Peripheral Neurology: GBS and MG

Ashok Verma, M.D., DM
Professor of Neurology
Director, Kessenich Family MDA ALS Center
and MDA Clinics
University of Miami Miller School of Medicine
Guillain-Barre Syndrome

- Landry’s Paralysis
- Guillain-Barre-Strohl Syndrome
- Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)
Guillain-Barre Syndrome

- Most common cause of acute or subacute generalized paralysis
- World-wide prevalence (2/100,000)
- Age, gender, season
EVENTS PRIOR TO GBS

- **Infections**
  - *Campylobacter jejuni, Mycoplasma pneumoniae*
  - Cytomegalovirus, Epstein-Barr virus, Influenza, Herpes, HIV, Vaccinia
  - *Borrelia burgdorferi*
  - Hepatitis Vaccine, Rabies

- **Antecedent Events**
  - Surgery/stress
  - Prior Hx of acute infectious process (1 – 3 wks prior)
  - Recent immunization with Swine influenza (1976). Not as much of a problem now
  - **HIGHER RISK PTS**
    - Lymphoma, Hodgkin's Disease, HIV, SLE
Guillain-Barre Syndrome
Myelinopathy

- Primary attack is on the myelin sheath
- Produces random/segmental demyelination
Segmental demyelination
Segmental demyelination
Guillain-Barre Syndrome

Clinical features

- Motor weakness: Proximal and distal
- Impaired reflexes: Early and prominent
- Sensory symptoms: Minimum loss, pain
- Autonomic symptoms: Cardiovascular
Guillain-Barre Syndrome

Clinical variants (focal/functional)

- Miller-Fisher syndrome (ophthalmoplegia, ataxia, areflexia)
- Paraparetic form
- Oculopharyngeal weakness
- Bifacial or abducens palsy with distal paresthesia
- Pharyngeal-cervical-brachial
- Pure sensory, autonomic, or ataxic form
Guillain-Barre Syndrome

Clinical variants (axonal)

- Acute motor axonal neuropathy (AMAN) (60% GM1 ab, *C. jejuni* infection)
- Acute motor and sensory axonal neuropathy (AMSAN)
- Acute multifocal motor neuropathy?
Guillain-Barre Syndrome

Clinical course

- Evolves from a few days to two weeks
- 25 - 30% will require ventilatory assistance
- Improvement occurs after plateau is reached
GUILLAIN BARRE SYNDROME

Investigations

**CSF analysis:**

Increased protein concentration with a normal cell count-
albuminocytological dissociation (elevated CSF protein, typically ranging from 46 to 300 mg/dl)

**EMG/NCS examination:**

Very often changes strongly suggestive of demyelination, such as conduction block, differential slowing, or focal slowing, are seen on assessment of one or more nerves.

**MRI with gadolinium**

Enhancement of cauda equina roots in two third cases
Nerve Conduction

H reflex

F wave
There is no known prevention for sporadic GBS.

The treatment of GBS has two components:

1. **Supportive care**
   - Respiratory support (about 25%)
   - BP, electrolytes, infection, GI, PE
   - Skin care to prevent ulcers
   - PT after plateau of disease course

2. **Specific therapy** (no change in mortality, but get better faster and less severe disease)
   - Plasmapheresis (200 ml/kg wt, 40 ml/kg wt/day x 5 sessions on alternate days)
   - IVIg therapy (2 gm/kg wt; 0.4 gm/kg wt/day x 5 consecutive days)
Guillain-Barre Syndrome
Prognosis and Recovery

- 85% recover fully
- 10% variable residual deficits (outlook is worse for those pts with severe proximal motor and sensory axonal damage (i.e., not just demyelinating))
- 3 – 5% mortality (pulmonary, cardiovascular)
- 5 - 10% recurrence of neuropathy (subacute IDP, CIDP)
Guillain-Barre Syndrome

Salient features

- Most common cause of acute or subacute generalized weakness
- Proximal and distal weakness
- Areflexia
- CSF, NCS and MRI help in diagnosis
- Majority of GBS patients plateau within 2 wks followed by recovery
- Greater potential for rapid recovery with Rx
Myasthenia Gravis

NEUROMUSCULAR JUNCTION

MORPHOLOGY

- presynaptic nerve terminal ending
- primary synaptic cleft
- postsynaptic membrane folds
- receptors

BIOCHEMISTRY

- ChAT = choline acetyltransferase
- CoA = coenzyme A
- AchR = acetylcholine receptor
- AchE = acetylcholinesterase

