Dysferlinopathies
LGMD2B, Miyoshi & Others

2B Empowered Conference
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Professor of Neurology and Pediatrics
Penn State Health
May 24, 2015
Outline

A. Empower you with knowledge about your diagnosis.

B. Explain why the diagnosis may have been hard for your doctors.

1. Dysferlinopathies, what do they look like?
2. What else looks like dysferlinopathies?
3. How common are dysferlinopathies?
4. How do we diagnose dysferlinopathies?
5. Why remain hooked into your doctor?
Dysferlinopathies, what do they look like?

Evidence-based guideline summary: Diagnosis and treatment of limb-girdle and distal dystrophies


ABSTRACT

Objective: To review the current evidence and make practice recommendations regarding the diagnosis and treatment of limb-girdle muscular dystrophies (LGMDs).

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Dysferlinopathy

• **Phenotype** (What are the physical characteristics?)
  - Limb girdle pattern (143/293 cases)
  - Also *distal myopathies*: (150/293 cases)
    • Miyoshi myopathy *(gastrosoleus complex)*
    • Distal anterior compartment myopathy *(tib ant)*
      - Scapuloperoneal or proximodistal pattern
      - Biceps atrophy
      - Bent spine syndrome
      - Carriers may be symptomatic

• Identical genetic mutations may present with different phenotypes
  - Even within the same family

Mahjneh et al
Neuromusc Disord 2001;11:20-26
Dysferlinopathy

- Onset – mean 18-32 yrs (range 0-73 yrs)
- Most have:
  - Some **distal**, calf weakness
  - Calf atrophy common (inability to stand on toes)
  - Asymmetries (side to side differences)
- No scapular winging, dysphagia, dysarthria, contractures or cardiac dysfunction
- PFTs ↓ over decades
  - Rarely symptomatic

Mahjneh et al
Neuromusc Disord 2001;11:20-26
Dysferlinopathy

- Anterior tibial
  - 13/76 cases
Dysferlinopathy

Calf hypertrophy early in course

Prominent deltoids with biceps atrophy

Rosales, X
Muscle Nerve 2010;42:14
Dysferlinopathy

Diamond on Quadriceps Sign
- 21/33 cases

Pradhan, S
Neurology 2008;70:332

Pradhan, S
Neurology India 2009;57:172
Dysferlinopathy

Paradas, C
Neurology 2010;75:316
Dysferlinopathy

Paradas, C
Neurology 2010;75:316
Dysferlinopathy

- Mechanism of action
  - Dysferlin-associated membrane repair
  - Mitochondrial health
  - Stabilizes stress-induced Ca\(^{2+}\) signaling in the T-tubule membrane
    - Diltiazem ↓ muscle fiber inflammation & injury

Bansal and Campbell
Dysferlinopathies

- CK may be markedly elevated
  - Mean = 3800 U/L
    (generally 1,000-30,000 U/L)

- Biopsies:
  - **Inflammation** (common)
    - Treatment refractory polymyositis
    - Deflazacort not effective
  - Amyloid (20-30%)

Gallardo, E
Neurology 2001;57:2136

Spuler, S
Ann Neurol 2008;63:323
Dysferlin

Polymyositis

Duchenne Muscular Dystrophy
Dysferlinopathy

- Immunostaining variable in dysferlinopathies
  - Absent
  - Diminished sarcolemmal
  - Sarcoplasmic accumulation

- Abnormal staining in other muscle disorders also
Dysferlinopathy

• Diagnosis
  – Western blot on muscle or monocytes

• Best to use genetic testing
  – Gene sequencing
  – Next generation gene panel
  – Exome/genome sequencing
What else looks like dysferlinopathies?

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Limb Girdle, Distal, or what?

- 19 autosomal recessive LGMDs
- 8 autosomal dominant LGMDs
Limb Girdle, Distal, or what?

- 19 autosomal recessive LGMDs
- 6 autosomal dominant LGMDs
- 9 distal myopathies
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- 7 myofibrillar myopathies

Nearly 50 genes in total
How common are dysferlinopathies?

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LGMD Regional Variability

- Northern Europe – LGMD 2A, 2I & 2L
- Southern Europe – LGMD 2A
- North Africa – LGMD 2B-F
- Asia – 2B & 2A
- South America – LGMD 2A-F
- North America – LGMD 1B & 2A-F
  - East Coast => LGMD 2A
  - West Coast => LGMD 2B
Relative Prevalence – USA

Dysferlinopathies:
• 10-20% (0.6%-33%) of LGMD/distal myopathies
How do we diagnose dysferlinopathies?
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)
- Dystrophin gene testing
  - Including in women
- Pompe disease testing – *free*
Free Genetic Sequencing

The Quiz, or questionnaire, on this website was designed to determine whether you may have a type of muscular dystrophy. To help identify individuals who may have one of the diseases studied by the foundations in our consortium, we sponsor genetic sequencing for the diseases listed below. After taking the quiz, we will contact you if your answers suggest that you may have one of the diseases covered by our sequencing program and invite you to participate in our diagnosis program at no cost to you.

