhythmias
- Sudden presumptively arrhythmic death occurs, frequency?
- Mechanism of sudden death (bradycardia?, tachycardia?)

Management of Arrhythmias in DM1 unclear
- Neurology referral to cardiology? When? Risk factors?
- Prophylactic pacemaker implant?
- North American data - single site studies, limited follow-up
- Cardiology studies: referral bias
The Arrhythmias in DM1 Registry
Aims (1996)

In DM1:

- To determine the natural history and risk factors for cardiac and arrhythmia involvement
- To develop cardiac referral guidelines for neurologists
- To study interventions to improve arrhythmia diagnosis
- To study interventions to improve arrhythmia treatment

Long-Term Goal:

To decrease the unacceptable rates of sudden death and arrhythmia morbidity in DM1
The Arrhythmias in DM1 Registry

Methods (1996)

- Multicenter prospective, observational cohort - MDA Clinics
- Enroll adult patients with clinical diagnosis of DM
- Registry data collected
  - Questionnaires – neurological, cardiac history
  - Muscular disability (by neurologists)
  - Confirmation of DM1 by genetic testing (peripheral leukocytes)
  - 12-Lead ECG (q Yr), 24-hr ambulatory ECG, echocardiography

- Registry Follow-Up (study observed did not recommend or intervene)
  - Follow-up on yearly basis or with event
  - Event – death, sudden death, unexplained syncope, pacemaker or ICD implantation, arrhythmia, heart failure, etc.
Recruiting Sites in the Arrhythmias in DM1 Study
The Arrhythmias in DM1 Registry:

Patients: (at 23 sites, with genetic confirmation)

- IRB: February 1997
- 1st Patient: April 1997
- 85
- 258
- 301
- 339
- 362
- 388
- 393
- 401
- 406

Closed to enrollment

[cumulative patients]
Electrocardiographic Abnormalities and Sudden Death in Myotonic Dystrophy Type 1

William J. Groh, M.D., M.P.H., Mriam R. Groh, M.S., Chandan Saha, Ph.D., John C. Kincaid, M.D., Zachary Simmons, M.D., Emma Caflansen, M.D., Rahman Pourmand, M.D., Richard F. Otten, M.D., Deepak Bhakta, M.D., Girish V. Nair, M.D., M.S., Mohammad M. Marashdeh, M.D., Douglas P. Zipes, M.D., and Robert M. Pascuzzi, M.D.

ABSTRACT

BACKGROUND

Sudden death can occur as a consequence of cardiac-conduction abnormalities in the neuromuscular disease myotonic dystrophy type 1. The determinants of the risk of sudden death remain imprecise.

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

Patients with severe abnormalities according to the entry ECG were older than patients without severe abnormalities, had more severe skeletal-muscle impairment, and were more likely to have heart failure, left ventricular systolic dysfunction, or atrial tachycardia. Such patients were more likely to receive a pacemaker or an implantable cardioverter-defibrillator during the follow-up period. During a mean follow-up period of 5.7 years, 81 patients died; there were 27 sudden deaths, 32 deaths from progressive neuromuscular respiratory failure, 5 nonfatal deaths from cardiac causes, and 17 deaths from other causes. Among the 17 patients who died suddenly in whom postcollapse rhythm was evaluated, a ventricular tachycardia was observed in 9. A severe ECG abnormality (relative risk, 3.39; 95% confidence interval [CI], 1.24 to 9.28) and a clinical diagnosis of atrial tachycardia (relative risk, 5.3; 95% CI, 2.28 to 11.77) were independent risk factors for sudden death.

