GUILLAIN BARRE SYNDROME

Background
1. Definitions:1-3
   o Guillain-Barre Syndrome (GBS)
     - Life threatening autoimmune disorder
     - Immune system attacks part of nervous system,
     - Causes nerve inflammation leading to muscle weakness
   o Also known as: Landry-Guillain-Barre syndrome; Acute idiopathic polyneuritis; Infectious polyneuritis; Acute inflammatory polyneuropathy; Acute inflammatory demyelinating polyneuropathy (AIDP).

2. General Information:1-3
   o Guillain-Barre Syndrome (GBS) often follows minor respiratory or gastrointestinal infection; usually presents after the signs of original infection have disappeared.
   o Immune system attacks nerve coverings (myelin sheath) causing demyelination; results in nerve signal slowing
   o In severe cases, damage can be more extensive, resulting in complete loss of nerve function.
     - Subtypes:
       - Acute inflammatory demyelinating polyradiculopathy (AIDP)
       - Acute motor axonal neuropathy (AMAN)
       - Acute motor sensory axonal neuropathy (AMSAN)
       - Miller Fisher syndrome
       - Acute panautonomic neuropathy (rarest of subtypes)

Pathophysiology
1. Pathology of Disease4
   o Guillain-Barre Syndrome (GBS) primarily involves peripheral nervous system.
   o Autoantibodies bind to gangliosides of nerve tissue and activate immune response; leads to inflammatory axon infiltration and secondary myelin impairment.
   o Pathologic findings include lymphocyte infiltration of spinal roots and peripheral nerves with subsequent macrophage-mediated stripping of myelin

2. Incidence and Prevalence
   o Incidence ranges from 0.62 cases/100,000 person-years (ages 0-9) to 2.66 cases/100,000 person-years (ages 80-89) in North America and Europe.5
   o Relative risk for males 1.78 compared to females.5
   o Incidence thought to be higher in parts of Asia.5

3. Risk Factors6
   o Risk factors for GBS may include:
     - Age: Increased incidence in late adolescence/young adult and elderly
     - Men > Women
- Recent gastrointestinal/respiratory infection by viruses/bacteria within 6 weeks
  - Usual pathogens include Epstein-Barr, Mycoplasma pneumoniae, Campylobacter jejuni and cytomegalovirus
- Recent vaccination (especially influenza and meningococcal)
  - Swine flu vaccine, given from 1976-1977, linked to excess GBS cases.
  - Since that time, influenza virus vaccines associated with only marginally increased GBS risk
- Recent surgery
- History of lymphoma, lupus, or AIDS.

4. Morbidity / Mortality
   - In one study of 76 patients admitted to ICU with confirmed GBS:
     - ICU stay averaged 21 days
     - Mechanical ventilation (MV) required in 78% (median duration 28 days)
     - 2/3 suffered at least one major complication, most commonly pneumonia (54%)
     - Morbidity strongly associated with mechanical ventilation and male sex
     - Over an average 3 years follow-up, recovery of independent ambulation seen in 75% of patients
       - Time to ambulate was median of 198 days; although seen as late as 10 years after onset
     - Prolonged mechanical ventilation and severe axonal loss did not preclude favorable recovery.
     - Slower recovery associated with ICU complications, prolonged MV, and early axonal abnormalities.
     - Mortality occurred in 6.5% of patients

Diagnostics
1. History
   - GBS often begins subtly, starting with tingling and weakness in feet and legs and subsequent ascending spread to upper body, arms, fingers and face.
   - In some people, symptoms begin in arms or even face.
   - As disorder progresses, muscle weakness can evolve into paralysis.
   - Lower cranial nerves may be affected, with difficulty swallowing, drooling, maintaining open airway and respiratory problems.
   - 73% of patients reach peak of symptoms at one week; 98% at four weeks.
   - In some cases, signs and symptoms may progress very rapidly, with complete paralysis of legs, arms and breathing muscles over the course of a few hours.
- Signs and symptoms of Guillain-Barre Syndrome may include:
  - Prickling, "pins and needles" sensations in fingers, toes or both
  - Weakness or tingling sensations in legs that spread to upper body
  - Unsteady walking, or inability to walk
  - Difficulty with eye movement, facial movement, speaking, chewing or swallowing
  - Severe pain in shoulders, back and posterior thighs
• Difficulty with bladder or intestinal functions
• Rapid heart rate
• Low or high blood pressure
• Difficulty breathing

