Muscular Dystrophies in Adulthood

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Disclosure Information

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  - Honoraria from: None
  - Employee of: None

- Disclosure of Off-Label and/or Investigative Uses
  - I may discuss the following off label use and/or investigational use in my presentation: Corticosteroids and genetic-based therapies in muscular dystrophies.

Definition

- Muscular dystrophies are genetic, progressive, degenerative disorders of muscle
  - Muscle weakness is the primary symptom
  - Clinical and histologic criteria have been used in the past for classification
Definition

- Now muscular dystrophies are mostly classified on a genetic basis
- Thus, we often refer to them by the broader moniker of: Genetic muscle diseases

Why Should We Care?

- 200+ genetic muscle diseases
- Overall minimum prevalence of symptomatic disease ~1 in 1,000
  - Similar to multiple sclerosis
  - Dystrophinopathies – 23/100,000
  - Myotonic dystrophies 1 & 2 – 14/100,000
  - FSHD – 11/100,000
  - LGMD – 7/100,000

Pathology Throughout the Myofiber

- Extracellular matrix
  - Sarcolemma
    - Sarcolemmal repair / maintenance / trafficking / signal transduction
  - Sarcoplasma
  - Sarcomere
  - Intermediate filaments
  - Nucleus
Pattern of Weakness Varies

Dystrophinopathies

- Multiple phenotypes
  - Duchenne (1:5,000)
  - Loss of independent ambulation <12 years
  - Becker (1:10,000)
  - Walk past 16th birthday
  - Manifesting female carriers (1:20,000)
  - HyperCKemia or myalgias
  - X-linked dilated cardiomyopathy
  - Cognitive disorders

Duchenne

- Motor
  - Slightly late to walk
  - Improve until 6-8 years
  - Stop walking 7-11 years
  - Continued loss of distal strength in 20s and 30s

Systemic

- Dilated cardiomyopathy
  - ACE inhibitor, b-blocker
- Restrictive lung disease
  - NIV, ventilators
- Gastroparesis/megacolon
  - G-J tubes
- Cognitive dysfunction
  - Language/Asperger/autism
- Developmental pediatrician
- Osteoporosis & fractures
Duchenne

Corticosteroid therapy:
- > 29 dosing regimens
  - Pred 0.75mg/kg/d
  - Deflazacort 0.9mg/kg/d
  - Pred 2.5mg/kg/d on Saturday and Sunday
- Start 3-8 years of age

Treated boys:
- Walk 1-3 years longer
- Fewer falls
- Better pulmonary function
- Less scoliosis, but more fractures
- Probable improvement in cognitive & cardiac function

Weight gain, behavioral changes, growth retardation, hypertension, glucose intolerance, peptic ulcer disease, cataracts, acne, fractures

Dystrophinopathies

Becker
- Highly variable severity
- Skeletal and cardiac muscle involvement may be quite disparate
- Cardiac transplantation a reasonable option
- Pulmonary milder
- Cognitively normal

Female carriers
- Underappreciated
- CK elevated in 30-60%
- 20% with weakness
- 20% with abnormalities on cardiac testing
- 10% with symptomatic dilated cardiomyopathy

Males and females with a limb girdle pattern of weakness should be evaluated for dystrophinopathies

Dystrophinopathies

- DMD
  - Largest gene in human genome
    - 2.3 megabases
    - 79 exons
    - 8 isoforms
  - Dystrophin
    - 3685 AAs
    - 427 kilodaltons

Dystrophin

- 8 isoforms
- 427 kilodaltons

Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Duchenne</th>
<th>Becker</th>
<th>Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>3-5 years</td>
<td>6-60 years</td>
<td>30-70 years</td>
</tr>
<tr>
<td>Weakness</td>
<td>Severe</td>
<td>Variable</td>
<td>~20%</td>
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<tr>
<td>CK</td>
<td>2,000-40,000</td>
<td>300-20,000</td>
<td>↑ in ~1/3</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Absent</td>
<td>Decreased</td>
<td>Nil or ↓</td>
</tr>
<tr>
<td>Immunostains</td>
<td></td>
<td></td>
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</tbody>
</table>
Diagnosis