CONCLUSIONS

Patients with adult myotonic dystrophy type 1 are at high risk for arrhythmias and sudden death. A severe abnormality on the ECG and a diagnosis of an atrial tachycardia predict sudden death. (ClinicalTrials.gov number, NCT00622453.)
The Arrhythmias in DM1 Registry Status

- 443 patients with a clinical diagnosis of myotonic dystrophy enrolled at 23 / 25 centers
- 406 patients with a confirmatory genetic test for DM1
- Study entry characteristics:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (18-78)</td>
<td>42 ± 12</td>
</tr>
<tr>
<td>Age at diagnosis, years (0-72)</td>
<td>31 ± 13</td>
</tr>
<tr>
<td>Gender</td>
<td>153 (49.4%) males</td>
</tr>
<tr>
<td>Muscular disability rating (1-5)</td>
<td>3.2 ± 1.0</td>
</tr>
<tr>
<td>1, 2 - No or minimal muscle impairment</td>
<td>107 (26.4%)</td>
</tr>
<tr>
<td>3 - Distal muscle weakness</td>
<td>117 (28.8%)</td>
</tr>
<tr>
<td>4 - Proximal muscle weakness (mild-mod)</td>
<td>155 (38.2%)</td>
</tr>
<tr>
<td>5 - Proximal muscle weakness (Severe)</td>
<td>27 (6.7%)</td>
</tr>
</tbody>
</table>

Mathieu J: Neurology 2001
DM1 - Genetics

- **Chromosome 19q13.3**
  - Amplification of an unstable CTG repeat sequence (38-2000)
  - DM2 (3q12, unstable CCTG amplification)

- **Genetic anticipation**
  - Earlier age of onset and increasingly severe muscle symptoms in succeeding generations
  - Increased number of CTG repeats each generation

Groh WJ: J Cardiovasc Electrophysiol 1999
DM1 - Genetics

Cardiac Pathogenesis?
- Troponin T
- KCNAB1
- Titin
- α-actinin-associated LIM protein
- ZASP
- PKC-mediated
- microRNA (miR-1)

Mankodi A: Circ Res 2005
CTG Length and DM1 Clinical Severity

CTG repeat length
Mean ± SD: 629 ± 386
Range (54 to 1965)
n = 406

Age at Diagnosis

CTG Repeat Length
CTG Length and DM1 Clinical Severity

CTG repeat length
Mean ± SD: 629 ± 386
Range (54 to 1965)
n = 406
CTG Length and Anticipation

CTG Repeat Length (lymphocytes)

Parent
292 ± 287

Offspring
709 ± 358

P = 0.03

n = 61
CTG Offspring – CTG Parent

Paternal Transmission

\( n = 61 \)

Maternal Transmission

CTG Parent
The Electrocardiogram (ECG): A Useful Screening Tool in DM1?

12-lead ECG: impulse formation, conduction, repolarization, arrhythmia

Hypothesis: A severe ECG conduction abnormality will predict a higher risk of sudden death in DM1 patients.

Normal
PR ≤ 200 ms, QRS≤100 ms
Resting 12-lead ECG
Abnormal: 65.1 %
Abnormal PR int: 41.9 %
Abnormal QRS dur: 19.6 %
CTG Length and Cardiac Muscle Involvement

Groh WJ: J Cardiovasc Electrophysiol 2002

n = 372
## DM1 Registry - Follow-up

### Mean 11.2 ± 4.2 years

* n = 406

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Last Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV dysfunction on imaging</td>
<td>9.5%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>7.0%</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>12.1%</td>
</tr>
<tr>
<td>Cardioverter-defibrillator</td>
<td>6.7%</td>
</tr>
<tr>
<td>Sinus node dysfunction</td>
<td>4.1%</td>
</tr>
<tr>
<td>High-degree AVB</td>
<td>5.4%</td>
</tr>
<tr>
<td>Atrial arrhythmia</td>
<td>15.5%</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>3.6%</td>
</tr>
<tr>
<td>Death, non-sudden cardiac</td>
<td>2.1%</td>
</tr>
<tr>
<td>Death, sudden cardiac</td>
<td>10.8%</td>
</tr>
</tbody>
</table>
DM1 Registry - Follow-up
Mean 11.2 ± 4.2 years

n = 406
SURVIVAL AND CTG REPEAT EXPANSION IN ADULTS WITH MYOTONIC DYSTROPHY TYPE 1

WILLIAM J. GROH, MD, MPH,1 MIRIAM R. GROH, MS,1 CHANGYU SHEN, PhD,2 DARREN G. MONCKTON, PhD,2 CYNTHIA L. BOOKIN, MD,3 and ROBERT M. PASCUZZI, MD4

