DM 101: GETTING A HANDLE ON THE BASICS

Jacinda Sampson MD PhD
Myotonic dystrophy: what’s in a name?

- Myotonic = inability of muscles to relax after contracting them
Myotonic dystrophy: what’s in a name?

- Dystrophy = degeneration of the muscle fibers
  - Causes progressive muscle weakness

Carpenter & Karpati, *Pathology of Skeletal Muscle* 2nd ed. 2001
How many types of DM are there?

- **Myotonic dystrophy type 1 = Dystrophia myotonica type 1 (DM1)**
  - Congenital myotonic dystrophy = DM1 with onset in infancy

- **Myotonic dystrophy type 2 = Dystrophia myotonica type 2 (DM2) = Proximal Myotonic Myopathy (PROMM)**
  - No identified infancy onset form
Are there other types of myotonia?

- Non-dystrophic myotonias include:
  - Myotonia congenita (not to be confused with congenital myotonic dystrophy) =
    - Becker myotonia
    - Thompson myotonia
Who discovered DM1?

- **DM1**
  - Described 1909 by Hans Steinert
  - Congenital form described 1970
  - Prevalence 13/100,000
  - Most common adult muscular dystrophy
- **Male = female**
Who were the discoverers of DM2?

- **Proximal Myotonic Myopathy (PROMM)** was described by Richard Moxley
- **DM2** may be as common as **DM1**, but underrecognized
- **Mutation** discovered only 15 yr ago!

Richard Moxley  
John Day  
Laura Ranum  
Christina Liquori
What is a ____-nucleotide repeat?

- Poly = many
- tri = three
- Tetra = four
- Penta = five
- ...etc

- In the DNA, these nucleotides get repeated over and over
What is a polynucleotide repeat?

- **Non-coding repeat:**
  - RNA regions that don’t code (“spell”) the amino acids that make the protein
  - DM1 and DM2 have non-coding repeats

- **Coding repeat:**
  - RNA regions do code (“spell”) amino acids
Are there other polynucleotide repeat diseases?

- Yes, there are several different disorders, including:
  - Several Spinocerebellar ataxias
  - Friedreich’s ataxia
  - Huntington’s disease
  - Certain forms of amyotrophic lateral sclerosis (Lou Gehrig’s disease)
    - Caused by C9ORF72
    - Spinobulbar muscular atrophy (SBMA)
  - Oculopharyngeal muscular dystrophy (OPMD)
What gene mutation causes DM1?

- DMPK (dystrophica myotonia protein kinase) gene
- Non-coding Trinucleotide repeat
  
  ...CTG CTG CTG CTG CTG CTG...
Myotonic Dystrophy Type 1

- CTG
  - 5-37 repeats: No Myotonic Dystrophy
  - 38-49 repeats: No symptoms
  - ~50-150 repeats: Mild Myotonic Dystrophy
  - ~100-1000 repeats: Classic Myotonic Dystrophy
  - 730-4300 repeats: Congenital Myotonic Dystrophy
What gene mutation cause DM2?

- Zinc finger 9 (ZNF9) gene = cellular retroviral nucleic acid binding protein 1 (CNBP)

- Non-coding Tetranucleotide repeat
- …CCTG CCTG CCTG CCTG …
Myotonic Dystrophy type 2

CCTG

11-26 repeats

Normal repeat number

27-74 repeats

Borderline expansions

Range where expansion or contraction is possible

75-11,000 repeats

Myotonic dystrophy type 2
So to review:

- **Myotonic dystrophies-**
  - Caused by polynucleotide repeat expansions

- **Myotonic dystrophy type 1**
  - CTG repeats in DMPK

- **Myotonic dystrophy type 2**
  - CCTG repeats in ZNF9 gene

- **Non-dystrophic myotonias,**
  - or **Myotonia congenita-**
  - Caused by chloride or sodium channel mutations

- **Thomson myotonia**

- **Becker myotonia**
What is “mild” DM?

- used to describe the severity of symptoms
- Some doctors use it to describe DM1 with lower repeat size and later onset
- Some doctors use it to describe DM2 compared to DM1

- Either way, these people’s experience compared to unaffected people may not feel “mild”!
How do you test for DM?

Fig. 1: Detection of CTG repeat instability in blood from a 27 year-old DM1 patient carrying more than 170 CTG repeat

SP-PCR was performed as described by Gomes-Pereira et al., 2004. An average of 250, 50 and 10 genome equivalents (g.e.) were amplified in each replicate reaction, as indicated above the lanes. The membrane was hybridized with a non-radioactive CAG oligonucleotide probe. The medical RX autoradiography film was exposed for 5 minutes at room temperature.

Non-Radioactive Detection of Trinucleotide Repeat Size Variability...
Can DM2 turn into DM1?

- Nope. The repeats can change length, but can't change genes.
Where did DM come from?

- **DM1**
  - Out of Africa migration

- **DM2**
  - 1,000- 2,000 BC
How is it inherited?

Dominant inheritance
Dominant inheritance

- 50% chance of inheriting abnormal gene
- 50% chance at each pregnancy
- Does not alternate or “even out”
Dominant inheritance

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What is anticipation?

