NEUROMUSCULAR JUNCTION DISORDERS

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Lecture Objectives

- NMJ Anatomy
- MG
  - Pathophysiology
  - Autoimmune dysfunction
  - Epidemiology
  - Clinical Presentation
  - Work-up
  - Electrodiagnostic studies
  - Treatment
- Differential Diagnosis
  - LEMS

NMJ Anatomy

- Neuromuscular Junction (NMJ)
  - The Acetylcholine receptor (AChR) is a sodium channel that opens when bound by ACh
    - There is a partial depolarization of the postsynaptic membrane and this causes an excitatory postsynaptic potential (EPSP)
    - If enough sodium channels open and a threshold potential is reached, a muscle action potential is generated in the postsynaptic membrane

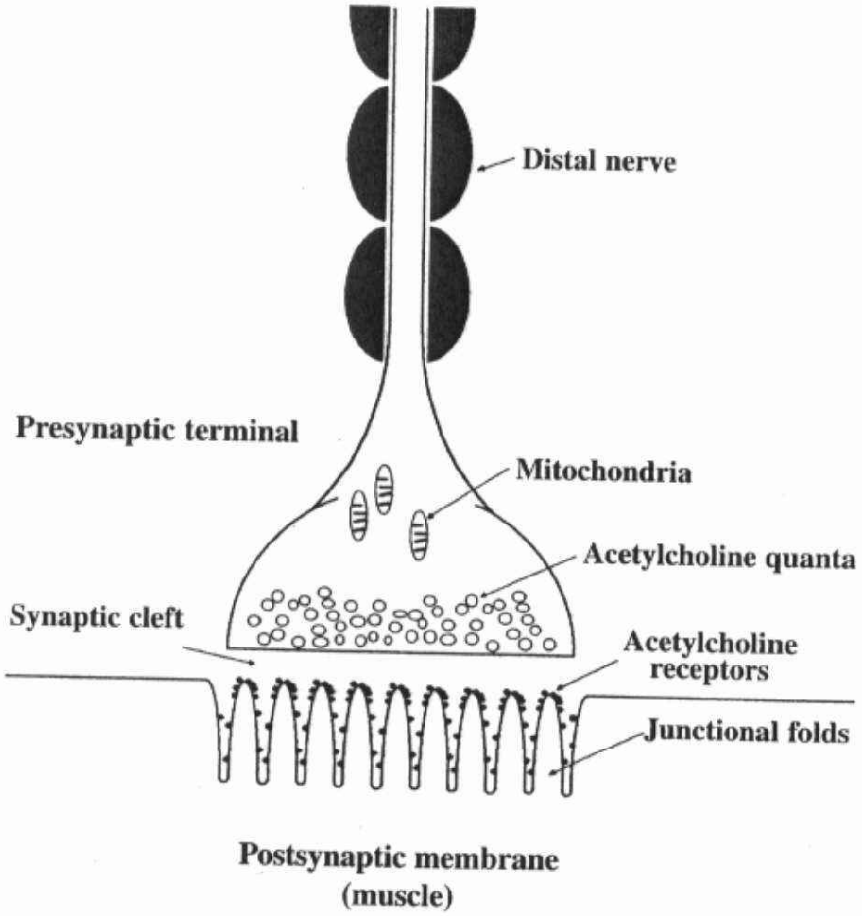
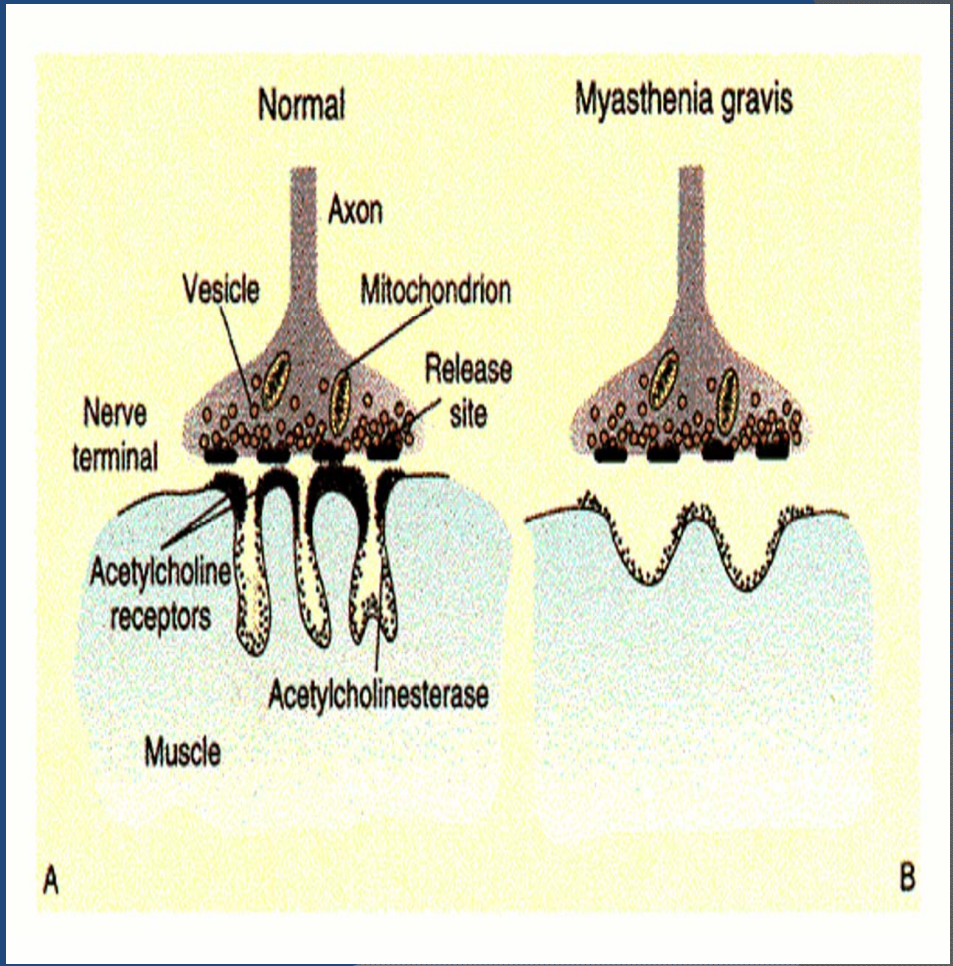


