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Neuromuscular Junction Disorders

Peter D. Donofrio, M.D.
Professor of Neurology
Vanderbilt University Medical Center
Neuromuscular Junction
Genetic and Antibody Targets

Figure 1

Antibody targets
- VGKC
- VGCC
- nAChR
- MuSK

Genetic targets
- VGKC
- VGCC
- CHAT
- AChE
- nAChR
- Rapsyn

Key:
- nAChR
- VGNaC
- VGCC
- VGKC
- MuSK
- CHAT
- AChE
- Rapsyn

Muscle fibre

Synaptic vesicle
Neuromuscular Junction

- Synaptic bouton contains vesicles with ACh.
- In synaptic cleft is AChE and proteins involved in stabilizing NMJ.
- Postsynaptic membrane has deep folds, and AChR is densely packed in at the top.
- When action potential reaches NMJ, ACh is released, binds to AChR, activating Na+ voltage gated channels.
**Myasthenia Gravis**

**Model: Post-Synaptic Junction**

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*Figure 3.* Acetylcholine opens receptor channels. Without acetylcholine, receptor channels are closed, *a.*, and no muscle contraction occurs. But when the receptors bind acetylcholine, *b.*, a channel into the cell is opened, bringing about a chemical change that causes the muscle cell to contract. (From The Salk Institute Newsletter, Fall 1983, artist Jamie Simon.)
Myasthenia Gravis
Clinical Features

• Demography
  – Occurs in approximately 20.4 per 100,000
  – Prevalence estimated at 40,000 -70,000 in U.S.
  – Occurs in 2 population peaks: young women and persons over 60 (more men than women). 11% are children.

• Clinical Presentation
  – Ocular: Ptosis and diplopia
  – Bulbar: Facial weakness, dysfunction of chewing, swallowing, and speech
  – Extremities: Fatiguable weakness, proximal weakness
  – Respiratory: SOB at rest or with exertion
Myasthenia Gravis

Laboratory Testing

- Edrophonium (Tensilon Test)
- Antibodies against acetylcholine receptor
- Antibodies against muscle specific kinase
- Thyroid function studies
- Serum K, Ca, Mg
- Chest CT or MRI scan
Figure 7-1. Examples of a positive response to edrophonium (Tensilon) in diagnostic testing for myasthenia. A patient with bilateral ptosis (A) regains normal lid elevation (B). In a second patient with unilateral ptosis and bilateral elevator palsies (C), administration of edrophonium eliminates the ptosis and restores normal vertical eye movement (D). In both cases, the original deficit returned within 10 minutes. (Courtesy of Dr. Norman Schatz.)
Myasthenia Gravis
Antibody Testing

- Acetylcholine Antibody (AChR-Ab)
  - Blocking
  - Binding
  - Modulating
- Binding and Modulating same frequency: 86%
- Blocking: 52%
- Sensitivity improves by assaying binding and modulating (8% of patients had only one positive)
- Blocking antibodies often associated with modulating antibodies-correlate better with clinical symptoms.

- Muscle Specific Kinase Antibodies
  - 40% of Seronegative MG patients
Myasthenia Gravis
Muscle Specific Kinase

- Approximately 15% of generalized myasthenia gravis (MG) and 50% of ocular myasthenia patients have no detectable antibodies to the acetylcholine receptor (AchR)
- In 2001 Hoch et al. found antibodies to muscle specific kinase (MuSK) in 66% of patients with generalized MG who were sero-negative for acetylcholine receptor antibodies
- MuSK sero-positivity not seen in AchR+ patients
- Only other antibodies associated with myasthenia have been: anti-striated muscle seen in patients with thymoma and anti-rapsyn antibody
Clinical Characteristics of MuSK+ Myasthenia Gravis

- Female predominance
- Young (6-68, peak 20-40)
- Bulbar symptoms more common
- Respiratory failure more common (75% v. 4%)
- Muscle atrophy more common
- Minimal thymic abnormalities
- MuSK antibodies in 30-40% of seronegative MG patients in UK, USA, Japan
Electrodiagnostic Testing for Myasthenia Gravis

• Repetitive Nerve Stimulation: usually the first electrophysiologic testing ordered
  – Ulnar nerve
  – Spinal Accessory nerve
  – Facial nerve

• Single Fiber EMG (SFEMG): if repetitive nerve stimulation is normal or equivocal
  – EDC
  – Frontalis
  – Masseter
  – Biceps Brachii
Myasthenia Gravis
Repetitive Nerve Stimulation