- Earlier onset of symptoms with successive generations
What is anticipation in DM1?

- < 35 repeats   normal
- <50 repeats   premutation
- 50-4,000 repeats   disease
- ~1000 (>730) repeats   congenital form
What is anticipation?
Myotonic Dystrophy Type 1

CTG

5-37 repeats
No Myotonic Dystrophy

Range where expansion is possible

38-49 repeats
No symptoms

~50-150 repeats
Mild Myotonic Dystrophy

~100-1000 repeats
Classic Myotonic Dystrophy

730-4300 repeats
Congenital Myotonic Dystrophy
Sperm repeat expansion

- Repeat expansions <100 are more unstable when inherited from the father’s side
- Even NORMAL repeat sizes show repeat number variation in sperm

http://oscss-biology.wikispaces.com/Images
Egg repeat expansion

- Occurred prior to fertilization
- Somatic mosaicism
  - Different tissues have different repeat sizes
  - Repeat size increases during development
  - Somatic expansion observed at 13-16 weeks

http://oscss-biology.wikispaces.com/Images
What is somatic mosaicism?

- Repeat size can vary between:
  - Cells
  - Tissues
  - Organs
How does DM cause disease?

- There are several hypotheses...
Review: DNA, RNA, and protein
What is a spliceopathy?

RNA must be cut and pasted (spliced) before it can be translated into a protein.

Choosing different exons can vary the protein sequence.
What is the toxic RNA hypothesis?

- Polynucleotide repeat bind up RNA splicing proteins
  - MBNL1 (Muscleblind 1)
  - CUGBP (CUG binding protein)
- Incorrect RNA splicing occurs
- Many RNAs, encoding many proteins for many tissues, are affected!

Splicing proteins get stuck in nucleus in "foci"

RNA detection  MBNL1 detection  Both RNA and MBNL1

DM1 neurons

Normal neurons

How is DM multisystemic?

- Muscle
- Brain
- Eyes
- Heart
- Lungs
How is DM multisystemic?

- Gastrointestinal tract
- Skin and hair
- Hormones
- Pregnancy
- Anesthesia
How does it affect the muscles?

- **DM1** – distal muscles
  - Hands, ankles, but also neck

- **DM2** – proximal muscles
  - Hips and shoulders

Saturday 11 AM: Occupational Therapy: Getting a Grip on Daily Activity Cynthia Gagnon, PhD

Saturday, 10 AM: DM & Exercise: A Panel Discussion
Katy Eichinger, DPT and community panelists
How does it affect the eyes?

- Cataracts
  - “Christmas tree”
  - tinsel effect

www.neuro.wustl.edu/neuromuscular
How does it affect the brain?

- **Congenital DM1**
  - Increased incidence of:
    - intellectual disability
    - Attention deficit disorder

- **Adult onset DM1**
  - Frontal and executive tasks

Saturday 2:30 – 3:15 PM: **DM & the Brain: Science & Symptoms**
John Day, PhD; David Moser, PhD; Giovanni Meola, MD, PhD
How does it affect the heart?

- Heart rhythm (arrhythmia)
  - Conduction block
  - Atrial flutter or fibrillation
  - Risk of sudden cardiac death

- Cardiomyopathy
  - Decreased strength of heart muscle
How does it affect the gastrointestinal tract?

- Swallowing difficulties (dysphagia)
  - Can lead to choking, aspiration

- Constipation
- Pseudo-obstruction
- Diarrhea
- Irritable bowel syndrome (IBS)- like symptoms
How does it affect the lungs?

- The muscles of breathing
  - Diaphragm
  - Intercostal muscles (muscles between the ribs)
- Brain control of breathing in sleep
  - Sleep apnea
- Aspiration pneumonia
How does it affect the hormones?

- irregular or absent menstrual periods
- Testicular atrophy
- Growth hormone
- Parathyroid hormone imbalance
- Thyroid hormone imbalance
How does it affect sleep?

- Increased sleep requirement (hypersomnolence)
- Daytime sleepiness
- Sleep apnea and snoring
  - Obstructive
    - weak tongue and throat muscles collapse during sleep
  - Central
    - brain directing breathing rhythm
- fatigue
What are the anesthesia effects of DM?

- Different types of anesthesia have different risks:
  - Weaken breathing, coughing, swallowing
  - Confusion/delerium
  - Constipation
  - Cause all-over myotonia

- See myotonic.org website for anesthesia recommendations
What can I do about it?

- Learn about it!
  - Which is what you are doing!
- Establish a medical care team
- Do your preventative care
- Support groups - support each other
- Consider research – see what is right for you
  - Registries
  - Surveys
  - Observational studies
  - Treatment studies
What research is being done?

Saturday, 3:15: Early Stage DM Therapy Development Update
Matt Disney, PhD; Roberto Guerciolini, MD; Lauren Wood, PhD

Saturday 4:00: DM Clinical Trial Updates
Ionis Pharmaceuticals, Laury Mignon, PhD; AMO Pharma, Joseph Horrigan, MD
The end-Questions?
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