Introduction to Neuromuscular Junction Disorders

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NMJ Disorders

1. Intro to NMJ Disorders – Kelly Gwathmey
2. Electrodiagnostic Approach to NMJ Disorders- Hans Katzberg
3. Treatment of NMJ Disorders- Amanda Guidon
4. NMJ Disorder Cases- Michael Hehir
Outline

Postsynaptic Neuromuscular Junction Disorder (Myasthenia Gravis)
  o Pathophysiology
  o Clinical Presentation and Examination
  o Myasthenia Gravis Subgroups
    • Early onset, Late onset, Ocular, Thymomatous, MuSK, LRP4, and Seronegative
  o Myasthenic Crisis

Presynaptic Neuromuscular Junction Disorders
  o Lambert-Eaton Myasthenic Syndrome (LEMS)
  o Botulism
Myasthenia Gravis

• Autoimmune disorder resulting from antibodies directed toward postsynaptic neuromuscular junction proteins, often the acetylcholine receptor (AChR).
• Impaired neuromuscular transmission ➔ skeletal muscle weakness
• Diagnosis hinges on combination of symptoms and signs of the disease in combination with specific autoantibodies.
• If autoantibodies are absent, then electrophysiological tests will secure the diagnosis.
Myasthenia Gravis Epidemiology

• Incidence approximately 10 per 1,000,000*
• Prevalence is 150-250 per 1,000,000*
• Women affected more than men (2:1-3:1), ratio becomes equal after age 40**


Pathophysiology

• Autoantibodies target the NMJ, resulting in reduced AChR on the postsynaptic muscle surface.

• Autoantibodies:
  - AChR 80%
  - MuSK 1-10%
  - LRP4 1-5%
  - Seronegative: low level antibodies not testable with current assay or antibodies that bind other components of the NMJ.
Myasthenia Gravis Autoantibodies
Acetylcholine Receptor

Cells. 2019 Jul 2;8(7).
How are the postsynaptic AChRs affected by anti-AChR antibodies?

Anti-AChR AB

Anti-AChR AB

AChR Receptor

Crosslinking

Endocytosis

Degradation

Complement Binding

MAC formation

Post-junctional membrane damage

https://neuromuscular.wustl.edu/mtime/modulation.htm#complement
Simplification of Postsynaptic Membrane in MG

Fig 2  Ultrastructural localisation of AChR at intercostal muscle end-plate from control subject (A) and in moderately severe, generalised MG (B). In B, only short segments of simplified postsynaptic membrane react for AChR. Presynaptic staining, seen in A, is virtually absent in B. A, B ×22 300. (Reproduced from ref 5, by permission.)
How are the postsynaptic AChRs affected by anti-AChR antibodies?

Direct Inhibition by AChR AB

https://neuromuscular.wustl.edu/mtime/modulation.htm#complement

Ann N.Y.Acad. 1987, 505, 526-538
J. Neuroimmunol. 1983, 5, 1-9
Anti- AChR autoantibodies

**Binding antibodies** - measure of IgG and IgM antibodies that bind AChR

- Relatively sensitive and specific

**Blocking antibodies** - block binding site for ACh on AChR

- Lower specificity for MG

**Modulating antibodies** - Anti-AChR antibodies cross-link AChRs on postsynaptic membrane.

- Low specificity for MG (hemolysis, muscle relaxers, arthrogryposis)

- Detected with Radioimmunoprecipitation Assay
- IgG1 and variably IgG3 subclass and activate complement
Myasthenia Gravis Autoantibodies

Anti-MuSK and anti-LRP4 antibodies block the intermolecular interactions of MuSK or LRP4 respectively.

This inhibits the normal mechanisms for maintenance and organization of the neuromuscular junction.
Clinical hallmark is fluctuating and fatigable weakness with repeated activity.
Initial Symptoms in Myasthenia Gravis

• **Ocular – 80%**
  - Diplopia, ptosis
  - Usually asymmetric, fluctuating, fatigable
• **Bulbar – 10%**
  - Swallowing
    - Frequent choking, nasal regurgitation, chewing fatigue
  - Speaking
    - Slurred speech, fatigable
• **Axial – 5%**
  - Neck weakness
• **Limb – 5%**
  - Proximal
• **Respiratory - <1%**
Symptoms in Generalized MG

• **Ocular**
  - Ptosis – 90%
  - Diplopia – 80%

• **Bulbar and Breathing**
  - Dysphagia – 70%
  - Dysarthria – 70%
  - Dyspnea – 40%

