Faculty/Presenter Disclosure
Slide 1

• Faculty: Blaine Foell

• Relationships with commercial interests:
  – Grants/Research Support: None
  – Speakers Bureau/Honoraria: None
  – Consulting Fees: None
  – Other: None
Disclosure of Commercial Support
Slide 2

• This program has received no financial support
• This program has received no in-kind support

• **Potential for conflict(s) of interest:**
  - None
Mitigating Potential Bias
Slide 3

• Not applicable
Objectives

1. Review the physiology and disorders of Neuromuscular Transmission

2. Learn an approach to diagnosing Myasthenia Gravis

3. Understand the management of Myasthenia Gravis patients.
Neuromuscular transmission

PRESYNAPTIC
Nerve terminal

SYNAPTIC
Basal lamina

POST-
SYNAPTIC
Muscle endplate
Neuromuscular transmission

- Depolarization of nerve terminal
  - $\text{Na}^+$ influx
- Repolarization
  - $\text{K}^+$ efflux (VGKC)
Neuromuscular transmission

- Activation of VGCC and Ca$^{++}$ influx
  - P/Q-type VGCC
  - Brief local increase in Ca$^{++}$
  - Then calcium diffuses away
Neuromuscular transmission

- Migration of vesicles containing acetylcholine (ACh) and fusion with pre-synaptic membrane...
Neuromuscular transmission

- Release of acetylcholine into neuromuscular junction:
  - Binds to AChR
  - Diffuses away before reaching AChR
  - Metabolized by AChE and doesn’t reach AChR
Neuromuscular transmission

- Opening of acetylcholine receptors (AChR) and entry of cations (mostly Na\(^+\)) into muscle, eventually leading to excitation-contraction coupling and muscle contraction.
Summary

• Pre-synaptic
  • Nerve action potential - influx Na\(^+\) (depolarization) and efflux of K\(^+\) (repolarization)
  • Depolarization of nerve terminal – VGCC open
  • Ca\(^{++}\) influx into nerve terminal
  • Migration of vesicles containing ACh and release

• Synaptic
  • ACh in NMJ is either metabolized, diffuses out of NMJ or binds to AChR

• Post-synaptic
  • ACh binds to AChR on muscle surface
  • AChR open - influx of Na\(^+\) into muscle
  • Excitation-contraction coupling (Ca\(^{++}\) dependent)
1 vesicle = 1 quantum = 10,000 ACh molecules, which when released spontaneously @ 0.2 Hz opens ≈1500 AChRs, producing a miniature end plate potential (MEPP) of 0.5-1.0 mV (i.e. end plate ‘noise’)

Depolarization of nerve terminal results in release of quantal content = 50-100 vesicles producing an end plate potential EPP of 50-60 mV
MEPPS, EPPs and action potential generation

If EPP is of sufficient amplitude it will trigger an all or none action potential.

Membrane potential (mV)

Threshold

MEPP’s

EPP

Action potential

Time
Neuromuscular Junction

• Contains a lot more than the AChR!
  • For almost every protein at the NMJ there can be
    • A mutation – causing a congenital myasthenic syndrome
      • Pre-synaptic – VGCC or vesicle trafficking
      • Synaptic - AChE
      • Post-synaptic – AChR itself (structure or function) or other proteins influencing function of AChR (MuSK, Rapsyn etc.)
Disorders of Neuromuscular Transmission

• In myasthenia gravis antibodies reduce the numbers of or availability of AChRs
  - Antibodies against acetylcholine receptor, MuSK or Lrp4 on the post-synaptic muscle surface

• In the Lambert Eaton Myasthenic Syndrome (LEMS) antibodies reduce the amount of ACh that is released
  - Antibodies against voltage-gated calcium channels (VGCC) on the pre-synaptic nerve terminal reduce Ca^{++} influx into the nerve terminal
Neuromuscular transmission in MG

Anti-AChR abs in MG
Neuromuscular transmission in LEMS

Anti-VGCC abs in LEMS
Two additional phenomena that occur normally that explain decrement (and fatigue) and increment when NMT is impaired

