

# Guillain Barre Syndrome and Its Variants<sup>1</sup>

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## **I. Introduction<sup>1</sup>**

a. Guillain Barre Syndrome most commonly characterized by some combination of limb paresthesias, generalized weakness, and areflexia.

## **II. Pathogenesis of GBS** not yet fully understood and current thinking is that GBS may not be a single disease, but a variety of acute neuropathies with a number of related immune-mediated pathogenetic mechanisms.

- a. Most common immunopathologic finding: endoneurial inflammation in spinal nerves roots, distal nerve segments, or around potential nerve entrapment sites.
- b. Target antigens appear to be common to the axon, myelin sheath, or both. The exact antigens, the precipitating event, and the resultant mechanism of injury somewhat unclear.

## **III. Etiology<sup>1</sup>**

- a. GBS common to all races and ages; mild increase in frequency in patients between ages 30-50; GBS is less common in infants or the elderly.
- b. Slight increased frequency in men and Caucasians.
- c. GBS has a yearly incidence of 0.6-1.9 cases/100,000 population.
- d. No apparent genetic susceptibility to developing GBS.
- e. Risk of GBS after vaccination may be slightly higher (1-2 additional cases per one million flue vaccinated persons) than general population.
- f. Prior infection is well established as a precipitating event in the development of GBS.
  - i. GBS preceded by an acute illness, 1-4 weeks before, in about 75% of cases.
    1. GBS may **rarely** develop within a day or two, or after 4-6 weeks, of an acute illness.
    2. Most antecedent illnesses associated with GBS affect the upper respiratory or GI tracts.
      - a. URI may precede GBS in 50% of cases.
      - b. The presence of an antecedent illness is more often determined by serologic evidence, than the presence of systemic symptoms.
    3. Cytomegalovirus (CMV) is the most common viral antecedent infection with serologic evidence in up to 15% of cases
      - a. CMV induced GBS tends to occur in younger patients and is often severe with respiratory failure, marked sensory and cranial nerve dysfunction, and elevated antibodies against ganglioside GM2.

4. Epstein Barr (EBV) infection may precede GBS in about 10% of cases; preceding clinical signs include mononucleosis, hepatitis, or pharyngitis.
5. GBS may occur with HIV seroconversion.
  - a. Aside from a CSF pleocytosis, HIV-GBS is clinically and EDX indistinguishable from non-HIV GBS.
6. *Campylobacter jejuni* (*C. jejuni*) is, overall, the most common antecedent infection and has been reported in up to 32% of cases.
  - a. *C. jejuni* enteritis is characterized by watery diarrhea and abdominal cramping.
    - i. Clinical enteritis may be absent in 30% of *C. jejuni* associated GBS. In these cases there is only serologic evidence of the prior bacterial infection.
  - b. *C. jejuni*-GBS has marked motor axon degeneration, an elevated anti-GM1 antibodies, and a delayed and often incomplete recovery.
  - c. There appears to be an over-representation of certain strains of *C. jejuni* (Penner 19, Lior 11) suggesting that the lipopolysaccharides of these organisms share ganglioside-like epitopes with peripheral nerves. This molecular mimicry appears to confuse the immune system resulting in mistaken attack against neural antigens.
  - d. Other potential antecedent conditions include mycoplasma pneumoniae (5%); possibly Lyme disease, Hodgkin's disease, lung cancer, thyroid disease, SLE, paraproteinemia, and sarcoidosis.
7. GBS may possibly occur after surgery, trauma, and in the post-partum period.

#### IV. Pathogenesis<sup>1</sup>

- a. GBS pathogenesis is likely to be multifactorial, with complex interactions involving humoral and cellular immunity, complement deposition, cytokines, and other, yet identified, inflammatory mediators.
  - i. The animal model of GBS is experimental autoimmune neuritis (EAN).
    1. the inflammatory response in EAN is mediated by T cells directed against PNS myelin epitopes
    2. key immuno-pathogenetic occurrence is macrophage invasion and demyelination
  - ii. It has been suggested that T cells, activated by a preceding infection and are stimulated by antigen-presenting cells that express major histocompatibility class II antigens, cause a disruption of the blood-nerve barrier by the release of

inflammatory cytokines such as interleukin-2 and tumor necrosis factor.

