NMJ disorders: Myasthenia Gravis

Dr. Mohammed Alanazy

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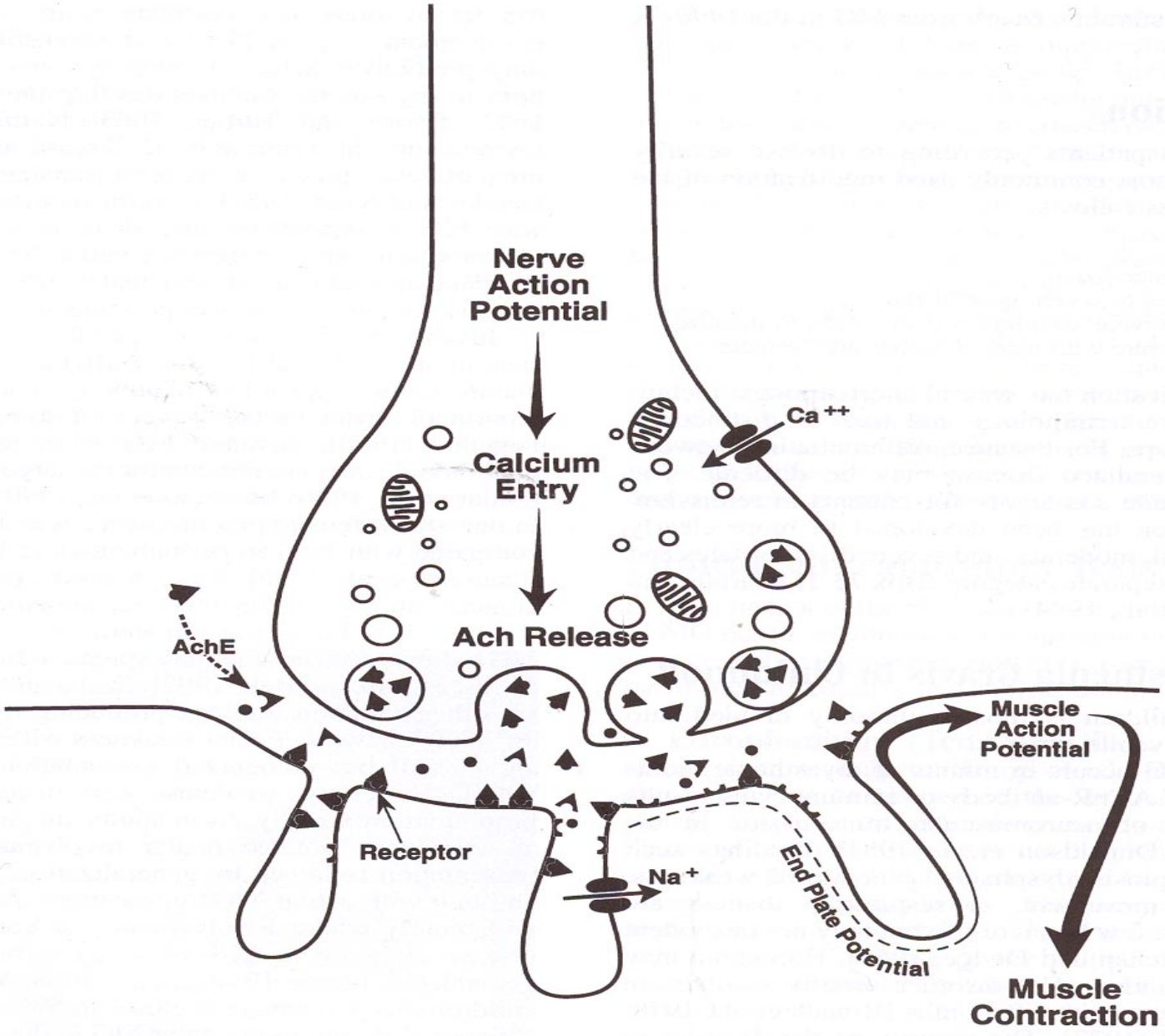
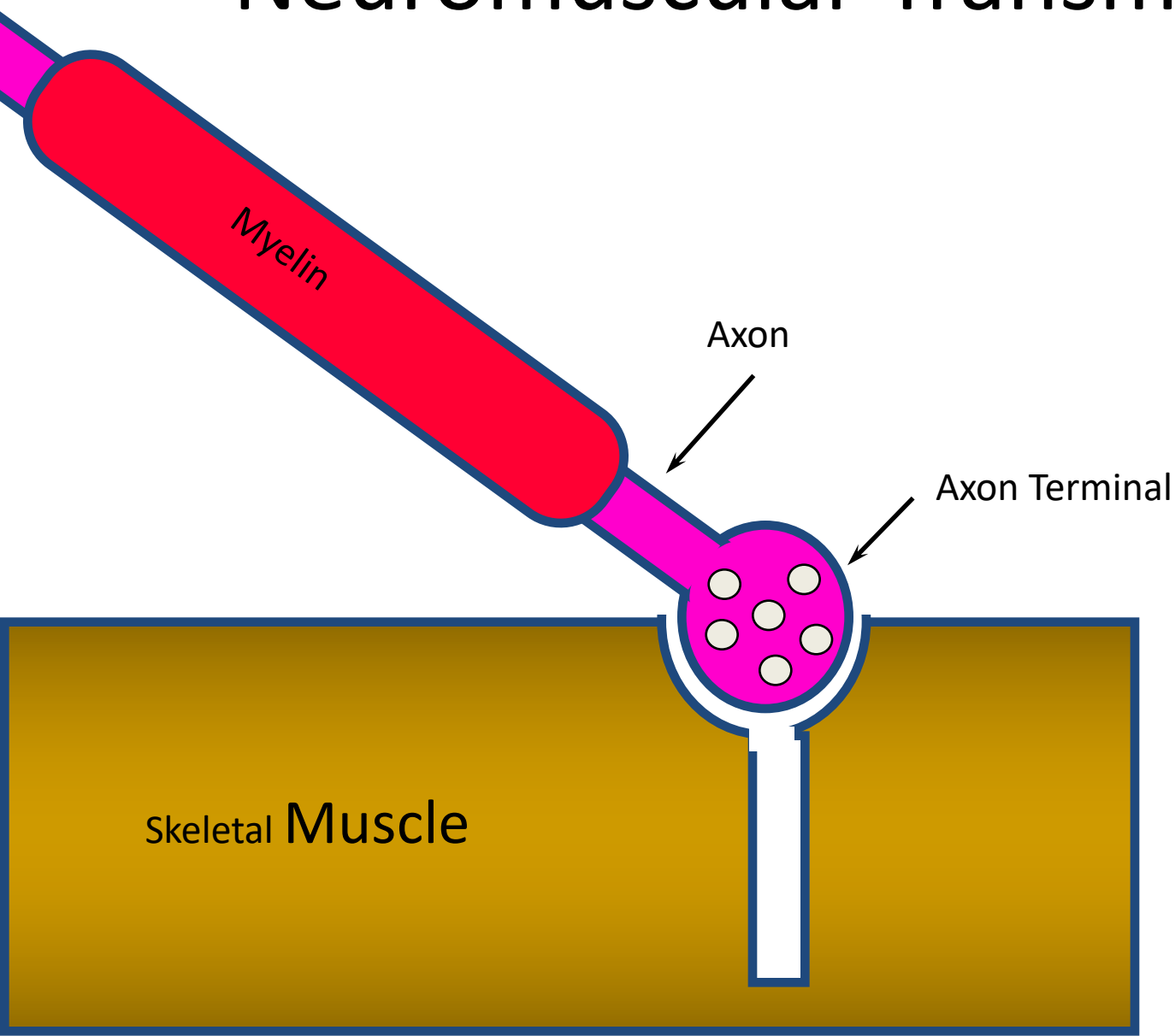
Objectives

By the end of the lecture the student should be able to:

1. Recognize the symptoms and signs of neuromuscular junction disorders (e.g., myasthenia gravis, MG)
2. Understand the pathophysiology of MG.
3. List the appropriate workup for MG.
4. List management options for MG.


Nerve
Action
Potential
Ca ++
Calcium
Entry
Ach Release
AchE
Muscle
Action
Potential
Receptor
Na +
End Plate Potential
Muscle
Contraction

