MYASTHENIA GRAVIS

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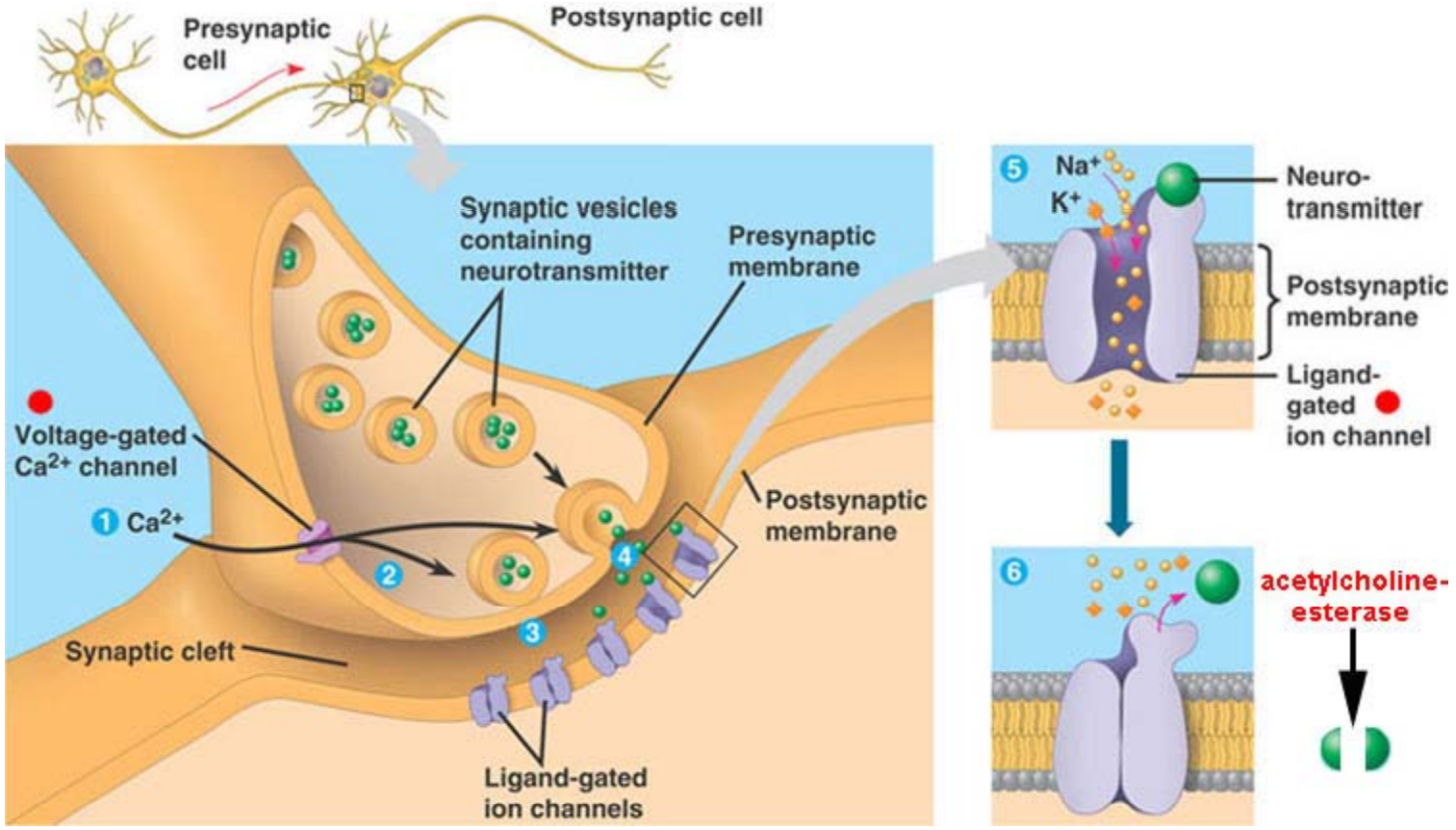
Overview

- An autoimmune neuromuscular disorder
- Common symptoms
  - A drooping eyelid
  - Blurred or double vision
  - Slurred speech
  - Difficulty chewing and swallowing
  - Weakness in the arms and legs
  - Chronic muscle fatigue
  - Difficulty breathing
- MG is not directly inherited nor contagious

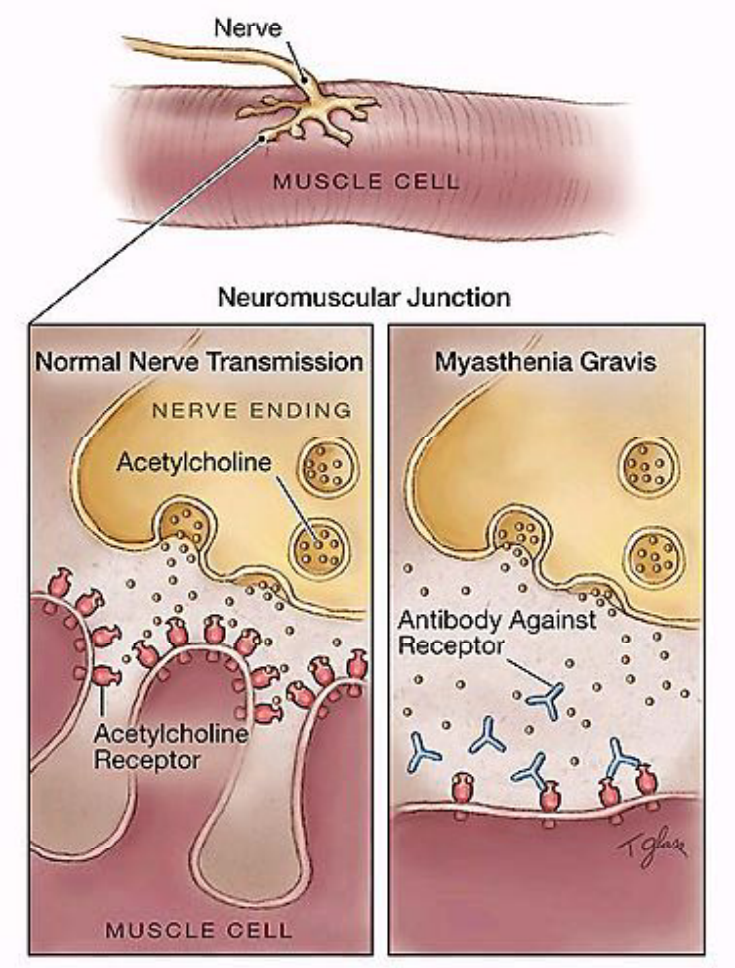
Epidemiology

- Prevalence
  - 20 per 100,000
- Onset age
  - **Bimodal pattern**
    - Early 2nd-3rd decade
      - Female > Male
    - Late 6th-7th decade
      - Male > Female
  - Childhood onset: ~ 30% in Asia
  - Neonatal: 12%
- Familiar MG: rare

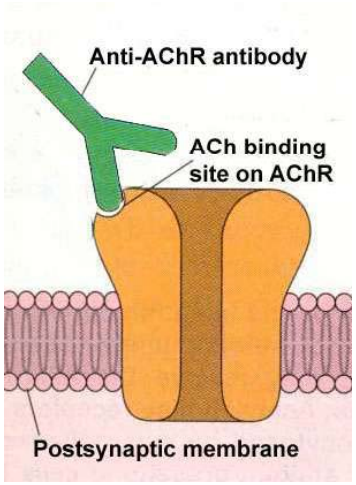
Neuromuscular Junction



Autoimmune Disease



- Autoantibody attacks acetylcholine receptor
- B cells → Plasma Cells
  - T helper cells
- T cells are activated by antigen (acetylcholine receptor)