1. released cytokines attract macrophages which invade nerves causing demyelination and Schwann cell injury.
- b. **Humoral factors** are also suspected to have a significant pathogenetic role in GBS.
- i. Experimental passive transfer studies have demonstrated that sera from GBS patients can cause nerve demyelination.
  - ii. A correlation between clinical severity and serum levels of complement fixing antimyelin antibodies has been demonstrated.
  - iii. C3d binding to motor nerve fiber axolemma has been demonstrated in GBS patients with prominent axonal loss.
  - iv. Clinical recovery after plasma exchange or IVIg has suggested that humoral factors play a prominent role.
  - v. If, and how, the varied immune processes affect the clinical and EDX findings remains uncertain.

## V. Clinical Features<sup>1</sup>

- a. **“Typical” GBS** is an acute, predominantly motor neuropathy involving distal limb paresthesias, relatively symmetric leg weakness, and frequent gait ataxia.
- i. Most cases will have subsequent arm weakness, and possibly weakness of facial, ocular, and oropharyngeal muscles.
- b. **Weakness** is always bilateral, although some asymmetry in onset and severity is common.
- i. Proximal muscles weakness very frequent, especially initially, with subsequent distal arm and leg weakness.
  - ii. GBS with a descending pattern of weakness seen in 14% cases; onset initially with cranial nerve or arm muscle weakness, followed by leg weakness.
  - iii. In 1/3 of cases, the degree of weakness in the arms and legs is roughly equal.
- c. **Reduced or absent reflexes characterize GBS.**
- i. Early loss of reflexes may be due to desynchronization of afferent impulses in reflex arc due to non-uniform demyelination.
  - ii. About 70% of patients present with loss of reflexes; less than 5% retained all reflexes during the illness;
  - iii. The presence of intact reflexes should suggest an alternative diagnosis other than GBS.
- d. **Sensory disturbance**
- i. >50% will present with symmetric distal limb paresthesias, before clinically evident limb weakness. Early finger paresthesias suggest a patchy process, unlike the pattern seen with distal axonopathies.
    1. paresthesias of trunk or face unusual, but sensory loss over the trunk frequent and a pseudolevel may be evident
      - a. beware if definite sensory level present as this may suggest structural cord disease

2. large diameter afferent modalities (JPS, vibration) are most severely affected.
3. an early sensory ataxia may not be obscured by concurrent limb weakness

**e. Pain**

- i. Some discomfort reported in 2/3 of patients which may take one of the following forms:
  1. deep muscle aching in back, hips or proximal legs,
  2. sharp radicular pain into the legs,
  3. severe burning dyesthetic pain in feet or hands.
- ii. Radicular pain can occasionally be a presenting complaint obscuring the true diagnosis.

**f. Cranial nerve involvement**

- i. 1/2 of GBS patients have some degree of cranial nerve dysfunction during their illness.
- ii. Facial weakness most common, especially if substantial limb weakness present.
  1. normal facial strength in the presence of marked quadriparesis very unusual in typical GBS.
  2. facial weakness usually bilateral but may be unequal in severity; only rarely truly unilateral.
- iii. Ophthalmoparesis seen in 10-20% of patients.
  1. abducens palsy most common; usually bilateral.
- iv. Oropharyngeal weakness present in almost 1/2 of cases increasing the risk of aspiration.
  1. rarely, patients with GBS may appear locked-in, due to paralysis of all cranial muscles, ventilatory failure, and flaccid paralysis.

**g. Respiratory dysfunction** due to diaphragmatic weakness occurs in about 1/3 of patients.

- i. Diaphragmatic weakness common in patients with severe quadriparesis; may also occur early on in patients with bibrachial weakness.
- ii. Patients with weakness of neck muscles, tongue and palate often have concomitant diaphragmatic and respiratory muscle involvement.
- iii. Pathogenesis of respiratory failure:
  1. atelectasis results from reduced vital capacity, inspiratory force and tidal volume due to diaphragmatic weakness.
  2. atelectasis worsened by impaired cough; result is arteriovenous shunting and hypoxia.
  3. the resultant tachypnea and increased work of breathing
  4. early reduction in CO<sub>2</sub> levels due to tachypnea, but with increasing weakness hypercarbia and respiratory arrest may occur

5. if diaphragmatic and respiratory muscle weakness has not occurred by 2 weeks into illness then assisted ventilation usually unnecessary.
6. patients requiring ventilator support have less favorable prognosis for neurologic recovery, have longer hospitalizations, and higher mortality.