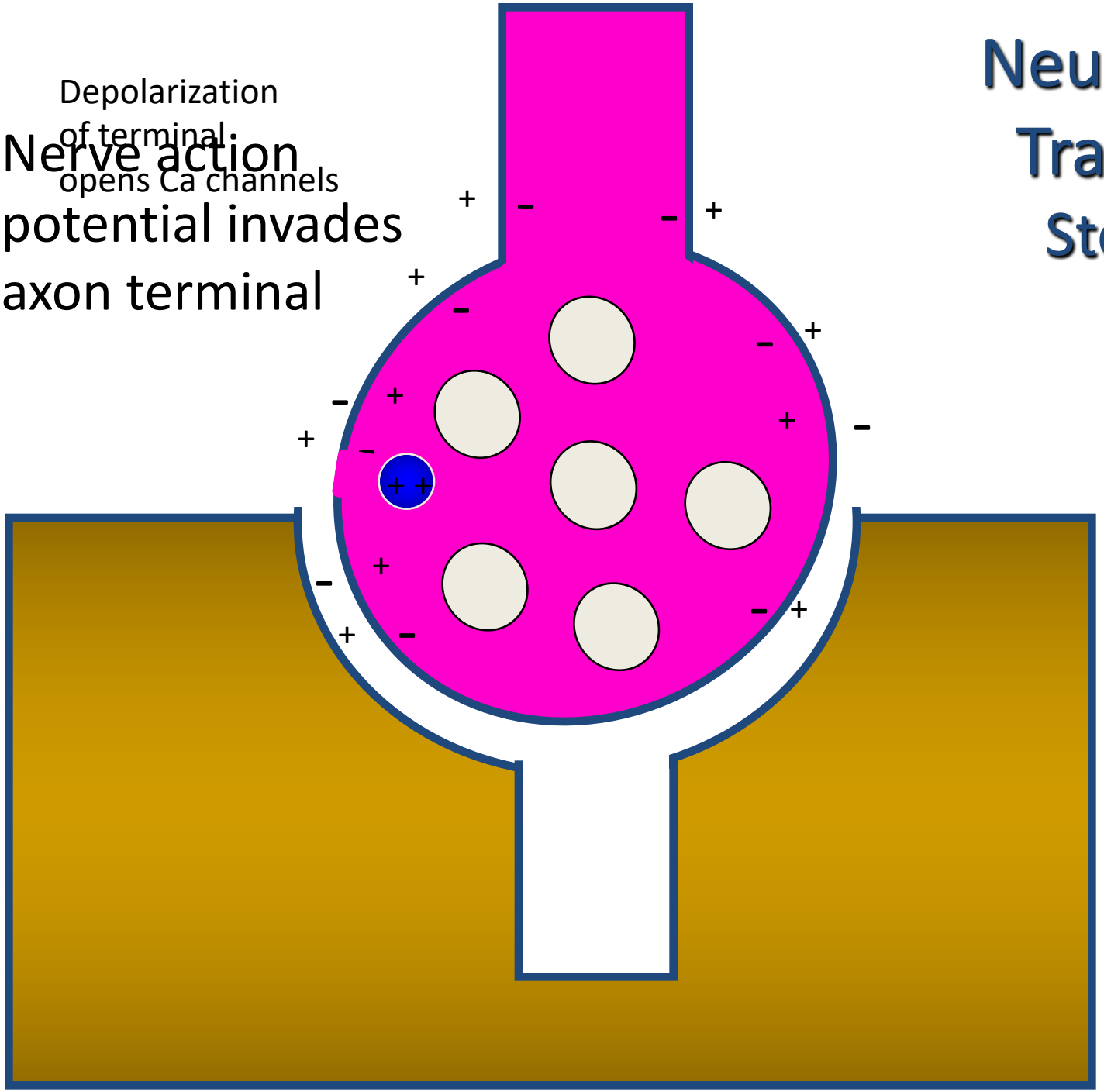
Neuromuscular Transmission

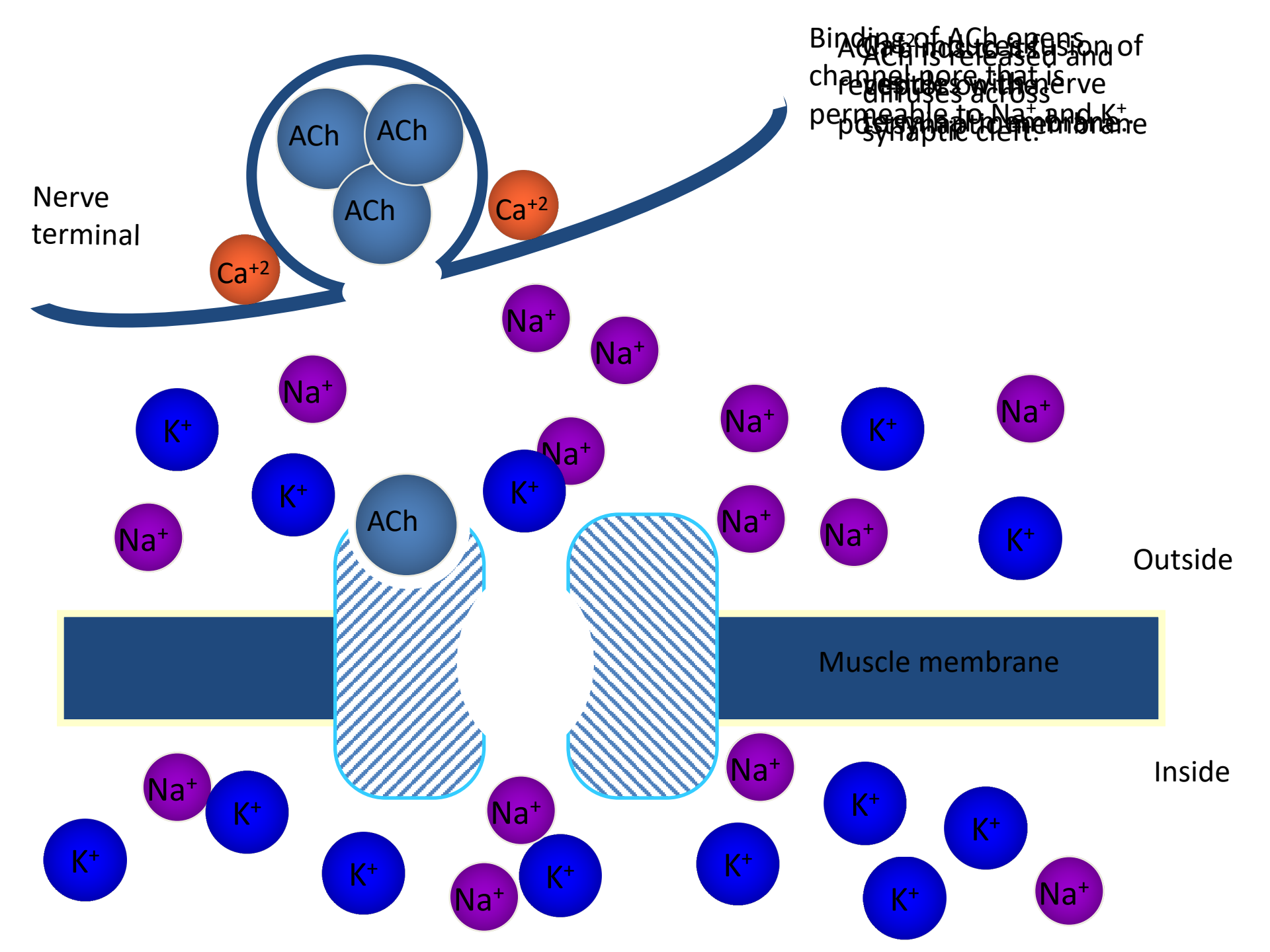


Neuromuscular Transmission:
Step by Step

Nerve action potential invades axon terminal

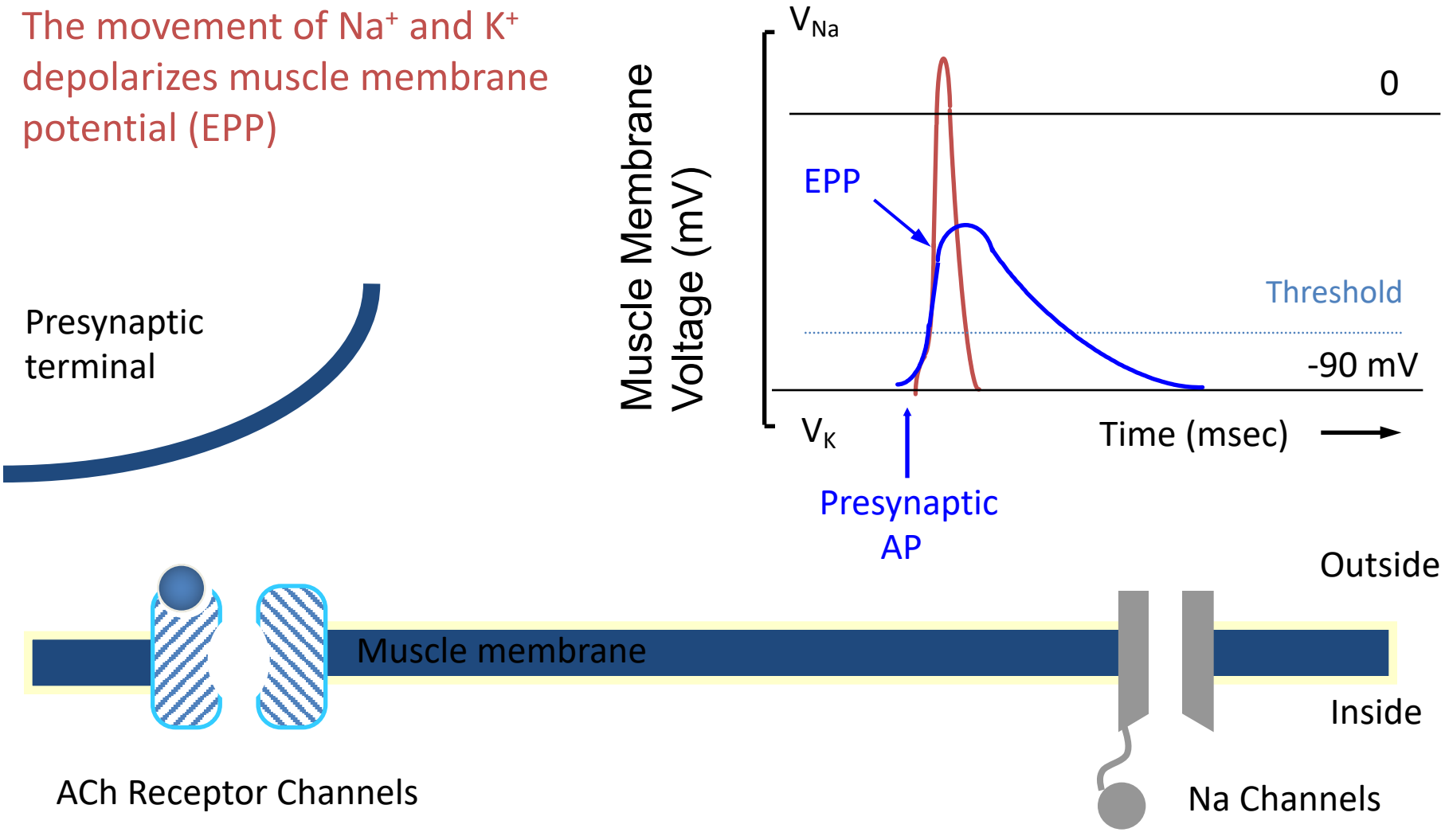
Depolarization of terminal opens Ca channels



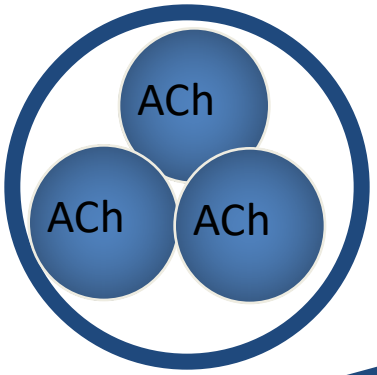

Binding of ACh opens channel pore that is permeable to Na+ and K+
ACh is released and diffuses across synaptic cleft.
Nerve terminal
ACh
ACh
ACh
Ca+2
Ca+2
Na+
Na+
Na+
K+
K+
Na+
K+
Na+
Na+
K+
Na+
Na+
K+
ACh
Outside
Muscle membrane
Inside
Na+
K+
Na+
K+
K+
Na+
K+
Na+
K+
K+
K+
Na+

End Plate Potential (EPP)

The movement of Na^+ and K^+ depolarizes muscle membrane potential (EPP)



Meanwhile ...



Nerve terminal

Choline is taken up into nerve terminal and recycled into vesicle

ACh is hydrolysed by AChE into Choline and acetate

ACh diffuses from its receptor so the channel closes

Acetate

Outside

Muscle membrane

Inside

Classification

- Presynaptic
  - Lambert Eaton Syndrome
  - Botulism
  - Congenital myasthenic syndrome
  - Hypermagnesemia
  - Envenomation
  - Aminoglycosides
- Synaptic
  - Congenital myasthenic syndromes
  - Cholinesterase inhibitors
  - Organophosphate
- Post-synaptic
  - Myasthenia gravis
  - Congenital myasthenic syndromes
  - Penicillamine

Myasthenia Gravis (MG)

Epidemiology

- Incidence: 10 – 20 per 1,000,000/ year
- Prevalence: 20 per 100,000
- Gender and age influence the incidence of MG
  - women are affected nearly three times more often than men before age 40
  - the incidence is higher in males after age 50 and roughly equal during and before puberty.

Clinical presentation

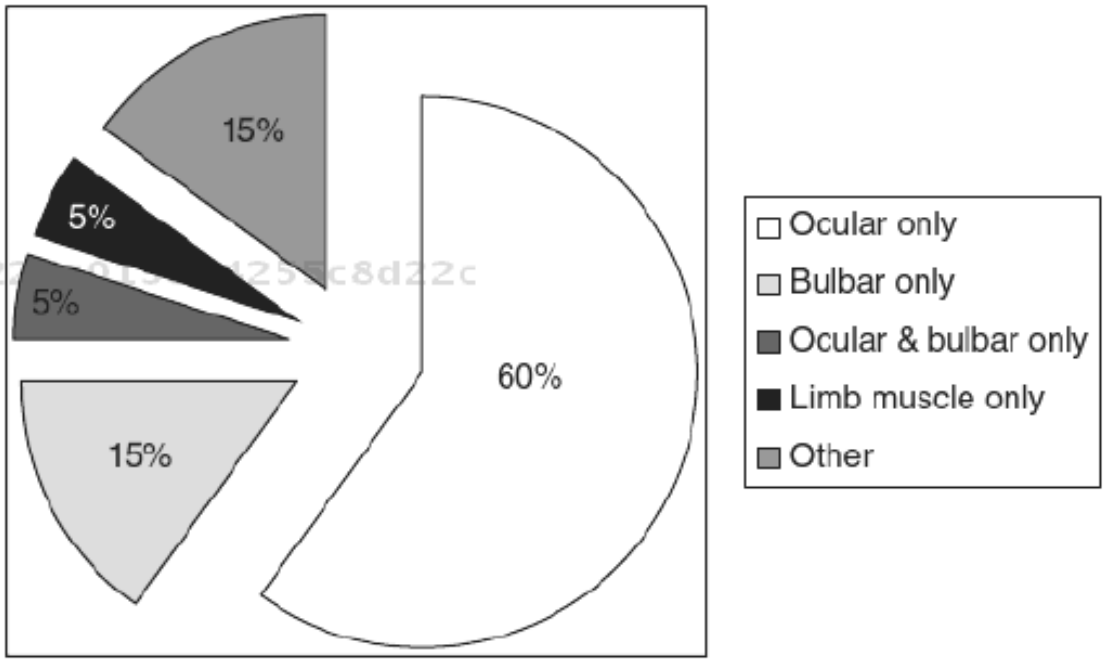


Figure 15.1. Initial symptoms in 919 patients with myasthenia gravis seen at the Duke University myasthenia gravis clinic (Sanders DB and Massey JM, unpublished data). Seventy percent had ocular symptoms (ptosis, diplopia, or blurred vision) at onset, and these were the only initial symptoms in 60%. Twenty-two percent had bulbar symptoms (dysarthria, dysphagia, or facial weakness), and these were the only symptoms in 15%; 5% had ocular and bulbar symptoms, and these were the only initial symptoms in 4%; and 5% had isolated weakness of limb or axial muscles alone. Twelve percent had initial symptoms of generalized weakness or fatigue, with or without other symptoms.

- Usually progresses for weeks-months, and maximum severity is usually in first year of disease

- 80% of ocular MG progress to generalized MG within 2 years.

- After 2 years with no limb Sx, disease usually remains purely ocular.

TABLE 1-2 Distribution of Weakness in a Large Cohort of Patients With Generalized Myasthenia Gravis (n = 609)

Distribution of Weakness	Percentage of Patients
Localized ocular	17%
Ocular and generalized	50%
Ocular and bulbar	13%
Ocular and limb	20%

Data from Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve 2008;37(2):141–149.

