Guillain–Barré syndrome and *Campylobacter jejuni* infection

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1. SUMMARY

Guillain–Barré syndrome (GBS) is the most common cause of acute neuromuscular paralysis, usually due to acute inflammatory demyelinating polyradiculoneuropathy. The presence of activated T lymphocytes and antibodies against peripheral nerve myelin suggests an autoimmune pathogenesis, although there is wide heterogeneity. Gangliosides are sialylated glycolipids widely distributed in nervous system membranes. GBS is usually preceded by an infection, most frequently *Campylobacter jejuni* enteritis, but also cytomegalovirus, *Mycoplasma pneumoniae* or Epstein–Barr virus. Patients with GBS and *C. jejuni* infection are more likely to have neurophysiological features of axonal neuropathy, antibodies to ganglioside GM1, pure motor GBS, a less elevated CSF protein concentration and a worse outcome than other GBS patients. Although molecular mimicry between peripheral nerve gangliosides and epitopes present on *C. jejuni* lipopolysaccharide could explain some of these associations, this hypothesis is inadequate to account for many aspects of the pathogenesis of GBS.

2. INTRODUCTION

Guillain–Barré syndrome (GBS) is characterized by temporary paralysis due to acute autoimmune inflammatory polyradiculoneuropathy. It is usually preceded by an infection, the commonest of which is *Campylobacter jejuni* enteritis. Patients with *C. jejuni*-associated GBS are more likely to have antibodies to ganglioside GM1, neurophysiology suggesting axonal neuropathy and a worse outcome than GBS preceded by other infections.

3. GUILLAIN–BARRÉ SYNDROME

3.1. Clinical features

Guillain–Barré syndrome is defined clinically by progressive weakness of two or more limbs due to neuropathy, reduced or absent tendon reflexes, $< 50$ mononuclear leucocytes per $\mu l$ cerebrospinal fluid (CSF), and absence of other known causes of acute neuropathy (Asbury and Cornblath 1990). The duration of worsening of disease was later arbitrarily defined as less than 4 weeks to distinguish GBS...
from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Symptoms typically begin with weakness, sensory disturbance or pain, and most patients develop rapidly progressive symmetrical weakness, worse in legs than arms (Winer et al. 1988b). Weakness classically follows an ascending temporal pattern, starting in the lower limbs and then spreading to involve upper limbs and cranial nerves, but other patterns are recognized. Most patients have numbness, tingling and pain, and many have bladder disturbance, facial weakness and difficulty swallowing (Hughes 1990). The CSF protein concentration is elevated in 80% of patients. Autonomic disturbance is common, with fluctuations in blood pressure, heart rate and bowel function. Weakness is usually maximal 1–2 weeks from onset, when approximately 20% of patients require artificial ventilation because of respiratory muscle weakness, 40% are bedbound, 20% can walk only with assistance, 10% can walk but not run, and 10% have only mild symptoms.

Several variant patterns are recognized, although there is considerable overlap. Pure motor GBS occurs in 18% of patients, who tend to have predominantly distal weakness and sparing of the cranial nerves (Visser et al. 1995). The Fisher syndrome is characterized by ophthalmoplegia, ataxia and areflexia, and probably caused by selective involvement of the ocular motor and subsets of afferent nerve fibres.

3.2. Pathology

The pathology of most European cases of GBS is perivascular multifocal lymphocytic infiltration with demyelination (Asbury et al. 1969), termed acute inflammatory demyelinating polyradiculoneuropathy (AIDP). Macrophages penetrate the Schwann cell basal lamina and strip myelin lamellae. An axonal form of GBS without inflammation or demyelination has been particularly studied in China where acute motor axonal neuropathy (AMAN) is as common as AIDP (Ho et al. 1995). Severe axonal degeneration may be secondary to primary autoimmune attack on either axon or myelin.