- microtubules and microfilaments
- mitochondrion
- synaptic vesicles
- active zone
- acetyl

- ChAT
- CoA
- acetylcholine
- choline
- acetylcholine
- acetate
- AchE
Blocking, Cross-linking

COMPETITIVE BLOCKER

RECEPTOR DEGENERATION

COMPLEMENT DEPENDENT DESTRUCTION

Lytic
Myasthenia Gravis

Epidemiology

- 50 to 125 cases/million or 30,000 cases in the United States
- Occurs at any age with peaks in the 3rd and 6th decades
- Women > Men from age 10-40
- Men > Women over 40
Diseases Associated with Myasthenia Gravis

- Thymic hyperplasia
- Thymoma
- Thyroid disorders
- Rheumatoid arthritis
- SLE
- Ulcerative colitis
- Vitiligo
- Pemphigus
- Multiple sclerosis

- Hemolytic anemia
- Pernicious anemia
- Red cell aplasia
- ITP
- Sarcoidosis
- Leukemia/lymphoma
Myasthenia Gravis

Clinical features

- Weakness and fatigability
  - Ocular: diplopia, ptosis
  - Masticatory: chewing difficulty
  - Bulbar: dysarthria, dysphagia
  - Extremities: proximal > distal limb weakness, neck weakness
  - Respiratory muscles: dyspnea
- Symptoms are worsened as day wears and by a rise in body temperature.
Myasthenia Gravis
Grading system (Osserman)

- Grade 0 - Remission
- Grade 1 - Ocular
- Grade 2A - Mild generalized
- Grade 2B - Moderate generalized
- Grade 3 - Severe generalized (crisis)
- Grade 4 – Late generalized
Myasthenia Gravis

Diagnosis

- History
- Neurological Exam
- Tensilon Test
- Electrodiagnostic studies
- Serological test (AChR, MuSK antibodies)
- Chest CT
- Thyroid function studies
Myasthenia Gravis

Key points on neuro exam

- Measure palpebral fissure distance at rest and following one minute of upward gaze.
- Test orbicularis oculi strength.
- Test for diplopia by prolonged lateral gaze.
- Test for dysarthria by having patient read aloud.
- Test strength of neck and extremity muscles.
- Should have normal pupillary reactions, sensation, and DTRs.
Myasthenia Gravis

Tensilon test

- Edrophonium inhibits cholinesterase to prolong Ach activity.
- Must have something objective to measure:
  - Usually degree of ptosis
  - Occasionally dysarthria/dysphagia
  - Not extremity strength, fatigue or diplopia
- Not required in all MG patients.
- Can rarely be “positive” in other diseases.
Myasthenia Gravis
Tensilon test

- Load 1 cc (10 mg) Tensilon in TB syringe.
- Inject directly into antecubital vein in 3 steps: 0.1 cc, 0.5cc, 1.0cc.
- When patient feels effect (sweating, nausea, fasciculations), stop injection.
- Consider cardiac/blood pressure monitoring in elderly patients.
- Use with caution in patients with prominent bulbar symptoms.
Myasthenia Gravis
Acetylcholine receptor antibody

- Most specific test for MG
- %+:
  - 85% generalized MG
  - 60% ocular MG
- “Binding” RIA most often used
  (nl <0.03 to 0.5 nmol/L)
- Correlate poorly with disease severity
- Therapeutic approach to antibody negative patients is the same.
Myasthenia Gravis
MuSK antibody

- MuSK is a muscle specific kinase essential for the development of the NMJ.
- Seen in 40-70% of generalized MG patients who are acetylcholine receptor Ab negative.
Myasthenia Gravis
Repetitive stimulation

- Perform at 2-3 Hz using a supramaximal stimulus.*
- Decrement > 10% indicates neuromuscular transmission defect.*
- Decrement more likely to be demonstrated in weak muscles (usually proximal).
- Look for post-exercise facilitation and exhaustion, especially if no decrement at rest.
- Decrement may improve with cold exposure - be sure upper extremity temperature is at least 34°C.
In normal subjects, repetitive stimulation at rates of 2 - 5 per second evokes consecutive muscle action potentials of the same size.

In subjects with myasthenia gravis, repetitive stimulation evokes muscle action potentials from involved muscles that progressively decrease in size over several responses as transmission fails at neuromuscular synapses.
Myasthenia Gravis

Needle EMG

- Insertional activity is typically normal.*
  Fasciculations may be present in patients on Mestinon.
- Motor unit morphology and recruitment is normal.
- Motor units characteristically show variability in amplitude.*
Records individual muscle fiber potentials.