- Weakness in MG
  - The distinguishing clinical feature in MG is fatigable weakness.
  - Weakness: better in the morning and after rest.
  - **Asymmetric** ptosis and EOM weakness
  - Pupils spared
  - Weak eye closure.
  - Breathy nasal speech (palatal weakness)
  - Dysphagia and difficulty clearing secretions.
  - Jaw muscle weakness (prolonged chewing)
  - SOB due to diaphragm weakness (orthopnea)
  - Neck weakness: NF > NE (Musk : NE>NF)
  - Limb weakness: Proximal > distal, usually **symmetric**.
    - UL: Deltoid, triceps, WE, and FE
    - LL: HF, and Ank. DF

ABLE 1-1 Fatiguing Maneuvers in Suspected Myasthenia Gravis

Clinical Fatiguing Maneuver	Manifestation in Symptomatic Myasthenia Gravis	Comments
Sustained upgaze (30 to 60 seconds)	Enhances ptosis and elicits medial rectus weakness	Medial rectus muscle is usually most severely involved extraocular muscle
Sustained abduction of the arms (120 seconds)	Patient can no longer hold arms up, or weakness becomes apparent with subsequent manual testing	Dysarthria or shortness of breath may be enhanced
Sustained elevation of leg while lying supine (90 seconds)	Patient can no longer hold leg up, or weakness becomes apparent with subsequent manual testing	Dysarthria or shortness of breath may be enhanced
Repeated arising from chair without use of arms (up to 20)	Fatigues after several attempts	Early/mild weakness may cause exaggerated lean-forward and ''buttocks-first'' maneuver
Counting aloud (1 to 50)	Enhances dysarthria	Nasal, lingual, or labial

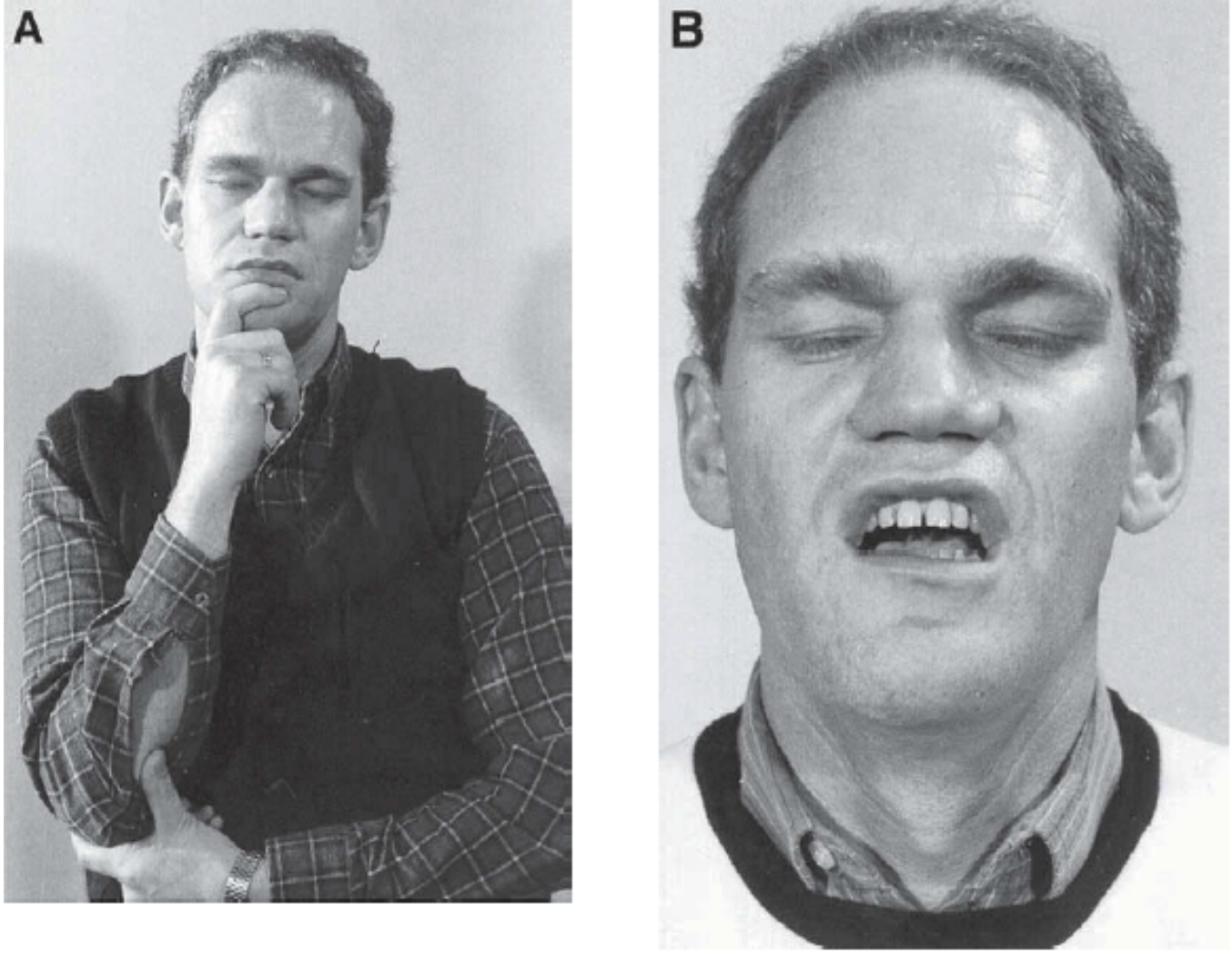


Fig. 1. A 36-year-old man with typical facial weakness. **(A)** He needs to support his jaw by holding his mouth closed. **(B)** When he attempts to close his eyelids firmly, his eyelashes remain visible, and the orbicularis oris weakness is evidenced by the straight smile.

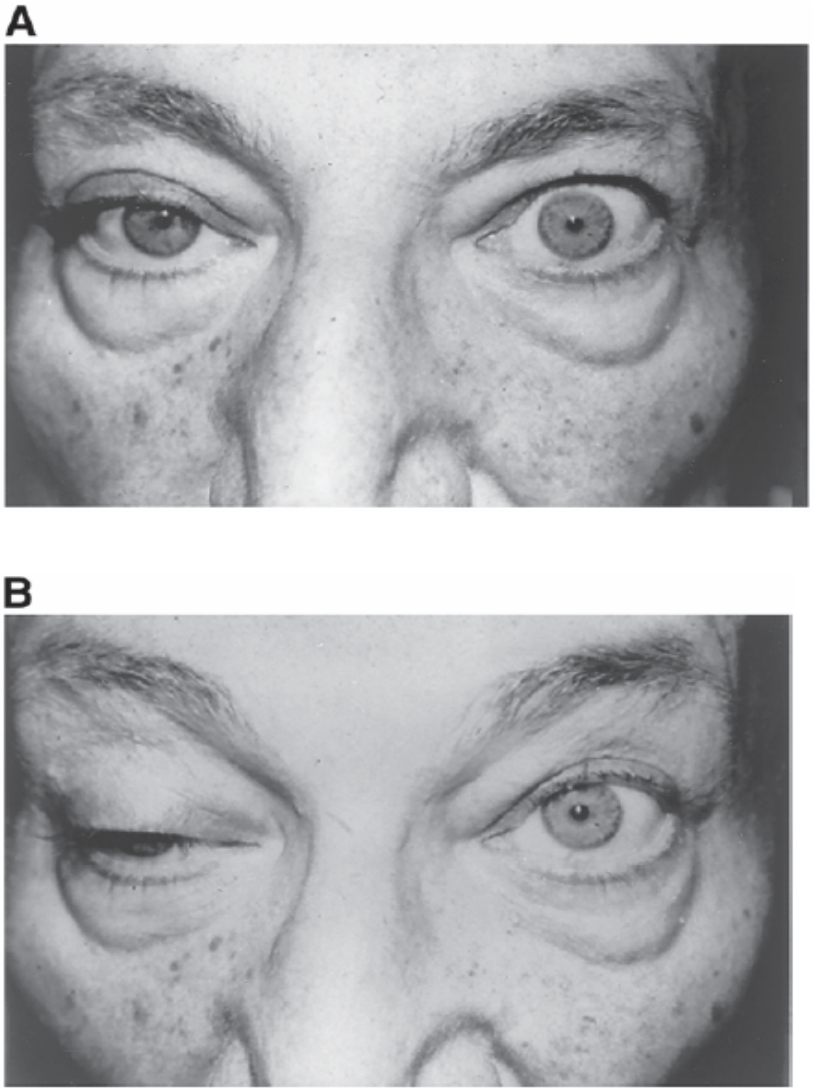
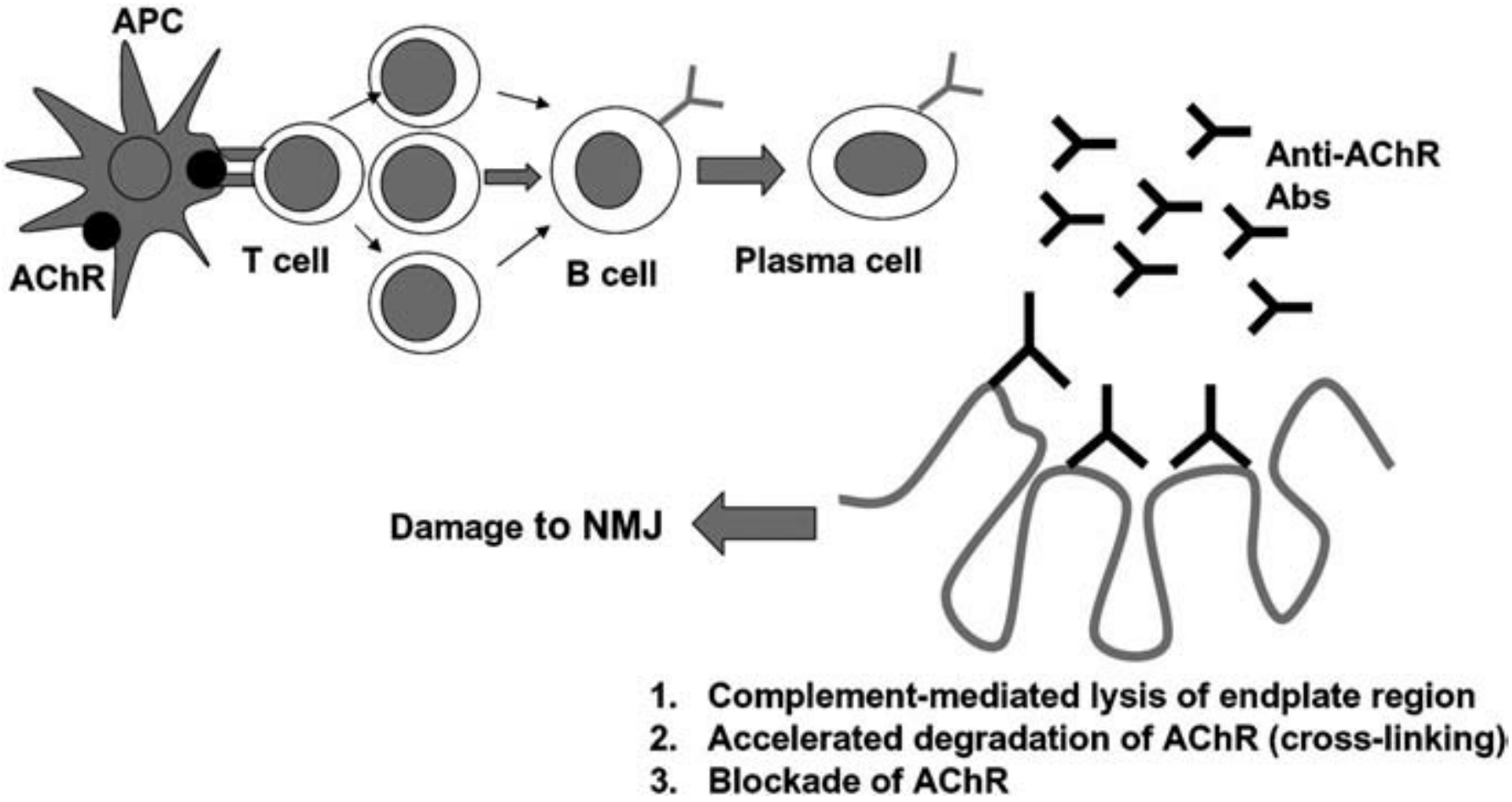