Figure 2.13 Neuromuscular junction. The neuromuscular junction is a specialized junction between the terminal axon and muscle fiber. When the nerve action potential invades the presynaptic terminal, acetylcholine is released and diffuses across the synaptic cleft to bind to acetylcholine receptors on the muscle membrane. This binding results in a muscle end-plate potential, which, once threshold is reached, causes the generation of a muscle fiber action potential.

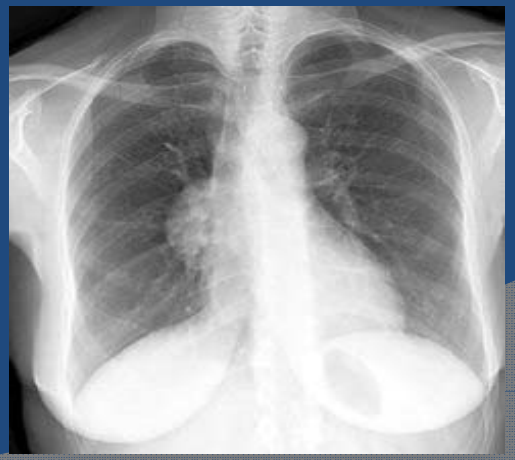
Myasthenia Gravis Pathophysiology

- In MG, antibodies are directed toward the acetylcholine receptor at the neuromuscular junction of skeletal muscles
- Results in:
  - Decreased number of nicotinic acetylcholine receptors at the motor end-plate
  - Reduced postsynaptic membrane folds
  - Widened synaptic cleft



Autoimmune Dysfunction

- Evidence of B-cell mediated disease:
  - Anti-AChR antibody is found in 80-90% of patients with MG
  - Proven with passive transfer experiments
- Evidence of dysfunction of T-cell mediated immunity:
  - Thymic hyperplasia and thymomas