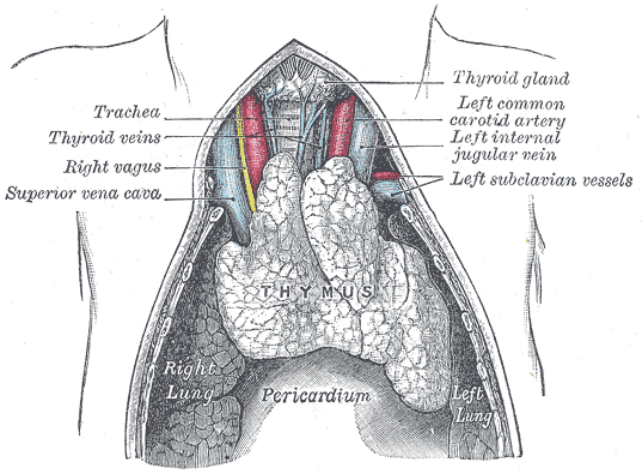
Autoimmune Disease

- Autoantibody against muscle specific kinas (MuSK)
  - A tyrosine kinas receptor required for the formation of the neuromuscular junction

- Anti-MuSK antibody inhibits the signaling of MuSK
  - decrease in potency of the neuromuscular junction
  - consequent symptoms of MG

The Role of Thymus

- 75% of thymus abnormality
- 25% of thymoma
- The disease remains stationary after thymectomy



Genetic Factors

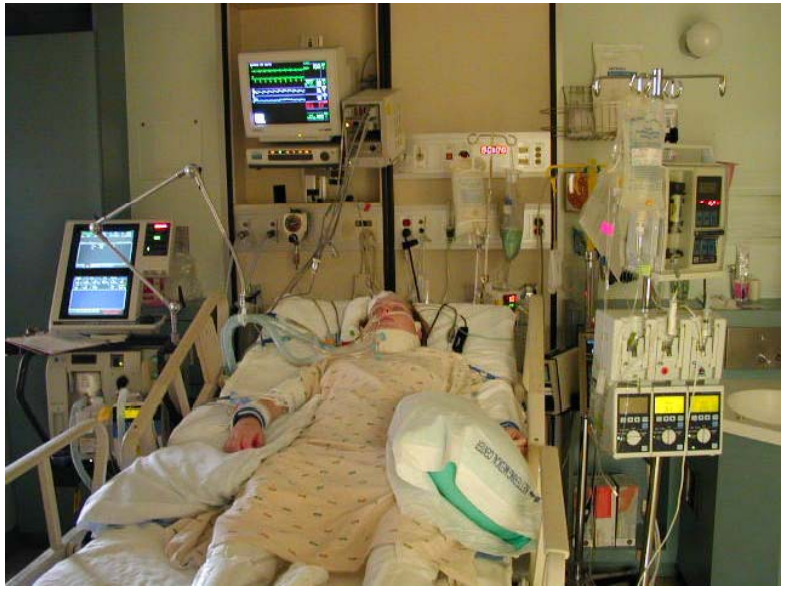
- 5% of the cases
- HLA-B8 and DR3
- Co-existing autoimmune diseases

Signs and symptoms

- Fatigability
- Eye, facial and bulbar muscles
  - Eye and eyelid movement
  - Facial expression
  - Chewing, swallowing
  - Talking
- Breathing muscle
- Neck muscle
- Limb muscles
- Insidious or sudden onset
- Intermittent and fluctuating
- Symptoms vary
  - ocular vs generalized

Myasthenia Crisis

- Paralysis of respiratory muscles
- Necessitating assisted ventilation
- Triggering factors
  - Infection
  - Fever
  - Adverse reaction to medication
  - Emotional stress



Diagnosis

- Diagnosis can be a difficult diagnosis
  - Symptoms are subtle
  - Other neurological disorders

- A thorough physical examination
  - Fatigability
    - Improving after rest and worsening again on repeat of exertion testing
  - Ice testing
    - Improvement in strength of weak muscles

Edrophonium (Tensilon, Reversol) Test

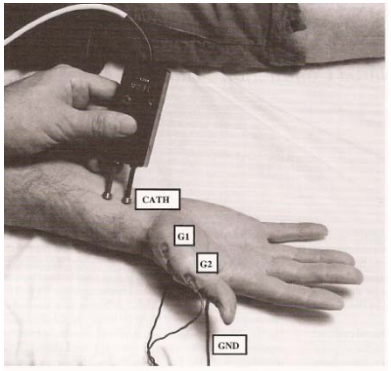
- Acetylcholinesterase inhibitor
  - Blocks the breakdown of acetylcholine by cholinesterase
  - temporarily increases the levels of acetylcholine at the neuromuscular junction
- Intravenous administration
- Rapid effect and short-acting

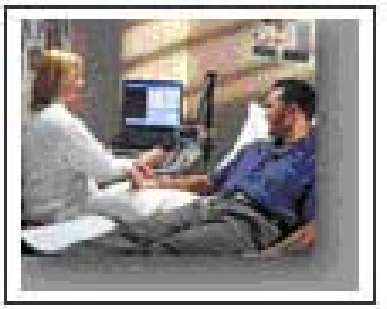
Blood Tests

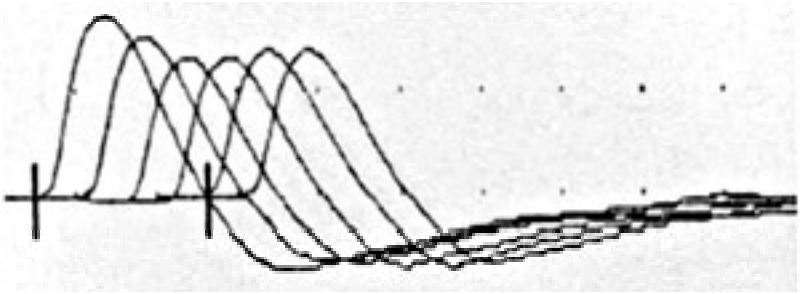
- Anti-acetylcholine receptor antibodies
  - 80–90 of generalized MG
  - 50% of ocular MG
- Anti-MuSK antibodies
  - 50% of AChR Ab-negative patients
- Anti-striational antibodies
  - with thymoma

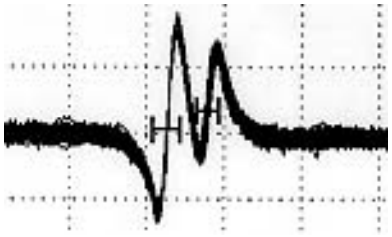
Clinical Neurophysiology

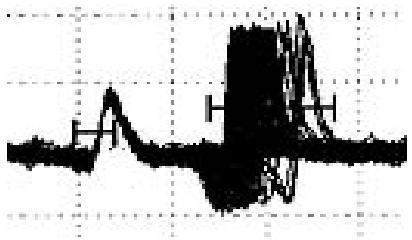
- Repetitive nerve stimulation
  - Decrements of amplitudes
- Single fiber electromyography
  - Increases in 'jitter'





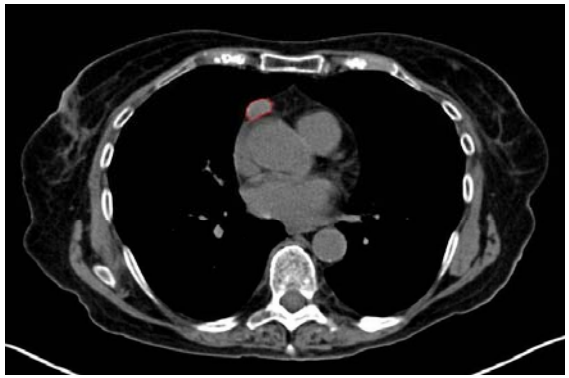






Imaging

- Chest CT scan
- Thymoma (red circle)