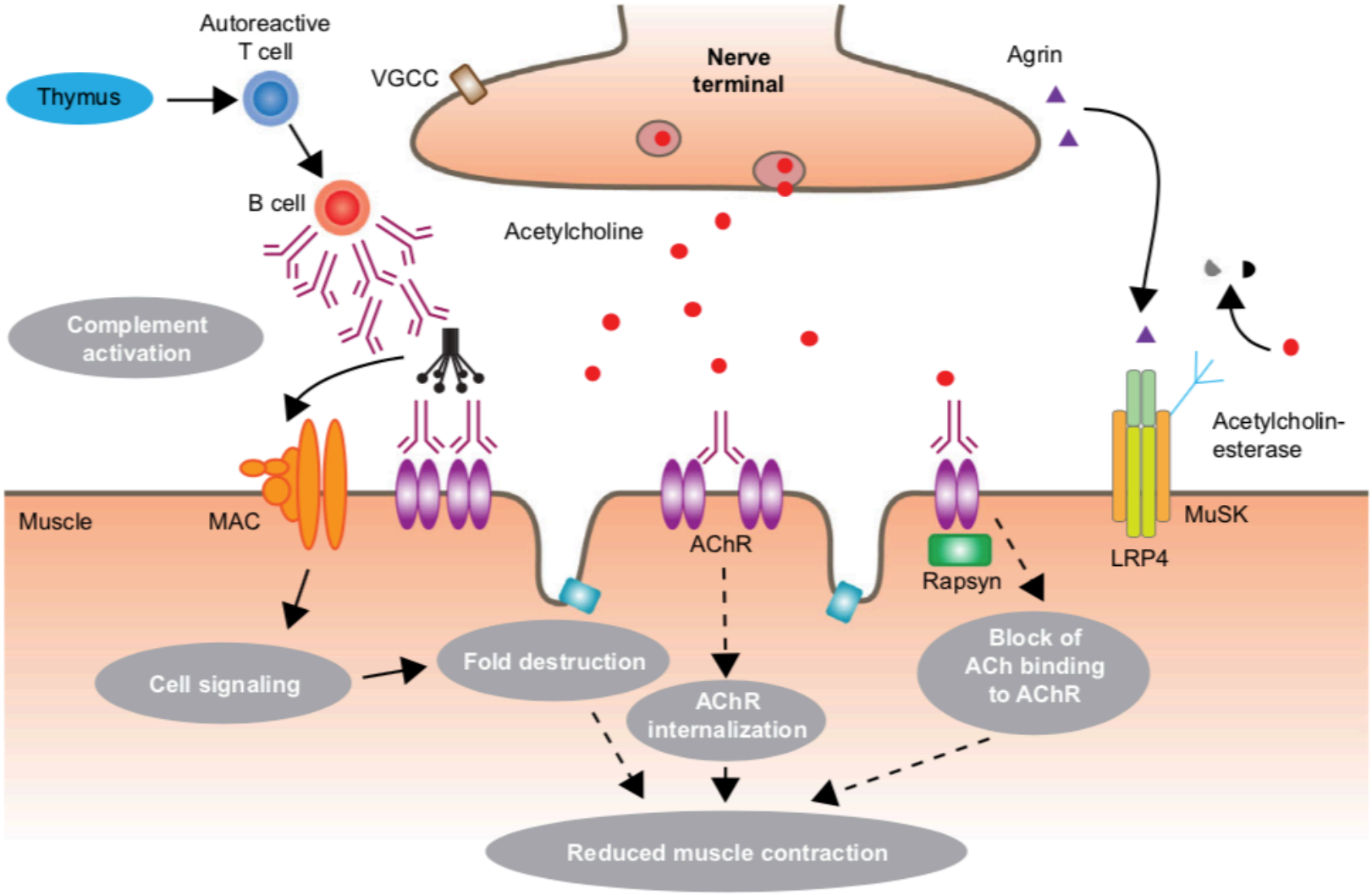
Fig. 1. (A) The patient is attempting to look up, evidenced by the contraction of the frontalis muscle. Note the slight right ptosis and left lid retraction. (B) Lid fatigue that developed during the sustained upward gaze, manifested by marked ptosis on the right, and lessening of the lid retraction on the left. (Photos courtesy of Dr. J. Lawton Smith.)

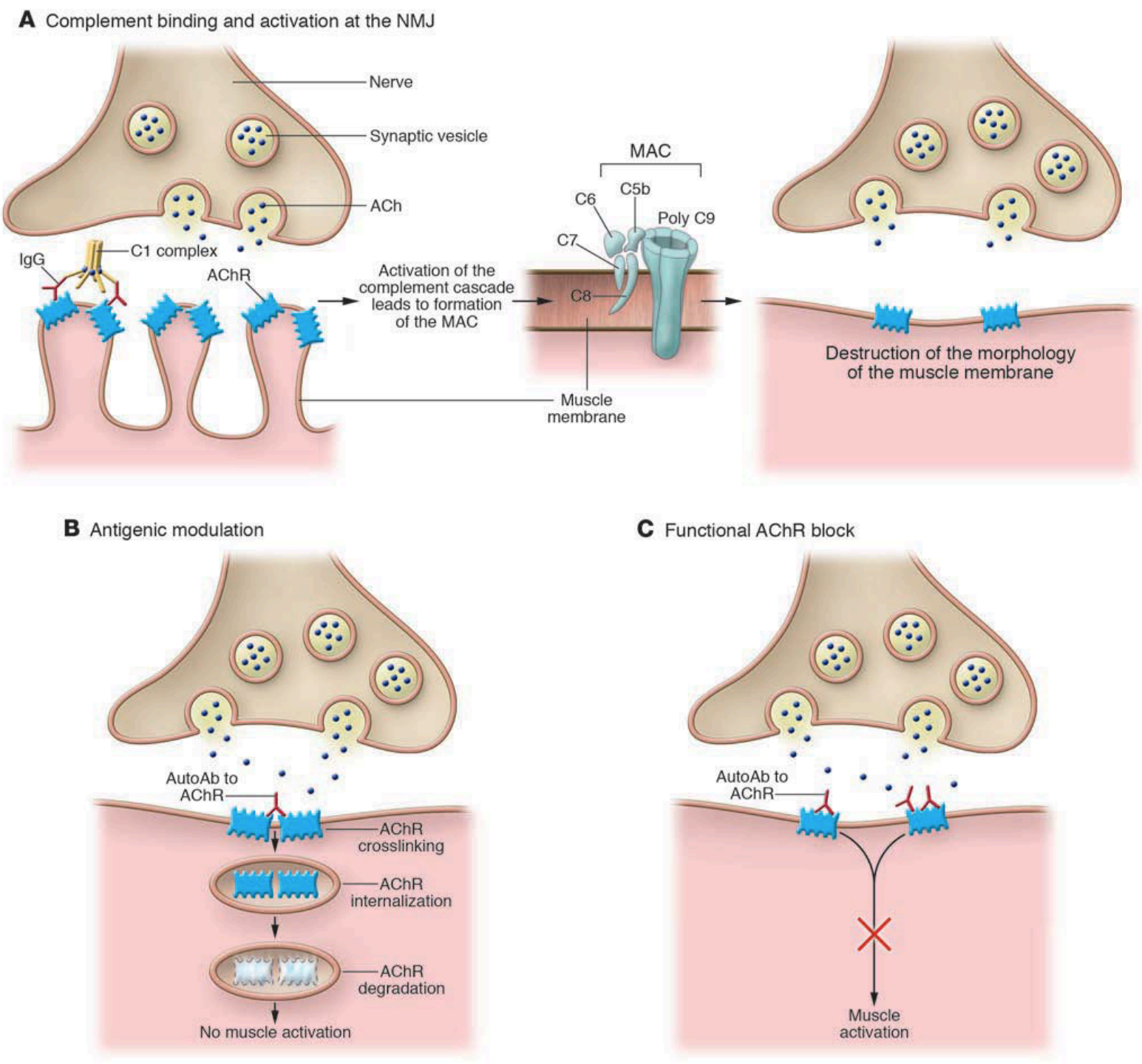
Myasthenia Gravis and related disorders,
Henry Kaminski, MD

Pathogenesis



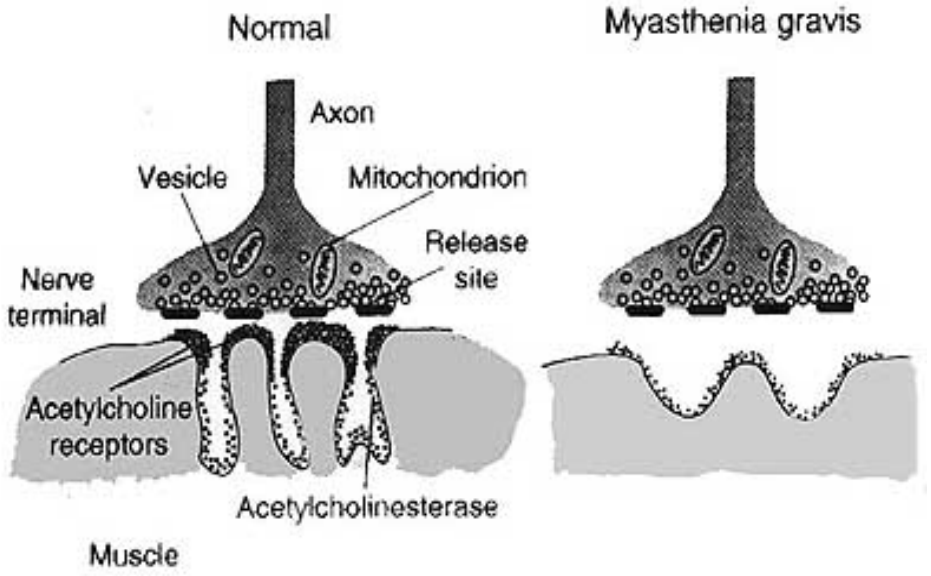
Pathophysiology of anti-AChR+ MG




A Complement binding and activation at the NMJ
Nerve
Synaptic vesicle
ACh
C1 complex
IgG
AChR
Activation of the complement cascade leads to formation of the MAC
MAC
C5b
C6
Poly C9
C7
C8
Muscle membrane
Destruction of the morphology of the muscle membrane
B Antigenic modulation
AutoAb to AChR
AChR crosslinking
AChR internalization
AChR degradation
No muscle activation
C Functional AChR block
AutoAb to AChR
Muscle activation

What Happens in MG

- Simplified postsynaptic membrane
- Decreased # of AchR's
- Remaining AchR's not localized to peaks
- Lower safety factor



Investigations

- CBC, LFT, RFT, CK, TSH, ESR, ANA
- Edrophonium Chloride (Tensilon) Test
- Ocular Cooling/“ice-pack” test
- Actylcholine Receptor (AChR) Antibodies.
- Anti-MUSK Antibodies.
- Repetitive nerve stimulation (RNS)
- SFEMG
- CT chest

Edrophonium Chloride (Tensilon) Test

- Inhibits the action of acetylcholinesterase, thus allowing ACh to diffuse more widely throughout the synaptic cleft and to have a more prolonged interaction with AChR on the postsynaptic muscle membrane

- The test is most reliable when the patient has ptosis or diplopia, and is positive in more than 90% of patients with MG.

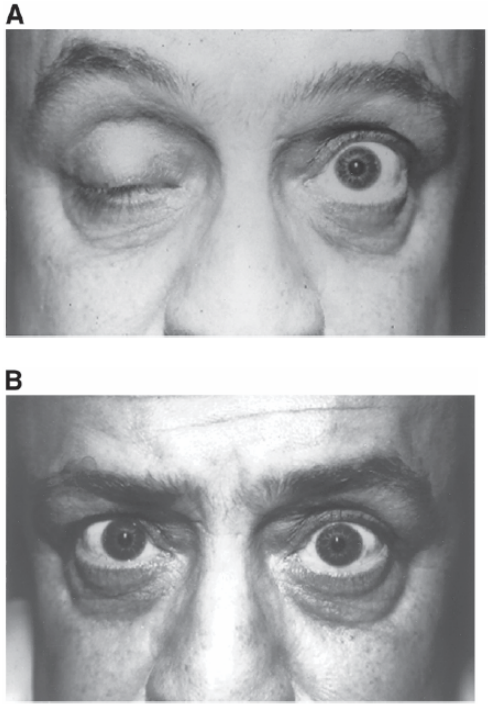


Fig. 2. (**A**) An almost complete right ptosis in a patient with ocular myasthenia. The frontalis muscle contraction, elevating the eyebrows, reflects the patient's effort to keep the lids open. (**B**) After administration of intravenous edrophonium chloride (Tensilon), the right ptosis is resolved. (Photos courtesy of Dr. J. Lawton Smith.)