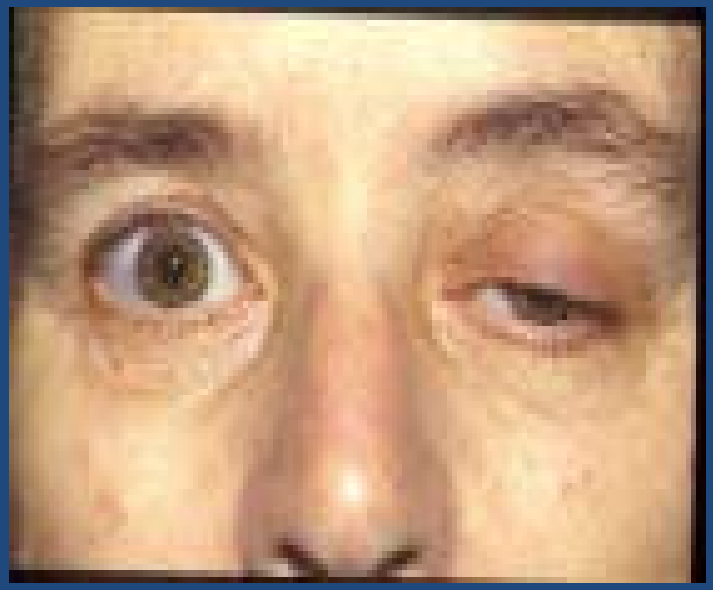
Epidemiology

- Frequency
  - Annual incidence in US- 2/1,000,000
  - Worldwide prevalence 1/10,000
- Mortality/morbidity
  - Recent decrease in mortality rate due to advances in treatment
    - 3-4% (as high as 30-40%)
  - Risk factors
    - Age > 40
    - Short history of disease
    - Thymoma
- Sex
  - F-M (6:4)
  - Mean age of onset (M-42, F-28)
  - Incidence peaks: M- 6-7th decade F- 3rd decade

Clinical Presentation

- Fluctuating weakness increased by exertion
  - Weakness increases during the day and improves with rest
- 40% have ONLY ocular symptoms
  - Only 16% of those with ocular symptoms at onset remain exclusively ocular at the end of 2 years
- Extraocular muscle weakness
  - Ptosis is present initially in 50% of patients and during the course of disease in 90% of patients
  - The disease remains ocular in 16% of patients
- Head extension and flexion weakness
- Respiratory fatigue (counting)
- Sensory examination and DTR's are normal

Clinical presentation



- Facial muscle weakness is almost always present, usually symmetric
- Ocular muscle weakness
  - Asymmetric
    - Usually affects more than one extraocular muscle and is not limited to muscles innervated by one cranial nerve
    - Weakness of lateral and medial recti may produce a pseudo-intranuclear ophthalmoplegia
      - Limited adduction of one eye with nystagmus of the abducting eye on attempted lateral gaze
  - Ptosis caused by eyelid weakness
  - Diplopia is very common

Clinical presentation

- Bulbar muscle weakness
  - Palatal muscles
    - “Nasal voice”, nasal regurgitation
    - Chewing may become difficult
    - Severe jaw weakness may cause jaw to hang open
    - Swallowing may be difficult and aspiration may occur with fluids—coughing and choking while drinking
  - Neck muscles
    - Neck flexors affected more than extensors

Clinical presentation

- Limb muscle weakness
  - Upper limbs more common than lower limbs

Upper Extremities
Deltoids
Wrist extensors
Finger extensors
Triceps > Biceps

Lower Extremities
Hip flexors (most common)
Quadriceps
Hamstrings
Foot dorsiflexors
Plantar flexors

Clinical presentation

- Respiratory muscle weakness-potential emergency
  - Weakness of the *intercostal muscles* and the *diaphragm* may result in CO2 retention due to hypoventilation
    - Bedside counts in 1 breath-rough estimate of VC
  - Weakness of *pharyngeal muscles* may collapse the upper airway
    - Monitor negative inspiratory force, vital capacity and tidal volume
    - Do NOT rely on pulse oximetry
      - Arterial blood oxygenation may be normal while CO2 is retained