Pulmonary Function Test

- Spirometry assesses respiratory function

- Forced vital capacity (FVC) at intervals
  - To monitor worsening of respiratory function

Pathological Findings

- Muscle biopsy is only performed if the diagnosis is in doubt and a muscular disease is suspected
- Immunofluorescence shows IgG antibodies on the neuromuscular junction.
- Electron microscopy shows receptor loss of the tips of the folds and widening of the synaptic clefts

Treatment

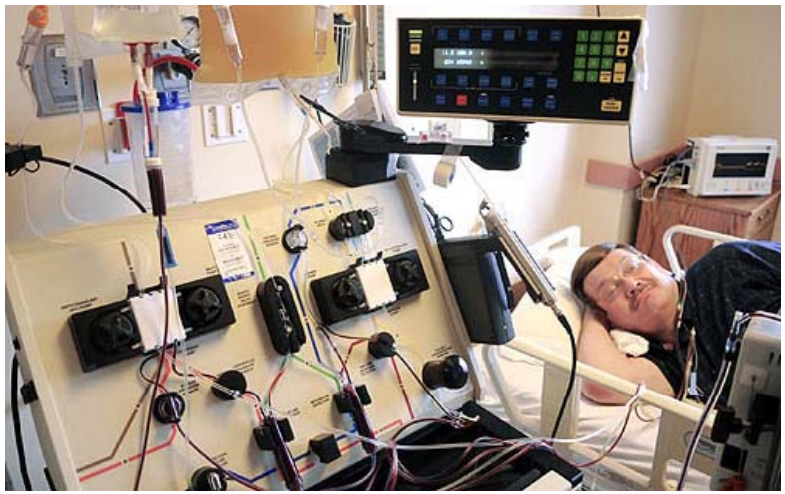
- Medication
  - Acetylcholinesterase inhibitors to directly improve muscle function
  - Immunosuppressant drugs to reduce the autoimmune process
- Thymectomy
- Emergency treatment
  - Plasmapheresis or IVIG
  - Temporary removal of antibodies from the blood circulation

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

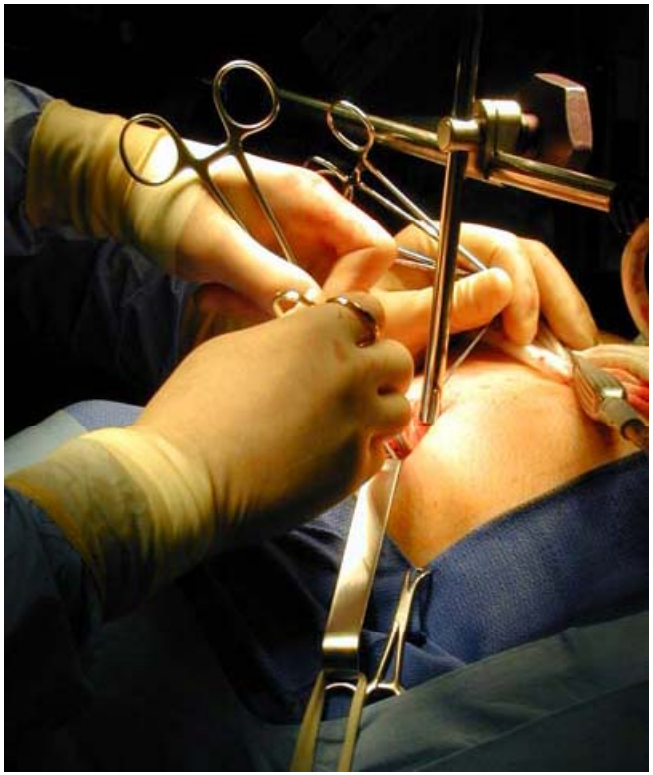
Plasmapheresis

- Myasthenia crisis or relapse
- To remove the putative antibody from the circulation
- Relatively short-lived benefits, typically measured in weeks



Thymectomy

- Indications
  - Thymoma
  - Generalized MG
  - Age of 18-55
- Long-term benefits



Prognosis

- MG is not usually a progressive disease
- Normal life expectancy
  - Except for those with a malignant thymoma
- Quality of life can vary depending on the severity
- The drugs either diminish in effectiveness over time (cholinesterase inhibitors) or cause severe side effects (immunosuppressant)
- Most patients need treatment for the remainder of their lives

Mycophenolate mofetil (CellCpt)

- Selectively inhibits the proliferation of activated B and T lymphocytes
- A potential role for CellCept as a steroid-sparing agent and as adjunctive or primary therapy in refractory MG
- Clinical trials are currently underway

Pregnancy

- MG does not affect the normal growth and development of the fetus
  - Many women with MG have successful pregnancies
- Neonatal myasthenia
  - Antibodies attack child's acetylcholine receptors
  - 12-20% incidence of in infants born to mothers with MG
  - A temporary general weakness in a baby
    - Occurs within the first 24 to 48 hours after birth
    - Usually self-limited, lasting three to five weeks, but occasionally lasts longer
  - Typically responds very well to acetylcholinesterase inhibitors

Flu shot?

- Flu shot is not a live vaccine
- Not strictly forbidden for people with MG
- Some instances in which the vaccine is not advised
  - Myasthenia crisis?

Medications You Should Avoid

- Antibiotics (aminoglycosides, ciprofloxacin, erythromycin, ampicillin)
- Beta blocking agents (propranolol, oxprenolol,Timolol)
- Lithium
- Magnesium
- Procainamide
- Verapamil
- Quinidine
- Chloroquine
- Anticholinergics (trihexyphenidyl)
- Neuromuscular blocking agents (vacuronium and curare)

Clinical Trials

- EN101antisense
- rEV576
- Rituximab
- Stem cell

EN101 antisense

- Antisense is a synthetic, short segment of DNA that locks onto a strand of mRNA and blocks production of acetylcholine esterase
- A small trial by Zohar Argov, MD, Hadassah Hebrew University Medical Center, Jerusalem, Israel
  - 16 people with MG were given daily doses for four days. Four of the people later took the drug for a month
  - Reduced disease severity by 46%, improved muscle function, improved swallowing and disappearance of a drooping eyelid
  - Side effects: dryness of eyes and mouth
- A large clinical trial

rEV576

- A protein found in tick saliva
- Complement (C5) inhibitor

- Henry J. Kaminski, M.D., Saint Louis University School of Medicine
  - Tested on rats with mild and severe experimental MG
  - Reduced weakness and weight loss

- rEV576 could have therapeutic value in human MG

Rituximab

- Rituximab for myasthenia gravis
- Monoclonal antibody against CD20+ cells that causes prolonged B cell depletion
- Stieglbauer K. at Academic Teaching Hospital, Linz, Austria
  - In all three patients, treatment with rituximab led to clinical improvement and discontinuation or reduction of prednisolone and other drugs
  - Rituximab was well tolerated.
- More studies and clinical trials

Stem Cell Therapy

- University of California, San Diego Medical Center
- Reprogrammed the patient's stem cells by destroying them with chemotherapy before re-introducing the purified stem cells
- After the transplant, the modified stem cells build new bone marrow, renewing the immune system with cells that don't attack the body
- Patients breathed easier