Mutation Analysis

- Mutations
  - Deletions ~55%
  - Duplications ~10%
  - Point (missense & nonsense) ~25%
  - Splice site ~5%

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Duchenne</th>
<th>Becker</th>
<th>Carrier</th>
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<tr>
<td>Out of frame</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In frame</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reading frame rule holes in ~80-90% of cases
Reading Frame Rule

[Diagram showing normal and abnormal pathways involving extracellular matrix and cytoplasmic bridges]

Reading Frame Rule

[Diagram showing normal and abnormal pathways involving extracellular matrix and cytoplasmic bridges]
Myotonic Dystrophies

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
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<tbody>
<tr>
<td>Weakness</td>
<td>Distal</td>
<td>Proximal</td>
</tr>
<tr>
<td>Clinical Myotonia</td>
<td>Prominent</td>
<td>Not usually</td>
</tr>
<tr>
<td>Other Organs</td>
<td>Prominent</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Pain</td>
<td>Uncommon</td>
<td>Frequent</td>
</tr>
<tr>
<td>EMG (Myotonia)</td>
<td>NL-5x</td>
<td>NL-5x</td>
</tr>
<tr>
<td>Gene</td>
<td>DMPK</td>
<td>ZNF9</td>
</tr>
<tr>
<td>Mutation</td>
<td>CTG repeat (3’ untranslated region)</td>
<td>CCTG repeat (Itron1)</td>
</tr>
<tr>
<td>Anticipation</td>
<td>Yes (especially ♀)</td>
<td>No, variable</td>
</tr>
</tbody>
</table>
DM1
"Christmas Tree Cataracts"

Temporal Tip White Matter Hyperintensities

DM1
Temporal Tip White Matter Hyperintensities

DM2
Multiple internal nuclei
Nuclear clumps

Genetics in DM1

• (CTG)n repeat length matters:
  - 4–37 => NL
  - 38–50 => stable, asymptomatic or minimal symptoms late in life
  - 51–100 => minimal symptoms late (e.g. cataracts)
  - 101–1,000 => classic adult onset DM1
  - 1,001 – 4,000 => severe ± congenital onset

[Image of eye with cataracts]
[Image of MRI scans]
[Image of histological section]
Genetics

- In DM1, larger repeat length correlates with:
  - Earlier onset of disease
  - More severe manifestations of disease
  - More severe cardiac involvement
- In DM2, there is no good correlate of repeat length with disease severity

Myotonic Dystrophies

Takeaway points

- DM1
  - Clinical myotonia or EMG
decrescendo/crescendo myotonic
discharges should spur genetic
testing for DM1
  - 1 in 4 children born to a woman with
DM1 will have congenital DM1
  - The word “pacemaker” should never
be uttered without “defibrillator”
- DM2
  - Consider this diagnosis in 30-50 year
old patients with pain, myalgias ±
weakness
  - Myotonic discharges may not be
appreciated on the first EMG in 15-
25% of cases

FSHD

(Facioscapulohumeral muscular dystrophy)

- Up to 30% sporadic
- Onset in teens
- Facial involvement may be mild (5-10%)
FSHD (Facioscapulohumeral muscular dystrophy)

- Up to 30% sporadic
- Onset in teens
- Facial involvement may be mild
- Asymmetries
- “Triple hump sign”
- Reversal of the anterior axillary folds
Diagnosis

- Autosomal dominant
- Clinical features
  - CK = NL to 5x ULN
  - EMG => myopathy or irritable myopathy
  - Biopsy almost always not necessary
    - Often inflammation associated with dystrophic features
  - Genetic testing

Genetics

- Reduction in the number of 3.3 kilobase (kb) tandem repeats (termed D4Z4) on chromosome 4q35
  - Normal >11
  - Shorter repeat length correlates with:
    - Earlier onset
    - More severe disease