Work-up

- Bedside: Ice pack, tensilon test
  - Edrophonium is a short acting Acetylcholine Esterase Inhibitor that improves muscle weakness (ptosis)
- Lab studies
  - Anti-acetylcholine receptor antibody
    - 85% in generalized myasthenia
    - 50% of patients with pure ocular myasthenia
  - Anti-muscle-specific tyrosine kinase (MUSK) antibody
    - Present in one-half to two-thirds of patients with “seronegative” generalized myasthenia
    - Unknown (but lower) frequency in pure ocular myasthenia

Work-up

- Co-existing autoimmune diseases
  - Hyperthyroidism
    - Occurs in 10-15% MG patients
      - Exophthalmos and tachycardia point to hyperthyroidism
      - Weakness may not improve with treatment of MG alone in patients with co-existing hyperthyroidism
  - Rheumatoid arthritis
  - Scleroderma
  - Lupus

Work-up

- Imaging studies
  - High resolution Chest CT scan (with and without contrast) is mandatory to identify thymoma
  - MRI of the brain and orbits may help to rule out other causes of cranial nerve deficits but should not be used routinely

Electrodiagnostic studies

- Repetitive nerve stimulation
  - Several factors can affect RNS results
    - Lower temperature increases the amplitude of the compound muscle action potential
    - Many patients report clinically significant improvement in cold temperatures
    - AChE inhibitors prior to testing may mask the abnormalities and should be avoided for at least 1 day prior to testing
- Single fiber electromyography (SFEMG)
  - SFEMG is more sensitive than RNS in MG

Neuromuscular Junction (NMJ)

- Synaptic vesicles 5,000-10,000 molecules of Ach (quantum)
- Each vesicle released causes a 1mV change in the post-synaptic membrane. This occurs spontaneously and is the the MEPP
- m=pn
  - m= the number of vesicles released after a nerve action potential reaches the NMJ
  - p= the probability of release
    - Proportional to the [Ca2+], typically 20%
  - n= the number of vesicles available

Vesicle stores

- Primary store- immediately available- 1000 vesicles
- Secondary store- mobilization, replenishes primary store after 1-2 seconds- 10,000 vesicles
- Tertiary store- reserve, found in the axon and cell body- 100,000 vesicles

Safety Factor

- The difference between the EPP and the threshold required for initiating a muscle fiber action potential.
  - Influenced by vesicle release, AchR conduction properties/density, postsynaptic folds that focus end plate current on voltage gated sodium channels

Role of calcium

- Pre-synaptic depolarization leads to calcium influx that leads to vesicular docking and Ach release
- Calcium diffuses slowly out of the pre-synaptic terminal at a rate of 100-200 ms.
- RNS < 5 Hz -calcium's role in vesicular release is not enhanced
- RNS > 10 Hz increased calcium greatly increases the probability that a vesicle will be released

Normal RNS

- In normals, with slow RNS, the EPP falls as vesicles are slowly depleted, but because of a normal safety factor, threshold is achieved and a muscle fiber action potential is generated
- With fast RNS (or exercise-preferred), the depletion of vesicles is counterbalanced by an accumulation of calcium, and there is an increase in the EPP

Post-Synaptic Disorders

- MG
  - The baseline EPP and safety factor are reduced, however threshold is still reached and the CMAP is normal
  - Slow RNS- The EPP falls further, some become subthreshold, muscle fiber action potentials fail and the CMAP drops (10%)
  - The greatest drop is seen between stimulus 1 & 4. By stimulus 5 the CMAP may increase with mobilization of the 2nd store
  - There may be a repair of the decrement after 10 seconds of exercise- "Post Exercise Facilitation"
  - Without a decrement, slow RNS should be repeated every minute after one minute of exercise- "Post Exercise Exhaustion"