2. Physical Examination
   o Ascending motor weakness with areflexia.
     • Weakness tends to be symmetric and usually begins in the legs.
   o Ataxia reported in about half of cases.
   o Cranial neuropathies also common:
     • Most commonly involve facial nerve, although ophthalmoplegia also frequently reported.
   o Autonomic neuropathy involving both sympathetic and parasympathetic systems also frequently seen.
     • Manifestations can include orthostatic hypotension, pupillary dysfunction, sweating abnormalities, and sinus tachycardia.
   o Respiratory failure due to respiratory muscle involvement results in ventilator dependence in about 1/4 of patients.

3. Diagnostic Testing
   o Common diagnostic tests include blood tests (CBC, BMP, ESR, CRP), urine tests, x-rays, CT or MRI scans, lumbar puncture, nerve conduction velocities (NCV), electromyogram (EMG) and electrocardiogram (ECG).
   o Lumbar puncture - excess protein (often more than 1g with no increase in CSF white blood cells) indicative of patient suffering from GBS.
     • CSF WBCs up to 50/μL permitted for diagnosis; must consider other disorders if CSF leukocytosis exceeds 50/μL.
   o Nerve Conduction Velocity test (NCV) reveals slow transmission in nerves with damaged myelin sheath and completely absent transmission with destroyed axons.
   o Electromyogram (EMG) evaluates muscle activity and indicate signs of slow or blocked nerve conduction
     • Test also used to differentiate between muscle disorders and muscle weakness caused by neurologic disorders.
   o Electrocardiogram (ECG) to rule out other sources of cardiovascular dysfunction
   o Nerve biopsy to determine damage to nerve and/or axon.

4. Laboratory evaluation
   o HIV test done in patients who have risk factors for HIV or CSF pleocytosis
   o Serologic tests for antibodies are not clinically available with 1 exception: Serum IgG antibodies to GQ1b for diagnosis of Miller Fisher Syndrome.
   o CSF findings:
     • Often normal when symptoms present for < 48 hours
     • By end of the first week, protein level usually elevated.
     • CSF protein 1–10 g/L (100–1000 mg/dL) without accompanying pleocytosis after first week; usually normal CSF in first week
     • Occasionally, transient mild increase in CSF white cell count (10–100/μL) occurs early in the GBS course of; clinical trial permit CSF cell counts up to 50 cells/mm
• Sustained CSF pleocytosis suggests alternative diagnosis (e.g., viral myelitis) or concurrent diagnosis (e.g., unrecognized HIV infection).  

5. Diagnostic imaging
   o Not indicated unless needed to rule out other diagnoses

6. Other studies
   o Electrodiagnostic features\(^4,8,10\)
     • AIDP = findings of demyelination (consider Miller Fisher syndrome)
     • AMAN = findings of acute motor axonal neuropathy (normal sensory nerves)
     • AMSAN = similar to AMAN except affects sensory nerves and roots (Wallerian-like degeneration of myelinated motor and sensory fibers)
     • Miller Fisher syndrome = reduced or absent sensory nerve action potentials; demyelination and inflammation of cranial nerve III and VI, spinal ganglia and peripheral nerves
     • Acute panautonomic neuropathy – cardiovascular involvement common
     o Abnormalities mild or absent in early stages and lag behind the clinical evolution
     o In cases with demyelination, usual features include: prolonged distal latencies, conduction velocity slowing, evidence of conduction block, and temporal dispersion of compound action potential
     o In cases with primary axonal pathology, principal finding is reduced amplitude of compound action potentials. Conduction slowing and of distal latency prolongation are absent.
     o Electrodiagnostic testing can be helpful in rare instances when muscular (e.g., polymyositis) or neuromuscular junction (e.g., myasthenia gravis) disorder must be ruled out.

