NEUROMUSCULAR DISORDERS
Myasthenia gravis and friends

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Q -All you need

- How do you make the diagnosis of myaesthenia
- Discuss all Treatment options in MG pt
- Differential diagnosis of MG
- Causes of relapse in MG
- LIST Drugs that worsen myaesthenia
- WRITE Short notes on Eaton lambert or Botulism

Myasthenia Gravis

- Myasthenia gravis (MG) - acquired autoimmune disease of the neuromuscular junction.

- Target of the autoimmune attack is the nicotinic acetylcholine receptor (AChR) located in the postsynaptic muscle endplate membrane

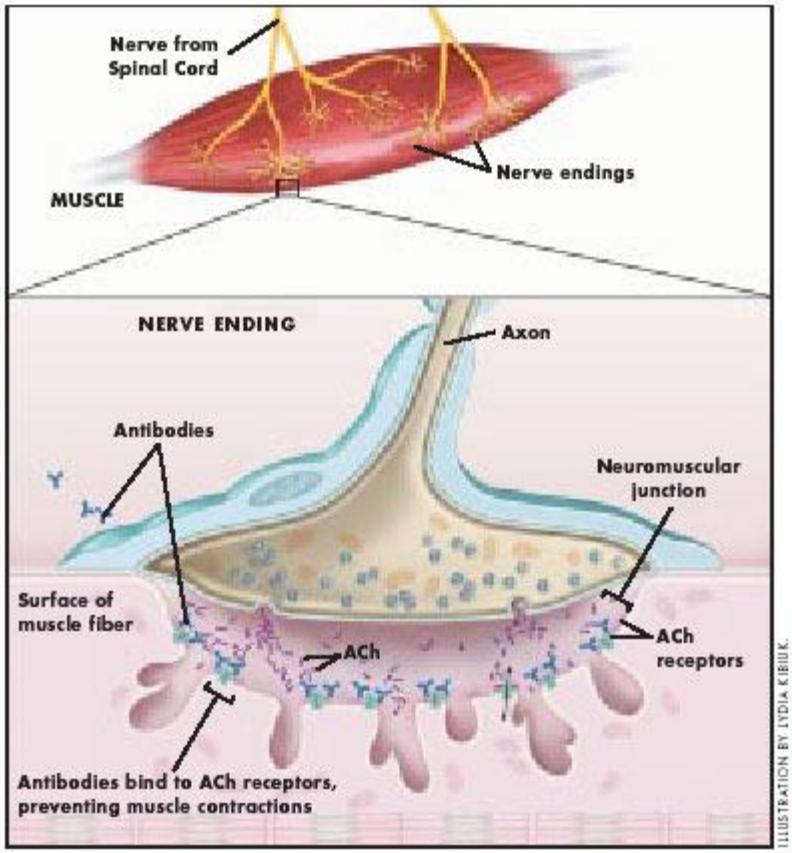
Differential Diagnosis of MG

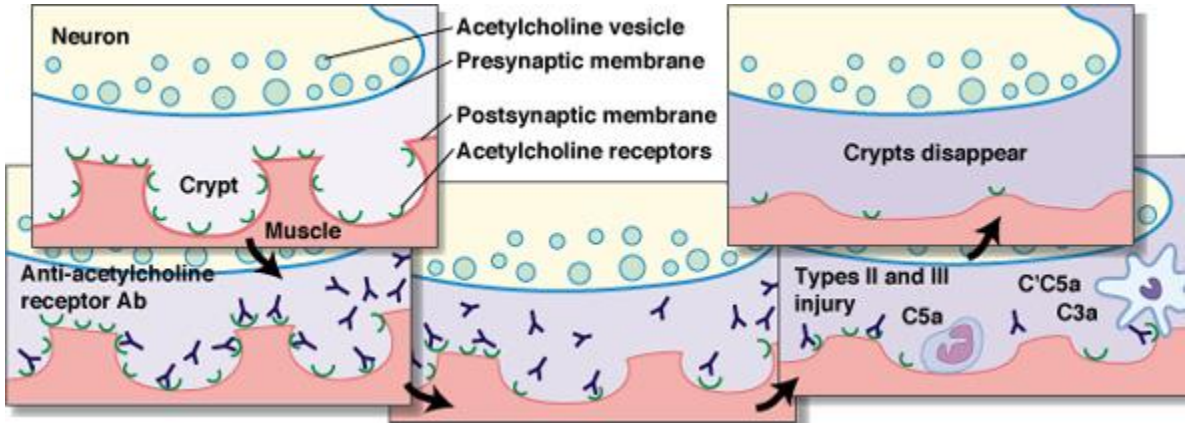
- Lambert Eaton Syndrome
- Botulism
- Oculopharyngeal muscular dystrophy
- Mitochondrial myopathy-CPEO
- Miller Fischer syndrome
- Psychiatric
- Brainstem lesion

Other Disorders of the Neuromuscular Junction

- Lambert-Eaton (myasthenic) syndrome
- Congenital (genetic) myasthenic syndromes
- Drugs impairing neuromuscular transmission
- Organophosphates
- Botulism
- Snake toxins

Pathophysiology





pathophysiology

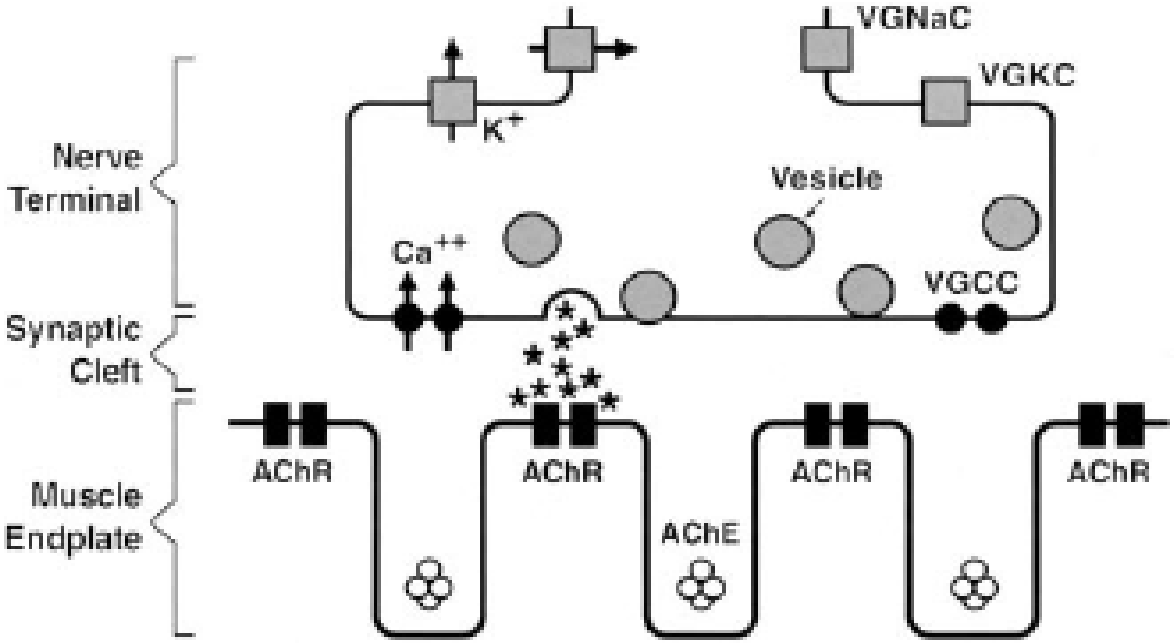


Figure 1. Diagram of the presynaptic and postsynaptic components of the neuromuscular junction. VGNaC = voltage-gated sodium channel; VGKC = voltage-gated potassium channel; VGCC = voltage-gated calcium channel; AChR = acetylcholine receptor; AChE = acetylcholine esterase.

