Myasthenia Gravis

Myasthenia Gravis is a disease characterized by autoimmune mediated destruction of post junctional nicotinic acetylcholine receptors at the neuromuscular junction, resulting in a fluctuating course of muscle weakness and fatigability.

ANESTHETIC CONSIDERATIONS:

- Neuromuscular weakness
  - Perioperative **respiratory failure** (weak, poor cough / clearance, risk postoperative ventilation)
  - **Increased risk of aspiration**
- Risk of **myasthenic crisis** or **cholinergic crisis**
- Associated disease processes
  - Thymoma: **anterior mediastinal mass**
  - Cardiac: myocarditis (if thymoma present), cardiomyopathies, atrial fibrillation, heart block
  - Endocrine / autoimmune: hypothyroidism, RA, SLE, ankylosing spondilitis, Crohn's, UC
- Co-Morbidities
  - Immune / adrenal suppression from steroid use
  - Type I DM has been associated with MG
  - restrictive pulmonary disease
- Altered pharmacology
  - Exquisitely sensitive to non depolarizing muscle relaxants
  - Resistant & unpredictable response to SCh with prolongation of response
- Anesthetic considerations of drug therapies
  - **Steroids** – may need supplementation intraoperatively
  - Immunosuppressants
  - Plasmapheresis
  - Anticholinesterases: prolonged duration of succinylcholine and mivacurium

ANESTHETIC GOALS:

- Preoperative optimization of neuromuscular function - consider neurology consult
- Prevent aspiration – Rapid Sequence Induction
- Risk stratification for possible post-op ventilation for respiratory failure
- Careful titration of neuromuscular blockade
- Treat relative adrenal insufficiency from long term steroid use

HISTORY

- Determine natural history and current condition of patient's disease (Osserman Classification) preferably in consultation with pt's neurologist

TABLE 2. *Modified Osserman and Genkins classification of myasthenia gravis.*

Stage I	Ocular myasthenia gravis: involvement restricted to extraocular muscles
Stage IIA	Mild generalized MG: generalized weakness without respiratory muscle involvement
Stage IIB	Moderately generalized MG: more severe generalized involvement, bulbar symptoms common and relative sparing of respiratory muscles
Stage III	Acute fulminating MG: rapid onset (within 6 months) of respiratory muscle involvement
Stage IV	Late severe MG: severe symptoms that have progressed for more than 2 years after onset of ocular or mild generalized MG

MG, myasthenia gravis.

  - Evidence of bulbar dysfunction (aspiration risk)
    - Limited facial muscle movement
    - Oropharyngeal weakness: dysarthria, nasal speech, dysphagia, aspiration, difficulty clearing secretions
  - Postoperative ventilation (Leventhal Criteria)
    - Disease duration > 6yrs
    - Concomitant pulmonary disease not due to MG
    - VC < 40 cc/kg (VC < 2.9L)
    - Pyridostigmine dose > 750 mg/day
  - Functional capacity to indicate respiratory muscle involvement
- Co-existing medical illness
  - Cardiac: myocardial function, palpitations
- Current treatment regime and complications
  - Anticholinesterases
  - Immunosuppressives: Corticosteroids, Azathioprine, Cyclosporine
  - Thymectomy
  - Plasmapheresis
  - IVIG

PHYSICAL

- **RESP** – head lift > 5 sec, paradoxical inspiratory motion, decreased ventilation to lung bases

- **MSK** – arm adduction time (> 1 min)

INVESTIGATIONS

- **Labs**
  - CBC, lytes, BUN, Cr if on immunosuppressives
  - TSH to rule out hypothyroidism
- **Imaging**
  - EKG (conduction abnormalities)
  - CXR if mediastinal mass (or CT)
- **Special**
  - PFT to document VC

OPTIMIZATION

- Elective cases should be done when patient in remission
- Management of anticholinesterases
  - Preoperative administration of pyridostigmine would likely avoid myasthenic crisis
- Optimization if myasthenic crisis:
  - Plasmapheresis
  - IVIG
  - steroids