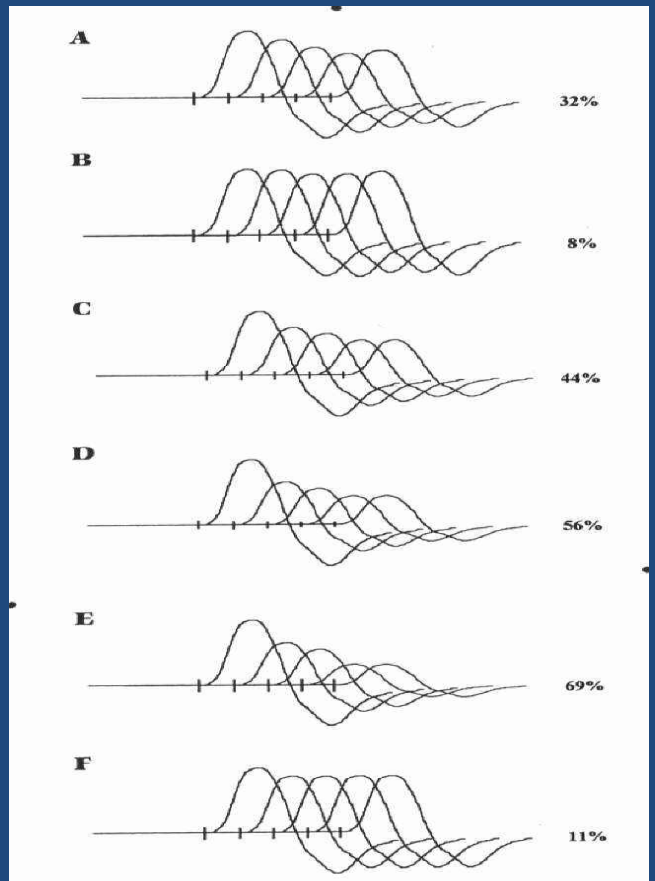


Figure 6.3 Postexercise facilitation and exhaustion. 3-Hz repetitive nerve stimulation in a patient with myasthenia gravis. A. Decrement of compound muscle action potential (CMAP) amplitude at rest. B. Postexercise facilitation: decrement of CMAP immediately after 10 secs of maximal voluntary exercise. Decrement has repaired toward normal. C–E. Postexercise exhaustion: decrements of CMAP 1, 2, and 3 mins after 1 min of maximal voluntary exercise. Decrement becomes progressively more marked over the baseline decrement. F. Postexercise facilitation after a decrement: Immediately after another 10 secs of maximal voluntary exercise, the decrement, which has worsened as a result of postexercise exhaustion, repairs toward normal.

Single-fiber electromyography

- Jitter- variability of the time interval between two muscle fiber action potentials innervated by the same motor unit
- Blocking- the failure of transmission leading to an absent muscle fiber action potential in a pair
- Generalized MG
  - Abnormal extensor digiti minimi found in 87%
  - Examination of a second abnormal muscle will increase sensitivity to 99%
- Ocular MG
  - Frontalis muscle is abnormal in almost 100%
  - More sensitive than EDC (60%)