Stem Cell Therapy

- Hematopoietic stem cell therapy for patients with refractory myasthenia gravis

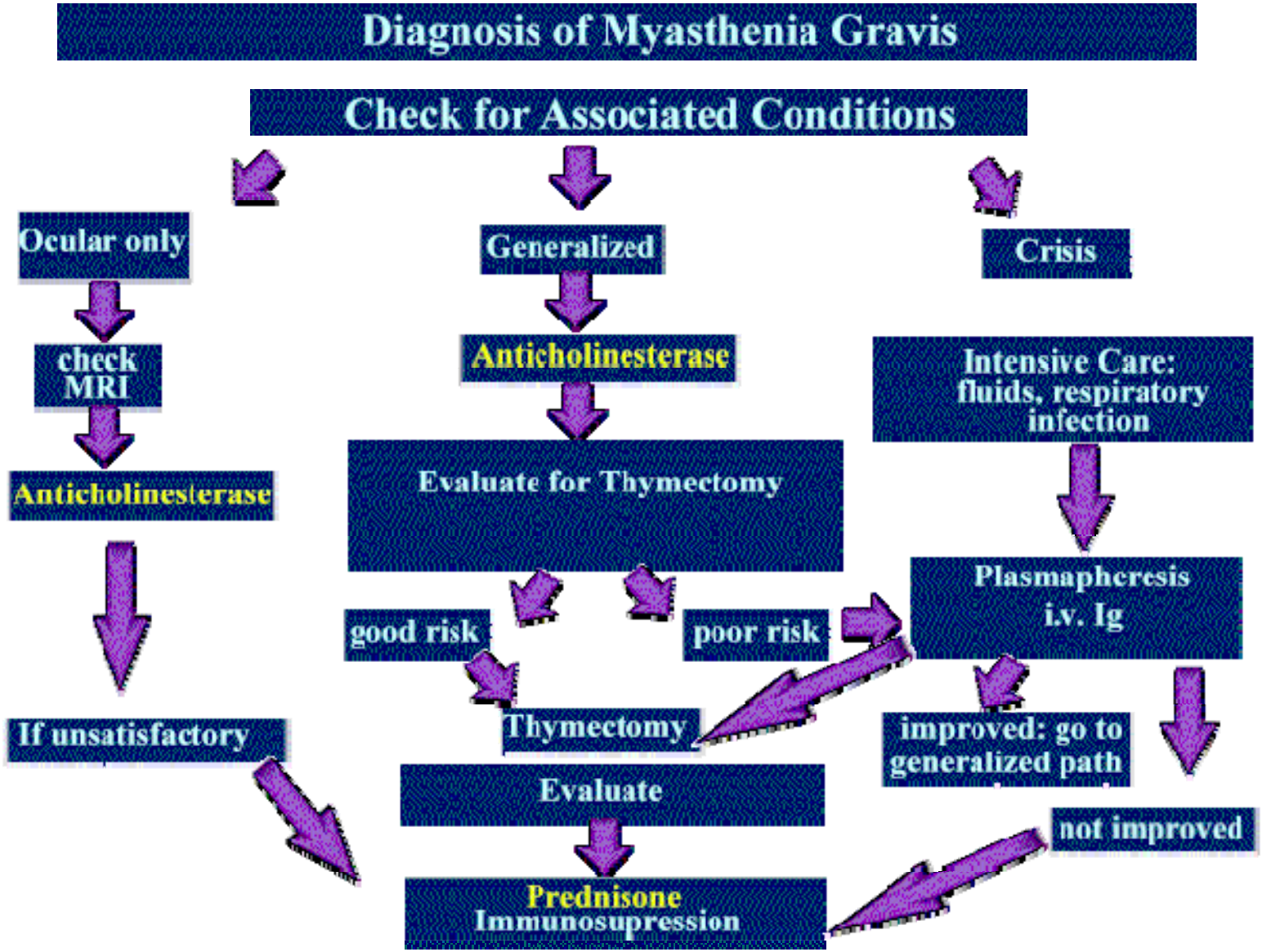
- Northwestern University and Northwestern Memorial Hospital
  PI: Richard Burt, MD

- Procedure: Hematopoietic Stem Cell Transplantation Autologous Hematopoietic Stem Cell Transplantation

- 2002 -

Future Strategy

- Immune tolerance
- Specific targets
  - Antigen-specific T or B cells
  - Bioengineering
- Stem cell Therapy


Diagnosis of Myasthenia Gravis
Check for Associated Conditions
Ocular only
Generalized
Crisis
check MRI
Anticholinesterase
Intensive Care: fluids, respiratory infection
Anticholinesterase
Evaluate for Thymectomy
Plasmapheresis i.v. Ig
good risk
poor risk
Thymectomy
If unsatisfactory
improved: go to generalized path
Evaluate
not improved
Prednisone
Immunosupression

GUILLAIN-BARRÉ SYNDROME

GBS Historical background

Early descriptions

1834 **James Wardrop**

1859 **Jean-Baptiste Octave Landry**

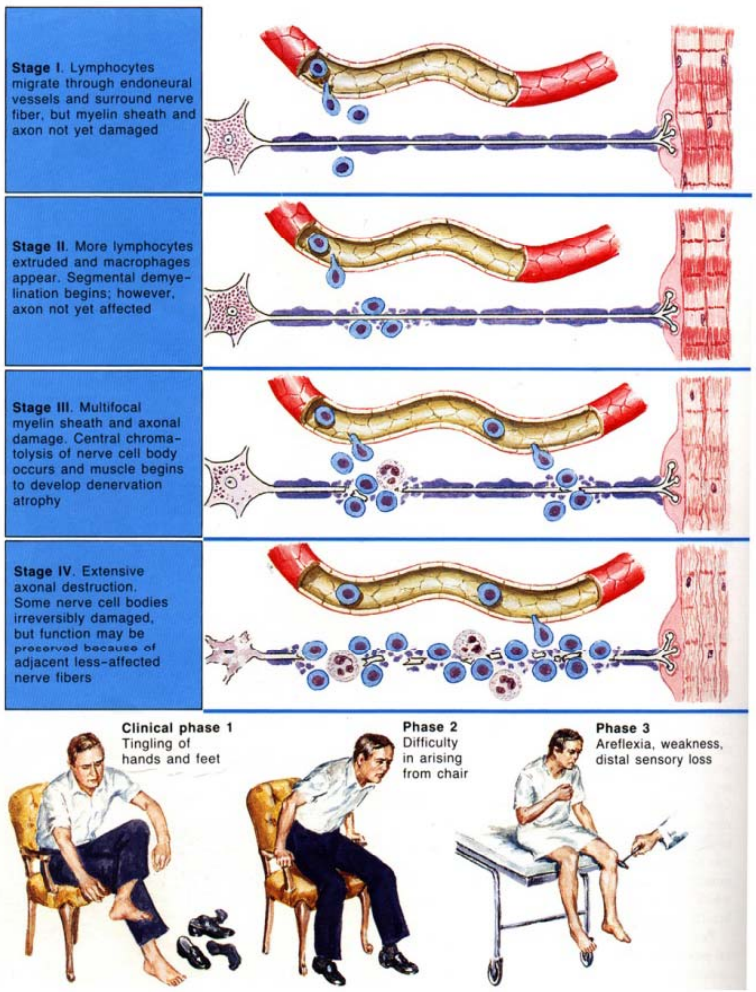
"Landry's paralysis"