Ocular Cooling/“ice-pack” test

- Place an ice pack over the ptotic eyelid for 2 minutes.
- Positive responses can occur even when edrophonium tests are negative.
- A meta-analysis showed his test to have high sensitivity and specificity in MG, suggesting that it may be useful in patients with lid ptosis, particularly if the edrophonium test is negative or contraindicated

ACETYLCHOLINE RECEPTOR (AChR) ANTIBODIES

- Sensitivity
  - 85% for GMG
  - 50% for OMG

ANTI-MUSK ANTIBODIES

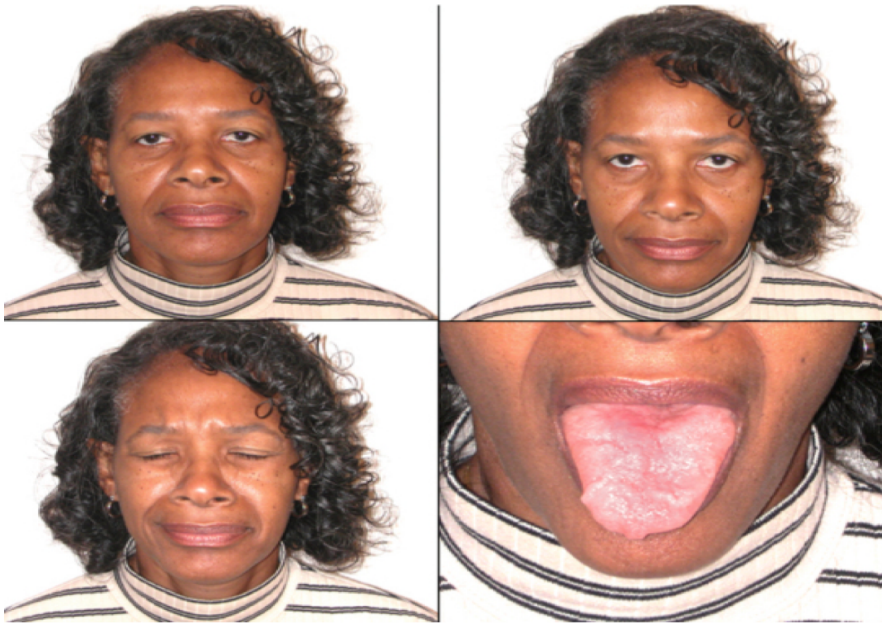
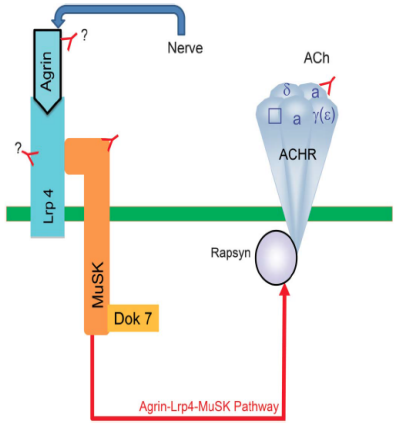


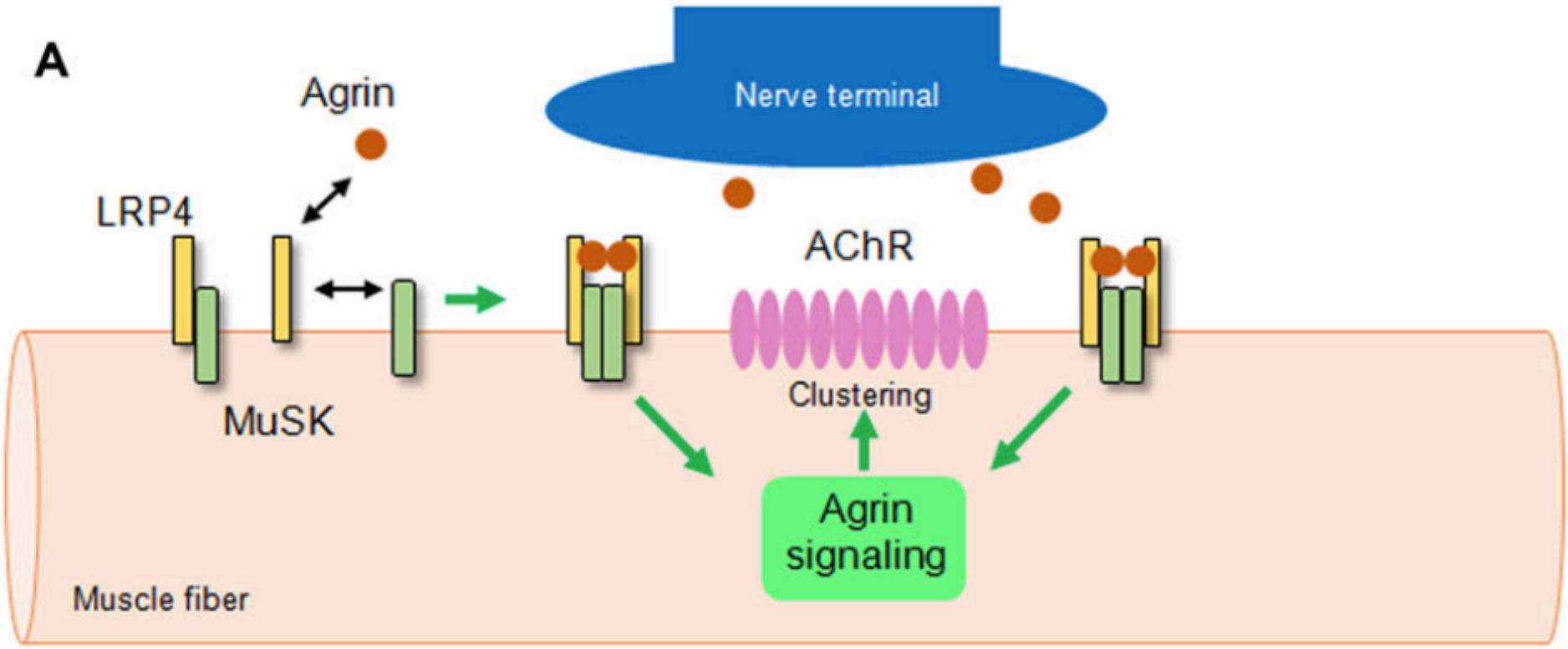
Figure Role of agrin



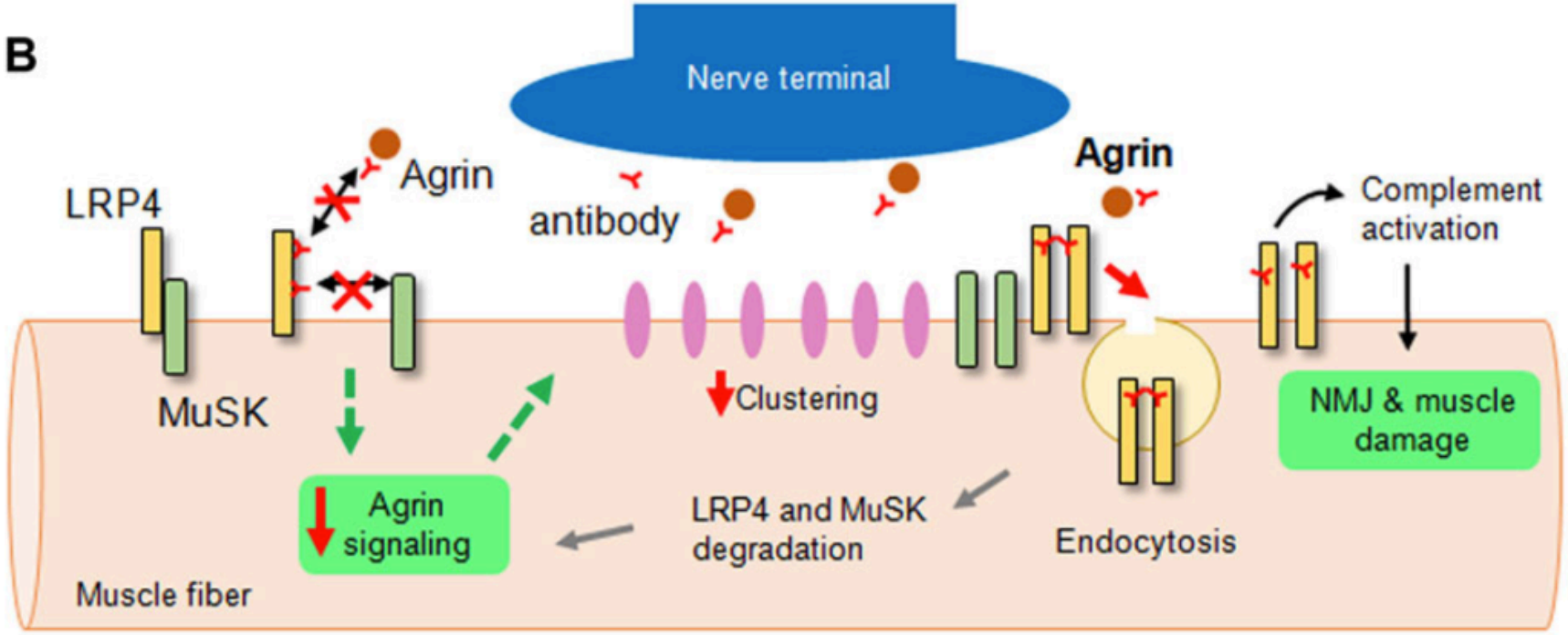
Agrin released from the nerve binds to LRP4, and through a complex with MuSK induces clustering of AChRs, which is further stabilized by rapsyn. Dok7 is required for proper activation of MuSK by nerve-derived agrin. See text re autoantibodies that have been demonstrated to produce myasthenia gravis and those that have yet to achieve requirements for confirmation as pathogenic antibodies. ACh = acetylcholine; AChR = acetylcholine receptor; Dok7 = docking protein 7; LRP4 = low-density lipoprotein-related receptor 4; MuSK = muscle-specific protein kinase.

- Present in up to 40 % of GMG patients who are seronegative for AChR antibodies and in some patients with OMG.

AChR clustering

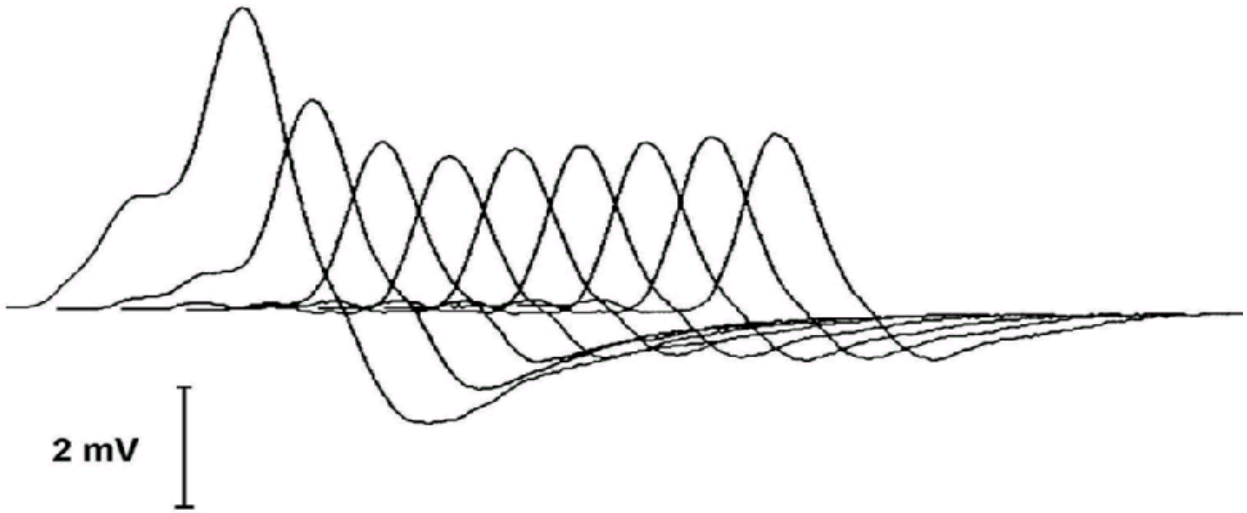


Potential mechanisms for anti LRP4 and anti-agrin antibodies

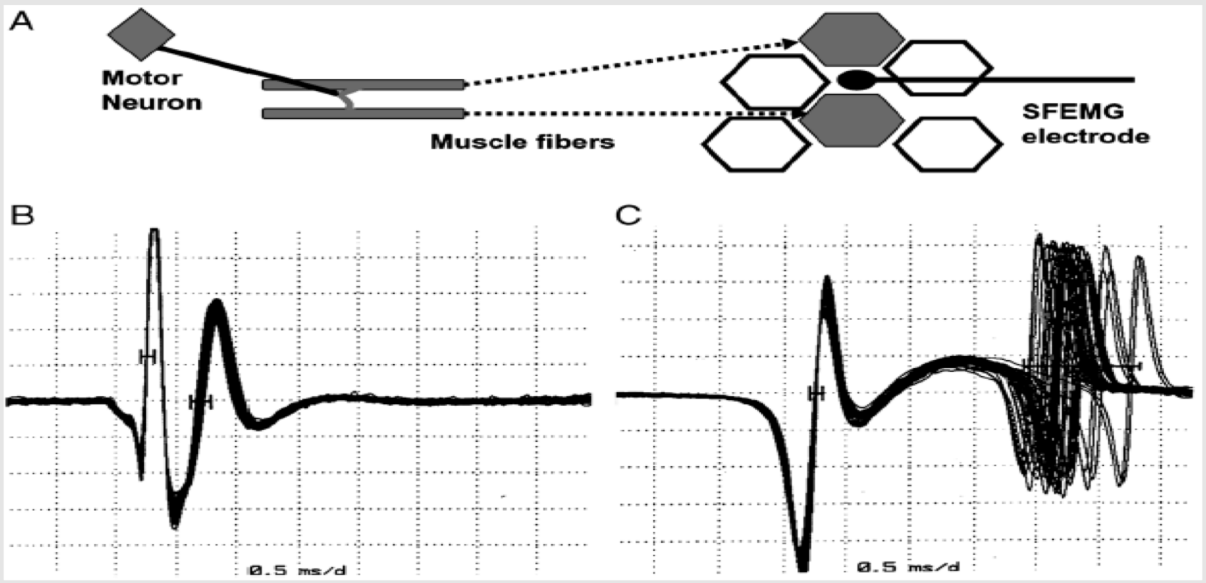


Repetitive nerve stimulation (RNS)

