

# Myasthenia Gravis

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# Overview

- Background
- Pathogenesis
- Clinical Manifestations
- Diagnosis
- Treatment
- Associated Conditions

# Background

- “Severe muscle disease”
- Most common disorder of neuromuscular transmission
- Annual incidence of 10-20 new cases per million
- Prevalence 1 in 7500
- Age of onset has a bimodal distribution
  - Second and third decades (female predominance)
  - Sixth to eighth decade (male predominance)

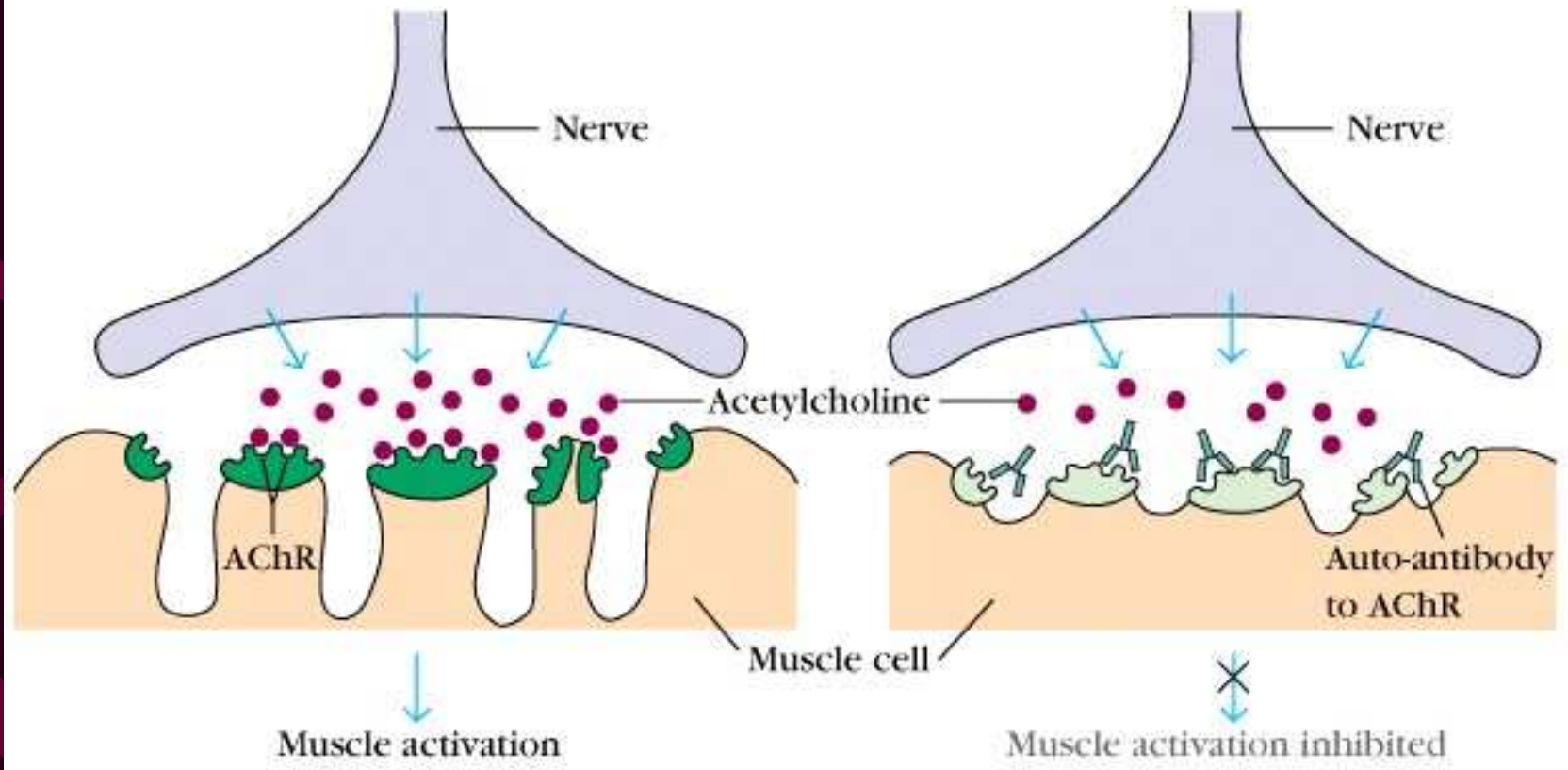
# Two Clinical Forms

- Ocular
  - Weakness limited to eyelids and extraocular muscles
  - Half of these patients have AChR antibodies
- Generalized
  - Also commonly affects ocular muscles
  - Bulbar, limb, and respiratory muscle involvement
  - Four-fifths of these patients have AChR antibodies

# Pathogenesis

- In MG, underlying defect is a decrease in the number of available acetylcholine receptors (AChR) at postsynaptic muscle membrane
- Postsynaptic folds are flattened or “simplified”, causing less efficient neuromuscular transmission

### BLOCKING AUTO-ANTIBODIES (Myasthenia gravis)



# Pathogenesis

- Autoimmune response mediated by anti-AChR antibodies
- Pathogenic antibodies are IgG and T cell dependent
- Thymus plays a role
  - Abnormal in 75% of pt's with MG
  - Hyperplastic in 65%
  - Thymoma in 10%

# Clinical Features

- Weakness and fatigability
- Cranial muscles, particularly eyelids and extraocular muscles, often involved early
- Diplopia and ptosis are common early complaints
- Weakness chewing (“I can’t chew meat”)
- Dysarthria
- Dysphagia



# Clinical Features

- “Snarling” expression when patient attempts to smile (“myasthenia sneer”)
- Weakness becomes generalized in 85%
- Limb weakness is often proximal, may be asymmetric
- Respiratory muscle weakness (“myasthenic crisis”)
- Deep tendon reflexes and sensation are preserved