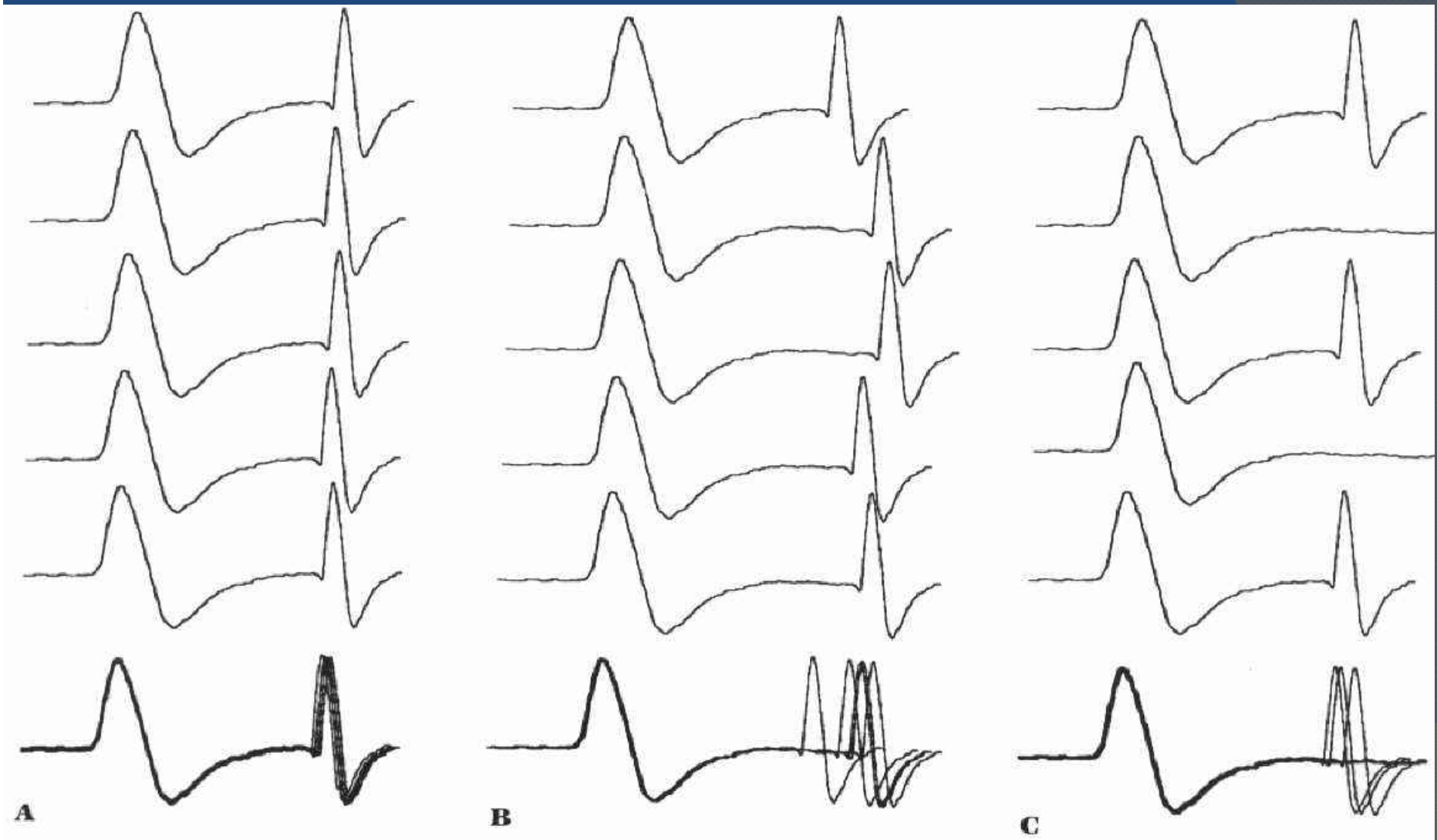
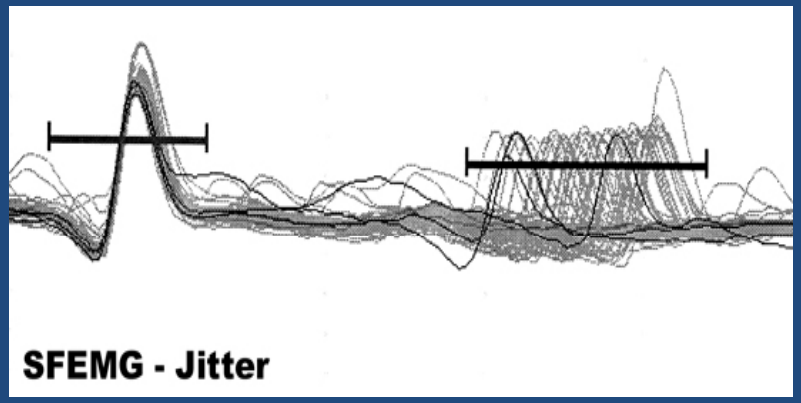
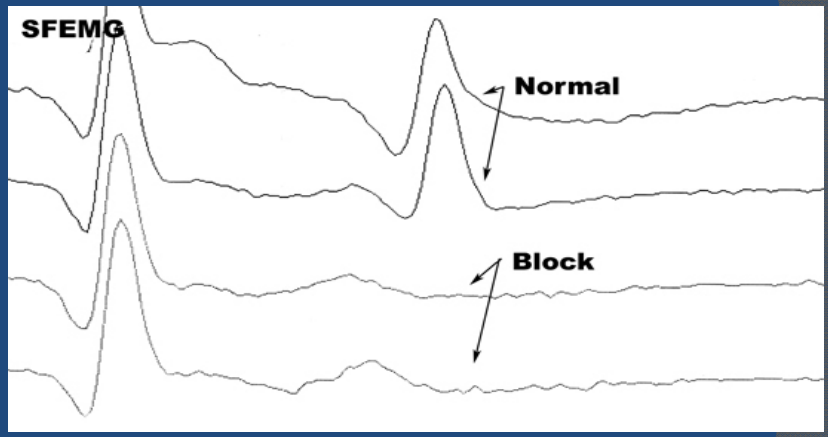