3.3. Epidemiology

The median incidence of GBS was 1.3 per 100 000 per year (range 0.4–4.0) in a review of 35 epidemiological series throughout the world (Hughes and Rees 1997). It may occur at any age but becomes more frequent with increasing age, possibly due to failure of suppression of autoimmunity. It is slightly more common in males than females by a factor of about 1:25, in contrast to the female preponderance in most other autoimmune diseases.

Guillain–Barré syndrome is rarely triggered by immunizations, of which the only proven associations are with rabies vaccines derived from animal brains (no longer used), the 1976 batch of 'swine' influenza vaccine, and possibly one in a million recipients of modern influenza vaccine.

4. AUTOIMMUNE PATHOGENESIS OF GUILLAINE–BARRÉ SYNDROME

4.1. Preceding infections

There is an increased incidence of certain infections in the weeks before onset of GBS. Most patients describe influenza, a respiratory infection or diarrhoea, although the organism is positively identified in only about half. The infecting organism has usually been eliminated from the body when neurological symptoms start and is rarely isolated directly. Different serological studies have shown the occurrence of Campylobacter jejuni enteritis in 13–72% of patients with GBS (Table 1), cytomegalovirus (CMV) infection in 5–22%, Mycoplasma pneumoniae in 5% and Epstein–Barr virus (EBV) in 2–10% (Winer et al. 1988a; Hao et al. 1998; Jacobs et al. 1998). Because all these infections (and IgG antibodies to them) are very common in the general population, it may be difficult to distinguish acute from previous infection, and part of the variability in estimates is due to differing specificities of each assay method.

Patients with cytomegalovirus-associated GBS were younger with prominent sensory involvement and more severe disease than GBS with no identified infection (Visser et al. 1996). Patients with CMV infection were more likely than others to have raised concentrations of adhesion molecules important in T-lymphocyte activation and migration: sICAM-1, sVCAM-1, sL-selectin and sIL-2R (Hadden et al. 2001).

4.2. Mechanism of pathogenesis

Different infections have been associated with differences in clinical and immunological features, leading to the hypothesis that the infections might contribute to pathogenesis and provide a basis for classification. Infecting organisms might activate autoreactive T cells to induce autoimmune disease by several mechanisms. Molecular mimicry between myelin, Schwann cell or axonal epitopes and antigens on different infective agents might produce the autoimmune response and explain the heterogeneous clinical features. In addition, some organisms cause upregulation of Th1 cytokines and induce MHC expression, microbial superantigens may selectively activate subsets of T cells, viral-induced damage may expose new self epitopes allowing epitope spreading, and viruses may activate or destroy particular T-cell subsets by direct infection (Oldstone 1998).

Activated autoreactive T cells that escape the normal mechanisms of tolerance may clonally proliferate, spread...
throughout the body and cross the blood–nerve barrier. Most T cells in GBS sural nerve biopsies express the αβ receptor but a few express the γδ receptor. γδ cells (and some double-negative αβ cells) recognize nonclassical antigens (such as carbohydrates and glycolipids) presented by CD1 molecules. CD1 molecules are present on endoneurial macrophages and possibly Schwann cells and are upregulated in GBS and other inflammatory neuropathies.

Once inside the endoneurium, T cells are further activated and start to orchestrate the inflammatory response. There is upregulation of matrix metalloproteinases (Kieseier et al. 1998), chemokines, and reactive oxygen and nitrogen species (Smith et al. 1999). Nitric oxide donors may block conduction in normal or demyelinated axons. Schwann cells may be actively involved, and may present antigens, secrete pro-inflammatory cytokines and express a changing pattern of integrins during demyelination and axonal loss. The final damage to myelin appears morphologically to be done by macrophages, probably targeted by opsonins like antibody and C3b (Smith 1999). During the recovery phase, most activated T cells die by apoptosis and other inflammatory cells are suppressed by cytokines such as TGF-β, interferon-β, prostaglandin-E, IL-4 and IL-10. Fas and its ligand may be responsible for apoptosis of Schwann cells or T cells.