Genetics

- Obligate conditions for FSHD
  1. Chromosome 4q35 (not chromosome 10q)
  2. 1-10 D4Z4 repeats
  3. 4qA variant at the terminus (not 4qB)
  4. Presence of one of three permissive simple sequence length polymorphisms – SSLPs (4A159, 4A161 or 4A168)
- Hypomethylation allowing DUX4 activity
- ~5% with FSHD phenotype not have the above
- FSHD2 – hypomethylation of D4Z4 repeats
- SMCHD1

Prognosis

- Indolently progressive weakness
  - Patients may comment on periods of quiescence interrupted by rapid deterioration
  - 20% eventually require wheelchair use
  - Women less severely affected than men
  - Rough correlation between disease severity and size of deletion
  - Normal life expectancy
Treatment

- No medical therapy
  - Prednisone, albuterol and creatine did not yield functional improvements
- Exercise is OK
- Pain management
- High frequency hearing loss screening
- Assistive devices like AFOs for foot drop
- Surgical scapular stabilization procedures

Limb Girdle Muscular Dystrophies

- Recessive:
  - More common (~85%)
  - Higher CK levels
  - Often appears sporadic in smaller families
- Dominant:
  - Passed generation to generation
  - NL or mildly elevated CK levels

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>LINKAGE</th>
<th>GENE</th>
<th>GENE PRODUCT</th>
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<tbody>
<tr>
<td>LGMD1A</td>
<td>1q11-11.2</td>
<td>LMNA</td>
<td>Lamin A/C</td>
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<td>LGMD1B</td>
<td>1q21-21.3</td>
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<td>Lamin A/C</td>
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<td>LGMD1C</td>
<td>3p11.22</td>
<td>DYSF</td>
<td>Dysferin</td>
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<tr>
<td>LGMD2A</td>
<td>1q21-12</td>
<td>SCG2</td>
<td>G-protein gamma</td>
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<td>G-protein gamma</td>
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<td>SGC4</td>
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<td>LGMD2F</td>
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<td>SGC5</td>
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<td>LGMD2G</td>
<td>3p11.1</td>
<td>FKRP</td>
<td>FK-Bet protein</td>
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<td>LGMD2H</td>
<td>3p12.3</td>
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<td>FK-Bet protein</td>
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<td>FK-Bet protein</td>
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<td>FK-Bet protein</td>
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<td>FKRP</td>
<td>FK-Bet protein</td>
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Relative Prevalence in USA

- Calpain 25%
- Sarcoglycans 15%
- Dysferlin 15%
- FKRP 15%
- Anoctamin 10%
- Lamin A/C 10%
- All others 10%

LGMD2A - Calpain

- Overall most common LGMD, ~20-30%
- Onset 2nd or 3rd decade (2-55 years)
- Hip extensors, knee flexors and hip adductors most involved
- ~50% wheelchair confined after 20 years of disease
- Scapular winging
- Finger extensor weakness
- May be confused clinically with DMD/BMD
- Lack of cardiac involvement

Pollitt et al. Neuromusc Disord 2001;11:287-296
Calpainopathy

- CK
  - 1000-5000 U/L
    (450-12,500 U/L)
- Muscle biopsy
  - Dystrophic
  - Lobulated fibers
  - Eosinophilic myositis
  - Early in disease

Dysferlinopathy

- Phenotypes
  - Limb girdle pattern
  - Also causes distal myopathies:
    - Miyoshi myopathy (posterior complex)
    - Distal anterior compartment myopathy (tab. ant)
    - Scapuloperoneal or proximodistal pattern
    - Biceps atrophy
    - Bent spine syndrome
    - Carriers may be symptomatic
- Identical mutations may present with different phenotypes
  - Even within the same family
Dysferlin's Function

- Membrane repair
  - Satellite cells
- T-tubules
- Mitochondria

Dysferlinopathy

- Onset – 2nd & 3rd decades (0-73 yrs)
  - Most have some distal, calf weakness
  - No cardiac manifestations
  - CK may be markedly elevated
    - Mean = 3800 U/L (generally 1,000-30,000 U/L)
- Biopsies:
  - Inflammation
  - Treatment refractory polymyositis
  - Amyloid
- Prevalence:
  - 20-30%