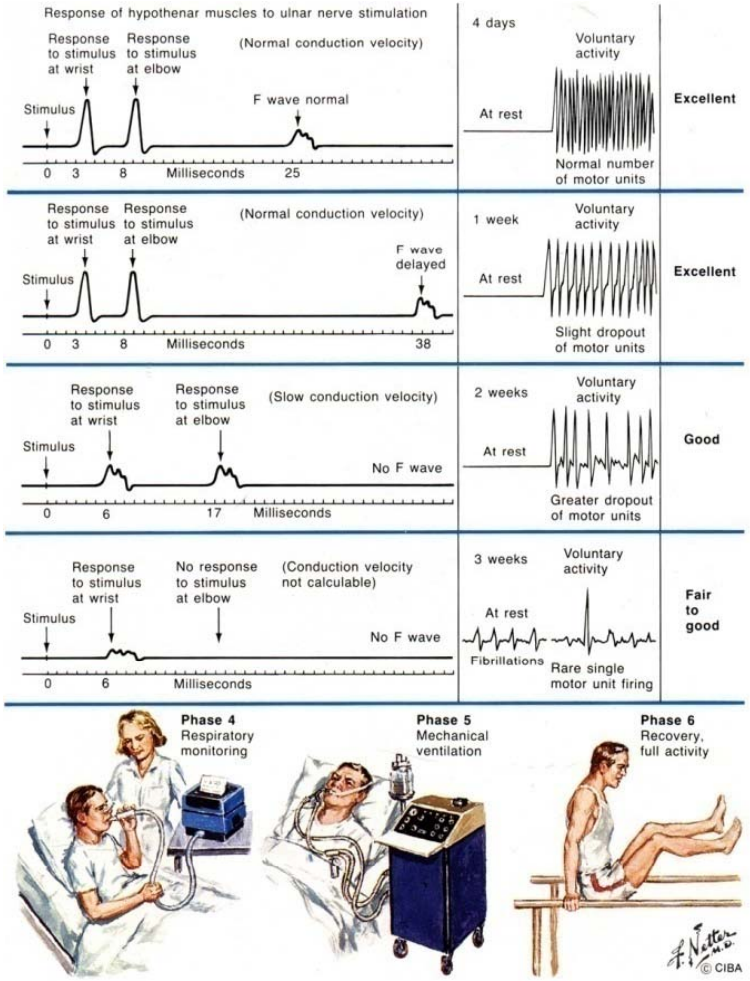
GBS Historical background

1916 **Guillain, Barré, Strohl**

"Radiculitis with hyperalbuminosis of the cerebrospinal fluid without cellular reaction"

Acute inflammatory demyelinating polyneuropathy **GBS**





Guillan-Barré Syndrome—Clinical Features

Condition	Frequency	
	Initially	In fully developed illness
Paresthesias	70%	85%
Weakness		
Arms	20	90
Legs	60	95
Face	35	60
Oropharynx	25	50
Ophthalmoparesis	5	15
Sphincter dysfunction	15	5
Ataxia	10	15
Areflexia	75	90
Pain	25	30
Sensory loss	40	75
Respiratory failure	10	30

Source: Adapted from Ropper, 1992.

GBS Preceding and associated conditions

- Infections
  - Viral (EBV 10%, CMV 15%)
  - Bacterial (Campylobacter)
- Surgery/trauma
- Immunizations
- Systemic conditions
  - Malignancy
  - Endocrinopathies
  - Systemic lupus erythematosus
- Pregnancy
- Drug-induced (D-Penicillamine, Zimeldine, Gold)

GBS Variants

- Miller-Fisher syndrome
- GBS/Bickerstaff's brain stem encephalitis
- Pharyngeal-cervical-brachial paralysis
- Paraparetic form
- Pure motor form
- Pure sensory form
- Acute dysautonomic neuropathy
- Axonal GBS

GBS Differential diagnosis

- Acute/subacute myelopathy
  - Cord compression
  - Transverse myelitis
- Cauda equina syndrome
- Poliomyelitis, Diptheria
- Myasthenia gravis, Botulism
- Porphyria
- Acute rhabdomyolysis
- Acute myopathy induced by steroid/nondepolarizing neuromuscular blocking agents
- Critical illness polyneuropathy

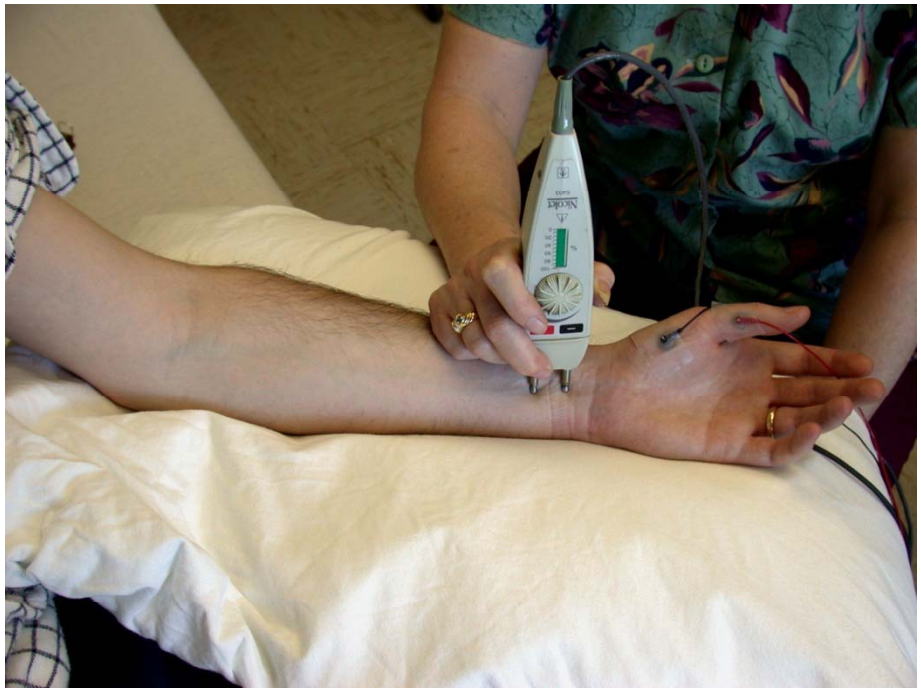
GBS Differential diagnosis cont'd

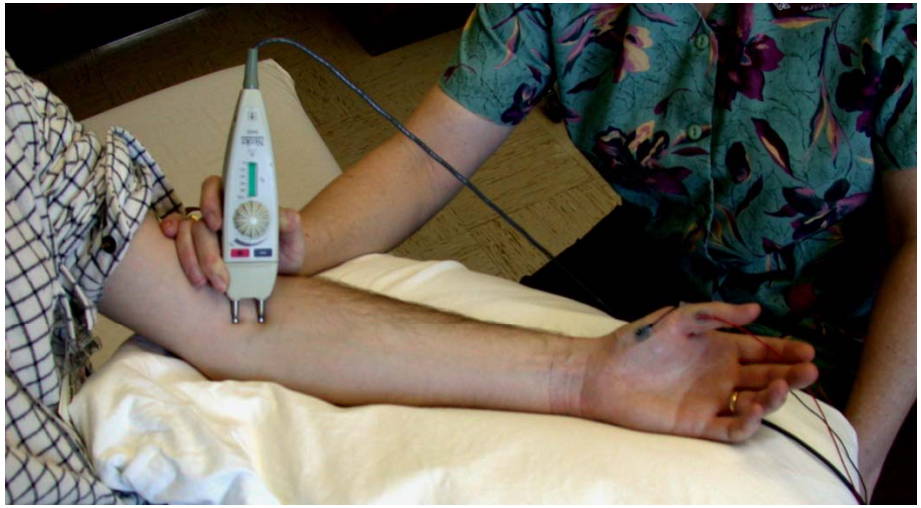
- Organophosphate intoxication
- Periodic paralyses
- Lyme Disease
- Tick Paralysis
- Acute toxic neuropathies (arsenic, thallium, lead, barium, hexacarbon, dapsone, nitrofurantoin, etc.)
- Hypophosphatemia
- Hypermagnesemia
- Carcinomatous meningitis
- Acute pontine ischemia