Figure 30.4 Single-fiber electromyography recordings. A. Normal. B. Increased jitter. C. Blocking. Each set: five rastered traces (top); superimposed traces (bottom). Both increased jitter and blocking are seen in neuromuscular junction disorders.

Jitter and block





Approach to treating MG

- Untreated MG carries a mortality rate of 25-31%; Treated MG has a 4% mortality rate
- Spontaneous remissions are rare
  - Most remissions with treatment occur within the first three years
- Treat any exacerbating factors
  - Infections, medication effect, endocrine disease
- Thymectomy- thymoma
- Standard RX:
  - Acetylcholinesterase inhibitors
  - Immunosuppressants
    - Prednisone
    - Azathioprine; Cyclosporine
  - Plasma exchange/ intravenous immunoglobulin

Treatment

- AChE inhibitor
  - Pyridostigmine bromide (Mestinon)
    - Starts working in 30-60 minutes and lasts 3-6 hours; individualize dose
    - Average dose:
      - 90 mg TID, plus 180 Timespan QHS
    - May cause cholinergic crisis, which can exacerbate pulmonary symptoms during acute crisis

Immunosuppressants

- Prednisone
  - Significant improvement is often seen after a decreased antibody titer which is usually 1-4 months
  - No single dose regimen is accepted
    - Outpatient regimen: start at 10 mg QD; increase by 5 mg every 3 days, to a maximum of 50 mg QD
    - Inpatient- can start at 20 and increase by 5 Q3d to max of 50; personally, if patient already intubated, will start higher.
  - Transient initial severe exacerbation, usually after 1 to 3 weeks (2% to 5%)
- Steroid Sparing agents:
  - Azathiproine- Maintenance dose 2-3 mg/kg; average dose: 140 and 210 mg qd; can take between 6-24 months for onset of action
  - Cyclosporine- more toxic; onset between 1-3 months

Differentials

- Lambert-Eaton Myasthenic Syndrome (LEMS)
- Botulism
- Amyotrophic Lateral Sclerosis (ALS)
- Dermatomyositis
- Multiple Sclerosis
- Sarcoidosis
- Thyroid disease
- Basilar Artery Thrombosis
- Brainstem gliomas
- Cavernous sinus syndromes
- Oculopharyngeal muscular dystrophy
- Brainstem syndromes

Lambert-Eaton Myasthenic Syndrome (LEMS)

- Clinical features:
  - Mimics MG, often affects older males
  - Proximal weakness (initially LE, then UE), areflexia or hyporeflexia Respiratory and craniobulbar involvement uncommon
  - Autonomic dysfunction prominent
    - dry mouth, dry eyes, impotence, orthostatic hypotension, hyperhidrosis
- Presynaptic disorder of neuromuscular transmission
- >92% with antibodies against P/Q-type voltage-gated calcium channels (presynaptic)
- Impaired influx of calcium into nerve terminal with reduced neuromuscular junction transmission
- Facilitation with sustained contraction
- >100% CMAP increase with repetitive stimulation

Lambert-Eaton Myasthenic Syndrome (LEMS)