Dysferlin

Polymyositis

Duchenne Muscular Dystrophy

LGMD2I – FKRP

- Fukutin-related protein (FKRP)
  - Prevalence = 6-40%
    - Highly prevalent LGMD subtype in Northern Europeans
    - 8% in US study
  - Phenotypes:
    - Congenital muscular dystrophy – Fetal / neonatal
    - LGMD – Onset 3-55 years
    - Asymptomatic hyperCKemia

Gallardo, E Neurology 2001;57:2136
Spuler, S Ann Neurol 2008;63:323
Defective glycosylation in muscular dystrophy

Defective glycosylation in muscular dystrophy

LGMD2I - FKRP

- Highly variable progression
- Calf and tongue hypertrophy
- Muscle pain & cramps
- Cardiac dysfunction
- Respiratory involvement
  - Nocturnal ventilation in 30-50%
  - Myoglobinuria not uncommon
- CK = NL <= 50 x ULN
- May be confused with DMD/BMD
LGMD2C-F - Sarcoglycans

- \(\gamma\), \(\alpha\), \(\beta\), and \(\delta\)-sarcoglycan
- \(~15\text{-}20\%\) of LGMD
- Form a tetrameric transmembrane subcomplex within the dystrophin glycoprotein complex
  - links the extracellular matrix to the subsarcolemmal cytoskeletal proteins

Sarcoglycanopathies

- Onset
  - In first decade in lower extremities
- Phenotypes
  - SCARMD (Duchenne-like)
  - Mild, later onset (Becker-like)
  - Aches/pains/cramps syndrome
  - Recurrent myoglobinuria
  - Asymptomatic hyperCKemia
  - Dilated cardiomyopathy
  - Calf hypertrophy in \(\frac{1}{2}\)
  - Scapular winging frequent

- May develop cardiac dysfunction (conduction defect and/or dilated cardiomyopathy)
- CK markedly elevated 1,000-25,000 IU
- Muscle biopsy dystrophic
  - Eosinophic myositis reported early in \(\gamma\)-sarcoglycanopathy
LGMD2L – Anoctamin 5

• ANO5 – Anoctamin 5
• Putative calcium-activated chloride channel
  ▫ Involved in membrane repair
• More common than dysferlinopathy in Northern England

LGMD2L – Anoctamin 5

• AR inheritance:
  ▪ LGMD2L
  ▪ Dermal myopathy (MM2D)
  ▪ Asymptomatic hyperCKemia
• LGMD clinical
  ▪ Onset 11-55 years of age
  ▪ Quadriceps & biceps atrophy
  ▪ Muscle pain in 85%
  ▪ Most remain ambulatory
  ▪ CE = NC to 50 fold normal
  ▪ AS = Dystrophic
  ▪ AD mutations => gnathodiaphyseal dysplasia (GDD)

LGMD1B – Lamin A/C

• ~7-10% of LGMD
• Onset:
  ▪ Congenital – 3rd decade
• Contractures
  ▪ Elbows
  ▪ Achilles
  ▪ Neck extensors
  ▪ Hip flexors
  ▪ Rigidity of the spine
  ▪ Scapular winging
  ▪ Variable rates of progression
  ▪ Frequent cardiac involvement

LGMD2L

• A-D – Atrophy of thighs & medial gastrocs
• E – Biceps atrophy
• F-H – Severe quad & hamstring wasting
• I – Hyperextension of knee

LGMD1B – Lamin A/C
Laminopathy

- 57 yo Grandfather without weakness, but required pacemaker in early 30’s
- 32 yo Mother asymptomatic
- 10 yo proband with typical muscular dystrophy requiring wheelchair
- All with the same mutation

Lamin A/C

- Mutations in LMNA also cause:
  - AR LGMD
  - Familial partial lipodystrophy
  - AD & AR axonal polyneuropathies
  - Mandibuloacral dysplasia syndrome
  - Progeria syndromes
  - Isolated dilated cardiomyopathy with A-V block (CMD1A)
  - Heart-hand syndrome of the Slovenian type
  - Metabolic syndrome
  - Cerebral white matter disease
What else looks like LGMD?

