MYASTHENIA GRAVIS
PATHOPHYSIOLOGY AND ANESTHETIC IMPLICATIONS
Mary Golinski, PhD, CRNA

- Basic Terminology
  - MG Foundation of America

Originates from Greek and Latin words meaning "grave muscular weakness"

Becoming familiar once again with normal anatomy and functioning of the NMJ
- The nerve terminal of the motor nerve enlarges at its end to form the "bouton terminale" AKA terminal bulb
- Bulb lies within a groove or indentation along the muscle fiber
- Presynaptic membrane (on the nerve), postsynaptic membrane (on the muscle membrane), and the synaptic cleft (the space between the 2 membranes) together constitute the NMJ
Enzyme Acetylcholinesterase (Ache)

- Hydrolyzes Acetylcholine
- Is abundantly present at the NMJ
- The surface area of the postsynaptic membrane is increased by infolding of the membrane adjacent to the nerve terminal
- An ↑ in SA does what?
  - Enables the NMJ to utilize the ACh fully!
  - Remember, AChRs are present in small quantities over most of the muscle membrane surface but are concentrated heavily at the tips of the NMJs
- IT ALL MAKES SENSE NOW!

The Phenomenon of ‘Rundown’

- With every nerve impulse, the amount of ACh released by the presynaptic motor neuron normally decreases because of a temporary depletion of the presynaptic ACh stores
MG — Reduction in the # of AChRs Available

- Specifically at the muscle endplate and (within) flattening of the postsynaptic folds
- Even if a normal amount of ACh is released → fewer endplate potentials will be produced
- What happens next?
  - Potentials fall below the threshold value for generation of an action potential
  
End result of this process = inefficient neuromuscular transmission

Pathophysiology

Relatively rare autoimmune disorder

Autoimmunity: production of antibodies against the tissues of your own body, produces autoimmune disease or hypersensitivity reactions.

Antibodies form against acetylcholine, *nicotinic* postsynaptic receptors at the neuromuscular junction of skeletal muscles.
The Fatigability of MG

Inefficient neuromuscular transmission AND with the normally present presynaptic rundown phenomenon = a progressive decrease in the amount of muscle fibers being activated by successive nerve fiber impulses

FATIGUE is the RESULT

When do you become symptomatic?

- When the number of AChRs is reduced to approximately 30% of normal

- Question – Why doesn’t this happen to the cholinergic receptors of smooth and cardiac muscle?

  - Answer - they have a different antigenicity than skeletal muscle and therefore usually are not affected by the disease
Acetylcholine Receptors

- 2 types of acetylcholine receptors (AChR) that bind acetylcholine and transmit its signal:
  - Muscarinic AChRs
  - Nicotinic AChRs
- Functionally different:
  - **Muscarinic type**: G-protein coupled receptors (GPCRs) that mediate a slow metabolic response via second messenger cascades
  - **Nicotinic type**: are ligand-gated ion channels that mediate a fast synaptic transmission of the neurotransmitter

Nicotinic cholinergic receptors

The binding of acetylcholine to nicotinic AChRs = Activation

- 2 molecules of acetylcholine bind a nicotinic AchR, a conformational change occurs in the receptor, resulting in the formation of an ion pore
- At the NMJ - the opening of a pore produces rapid ↑ in cellular permeability of Na⁺ and Ca⁺⁺ ions
- The result? depolarization and excitation of the muscle cell, thereby producing a muscular contraction
The Autoimmune Process of MG

Autoimmunity causes anti-AChR antibodies to be produced; this decreases the numbers of post synaptic receptors.

Blockage of target receptors leads to a ‘turnover process’ of the receptors, and damage occurs of the post synaptic membranes in a complement-mediated manner.

B Cell or T Cell Mediated Immunity?

Anti-AChR antibody is found in approximately 80-90% of patients with MG.

- can be considered a B cell–mediated disease, in that it derives from antibodies (a B cell product) against AChR.

- the importance of T cells in the pathogenesis of MG is becoming increasingly apparent
  - thymus is the central organ in T cell–mediated immunity, and thymic abnormalities such as thymic hyperplasia or thymoma are well recognized in myasthenic patients.