Antibodies to various components of peripheral nerve have been found in many patients with GBS (Hughes et al. 1999). Antibodies may contribute to the pathogenesis and cause demyelination through antibody-dependent cell-mediated cytotoxicity or complement activation. A sensitive adaptation of the complement fixation test, the ‘C1 fixation and transfer’ assay, detected IgM antibodies to whole nerve in almost all GBS patients and no controls (Vriesendorp et al. 1993). However, the overall significance of antibodies to myelin is uncertain because many have also been found in normal controls, and many patients with GBS have no detectable antibodies by most methods.

### Table 1 Reported associations with C. jejuni-associated GBS

<table>
<thead>
<tr>
<th>Country</th>
<th>GBS n</th>
<th>C. jejuni % of GBS</th>
<th>C. jejuni % of controls</th>
<th>EMG types: % of C. jejuni GBS</th>
<th>GM1 abs: % of C. jejuni GBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaldor and Speed 1984</td>
<td>Australia</td>
<td>56</td>
<td>38</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Ropper 1988</td>
<td>USA</td>
<td>106</td>
<td>4*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Winer et al. 1988a</td>
<td>UK</td>
<td>99</td>
<td>14</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Boucquey et al. 1991</td>
<td>Belgium</td>
<td>42</td>
<td>13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gruenewald et al. 1991</td>
<td>USA</td>
<td>17</td>
<td>18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Enders et al. 1993</td>
<td>Germany</td>
<td>38</td>
<td>39</td>
<td>18</td>
<td>–</td>
</tr>
<tr>
<td>Gregson et al. 1993</td>
<td>UK</td>
<td>42</td>
<td>35</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Kuroki et al. 1993</td>
<td>Japan</td>
<td>46</td>
<td>41</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Mishu et al. 1993</td>
<td>USA</td>
<td>118</td>
<td>36</td>
<td>10</td>
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</tr>
<tr>
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<td>USA</td>
<td>58</td>
<td>17</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Von Wulffen et al. 1994</td>
<td>Germany</td>
<td>42</td>
<td>26</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Ho et al. 1995</td>
<td>China</td>
<td>38</td>
<td>66</td>
<td>16</td>
<td>64 AMAN</td>
</tr>
<tr>
<td>Rees et al. 1995a</td>
<td>UK</td>
<td>96</td>
<td>26</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Jacobs et al. 1996</td>
<td>Netherlands</td>
<td>154</td>
<td>32</td>
<td>8</td>
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</tr>
<tr>
<td>Guarino et al. 1998</td>
<td>Italy</td>
<td>60</td>
<td>15</td>
<td>5</td>
<td>–</td>
</tr>
<tr>
<td>Hao et al. 1998</td>
<td>Japan</td>
<td>205</td>
<td>45</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Koga et al. 1998</td>
<td>Japan</td>
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<td>31</td>
<td>4</td>
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<tr>
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<td>Japan</td>
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<td>52</td>
<td>–</td>
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<tr>
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<td>16</td>
<td>59 AMAN</td>
</tr>
<tr>
<td>Koga et al. 1999</td>
<td>Japan</td>
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<td>24</td>
<td>9</td>
<td>–</td>
</tr>
<tr>
<td>Yuki et al. 1999</td>
<td>China</td>
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<td>47</td>
<td>5</td>
<td>58 AMAN</td>
</tr>
<tr>
<td>Hadden et al. 2001</td>
<td>Austria USA</td>
<td>229</td>
<td>23</td>
<td>–</td>
<td>10 axonal</td>
</tr>
</tbody>
</table>

– , not described, *identified by stool culture only.
4.3. Animal models of autoimmune neuropathy

Proof that a demyelinating polyradiculoneuropathy could be caused by an autoimmune mechanism came from the development of experimental autoimmune (or allergic) neuritis (EAN) of the rat (Waksman and Adams 1955). This is the closest animal model of GBS and the one best understood. Injection of homogenized peripheral nerve together with Freund’s complete adjuvant causes an acute monophasic illness with multifocal inflammatory demyelination of peripheral nerves. Clinical features include weight loss, and weakness of the tail and hind limbs, usually followed by recovery back to normal. Neurophysiological abnormalities in EAN are similar to GBS.