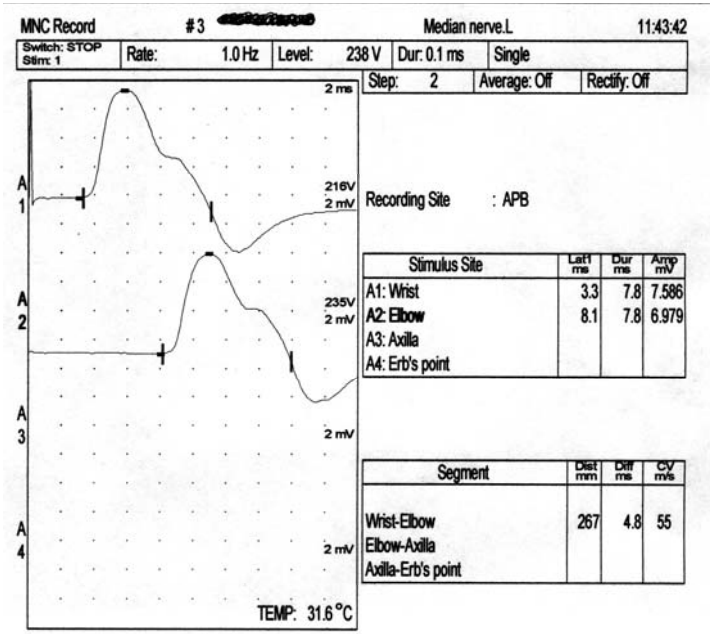
GBS Etiology/Pathogenesis

- Immune mechanisms
- Humoral and cellular immunity
- Complement deposition
- Proinflammatory cytokines
- AIDP – immune-mediated demyelination
- AMAN/AMSAN – immune mediated – axonal degeneration (molecular mimicry between C. jejuni lipopolysacharides and ganglioside-like epitopes of peripheral nerves (e.g.GM1)

NERVE CONDUCTION STUDIES



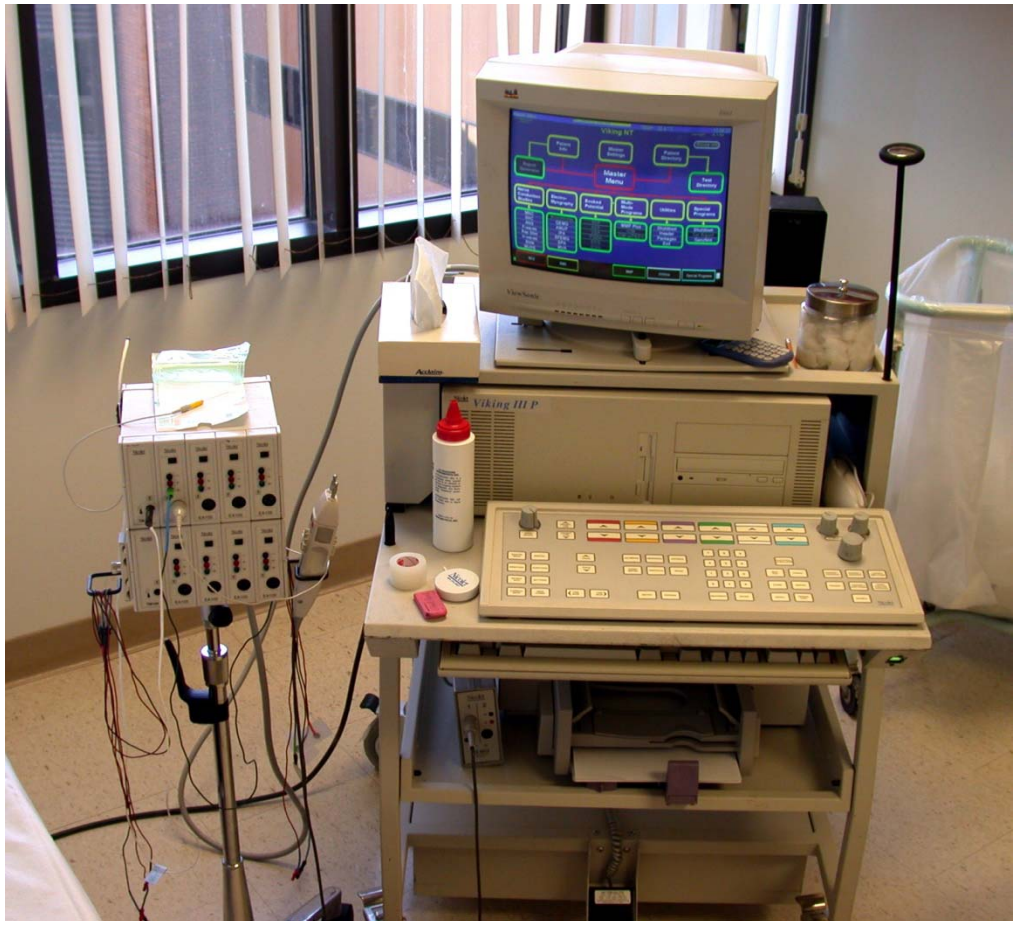


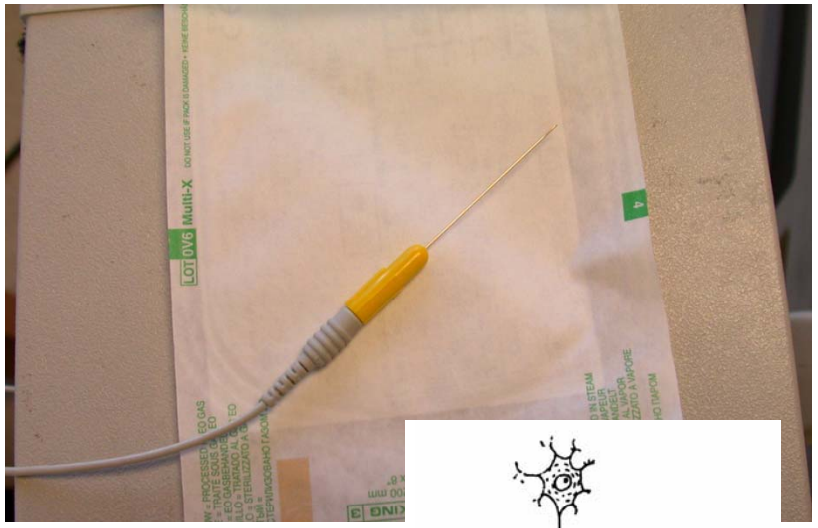


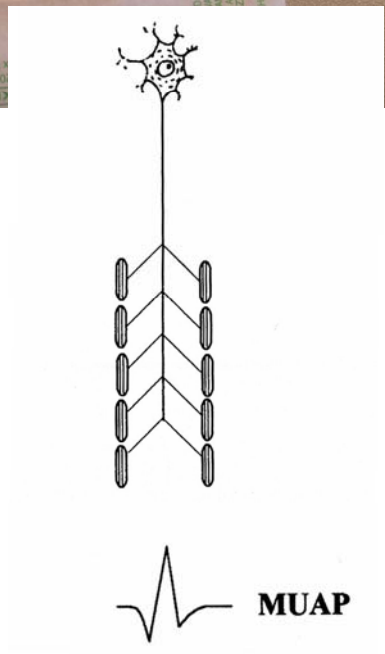
Median nerve
motor conduction study

Recording from the thenar muscles

Electromyography







GBS Electrodiagnostic studies

- Electrophysiologic studies (NCS/EMG) are diagnostic in 95 % of patients at some time during the course of the illness.
- Electrophysiologic evidence of demyelination is the hallmark of GBS
- Early in the course nerve conduction velocities and distal latencies may be normal

