

The Guillain-Barré Syndrome

A subacute onset of areflexic paralysis with recovery accompanied by acellular cerebrospinal fluid with an elevated protein was described in two soldiers in 1916 by the French neurologists Georges Guillain, Jean-Alexandre Barré, and Andre Strohl. The eponym Guillain-Barré Syndrome (GBS) covers a spectrum of presentations and pathologies.

Classification (see Figure 1)

Classification is according to clinical features; time course, predominance of sensory or motor involvement, and involvement of cranial nerves.¹ Nerve conduction usually distinguishes between demyelination and primary axonal degeneration, but the timing of nerve conduction studies is important - indices may be normal in the very early stages and when the illness is very advanced the nerves may be unexcitable. By definition the onset phase (the time from first to worst symptoms) in GBS is less than four weeks. Classification of variants based upon antibody profile rather than clinical features and neurophysiology has been proposed.²

Epidemiology

Worldwide, the incidence of GBS is 0.6-4.0 per 100,000. Men are 1.5 times more likely to be affected. In the West,

incidence increases with age, but in China the incidence of all forms across age groups is more uniform. Acute motor axonal neuropathy (AMAN) is the commonest form in China and shows a marked seasonal variation and paediatric predominance;³ elsewhere, cases are mostly sporadic but clusters and epidemics do occur, often in association with outbreaks of bacterial enteritis. Rabies vaccination (which contains brain material) is followed by GBS in about one in a thousand cases. There may be a very small increase (one per million over background) in risk of GBS after influenza vaccination. A small proportion of patients report symptom recurrence after routine immunisation but relapse is rare.⁴ Evidence of preceding *Campylobacter jejuni* infection is found in about 25% of GBS cases. Cytomegalovirus and Epstein-Barr virus occur in about 10% of cases.⁵

Pathogenesis¹

Antibodies generated by the immune response to infection and directed against neural epitopes (the molecular mimicry hypothesis) may be the basis of axonal GBS and Miller-Fisher Syndrome (MFS). Strains of *C jejuni* which trigger GBS are more likely to possess lipo-oligosaccharide epitopes similar to gangliosides GM1, GD1a or



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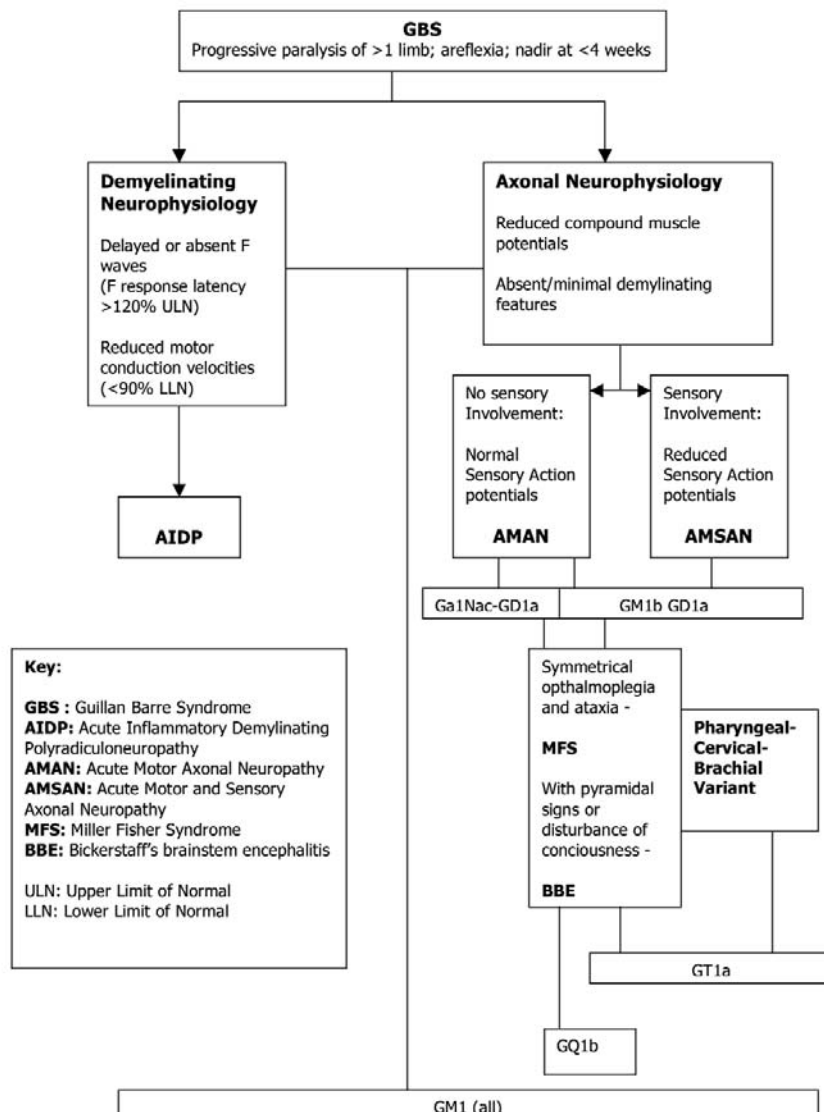