Diagnosed but negative for the IgG antibodies?

- Antibodies exist that are specific to the muscle receptor kinase at the NMJ.
- Destruction against this muscle specific kinase = developmental abnormalities of the NMJ.

- The result?
  - FUNCTIONAL LACK OF ACETYLCHOLINE RECEPTORS.
The Myasthenic Crisis – Endotracheal intubation; need for Mechanical Ventilation

Skeletal Muscles of Respiration

**Contraction of External Intercostal Muscles**

Elevation of ribs & sternum > increased front-to-back dimension of thoracic cavity > lowers air pressure in lungs > air into lungs

**Diaphragm**

Moves downward > increases vertical dimension of thoracic cavity > lowers air pressure in lungs > air moves into lungs
Diagnosing

Based on the clinical features:

✓ the benefit of the cholinesterase inhibitors
✓ the detection of specific autoantibodies
  ✓ (anti-AChR, anti-MuSK or anti-LRP4)
✓ significant decrement evidenced by electrophysiological tests

Management Options

• Pharmacologic
  • Anti cholinesterases
    • Neostigmine
    • Pyridostigmine
  • Immunosuppressives
    • Prednisone
    • Azathioprine
    • Cyclosporin
    • Mycophenolate mofetil
    • Tacrolimus

• Surgery
  • Thymectomy

• Short term immunotherapies
  ▶ plasma exchange
  ▶ intravenous immune globulin

MOA Pharmacologic Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time to Clinical Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridostigmine</td>
<td>15 minutes</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>1-3 days</td>
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<tr>
<td>Mg</td>
<td>1-4 weeks</td>
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<tr>
<td>Prednisone</td>
<td>2-6 weeks</td>
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<tr>
<td>Azathioprine</td>
<td>2-6 months</td>
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<tr>
<td>Cyclosporine</td>
<td>2-6 months</td>
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<tr>
<td>Mycophenolate mofetil</td>
<td>3-12 months</td>
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The Anticholinesterase Agents

- Neostigmine (Prostigmin®) and Pyridostigmine (Mestinon®)
- Prevent ACh destruction and increase the accumulation of ACh at neuromuscular junctions, improving the ability of the muscles to contract

Anti-acetylcholinesterase agents

- First line of treatment
- May be given initially to enhance the function of the remaining normal acetylcholine receptors
- Use of anti-acetylcholinesterase drugs is limited to the treatment of mild myasthenia

Pyridostigmine (Mestinon)

- Most widely used
- PO administration
- Onset ▶ 30 minutes
- Peaks ~ 2 hours, gradually declines
- Half life ~ 4 hours
- Dosage and schedule tailored
- Maximal useful dosage rarely exceeds 120 mg every 3 hours
- Higher doses increase weakness
  - Why?
**MOA-Anticholinesterases**

- Reversibly inhibit acetylcholinesterase
  - Acetylcholinesterase → enzyme which deactivates acetylcholine
  - Acetylcholinesterase inhibition → acetylcholine not destroyed as quickly → remains active for a longer duration at motor endplate

- ↑ duration of action = ↑ number of interactions between the transmitter and receptors = muscular strength and response to repetitive nerve stimulation is improved

**Pre operative Suggestions and Pyridostigmine**

- Continue the drug v hold the morning of surgery! (will you be using non depolarizing MR?)
- Intravenous supplementation
  - Dose conversation from IV to PO 1:30 owing to first pass metabolism
  - 1:90 also reported

Overdose? Flaccid paralysis and autonomic symptoms
  - i.e. bronchospasm

**Myasthenic Crisis v Overdosage**

- Failure of patients to show clinical improvement may reflect underdosage -- it can also be indicative of overdosage!!!

- It is important to differentiate between myasthenic crisis and cholinergic crisis caused by overdosage of pyridostigmine
  - Both conditions result in extreme muscle weakness but require radically different treatment
Symptoms And Treatment Of Overdose:

Overdosage of pyridostigmine → cholinergic crisis
- an over-stimulation at a neuromuscular junction
- due to an excess of acetylcholine (ACh), as a result of the inactivity (perhaps even inhibition) of the AChE enzyme
- Characterized by → ↑ muscle weakness w/ involvement of the muscles of respiration, may result in → death

Result of cholinergic crisis?