- What happens during low frequency stimulation (LFS; 2-5 Hz)
- What happens during high frequency stimulation (HFS; 20-40 Hz) or maximal voluntary contraction (MVC)
  - NB – during MVC the nerve supplying that muscle fires at \( \approx 20-30\text{Hz} \) – in effect the same as high frequency stimulation of the nerve supplying that muscle
Low frequency stimulation (LFS)

- During low frequency repetitive stimulation (e.g. 3 Hz) there is a gradual reduction in the amount of ACh released from the presynaptic nerve terminal even in normals.
- Initial ACh released comes from pre-formed vesicles.
Effects of LFS - normal NMT

- **Safety margin** in NMT
  - In humans, the product of:
    
    \[ \text{[ACh released]} \times \text{[#s of AChRs available]} \]
    
    determines probability that there will be an action potential at that muscle fibre, and in humans is > 3x needed

- So – when NMT is normal, even though there is a gradual reduction in [ACh released] with LFS, this product never falls below safety margin and there is no decrement (electrophysiologically) or weakness (clinically)
Effects of LFS - MG or LEMS

• In **MG** the number of AChRs is reduced, so if [ACh released] falls below critical level as a result of LFS
  
  OR

• In **LEMS** [ACh released] is reduced, so if [ACh released] is reduced even more as a result of LFS then:

  • An action potential is not produced at that muscle fibre.

  • If this happens at a single muscle fibre it can be detected with SFEMG as blocking and if enough muscle fibre action potentials fail, detected during LFS as decrement (and weakness clinically).
LFS - Myasthenia

Normal

MG
High frequency stimulation

- Normally, after nerve depolarization there is a **transient** (100-200 µsec) **increase** in [Ca$$^{++}$$] in the nerve terminal.

- During **high** frequency repetitive stimulation (20-40 Hz) or maximal voluntary contraction (MVC) another depolarization arrives while the [Ca$$^{++}$$] is still increased, this increases the [Ca$$^{++}$$] in nerve terminal and increases ACh release.

- At stimulation rates < 10 Hz successive stimuli **don’t** fall within 100-200 µsec window - calcium diffuses away and no increase in ACh release.
LFS - Myasthenia

Post-exercise repair
- Increased amplitude of first stimulation
- Reduced decrement

Post-exercise exhaustion
- $\pm$ decreased amplitude of first stimulation
- Increased decrement
Lambert Eaton Myasthenic Syndrome ‘LEMS’

LFS – pre MVC

LFS – post MVC

Repair

HFS

Increment

LFS

Decrement

Thenar Recording

(3Hz)

(40Hz)
Myasthenia Gravis

- Autoimmune
- Antibodies against proteins at neuromuscular junction
  - AChR - ≈ 50% in ocular, ≈ 85% in generalized
  - MuSK (skeletal muscle specific tyrosine kinase) - 0-70% of remaining generalized seronegative so 0-10% overall
  - Lrp4 (Low density lipoprotein-receptor related protein) 2-50% of AChR/MuSK neg ≈ 2-3% overall?
  - Other targets?
- Uncommon
  - Prevalence : 1 in 10,000
  - Incidence : 6 in 10^6
  - Increasing in the elderly
Mechanisms of AChR abs

- **Blockade**: AChRs still there but blocked
- **Cross-link and internalization**: AChRs reduced but can be replenished
- **Complement binding and destruction**: AChRs reduced and may or may not be replenished
Clinical features of Myasthenia Gravis

- **Ocular**
  - Diplopia, ptosis
- **Bulbar**
  - Facial weakness, dysarthria, dysphagia, jaw (closure) weakness
- **Axial**
  - Neck flexion or extension (head drop)
- **Respiratory**
  - Orthopnea, dyspnea bending over
- **Extremity**
  - Proximal arm > leg
  - Distal/asymmetric can occur
Clinical features of Myasthenia Gravis

- **Fluctuation and fatigue** – characteristic for MG
  - Diurnal fluctuation - worse at end of day
    - Ptosis - OK in morning, worse watching TV at day’s end.
    - Bulbar
      - Slurred speech, worsening during conversation
      - Dysphagia not there or mild at breakfast, worse at lunch and much worse with dinner
  - Fluctuation over time
    - Previous episode of something similar months-years earlier that resolved spontaneously
    - There some days/weeks and not (or less) on others
- Fluctuation/fatigue NOT present in all MG pts
- ....and if asked directly most patients who have weakness but don’t have MG will say it’s worse at end of day
Diagnosis of MG