Figure 1: Clinical and neurophysiological classification of GBS and variants showing antibody associations.

Figure 2: Differential diagnosis of GBS

Syndrome	Aetiology	Suggestive Features
Brainstem	Stroke Encephalitis	Cranial nerve involvement Encephalopathy Upper motor neurone signs
Myelopathy	Acute compressive lesion Myelitis	No signs or symptoms above neck Sensory (and motor) level Sphincter involvement Localising symptoms and signs Inflammatory CSF
Anterior Horn	Poliovirus Other enteroviruses	Endemic area. Typically in children. Acute febrile illness. Meningism. Asymmetric paresis Absence of sensory involvement
Peripheral Neuropathy	Diphtheria Lyme disease Porphyria Vasculitis Lymphoma Paraneoplastic HIV sero-conversion Toxic	Palatal palsy, bulbar dysfunction. Cellular CSF. Raised CSF protein Exposure, headache, arthralgia, erythema migrans rash, facial weakness Abdominal pain, psychiatric illness. Lymphocytic CSF Systemic disease, rash, painful. No systemic markers if vasculitis is confined to peripheral nerves Systemic disease. Rash. Elevated ESR. Lymphocytic CSF large fibre involvement A form of GBS. Recent exposure. Mild lymphocytic pleocytosis. Probably under-diagnosed Sub-acute axonopathy. Exposure (could be iatrogenic / occupational / environmental / intentional)
Neuromuscular junction	Myasthenia Botulism	Absence of sensory symptoms or signs Bowel symptoms, dysphagia, autonomic features, mydriasis, pure motor
Muscle	Inflammatory myopathy Hypokalaemic periodic paralyses	Reflexes may be preserved. Very elevated CK Episodic. Inherited (AD). May wake with weakness. Cranial nerves typically spared

GQ1b. These antigens seem to induce neuropathy-causing ganglioside antibodies in animal models. The titre of anti-GQ1b correlates with disease severity in MFS, and GQ1b ganglioside is concentrated in nerves supplying extra-ocular muscles.

The pathophysiology of the more common acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is less well understood. T cells appear to play an important part in inducing macrophage attack against Schwann cells or myelin. The correlation between neurophysiology and clinical and immunological markers is only approximate.

Presenting features and diagnosis

Although GBS is generally considered a straight-forward diagnosis by neurologists, multiple physician assessments prior to correct diagnosis are common.⁶ Patients may have been screened and signs matured by the time they reach neurological evaluation. In a casualty case series, less than 50% of patients had weakness as their main complaint, with a

minority presenting with the 'typical' symptoms of weakness and numbness. One fifth presented initially with only sensory complaints.⁶

Whilst most patients presenting with an acute flaccid paralysis will have GBS, the differential is wide. GBS is a clinical diagnosis, and in practice, investigations are employed to exclude alternative possibilities. (See Figure 2)

Management

i) Supportive⁷ (see Figure 3)

There are no studies specifically addressing thromboprophylaxis in GBS, however this is an important aspect of supportive care.

Dysautonomia - which includes paralytic ileus and bronchial dysfunction as well as instability of pulse and blood pressure - occurs in 20% of patients with GBS. Wide blood pressure swings may augur severe bradycardia, which can precede asystole.

These complications occur mostly in severely affected patients with generalised weakness and respiratory failure.

Neuromuscular respiratory insufficiency ensues in 17-30% of patients with GBS. Accumulating secretions secondary to bulbar and bronchial mucosal dysfunction may further compromise gas-exchange. Rapid progression and pattern of involvement signal risk of respiratory compromise,⁸ (see Figure 4).