If T lymphocytes from the lymph nodes or spleen of an animal with EAN are appropriately stimulated in culture with a neuritogenic antigen such as P2 protein, the intravenous injection of these T cells alone into a second syngeneic animal will cause a similar illness, termed ‘passive’ or ‘adoptive transfer’ (AT-)EAN. Adoptive transfer EAN was initially developed in an attempt to prove that T cells were more important than antibodies in the pathogenesis of GBS and EAN, but has some differences from the original disease.

An animal model of C. jejuni-induced neuritis has been described, in which chickens developed acute axonal neuropathy after being fed with C. jejuni (Penner serotype O:19) from a Chinese patient with acute motor axonal neuropathy (AMAN) (Li et al. 1996). Almost all 99 chickens developed diarrhoea, and 33% developed weakness at a median 12 d after feeding. The sciatric nerves of weak chickens showed axonal degeneration without demyelination or lymphocytic infiltration, or no pathological abnormality, similar to human AMAN. Immunization with lipopolysaccharide from the same C. jejuni organism also caused acute axonal neuropathy in one of eight rabbits. These models have not been replicated. Although C. jejuni may asymptptomatically colonize the intestines of many animals, it does not cause enteritis in most laboratory animals, with the exception of immunodeficient mice. Subcutaneous immunization with C. jejuni causes an antibody response without neuropathy or weakness.

4.4. Immunogenetic factors

The expectation of host susceptibility factors in an autoimmune disease prompted the search for immunogenetic risk factors. Although this has not revealed any unifying hypothesis, there were weak unconfirmed subgroup associations of C. jejuni-associated GBS with HLA DQB1*03 (Rees et al. 1995c), HLA B35 and the tumour necrosis factor α2 allele, and of AIDP with HLA DRB1*1301. Associations with HLA DQ and DR imply an important role for MHC class II molecules and T cells, and with HLA B imply a role for MHC class I molecules.

5. ASSOCIATION BETWEEN GUILLAIN–BARRÉ SYNDROME AND CAMPYLOBACTER JEJUNI INFECTION

An antibody response to C. jejuni has been reported in 13–72% of GBS patients, but also in 0–18% of normal controls, reflecting the differing specificities of methods used and the fact that C. jejuni is extremely common in rural China (Table 1) (Hughes and Rees 1997).

The organism is detectable by stool culture for a median of 16 d from diarrhoea onset, but the time from diarrhoea until GBS onset is 11 ± 5 d (mean ± S.D.), so the organism may have been cleared by the time many GBS patients reach hospital. The organism was isolated from the stool of 4% of GBS patients (Ropper 1988). Serological diagnosis is therefore more reliable.

Guillain–Barré syndrome is often associated with serotypes less common in uncomplicated enteritis. The Penner serotype is determined by a capsular polysaccharide that is distinct from the lipopolysaccharide (Karlyshev et al. 2000). In Japan 52%–77% of patients with C. jejuni-associated GBS had serotype Penner O:19 (Yuki et al. 1997; Hao et al. 1998), in Germany 93% had Lior 11 (Enders et al. 1993) and in South Africa 53% had the same genotypic clone of Penner O:41 (Lastovica et al. 1997).

Patients with C. jejuni enteritis often (but not always) develop low titres of systemic antibody to C. jejuni, yet only one in a thousand subsequently develops GBS (Allos 1997), usually with higher titres of antibody. The reasons for this are unknown, but may relate to organism virulence and host susceptibility, and possibly subtle differences in the interaction between different strains of C. jejuni, the host T cell receptor and MHC class II. Antibodies to C. jejuni have been found in the CSF but appeared later than in serum.