- Clinical suspicion
  - Often biggest barrier to diagnosis
  - Testing for fatigue
    - Counting out loud to 30 – dysarthria
    - Sustained up gaze for > 60 seconds – ptosis
    - Resisted deltoids for 5 contractions – increased weakness

- Reversal of clinical features
  - Tensilon, Ice Pack

- Electrophysiological
  - Repetitive nerve stimulation, single fibre EMG

- Serological
  - AChR – 85% of generalized, 50% of ocular
  - MuSK – 0-10% of generalized
  - Lrp4 - 2-50% of AChR/MuSk neg

RNS: Decrement
Ice Pack Test

- Ice on ptotic lid for 5 minutes
  - Rest + cold temperature improves NM transmission
- Assess ptosis before and after
- Sensitivity and specificity \( \approx \) Tensilon
- Minimal adverse
Diagnostic tests in MG

Sensitivity

* Not usually done in generalized MG
Diagnostic tests in MG

Specificity

- Tensilon
- Ice Pack
- RNS
- SFEMG
- AChR Abs

99%
MuSK positive MG

- “MuSK phenotype”
  - Female, bulbar, early onset
    - But in individual patients hard to predict – can be same oculobulbar/axial/limb as AChR+ MG
  - ?? More often ‘oligosymptomatic’
    - Just head drop, isolated dyspnea, dysphagia
  - More severe?
  - Very rare in pure ocular
  - Less responsive to Mestinon ± worsen?
  - Less responsive to IVIG?
MuSK Myasthenia Gravis

- MuSK MG not associated with thymic pathology?

- Electrophysiology different
  - Yield higher in facial/proximal muscles (RNS and SFEMG)
  - ‘myopathic’ changes on needle EMG
Lrp4 MG

• Newly discovered ab against lipoprotein receptor-related protein (Lrp4)

• Prevalence
  • Found in 2-50% of AChR & MuSK negative generalized (15-20% overall?)
  • F:M 2.5:1 (slightly more ♀ than AChR+ MG?), mostly early onset (average age 33.4 ♀ 41.9 ♂)

• Clinical phenotype
  • Ocular - found in 27% of AChR/MuSK neg ocular MG in one series (Zisimopoulou et al 2013) vs MuSK abs - very rare in ocular MG
  • Milder (MGFA I or II) MG than AChR or MuSK
  • Bulbar/neck in some
  • Double positives (Lrp4 + AChR, Lrp4 + MuSK) found and associated with more severe disease

• Thymus
  • Lrp4 rarely/never associated with thymoma, sometimes (⅓) with thymic hyperplasia (similar to AChR/MuSK neg)

• Treatment
  • Similar response to treatment as AChR+ MG?
Diagnostic pitfalls in MG

- Seropositive MG (AChR or MuSK)
  - They have MG!
    - Abs 99% specific
  - but…. are symptoms secondary to MG?

- Seronegative MG
  - MG but seronegative
  - Not MG!
    - Mitochondrial
    - Other muscle
    - Other nerve
Lambert Eaton Myasthenic Syndrome ‘LEMS’

1° Autoimmune or paraneoplastic
- Prevalence – ½ 1° autoimmune; ½ paraneoplastic
- Incidence – 10% autoimmune; 90% paraneoplastic
- Paraneoplastic – almost always SCLC
  - If you find another malignancy keep looking

Pathophysiology
- Antibodies against voltage-gated calcium channels (VGCC) in both

Epidemiology
- Incidence 0.4/10^6 (1/15 of MG)
- Prevalence 2.5/10^6 (1/30-45 MG)
  - Reduced survival vs MG
LEMS vs MG

• Clinical

• MG – starts at head and descends
  • Ocular, bulbar, axial/resp, arm, leg
  • Reflexes normal