GBS Electrodiagnostic studies

- Prolongation or absence of F-waves may be the only abnormality in some GBS cases especially early in the course of the disease
- Slowing of motor conduction velocity
- Prolongation of distal latencies
- Conduction block or temporal dispersion
- 25-75% of GBS cases will have abnormal sensory NCS. (sural SNAP frequently spared, despite reduced or absent median or ulnar SNAPs)

GBS
Electrodiagnostic studies

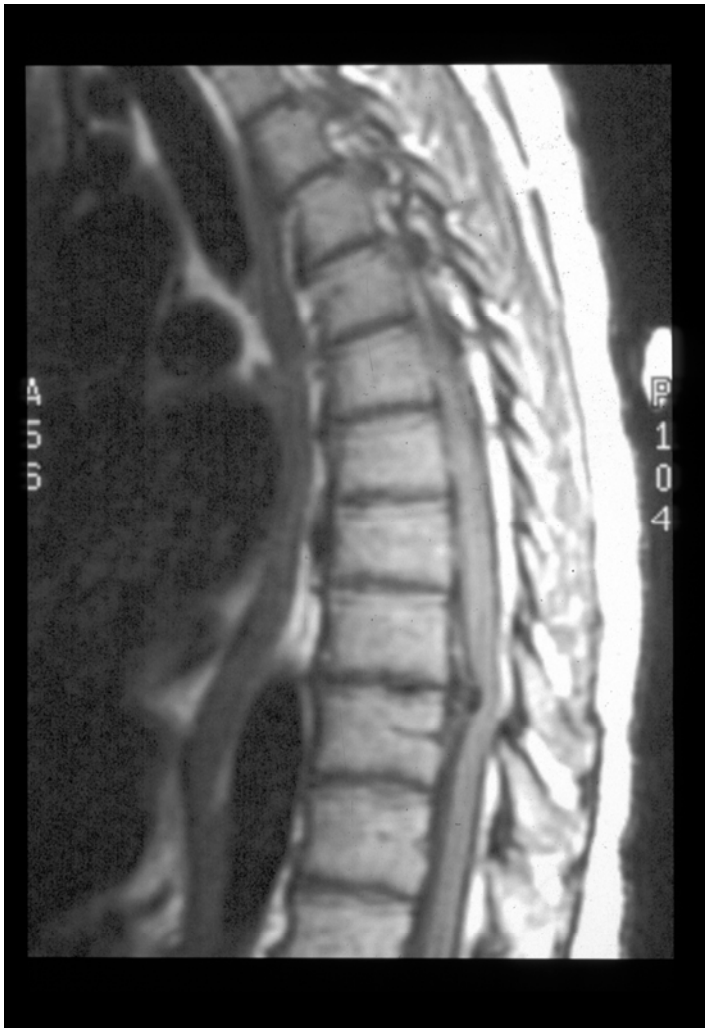
- Small amplitudes of CMAPs, if not associated with conduction block or temporal dispersion indicate severe axonal damage.
- Needle EMG – less helpful in early GBS (especially within first 2 weeks)
- Abnormal recruitment pattern – high firing frequencies with decreased numbers of motor unit potentials may be the only abnormality in purely demyelinating GBS cases.
- Detection of spontaneous activity indicates coexisting axonal damage (20-64% cases within 4 weeks)

GBS
CSF studies

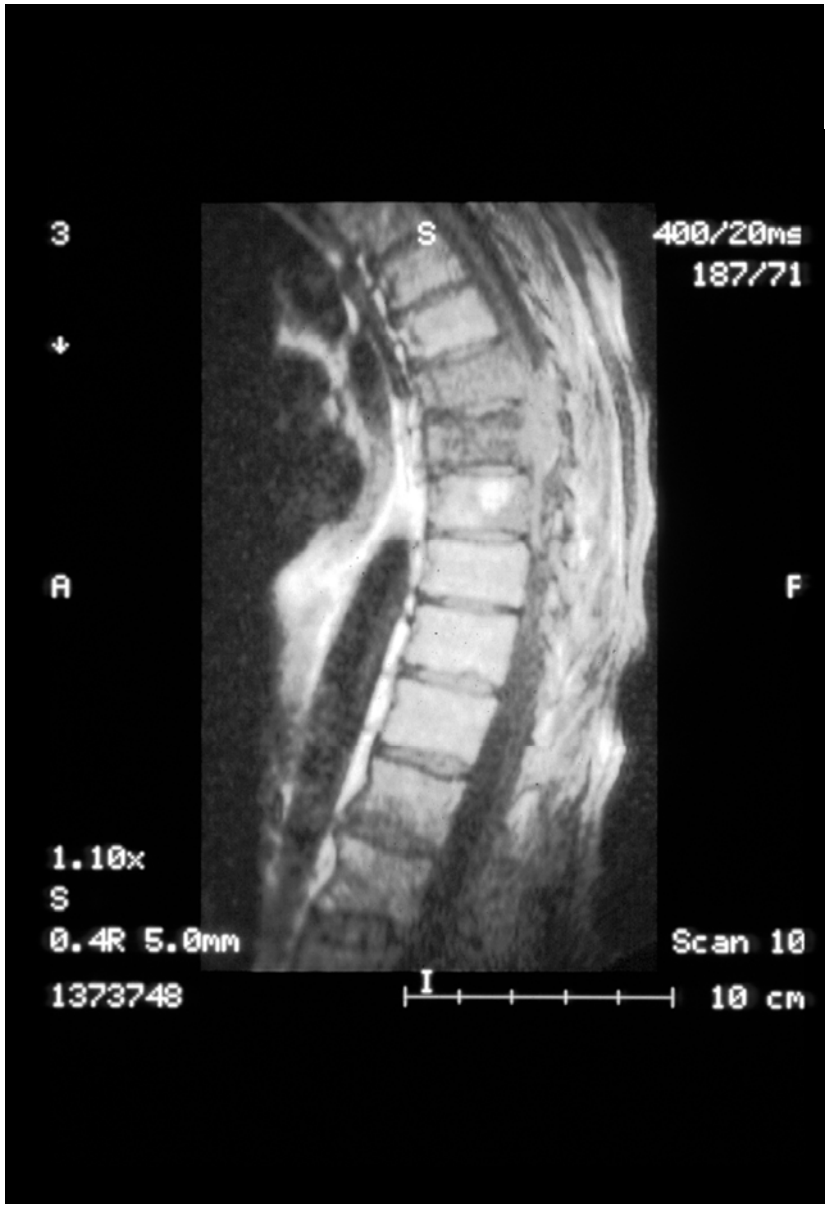
- CSF profile of cytoalbuminemic dissociation
- Markedly elevated protein (typically >100 mg/dl but may be greater than 1000 mg/dl).
- Protein content is the highest typically between 1st and 3rd week from the onset of symptoms.
- Cell count typically less than 10 mononuclear cells/mm^3
- Less than 10% of GBS cases may have higher cell count (more than 10 cells/mm^3)
- Lyme or HIV associated GBS may have markedly higher cell count (?meningeal inflammatory reaction)
- Other CSF studies may be necessary depending on clinical situations (e.g. to rule out infectious, CNS demyelinating or malignant processes)
-

MRI of the spine or brain is frequently obtained to rule out alternative diagnoses