The sensitivity of RNS for diagnosing MG reportedly ranges from 53% to 100% in GMG and 10% to 48% in OMG

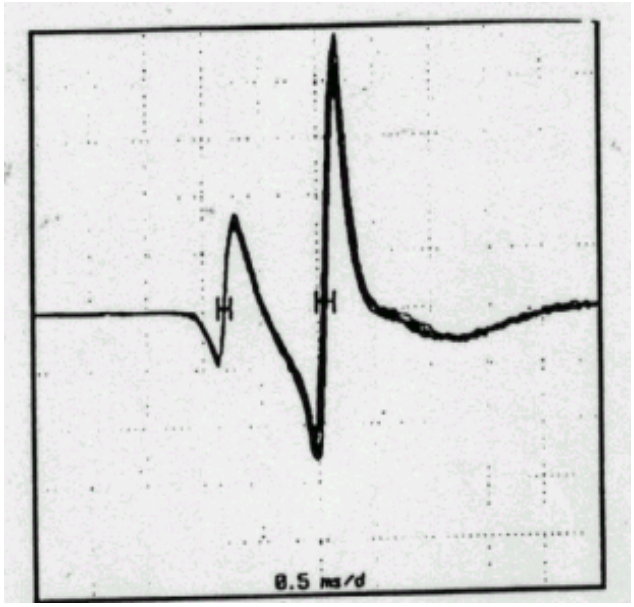


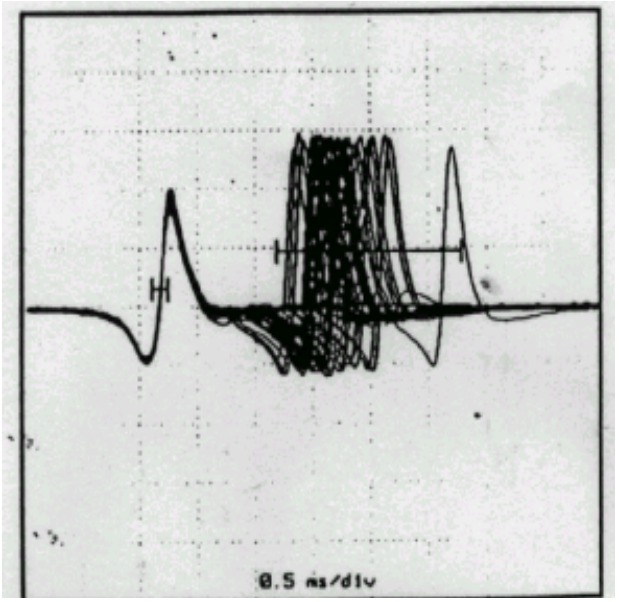
SFEMG

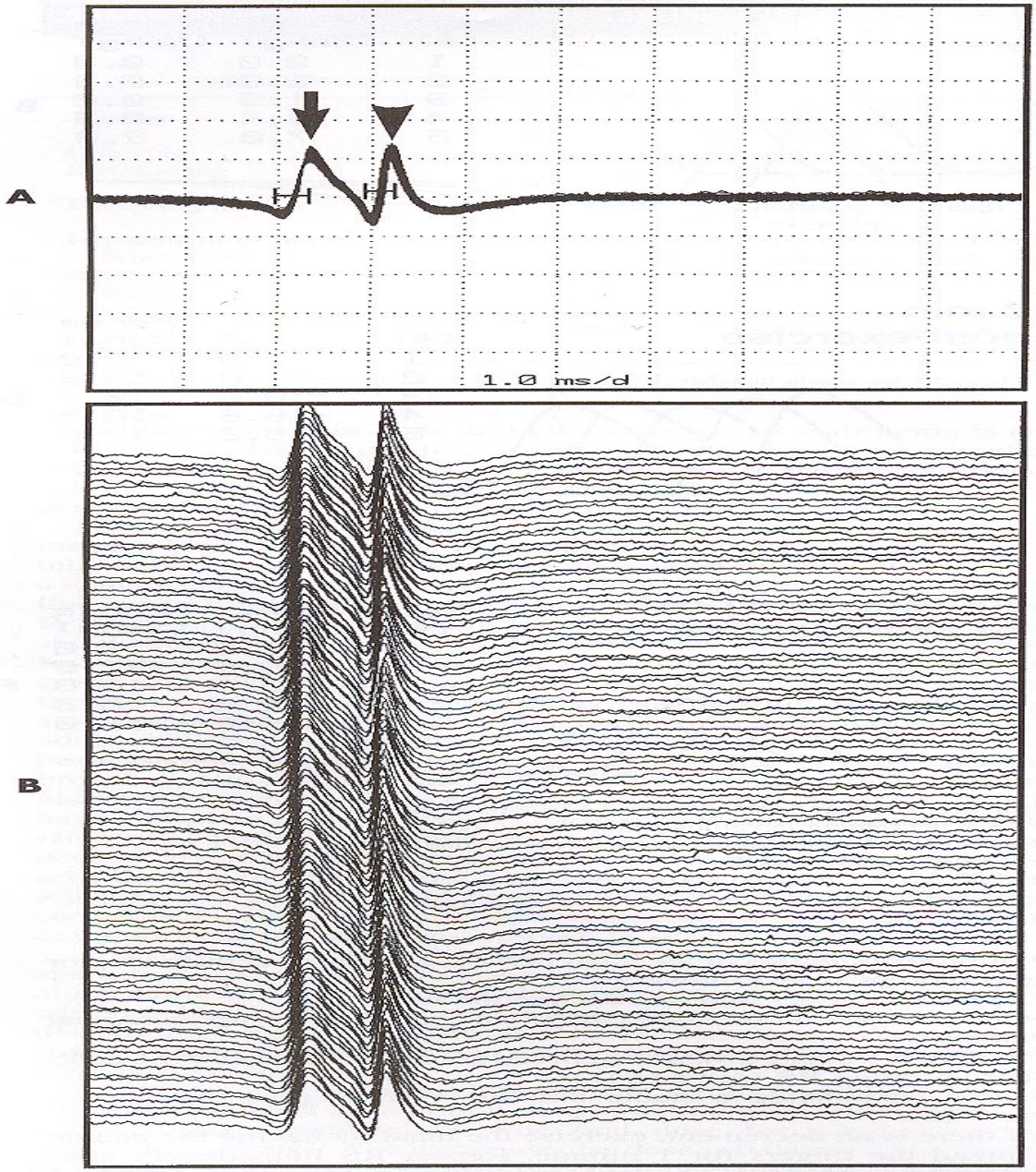


IGURE 2-4 *A,* In single fiber EMG (SFEMG) testing, the recording electrode is positioned to record from two or more time-locked potentials. Jitter is measured as the variation in the time interval between the two action potentials in the pair. *B,* An example of normal jitter; 40 consecutive discharges are superimposed. *C,* Abnormal jitter; 50 consecutive discharges are superimposed.

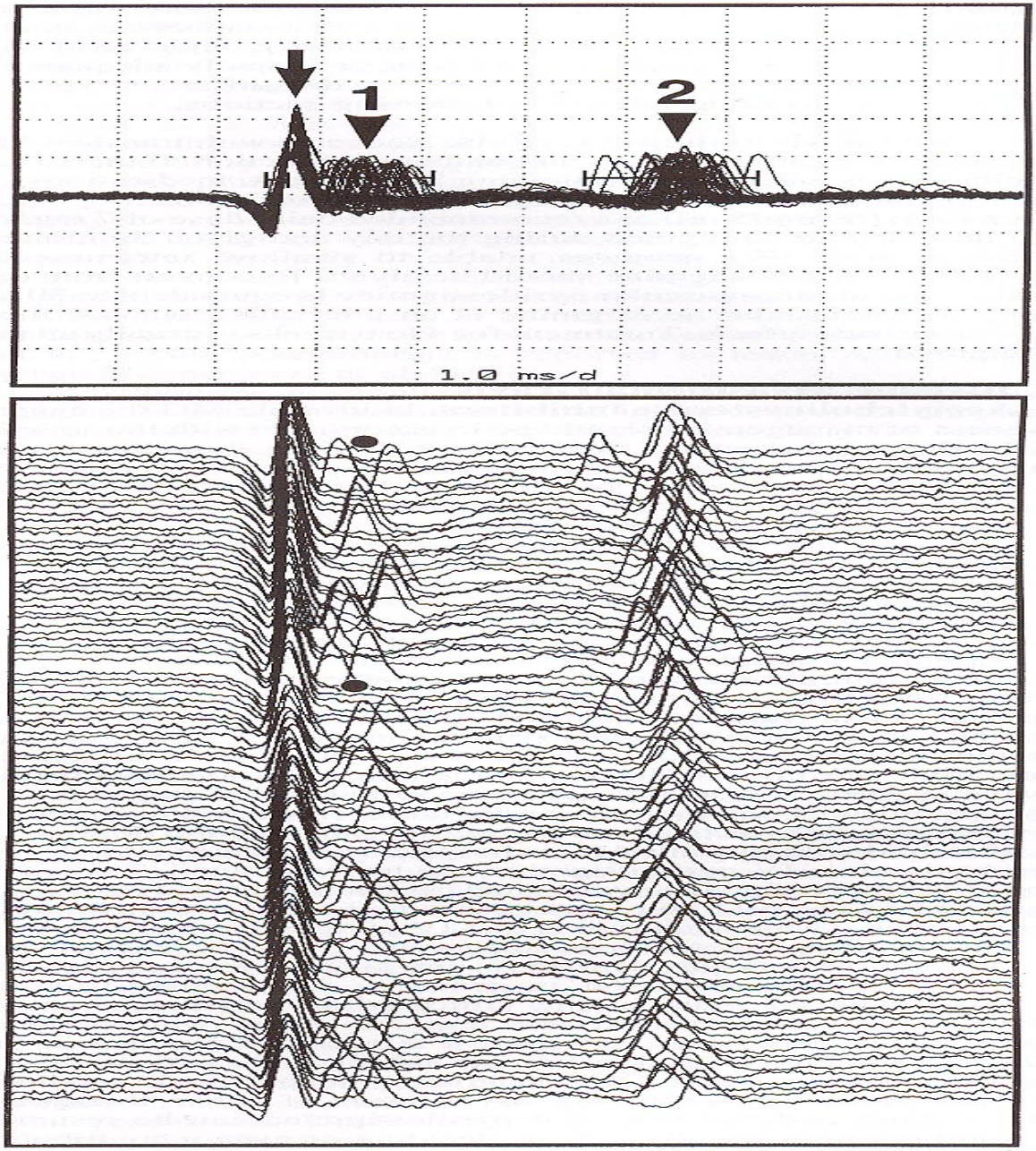
- Decreased # of interactions between Ach and receptors → takes longer to reach threshold
- Time required for EPP to reach threshold varies – JITTER
- Sometimes EPP fails to reach threshold – BLOCKING