Epidemiology

- Increasing prevalence
- Women in twenties /men in sixties

Clinical presentation

- Muscle weakness
- Ptosis or diplopia (both within 2yrs 100%)
- Difficulty chewing ,swallowing,talking(15%)
- Limb weakness (10%)

- Fluctuating weakness – time of day reading, tv, driving, light sensitivity ,food, singing

Course

- Restricted to ocular in 10%
- Progressive weakness over 2yrs
- Maximum weakness in 1yr

- Rule of 1/3
- Die
- Progressive disease
- Spontaneous improvement

Worsening symptoms

- Stress-emotional upset
- Systemic illness
- Hypothyroidism/hyperthyroidism
- Pregnancy/menstrual cycle
- Drugs - not taking,taking Too much,taking other drugs

Drugs which worsen MG

- Magnesium salts—often in vitamin supplements
- Quinidine/procainamide/phenytoin/verapamil/
- Thyroid
- Aminoglycosides/erthyromycin/tetracyclines
- Cimetidine
- Statins
- Beta blockers
- Lithium/chlorpromazine

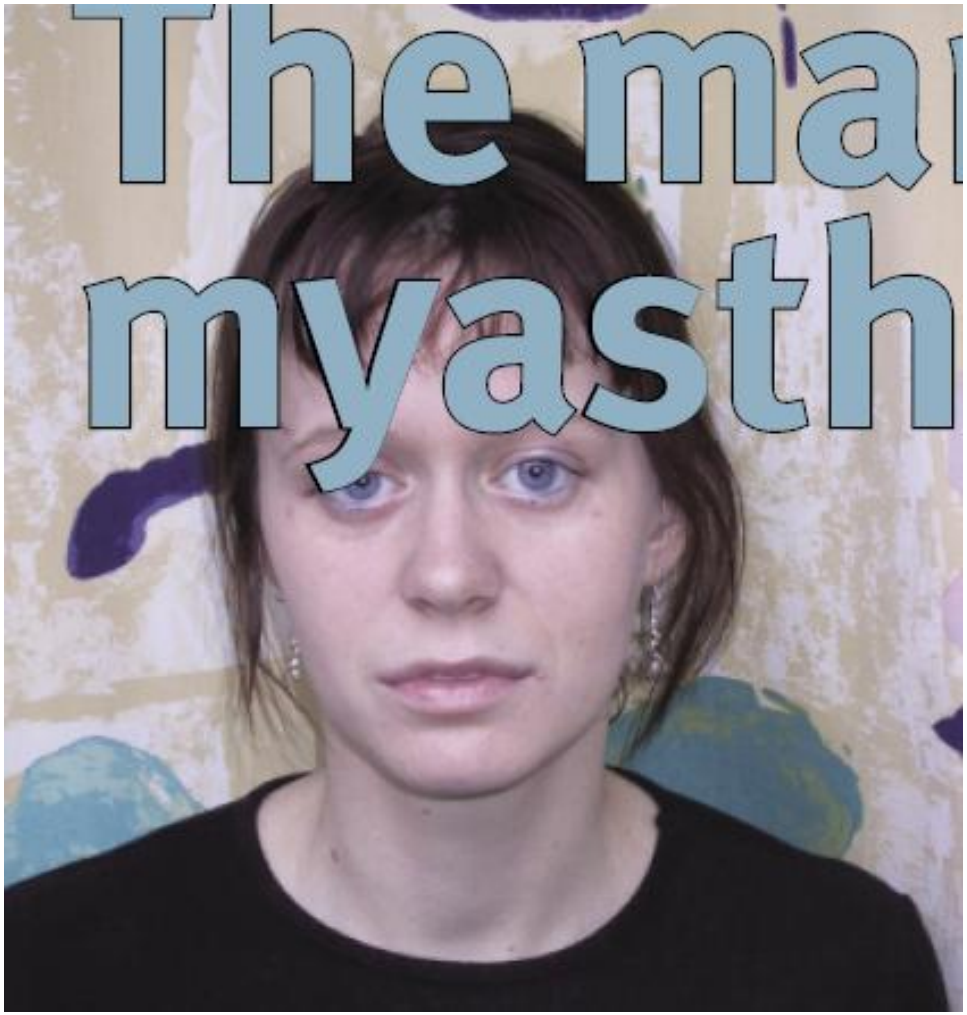
Examination

- Assess strength fluctuations during maximum effort and after rest
- Eyes and bulbar and LIMB muscles

- Fatigability diagnostic
- No sensory abnormalities

Ocular muscles

- Asymmetrical weakness of several muscles in both eyes .Not characteristic of single nerve
- Pupil sparing
- Medial rectus
- Ptosis asymmetrical and varies
- Frontalis overactivity
- Weakness of eye closure



Oropharyngeal weakness

- Voice changes –”100 eeeee”
- Difficulty swallowing/chewing
- Myaesthenic snarl
- Jaw weakness
- Eye closure weakness even with treatment

Limb muscles

- Some more than others
- Neck flexors
- Deltoids,triceps,extensors of wrist and fingers,ankle dorsiflexors

MG Activities of Daily Living Scale

Grade	0	1	2	3	Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	

Total score _____

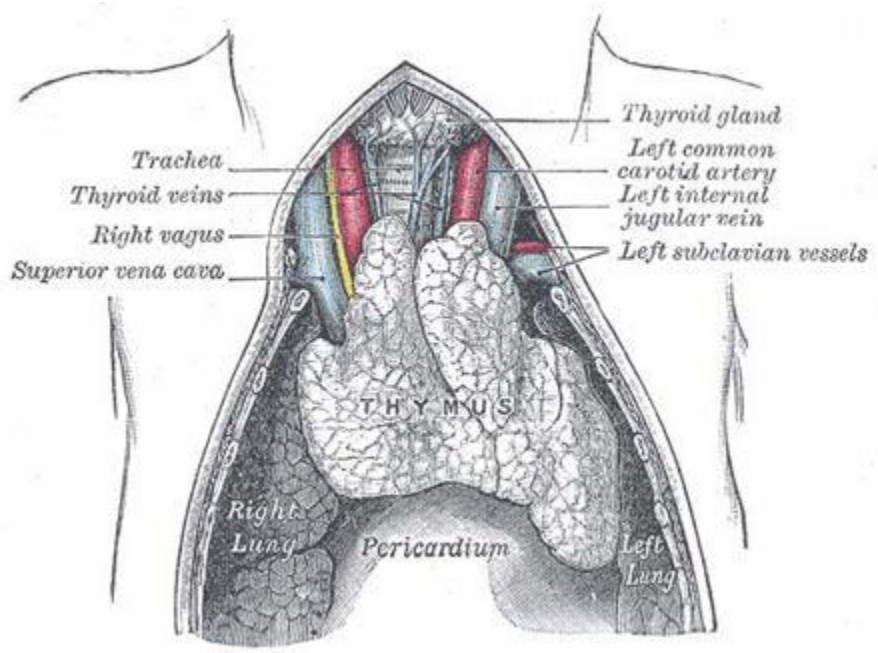
Grade	0	1	2	3	Score
Double vision (lateral gaze) sec.	>60	11-60	1-10	Spontaneous	
Ptosis (upward gaze) sec.	>60	11-60	1-10	Spontaneous	
Facial Muscles	Normal lid closure	Complete, weak, some resistance	Complete, without resistance	Incomplete	
Swallowing	Normal	Occasional choking	Consistent choking	Cannot swallow	
Head, lifted (45° supine) sec.	>120	>30-120	>0-30	0	
Right arm outstretched (90° standing) sec.	>240	>90-240	>10-90	0-10	
Left arm outstretched (90° standing) sec.	>240	>90-240	>10-90	0-10	
Speech following counting aloud from 1-50 (onset of dysarthria)	None at #50	Dysarthria at #30-49	Dysarthria at #10-29	Dysarthria at #9	
Right leg outstretched (45° supine) sec.	>100	31-100	1-30	0	
Left leg outstretched (45° supine) sec.	>100	31-100	1-30	0	
Vital capacity (l): male female	>3.5 >2.5	>2.5-3.5 >1.8-2.5	1.5-2.5 1.2-1.8	<1.5 <1.2	
Rt hand grip: male (Kg force) female	>45 >31	>15-45 >10-30	5-15 5-10	<5 <5	
Left hand grip: male (Kg force) female	>35 >25	>15-35 >10-25	5-15 5-10	<5 <5	