ANESTHETIC OPTIONS

- Local, regional, general
- Regional
  - Prefer amide LA vs. ester LA (prolonged duration d/t anticholinesterases); min sedation
- Consider epidural analgesia in sternal thymectomy
- Aspiration prophylaxis
  - Metoclopramide, Na Citrate and H_2 blocker preoperatively

ANESTHETIC SETUP

- **Drugs**
  - Minimize use of SCh and NDMRs if possible
  - Hold anticholinesterase 2-4 hours preoperatively if patient will tolerate
- **Equipment**
  - Standard CAS
  - PNS (TOF)
  - Spirometry if available

MANAGEMENT OF ANESTHESIA

- **Induction**
  - **Modified rapid sequence induction (aspiration risk)**
  - Consider Intubation without muscle relaxation
    - ETT preferred to LMA d/t risk of aspiration
    - Deep propofol induction
  - Minimize use of NMBs if possible
    - SCh - unpredictable effect
      - Resistant to Succinylcholine due to decrease in number of functional Ach receptors
      - ED95 is 2.6 x normal
      - Duration of action may be increased in patients taking pyridostigmine
    - NDMRs
      - If use absolutely necessary, use small dose of short acting agent (cisatracurium, mivacurium, rocuronium, atracurium)
      - Should receive 1/10 to 1/20 of normal intubating dose (i.e. a defasciculating dose) as this can produce profound muscle weakness
      - Titrate with **neuromuscular monitoring and nerve stimulator**
  - Minimize respiratory depressants
- **Maintenance**
  - **Consider TIVA** as will not prolong neuromuscular weakness
  - **Often inhalational anesthetics provide enough muscle relaxation for surgery**
- **Emergence**
  - Consider IV neostigmine 1h before emergence at 1/30-1/60 daily pyridostigmine dose; infuse over 24h
    - Some advocate spontaneous recovery (avoiding neostigmine)
  - Extubate only after thorough evaluation of ventilatory function and reversal of paralysis

DISPOSITION & MONITORING

- Consider risk of post-operative ventilation when deciding upon postoperative disposition
- Be wary of medications / conditions that prolong muscle weakness:
  - Residual blockade
  - Acidosis, **hypothermia**
  - **Hypermagnesemia**, hypocalcemia, hypokalemia, hyponatremia
  - Volatiles
  - Local anesthetics: lidocaine, procaine
  - Aminoglycosides: gentamicin, neomycin, clindamycin, streptomycin, lincomycin, tetracycline, polymixin B

- Cardiac: CCBs, procainamide, quinidine
- ?Opioids decrease respiratory drive and may exacerbate postoperatively respiratory weakness

- Increased risk of postoperative pneumonia (poor cough and secretion clearance) & aspiration

COMPLICATIONS

- **Post-operative weakness**
  - Need to differentiate between myasthenic crisis and cholinergic crisis
    - **Cholinergic crisis** is associated with muscarinic side effects (excessive anticholinesterase): increased weakness, bradycardia, salivation, miosis
    - Differentiate by administering edrophonium as myasthenic crisis will improve and anticholinergic crisis will worsen
  - Also consider other factors (listed above)

MYASTHENIA IN PREGNANCY

- 1/3 improve, 1/3 stay the same and 1/3 get worse
- ~30% experience relapse postpartum
- Monitor for weakness during labor
- Magnesium is relatively contraindicated
- Neonatal myasthenia in 16% due to transfer of maternal antibodies across the placenta → resolves in 3 – 4 weeks
- Generally, neuraxial anesthesia preferred (for labor & C/S) unless severe bulbar or respiratory involvement, then consider GA for C/S

MYASTHENIC SYNDROME (LAMBERT-EATON)