The CSF protein concentration was slightly lower in patients with C. jejuni infection than others in one study (Hadden et al. 2001) but not another (Kaldor and Speed 1984). A lower CSF protein would suggest a lesser degree of inflammation in the intrathecal portion of the spinal roots, or less opening of the blood–CSF barrier.

6. CAMPYLOBACTER JEJUNI AND ANTIBODIES TO GANGLIOSIDE GM1

6.1. Gangliosides

Lipid makes up 70–80% of the dry weight of myelin, comprising mainly cholesterol, galactocerebroside and phospholipids, as well as small amounts of sulphatide and gangliosides. Gangliosides are acidic glycosphingolipids,
consisting of ceramide attached to an oligosaccharide and sialic acid (= N-acetyllactosamine) residues. The nomenclature codifies the number of sialic acid residues (M = mono = 1, D = di = 2, T = tri = 3, Q = quad = 4), and the chromatographic migration speed, GM1 migrating more slowly than GM2 (Willison 1994). The various permutations give a range of gangliosides occurring with different frequencies in different parts of the nervous system, the most common being GM1, GD1a, GD1b and GT1b. Antigenic cross-reactivity between different gangliosides or between gangliosides and glycoproteins is common because of shared sequences.

Ganglioside GM1 is distributed widely in the nervous system and other tissues. Monoclonal antibodies to ganglioside GM1 bind to compact myelin, Schwann cell and axonal membranes, dorsal and ventral roots, nodes of Ranvier and motor nerve terminals, as well as to the surface of most central nervous system neurones. Cholera toxin binds to ganglioside GM1 and has been used to identify sites that are inaccessible to antibodies. Gangliosides have multiple effects on signal transduction, and interact with ion channels, growth factor receptors and adhesion molecules.

**6.2. Antibodies to gangliosides in GBS**

GM1 is the ganglioside most commonly implicated in GBS. Most frequently, IgG, but also IgM and IgA, antibodies to GM1 have been detected in 10–20% of GBS patients in most studies, but also in a few normal controls (Hughes et al. 1999). They also occur in other lower motor neurone diseases such as amyotrophic lateral sclerosis and multifocal motor neuropathy with conduction block, in which they usually belong to the IgM class. Antiganglioside GM1 antibodies differ in their cross-reactivity with other ganglioside epitopes, but the most relevant specificity is unknown.

In some cases of axonal GBS an immune response to gangliosides may be directly pathogenic. Therapeutic injection of gangliosides was associated with an increased risk of developing GBS in a large epidemiological survey. Of seven such GBS patients studied in detail, all had AMAN and IgG antibodies to gangliosides (mostly GM1) whereas these antibodies were not present in any of eight subjects who received gangliosides without developing GBS (Illa et al. 1995). Immunization of animals with gangliosides gives an antibody response but almost never induces neurological disease.

Antibodies to certain gangliosides have been associated with different subtypes of GBS. Antibodies to ganglioside GM1 were associated with motor nerve involvement, whereas antiganglioside GQ1b antibodies were associated with involvement of sensory axons. Fisher syndrome is associated with IgG1 antibodies to ganglioside GQ1b, acute oropharyngeal palsy with antibodies to gangliosides GT1a and GQ1b, and AMAN variably with antibodies to gangliosides GM1, GM1b, GD1a or N-acetylgalactosaminyl GD1a (GalNAc-GD1a). However, these antibodies vary in the degree to which they cross-react with more than one ganglioside and it has been suggested that this fine specificity might explain some of the phenotypic variability.

Although antibodies to ganglioside GQ1b are closely associated with Fisher syndrome and probably pathogenic (Plomp et al. 1999), the role of antibodies to gangliosides in the pathogenesis of GBS remains controversial. The pathogenic potential of antibodies to ganglioside GM1 is likely to be modified by the pattern of cross-reactivity with shared epitopes on other molecules, protection of GM1 antigens by the local neural microenvironment, differences in the pathophysiological effect of binding, and the greater penetrance and affinity of IgG than IgM (Willison et al. 1997).