Total score _____

Thymus in myaesthenia

- Role in induction of tolerance to self antigens
- Myoid cells express AChR antigen,antigen presenting cells,immunocompetent T cells
- Thymic tumour 10%-20%
- Thymic hyperplasia - 70%

Thymus



Diagnostic procedures

- 1.FATIGABILITY

- 2.Tensilon test
- IV edrophonium chloride
- Need maximum effort before and after drug to assess effect
- Blinded/double blinded

- Oral pyridostigmine over several days

Edrophonium test

- Positive test requires a measurable change in some sign such as ptosis,gaze paresis,grip strength or respiratory function after injection
- Compare result to placebo
- False positive results common

- Oral pyridostigmine after meal and assess 1hr later

False-positive Edrophonium Tests

- Lambert-Eaton syndrome (37% positive)
- Botulism (27% positive)
- Congenital end-plate acetylcholine receptor deficiency
- Guillain-Barré
- Amyotrophic lateral sclerosis
- Brain stem glioma

Diagnostic procedures

- 3.Antibodies against acetylcholine receptors
- Acquired generalised 80%
- Ocular myaesthenia- 55%
- Repeat as may be low at symptom onset
- False positive

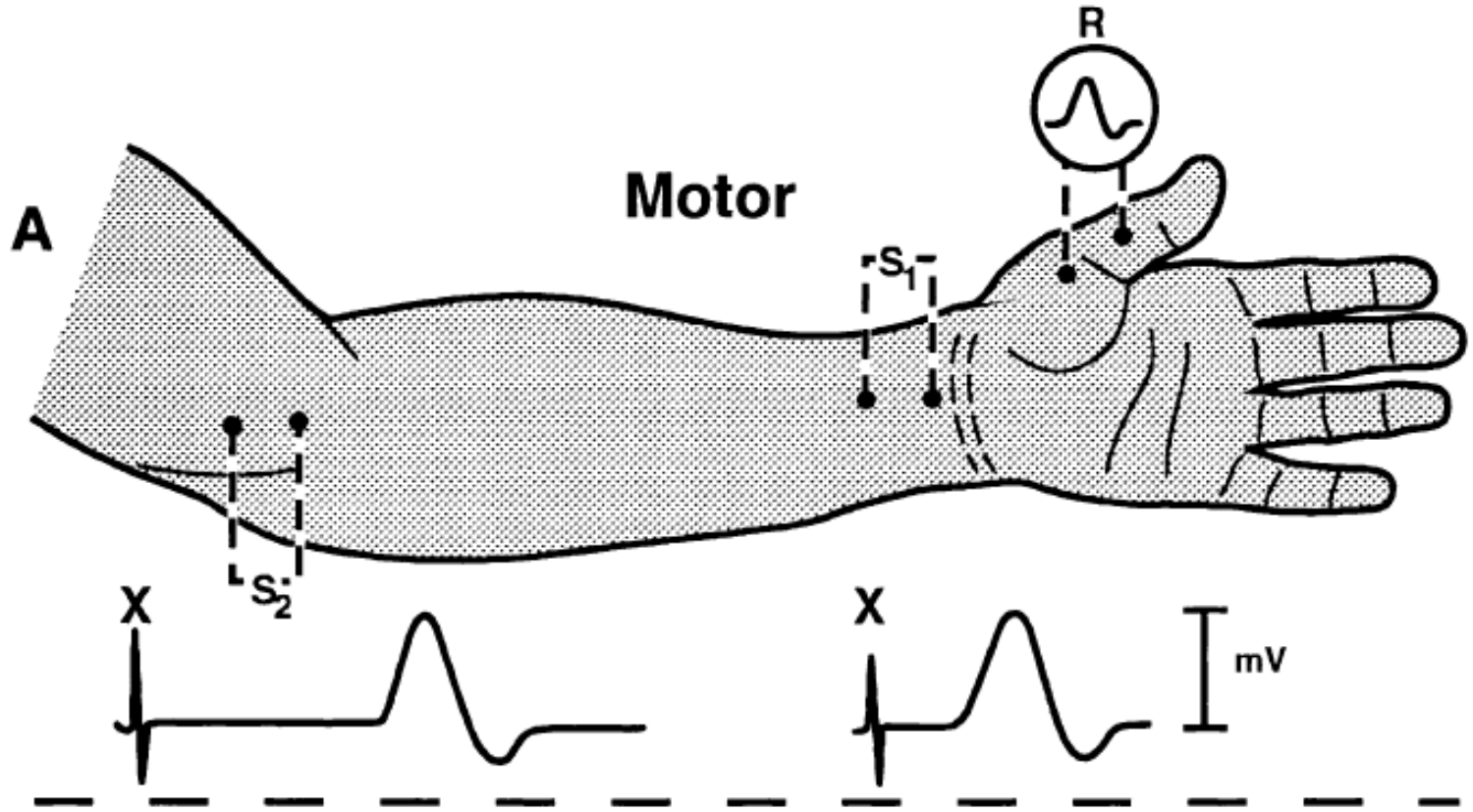
Other antigens in MG

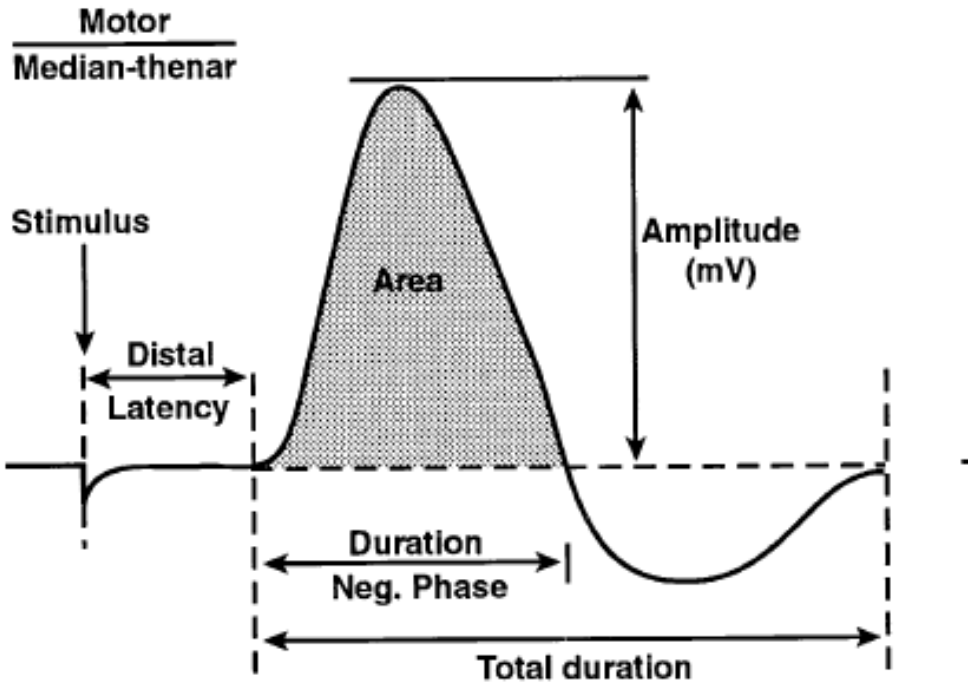
- Other neuromuscular junction antigens, distinct from AChR
- The characteristics of this disorder, seronegative MG (more accurately AChR antibody–negative MG), identical to AChR antibodies +
- In patients in whom only the extraocular muscles are involved, so called ocular myasthenia, this proportion is approximately 50%.
- Serum antibodies directed against a distinct endplate membrane intrinsic protein, muscle-specific receptor tyrosine kinase (MuSK) 50% of generalised seronegative disease