#### **h. Dysautonomia**

- i. occurs in about 65% of cases
- ii. more frequent in patients with severe paralysis and ventilatory difficulties but may develop in mild cases.
- iii. Most common manifestations include cardiac dysfunction such as sinus tachycardia, sinus bradycardia, sinus arrest and other supraventricular arrhythmias, paroxysmal hypertension, and hypotension (especially postural),
- iv. ICU monitoring necessary because of possible cardiac complications.
- v. Other features: ileus, urinary retention (1/4 cases), inappropriate ADH, altered sweating, mild orthostatic hypotension.

### **VI. Variations of Typical Presentation<sup>1</sup>**

#### **a. Acute Motor and Sensory Axonal Neuropathy (AMSAN)**

- i. Initially described by Feasby as axonal GBS.
- ii. Characterized by acute quadriplegia, areflexia, distal sensory loss, and respiratory insufficiency.
- iii. CSF with increased CSF; EDX shows loss of motor and sensory potentials with diffuse active denervation. No evidence of primary demyelination
- iv. Postmortem evidence of diffuse axonal degeneration without associated inflammatory response, or demyelination.
- v. Condition now labeled acute motor-sensory axonal neuropathy (AMSAN)
  1. although thought to be a variant of GBS, it is clinical indistinguishable from severe, typical, mixed demyelinating GBS in which there is a substantial degree of axonal loss.
  2. AMSAN is usually severe with quadriplegia, respiratory insufficiency and delayed, incomplete recovery.
  3. EDX studies differentiate from typical GBS by showing evidence of only axonal degeneration, without demyelination.
    - a. Originally some controversy whether the inexcitable nerves were due to axonal degeneration or severe distal conduction block
    - b. Pathologic specimens have confirmed the presence of distal axonal degeneration, or severe radicular demyelination, with subsequent wallerian degeneration.

**b. Acute Motor Axonal Neuropathy (AMAN)**

- i. Originally described in patients from northern China, particularly children.
- ii. Characterized by acute/subacute onset of relatively symmetric limb weakness, diffuse areflexia, facial and oropharyngeal muscle weakness, and respiratory insufficiency.
- iii. Clinically purely motor deficits; normal EOMs.
- iv. Associated with gastric enteritis due to *C. jejuni* with elevated anti-GM1 and anti-GD1a antibodies to *C. jejuni*.
- v. EDX studies show evidence of motor axon loss sparing sensory fibers. No evidence of demyelination. Needle EMG shows diffuse denervation. Elevated CSF protein.
- vi. Postmortem studies correlate with EDX results, with diffuse motor axon degeneration without inflammatory response or evidence of demyelination.
- vii. Pathogenesis unclear; possible antibody and complement mediated attack at terminal motor nerve endings. Presence of macrophages in periaxonal space of myelinated internodes suggest pathogenetic role.
- viii. Occasionally, some patients make relatively rapid recovery, possibly due to reversible changes at nodes of Ranvier, or regeneration of intramuscular nerve endings.

**c. Miller-Fisher Variant**

- i. Classic triad of ophthalmoplegia, ataxia, and areflexia described by C. Miller Fisher in 1956
- ii. Occurs in about 5% of GBS cases
  1. some of what appears to be Fisher syndrome subsequently incorporate findings of typical GBS raising the possibility of a clinical spectrum between GBS and Fisher syndrome.
- iii. Diplopia usually initial symptom, followed by limb or gait ataxia.
- iv. Occasionally there may be mild sensory symptoms, swallowing difficulties, or proximal limb weakness in up to 1/3 or 1/2 of cases.
- v. abducens palsy usually initial EOM deficit, which may progress to complete ophthalmoplegia.
  1. ptosis frequent, but papillary function usually spared.
- vi. Limb and gait ataxia common, although possibly asymmetric limb involvement initially.
  1. limb ataxia may resemble that seen with cerebellar disease
- vii. Areflexia is usual.
- viii. Although CSF protein is mildly elevated, it is less so than in typical GBS.
- ix. EDX shows loss of sensory potentials, with milder axonal degeneration. Some studies have shown a demyelinating neuropathy, while others suggest purely an axonal process.
- x. May clinically resemble brainstem inflammatory or ischemic disease.