7. Diagnostic Criteria\(^8\)
   o **Features required for diagnosis**
     • Progressive weakness in both arms and legs; areflexia
   o **Features strongly supporting diagnosis**
     • Progression of symptoms over days, up to four weeks
     • Relative symptom symmetry
     • Mild sensory signs/symptoms
     • Cranial nerve involvement, especially bilateral facial muscle weakness
     • Recovery beginning two to four weeks after progression ceases
     • Autonomic dysfunction
     • Absence of fever at onset
     • High concentration of protein in cerebrospinal fluid, with fewer than 10 cells per cubic millimeter
     • Typical electrodiagnostic features
   o **Features excluding diagnosis**
     • Diagnosis of botulism, myasthenia, poliomyelitis or toxic neuropathy
     • Abnormal porphyrin metabolism
     • Recent diphtheria
     • Purely sensory syndrome, without weakness.
**Differential Diagnosis**$^{8,10}$

1. Key Differential Diagnoses (when neuropathy identified)
   - Infection (Lyme, Diptheria)
   - Inflammatory (neurosarcoïd)
   - Paraneoplastic (chronic)
   - Malignant (infiltration of roots)
   - Vasculitic (mononeuropathy)
   - Metabolic (vitamin B1 deficiency)

2. Extensive Differential Diagnoses$^8$
   - Basilar artery occlusion (asymmetric limb paresis)
   - Botulism (descending paralysis)
   - Heavy metal intoxication (confusion, psychosis, organic brain syndrome)
   - Hypophosphatemia (irritable, apprehensive, hyperventilation, normal CSF)
   - Metabolic myopathies (cerebral and cerebellar symptoms)
   - Myasthenia gravis (weakness and fatigue that improves with rest)
   - Neoplastic meningitis (asymmetric spastic paralysis)
   - Neurotoxic fish poisoning (spontaneous recovery within 24 hours)
   - Poliomyelitis (purely motor disorder with meningitis)
   - Polymyositis (chronic, affects proximal limb muscles)
   - Spinal cord compression (asymmetric)
   - Tick paralysis (sensory changes absent, normal cerebrospinal fluid)
   - Transverse myelitis (abrupt bilateral leg weakness, ascending sensory)

**Therapeutics**

1. Acute Treatment$^{4,6,8}$
   - Treatment of GBS has two facets: supportive and specific therapy
   - Supportive care goal to lessen illness severity and includes:
     - Hospital admission to observe for clinical deterioration (respiratory failure, circulatory collapse, GI obstruction, urinary retention)
     - Monitor vital capacity (VC); use mechanical ventilation when VC less than 15-20 mL/kg
     - Early intubation should be considered in following circumstances:
       - Negative Inspiratory force (NIF) < -25 cm H2O
       - > 30% decrease in either VC or NIF within 24hrs
       - Rapid progression of disease
       - Autonomic instability
     - Monitor blood pressure and pulse to detect/treat hypotension/dysrhythmias
   - Deep Venous Thrombosis/VTE prophylaxis
   - Specific therapy goal: lessening or reversing nerve damage and includes:$^4$
     - Plasma exchange of 4 to 6 plasma volumes over 2 weeks (first treatment found to be effective)
     - Extract plasma from blood and use blood separators to remove immune complexes and autoantibodies (plasma then reinjected into patient with 5% albumin)
• Reduces percentage of patients requiring mechanical ventilation at
  4 weeks from 27% to 14%\(^6\)
• Effective if given within 4 weeks of first motor symptom
• Post-treatment worsening seen in 10% of patients

