

Guillain-Barré Syndrome: Clinical Spectrum and Therapeutic Possibilities

Guillain-Barré syndrome (GBS) is the foremost cause of post-infectious neuromuscular paralysis worldwide, with a global incidence of $\sim 1.5/10^5$ spread across all age groups [Hughes and Cornblath 2005]. The lifetime likelihood of any one individual acquiring the disease is approximately 1 in 1000. Onset is rapid, and in $\sim 20\%$ of cases leads to total paralysis, occasionally requiring prolonged intensive care and mechanical ventilation. There remains a need to fully understand GBS pathogenesis as a prerequisite to developing effective contemporary immunotherapies. The therapeutic window for GBS is short and the current optimal treatment with whole plasma exchange (PE) or intravenous immunoglobulin (IVIg) therapy only halves disease severity. These approaches lack immunological specificity, and it is hoped that therapies directed against specific immunological targets will result in improved treatment efficacy.

Patterns of disease

The clinical presentation of progressive, relatively symmetrical motor weakness developing rapidly to peak within four weeks of onset is well known to all neurologists. Sensory symptoms and signs are common, but generally mild. Cranial nerves are frequently affected, especially the facial nerve. Although areflexia is generally the rule, it may not be fully developed at presentation, and reflexes may occasionally be preserved, especially in variant forms of GBS. Autonomic features affecting cardiac, bowel and bladder function may be present. Acute inflammatory demyelinating polyneuropathy (AIDP), by far the commonest form of GBS, arises from segmental demyelination of the peripheral nerves. This is executed in part by macrophage-mediated stripping of the myelin sheath triggered by antibody and complement deposition on Schwann cell and myelin membranes [Hafer-Macko et al. 1996b]. The role of other inflammatory factors including T cells, nitric oxide and other soluble mediators is

unknown in the human disease, but supported by some experimental evidence. The primary antigenic target(s) for immune attack in AIDP remains unknown, despite considerable research effort. In AIDP, demyelination may be extensive throughout the length of the nerve, but is especially prominent in proximal nerve roots and the distal intramuscular nerve segments where the blood nerve barrier (BNB) is weak. Axons are generally unaffected in AIDP, although may suffer so-called bystander injury, the mechanisms for which remain unclear.

In the GBS variant, acute motor (and sensory) axonal neuropathy (AMAN, AMSAN), the primary target is the motor and/or sensory nerve axolemmal membrane [Feasby et al. 1986]. Patients present with pure motor weakness and denervation atrophy often becomes evident as the illness evolves. In AMSAN, sensory symptoms and signs are also present. In AMAN, the inflammatory process occurs predominantly either in the nerve roots or distal nerve terminals [Hafer-Macko et al. 1996a; Ho et al. 1997]. Immune attack can lead to reversible axonal conduction block due to reversible axonal injury, or complete axonal transection. The relative extent of each of these processes is likely to dictate the clinical outcome, which will be especially poor if axonal transection occurs proximally at the level of nerve roots. Wallerian degeneration will occur distal to the site of axonal transection, but otherwise myelin is unaffected. AMAN is highly associated with anti-ganglioside antibodies to GM1a, GM1b, GD1a, and GalNAc-GD1a [Ho et al. 1999; Ogawara et al. 2000]. Representative structures are shown in Figure 1. In addition, intriguing new evidence suggests ganglioside complexes composed of two interacting gangliosides might form important antigenic targets [Kaida et al. 2004; Kaida et al. 2006].

The regional variants of GBS only paralyse specific areas of the body, such as the eyes or face, or the afferent sensory and autonomic systems [Ropper 1994]. The most widely studied of these variants is the Miller Fisher syndrome (MFS), the pathogenesis of which was advanced



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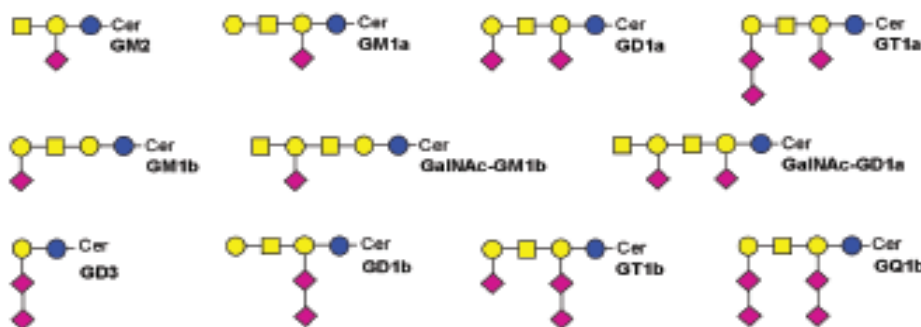


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A. Ganglioside targets in GBS



B. *Campylobacter jejuni* species and LOS structures

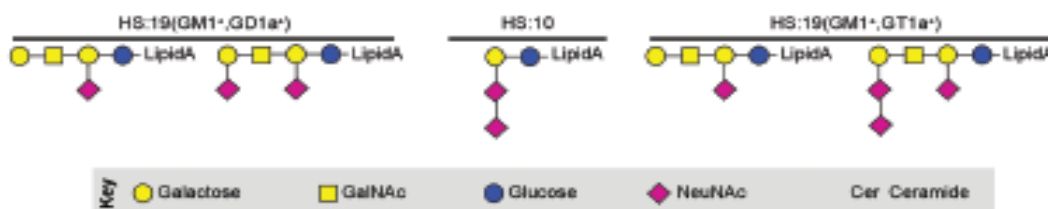


Figure 1: Representative examples of ganglioside and lipooligosaccharide structures targeted by anti-ganglioside antibodies in GBS.

greatly by the discovery of the anti-GQ1b antibody marker [Chiba et al. 1992]. Anti-GQ1b antibody testing has allowed investigators to identify closely related 'forme frustes', including varying degrees of acute cranial motor neuropathy with or without ataxia, but associated with anti-GQ1b antibodies (the 'anti-GQ1b antibody syndromes'), and the pharyngeal-cervical-brachial variant closely associated with anti-GT1a IgG (which is structurally similar to anti-GQ1b, and often cross-reacts with it). The selective affliction of cranial and in particular extraocular nerves in the anti-GQ1b antibody syndromes is believed due to enrichment of the target antigen(s) in affected sites.