Muscles stop responding to the bombardment of Ach → FLACCID PARALYSIS, RESPIRATORY FAILURE, AND...OTHER S/S
INCLUDING:
- increased sweating
- salivation
- bronchial secretions
- miosis (pupillary constriction)

This crisis may be masked → concomitant use of ATROPINE combined with anticholinesterase inhibitors

Flaccid paralysis resulting from cholinergic crisis can be distinguished from myasthenia gravis by the use of edrophonium (Tensilon), which worsens the paralysis caused by cholinergic crisis, but strengthens the muscle in the case of myasthenia gravis

Myasthenic crisis

Due to an increase in the severity of the disease
- accompanied by extreme muscle weakness
- may be difficult to distinguish from cholinergic crisis on a symptomatic basis

Differentiation is important!

Increases in the dose of pyridostigmine or other drugs in this class-- in the presence of cholinergic crisis or of a refractory or "insensitive" state-- could have grave consequences

The two types of crises may be differentiated by use of edrophonium chloride as well as clinical judgment

AKA 'tensilon test'
Atropine?

Some elements of cholinergic crisis can be treated with antimuscarinics i.e. atropine → respiratory arrest cannot

Atropine blocks muscarinic acetylcholine receptors (the different subtype) → will NOT improve the muscle strength and ability to breathe in someone with cholinergic crisis

WILL require mechanical ventilation support until the crisis resolves on own. The respiratory compromise from cholinergic crisis → no pharmacologic solution or therapy

Let’s talk steroids

• MOA for Steroid Therapy
  • Theory: May ↓ acetylcholine-receptor antibody levels
    • and diminish the anti-acetylcholine-receptor reactivity of peripheral blood lymphocytes
  • ~ may reduce acetylcholine receptors in (cultured muscle cells) and may ↑ neuromuscular transmission
    • The clinical relevance for this has not been established

Immunosuppression with Azathioprine

A prodrug (a precursor of a drug) - converted in the body to its active form - mercaptopurine (Purinethol)

• The exact mechanism of action of azathioprine is not known

However...................
Immunosuppression with Azathioprine

- Action appears predominantly on T cells
  - suppresses the proliferation of T and B lymphocytes
- Effectiveness assumes production of acetylcholine-receptor antibody is T cell dependent
  - Most use in those where steroids are contraindicated or insufficient response to steroids
- Two drawbacks:
  - Causes flu like reaction
  - Requires months to year for adequate trial – clinical results

Other Immunosuppressants

- Cyclosporine
- Tacrolimus
- Mycophenolate mofetil

Journal of Neurology September 1997, V 244, pp 542-547
Long-term cyclosporine treatment in a group of severe Myasthenia gravis patients

7 of 9 – improved muscle strength and functional score.

Short term immunotherapies

- IV immune globulin therapy
  - is an immunomodulating agent with multiple activities
  - Suppression of idiotypic antibodies
Therapeutic plasma exchange (TPE, plasmapheresis)

- an extracorporeal treatment that can be performed by centrifugation or filtration and is designed for the removal of pathogenic substances, such as antibodies, immune complexes, or large molecular weight substances from the plasma.

Plasma Exchange

used as a short-term intervention with sudden worsening of myasthenic symptoms for any reason

to rapidly improve strength before surgery

and as a chronic intermittent treatment for patients who are refractory to all other treatments

The need for plasma exchange, and its frequency of use is determined by the clinical response in the individual patient. Almost all with acquired MG improve temporarily following plasma exchange. Maximum improvement may be reached as early as after the first exchange or as late as the fourteenth. Improvement lasts for weeks or months and then the effect is lost unless the exchange is followed by thymectomy or immunosuppressive therapy. Most patients who respond to the first plasma exchange will respond again to subsequent courses. Repeated exchanges do not have a cumulative benefit.

When suffering an acute exacerbation.....

Plasma exchange?