**6.3. Epidemiological association of Campylobacter jejuni and antibodies to ganglioside GM1**

Probably because of molecular mimicry between ganglioside GM1 and the lipopolysaccharide of *C. jejuni*, antibodies to ganglioside GM1 have been found in 20–71% of patients with *C. jejuni*-associated GBS, significantly more frequently than in other cases of GBS (Table 1). Patients with *C. jejuni* infection who develop GBS generally produce a stronger antibody response than those who have uncomplicated enteritis. Most studies have failed to detect antibodies to ganglioside GM1 in patients with uncomplicated *C. jejuni* enteritis (Rees et al. 1995a). IgA antibodies to ganglioside GM1 were of the IgA1 type indicating production in bone marrow rather than in the gut, and were more closely associated with *C. jejuni* infection and poor prognosis than IgG or IgM antibodies (Koga et al. 1999).

GBS patients with antibodies to ganglioside GM1 are more likely to have axonal neurophysiology and pure motor GBS (Jacobs et al. 1996; Hadden et al. 1998). Antibodies to ganglioside GD1a or GalNAc-GD1a may be linked to axonal neurophysiology even more strongly (Ho et al. 1999).

**6.4. Molecular mimicry**

6.4.1. Structural mimicry. Molecular mimicry may be defined as the sharing of similar structures by molecules derived from dissimilar genes. It was first recognized during the development of monoclonal antibody technology that an antibody might cross-react with both human and viral antigens, and molecular mimicry has subsequently been shown in many diseases. It is not clear whether or not this is mimicry in the Batesian sense, but if so then it may be the host that ‘benefits’.

Many strains of *C. jejuni* are able to synthesize sialic acid and have sialylated carbohydrate residues identical to human gangliosides GM1, GD1a, GD3 or GT1a in the lipo-oligosaccharide of their cell wall. This was originally shown in organisms of Penner serotype O:19 cultured from Japanese patients with GBS (Yuki et al. 1993). These observations gave support to the molecular mimicry hypothesis that the immune response to *C. jejuni* infection could generate antibodies cross-reactive with neural antigens, which might be responsible for the pathogenesis of GBS.

Molecules other than the lipo-oligosaccharide might be responsible for molecular mimicry in *C. jejuni* (Linton et al. 2000). Sialylated oligosaccharides have also been shown on flagellin, the major constituent of the flagellum, and *C. jejuni* has many more glycosylated proteins than most bacteria, although it is not known whether these molecules contain ganglioside-like epitopes.

### 6.4.2. Antibody cross-reactivity

The antiganglioside GM1 activity of IgG from Dutch patients with GBS was inhibited by absorption with whole *C. jejuni* of serotypes O:4, O:22 and O:41, and different strains inhibited different sera (Oomes et al. 1995). Similar cross-reactivity was shown in patients with Fisher syndrome, whose serum IgG antibodies to ganglioside GGQ1b bound to surface epitopes on their own isolate of *C. jejuni*. Antibodies to *C. jejuni* LPS that did not cross-react with GM1 (i.e. were not inhibited by cholera toxin) were usually of subclass IgG2 (T-cell independent), whereas antibodies that cross-reacted with both *C. jejuni* LPS and GM1 were generally of subclass IgG1 (T-cell dependent) (Gregson et al. 1997).

Cross-reactive antibody was shown to be pathogenic in mouse nerve (Goodyear et al. 1999). A monoclonal IgM antibody was generated by immunizing mice with lipopolysaccharide of *C. jejuni* isolated from a patient with GBS. This antibody bound *in vitro* to gangliosides GT1a, GQ1b and GD3 as well as to *C. jejuni* lipopolysaccharide. It bound to sections of mouse motor nerve terminals, nodes of Ranvier and dorsal root ganglia. In the *ex vivo* mouse phrenic nerve diaphragm preparation, it caused complement-dependent depolarizing (α-latrotoxin-like) neuromuscular transmission block. Another group found that GBS serum also caused neuromuscular transmission block, but with important differences, in that the effect was complement-independent, related to IgG not IgM, and did not cause initial depolarization (Buchwald et al. 1998).