- xi. Elevated antibodies to GQ1b suggest an immune attack against GQ1b gangliosides which are concentrated in the paranodal regions of extraocular nerves.
  - 1. Typical GBS with ophthalmoplegia also display elevated antibodies to GQ1b.
  - 2. Motor nerve terminal blockade suggested as explanation for the generalized weakness; supported by experimental evidence showing that sera with anti-GQ1b antibodies cause reversible failure of ACh release from presynaptic motor nerve terminals.

**d. Pure Motor Variants**

- i. Acute, progressive, symmetric limb weakness, no sensory loss, areflexia.
- ii. 18% cases in one series; 3% in another.
- iii. Dx suggested by acute, predominantly distal limb weakness, normal cranial nerve function, and elevated anti-GM1 titers due to preceding *C. jejuni* infection.
- iv. Course and recovery similar to typical GBS.
- v. CSF protein elevated.
- vi. EDX shows marked axonal degeneration with some accompanying demyelinating features.
- vii. Differential Dx: poliomyelitis, porphyria, acute fulminant myasthenia gravis, tick paralysis.

**e. Pure Sensory Variants**

- i. Rare occurrence of acute sensory polyneuropathy with elevated CSF protein, and demyelinating features on EDX studies.
- ii. Rapid onset of large fiber sensory loss with resultant sensory ataxia.
- iii. Positive Romberg sign, pseudoathetosis, tremor, lesser involvement of small fiber sensory function; dysautonomia.
- iv. Sensory dysfunction may involve the face and torso in severe cases.
- v. Differential Dx: cervical myelopathy, malignant and non-malignant sensory neuronopathy, Sjogren's syndrome, ciguatera poisoning.

**f. Pure Dysautonomia Variant**

- i. Acute dysautonomia considered to be a rare variant of GBS.
- ii. Initial symptoms usually GI, such as abdominal pain, vomiting, and constipation or diarrhea. Possible hx of preceding viral infection.
- iii. Possible gastroparesis with abdominal distention and ileus.
- iv. Orthostatic hypotension and syncope may be disabling.
- v. Other associated deficits include erectile dysfunction, urinary urgency or retention, and vasomotor instability.
- vi. Characteristically, limbs are strong, although areflexia and mild distal sensory symptoms may be evident.

- vii. Routine EDX studies are normal; autonomic testing such as heart rate variability, tilt-table testing, sympathetic skin responses, and sweat testing (QSART) may be abnormal.
- viii. Syndrome characteristically progresses and then plateaus after few weeks
- ix. About ½ recover slowly after several months.

**g. Pharyngeal-Cervical-Brachial Variant**

- i. Regional GBS variant affecting cervical, brachial or oropharyngeal muscles exclusively.
- ii. Possible high titers to GT1a antibodies.
- iii. May have initial severe involvement of pharyngeal and neck muscles with later spread to limbs after several weeks; leg muscles may be entirely spared.
- iv. Severe facial weakness, ptosis and ophthalmoparesis may mistakenly suggest myasthenia gravis.
- v. CSF protein elevated.
- vi. EDX may be normal, or show demyelinating changes in upper limbs.
- vii. Delayed and, at times, incomplete recovery.

**h. Paraparetic Variant**

- i. Regional variant with isolated leg weakness and areflexia.
  - 1. upper limbs, cranial nerves and sphincters spared.
  - 2. radicular pain common
- ii. CSF protein elevated.
- iii. EDX shows demyelinating changes in lower limb nerves. MRI of spinal cord and lumbar roots to exclude lesion of distal cord and cauda equina is suggested.

**i. Other less common variants**

- i. Acral paresthesias with diminished reflexes in either arms or legs.
- ii. Facial diplegia or abducens palsies with distal paresthesias
- iii. Isolated postinfectious ophthalmoplegia.
- iv. Bilateral foot-drop with upper limb paresthesias.
- v. Acute ataxia without ophthalmoplegia.