Diseases Tested by our Genetic Sequencing
- Limb girdle muscular dystrophies (LGMD1A-F and LGMD2A-Q)
- Nonaka/HIBM, Tibial muscular dystrophy
- Becker muscular dystrophy (BMD)
- Duchene muscular dystrophy (DMD)
- Facioscapulohumeral muscular dystrophy (FSHD)
- Emery-Dreifuss muscular dystrophy (EDMD)
- ISPD
- Pompe
- Bethlem myopathy

Associated Genes
- MYOT, LMNA, CAV3, DNAJB6, DES, TNPO3, CAPN3, DYSF, SGCG, SGCA, SGCB, SGCD, TCAP, TRIM32, FKRP, TTN, POMT1, ANOS1, FKTN, POMT2, POMGnT1, DAG1, PLEC1, GNE, DMD, FSHD1, FSHD2, EMD, FHL1, SYNE1, SYNE2, ISPD, GAA, COL6A1, COL6A2, COL6A3
Diagnostic Strategies

• Muscle biopsy?
  – Muscle biopsy with immunostains - $7,000-$12,000
  – Or… multiple mutation analyses
    • Commercially 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

• Jain Foundation in concert with this LGMD consortium now offering same panel of 35 genes to >5,000 LGMD patients registered throughout the USA.

  – An explosion of diagnoses over the upcoming year!
  – Who knows what we’ll find???
“Whilst looking down the rabbit hole, all I saw was bunnies. But once my eyes gazed ‘bout the glen, the panoply of species I did see.”

(Old English Fairy Tale)
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“The accurate diagnosis of genetic muscle diseases is important for patients, their families, and for efficient and cost-effective use of medical resources. It assists in defining the long-term prognosis, since some dystrophies are more rapidly progressive, involve the cardiorespiratory systems more frequently, or are associated with other organ system problems. The identification of these dystrophies through genetic testing will not only inform long-term prognosis but will also assist in directing care more efficiently (e.g., more frequent cardiorespiratory monitoring and prophylactic treatments such as pacer/defibrillator placement for those disorders known to be associated with cardiac involvement). Precise identification of the disorder also eliminates the need for repeated testing for an acquired, treatable disorder such as an inflammatory myopathy, because some dystrophies may have inflammation on some muscle biopsies. This makes diagnosis difficult on the basis of routine biopsy findings. The cost of a repeat muscle biopsy, slide preparation and staining, along with pathologic interpretation costs $7,000-$12,000. The cost of genetic testing is now much lower and provides a definitive diagnosis. Although establishing a genetic diagnosis is somewhat costly on the front end, the costs of continued investigation for other causes and monitoring for cardiorespiratory involvement (Cardiology consultation with EKG, echocardiogram and Holter monitor plus Pulmonary consultation along with pulmonary function testing), and the risks and expenses associated with empiric trials of immunosuppressants make a strong case for establishing a genetic diagnosis. A genetic diagnosis also provides patients a sense of “closure”. Establishing a genetic diagnosis is crucial for genetic counseling to inform decision making about having children and for screening of offspring. Treatment of cardiomyopathy, arrhythmias, and ventilatory failure prolongs life and improves quality of life in patients with other neuromuscular diseases.”
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“Patients can remain engaged in their own care, and in further disease discovery, through regular evaluations with their neuromuscular specialist, and through participation in research trials on natural history and/or treatment.”

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Recommendations for Future Research

As the category of LGMDs expands with advances in molecular diagnostics and new disorders are identified, there is need for research in the following areas.

1. **Large prospective, long-term, population-based studies** to establish the prevalence of these disorders, identify the ethnic populations among which they are most prevalent, and evaluate their long-term course, including the incidence of cardiorespiratory complications.

2. **Studies of genotype/phenotype correlation** to establish phenotypic patterns based on genotype, and to describe the phenotypes caused by each genotype.

3. **Optimal management of other organ system involvement** (e.g., frequency and types of screening, effective treatments).

4. Well-designed studies of the **effectiveness of exercise programs, physical therapy, and endurance training**.

5. Studies of treatments, including **symptomatic treatments** such as orthotics for contractures (nonsurgical/surgical) on mobility and quality of life, as well as **disease-modifying treatments** such as gene therapy and stem cell therapy.

6. Preliminary data suggest **corticosteroids** may benefit α-dystroglycanopathies but not dysferlinopathies. These results need replication in larger, controlled studies.
Engagement Empowers

• Encourage diagnosis.
• Engulf education about dysferlinopathies.
• Employ knowledge to optimize quality of life.
• Enable through community efforts.
• Endow all with your enthusiasm.
• Embolden research.
• Envision no dysferlinopathies…
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