### 6.4.3. T-cell receptor cross-reactivity

The T-cell receptor is less antigen-specific than an antibody, and one T-cell clone may respond to many peptides in which some or even all amino acids differ (Mason 1998). T cells therefore respond to multiple antigens with a broad affinity spectrum. During thymic selection, T cells with high affinity for self antigens undergo apoptosis, those with low affinity die by neglect, and those with intermediate affinity expand and are present in normal humans. A viral infection activates T cells with higher affinity for viral peptides than self antigens. These T cells probably do not cause autoimmune disease except in the presence of enhancing factors, such as the T cells being of the memory/effector phenotype (perhaps due to a previous infection), activation of antigen-presenting cells (with upregulation of MHC and costimulatory molecules) and/or increased amounts of antigens exposed during tissue damage.

### 6.5. Limitations of molecular mimicry hypothesis

Unfortunately, the molecular mimicry hypothesis is an oversimplification and does not explain many observations. Many GBS patients with anti-GM1 antibodies have not had *C. jejuni* infection (Hao et al. 1998). Furthermore, *C. jejuni* that express GM1 epitopes have sometimes been isolated from GBS patients without serum antibodies to GM1, and vice versa (Gregson et al. 1997), although the expression of surface molecules by *C. jejuni* may be affected by the culture conditions. *C. jejuni* isolated from patients with GBS and with enteritis alone have similar ganglioside-like moieties, yet patients with *C. jejuni* enteritis do not develop antibodies to gangliosides (Gregson et al. 1997; Sheikh et al. 1998). Serotypes associated with GBS are somewhat more likely to have GM1-like epitopes than serotypes not associated with GBS (38% vs. 15%) (Nachamkin et al. 1999), but anti-GM1 antibodies have been found in only two of six GBS patients infected with clonally identical *C. jejuni* Penner O:41 (Gregson and Lastovica 1999). Sialylated lipo-oligosaccharide is found in a few other bacterial species including *Neisseria* and *Haemophilus*, and may confer resistance to complement-mediated killing and phagocytosis, but these species have not been shown to be associated with GBS. These lines of evidence suggests that antibody generation cannot always be explained by a simple theory of mimicry, and that host susceptibility factors are probably important.

### 7. CAMPYLOBACTER JEJUNI AND NEUROPHYSIOLOGICAL SUBTYPES OF GUILLAIN–BARRÉ SYNDROME

Nerve conduction studies are used to support the diagnosis of GBS, distinguish axonal and demyelinating subtypes and help predict the outcome. By stimulating a nerve at different sites and recording the latency and amplitude of the compound muscle action potential (CMAP), it is possible to identify conduction slowing or block (characteristic of demyelination) and to infer axonal loss (by reduced CMAP...
amplitude). The pattern of abnormality depends on the time from disease onset. Motor amplitude is the measure most closely related to clinical symptoms, and is severely affected from the first week, whereas sensory amplitude, motor velocity and F-wave latency are not severely affected until the third week. Most measures reach a nadir between 3 and 4 weeks.

By neurophysiological criteria to classify GBS patients from Europe and North America, 69% had features of demyelinating neuropathy, 3% axonal neuropathy, 3% inexcitable nerves, 2% normal neurophysiology and 23% were unclassifiable (Hadden et al. 1998). Patients with absent action potentials may have either demyelinating or axonal pathology that cannot be distinguished neurophysiologically.

Patients with C. jejuni-associated GBS are more likely than other GBS patients to have primary axonal GBS (Hadden et al. 2001; Ho et al. 1999), secondary axonal degeneration (Rees et al. 1995b) or inexcitable nerves (Table 1). However, most Western patients with C. jejuni infection have demyelinating neuropathy. The pathological process is likely to depend not only on the immunogenic components of the infecting organism, but also on host factors, including regulation of the immune response and properties of the peripheral nervous system.