• LEMS – starts in legs and ascends
  • Legs, arms, bulbar, ocular
  • NB – ptosis and diplopia DO occur in LEMS – just later
  • LEMS ‘never’ starts with isolated diplopia/ptosis
  • Reflexes reduced or absent
  • Autonomic – dry mouth, constipation, ED, postural hypotension
Treatment of LEMS

- 3,4-diaminopyridine (3,4-DAP)
  - Inhibits VGKC on nerve – prolonging nerve depolarization and increasing ACh release
  - Mestinon alone or with 3,4-DAP contributes little
  - ± Immunosuppression
  - Risks in someone with underlying malignancy
Neuromuscular transmission

- Depolarization of nerve terminal
  - $\text{Na}^+$ influx
- Repolarization
  - $\text{K}^+$ efflux (VGKC)
Treatment options in MG

- **Symptomatic**
  - Pyridostigmine (Mestinon)

- **Immunosuppression**
  - Prednisone
  - Azathioprine (Imuran)
  - Mycophenolate (Cellcept, Myfortic)
  - Methotrexate
  - Cyclophosphamide
  - Tacrolimus
  - Anti-B lymphocyte abs
    - Rituximab etc..

- **Immunomodulation**
  - Intravenous immunoglobulin
  - Plasma exchange
Commonly used therapies for myasthenia gravis

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Time to onset of effect*</th>
<th>Time to maximal effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptomatic therapy</strong></td>
<td></td>
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</tr>
<tr>
<td>Pyridostigmine</td>
<td>10 to 15 minutes</td>
<td>2 hours</td>
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<tr>
<td><strong>Chronic immunotherapies</strong></td>
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</tr>
<tr>
<td>Prednisone</td>
<td>2 to 3 weeks</td>
<td>5 to 6 months</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>~12 months</td>
<td>1 to 2 years</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>6 to 12 months</td>
<td>1 to 2 years</td>
</tr>
<tr>
<td>Cyclosporine and tacrolimus</td>
<td>~6 months</td>
<td>~12 months</td>
</tr>
<tr>
<td><strong>Rapid immunotherapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1 to 7 days</td>
<td>1 to 3 weeks</td>
</tr>
<tr>
<td>Intravenous immune globulin</td>
<td>1 to 2 weeks</td>
<td>1 to 3 weeks</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
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</tr>
<tr>
<td>Thymectomy</td>
<td>1 to 10 years</td>
<td>1 to 10 years</td>
</tr>
</tbody>
</table>

* Estimated times are rough guidelines based upon clinical experience in myasthenia gravis.
Common Approach

- **Ocular or mild generalized**
  - Mestinon x 2 weeks (30 qid x 3 then 60 qid)
  - Then prednisone 25 eod
  - + azathioprine (25—50—100—150 mg/d q 2 weeks) if comorbidities/want to reduce exposure to prednisone
  - $\pm$ add azathioprine at 6 months if not doing well
  - Reduce in reverse order

- **Moderate to severe**
  - Mestinon + prednisone (10—20—30—40—50) increasing every 3 days
  - Azathioprine often at same time esp. if co-morbidities
  - IVIg or PLEEx if bulbar or respiratory
Mestinon

- **Pearls**
  - Not a great drug
    - Doesn’t work in everyone or forever
    - MuSK MG may not respond (or worsen)
    - May not work for ocular symptoms
  - Least toxicity and (if it works) it works quickly - within hours/days
  - Imodium useful for GI adverse
  - Significant placebo effect in MG and non-MG
    - Do NOT use response to Dx MG
Prednisone

**Pearls**

- Good/great drug – potentially significant toxicity
- Patience!
  - Months – not days or weeks
- Lower doses in ocular MG
- Lower doses + patience

- Do NOT start high doses with bulbar or respiratory involvement
  - 40% will worsen, 25% of these (10%) significantly
- Alternate day - ? Any real benefit to reduce toxicity
- Bisphosphonate prophylaxis from outset in most
Azathioprine