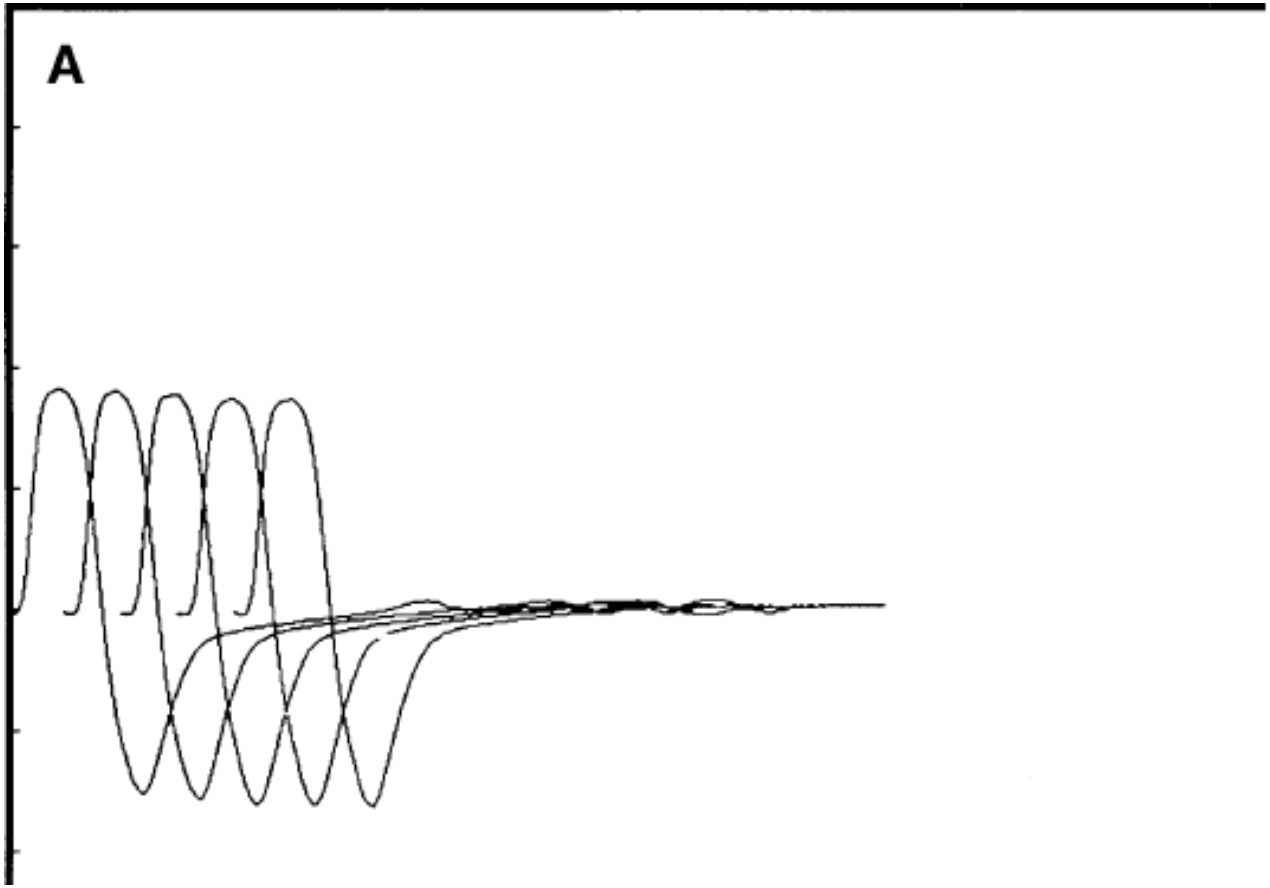
Diagnostic procedures

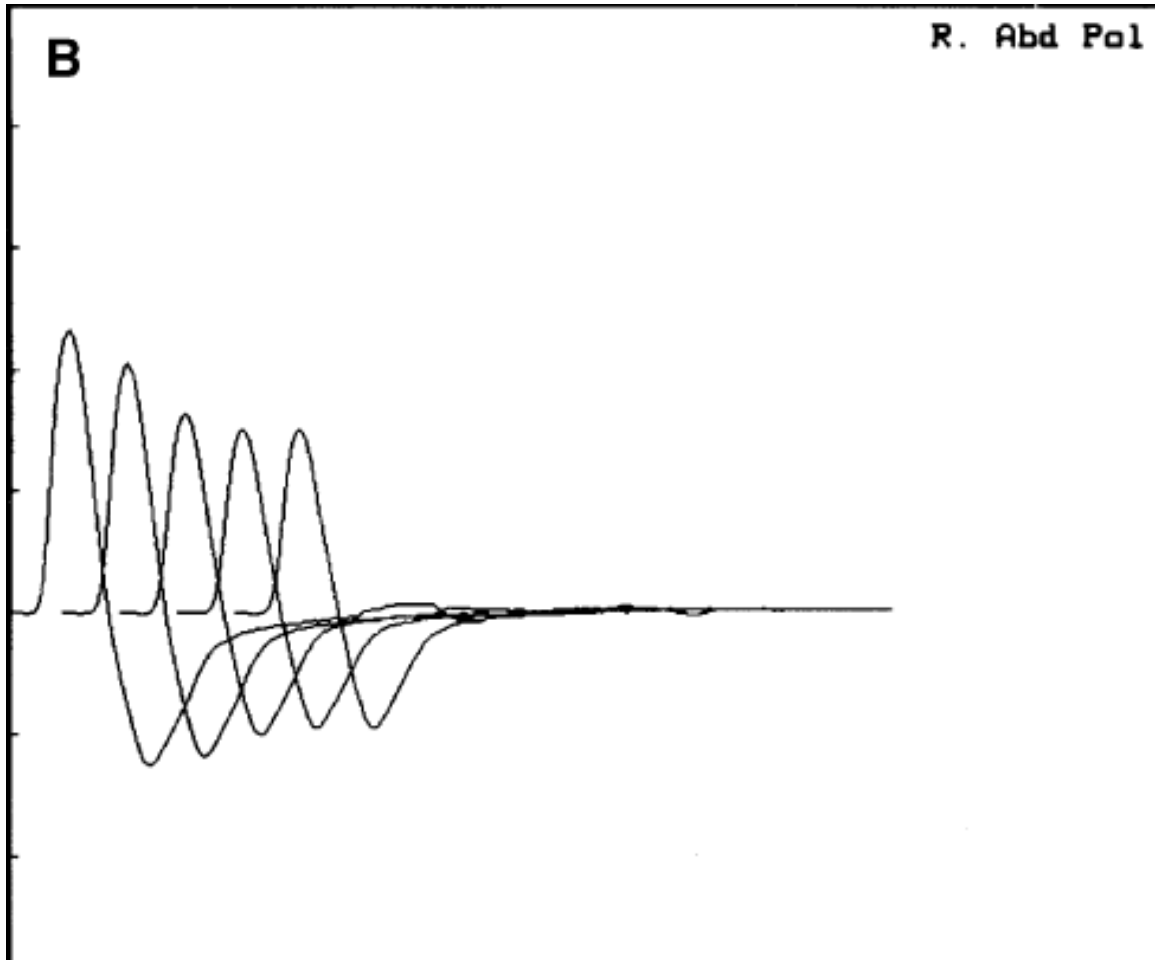
4.Repetitive nerve stimulation

- Repetitive nerve stimulation of a nerve supplying a symptomatic muscle
- Stop acetylcholinesterase inh
- Reproducible 10% decrement from first to 4^{th} or 5^{th}
- Decremental response seen more often in facial,biceps,deltoid and trapezius









$$\%\ \text{Decrement} = \frac{\text{Amplitude(1st response)} - \text{Amplitude(3rd/4th response)}}{\text{Amplitude(1st response)}} \times 100$$

Comparison of diagnostic techniques

- Tensilon test - ptosis,opthalmoparesis
- Negative acetylcholine receptor antibodies does not exclude diagnosis
- RNS normal in ocular disease and not specific for myaesthenia

Other investigations

- Thyroid function
- CT chest
- Fbc ,electrolytes,glucose

Lessons from other autoimmune diseases.

- Follow a relapsing and remitting course.
- Goal of treatment for patients with these diseases is to induce and support the quiescent stage and to prevent the exacerbation stage.
- Initiating factors in the relatively recent past have been infection and surgery.
- Immunosuppressives the majority of patients are essentially symptom free while given high doses.
- Symptoms return,when doses are reduced below a certain level.

***Principles* of Management**

- Symptomatic treatment;
- Immunomodulatory therapy;
- Immunosuppressant therapy.

TREATMENT

Treatment

- Individualise treatment goals
- Severity
- Age and gender
- Degree of functional impairment

- number of drugs or conditions may have a direct pharmacologic effect on the neuromuscular junction.

Symptomatic (nonimmune) treatments of autoimmune MG.

- Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors

- Increased concentration of ACh (caused by blocking the acetylcholinesterase) inducing the remaining AChRs to be maximally activated.

- Muscarinic side effects are gut hypermotility (abdominal cramps, diarrhea), excessive perspiration, excessive respiratory and gastrointestinal secretions, and bradycardia.
- Nicotinic effects can be muscle fasciculations and increased blockade of neuromuscular transmission (so-called cholinergic crisis).

- The muscarinic side effects can be reduced by addition of muscarinic antagonists, such as propantheline.

ANTICHOLINESTERASE (PYRIDOSTIGMINE) THERAPY

- Pyridostigmine tablets are 60 mg.
- They are scored and so can be divided into quarters (15 mg).
