Neuromuscular Disorders: The Road from Detection to Diagnosis

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Disclosures

- No relevant disclosures
Objectives

• Define neuromuscular diseases
• Describe the approach to diagnosing neuromuscular diseases
• Discuss common, relevant disorders
• Understand the importance of recognizing neuromuscular disease by all practitioners.
First things first...

- What are neuromuscular disorders?
  - Heterogeneous group of disorders affecting the peripheral nervous system
    - Muscle diseases
    - Nerve diseases
    - Neuromuscular junction diseases
  - Not synonymous with Movement Disorders
# Limb-Girdle Muscular Dystrophy (LGMD) Syndromes

## Limb girdle dystrophies: **Dominant**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Myotilin; 5q31; Dysarthria</td>
</tr>
<tr>
<td>1B</td>
<td>Lamin A/C; 1q21; + Cardiac</td>
</tr>
<tr>
<td>1C</td>
<td>Caveolin-3; 3p25; Child onset</td>
</tr>
<tr>
<td>1D</td>
<td>DNAJB6; 7q36</td>
</tr>
<tr>
<td>1E</td>
<td>Desmin; 2q35</td>
</tr>
<tr>
<td>1F</td>
<td>TNPO3; 7q32</td>
</tr>
<tr>
<td>1G</td>
<td>HNRNPD1; 4q21</td>
</tr>
<tr>
<td>1H</td>
<td>3p23</td>
</tr>
</tbody>
</table>

**Ankle contractures & High CK**

Bethelm, 1

- COL6A1: 21q22
- COL6A2: 21q22
- COL6A3: 2q37

Bethelm, 2: COL12A1; 6q13

**Central core**

RYR1: 19q13

**Cytoplasmic body**

- 2q24; 2q21 +...

**Distal myopathies**

- MPD2: MATR3; 5q31
- Emery-Dreifuss

**Lamin A/C**

- 1q21

**SYNE1**

- 6q25

**SYNE2**

- 14q23

**Facioscapulohumeral**

- 1A: DUX4; 4q35
- 1B: DUX4; 10qter
- 2: SMCHD1; 18p11

**Myofibrillar (Desmin storage)**

- MF1M: Desmin; 2q35; AD or AR
- MF1M: CRYAB; 11q22
- MF3M (LGMD 1A): Myotilin; 5q31
- MF3M: ZASP; 10q23
- MF5M: Filamin C; 7q32
- MF6M: BAG3; 10q25
- Congenital: SEPN1; 1p36
- Other

**Myosin storage**

- MYH7; 14q11

**Myotonic (DM1)**

- DMPK; 19q13

**Myotonic (DM2)**

- ZNF9; 3q21
- Oculopharyngeal: PABP2; 14q11

## Limb girdle dystrophies: **Recessive**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>2A</td>
<td>Calpain-3; 15q15</td>
</tr>
<tr>
<td>2B</td>
<td>DF3; 2p13</td>
</tr>
<tr>
<td>2C</td>
<td>y-Sarcoglycan; 13q12</td>
</tr>
<tr>
<td>2D</td>
<td>a-Sarcoglycan; 17q21</td>
</tr>
<tr>
<td>2E</td>
<td>b-Sarcoglycan; 4q12</td>
</tr>
<tr>
<td>2F</td>
<td>f-Sarcoglycan; 5q33</td>
</tr>
<tr>
<td>2G</td>
<td>Telethonin; 17q12</td>
</tr>
<tr>
<td>2H</td>
<td>TRIM32; 5q33</td>
</tr>
<tr>
<td>2I</td>
<td>MDDGC5; FKRP; 19q13</td>
</tr>
<tr>
<td>2J</td>
<td>Titin; 2q24</td>
</tr>
<tr>
<td>2K</td>
<td>MDDGC1; POMT1; 9q34</td>
</tr>
<tr>
<td>2L</td>
<td>ANOS; 11p14</td>
</tr>
<tr>
<td>2M</td>
<td>MDDGC4; Fukutin; 9q31</td>
</tr>
<tr>
<td>2N</td>
<td>MDDGC2; POMT2; 14q24</td>
</tr>
<tr>
<td>2Q</td>
<td>MDDGC3; POMGnT1; 1p32</td>
</tr>
<tr>
<td>2P</td>
<td>MDDGC9; DAG1; 3p21</td>
</tr>
<tr>
<td>2Q</td>
<td>Plectin II; 8q24</td>
</tr>
<tr>
<td>2R</td>
<td>Desmin; 2q35</td>
</tr>
<tr>
<td>2S</td>
<td>TRAPPC11; 4q35</td>
</tr>
<tr>
<td>2T</td>
<td>GMPPB; 3p21</td>
</tr>
<tr>
<td>2U</td>
<td>Cerebellum small; ISPD; 7p21</td>
</tr>
<tr>
<td>2V</td>
<td>GAA; 17q25</td>
</tr>
<tr>
<td>2W</td>
<td>LIMS2; 2q14</td>
</tr>
<tr>
<td>2X</td>
<td>POPDC1; 6q21</td>
</tr>
<tr>
<td>2Y</td>
<td>TOR1AIP1; 1q25</td>
</tr>
<tr>
<td>2Z</td>
<td>MDDGC12; POMK; 8p11</td>
</tr>
</tbody>
</table>

