Myasthenia Gravis
Case

- Mrs. C. is a 81yr old right-handed woman
- Presents with gradual SOB slowly progressing over past 2 years, until having an acute episode assoc. with chest heaviness.
- Admitted, decompensated, required intubation.
- Later improved, extubated, seen by neurology.
- History revealed also had been getting weakness in legs, and felt slightly off balance.
- Weight Loss (10-15lbs over last year)
- Described difficulties swallowing solids and need to mince food.
- Diplopia when looking around.
- Mild ptosis bilaterally.
- No paresthesias in hands or feet, no back or neck pain.
PAST MEDICAL HISTORY:
- Angina
- HTN
- Borderline Type II DM
- Osteoarthritis
- GERD
- Cataracts With Implants

MEDICATIONS:
- Diltiazem
- Metoprolol
- Slow-K
- ASA
- Ranitidine
- Zocor
- Nitro-Dur
- Nitro-Spray
ALLERGIES:
NKDA

SMOKING:
Nil

ETHANOL:
One glass wine daily.
PHYSICAL EXAM:
Cardiac: Normal
Resp: Difficulty taking deep breath, Otherwise normal.
-Neuro Exam:
Normal mental status.
No aphasia.
CN exam completely normal except a partial bilateral ophthalmoplegia.
MOTOR EXAM:
- Upper: shoulder abd., flexion, extension=4
- Wrist flexion, extension, grip=4
- Left first interosseous=4- (with atrophy)
- Lower: Quadriceps=36 degree extensor lag
- Hip Flexors=4-
- “Give Away Weakness” distally in feet, but Inversion, Eversion, Plantar/Dorsiflexion=4
- Reflexes all 2+.
- Toes Downgoing.
- Vibration mod. Impaired.
- Stocking loss to pain and temp from MTP to mid upper calf.
EMG:
-A few serrated potentials in deltoids and in left tibialis anterior. Otherwise normal.

Repetitive Stimulation EMG:
-Normal amplitude response.
-Did not increase during exercise
-In exhaustive phase, drop in amplitude of 15% (suggests a conduction block).
Myasthenia Gravis

Definition:
- Neuromuscular disorder characterized by weakness and fatigability of skeletal muscles.
- Underlying defect is decrease in # of available Acetylcholine receptors at NMJ, due to antibody mediated autoimmune attack. (Harrison’s Principles of Internal Medicine, 15th edition.)

Epidemiology:
- Prevalence of 1 in 7500
- Affects all age groups.
- Peak Incidence in 20’s and 30’s in women
- 50’s and 60’s in men.
- Female:Male=3:2
- 16% experience a “Myasthenic Crisis”
-6-10% mortality from Myasthenia complications (resp. failure)

-Before 1950’s only 50% chance of surviving Myasthenic Crisis


Associated Diseases (autoimmune disorders):
- Thyroid disease
- Type I Diabetes
- Vitiligo
- 10% have an associated Thymoma
- 65-70% have thymic hyperplasia

CLASSIFICATION:
- Group I: Ocular (20%)
- Group IIa: Mild Generalized (30%)
- Group III: Acute Fulminating (11%) (rapid onset, early resp. involvement, high mortality).
- Group IV: Late Severe (9%)
Pathophysiology

- Acquired disease of neuromuscular transmission
- Deficit and Dysfunction of Ach-R
- Associated with abnormal muscle weakness and fatigue on exertion
CHOLINERGIC RECEPTORS

- **Somatic nervous system**
  - CNS
  - Effector organ
  - ACh

- **Autonomic nervous system: Parasympathetic division**
  - CNS
  - Ganglion
  - ACh
  - Effector organ

- **Autonomic nervous system: Sympathetic division**
  - CNS
  - Ganglion
  - ACh
  - NE
  - (via bloodstream)
  - Epi (also NE, DA, peptides)
  - Effector organ
TYPES OF CHOLINERGIC RECEPTORS

- **AGONISTS**
  - Oxotremorine
  - Methacholine
  - Muscarine
  - Carbamylcholine
  - Acetylcholine
  - DMPP
  - Succinylcholine

- **MUSCARINIC**
  - M1 ganglia
  - M2 target organs
  - Nn ganglia
  - Nm NMJ

- **NICOTINIC**
  - N-methylatropine
  - Atropine
  - Pirenzepine
  - Nicotine
  - Hexamethonium
  - Trimethaphan
  - TEA
  - Tubocurarine

- **ANTAGONISTS**
  - McN-A-343
NEUROMUSCULAR JUNCTION

Diagram showing the structure of a neuromuscular junction with labels for AChE, ACh receptors, synaptic vesicles, Ca²⁺, Na⁺, and K⁺.
WHAT GENERATES AB PRODUCTION?