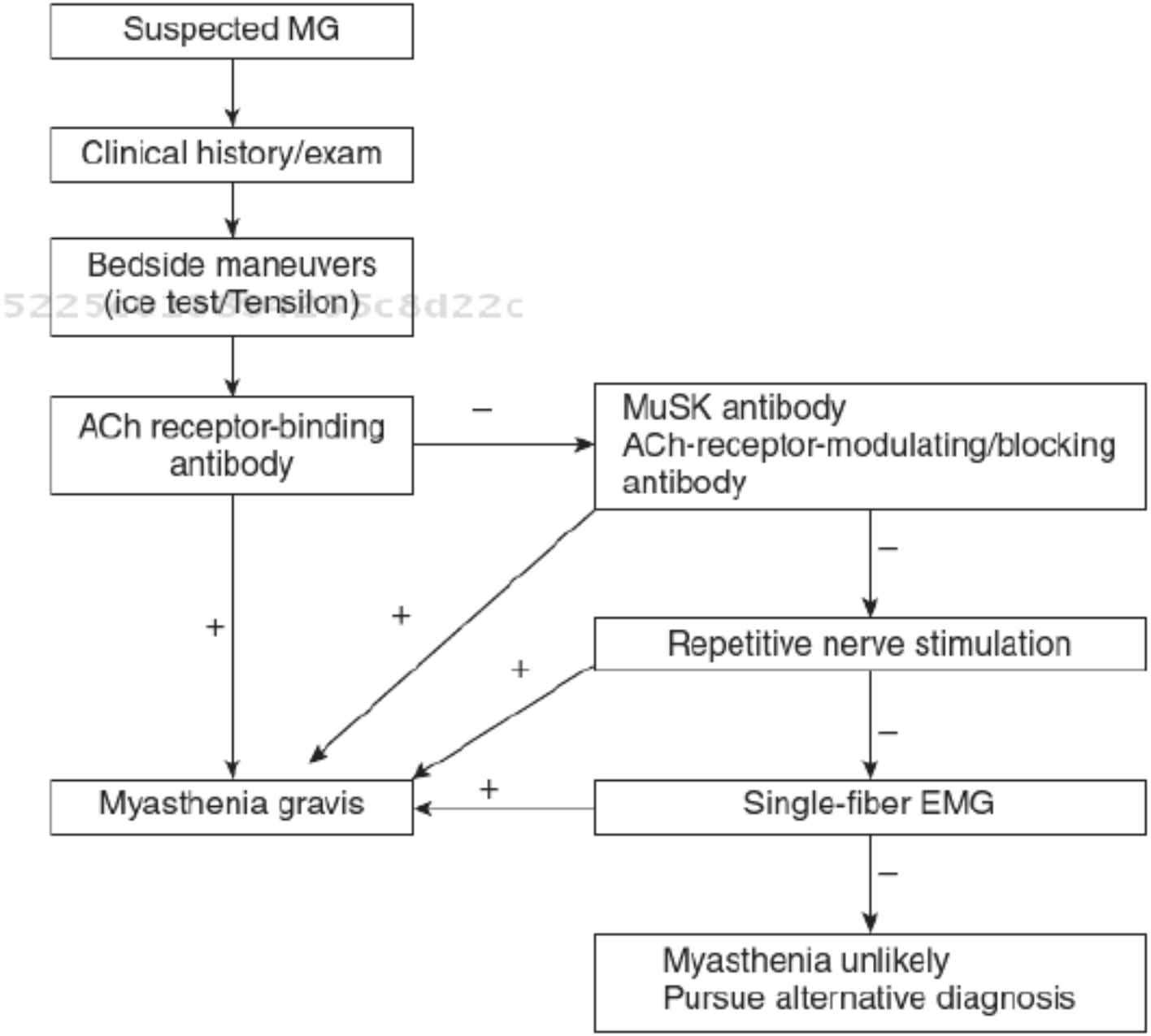


MCD=14.3 µsec



MCD #1 = 270 µsec
50% blocking

MCD #2 = 187 µsec


Suspected MG
Clinical history/exam
Bedside maneuvers
(ice test/Tensilon)
ACh receptor-binding
antibody
–
MuSK antibody
ACh-receptor-modulating/blocking
antibody
+
+
+
–
–
–
Repetitive nerve stimulation
Myasthenia gravis
+
Single-fiber EMG
Myasthenia unlikely
Pursue alternative diagnosis

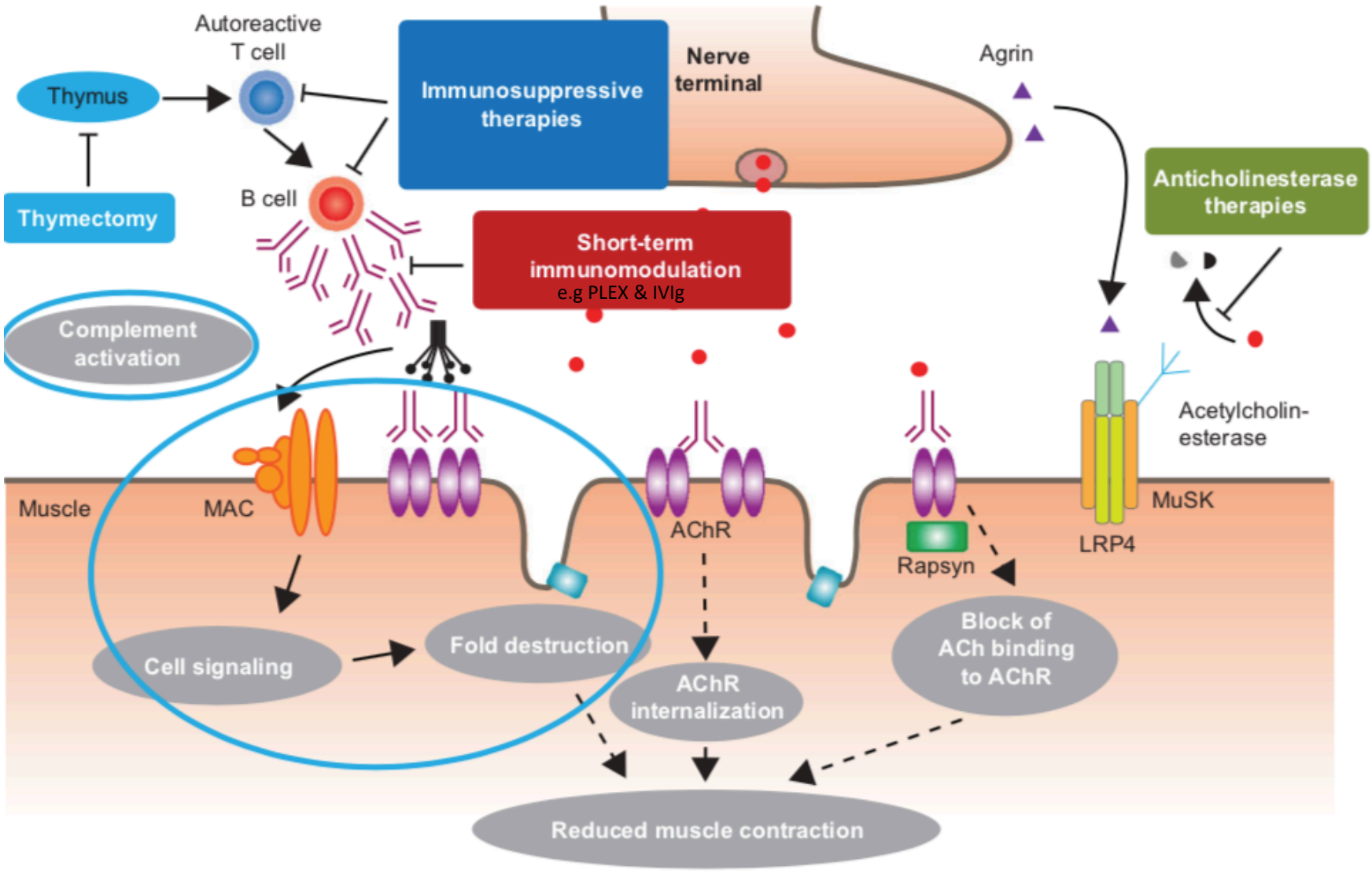
Differential diagnosis for MG

- Muscle disease
  - Thyroid ophthalmopathy
  - Ocular pharyngeal muscular dystrophy (OPMD)
  - Myotonic dystrophy
  - Progressive external ophthalmoplegia
- NMJ disorder
  - LEMS
  - Botulism
  - Congenital MG
  - Penicillamine-induced myasthenia
  - Tick paralysis
- Peripheral nerve
  - Oculomotor cranial nerve pathology
  - GBS, and CIDP
  - Cavernous sinus pathology
- Motor neuron disease
  - ALS, PMA
- Brainstem pathology
  - Stroke
  - MS
  - Tumors
  - Infections
- Other
  - Isolated ptosis (? Weak tissues)
  - Isolated dysconjugate gaze (decompensated strabismus)

TREATMENT OF MG

- **Cholinesterase Inhibitors**
  - Pyridostigmine (Mestinon)
- **Immunosuppressive Therapies (IST)**
  - **Prednisone**
  - Azathioprine (Imuran), Mycophenolate (cellcept)
  - Methotrexate, Tacrolims, Cyclosporine, Cyclophosphamide
- **Refractory MG**
  - Eculizumab, rituximab, maintenance IVIG or PLEX, steroids +/- other IST
- **MG crisis**
  - Intravenous Immune Globulin (IVIG)
  - Plasmapheresis
- **Surgery**
  - Thymectomy

Mechanisms of action of MG therapies



TREATMENT OF MYASTHENIA GRAVIS

TYPICAL TIME TO CLINICAL EFFECT AFTER INITIATING THERAPY

THERAPY	TIME
Edrophonium (not used as therapy)	1-2 minutes
Pyridostigmine	10-15 minutes
Plasmapheresis	1-14 days
IVIG	1-4 weeks
Prednisone	2-8 weeks
Mycophenolate	2-6 months
Cyclosporine	2-6 months
Azathioprine	3-18 months
Thymectomy	Several months to several years

Box 1 Factors exacerbating weakness in myasthenia gravis and potentially triggering myasthenic crisis

- Infections
- Stress—trauma, postoperative
- Withdrawal of cholinesterase inhibitors (when symptoms not fully controlled)
- Rapid introduction or increase of steroids
- Electrolyte imbalance—hypokalaemia, hypophosphataemia
- Anaemia
- Medications: most are rarely implicated, except those highlighted
  - Antibiotics
    - Aminoglycosides: **gentamicin**, amikacin, **telithromycin**, etc
    - Quinolones: ciprofloxacin, norfloxacin, etc
    - Tetracyclines: doxycycline, minocycline, etc
    - Antimalarials: **chloroquine**
  - Antirheumatic drugs: **penicillamine**
  - Anaesthetic agents: **succinylcholine**
  - Antiarrhythmic drugs: quinidine, procainamide
  - Antihypertensives: β blockers and calcium channel blockers
  - Neuropsychiatric drugs: lithium, chlorpromazine, phenytoin
  - Chemotherapy: cisplatin
  - **Botulinum toxin**