• **Limb and Neck**
  - Neck flexion – 70%
  - Proximal arms – 70%
  - Proximal legs – 70%
## MGFA Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
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| I     | Any ocular muscle weakness  
May have weakness of eye closure  
All other muscle strength is normal |
| II    | Mild weakness affecting other than ocular muscles |
| IIa   | Predominantly affecting limb, axial muscles, or both  
May also have lesser involvement of oropharyngeal muscles |
| IIb   | Predominantly affecting oropharyngeal, respiratory muscles, or both |
| III   | Moderate weakness affecting other than ocular muscles  
May also have ocular muscle weakness of any severity |
| IIIa  | Predominantly affecting limb, axial muscle or both  
May also have lesser involvement of oropharyngeal muscles |
| IIIb  | Predominantly affecting oropharyngeal, respiratory muscles, or both  
May also have lesser or equal involvement of limb, axial muscles, or both |
| IV    | Severe weakness affecting other than ocular muscles  
May also have ocular muscle weakness of any severity |
| IVa   | Predominantly affecting limb and/or axial muscles  
May also have lesser involvement of oropharyngeal muscles |
| IVb   | Predominantly affecting oropharyngeal, respiratory muscles, or both  
May also have lesser or equal involvement of limb, axial muscles, or both |
| V     | Defined by intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb |
Ocular Examination

• Dysconjugate gaze can be elicited with sustained horizontal gaze.
  • Spares pupils
  • Does not follow cranial nerve distribution.
• Ptosis
  • Often unilateral or asymmetrical
  • Fatigues with sustained upgaze.
• Weak eye closure

https://www.aao.org/eyenet/article/when-muscles-falter-update-on-myasthenia-gravis
Examination Continued

- **Facial muscles**
  - expressionless face
  - myasthenic snarl with attempted smiling
- **Dysarthria**
  - nasal speech that worsens with prolonged speaking
- **Palate may not elevate**
- **Tongue weakness**
  - when patient is asked to push tongue against side of cheek
- **Neck weakness of flexion>extension** (may have dropped head)
- **Proximal predominant weakness of extremities**

http://neurosigns.org/wiki/Myasthenic_snarl
Neuromuscular Disorders 2015 25(5): 429-431
Myasthenia Gravis Subgroups

1) Age of onset
   - Early-onset MG (EOMG), onset below age 50, female predominant, often with thymic hyperplasia
   - Late-onset MG (LOMG), onset after 50, high fraction male patients
Myasthenia Gravis Subgroups

2) Distribution of manifestations
   - Ocular MG (OMG)
     - 15-20% of patients will remain ocular
     - 50% will have detectable AChR antibodies (not reported in MuSK)
     - 90% at 2 years will stay ocular
   - Generalized MG (GMG)
Myasthenia Gravis Subgroups

3) Thymic Status (thymomatous and non-thymomatous)
   - 10-20% will have a thymoma (increases with age)
   - More commonly thymic hyperplasia
Myasthenia Gravis Subgroups

4) Serology

- **AChR +**
- **MuSK +**
  - Affects primarily women
  - 2 presentations
    1. up to 50% with similar to AChR + MG
    2. severe craniobulbar weakness and atrophy
- **LRP4+**
  - Mild generalized or ocular symptoms
  - Double seropositive
    - more likely to have bulbar, respiratory, axial and extremity muscle weakness
- **Seronegative**

Myasthenic Crisis

• MG-related respiratory muscle weakness so severe that requires intubation and ventilation
• 15-20% of patients
• Most typically in first 3 years
• 30% of MuSK patients
What Exacerbates Myasthenia Gravis?

- Heat
- Stress
- Infection
- Medications- https://myasthenia.org/Portals/0/Cautionary%20Drugs.pdf
- Vaccines
Presynaptic Disorders
Lambert-Eaton Myasthenic Syndrome (LEMS)

- Most common presynaptic neuromuscular transmission disorder in adults
- Annual Incidence 0.48 per 1 million*
- Prevalence 2.32 per 1 million*
- Mean age of disease onset
  - Paraneoplastic LEMS 60 years (male predominant)
  - Non-paraneoplastic LEMS (2 peaks 35 and 60 years), men=women**
- 50% tumor associated*** (smoking associated small cell lung cancer)

In LEMS antibodies block the P/Q subtype of VGCC which prevents calcium influx.