• Theories
  – Majority (80%) of MG patients have thymic abnormalities
    • 60-70% hyperplasia
    • 10-12% thymoma
      – Myoid cells of thymus that normally express Ach® are altered during viral illness
        » Proximity to APC and helper T-cells facilitates production of an immune response
  – Molecular mimicry
    • Infection by a virus/bacteria with an Ag that may share epitopes with Ach® → Ab generalized against virus also recognizes Ach®

• Genetic factors
  • Certain HLA types associated with MG (HLA-DR3 and DQ2)
Autoimmune reaction
Ab-mediated destruction of the Ach Receptor

- Normal: Axon, Vesicle, Mitochondrion, Acetylcholine receptors, Acetylcholinesterase, Muscle
- Myasthenia gravis: Reduced number of Acetylcholine receptors, Muscle
CUMMULATIVE EFFECTS:

- Flattening of synaptic folds
- Widening of synaptic cleft

\[ \downarrow \text{#Ach®s} \]

\[ \uparrow \text{Chance that Ach will diffuse away or be degraded} \]

\[ \downarrow \text{Ach} \leftrightarrow \text{Ach®} \]
WEAKNESS IN MYASTHENIA GRAVIS

Synaptic widening

↓ # Ach ®s

↓ Ach ↔ Ach®

↓ Na+ influx

↓ amplitude of end-plate potential (EPP)

AP not triggered in some mm fibers

WEAK MM CONTRXN

↓ synaptic folding
FATIGUE IN MYASTHENIA GRAVIS

- Synaptic widening
- Synaptic folding

- ↓ # Ach®s
- ↓ # of NMJs generating sufficient EPP
- ↓ # of NMJs generating AP and contrxn

MM FATIGUE
Myasthenia Gravis: Signs & Symptoms

- Fluctuating weakness increased with exertion
- Eyes: ptosis, diplopia, proptosis, EOM weakness
- Facial muscle weakness: mask face, horizontal smile, myasthenic sneer
- Dysarthria, dysphagia, open jaw
- Respiratory muscle weakness
- Limb muscle weakness (upper > lower)
- Normal reflexes and sensation
The Faces of Myasthenia Gravis
The “Morning Rounds Post-Call Sign”

Hmmm, let’s see, what is my approach to muscle weakness?
Differential Diagnosis

- Cranial nerve and compressive lesions
- Graves disease
- Botulism
- Lambert-Eaton Myasthenic Syndrome
- Drugs
The Work-up

**Lab Studies:**
- Anti-acetylcholine receptor antibody
- Thyroid function and thyroid antibodies
- RF, ESR, ANA

**Imaging:**
- Chest X-Ray
- CT
Pharmacologic Challenge: Tensilon Test

- Give AChE (acetylcholinesterase) inhibitor
- Edrophonium (Tensilon) is short-acting
- Evaluate pre/post weakness
Repetitive Nerve Stimulation

Normal muscles: no change in compound AP amplitude
Myasthenia gravis: progressive decline with stimuli

RNS is positive in 75% of patients with Generalized MG
A decremental response is not specific for MG (LEMS and motor neuron disease)
**Single Fibre EMG:**

Principle: muscle fibres innervated by a single axon

Normal: These fibres activated with consistent latencies

NMJ disorders: increased variables of latencies among muscle fibres in a single motor unit = “jitters”
Therapy

- Anticholinesterase Inhibitors
- Steroids
- Immunosuppressive Agents
- Thymectomy
- Plasma Exchange
- Intravenous Immune Globulin
Old School

1934: Neostigmine introduced by Mary Walker

1935: ACTH administration shown to improve MG symptoms and shrink thymoma
  - Simon HE. Myasthenia gravis: Effect of treatment with anterior pituitary extract. JAMA 1935;104:2065-2066

1969: azathiaprine administered

1971: first successful corticosteroid trial
Cholinesterase Inhibitors

- Increases availability of Ach
- Helps control symptoms but not curative
- Most commonly used drug is pyridostigmine
- High concentrations may produce “cholinergic crisis”
- Most side effects related to increased cholinergic tone:
  - Miosis
  - Bradycardia
  - Hypersalivation
  - Brochoconstriction
  - Lacrimation
  - Sweating
Immunosuppression

- Prednisolone is mainstay of treatment
- Often started at low dose and gradually increased
- Once remission achieved, dose is gradually reduced to determine minimum effective dose
- Azathioprine may be added initially or later
- Alternate therapies include cyclophosphamide, methotrexate and cyclosporin
Thymectomy

“for patients with nonthymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement”


Currently recommended for:
- Young onset
- AChR-antibody positive
- Generalised myasthenia (not ocular)
Plasma Exchange

- The technique consists of separating plasma from cells using membrane filtration or centrifugation.
- Cells are re infused while plasma is removed.
- Diluted albumin or colloids or crystalloids are used to maintain volume and oncotic equilibrium.
- Plasma exchange has significant constraints and morbidity. Specific devices and teams trained in the use of extracorporeal circulation are needed.
Plasma Exchange

- First used in 1976 as a short term therapy for acute exacerbations of myasthenia gravis
- Currently recommended for short term therapy of myasthenic crisis (no RCTs)
- No benefit from long term treatment
IVIG

- First used for myasthenia gravis in 1984

- Acts to “mop up” AChR antibodies

- Very few RCT but lots of case reports and practical experience suggest benefit in myasthenia crisis

- Probably as efficacious as plasma exchange

- No long term benefit