Electrophysiological findings

Where there is clinical doubt, electrophysiological findings are often very helpful in classification of GBS subtypes. Strict criteria have been set for research purposes. Importantly, electrophysiological patterns may evolve during the course of the illness, and may even be normal early in the course of AIDP. Repeat examination is thus often helpful. The characteristic electrophysiology of AIDP is of delayed or absent F waves (indicating proximal conduction slowing or block), reduced motor conduction velocities with temporal dispersion and prolonged distal motor latencies. Compound muscle action potential (CMAP) amplitudes may be reduced. Small, but otherwise well formed CMAPs, in the absence or marked paucity of demyelinating features are characteristic of AMAN. When nerves are completely inexcitable, classification into AIDP or AMAN is not possible. Sensory nerve action potential amplitudes may be reduced or absent in AIDP, AMSAN and MFS, but are (by definition) normal in AMAN.

Gangliosides and preceding infections

A wide range of infections are recognised as precipitating GBS. The discovery of ganglioside and glycolipid mimics on *Campylobacter jejuni* lipooligosaccharide (LOS) has led to a unifying view of molecular mimicry as the critical underlying concept in GBS [Yuki 2001]. Structures are shown in Figure 1. Both *Haemophilus influenzae* and *Mycoplasma pneumoniae* that often precede GBS also express glycolipid mimics. There are many structurally distinct gangliosides and other glycolipids in nerve that are synthesised in complex developmental, spatial and cell specific patterns [Kolter et al. 2002]. Some *Campylobacter* species express similar biosynthetic genes and thereby generate similar glycan structures to gangliosides [Godschalk et al. 2004]. Evidence from human and animal studies indicates a key role for this molecular mimicry in GBS pathogenesis [Bowes et al. 2002; Goodfellow et al. 2005; Goodyear et al. 1999], but in clinical practice specific infective triggers often fail to be identified, just as the antigenic targets that such putative triggers mimic remain elusive.

The mechanisms of nerve injury induced by anti-ganglioside antibodies

Anti-ganglioside antibodies could potentially bind any ganglioside-containing membranes, provided that they can gain access and binding

is not subject to steric inhibition locally in the membrane. Potentially important axonal and glial sites of injury are the ganglioside-dense axolemma at nodes of Ranvier and paranodal myelin in spinal roots and pre-synaptic nerve terminals - both sites are relatively unprotected by the blood nerve barrier and thus accessible to circulating antibodies. Considerable human and animal data support these as key sites of injury [Willison and Yuki 2002; Yuki 2005].

It is clear that complement activation with membrane attack complex (MAC) formation drives at least part of the neural membrane injury in animal models of GBS and in humans, as elucidated from autopsy and biopsy tissues. [Halstead et al. 2004; Lu et al. 2000]. It would thus appear likely that blocking MAC formation locally should prevent MAC-dependent tissue injury, even if anti-ganglioside antibody is deposited on the membrane. One therapy that has been used to investigate this is the complement inhibitor, APT070, comprising the C3/C5 convertase inhibiting region of CR1 [Halstead et al. 2005]. Antibody neutralisation or removal using therapeutic immunoabsorption columns studded with relevant glycan epitopes are another attractive possibility that might supplement traditional plasma exchange [Willison et al. 2004]. These approaches both represent possible future directed and specific therapeutic interventions in GBS.

Prognosis and treatment

Gratifyingly, the majority of patients with all forms of GBS recover well, with 80% of affected patients walking independently by one year after onset. Recovery may continue for a considerable time (several years) in severely affected cases with extensive axonal degeneration, and a small proportion of cases are left permanently chair or bed-bound. Older age, rapid speed of onset, severe weakness at the peak of the illness and intercurrent illnesses (including complications of GBS) are all poor prognostic factors. Death is uncommon (5% or less). The mainstay of treatment is meticulous care to rapidly identify and avoid or treat the complications of bulbar and respiratory failure, autonomic dysfunction and motor debility. The role of both plasma exchange and intravenous immunoglobulin has been well documented, and either treatment, when administered within 2 weeks of diagnosis, approximately halves the number of patients requiring ventilation and doubles the speed of recovery. There is no evidence for any added benefit of combination therapy, and corticosteroids are ineffective.

Conclusions

Whilst MFS and AMAN have been partially solved pathophysiologically, progress is most especially needed in the search for the putative AIDP antigen(s) and antibodies. It is ironic that AIDP, the common form of GBS that is easily recognised by most neurologists, is considerably less well understood from a pathogenic perspective than its rarer variants. The optimisation of acute therapy is paramount in GBS, because it is unlikely to ever be preventable. An important consequence of identifying antibodies as the

main pathogenic mediators of GBS is that such knowledge should direct therapeutic approaches towards blockade of antibody-mediated effector pathways, such as complement inhibition or B cell suppression. Therapeutic progress in the GBS field is confounded by the fact that large trials are complex and time consuming to organise and execute. This reinforces the need to make rational choices for novel immunotherapy testing.

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