Facioscapulohumeral Dystrophy & Myotonic Dystrophy: Clinical Aspects

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Wellstone/NCH/OSUWMC Myology Training Course

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Disclosures

- Consultant for ISIS for clinical trial in DM1
- Consultant for aTyr for FSHD study
- Consultant for Cytokinetics for FSHD study
- Will be (sort of) discussing some off label uses of drugs and agents

- Will *not* be giving a comprehensive overview of DM and FSHD
Objectives

- Clinical overview of DM and FSHD (Types 1 and 2 for both)
  - In 30 minutes!
- Touch on molecular pathogenesis
  - As it relates to diagnosis
  - Serve as “set up man” for Dr. Harper
- Approach to management; treating untreatable
- Try to keep everyone awake!
  - Case presentations & lots of pictures/videos
  - Tough assignment with mixed audience!
48 yo OSU prof - slow healing after ankle fx.
? distal weakness and stiffness
Referred by orthopod. why won’t he heal?
Clumsy in high school; trouble keeping up in sports
Mild foot slap
EMG of Case 1

- Genetic testing positive for repeat of myotonic dystrophy type 1 (DM1)
Myotonic Dystrophy
Overview

- Most common adult MD
  - 15 cases/100,000
- A.D. high penetrance
- Presents < age 50
- Variable severity & progression
- Predominantly **distal** weakness!
- Clinical/EMG myotonia (lids, tongue, hands)
DM1 Tongue Myotonia
Myotonic Dystrophy
Non-Muscle Features

- Frontal balding/bossing
- Cataracts, ptosis
- Hypersomnia; OSA
- Cognitive/personality \( \Delta \)
- TMJ dysfunction
- Cholelithiasis/dysphagia
- Insulin resistance/DM; GH def; impotence; test. atrophy
- Cardiac conduction def.
  - Cardiomyopathy

Courtesy Neil Miller (NM Home Page)
abnormal contractile function

LV

LV

RV

LV

LV

RV

Scar by late gadolinium Enhancement (LGE) (white)

Courtesy Subha Raman
Cardiac MRI in DM1
T1 Mapping & Extracellular Volume (ECV)

- Myocardial ECV measured as % tissue comprised of EC space; correlates with collagen volume fraction (i.e. fibrosis).
  - ECV of normal myocardium 20.4-30.4%

- ECV mapping may be able to augment LGE imaging in cases with homogenously diffuse disease.
  - Raman, Campbell, Kissel, 2014
Myotonic Dystrophy
Genetics

- 19q13.3 expanded CTG repeat (nl < 35) in non-coding region of DMPK gene
  - Myotonin protein
- 98% of DM cases (DM1)
- Repeat size correlates with severity
- Congenital form inherited from mother
  - Onset in infancy
  - Death in 25%

Prior et al, 1995
Myotonic Dystrophy

- Repeat unstable, true genetic anticipation
- Typically 100–1000
- Minimal sx. 50–150
- Pre-symptomatic 35–50
- Congenital often > 750
  - Inherited from mother
  - ~25% of maternal births
  - Fatal in infancy in 25%
  - Mental retardation, severe disease
Congenital DM
Myotonic Dystrophy Pathogenesis

MBNL family regulate splicing of several hundred transcripts & regulates RNA transport and decay (CIC-1, insulin receptor, BIN1, dystrophin, and L-type calcium channels)

Elliot 2014
Myotonic Dystrophy
Type 2

- Less weakness, prox > distal (i.e. PROMM)
- Less myotonia, heart; more pain
- DM2 locus at 3q21 in 2% (90% of PROMM)
  - CCTG repeat in ZNF9 gene (Liquori, 2001)
- Similar pathogen to DM1
- ? other PROMM, DM3 not linked to either locus ? (but not IBMPFTD)
DM-Symptomatic Care
Multi-System Disease

- Myotonia - mexilitine, topamax, tocainide, gabapentin, carbamazepine, phenytoin
- Modafinil for excessive DS – but limited benefit!
- Glucose intolerance-oral hypoglycemics, insulin
- Impotence-testosterone
- Cataracts - evaluation for extraction
- No strength therapy – 2009 INSMED rhIGF1-bp study negative – major disappointment!
- ASO-mediated trials to reduce RNA loops
  - ISIS phase 1 study in progress!
Cardiac Evaluation in DM1
Groh et al, NEJM 2008

- 406 adult genetically confirmed DM1 pts
- 81 deaths over mean f/u of 5.7 years

- 32 cardiac deaths; 27 "sudden"

- Risk factor - atrial tachyarrhythmia & "severe EKG abnormality"

- Non-sinus rhythm -- QRS > 240 msec
- PR > 240 msec -- 2° or 3° AV block

- Frequent EKGs (at least yearly) a MUST!