**VII. Differential Diagnosis<sup>1</sup>**

**a. Acute peripheral neuropathies**

- i. Toxic: thallium, arsenic, lead, n-hexane, organophosphate
- ii. Drugs: amiodarone, perhexiline, gold
- iii. Alcohol
- iv. Porphyria
- v. Systemic vasculitis
- vi. Poliomyelitis
- vii. Diphtheria
- viii. Tick paralysis
- ix. Critical illness polyneuropathy

**b. Disorders of Neuromuscular Transmission**

- i. Botulism

- ii. Myasthenia gravis
- c. **Central Nervous System Disorders**
  - i. Basilar artery occlusion
  - ii. Acute cervical transverse myelitis

### VIII. Electrodiagnostic Studies<sup>1</sup>

- a. Diagnostic in 95% cases
- b. May be normal early on perhaps reflecting involvement of proximal nerve segments not accessible to conduction studies.
- c. Nature and severity of physiologic findings dependent on timing of study, number of nerves studied, and whether proximal nerve segments investigated.
- d. Typically, there is multifocal demyelination affecting proximal and distal nerve segments.
  - i. Earliest findings may be abnormalities of F waves and H reflex latencies. Prolonged or absent F waves may be initial sole abnormality in about 30-50% of cases studied.
  - ii. Conduction block in about 1/3 of cases; conduction slowing and temporal dispersion reflect demyelination.
- e. Evidence of sensory axon demyelination seen in about 25% of cases when studied in the first week, increasing to 75% after 3 weeks.
- f. Characteristic pattern is abnormal median and ulnar sensory potentials with spared sural potentials, reflecting random, multifocal demyelination.
- g. Most common needle EMG finding is reduced voluntary motor unit recruitment.
  - i. Active denervation present in 20-64% of cases by week 4.
  - ii. Myokymia, reflecting demyelination, occasionally present.
- h. Severe axonal GBS will show diffuse loss of sensory and motor responses with widespread active denervation.
  - i. Occasionally, patients that appear to have inexcitable nerves early on eventually show substantial clinical and physiologic recovery reflecting remyelination of distal nerve segments.
- i. Most important predictor of recovery is the degree of axonal degeneration, best reflected by the amplitude of the compound muscle action potential.
  - i. Motor potentials with amplitudes less than 20% normal suggest a prolonged, and often incomplete recovery.
  - ii. No correlation between the degree of conduction slowing and eventual recovery.
  - iii. Electrophysiologic evidence of demyelination may persist for years, despite adequate clinical recovery.

### IX. CSF<sup>1</sup>

- a. CSF protein levels elevated without accompanying pleocytosis in 80-90% of patients with GBS.
- b. Pleocytosis ( $>10$  cells/mm<sup>3</sup>), usually lymphocytic, present in about 10%.
- c. CSF in Lyme or HIV disease may have pleocytosis reflecting concurrent meningeal reaction.

- d. Protein concentration peaks in 2<sup>nd</sup> to 3<sup>rd</sup> week followed by slow decline toward normal that may take several months.
  - i. Patients may have normal CSF protein in first week.
- e. Elevated protein may be due to leaky blood-CSF barrier due to spinal nerve root inflammation.
- f. High protein levels (e.g. 1,500 mg/dl) may be associated with papilledema and pseudotumor cerebri.
- g. No correlation between CSF findings, clinical findings, EDX results, or clinical outcome.

## **X. Treatment and Management<sup>1</sup>**

### **a. Supportive Care**

- i. ICU monitoring
- ii. Basic medical management often determines mortality and morbidity.

### **b. Ventilatory Support**

- i. Atelectasis leads to hypoxia.
- ii. Hypercarbia later finding; arterial blood gases may be misleading.
- iii. Vital capacity, tidal volume and negative inspiratory force are best indicators of diaphragmatic function.
- iv. Progressive decline of these functions indicate an impending need for ventilatory assistance.
  - 1. mechanical ventilation usually required if VC drops below about 14 ml/kg; ultimate risk depending on age, presence of accompanying lung disease, aspiration risk, and assessment of respiratory muscle fatigue.
- v. Atelectasis treated initially by incentive spirometry, frequent suctioning, and chest physiotherapy to mobilize secretions.
- vi. Intubation may be necessary in patients with substantial oropharyngeal dysfunction to prevent aspiration.
- vii. Tracheostomy may be needed in patients intubated for 2 weeks who do not show improvement.