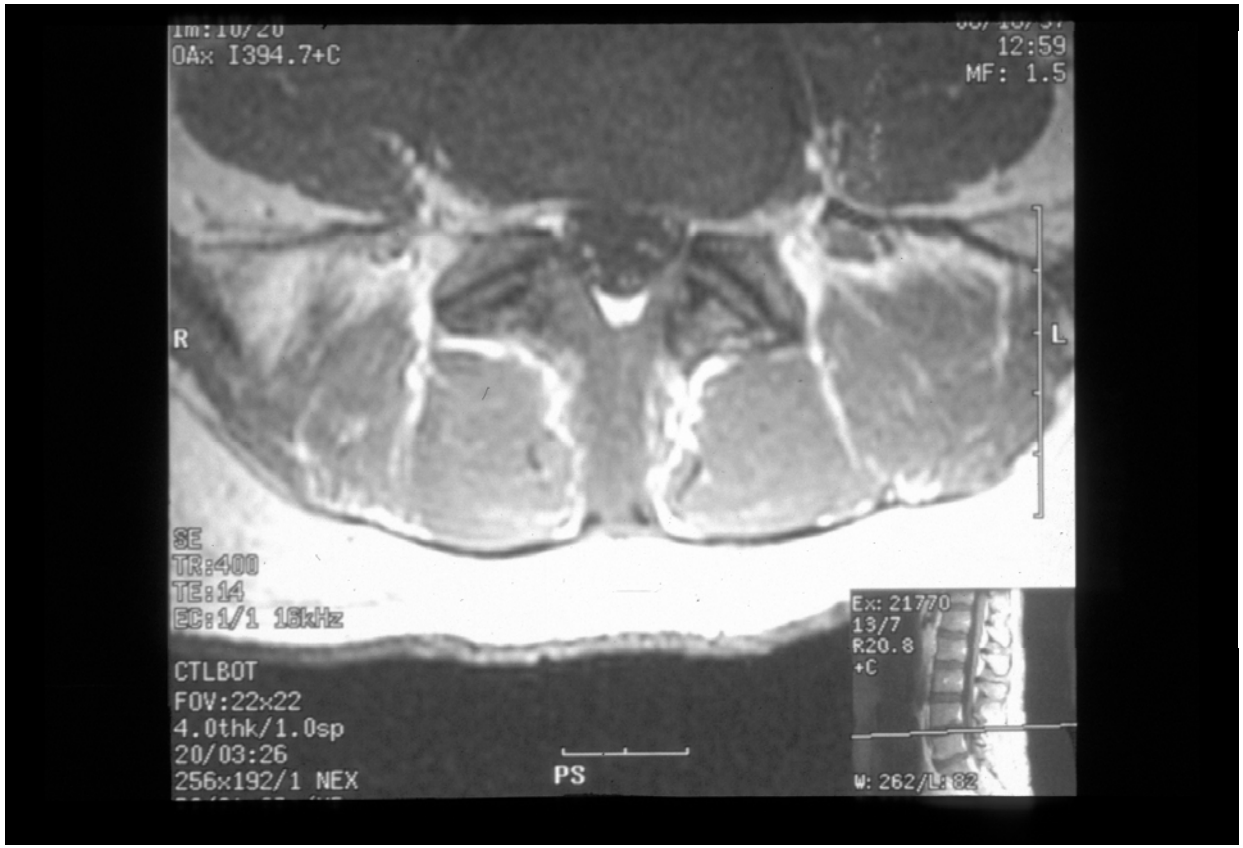
Thoracic disc herniation



Metastatic prostate cancer



HIV-related radiculitis



GBS Diagnostic studies

- The minimum laboratory work-up should include:
  - CBC, CMP
  - Sedimentation rate
  - Serum protein electrophoresis
  - Antinuclear antibodies (ANA), Rheumatoid factor (RF)
  - Lyme and HIV titers
  - Porphyria screen (in some cases)
  - Other labs depending on the clinical presentation (e.g. GQ1b, GM1 antibodies)

GBS

- Peripheral nerve biopsies are not routinely performed as part of diagnostic work-up, but may be considered in atypical cases.

GBS Supportive treatment

- Admit to ICU/ICU measures
- Monitor closely Vital Signs/Pulmonary Functions (VC,TV,NIF), at least every 4 hours.
- Baseline ABG in all ICU patients

GBS Supportive treatment

- Chest physiotherapy
- Chest X ray, baseline, then weekly or more often
- DVT/PE prophylaxis, SQ Heparin, venodynes
- GI bleeding prophylaxis – e.g. ranitidine IV 50 mg tid, or antacids, or sucralfate
- Prevent decubiti (air mattress)

GBS Supportive treatment cont'd

- Tube feedings in intubated patients or in patients with impaired swallowing
- Monitor for possible infections
- Monitor for possible hyponatremia
- Intermittent catheterization in urinary retention develops
- Prevent constipation (bulking agents, stool softeners)

GBS Supportive treatment cont'd

- Monitor for autonomic instability (hypotension/hypertension, bradycardia)
- Physical Therapy
- Pain Control
- Psychological Support

GBS Intubation Criteria

- Expiratory vital capacity reduced to 12-15 ml/kg
- PO2 falls below 70 mmHg with the patient breathing room air
- Severe oropharyngeal paresis develops (manifest by difficulty in clearing secretions, impaired swallowing, or aspiration)

GBS Supportive treatment cont'd

- Synchronized intermittent mandatory ventilation (SIMV)
- Patients who do not show sufficient respiratory improvement and require prolonged ventilation should undergo tracheostomy, usually after 7-14 days.

GBS Treatment

Immune therapy

- Plasma exchange
- Intravenous immunoglobulin
- PE and IVIG have probably equal efficacy (Dutch GBS Study Group, NEJM 1992)
- PE followed by IVIG provides no additional benefits (Plasma exchange/Sandoglobulin GBS Study Group. Lancet 1997;349:225-230)
- Corticosteroids are ineffective and may increase relapse rate (GBS Steroid Trial Group, Lancet 1993)

GBS Treatment

Plasma exchange

- Beneficial, if started within the first 2 weeks of illness
- Typically 3-5 exchanges; 20-50 ml/kg per exchange; over 7-14 days
- If relapse after initial improvement patients may respond to additional courses of PE

Plasma exchange

Possible complications

- Pneumothorax
- Sepsis
- Allergic reactions
- Hypotension
- Cardiac arrhythmias
- Congestive heart failure
- Venous thrombosis,
- Hemolysis
- Bleeding

GBS Treatment

Intravenous immunoglobulin

- 0.4gm/kg/day for 5 days
- Efficacy comparable to PE
- Low frequency of adverse effects
- Plasma exchange followed by IVIG provides no additional benefit

Intravenous immunoglobulin

Adverse reactions

- Headache
- Nausea, Chills, fever, Myalgia
- Anaphylactic reactions (predominately in patients with IgA deficiency)
- Allergic reaction (rash, hives)
- Aseptic meningitis
- Fluid overload/congestive heart failure
- Acute renal tubular necrosis
- Hypercoagulable state (risk of Stroke or MI)
- Risk of virus transmission – very small

GBS Prognosis

- With optimal treatment 75-80% of patients recover with little or no permanent disability
- 5-10 % have severe disability (severe weakness with wheelchair dependence, severe sensory deficit)
- 3-6 % of patients with typical GBS may develop chronic/relapsing course c/w CIDP
- Very rare patients may develop recurrent GBS (after long asymptomatic intervals)
- Mortality is less than 5%

GBS Prognosis

Factors suggesting poor outcome

- Age >60
- Need for ventilatory support
- Rapid evolution of neurological deficit
- Markedly reduced CMAP amplitude (<20% of lower limit of normal), indicating severe axonal degeneration