Jitter measures variability of rise time of end plate potential to reach threshold.

Jitter is measured in microseconds as the mean consecutive difference (MCD).

Blocking = failure of NMJ transmission; EPP does not reach threshold.

Normal average MCD of 20 pairs in the EDC is < 35 μsec and normal blocking = 0%. 
Myasthenia Gravis
Natural history

- Grob et al. 1,487 patients 1940-1985

- Initial Symptoms:
  - Ocular 53%
    - 25% ptosis, 25% diplopia, 3% blurred vision
  - Leg/Arm/Neck Weakness 20%
  - Bulbar 16%
    - 6% dysphagia, 5% dysarthria, 4% chewing
  - Respiratory Muscle Weakness 1%
  - Generalized fatigue 9%
Myasthenia Gravis

Natural history


- Ocular MG
  - 40% remain ocular at one year
  - 13% ultimately remain ocular

- Time to Progression to Generalized MG
  - 56% by 6 months
  - 78% by 1 year
  - 85% by 2 years
  - 92% by 3 years
Myasthenia Gravis

Treatment

- **Increase acetylcholine (anticholineserases):**
  - Mestinon
  - Neostigmine

- **Decrease antibodies against the acetylcholine receptor (immunosuppressants):**
  - Prednisone
  - Azathioprine
  - Cyclosporine
  - Mycophenolate mofetil
  - Cyclophosphamide
  - Plasmapheresis
  - IVIG

- **Acute myasthenia gravis (crisis):**
  - Plasma exchange (200 – 250 ml/kg wt over 5 – 7 sessions)
  - IVIg (0.4 gm/kg wt/day 3 –5 days)

- **Thymectomy**
Mestinon

- Oral acetylcholinesterase inhibitor which is used as first line therapy for MG
- Dose is variable
  - 60mg TID - QID
- If you need more, immunosuppressive therapy is warranted.
- Treat GI side effects with probanthine (30mg) or hyocyamine sulfate (Levsin/Anaspaz, 0.125mg)
- IV dosing is 1/30th oral dosing (1mg IV=30mg po)
Prednisone

- Start at 1-1.5mg/kg wt/day for 2-4 weeks, then taper to 100mg qod.
- Maintain same dose until significant improvement (preferably remission) then taper by 5 mg q 2 weeks as tolerated.
- Improvement usually begins in 2-4 weeks.
- Maximum benefit seen in 4-6 months.
- Transient worsening occurs in 20% of patients during first week.
- “Remission” is often steroid dependent.
Prednisone: Collateral program

- 1800 calorie/4 gram Na diet
- Avoid simple carbohydrates
- Vitamin D 400-800 IU/day
- Calcium supplementation
  - 1000mg/d pre-menopausal or male
  - 1500mg/d post-menopausal
- Initiate treatment with Fosamax if evidence of bone loss.
Myasthenia Gravis

IVIg and PE

- Improvement seen in 1-20 days.
- Duration of effect 1 – 4 months.
- Maintenance IVIg and PE.
Intravenous Immunoglobulin

Potential side effects

- Fever/chills
- Nausea/vomiting
- Headache
- Myalgias
- Hypotension
- Hypertension
- CHF
- Hepatitis C
- Anaphylaxis in IgA deficiency
- Aseptic meningitis
- Renal failure
- Stroke
- DVT
- Allergic reactions
Plasmapheresis

Limitations

- IV access - often requires large double lumen catheter
- Complications:
  - Pneumothorax
  - Hypotension
  - Sepsis
  - Pulmonary embolism
- Expensive
- Short-term benefit
Myasthenia Gravis

Thymectomy


- Time to remission in thymectomy patients:
  - 25% 1st year
  - 40% 2nd year
  - 55% 3rd year
Myasthenia Gravis

Immunotherapy pearls

- Poor response to immunotherapy is often due to inadequate doses for too short a duration.

- Patients with bulbar or generalized MG who are started on high dose prednisone should be hospitalized (because of early exacerbations).

- Immuran takes at least 6 months to kick in and works about half the time (be patient).

- Medications with the shortest duration of action should be reduced first.

- The faster the taper, the more likely the patient is to relapse.
Myasthenia Gravis

Drugs to avoid

- Calcium channel blockers
- Beta-blockers
- Quinine
- Quinidine
- Procainamide
- Lidocaine
- Aminoglycoside antibiotics
- Polymixin
- Morphine
- Barbiturates
- Neuromuscular blocking agents
- Magnesium
Thank You