From Cochrane Database, 2002.

OBJECTIVES: To examine the efficacy of plasma exchange in the short and long term treatment of myasthenia gravis.

REVIEWER'S CONCLUSIONS:

‘There are no adequate randomised controlled trials but many case series report short-term benefit from plasma exchange in myasthenia gravis, especially in myasthenic crisis. There are no adequate randomised controlled trials to determine whether plasma exchange improves the long-term outcome for myasthenia gravis. Further research is need to compare plasma exchange with alternative short-term treatments for myasthenic crisis and to determine the value of long-term plasma exchange for treating myasthenia gravis’.
Oops, I meant to mention: Plasma exchange

May result in a prolonged duration of action of succinylcholine (remember, drug requires plasma cholinesterase for metabolism)

Note: Drugs that rely on nonspecific plasma and tissue esterases: esmolol and remifentanil – should not have their duration affected to as great a degree!

Why am I being, or might be treated with IVIG?

‘IVIG might be prescribed for an individual with MG for one of several reasons. The first indication for use might be for a hospitalized patient who is extremely ill and might not be responding adequately to other treatments. Some patients with MG who are being treated with IVIG have improved quickly, thus allowing time for other treatments to begin working. Patients at home who are having significant symptoms (problems speaking, swallowing or walking) in spite of aggressive treatment with other drugs and treatments may be considered for treatment with IVIG also.

Planning the Anesthetic

- Consideration of the surgical procedure itself AND the pulmonary, muscular, and cardiovascular systems
- Consideration of other co morbidities
- Consideration of drug interactions
- Prior-to surgery medications and the anesthetic
- Consideration of anesthetic adjuncts: which drugs to avoid!
The extremely important pre operative patient and support system education

- Length of time from the last exacerbation?
- Severity of disease?
- FVC: total volume of air expired after a full inspiration
Patients with:
1) vital capacity > 20 ml/kg
2) a maximal expiratory pressure > 40 cm H2O
3) or a maximal inspiratory pressure > -40 cm H2O

are unlikely to require mechanical ventilation

A decline of 30% or more in maximal inspiratory pressure predicted a group at higher risk of requiring mechanical or noninvasive ventilation. Hypercapnia was frequent and was more common in patients who required mechanical ventilation. Worsening of these pulmonary function and blood gas values in patients with myasthenia gravis may guide decisions about intubation and ventilatory support. Muscle Nerve 2005 Nov;32(5):584-7.
Pulmonary function tests and blood gases in worsening myasthenia gravis.

More risk factors for respiratory insufficiency post operatively — nondescript list below

- Disease > 6 years?
- History of chronic respiratory disease
- Daily pyridostigmine doses? 750 mg
- Remember VC
- Large thymoma- risk of airway collapse; CT or MRI for tracheal compression
Increased weakness before surgery?

- Evaluate and treat
  - Possible therapies – increased dosing of medications to hospital admission for plasma exchange? IV immunoglobulin therapy – possible
  - Remember the complications of plasma exchange:
    - Associated with vascular access and fluid shifts
    - Venous thrombosis
    - Infection
    - Pneumothorax
    - Hypotension
    - Bradycardia
    - HF

The Risk Factors 2° to Disease Itself

- Pulmonary Aspiration
  - Pharyngeal and laryngeal muscle weakness
  - Dysphagia
  - Dysarthria
  - Inability to handle secretions
- Cardiovascular Involvement
  - Atrial fibrillation
  - Heart block
  - Cardiomyopathy
  - Hypertension
  - Other

Cardiovascular Involvement?

- Why?
  - The antibodies have an affinity for the β1 and β2 receptors
- Heart disease present?
  - ST- T wave abnormalities
  - Rhythm disturbances
  - HTN?
  - Medications?

Must have cardiovascular assessment! EKG at a minimum!
Sensitive to NDMR and Resistant to DMR????