1 Department of Medicine, Division Cardiology, Emannist Institute of Cardiology, Indiana University, 1800 North Capitol, Room E300C, Indianapolis, Indiana 46202, USA
2 Division of Biostatistics, Indiana University, Indianapolis, Indiana, USA
3 Division of Molecular Genetics, Faculty of Biomedical and Life Sciences, University of Glasgow, Glasgow, UK
4 Department of Neurology, Indiana University, Indianapolis, Indiana, USA

Accepted 4 October 2010

ABSTRACT: Introduction: An association is observed between the severity of myotonic dystrophy type 1 (DM1) and the genetic abnormality of cytosine-thymine-guanine (CTG) repeat expansion. It is unknown whether an association exists between survival and CTG repeat expansion. Methods: in an adult 406-patient DM1 cohort, the phenotype, including survival age, was evaluated in relation to CTG repeat expansion. Results: At study entry, age was 42 ± 12 (range 18–78) years, with a CTG repeat length of 629 ± 386 (range 54–1965). An inverse correlation was observed between CTG repeat length and the age at onset and younger DM1 phenotype. Over a follow-up of 9.2 ± 3.1 years, 116 (29.1%) patients died, including 80 of neuromuscular respiratory failure, 41 of cardiac causes, and 17 of non-neuromuscular, non-cardiac causes. There was an inverse relationship between all-cause survival and CTG length (relative risk 5.4 per log repeat, 95% confidence interval 2.9–10.2, P < .001). Conclusion: The data demonstrate a genotype–mortality association in DM1.

Muscle Nerve 43: 646–651, 2011
Electrocardiographic Abnormalities and Sudden Death in Myotonic Dystrophy Type 1

Clinical characteristics and the ECG are independent predictors of sudden cardiac death in DM1

- Age (per SD)
- Atrial Arrhythmia
- ECG with severe conduction disease*
- Pacemaker

*Rhythm other than sinus, or a PR interval ≥ 240 ms, or a QRS duration ≥ 120 ms, or second- or third-degree atrioventricular block.

Pacemaker and Implantable Cardioverter-Defibrillator Use in a US Myotonic Dystrophy Type 1 Population

DEEPAK BHAKTA, M.D.,* CHANGYU SHEN, Ph.D.,† JACK KRON, M.D.,‡ ANDREW E. EPSTEIN, M.D.,§ ROBERT M. PASCUZZI, M.D.,¶ and WILLIAM J. GROH, M.D., M.P.H.*

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**Figure:**

- **Y-axis:** Fraction of Patients with an Antiarrhythmia Device
- **X-axis:** Age - Yr
- **Graphs:**
  - Pacemaker
  - Defibrillator

**Table:**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Pacemaker</th>
<th>Defibrillator</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-30</td>
<td>405</td>
<td>406</td>
</tr>
<tr>
<td>30-40</td>
<td>377</td>
<td>378</td>
</tr>
<tr>
<td>40-50</td>
<td>304</td>
<td>307</td>
</tr>
<tr>
<td>50-60</td>
<td>171</td>
<td>176</td>
</tr>
<tr>
<td>60-70</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>70</td>
<td>19</td>
<td>25</td>
</tr>
</tbody>
</table>

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Bhakta D: J Cardiovasc Electrophysiol 2011
Benefit Pacemaker / ICD

2\textsuperscript{nd} or 3\textsuperscript{rd} –degree AVB
Sudden death / resuscitated VT/VF / ICD Tx
Not a non-sudden death or a DNR

Predictors

PR interval, QRS duration
QRS duration, atrial arrhythmias
Age, wheelchair-bound, heart failure
Myotonic Dystrophies and Cardiac Disease: Summary

1. Patients with myotonic dystrophy are at high risk for cardiac conduction disease, arrhythmias and sudden death.

2. CTG repeat expansion predicts the age at onset of cardiac involvement in a population but has too much variability to assist in an individual patient.

3. A smaller proportion of myotonic patients have heart failure / ventricular systolic dysfunction related to their neuromuscular disease.

Myotonic Muscular Dystrophy: Global Impact - Cardiac Involvement

Questions?