- Start with 15 mg qds.
- Increase (if necessary) after 2 days to 30 mg qds.
- Increase (if necessary) after 2 days to 60 mg qds.
- Maximum dose 360 mg daily- usually 90 mg qds
- but some patients may benefit from 60 mg × 6
- Add propantheline if gastrointestinal adverse effects

Immune-directed treatment

- Either modify AChR antibody production or modify the damage to the neuromuscular junction induced by the binding of these antibodies.

- 1. Rapid but Short-lived effect on the disease
- 2. Long-term effect.

- The strategy of treatment is to first induce a remission and then to maintain the remission, with the least possible cost-to-benefit ratio. (In this context, remission can be defined as complete or nearly complete absence of symptoms.)

Long-term immune-directed treatments

Thymectomy

- Effect is usually not apparent until after 1 year, and the full effect is not felt for 5 years.
- Neoplastic thymoma
- Thymic hyperplasia

- Increase remission and reduces long term immunosuppressive drugs.
- Most effective - first 2 years of disease.

Steroids

- Corticosteroids are main immune treatment
- Effective in inducing remission in at least 50%, but perhaps in as many as 80%
- High-dose steroids worsening of the disease. 7 to 14 days after initiation ,lasted less than 1 week.
- Gradually increasing the dose of steroids over 1 to 2 months reduces risk of early worsening of disease.

Steroids

- Goal should be to reach a high dose of steroids as rapidly as possible.
- Maximum dose is maintained until complete remission is accomplished.
- Improvement noted by 6 weeks and remission by 3 months.
- Once remission occurs, then tapering phase
- There is a lag of up to 3 months between a dose reduction and the exacerbation it induces

Steroids

- Once the patient is in remission (which in practice means minimal residual symptoms and signs) the pyridostigmine should be withdrawn gradually over 2–4 weeks.
- If symptoms and signs return, the patient is not in remission.
- The prednisolone should then be reduced gradually, trying to determine the minimum dose required to keep the disease under control

Azathioprine

- It acts by inhibiting purine synthesis and hence cell proliferation.
- steroid-sparing agent.
- Its use with high-dose steroids may increase the risk of opportunistic infections.
- The therapeutic dose of azathioprine is 2 to 3 mg/kg. (The initial dose should be 1 mg/kg with gradual increase to the therapeutic dose.)