- LEMS diagnosis warrants a thorough investigation for underlying carcinoma:
  - 45% to 60% associated with SCLC, reported also with renal cell carcinoma, lymphoma and breast
- Syndrome precedes tumor diagnosis by several months to years
- Careful observation and serial evaluations until tumor found
- Unlike most paraneoplastic syndromes LEMS usually responds to:
  - Plasmapheresis/ intravenous immunoglobin
  - Corticosteroids
  - 3,4 Diaminopyridine: 20 mg tid (orphan drug; can obtain as compassionate use from Jacobus Pharmaceutical Company, NJ; Phone: 609-921-7447; Fax: 609-799-1176)
  - Pyridostigmine
  - Immunosuppressants
- Long-term treatment often needed

Pre-Synaptic Disorders

- The baseline EPP is reduced and some are sub- threshold
- The baseline CMAP is reduced
- Slow RNS- the EPP falls further, fewer muscle fibers generate action potentials and the CMAP is reduced more
- Fast RNS- pre-synaptic calcium increases, more Ach is released, larger EPPs generate muscle fiber action potentials and the CMAP is increased
- LEMS- Increment often > 100-200%
- Botulism- smaller increment 30-100%

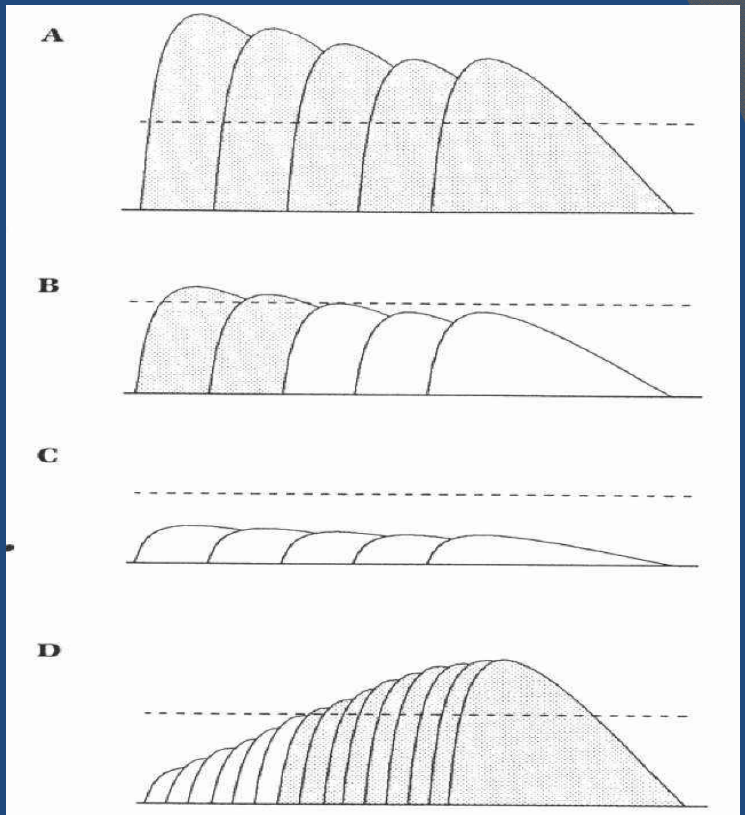


Figure 6.2 End-plate potentials. Threshold is represented by dashed line; shaded end-plate potentials (EPPs) are those that rise above threshold and generate a muscle fiber action potential. A. 3-Hz repetitive nerve stimulation (RNS), normal neuromuscular junction (NMJ): Note that all potentials remain well above threshold despite the normal decline in EPP amplitude (safety factor). B. 3-Hz RNS, postsynaptic NMJ disorder: note the lower EPP amplitudes. With further acetylcholine depletion, the last three potentials fall below threshold, and a muscle fiber action potential is not generated. C. 3-Hz RNS, presynaptic NMJ disorder: Note that all EPPs are below threshold and no muscle fiber action potentials are generated. The EPP declines in amplitude but not as markedly as in normal subjects or patients with postsynaptic NMJ disorders. D. 50-Hz RNS, presynaptic NMJ disorder: Note the progressive increment in the EPP amplitude to above threshold and the subsequent generation of muscle fiber action potentials