**Caveolin-3**

- Merosin (Laminin a2)
  - Absent: 6q22
  - Reduced

**Abnormal: LGMD 2I**

- **Myosin 2**

**Myosin 2**

- **Cardiomyopathy**

**Arrhythmia**

- POPDC1; 6q21
- Dilated: DPM3; 1q12
- Triangle tongue (2W): LIMS2; 2q14
- CNS: POMGnT2; 3p22
- Contractures: TOR1AIP1; 1q25
- Epilepsy: DPM2; 9q34

**Infant stiffness:** CRYAB; 11q22

## Other inherited myopathy syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>3: Dystroglycan disorders (MDDC)</td>
<td></td>
</tr>
<tr>
<td>APECED: AIRE; 21q22; Recessive</td>
<td></td>
</tr>
<tr>
<td>Autoimmunity</td>
<td></td>
</tr>
<tr>
<td>Excessive: VMA21; Xq28</td>
<td></td>
</tr>
<tr>
<td>Multisystem: CLN3; 16p11; Recessive</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Barnes myopathy: Dominant</td>
<td></td>
</tr>
<tr>
<td>Cardiac + Myopathy</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy-associated</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy (?) LGMD1B</td>
<td></td>
</tr>
<tr>
<td>LGMD 1E: Desmin; 2q35; Dominant</td>
<td></td>
</tr>
</tbody>
</table>

## LGMD: General features

**Muscle proteins**

- **Connective tissue**
- **Dystrophin & associated proteins**
- **Intermediate filaments**
- **Neuromuscular junction**
- **Nuclear envelope**
- **Structural & Contractile**

**Inclusion Body (IBM)**

- Distal + Respir: TTN; 2q31; Dominant
- IBM1: Desmin; 2q35; Dominant
- IBM2: GNE; 9p12; Recessive
- IBM3: MYH2; 17p13; Dominant
- IBM4: 7q22; Dominant
- LGMD 1D: DNAJB6; 7q36; Dominant
- IBM + Paed
- HMRF: Titin; 2q24; Dominant
- KFS4: MYO1B; 22q12; Recessive
- Lipid
- Mitochondrial
- Myotonic dystrophy
- Ophthalmoplegia: MYH2; 17p13; Recessive
- Other dystrophies
- Protein surplus: CASQ1; 1q23; Dominant
- Reducing body
- Respiratory failure
- Scapuloperoneal syndromes
- Skeletal + Myopathy: Dominant
- Bone fragility: MTAP; 9p21
- Paget (VCP; HNRNPA2B1; HNRNPC1)
- Dysphasia
- Diaphragm: TGFB1; 19q13
- Epiphysial: COL9A3; COL9A2; COMP
- Spheroid body (Myotilin)
- Strongman: DCST1; 1q22; Dominant
- Tubular aggregates
- Tubular arrays

http://neuromuscular.wustl.edu
Relevance

- Many diseases treatable
  - Myasthenia gravis
  - Guillain-Barre Syndrome
- Can be complications of other clinical scenarios
  - Chemotherapy
  - Critical illness
- Misdiagnoses lead to missed or excess treatment
  - ALS
General Symptoms

- Weakness
- Sensory disturbance
- Dysphagia
- Diplopia
- Dyspnea
- Dysarthria
- Muscle atrophy
- Falls
- Pain
Other History

- Disease course
- Detailed family history
- Diurnal variability
- Fasciculations
- Episodic symptoms
  - Cold
  - Exercise
  - Carbohydrates
- Autonomic symptoms
Approach

• Examination
  – Goals
    • Distinguish muscle, nerve and NMJ localization
    • Assess functional deficits
    • Identify uncommon and specific findings
  – Frequently diagnostic
Examination features