# Diagnosis

- History and Physical
- “Tensilon Test”
- Repetitive Nerve Stimulation
- AChR antibody testing
- Single Fiber EMG

# History and Physical

- Diplopia, ptosis
- Weakness in characteristic distribution
- Fatigability
- Reduced strength on exam
- Reduced vital capacity

# Tensilon Test

- Edrophonium is an AChE inhibitor
- Rapid onset (30s) and short duration of action (about 5 minutes)
- Focus on a weak muscle group and evaluate for change
- Initial dose of 2mg given IV. If no change, give additional 8mg IV
- Beware cholinergic effects (nausea, diarrhea, salivation, fasciculations, bradycardia)
- Have atropine at bedside

# Repetitive Nerve Stimulation

- Anti-AChE inhibitors stopped 6-24 hrs prior to testing
- 2-3 electric shocks/second delivered, action potentials recorded
- In normal individual, amplitude of evoked muscle action potential dose not change
- In pt with MG, rapid reduction in the amplitude of the evoked response of more than 10-15%

# AChR Antibodies

- Presence diagnostic of MG, but a negative test does not exclude disease
- Measured level does NOT correspond well with severity of disease
- In an individual patient, however, treatment-induced fall in the antibody level often correlates with clinical improvement

# Single Fiber EMG

- The most sensitive test for MG
- Electrode measures action potentials of two muscle fibers innervated by the same motor axon
- Variability in time of the 2<sup>nd</sup> action potential relative to the 1<sup>st</sup> is called “jitter”
- MG cause increased “jitter”

# Treatment

- AChE inhibitors
  - Pyridostigmine (Mestinon)
- Immunosuppression
- Rapid immunomodulating treatments
  - Plasma exchange
  - IVIG
- Thymectomy



# AChE inhibitors

- Pyridostigmine (Mestinon)
  - Effect starts in 15-30 minutes, lasts 3-4 hours
  - Titrate dosage to symptoms
  - Cholinergic symptoms can limit use