- **Pearls**
  - Good drug – mild toxicity
    - Flu-like 1-2%, increased liver enzymes 10%, myelosuppression (neutrophils) 5%
    - NB allopurinol – use ⅓ dose
  - Steroid-sparing
    - Synergistic with prednisone
  - Patience!
    - Can take longer than a year – 15-18 months optimal
  - Use sufficient dose: 2.5-3.5 mg/kg/day = 250-350 mg/day in 100 kg patient
  - Monitor CBC and diff + liver enzymes
    - Weekly x 8, monthly x 10 then q2-3 months
  - Discuss lymphoma but likely (?) not an issue in MG
  - Not teratogenic!
Treatment Failure in MG
The other 10%....Beyond the first three drugs

- Considerations:
  - Is it really MG?
  - Is MG really the cause of symptoms?
  - Are they on the right dose? For long enough?
    - Increase dose prednisone/wait longer
    - Increase dose azathioprine/wait longer
Treatment Failure in MG
The other 10%....Beyond the first three drugs

- If true treatment failure – other options
  - Regular use IVIg/PLEx - $$
  - Mycophenolate instead of azathioprine
    - Trials (flawed) showed that MMF ‘doesn’t’ work in MG
  - Other immunosuppressives (instead of azathioprine/mycophenolate)
    - Methotrexate – ongoing trial
    - Cyclosporine – good RCT evidence but toxic
    - Cyclophosphamide – probably effective but toxic
    - Tacrolimus
  - Other biologics
    - Rituximab
Thymectomy in MG

- **Why?**
  - Removal of lymphoid organ which (at least early in disease) is major source of T/B lymphocytes responsible for anti-AChR antibody production

- **Who - the ‘Ideal’ candidate**
  - Early onset
  - Generalized
  - AChR antibody positive
  - Within 2-3 years of disease onset
  - Well controlled before surgery
  - Thymoma
Thymectomy in MG

• Results
  • Natural history – 20% sustained remission on no Rx
  • After thymectomy in ideal circumstances
    • 40% sustained drug free remission (doubles chances of ‘cure’)
    • additional 40% ‘improved’ but still on Rx
  • may shorten exposure to Rx

• Controversies
  • Many – approach (cervical, trans-sternal, VATS), age, duration
Thymectomy in MG

- **Thymoma**
  - 10-15% of all MG, 30% if > 60
  - On average more severe MG
  - Removal gets rid of tumor – likely won’t help MG

- **Ocular MG**
  - On balance risks > benefits
  - But – 40-50% start with ocular only, 25% ocular only after 3 years – so most will generalize
Accurate diagnosis of MG important before exposing pt to potential side effects of Rx or performing thymectomy.

If seronegative & non-responsive – is it MG?

Treatment effective in most – if poor response:
- Not MG
- Symptoms not secondary to MG
- Not on enough Rx or for long enough
- MG and refractory
  - Novel treatments – other Immunosuppressant, Rituximab
## Drugs that may unmask or exacerbate myasthenia gravis

<table>
<thead>
<tr>
<th>Anesthetic agents</th>
<th>Antirheumatic drugs</th>
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<tbody>
<tr>
<td>Chloroprocaine</td>
<td>Chloroquine</td>
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<tr>
<td>Diazepam</td>
<td>Penicillamine</td>
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<td>Ether</td>
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<tr>
<td>Halothane</td>
<td>Cardiovascular drugs</td>
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<tr>
<td>Ketamine</td>
<td>Beta blockers</td>
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<tr>
<td>Lidocaine</td>
<td>Bretlyum</td>
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<tr>
<td>Neuromuscular blocking agents</td>
<td>Proccainamide</td>
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<td>Propanidid</td>
<td>Prepafenone</td>
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<tr>
<td>Procaine</td>
<td>Quinidine</td>
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<tr>
<td>Neomycin</td>
<td>Varapamal and calcium channel blockers</td>
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<tr>
<td>Neostigmine</td>
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<td>Paromomycin</td>
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<td>Pseudomonasynol</td>
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<td>Thymamycin</td>
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<td>Aminoglycosides</td>
<td>Fluoroquinolones</td>
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<td>Gentamcin</td>
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<td>Others</td>
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<td>Anticonvulsants</td>
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<td>Antipsychotics</td>
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<td>Lithium</td>
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<td>Phenothiazines</td>
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*Drugs listed here should be used with caution in patients with myasthenia gravis. Aminoglycosides should be used only if absolutely necessary with close monitoring. Please refer to the text for further information.*