Approximately 16% of GBS patients have no detectable abnormality of sensory nerve fibres and have been termed (pure) motor GBS. Pure motor GBS is more frequent in abnormality of sensory nerve fibres and have been termed response and properties of the peripheral nervous system.

Many studies have identified factors predictive of poor outcome by regression analysis. These include older age, factors related to pathogenesis (C. jejuni infection or diarrhoea, antiganglioside GM1 antibodies) and factors related to disease severity (rapid onset, more severe weakness of legs or arms, requirement for artificial ventilation and small or absent motor nerve action potentials) (McKhann et al. 1988; Visser et al. 1999). C. jejuni infection might cause a poor outcome because the resulting autoimmune response causes greater axonal degeneration than with other infections, perhaps due to molecular mimicry with axonal antigens. Neurophysiology suggestive of axonal neuropathy was previously considered to indicate a poor outcome, until patients with AMAN were shown to have a similar outcome to those with AIDP in China and western countries (McKhann et al. 1993; Hadden et al. 1998).

The death rate has varied from 2% to 18% in different series. The most common causes of death are cardiovascular autonomic complications, ventilator-associated pneumonia and pulmonary thromboembolism, predicted by older age and the presence of underlying lung disease.

### 8. CAMPYLOBACTER JEJUNI AND POOR OUTCOME IN GUILLAIN–BARRÉ SYNDROME

#### 8.1. Causes of poor outcome

Recovery from GBS is very variable. The median time from onset until improvement begins is 2 weeks, until walking unaided 2 months, and until complete recovery about 6 months. Less than 10% of patients have a temporary relapse about a month after starting to improve. Despite new treatments, some patients still have a poor long-term outcome. One year from onset, approximately one-third of GBS patients have returned to normal, one-third have minor symptoms or signs not affecting walking, one-sixth can walk but not run, 7–20% are unable to walk without assistance and 2–18% are dead (Winer et al. 1988b).

Mechanisms of poor outcome include axonal degeneration, fatigue and psychosocial factors, and the development of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Axonal degeneration may be caused by specific autoimmune attack on the axon, or by ‘bystander’ damage resulting from severe inflammation of any antigenic specificity. Axons may regenerate, but this is slow (less than 1 mm d\(^{-1}\)) and often incomplete.

#### 8.2. Treatment

Plasma exchange (PE) was the first disease-modifying therapy of proven efficacy (The Guillain–Barré Syndrome Study Group 1985). Intravenous immunoglobulin was later shown to be equally beneficial, safer and more convenient than PE (Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group 1997). Retrospective subgroup analysis in a Dutch study suggested that patients with C. jejuni or CMV infection, pure motor GBS, antiganglioside GM1 antibodies or rapid onset might have a better outcome if treated with immunoglobulin than with plasma exchange (Visser et al. 1999), but this was not confirmed in another study (Hadden et al. 2001).

Uncontrolled reports of seven cases suggested that treatment of C. jejuni infection with erythromycin did not prevent the development of GBS (Ropper 1988), but antibiotic therapy has never been formally tested in GBS. Some patients have prolonged gut colonization by the organism, which might continue to stimulate an immune response. It would seem worthwhile to do a randomised trial of antibiotic therapy in those with a positive stool culture.

### 9. CONCLUSIONS

GBS is the most common cause of acute neuromuscular paralysis and is likely to be an autoimmune disease. The
most frequent infection preceding GBS is \textit{C. jejuni}. Patients with GBS and \textit{C. jejuni} infection are more likely to have neurophysiological criteria of axonal neuropathy, antibodies to ganglioside GM1, pure motor GBS, a less elevated CSF protein concentration and a worse outcome than other GBS patients. The presence of ganglioside-like epitopes on the \textit{C. jejuni} lipopolysaccharide explains some of these associations, but such a molecular mimicry hypothesis is inadequate to account for many aspects of the pathogenesis of GBS.

10. REFERENCES


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