- Dystrophinopathies
- FSHD
- Bethlem myopathy
- X-linked EDMD
- Myofibrillar myopathies
- Mitochondrial myopathies
- Metabolic myopathies
- Pompe disease

### Pompe Disease
- Affects all ages
- Treatable disorder
- Enzyme replacement therapy

### Myopathy with Paget’s Disease
- Uncommon
- Adult onset – mean age of 42 years
- Slowly progressive proximodistal weakness
  - Early onset: Paget’s disease
  - Premature, frontotemporal dementia (FTD)
- 29yo F with AD proximodistal weakness and FH of Paget’s disease...
Extracellular Matrix-Related Myopathies

- Collagen VI
  - Bethlem and Ullrich
  - COL6A1/A2/A3
    - Hyperlaxity => contractures
    - Keloids
    - CK NL 2.5th U/L
    - Ultrasound “central cloud”
    - MRI – “outside-in” pattern
- Collagen XII
  - Similar features

Emery-Dreifuss

- Clinical triad:
  - Early and disproportionately prominent contractures
  - Elbows, spine and Achilles
  - Childhood onset of humeroperoneal weakness
  - Cardiac disease with arrhythmias, conduction block, and cardiomyopathy
  - Pacemaker/defibrillators
  - Manifesting female carriers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Mode of Inheritance</th>
<th>% of Cases</th>
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<tbody>
<tr>
<td>LMD</td>
<td>Emerin</td>
<td>X-linked recessive</td>
<td>17%</td>
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<tr>
<td>LMNA</td>
<td>Lamin A/C</td>
<td>Autosomal dominant</td>
<td>32%</td>
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<td>SYNE1</td>
<td>Nesprin-1</td>
<td>Autosomal dominant</td>
<td>Unknown</td>
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<td>SYNE2</td>
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<tr>
<td>FMAN2</td>
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<td>Unknown</td>
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OPMD
(OCulopharyngeal Muscular Dystrophy)

- Clusters of disease
  - French Canadians & New Mexico Hispanics
- Onset 40s-60s
- Ptosis & dysphagia
  - 2/3 ophthalmoplegia
  - limb weakness
  - 2/3 lower extremity
  - U/L upper extremity
  - CK – NL 1,000 U/L
  - Biopsy with vacuoles
  - (GCN)12-17 trinucleotide repeat expansion in exon 1 of PABPN1
What if the CK is very high?
(>10,000 U/L)
- LGMD2A - Calpain
- LGMD2B - Dysferlin
- LGMD2C - Sarcoglycans
- LGMD2I - FKRP
- LGMD2L - Anoctamin 5
- Dystrophinopathy (Duchenne/Becker)

Diagnostic Strategies
- If clinically FSHD, DM1 or OPMD => genetic testing
- If "limb-girdle" pattern of weakness
  - Use phenotype, PH, FH, CK & EMG => targeted genetic test(s)
  - Jain Foundation web-based "smart" algorithm (ALDA)
- Pompe disease testing – free through MDA
- Dystrophin gene testing
  - Including in women

Jain Foundation
LGMD Online Patient Diagnostic Tool
Diagnostic Strategies

- Muscle biopsy?
  - Muscle biopsy with immunostains - $7,000-$12,000
  - Or... multiple mutation analyses
    - Commerially available panels (33, 79 & 200+ genes)**
    - Or...
      - Exome sequencing – 3 affected & 3 unaffected family members***
      - Genome sequencing – now raw data available in < 1 week***
    - Cautionary tale...
  - "Inverted Diagnosis"

LGMD Genetic Testing through MDA

- MDA now offering same panel of 35 genes to >5,000 LGMD patients registered with the MDA.
  - An explosion of diagnoses over the upcoming year!