- Need for His bundle studies?
  - Controversial; more studies needed (Lau, 2015)

Whabi et al, JAMA 2012

Graph showing survival probability over follow-up years with invasive and noninvasive strategies.

No. at risk
- Invasive strategy: 341, 270, 205, 165, 106
- Noninvasive strategy: 145, 124, 98, 67, 43

P = .001
Myotonic Dystrophy Prognosis

- 50% wheelchair dependent
- Mean age death ~60
  - 30% cardiac
  - 30% pulmonary
  - 40% multifactorial
- Earlier death with longer repeat
- Profound morbidity!
  - COGNITIVE ISSUES!
50 y.o. WM fell & injured right shoulder

Referred for pain and “winging” of shoulder
  ➢ “Nerve palsy”

Life long history of raising arms
  ➢ High school gym class
  ➢ At work currently

Never could whistle
Case Presentation #2

Pattern 3: Scapuloperoneal Pattern
FSH Dystrophy

Clinical Picture

- AD; prevalence 12/100,000
  - Deenen et al, 2014
- Descending weakness of face, proximal arm
  - “Popeye arms”
  - Pectoral atrophy
- Distal leg weakness
  - Foot drop
- Asymmetric weakness
- Spares bulbar muscles
- Respiration spared
FSHD Clinical
Non-Muscle Involvement

- Clinically isolated to skeletal muscle
- No cardiac defects
- Hearing loss with large deletions (Lutz, 2013)
  - Often subclinical
  - Progresses with time
- Subclinical retinal involvement (?.)
- Coat’s retinal syndrome (< 5%)
Deletion in 3.3 kb repeat D4Z4 sequence at 4q35; "A" allele (permissive sequence); increased DUX4 gene expression

- 95% - short fragment (normal is 38-300 kb)
- FSH < 35 kb; inverse correlation with severity

- 5% FSHD2 - chrom 18 SMCHD1 gene mutation in 85%

- Structural maintenance of chromosomes flexible hinge domain containing 1

- Hypomethylation / increased DUX4 expression (allele A)

- May modify expression of FSHD1 (Sacconi, 2013) via second mutation/double trouble!

- Hypomethylation correlates with dx. Severity (Gaillard, 2014)

Statland & Tawil, Neurol Clinics, 2014
Evidence-Based Guideline
Tawil, Kissel, et al Neurology 2015

Suspected FSHD
Genetically confirmed 1st-degree relative?

Yes
FSHD1

No
Test for presence of D4Z4 contraction

Yes
Clinically typical FSHD?

Yes
FSHD1

No
Test for A allele on contracted D4Z4

Yes
FSHD1 confirmed

No
Other myopathies*:
- LGMD2A
- Acid maltase deficiency
- Mitochondrial myopathy
FSHD Variation
## Strength Therapy in FSHD

### Clinical Drug Trials

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MR fat infiltration as biomarker for diseased muscles

Distal fat infiltration/altered energy metabolism, then rapid fat replacement spreading over whole muscle.

Suggests early trial intervention (aTyr study; 2015)

Supportive Therapy
Evidence Based Guidelines 2015

- Limb, back pain
  - NSAIDs, muscle relaxants
  - Physical therapy
- Abdominal pain
  - LS corset/binder
- Fatigue in 60%
  - Kalkman, 2005
  - ? medications
Supportive Therapy  
Judicious Bracing

- Custom-molded AFOs for foot drop
  - Not off the shelf!
- Toe-off/Blue Rocker brace
- “Stance control” KAFOs for more proximal/quad weakness
  - Provides automatic release at knee during push-off phase
  - Lock during stance
FSHD - Supportive Therapy
Scapular Stabilization Surgery

- For some with good deltoid, bicep function
- Increases leverage arm but decreases ROM
- Complications - rib fx, hemothorax, pneumothorax, pleurisy, bleeding, failure, brachial plex.
- 10-12 weeks immobility
- Experienced surgeon!
- Motivated patient!!
Scapular Stabilization Surgery

Dr. Anthony Romeo, Chicago
Scapular Stabilization Surgery
“…to move things is all that mankind can do, for such the sole executant is \textit{muscle}, whether in whispering a syllable or in felling a forest.”

Charles Sherrington, 1924
“Wonderful! Just wonderful! ... So much for instilling them with a sense of awe.”

Thank you for your attention!