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 2^{nd}-3^{rd} decade
      - Female > Male
    - Late 6^{th}-7^{th} decade
      - Male > Female
  - Childhood onset: \sim 30\% in Asia

  - Neonatal: 12\%

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

- 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

- EN101 antisense
- rEV576
- Rituximab
- Stem cell
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

check MRI

Anticholinesterase

If unsatisfactory

Generalized

Anticholinesterase

Evaluate for Thymectomy

good risk

poor risk

Thymectomy

Evaluate

Prednisone

Immunosuppression

Crisis

Intensive Care: fluids, respiratory infection

Plasmapheresis i.v. Ig

improved: go to generalized path

not improved
GUILLAIN-BARRÉ SYNDROME
GBS Historical background

Early descriptions

1834 James Wardrop

1859 Jean-Baptiste Octave Landry
   “Landry’s paralysis”
1916  Guillain, Barré, Strohl

“Radiculitis with hyperalbuminosis of the cerebrospinal fluid without cellular reaction”
Acute inflammatory demyelinating polyneuropathy

**Stage I.** Lymphocytes migrate through endoneurial vessels and surround nerve fiber, but myelin sheath and axon not yet damaged.

**Stage II.** More lymphocytes extrude and macrophages appear. Segmental demyelination begins; however, axon not yet affected.

**Stage III.** Multifocal demyelination and axonal damage. Central chromatolysis of nerve cell body occurs and muscle begins to develop denervation atrophy.

**Stage IV.** Extensive axonal destruction. Some nerve cell bodies irreversibly damaged, but function may be preserved because of adjacent less-affected nerve fibers.

**Clinical phase 1** Tingling of hands and feet

**Phase 2** Difficulty in arising from chair

**Phase 3** Ankle weakness, distal sensory loss

**Phase 4** Respiratory monitoring

**Phase 5** Mechanical ventilation

**Phase 6** Recovery, full activity

Response of hypothenar muscles to ulnar nerve stimulation

<table>
<thead>
<tr>
<th>Response to stimulus at wrist</th>
<th>Response to stimulus at elbow</th>
</tr>
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<tbody>
<tr>
<td>(Normal conduction velocity)</td>
<td>(Normal conduction velocity)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>4 days</th>
<th>Voluntary activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>At rest</td>
</tr>
<tr>
<td>Normal number of motor units</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>1 week</th>
<th>Voluntary activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>At rest</td>
</tr>
<tr>
<td>Slight dropout of motor units</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2 weeks</th>
<th>Voluntary activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>At rest</td>
</tr>
<tr>
<td>Greater dropout of motor units</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3 weeks</th>
<th>Voluntary activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair to good</td>
<td>At rest</td>
</tr>
<tr>
<td>Rare single motor unit firing</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 5</th>
<th>Mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 6</td>
<td>Recovery, full activity</td>
</tr>
</tbody>
</table>
## Guillan-Barré Syndrome—Clinical Features

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initially</th>
<th>In fully developed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias</td>
<td>70%</td>
<td>85%</td>
</tr>
<tr>
<td>Weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arms</td>
<td>20</td>
<td>90</td>
</tr>
<tr>
<td>Legs</td>
<td>60</td>
<td>95</td>
</tr>
<tr>
<td>Face</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>25</td>
<td>50</td>
</tr>
<tr>
<td>Ophthalmoparesis</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Sphincter dysfunction</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Ataxia</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Areflexia</td>
<td>75</td>
<td>90</td>
</tr>
<tr>
<td>Pain</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>40</td>
<td>75</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

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 lipopolysaccharides 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 1\textsuperscript{st} and 3\textsuperscript{rd} week from the onset of symptoms.
- Cell count typically less than 10 mononuclear cells/mm\textsuperscript{3}
- Less than 10% of GBS cases may have higher cell count (more than 10 cells/mm\textsuperscript{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)
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