- Originally described in patients with Small Cell carcinoma of lung but also described in patients without cancer
- Proximal limb skeletal muscle weakness that often **improves** with exercise
- No bulbar or respiratory muscle involvement
- Autoimmune disorder: IgG antibodies to **presynaptic calcium channels preventing Ach release**
  - Presynaptic site of the neuromuscular junction is the target
  - Autonomic disturbances are seen in about 30% of patients with LEMS
  - Unlike MG, anticholinesterases are of little therapeutic value in LEMS
  - Improvement in muscle strength is seen after exercise
  - LEMS is differentiated from MG by electromyography, in which facilitation of the electromyographic response, rather than fade, occurs during high-frequency (30 to 50 Hz) stimulation
  - The two diseases can also be differentiated by antibody titer to specific channels
- Sensitive to **both SCh and NDMR**
- Plasmapheresis or IVIG give transient improvement
- 3,4-diaminopyridine results in significant improvement
- Pyridostigmine potentiates the response to 3,4-diaminopyridine
- Should be considered in patients undergoing procedures for suspected lung cancer

THYMECTOMY

- **Anesthetic Considerations:**
  - Myasthenia gravis
  - Anterior mediastinal mass
  - Sternotomy (apnea / lungs deflated during sternotomy, risk of laceration to RA, RV or great vessels, unrecognized pneumothorax, epidural for postoperatively pain control)

PATHOPHYSIOLOGY (MYASTHENIA GRAVIS)

- Autoimmune disorder of motor endplate caused by decrease in postsynaptic acetylcholine receptors at NMJ due to autoantibody destruction of alpha subunit of muscle type Ach receptor, resulting in muscular weakness & fatigability
- Pathophysiology
  1. Decreased number of post-synaptic nicotinic receptors due to:
     - Functional block – cross-linking of antibodies
     - ↑ degradation
     - Complement-mediated lysis of postsynaptic membrane
  2. Loss of post-synaptic membrane folds
  3. Increased distance of synaptic cleft
- Estimated loss of 70-80% of ACh receptors
- Normally 25-30% receptors needed for transmission ∴reduced margin of safety in MG
- Hallmark is **rapid exhaustion of voluntary skeletal muscles with repetitive activity and partial recovery with rest**
- Skeletal muscle innervated by cranial nerves are particularly susceptible **(pharyngeal / laryngeal), resulting in dysphagia, dysarthria, failure to clear secretions / airway obstruction**
- Thymus
  - **70% have thymic hyperplasia**
  - **10-15% have thymomas**
- Epidemiology:
  - Incidence 0.5-1/2000, prevalence 0.25-2/100,000
- Differential diagnosis
  - Drug-induced myasthenia gravis (penicillamine, aminoglycosides, procainamide)
  - Quadriplegic myopathy
  - Hyperthyroidism
  - Graves' disease
  - Botulism
  - Structural

Syndrome	Location	Mechanism	Etiology

Lambert-Eaton myasthenic syndrome	Presynaptic	Autoimmune	Antibodies to voltage-gated calcium channels at the motor nerve terminal
Congenital myasthenic syndromes		Genetic	
Choline acetyltransferase deficiency	Presynaptic		Mutations in choline acetyltransferase
Acetylcholinesterase deficiency	Synaptic		Mutations in the gene encoding the collagenic tail subunit (ColQ) of the enzyme that anchors acetylcholinesterase in the synaptic cleft
Slow- and fast-channel syndromes	Postsynaptic		Mutations in nAChR genes
nAChR deficiency	Postsynaptic		Mutations in nAChR genes or in rapsyn
Myasthenia gravis	Postsynaptic	Autoimmune	
-Seropositive			Antibodies to nicotinic ACh receptors
-Seronegative			Antibodies to MuSK
MuSK, muscle-specific kinase; nAChR, nicotinic acetylcholine receptor			

REFERENCES

- Miller 6th Edition – chapter 13
- Dillon, FX, Anesthesia Issues in the Perioperative Management of Myasthenia Gravis. Semin Neurol 2004 24: 83-94