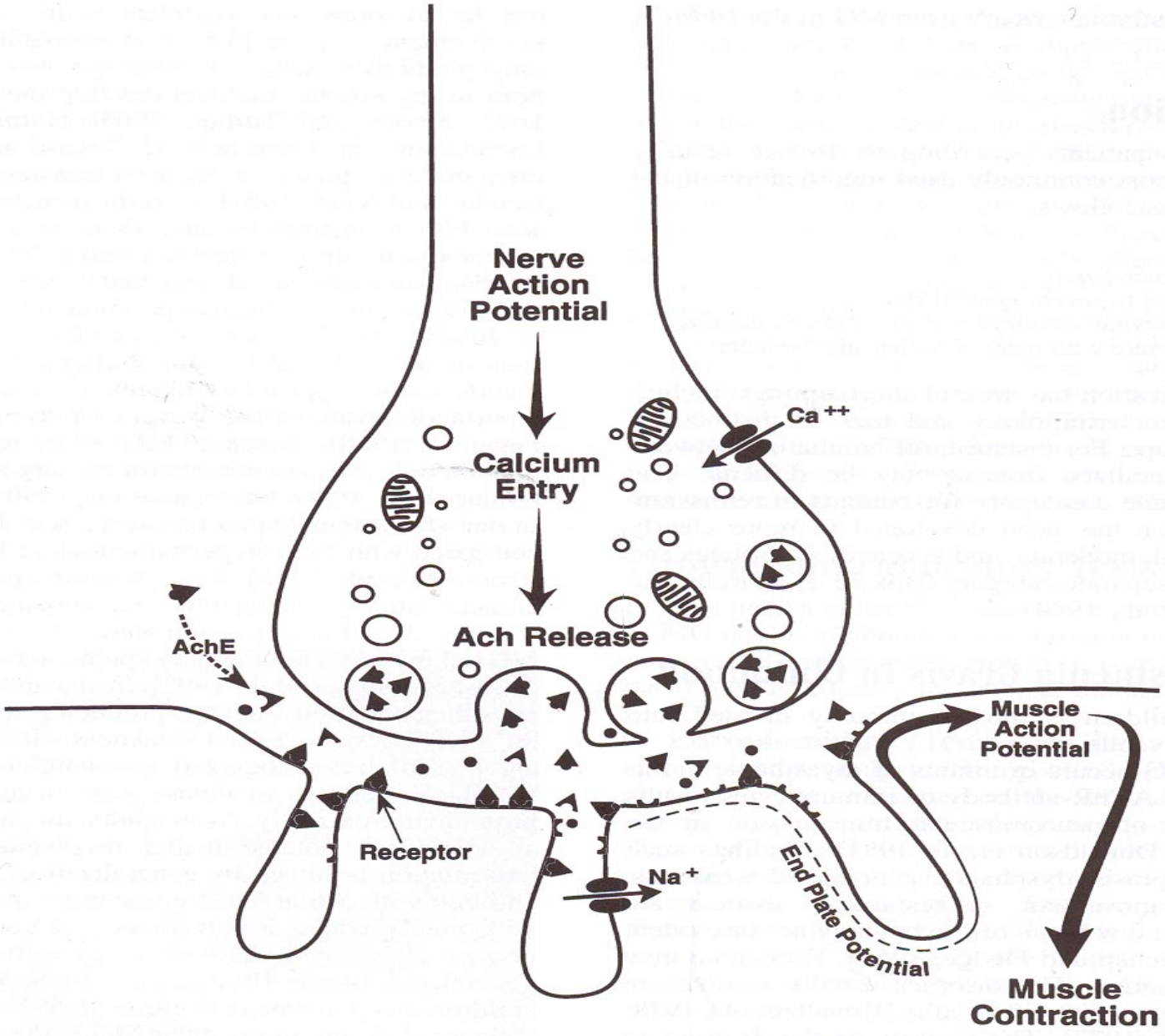
Neurology in practice, 2009;9:364–371

MG conclusions

- MG causes fatigable muscle weakness and often presents with ptosis and ophthalmoplegia.
- Early onset (<40 years) MG more commonly affects women, late onset is more common in men.
- AChR antibodies are found in 80–85% of generalised and 50% of ocular MG patients, MuSK antibodies in 5–8% of generalised MG.
- Decremental response to RNS and prolonged jitter or blocking on SFEMG are the neurophysiological hallmarks of MG.
- Monitoring of FVC is vital in patients with severe bulbar weakness.
- Myasthenic weakness is often exacerbated by infections and can lead to myasthenic crisis.
- Pyridostigmine, steroids and immunosuppressants are the mainstay of treatment.
- All patients with MG should be screened for thymoma.
- Thymectomy is often advised in mild to moderate AChR antibody positive generalised MG with onset less than 65 years of age.

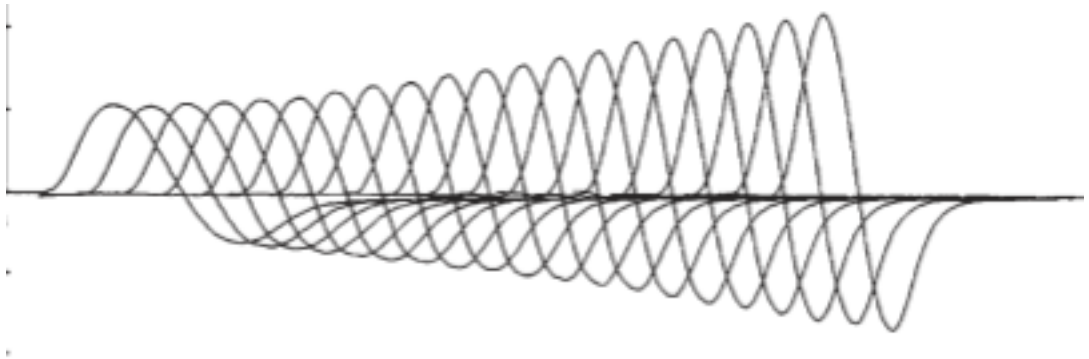
LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)

- Paraneoplastic (SCLC) and autoimmune.
- Voltage-Gated Ca++ Channel (VGCC) Ab's present in 90% of cases.
- Clinical features
  - Weakness/Fatigue in Limb-Girdle Distribution
  - Mild Ptosis, Diplopia, Dysphagia, Dysarthria may occur
  - Autonomic involvement: dry mouth, postural lightheadedness, sphincter disturbance or impotence.
  - Occas Paresthesias, Myalgias


Nerve
Action
Potential
Ca ++
Calcium
Entry
Ach Release
AchE
Muscle
Action
Potential
Receptor
Na +
End Plate Potential
Muscle
Contraction

- On Exam:
  - Proximal arm/leg weakness
  - Improvement after few secs of voluntary Contraction
  - Poorly reactive pupils
  - Hypo or areflexia
  - May have mild distal sensory loss in feet

- Incremental Response at High Rates RNS (20-50 Hz)



- 1st Rx Underlying Malignancy
- 2nd
  - 3,4 DAP (amifampridine)
  - Guanidine hydrochloride
  - Similar to MG treatment


Botulism

- Botulism is caused by a toxin produced by the anaerobic bacterium *Clostridium botulinum*
- Eight types of botulinum toxins (A, B, C_a, C_b, D, E, F, and G)
  - Types A and B are the cause of most cases of botulism in the United States.
  - Transmission of type E is in seafood.

- All forms of the toxin *block ACh release from the presynaptic motor nerve terminal* and the *parasympathetic* and *sympathetic* nerve ganglia.

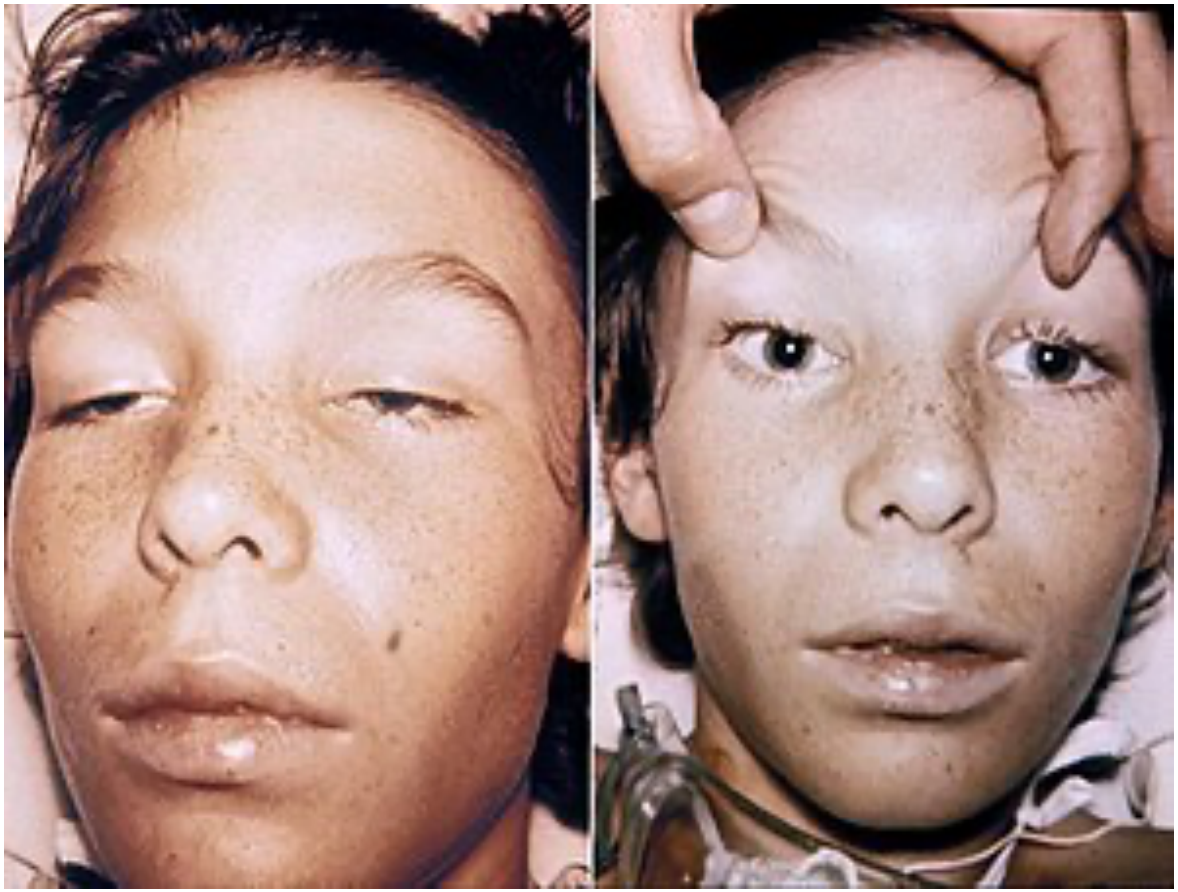
- The intracellular target is the SNARE proteins of the presynaptic membrane.

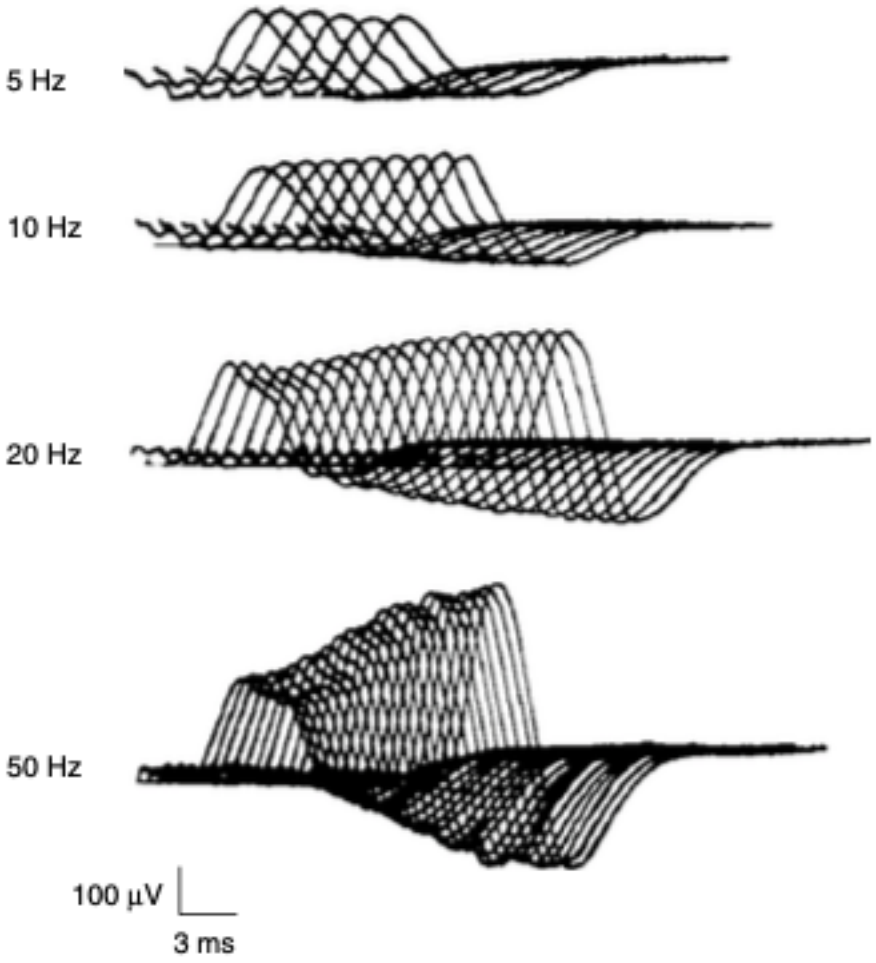
- Neuromuscular symptoms usually begin 12 to 36 hours after ingestion of contaminated food and are preceded by nausea and vomiting.

Clinical Classification of Botulism
Classic form
Infantile form
Wound botulism
Traumatic or surgical
Drug abuse
Intranasal
Intravenous
Hidden form

Clinical presentation

- Acute presentation
- Cranio-ocular symptoms begin at same time or soon after initial GI symptoms (nausea & vomiting) with ingested toxin.
- Descending weakness
- Pupils dilated and fixed in 50-75% of the patients.
- Blurred vision
- Ptosis, EOM weakness nearly universal, symmetrical (may improve a bit with Tensilon)
- Bulbar weakness: dysarthria, dysphagia, facial
- Limb weakness proximal > distal, symmetrical
- Respiratory weakness




5 Hz
10 Hz
20 Hz
50 Hz
100 μV
3 ms

Treatment

- Treatment consists of administration of bivalent (type A and B) or trivalent (A, B, and E) antitoxin.
- Supportive
- Infantile botulism: IV human botulism immune globulin (BIG-IV)