# Plasmapheresis and IVIG

- Plasmapheresis
  - Pathogenic antibodies removed
  - Usually a course of 5 exchanges over a 2 week period
  - Useful for temporary relief of symptoms
- IVIG
  - Rapid improvement
  - 2g/kg typically administered over 5 days

# Immunosuppression

- Glucocorticoids and cyclosporin generally produce improvement within 1-3 months
- Azathioprine and mycophenolate take up to a year to show effect

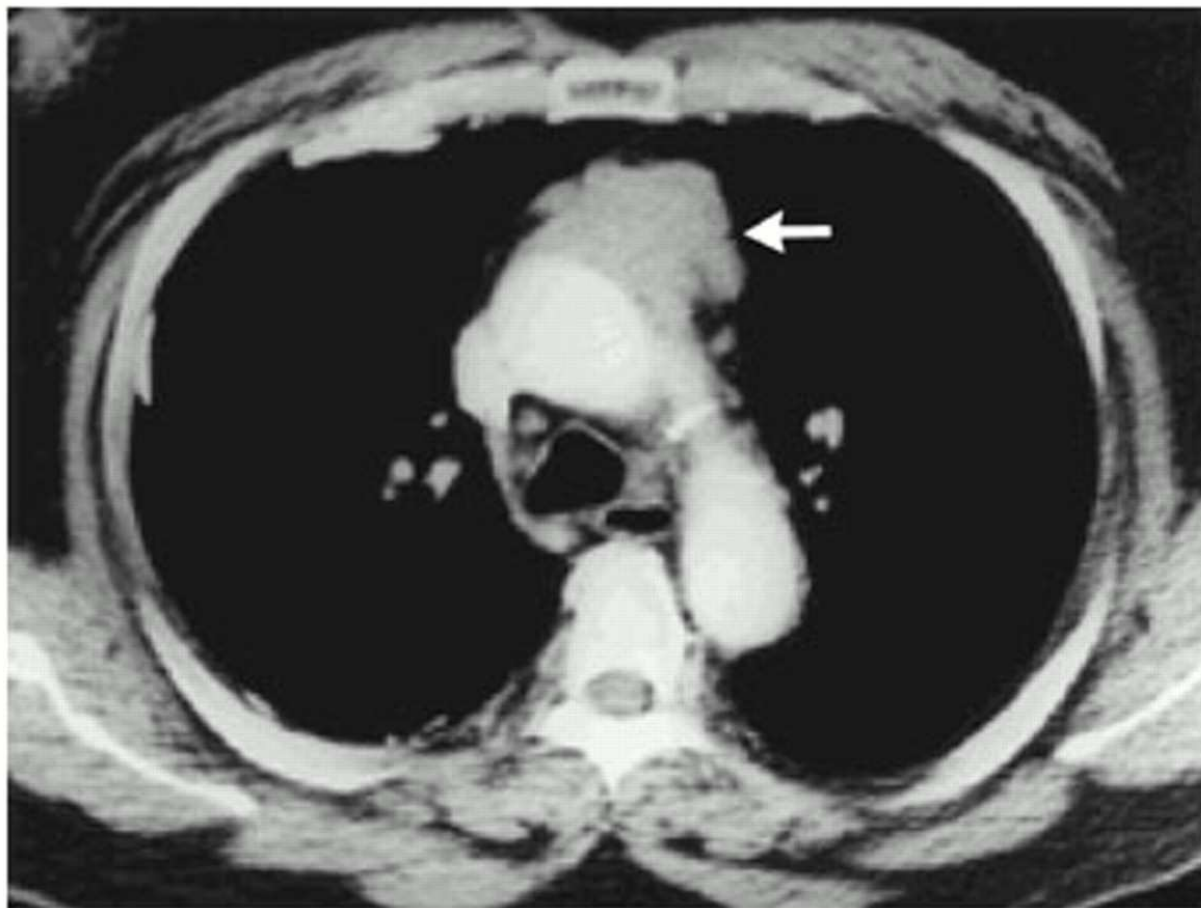
# Thymectomy

- In the absence of tumor, 85% of patients have improvement after thymectomy
- Improvement takes months to years