Think it through: Extra sensitive to NDMR – you don’t need as much!
- the dose of NDMR is suggested to be decreased by half, to 0.6mg/kg in pt's with MG.
If used do note:
  Onset short
  Duration longer

Receiving anticholinesterase therapy?
  a- Morning of OR dose given? Yes, then
  b- Increase NDMR dose (Vecuronium)

Resistant to Succinycholine

- ½ the crux of the sux contraindication is that due to the antibody mediated decreased # of ACh receptors, sux simply doesn’t have enough targets to create adequate paralysis for intubation.

- Multiple studies have shown that the dose of succinylcholine required to produce neuromuscular blockade is approximately double in patients with symptomatic MG. This was first performed in intubated patients in the OR, with ulnar nerve/hypothenar muscle EMG results plotted against slowly uptitrating succinylcholine doses. These studies versus controls demonstrated approximately double the amount of Sux was needed in pts with MG for neuromuscular blockage (0.8mg/kg vs 0.3mg/kg).

Neuromuscular Monitoring

Monitoring of neuromuscular blockade in one muscle group alone may not reflect recovery of total muscle function in patients with ocular MG

Rocuronium followed by Sugammadex
  Adductor pollicis muscle
  Recovery slower at CSM
  Opposite w/o diagnosis
About Succinylcholine?

- When used
  - At higher risk for a phase 2 block, especially with repeated doses

Phase II block - a complex phenomenon that occurs slowly at junctions continuously exposed to depolarizing agents. The junction is depolarized by the initial application of a depolarizing relaxant, but then the membrane potential gradually recovers toward normal, even though the junction is still exposed to drug. Seen with repeated doses -- Neurotransmission remains blocked throughout.

Considerations of Anesthesia Drugs

- **Volatile agents**
  - Enhance the effect of NDMR
- **Sevoflurane**
  - Potentiates the effects (NDMR) to the greatest degree
- **Intravenous agents**
  - Relatively non problematic
- **Opioids**
  - Be careful; respiratory depression
- **Beta blockers and corticosteroids** - hmmm… Maybe not…
  - Esmolol (RBC esterases)
  - Steroids - high dose early treatment = exacerbation.
  - Start low dose and gradually increase

Potentially Harmful Drugs

- Based on anecdotal case reports or in vitro studies
  - Beta blockers – pre existing autonomic instability? Hypotension?
    - Propranolol
    - Timolol
    - Atenolol
    - Labetalol
    - Metoprolol
    - Nadolol
    - Calcium Channel Blockers
      - Verapamil
Neuraxial anesthetics?
- Controversy still exists
- Esters; problematic
- So use reduced doses of amides

Local anesthetic of choice should be the one with the weakest concentration and least motor involvement (as appropriate)

Ester local anesthetic agents:
- Cocaine
- Procaine
- Methocaine
- Chloroprocaine

Esters
- relatively unstable in solution
- rapidly hydrolysed in the body by plasma cholinesterase (and other esterases)
- one of the main breakdown products is para-amino benzoate (PABA)
- which is associated with allergic phenomena and hypersensitivity reactions
Antibiotics that impair neuromuscular transmission and may increase weakness

- **Aminoglycosides**
  - Tobramycin
  - Gentamicin
  - Netilmicin
  - Neomycin
  - Streptomycin
  - Kanamycin

- **Other antibiotics**
  - Tetracyclines
  - Sulfonamides
  - Penicillins
  - Amino Acids
  - Macrolides
  - Azithromycin
  - Clarithromycin
  - Ritonavir

What is the planned surgical procedure? Thymectomy?

- Indications - significant symptoms
- Diagnostics – CT MRI etc
- Management Protocols
  - Based on H and P

- Surgical Approaches
  - Transternal
  - Extended transcervical
  - Transternal maximal thymectomy
  - Minimally invasive: transcervical or video assisted thoracoscopic thymectomy (robotic)

Other Surgical Interventions

- All aforementioned considered
The Use of Sugammadex

- Case reports in patients with MG document the successful use of Sugammadex:
  - The use of sugammadex in a patient with MG. Anaesthesia. 2010; 65 (3): 303-305
  - Successful use of rocuronium and sugammadex in a patient with myasthenia. Eur J Anaesthesiol. 2010;27 (9):917-918

Thank YOU!

I'll do my best to answer any questions you may have!