Short-term immune-directed treatments

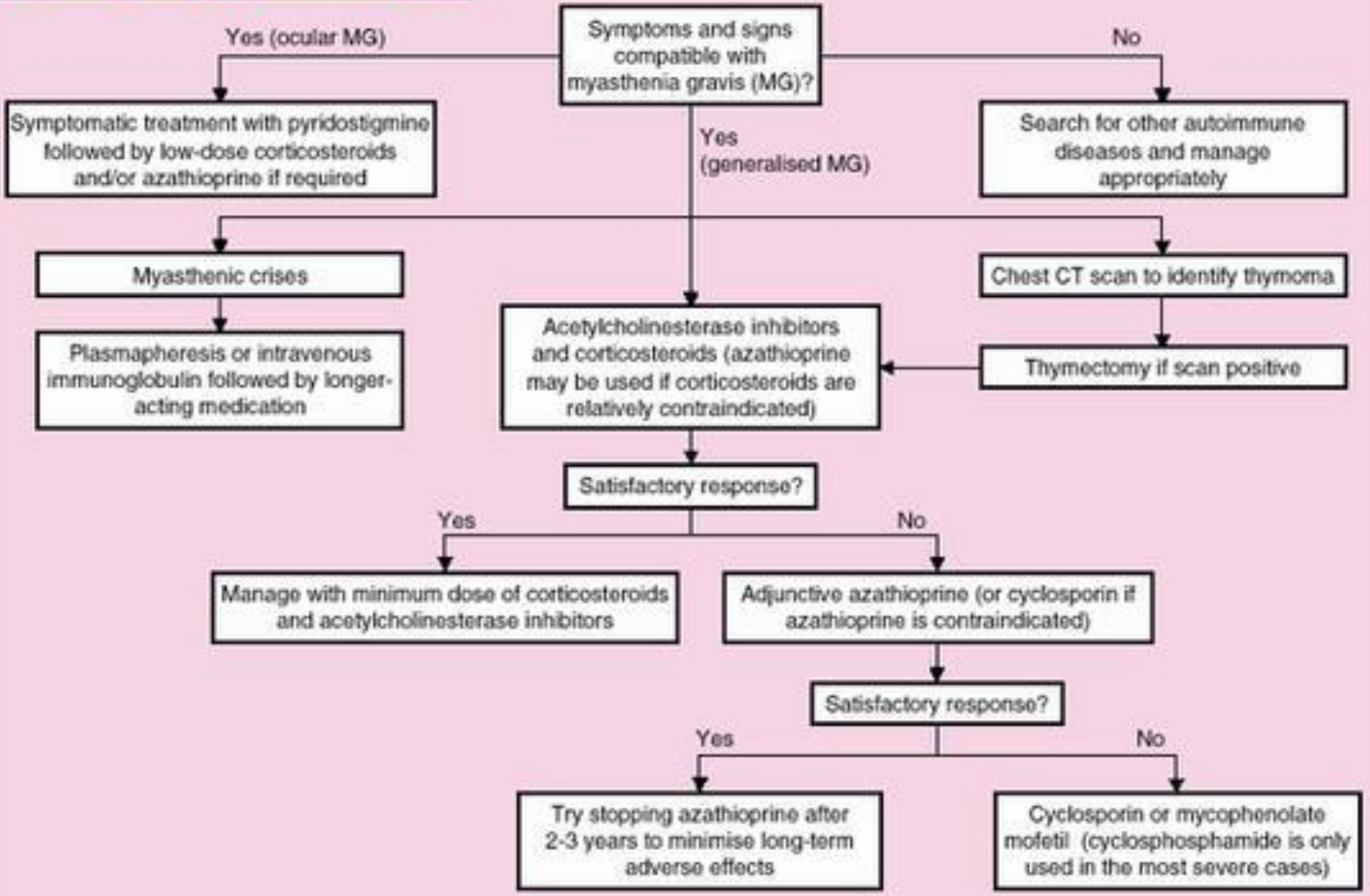
- **MYAESTHENIC CRISIS**
- Plasmapheresis and infusion of IV immunoglobulin (Ig)
- Immune-directed treatments - rapid onset of effect but short duration of action.
- Adverse effects

Deterioration in a myasthenia patient

- Spontaneous (which is not that uncommon and reflects the spontaneous fluctuation seen in many autoimmune disorders);
- Induced by ‘stress’ (e.g. infection, surgery,emotional issues, hormonal factors);
- Reduction or withdrawal of previously effective therapy ;
- precipitated by recent introduction of a drug that interferes with neuromuscular transmission.

Myaesthenic crisis

- Respiratory failure
- Definable precipitating event- infection,surgery,tapering of treatment
- Cholinergic crises – respiratory failure from overdose of ChE inhibitors
- ICU- support ventilation



Suggested strategy for management of patients with myasthenia gravis[1,2]

Therapy for Myasthenic Crisis and Respiratory Failure

Therapy	Agent	Usual adult dose	Time to onset of effect	Time to maximal effect	Adverse effects
Anticholinesterase	Pyridostigmine (Mestinon)	15-90 mg po q6h **OR** 1/30th of total daily oral dose given IV either in divided doses or as a continuous infusion	30 min	2 hours	Cholinergic crisis
	Neostigmine (Prostigmin)	7.5-45 mg q 2-6h			
Short-term immunosuppressive therapies	IV immune globulin	400 mg/kg for 5 days	3-5 days	1-3 weeks	Headache, fluid overload, renal failure (rare)
	Plasmapheresis	5 exchange treatments of 3-4 liters over 10-14 days	3-7 days	1-3 weeks	Line infection, hypotension thromboembolic disease
Immunosuppressive medications	Prednisone Methylprednisolone	15-20 mg/day, gradually increasing to 60-80 mg/day, eventually converting to every other day therapy	2-3 weeks	306 months	Immunosuppression, UGI bleeding, diabetes, osteopenia
	Cyclosporine	5 mg/kg/day in 2 divided doses (125-200 mg twice daily)	2-12 weeks	3-6 months	Nephrotoxicity, hypertension
	Azathioprine	2-3 mg/kg/day (100-250 mg/day)	3-12 months	1-2 years	Marrow suppression

Stress Reduction Kit

Directions:

1. Place kit on FIRM surface.
2. Follow directions in circle of kit.
3. Repeat step 2 as necessary, or until unconscious.
4. If unconscious, cease stress reduction activity.

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Lambert-Eaton myaesthenic syndrome

- Presynaptic abnormality of acetylcholine release
- Immune mediated process directed against voltage gated calcium channels
- Older than 40
- Underlying malignancy-80% sclc,years before or after symptoms of LEMS

Lambert-Eaton-Clinical

- Weakness of proximal muscles especially in legs
- Ache and tenderness
- Strength improves initially after exercise
- Tendon reflexes depressed or absent
- Mild oropharyngeal and ocular weakness
- Autonomic dysfunction- dry mouth,impotence,postural hypotension
- mild improvement with tensilon test

Lambert-Eaton

- Similar to MG worsening with drugs

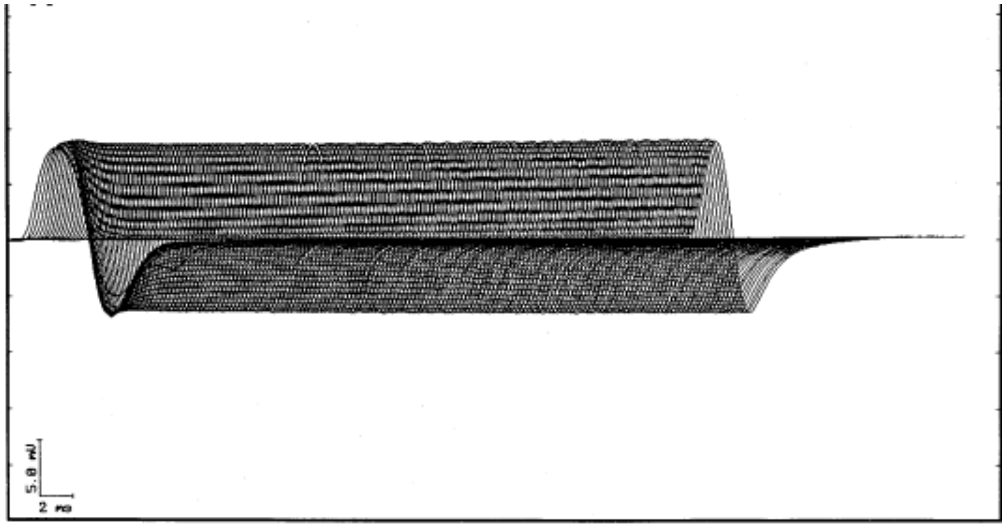
- Similarity to MG in nmj immune mediated disorder
- Distinct difference – resembles cachexia,polymyositis or paraneoplastic neuromuscular disease