# Associated Conditions

- Disorders of the thymus
  - Thymoma
  - Hyperplasia of thymus
- Autoimmune disorders
  - Thyroiditis
  - Autoimmune thyroid disease (3-8%)
  - RA
  - SLE
- MG can be exacerbated by hyper/hypothyroidism, occult infection, drugs

**CT Scan of the Chest Obtained Four Years before Admission, Showing a Lobulated Anterior Mediastinal Mass (Arrow)**



Siao P and Zukerberg L. N Engl J Med 2000;342:1508-1514



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## Sectioned Surface of the Thymic Tumor



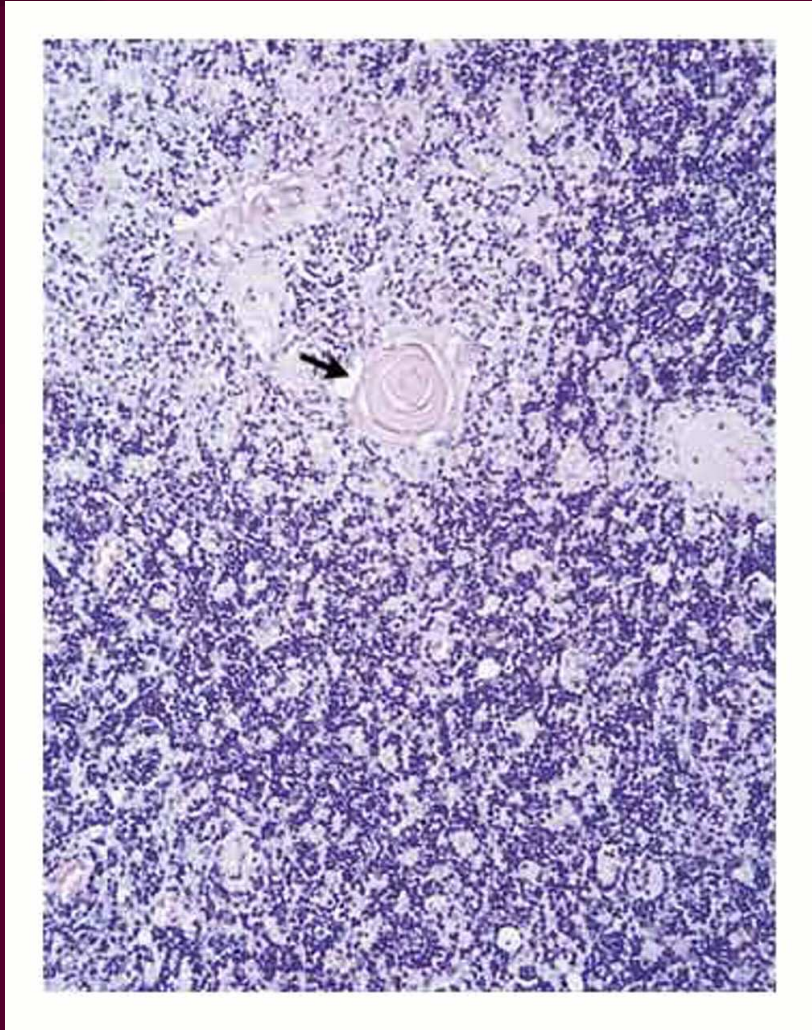
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Medullary Differentiation with a Hassall's Corpuscle (Arrow) (Hematoxylin and Eosin, x80)



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# Sources

- Harrison's Principles of Internal Medicine, 15<sup>th</sup> Edition. 2001
- Scully RE, Mark E. Case Records of the Massachusetts General Hospital. *The New England Journal of Medicine*. 1508-1514. May 2000.
- UptoDate. Myasthenia Gravis