Pain occurs in 90% of patients with GBS and at least six types of pain have been identified⁹ (see Figure 3). Commonly, sensory symptoms exceed the signs. Neurogenic pain may arise from the loss of inhibition of the substantia gelatinosa by larger myelinated fibres and from small unmyelinated C fibres. Radicular pain and meningeal irritation may be secondary to inflammation of spinal nerve roots. Weakness of paraspinal muscles may result in mechanical back pain. Rate related cardiac ischaemic pain and discomfort from constipation and urinary

Figure 3: Important aspects of supportive management in GBS

Thromboprophylaxis	Dysautonomia	Neuromuscular respiratory and bulbar compromise	Pain	Early rehabilitation
<ul style="list-style-type: none"> Low molecular weight heparin Compression stockings 	2-4 hourly monitoring of: <ul style="list-style-type: none"> Blood pressure Pulse (increase frequency depending upon severity and rate of progression. Cardiac monitor if non-ambulant.) Daily urine output 	<ul style="list-style-type: none"> Vital capacity - 12 hourly Respiratory rate - 2-4 hourly (increase frequency if deteriorating or evidence of respiratory distress (see Figure 4)) Daily assessment of facial strength and swallow Daily assessment of limb and neck strength 	Identify type of pain(s) <ul style="list-style-type: none"> Consider: Dysesthetic, radicular, meningitic, myalgic, arthralgic, visceral Choose simple analgesic or anti-neuropathic agent as appropriate. 	<ul style="list-style-type: none"> Mobilisation Prevent formation of contractures - splints Bed sore prevention Nutrition

Figure 4: Predictors of mechanical ventilation and warning signs of respiratory failure in GBS

Risk factors for mechanical ventilation	Warning signs of impending respiratory failure
<ul style="list-style-type: none"> • Rapid progression • Weak cough • Bilateral weakness • Inability to stand • Inability to lift elbow off bed • Inability to lift head off bed • Chest radiograph abnormalities • Elevated liver enzymes • Vital Capacity <20ml/Kg 	<ul style="list-style-type: none"> • Tachypnoea • Tachycardia • Sweating • Use of accessory muscles • Asynchronous movements of chest and abdomen • Rapidly declining vital capacity or vital capacity <50% of baseline or vital capacity approaching 15ml/Kg

retention could be mis-interpreted as radicular pains. Both carbamazepine and gabapentin are effective in reducing pain scores and requirement for opioid analgesia in GBS patients. Gabapentin seems to have a quicker onset and be most effective.¹⁰ Amitriptyline is also frequently used.

ii) Immunotherapy

When given to non-ambulant patients within four weeks of presentation, intra-venous immunoglobulin (IVIg) and plasma exchange (PE) have a similar efficacy both in terms of disability measured one month after treatment and long term outcome.¹¹ IVIg is usually used (0.4g/Kg body weight /day for five days) because of convenience despite the theoretical risk of transmission of virus or prion. IVIg may work by multiple mechanisms, including blocking Fc receptors, provision of anti-ideo-typic antibodies, interference with complement activation and T-cell regulation.

Monoclonal antibodies show promise as

future treatments. Eculizimab disrupts the complement cascade, protecting terminal motor nerves from anti-GQ1b antibody induced injury.¹²

Rehabilitation and outcome

Death or severe residual disability occurs in up to 17% of patients, and lesser degrees of disability and fatigue are common in the remainder; 35 to 45% report persisting adverse changes in their employment, domestic function and leisure activities.¹³ Outlook is poorer in the elderly, in those with previous diarrhoea, rapid onset, severe deficit at nadir, initial axonal involvement, unexcitable motor nerves, and C jejuni or CMV infection.⁵ One Chinese study with a large population of children showed no difference in recovery time between AMAN and AIDP, with a median time to regain the ability to walk with assistance being one month.³

Although 40% of patients require inpatient rehabilitation, there is a paucity of systematic research of rehabilitation strategies in GBS.

Medium term complications to be aware of in the rehabilitation setting include decubitus ulcers, peripheral nerve compression, hypercalcaemia, and disturbed central respiratory drive secondary to persistent ventilatory compromise.¹⁴ Decreased range of movement in joints may be caused by contractures, muscle injury, pain, thrombosis, fractures and heterotopic ossification (of which elevated alkaline phosphatase is a useful indicator).¹⁵ Patients should be advised that over-exercise may lead to paradoxical weakening.

Future directions

The clinical phenotype of GBS is likely to be due not only to the immunogenic components of the infecting organism, but also the host immune response and distribution of epitopes. Examination of the immune response in GBS variants will allow the development of more targeted therapies such as complement inhibition, anti-cytokine therapy and specific antibody adsorption.¹

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