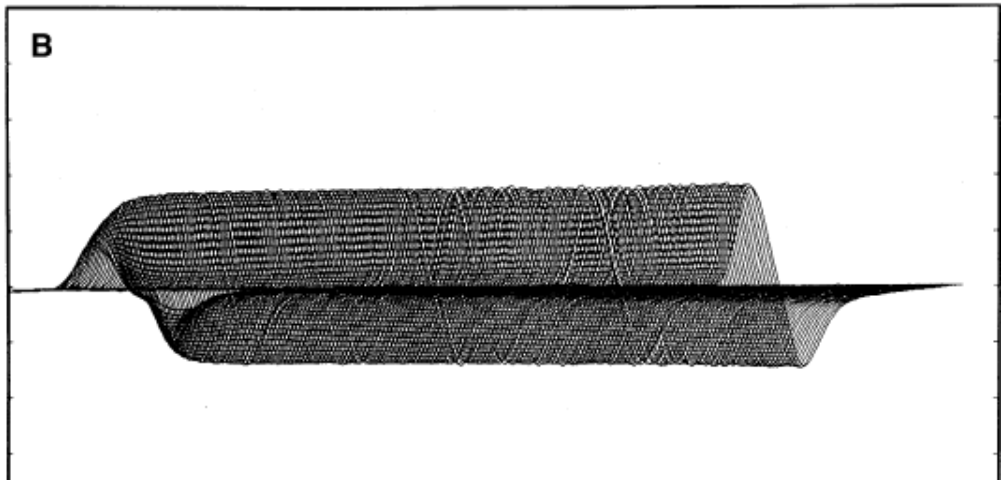
Diagnostic procedures

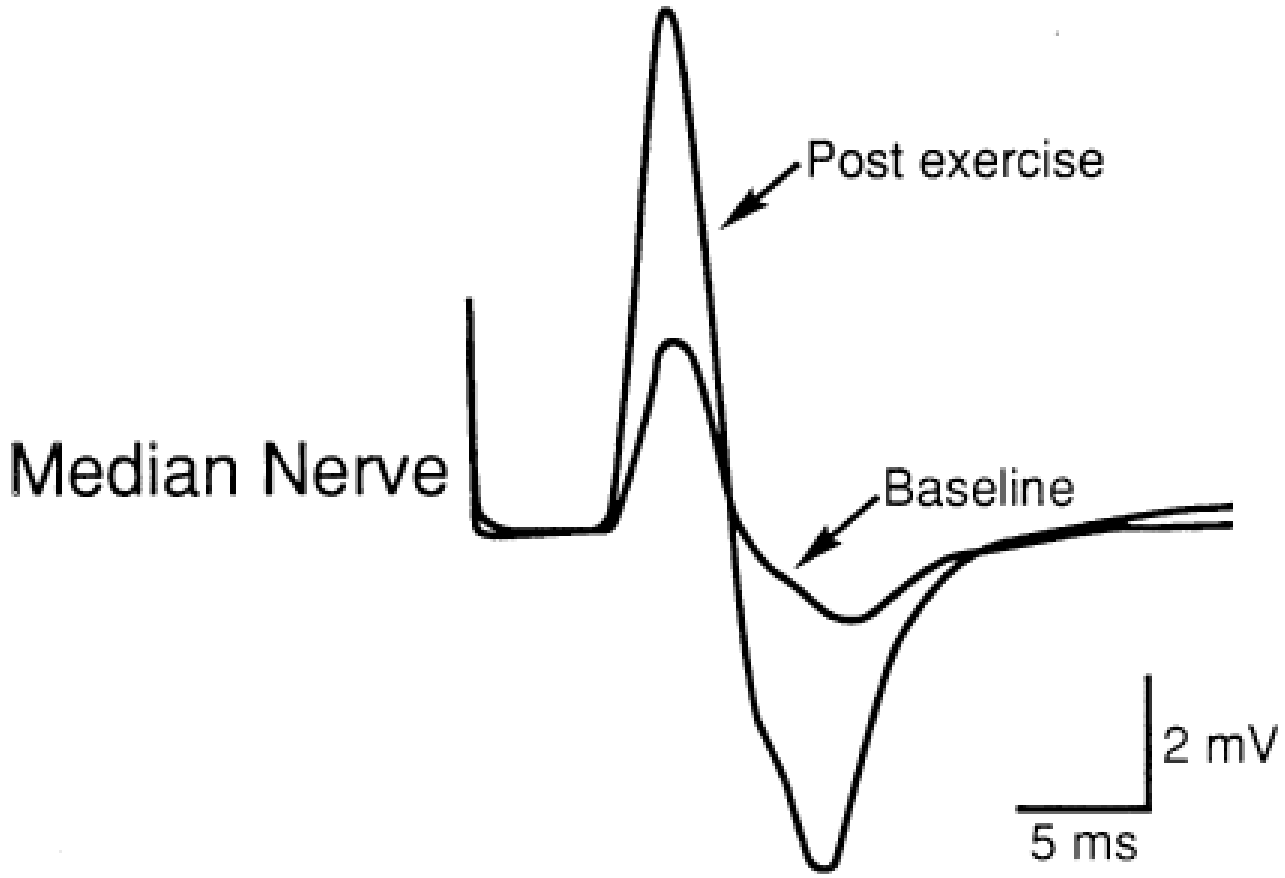
EMG

- decreased CMAP,
- size reduction in response to RNS(1-5hz),
- doubling of CMAP in RNS (20-50),
- transitory increase after brief maximum voluntary contraction