### **c. Autonomic dysfunction**

- i. Autonomic dysfunction may be self-limited; do not over-treat.
- ii. Sustained hypertension managed by angiotensin-converting enzyme inhibitor or beta blocking agent. Use short acting intravenous medication for labile hypertension requiring immediate therapy.
- iii. Postural hypotension treated with fluid bolus or positioning.
- iv. Urinary difficulties may require intermittent catheterization.

### **d. Nosocomial infections** usually involve pulmonary and urinary tracts.

- i. Occasionally central venous catheters become infected.
- ii. Antibiotic therapy should be reserved for those patients showing clinical infection rather than colonization of fluid or sputum specimens.

### **e. Venous thrombosis** due to immobilization poses great risk of thromboembolism.

- i. Subcutaneous heparin or intermittent pneumatic compression boots should be used.
- f. **Nutritional support** via nasogastric tube needed in patients who are intubated or have significant oropharyngeal weakness.
  - i. Hyperalimentation may be necessary in patients with ileus.
  - ii. Observe for inappropriate ADH.
- g. **Immune therapy**
  - i. **Plasma exchange (PE)** demonstrated to be beneficial if instituted within two weeks of illness.
    - 1. in North American study, treated patients improved more rapidly and regained ability to walk earlier.
      - a. Ventilator treated patients were weaned earlier with PE.
    - 2. even patients with with poor prognostic features showed some benefit from PE.
    - 3. efficacy of PE reduced if initiated after 3 weeks.
    - 4. improvement may occur in mild GBS with as few as 2 exchanges, but most require a minimum of 4 exchanges performed on alternate days.
    - 5. PE appears beneficial in typical GBS, and most variants of GBS.
  - ii. **Intravenous immunoglobulin (IVIg)**
    - 1. When compared to PE, IVIg shown to be as efficacious as PE and with few adverse effects (Sandoglobulin trial).
    - 2. No benefit to combined PE and subsequent IVIg over either alone.
    - 3. Mechanism of IVIg improvement not completely understood.
      - a. neutralization of proinflammatory cytokines
      - b. down regulation of pathogenic antibodies
      - c. modulation of Fc receptor-mediated phagocytosis
      - d. inhibition of complement deposition
      - e. promotion of remyelination
    - 4. side effects
      - a. headache most common
      - b. transient fever, serum sickness reaction, aseptic meningitis, elevated LFTs and WBCs, acute renal tubular necrosis, hypercoagulable state with risk myocardial infarction or stroke
      - c. anaphylaxis may occur in patients with IgA deficiency if IgA rich IVIg administered.
      - d. transmission of hepatitis C reported, but not HIV.
    - 5. relapse rate about 10% which is similar to PE
- h. **Corticosteroids** initially thought to be ineffective, especially prednisone

- i. Few reports of intravenous high-dose corticosteroid responsiveness, particularly after worsening during or after PE or IVIg.

## **XI. Prognosis<sup>1</sup>**

- a. Majority have progressive illness with nadir of clinical deficits at 4 weeks.
  - i. 3/4 reach nadir by 1 week.
- b. 15% have mild illness, remain ambulatory, and recovery after few weeks.
- c. 5-20% have fulminant course, develop flaccid paralysis, ventilator dependence, and axonal degeneration.
  - i. Such patients have delayed and incomplete recovery.
- d. Residual deficit: about 1/3 of cases require ventilator assistance, 1/2 are either chair or bed bound, and 7% have trouble walking. The remainder are ambulatory.
- e. Recovery at 1 year follow-up: 62% had recovered completely, 14% could walk but not run, 9% could not walk without assistance, 4% remained bed bound or ventilated, 8% died.
- f. Poor prognostic features
  - i. age greater than 60
  - ii. history of preceding diarrhea illness
  - iii. recent CMV infection
  - iv. fulminant and rapidly progressive course
  - v. ventilator dependence
  - vi. greatly reduced CMAP amplitudes or inexcitable nerves
- g. Mortality about 5-10% with aggressive ICU care.
- h. About 3-6% of patients with typical GBS have developed a chronic relapsing course consistent with CIDP.
  - i. No distinguishing features.
  - ii. Most relapses responsive to steroids.

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