• Muscle
  – Proximal >> Distal Muscle weakness
  – Reflexes generally preserved
  – Normal sensory exam
  – No or minimal atrophy
Muscle patterns

- Limb-girdle
- Scapuloperoneal
- Distal predominant
- Distal arm/proximal leg
- Ptosis with/without EOM involvement
- Bulbar involvement
Examination Features

• Peripheral nerve disorders
  – Distal weakness +/- Proximal weakness
  – Absent or markedly reduced reflexes
  – Careful sensory exam
Examination

• Neuromuscular junction
  – Fatigable weakness
  – Widespread pattern
    • Ocular and bulbar
  – No sensory loss
  – Often only mildly reduced reflexes despite profound weakness
Workup

- EMG
  - Useful to confirm nerve vs. muscle
  - Can characterize the neuropathy
  - May be useful for prognosis
  - Can distinguish pre-ganglionic from post-ganglionic lesion
  * Requires 10-14 days for changes to develop*
Labs

- **Muscle**
  - CPK, thyroid, ANA, ESR

- **Peripheral neuropathy**
  - HbA1C, Thyroid, ANA profile, RF, B12, ESR, IFE

- **NMJ**
  - Acetylcholine receptor antibodies
Biopsy

• Generally used to confirm diagnosis

• Muscle
  – Confirms inflammatory myopathy
    • Polymyositis vs. dermatomyositis
    • Necrotizing myopathy
  – Can be used to determine type of muscular dystrophy

• Nerve
  – Vasculitis
  – Amyloidosis
  – Inflammatory demyelinating
32 year old male with weakness
- 2 days ago developed numbness/tingling in feet
- Yesterday with back pain
- This morning awoke unable to walk without falling
- Now hands are tingling
- Viral URI 2 weeks ago
Case

Exam

- Normal MS and CN
  - Areflexic
  - 4/5 deltoids and intrinsic hand muscles
  - 3/5 hip flexors and dorsiflexors
  - Panmodality stocking/glove sensory loss

- Workup
  - Lumbar puncture: 2 cells (L), gluc 45, prot. 110
  - MRI L-spine w/ contrast: Enhancing nerve roots
AIDP

- Acute Inflammatory Demyelinating Polyradiculoneuropathy
  - Guillain-Barre Syndrome
- Autoimmune attack on proximal peripheral nerve
  - Humorally mediated
  - Multiple antibodies implicated
Classic AIDP

• Clinical history
  – Lower extremity paresthesias
    • Initial symptom in 50%
  – Back pain
  – Ascending weakness

• Associated symptoms
  – Dyspnea
  – Dysphagia
  – Autonomic symptoms
AIDP

- Frequent prodrome
  - URI
    - Mycoplasma
    - CMV
  - Gastroenteritis
    - Campylobacter jejuni
      - Linked to motor variants
  - Surgery
  - Vaccination
  - Post-partum
  - Seroconversion HIV
AIDP

- Laboratory
  - CSF
    - “albumino-cytologic dissociation”
    - If cells present should suspect HIV
    - OCBs may be present
  - Campylobacter serologies
  - Anti-GQ1b antibodies
  - EMG can be normal
AIDP

• Course
  – Self-limited (even without treatment)
  – Faster recovery with treatment
  – Usual nadir in 1st 10 days
  – Progression <4 weeks
AIDP

• Management
  – ICU or ICA monitoring
    • Tele because of risk of arrhythmia
  – Follow pulmonary functions q4-6 hours
    • Intubation indicated
      – Nif <25 mm Hg
      – FVC < 12-15 ml/kg (~1000 ml)
  – Swallow evaluation/Nutrition
  – Bowel/Bladder care
  – PT for ROM
AIDP

• Treatment - Acute
  – IVIG 2g/kg over 2-5 days
  – Plasma exchange 50mg/kg, 5 treatments over 5-15 days
  – Steroids “Contraindicated”

• Treatment – Long-term
  – Physical and occupational therapy
    • Compensatory devices
Critical Illness Neuromyopathy

• Increasingly recognized complication of ICU
  – Critical illness myopathy (CIM) and Critical illness polyneuropathy (CIP)
  – Most commonly concurrent

• Risk factors
  – Sepsis/SIRS (CIP)
  – Corticosteroid and NM blocking agents (CIM)
  – Severity and duration of ICU admission
CINM

• Presentation
  – Failure to wean
  – Severe weakness (often quadriplegia)
  – Severe atrophy (esp. CIP)
  – Areflexic

• Differential diagnosis
  – CNS disorders
  – Myasthenia Gravis
  – Botulism
  – Guillain-Barre
CINM

• Diagnosis
  – Onset and pre-admission history critical
  – Exam and typical history usually adequate
  – Muscle biopsy
    • Loss of thick filaments (CIM)
  – EMG
    • May show prolonged motor responses (CIM)
    • Absent sensory responses (CIP)

CINM

• Management
  – Supportive care
  – Long-term rehab needed.