2 Hz
Rbegin: Repetitive Nerve Stimulation

Myasthenia Gravis

Decremental response

Train 1

Post-tetanic potentiation

Train 2

Post-activation exhaustion

Train 3
Single Fiber EMG (SFEMG)

- Developed by Stalburg and Ekstedt in 1963
- Record simultaneously the potentials of two muscle fibers innervated by the same axon
- Measure the variability or “jitter” in latencies between the fibers
- Typical practice to measure variability in 20 pairs and take the average = mean consecutive difference (MCD)

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\frac{|\text{Int}_1 - \text{Int}_2| + |\text{Int}_2 - \text{Int}_3| + \ldots + |\text{Int}_{n-1} - \text{Int}_n|}{n-1}
\]
Single Fiber EMG
Model of Potential Pairs

Dahlback, Ekstedt, Stålberg, 1970
Myasthenia Gravis
Thymic Abnormalities

- Thymic abnormalities in 80%-85% of patients
- Majority have follicular hyperplasia
- Thymoma 10%-15%
Myasthenia Gravis

Treatment

- Acetylcholinesterase inhibitors (Pyridostigmine)
- Thymectomy
- Corticosteroids
- Other immunosuppressant medications
  - Azathioprine (Imuran)
  - Methotrexate
  - Cyclosporin (Sandimmune, Neoral)
  - Mycophenolate Mofetil (CellCept)
  - Tacrolimus
- Plasma exchange
- IVIG (intravenous immunoglobulin)
- Rituximab (Rituxan) - potential future treatment
• Patients undergoing thymectomy
  – More likely to achieve medication-free remission, relative rate (RR): 1.6
  – Become asymptomatic: RR 1.6
  – Improve: RR 1.7
  – Magnitude of improvement greater in more severe disease
  – Thymectomy technique: no conclusion
  – Younger age, female gender: More likely to benefit
Intravenous Immunoglobulin (IVIG)

Large trials in Myasthenia Gravis
AchR-ab+ patients

87 patients in exacerbation comparing IVIG vs. Plasma exchange
• 2 doses of IVIG used (0.4 g/kg daily for 3 days (1.2 g/kg) or 5 days (2 g/kg)
• Showed no difference between all 3 treatments, although IVIG groups had less complications.

2nd Trial: Zinman, Ng, Bril 2007.
Studied 51 patients, worsening myasthenia gravis
Randomized to 2g/kg IVIG or 5% dextrose H2O.
Quantitative MG Score, masked observer, day 14 and 28
IVIG-treated patients: clinically meaningful improvement in QMG at days 14 and 28
Greatest improvement in most severe disease
Lambert-Eaton Myasthenic Syndrome

Clinical Features

• Proximal Weakness, Slight Improvement with Exercise
• Areflexia
• Autonomic Disturbances
• Characteristic Repetitive Stimulation Abnormalities
• Association with Carcinoma
• Pre-synaptic Neuromuscular Junction Disorder
• Antibodies to Voltage-Gated Calcium Channels
Lambert-Eaton Syndrome
Repetitive Nerve Stimulation Testing
Lambert-Eaton Myasthenic Syndrome Treatment

• Evaluation for malignancy
• Guanidine: 30 mg/kg/day
• 3,4-diaminopyrididine
• Acetylcholinesterase inhibitors: pyridostigmine
• Immunologic Therapies
  – Plasma exchange
  – IVIG
  – Oral Immunosuppressive agents: Prednisone, mycophenolate, cyclosporine
Botulism

- Acute onset of dysphagia, dysarthria, ptosis
- Autonomic dysfunction
- Seen in illegal drug users; injuries (sometimes minor)
- Treatment: early diagnostic suspicion, antitoxin, wound debridement, penicillin, supportive therapy (for weeks)
Botulism - Repetitive Nerve Stimulation

Botulism

Therapy

- **Monitoring:** Vital signs especially RR, airway integrity, pulse oximetry, ABGs, ventilation
- **Equine serum botulism anti-toxin:** 7 known botox types A-G
  - 20% serum sickness
  - 3% anaphylaxis
- **Antibiotics for wound infections:** Pcn G 3 million units IV q4h or metronidazole 500 mg q8h.
Myasthenia Gravis & Related Disorders

Summary

• Myasthenia Gravis
  – Clinical Presentation
  – Electrophysiology, Antibody Testing
  – Role of the Thymus
  – Treatment

• Lambert-Eaton Syndrome

• Botulism.