DM 101: UNDERSTANDING THE BASICS

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Myotonic dystrophy (Dystrophia Myotonica)

1. **DM1 and DM2**: 2 types of diseases

2. **Inherited diseases** caused by a genetic abnormality

3. **Multi-systemic diseases**: not only the muscle is affected but multiple other organ systems
Myotonic dystrophy has been known as a neurological disease since 1909. While the clinical, genetic and biomolecular aspects of this disease have been thoroughly investigated, astonishingly little is known about Hans Steinert [2], who first described it 100 years ago. This anniversary is the reason for bringing together what can be ascertained about Steinert, from the scarce archival sources in the Leipzig University archives [10].

According to his handwritten application to qualify as a lecturer at Leipzig University (’Habilitation’), Hans Gustav Wilhelm Steinert was born in Dresden (Saxony) on 10 April 1875 into the family of lawyer Otto Steinert, a senior administrative official in the Royal services, and his wife Louise, née Westen. Between 1884 and 1893 Steinert attended grammar school in Dresden, before starting to study medicine and, at least initially, philosophy at the Universities of Leipzig, Freiburg, Berlin and Kiel. After his return to Leipzig he passed his medical finals, and defended his M.D. thesis on ‘Two Ovarian Embryonic Systems and a Testicular Dermoid Cyst’. From September 1898 until 1 July 1899 Steinert worked in Halle under the direction of Adolf Seeligmüller (1837–1912). Thereafter he worked in Berlin at the neurological clinic of Emmanuel Mendel (1839–1907), followed by brief assistantships at Leipzig University’s Institute of Pathology, the private neurological clinic of Leipzig neuropsychiatrist Franz Windscheid (1862–1910), and the Dresden City Hospital under Alfred Fiedler (1835–1921). Finally he was invited to work, starting in April 1901, at the Medical Clinic of Leipzig University under Heinrich Curschmann (1846–1910), who in 1888 had been appointed professor ordinarius of internal medicine, special pathology and therapy and head of the medical hospital of Leipzig University. Although primarily a specialist in cardiology and infectious diseases, he eagerly supported his assistants who took an interest in neurological diseases. Curschmann

1909
“Über das klinische und anatomische Bild des Muskelschwunds der Myotoniker.” in Dtsch Z Nervenheilkd

1994
“Proximal myotonic myopathy: a new dominant disorder with myotonia, muscle weakness, and cataracts.” in Neurology

2001
“Myotonic Dystrophy Type 2 Caused by a CCTG Expansion in Intron 1 of ZNF9” in Science
<table>
<thead>
<tr>
<th>Condition</th>
<th>DM 1</th>
<th>DM 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial weakness</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Difficulty swallowing, speaking</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>common</td>
<td>rare</td>
</tr>
<tr>
<td>Heart problems</td>
<td>common</td>
<td>variable</td>
</tr>
<tr>
<td>Pain</td>
<td>rare</td>
<td>common</td>
</tr>
<tr>
<td>Difficulty thinking, memory</td>
<td>common</td>
<td>uncommon</td>
</tr>
<tr>
<td>Congenital form</td>
<td>yes</td>
<td>No</td>
</tr>
</tbody>
</table>
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2 different chromosomes
2 different genes

DM1 is here

DM2 is here
DM 1
CTG repeat expansion

DM 2
CCTG repeat expansion

chromosome 19

DMPLK gene

\[ c + 6 \rightarrow 3 + 9 + 3 \rightarrow 3 + 9 + 3 \rightarrow \text{normal (5-37 CTG repeats)} \]

DM 1

chromosome 3

ZNF9 gene

\[ g + 3 + 9 + 3 + 3 \rightarrow \text{normal (11-26 CCTG repeats)} \]

DM 2

\[ 3 + 9 + 3 + 9 + 3 + 9 + 3 + 9 \rightarrow \text{50-2000 CTG repeats} \]
Review: DNA, RNA, and protein
Review: RNA Splicing

- DM2 on ZNF9
- DM1 on DMPK

Diagram:
- Exons and introns
- 5' Cap
- Poly-A Tail
- RNA splicing
How does the repeat expansion cause a problem?
How does the repeat expansion cause a problem?

RNA toxicity

Mankodi et al. 2001
DM1

DM2

RNA

MBNL

both

Mankodi et al. 2001
Splicopathy

DNA

DM1

DMWD

DMPK

SIX5

(CTG)_n

DM2

ZNF9

(CCTG)_n

Pre-mRNA

(CUG)_n

(CCUG)_n

Altered activity of RNA binding proteins regulating splicing, including CUG-BP and MBNL 1

Aberrant splicing

Insulin Resistance

Chloride Channel CLCN1

Cardiac Troponin T

RYR1

MTMR1

NMDAR1

Tau APP

Disease features

Insulin Receptor

Myotonia

?cardiac abnormalities

?Muscle weakness and wasting

CNS effects
Treatment Targets
2 concepts to explain differences in disease severity

- 1. Anticipation

- 2. Somatic instability
How is DM inherited?

DM1 and DM2: autosomal dominant
DM1: Anticipation

Harper 2001
A few concepts to explain differences in disease severity

- 1. Anticipation

- 2. Somatic instability
DM1: Somatic Instability

- CTG repeat expansion size changes in some body tissues throughout a patient's life.

- This happens at different rates in different types of cells, which leads to variability of repeat length in different tissues within one individual.
DM1: Somatic Instability

- Skeletal muscle: > 2,000 repeats by age 20, 40 years: average repeat length > 4,000 repeats, (3 to 25-fold larger than in blood)

- This may explain how the disease worsens in different ways in various organs over time.
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Multi-systemic Disease
MUSCLE

- Myotonia ("muscle stiffness") – delayed muscle relaxation
MUSCLE

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- Dystrophy – progressive weakness and loss of muscle mass

- Swallowing – difficulty swallowing with risk of aspiration and slurred
HEART

- Slow, fast or irregular heart beat
- Heart failure
- Can be present early with little other symptoms
- Yearly EKG
- Risk of sudden cardiac death
BREATHING

- Weakness of the diaphragm
- Disordered breathing in sleep
- Insufficient breathing at night (nocturnal hypoventilation)
- Monitoring breathing function at clinic visits
- Assisted breathing at night
SLEEP/hypersomnolence

- Excessive daytime sleepiness
- Hypersomnia (sleeping too much)
- Sleep is not restorative
- Due to abnormal sleep regulation
- Sleep study
GASTROINTESTINAL SYMPTOMS

- Risk of problems with gallbladder
- Bowel urgency with diarrhea, alternating with constipation (symptoms like irritable bowel syndrome)
ENDOCRINE SYSTEM

- Difficulty with fertility (more common in men)
- Balding
- Insulin resistance (risk for diabetes)
- Difficulty with problem solving
- Difficulty with emotions and behavior
- Changes on brain MRI

Gourdon, G and Meola, G. 2017
EYES - Cataract

- Cataract: clouding of the lens resulting in decreased vision
- In DM: Cataracts before age 55
- “Christmas tree cataract” – multicolored spots
Others

- **Pain**: DM2 > DM1

- **Cancer**: Increased risk of cancer → up to date with cancer screening

- **Anesthesia complications**: www.myotonic.org
What can you do?

- Learn about it and inform your family
- Establish an interdisciplinary medical care team
- Preventative care (cancer screening, diabetes)
- Support groups - support each other
- Consider research — see what is right for you
  - www.clinicaltrials.gov
  - Registries
  - Surveys
  - Observational studies
  - Treatment studies