  ▪ Intravenous immunoglobulin (IVIg) at 400 mg/kg daily for 5 days
  ▪ Inhibits autoantibodies and suppresses autoantibody production
  ▪ Prevents damage to nerves by macrophage phagocytosis
  ▪ Similar efficacy to Plasma exchange, but considerably safer;
    therefore, usually first line
  ▪ Improves outcomes when given early; no effectiveness >2 weeks
    after first motor symptom

  ▪ Combination of Plasma exchange + IVIg not more effective than either
    alone
  ▪ Corticosteroids not effective

2. Further Management (24 hrs)
  ▪ Neuropathy can advance so rapidly that mechanical ventilation support may be
    necessary within 24 hours onset.\(^8\)
  ▪ Physical/Occupational/Speech therapy – to improve activities of daily living
    function\(^6\)

3. Long-Term Care
  ▪ Autonomic nervous system dysfunction may manifest as fluctuations in blood
    pressure, cardiac dysrhythmias, gastrointestinal pseudo-obstruction, and urinary
    retention.\(^6\)
  ▪ Prophylaxis for deep venous thrombosis/VTE

Follow-Up

1. Return to Office
  ▪ Follow-up within 2 weeks after acute syndrome to evaluate for relapse, at which
    point repeat intravenous immunoglobulin or plasma exchange can be considered
  ▪ Thereafter, follow-up every 4 to 6 weeks for 6 months, then to 6 months for 1
    year, then yearly.
  ▪ Patient should continue working with physiotherapy, occupational and speech
    therapy as needed
  ▪ Patients should be educated to contact their physician with any worsening
    neurologic symptoms of weakness, numbness, paresthesia, facial weakness,
    difficulty swallowing or breathing, or worsening bladder function.

2. Refer to Specialist
  ▪ Outpatient follow-up with neurology, pulmonology, physical therapy, and
  ▪ occupational therapy may be necessary depending on extent of neurological
    damage.
  ▪ Patients should always follow up with their PCP soon after discharge.\(^8\)

Prognosis

1. Symptoms reach clinical nadir between 2 to 4 weeks\(^6\)
2. ~ 85 percent of patients with GBS achieve full and functional recovery within six to 12
   months; recovery maximal by 18 months post onset\(^8\)
3. Some patients have persistent minor weakness, areflexia, and paresthesia.
4. ~ 7 to 20 percent of patients have permanent neurologic sequelae including:\(^6,^8\)
   - bilateral footdrop,
   - intrinsic hand muscle wasting,
   - sensory ataxia, and
   - dysesthesia
5. Mortality rate < 5 percent in tertiary care centers with multidisciplinary team
   experienced in GBS management\(^8\)
   - 4-15 percent mortality within one year in general population\(^6\)
6. Causes of death include adult respiratory distress syndrome, sepsis, pulmonary emboli,
   cardiac arrest, intestinal perforation, infections associated with prolonged immobility and
   mechanical ventilation\(^7,^8\)
7. Predictors of subsequent poor recovery\(^6,^8\)
   - Age greater than 50 years
   - Severe, rapidly progressive disease
   - Low nerve conduction amplitudes suggesting axonal loss
   - Prolonged mechanical ventilation for more than one month
   - Preexisting pulmonary disease predict a poor outcome
   - Poor long-term prognosis directly related to severity of acute episode and delay in
     specific treatment
   - Relapse occurs in 3-5% of patients

**Prevention**
1. No definite preventive recommendations for GBS
2. Other immunizations not recommended during acute disease phase and are not suggested
   for period of \(\geq 1\) year after onset.\(^11\)

**Patient Information**
1. Aside from physical care, supporting patient and family and teaching them about GBS
   crucial.
2. Use of patient and family teaching guide is one strategy for providing education and
   support.\(^12\)
3. GBS Foundation International website:  www.gbs-cidp.org
4. United Kingdom website:  www.gbs.org.uk

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