• Prognosis
  – Limited studies
  – Most with long-term neurological sequelae
  – Improvement CIM > CIP
Amyotrophic Lateral Sclerosis

- Fatal neurodegenerative disease of the motor neuron
  - Described by Charcot in 1869
  - Causes bulborespiratory failure
  - Riluzole only treatment
ALS Epidemiology

- Worldwide incidence of 1-8/100,000
- Slight male predominance
- 5%-10% familial
- Peak incidence 6th-8th decades
- Lifetime risk 1:2000

\(^1\text{Clin Genet 2003;63(2):83-101}\)
Pathophysiology

- Multifactorial
  - Glutamate toxicity
  - Inflammation
  - Genetic
    - Monogenetic
    - Polygenetic
  - Mitochondrial
  - Toxic misfolded proteins
  - Environmental exposures

Motor neuron death
Clinical features

• Progressive weakness
  – Often asymmetric
  – May begin in bulbar, respiratory or limb
  – Painless
  – Occasionally pseudo-acute presentation to hospital

• Fasciculations

• Eventual failure to thrive and death
ALS Diagnosis

• Neurological examination – Primary means of dx
  – UMN and LMN signs
  – Fasciculations
  – Asymmetry
  – Normal sensation

• Ancillary tests to exclude alternative diseases
  – MRI
  – Serologic tests
  – EMG
  – Lumbar puncture rarely needed
ALS Exam

- **Upper motor neuron exam**
  - Spastic dysarthria
  - Slow tongue movements
  - Hyperactive gag, blink, jaw, deep tendon reflexes
  - Increased tone in limbs
  - Babinski (relatively uncommon) and Hoffman signs
  - Pseudobulbar affect

- **Lower motor neuron exam**
  - Flaccid dysarthria
  - Atrophy
  - Hyporeflexia
  - Decreased tone
  - Fasciculations
Variants

- Primary lateral sclerosis (PLS)
  - Pure upper motor neuron
- Progressive muscular atrophy (PMA)
  - Pure lower motor neuron

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>No of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic</td>
<td>404 (30.3)</td>
</tr>
<tr>
<td>Bulbar</td>
<td>456 (34.2)</td>
</tr>
<tr>
<td>Flail arm</td>
<td>74 (5.5)</td>
</tr>
<tr>
<td>Flail leg</td>
<td>173 (13.0)</td>
</tr>
<tr>
<td>Pyramidal</td>
<td>120 (9.1)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>14 (1.1)</td>
</tr>
<tr>
<td>PLMN</td>
<td>38 (2.9)</td>
</tr>
<tr>
<td>PUMN</td>
<td>53 (4.0)</td>
</tr>
<tr>
<td>Overall ALS</td>
<td>1332</td>
</tr>
</tbody>
</table>

JNNP, 2011. 82(7): p. 740-6
ALS management

- **Generally quality of life**¹
  - Cramps
    - Baclofen, Benzos
  - Saliva
    - TCA, Botox
  - Nutrition
    - PEG
  - Mobility
    - Power chair, hoyer

- Physical therapy
  - ROM, conditioning
- Psychosocial
  - Family, occupation
- Pulmonary
  - Non-invasive ventilation
    - Improves survival ²,³
    - Secretion management

¹ Neurology 73(15): 1218-1226
² J Neurol Sci 125 supp: 19-26
³ J Neurol Sci 164(1): 82-88
Challenge of Misdiagnosis

• “Risk factors”
  – Heterogeneous disease
  – Mimicked by much more common disorders
    • Radiculopathy
    • Entrapment neuropathy
  – Lack of provider experience
  – Lack of pain
Conclusion

- Neuromuscular diseases are a group of common and rare diseases of the peripheral nervous system.
- Careful clinical history and exam are the most important factor contributing to diagnosis.
  - Nerve, muscle and NMJ diseases have different exams.
  - Ancillary tests merely confirm clinical diagnosis.
- Treatment includes supportive care and immune directed treatments.
  - Treatment impacts prognosis and quality of life.
- Awareness by non-neuromuscular specialists critical.
Questions?

“I thought Google eliminated the need to ask questions out loud, but fine…”

Congratulations on 35 great years of the BNI Neuroscience Nursing Symposium!