Less acetylcholine vesicles are released from motor and autonomic cholinergic nerve terminals.
LEMS Pathophysiology

• VGCC are expressed on SCLC cell and other cancer cells.
• SCLC tumor cells have antigenic potential and trigger autoantibody production.
• 65% of nonparaneoplastic LEMS will have HLA-B8-DR3 haplotypes.
• 10-15% of LEMS are without P/Q type VGCC antibodies.
• Antibodies to SOX1 (a transcription factor belonging to SRY family of high-mobility group box proteins) is a diagnostic marker for LEMS and has high specificity for SCLC.
Paraneoplastic LEMS

• Screen for possible associated tumor with CT and/or PET

• Value in screening for other markers of SCLC including neuron specific enolase, pro-gastrin-releasing peptide (ProGRP), SOX1, and Hu proteins

• If malignancy screening initially negative- continue screening every 3-6 months for at least 2 years
DELTA-P Scoring System

- Dutch-English LEMS Tumor Association Prediction (DELTA-P)
- Prediction score for SCLC in LEMS
- Calculated based on age of onset, smoking habits, weight loss, bulbar involvement, ED, Karnofsky performance status
- Scores range 0-6
- Higher score, higher SCLC association
LEMS Clinical Presentation

• Clinical Triad
  1. Weakness
     o Leg weakness
  2. Autonomic Dysfunction
     o Dry mouth, blurred vision constipation, orthostatic hypotension, hypohydrosis
  3. Areflexia
     o Often facilitate with exercise

• Severe fatigue
• May look like CIDP but no sensory involvement
LEMS Prognosis

• Paraneoplastic LEMS
  ◦ prognosis is poor and depends on the stage of the malignancy
  ◦ most live a few years.

• Nonparaneoplastic LEMS
  ◦ live for more than 20 years
  ◦ respond well to immunotherapy
Botulism

• Rare, but potentially fatal syndrome caused by the neurotoxin from gram-positive, rod-shaped, spore forming, anaerobic bacterium *Clostridium botulinum*. 

https://www.cdc.gov/botulism/general.html
Botulism

• CDC has 4 categories of transmission of botulinum toxin
  1. Infantile
  2. Food-borne
  3. Wound
  4. Other (including bioterrorism and adult intestinal colonization)
• Between 2011-2015 average of 162 cases annually in US
  o 71-88% infant botulism
  o 1-20% foodborne botulism
  o 5-10% wound botulism

https://www-ncbi-nlm-nih-gov.proxy.library.vcu.edu/books/NBK459273/
Botulinum Toxin

- There are 8 distinct serotypes of botulinum neurotoxin
- Most cases in US are caused by Type A and B
- Infants will ingest or inhale spores, migrate across the mucosal barrier into the circulation. Toxins cross intestinal or pulmonary epithelium into circulation.
- Adults may ingest preformed toxin in improperly stored food.
- Wound botulism is the result of spore germination in devitalized tissue, often due to subcutaneous injection of illicit drugs with spore contamination.
Botulism Pathophysiology

Healthy neuromuscular transmission

A

Effect of botulinum neurotoxin (BoNT)

B

Presynaptic terminal

VAMP

Membrane fusion

SNARE complex

SNAP-25

Syntaxin

Synaptic cleft

ACh vesicle

Na+

ACh receptor

Muscle cell

BoNT Light chain

Light chain dissociates and targets SNARE complex

Membranes do not fuse

Heavy chain
Infantile Botulism

- Affects children 1-6 months of age
- Classically due to exposure to contaminated soil or honey
- Presenting symptoms: constipation, weakness, feeding difficulties, weak cry and drooling.
- On exam sluggish pupillary response, weakness of extremities and low tone.
- Autonomic dysfunction- constipation (key), urinary retention, dry mouth, blood pressure instability
- May need intubation and mechanical ventilation

Food-borne Botulism

• Prodrome of abdominal pain, nausea, vomiting beginning 12-72 hours after ingestion
• Blurred vision due to pupillary dilation, with diplopia and ptosis
• Bulbar dysfunction
• Symmetric descending weakness
• Gastrointestinal symptoms (nausea, vomiting, diarrhea)
• Other autonomic symptoms: blood pressure and heart rate variability
Botulism Diagnostic Testing

• Lab confirmation – serum and stool assays for the toxin. Stool microscopy for spores, stool culture, wound culture.
• Traditionally – mouse lethality assay – live mouse injected with stool/serum sample. – look for mouse to have signs of botulism and death.
• Many new testing options in pipeline.*
• Electrodiagnostic testing… more to come shortly

Treatment of Botulism

- Close monitoring in hospital and possible respiratory support
- Over one year- equine derived antitoxin.
- Under one year- human derived botulism immunoglobulin.
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