- ANTI BODY blood test





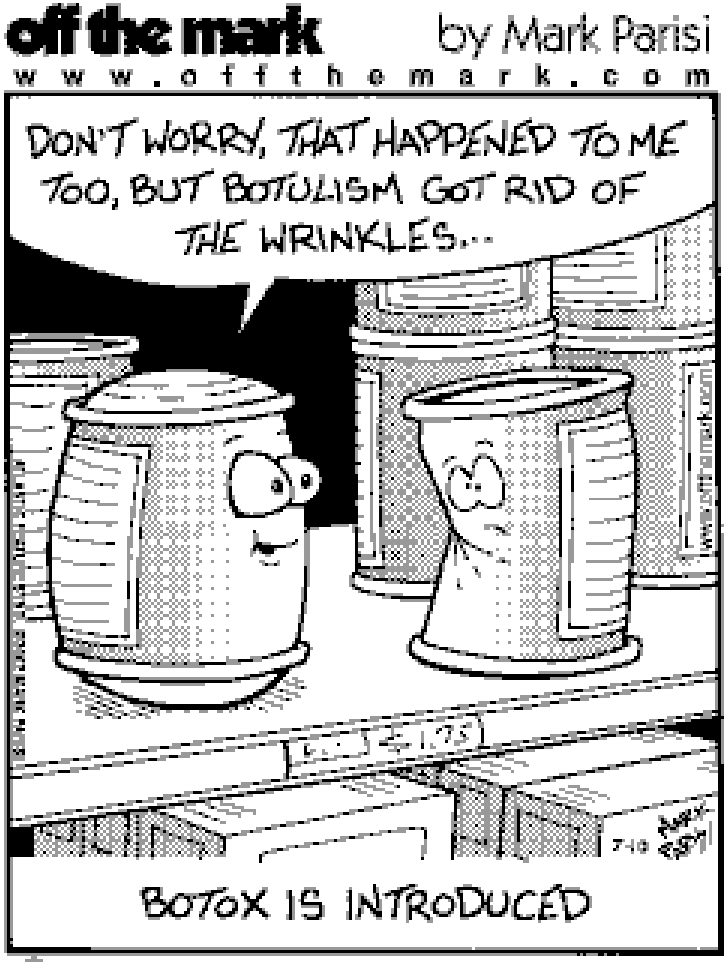


Treatment

- Search for underlying malignancy
- Avoid hot showers or baths
- ChE inhibitors
- Guanidine hydrochloride-increases release of acetylcholine
- Plasma exchange and immunoglobulin
- Immunotherapy-prednisone ,azathioprine,

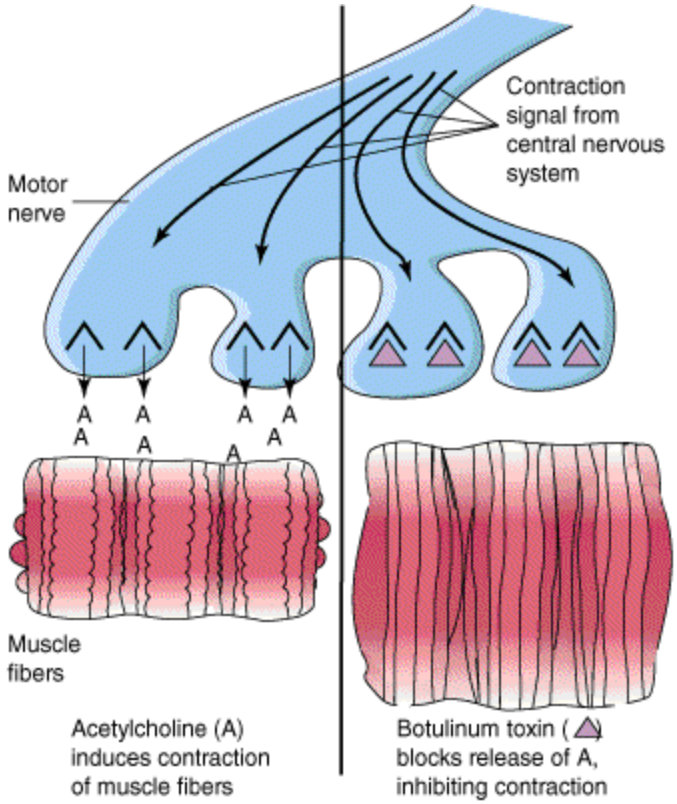
	Myasthenia gravis	LEMS
Ocular involvement	Prominent	Less prominent
Bulbar involvement	Common, prominent	Uncommon, subtle
Myotatic reflexes	Normal	Absent or depressed
Sensory symptoms	None	Paresthesia is common
Autonomic involvement	None	Dry mouth is common, but also impotence and gastroparesis
Tensilon test	Frequently positive	May be positive
Serum antibodies directed against	Postsynaptic acetylcholine receptors	Presynaptic voltage-gated calcium channels
Baseline CMAPs	Normal	Low in amplitude
Postexercise CMAPs	No change	Significant facilitation
Slow repetitive stimulation	Decrement	Decrement
Rapid repetitive stimulation	No change or decrement	Increment

BOTOX



Botulism

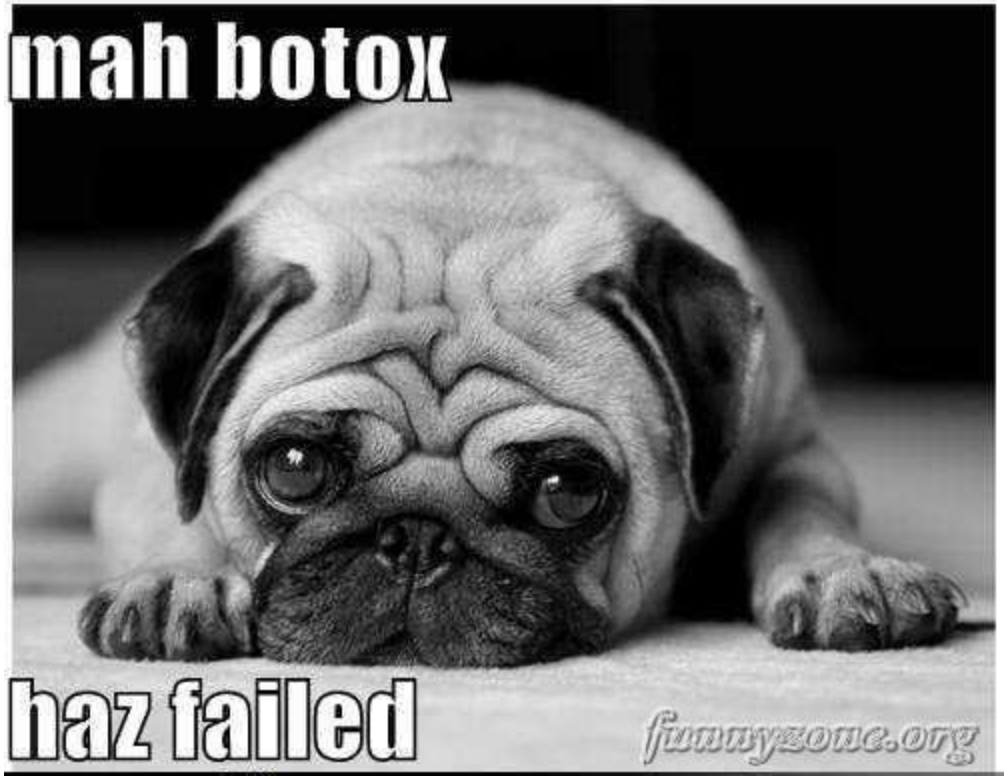
- Botulinum toxins produced by anaerobic bacterium Clostridium botulinum.
- Potent muscarinic and nicotinic cholinergic presynaptic toxins.
- Toxins bind to various plasma membrane and vesicle proteins essential for docking of the presynaptic vesicles at the presynaptic active zones of the nerve terminals, resulting in failure of Ach release and ultimate destruction of the presynaptic terminals.



Botulism

- Food born, infantile and wound botulism.
- Often presents with a rapid, usually descending, muscular weakness (ocular to bulbar to extremities)
- Autonomic symptoms (pupillary dilatation,constipation, dry mouth, urinary retention).
- Differential diagnosis of botulism includes MG, LEMS, Guillain-Barre´ syndrome (including the Miller-Fisher syndrome), tick paralysis, and diphtheritic polyneuropathy.

- Diagnosis confirmed by electrophysiological testing , identification of toxin in serum and stool, or identification of organism in stool cultures (in infantile and wound botulism).
- NERVE CONDUCTION- presynaptic defect of NMJ but differs from LEMS in that they may vary from day to day, may be normal during the first few days and may be only present in weakened muscles.



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