Guillain-Barré syndrome in the 100 years since its description by Guillain, Barré and Strohl

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Abbreviations: AIDP = acute inflammatory demyelinating polyradiculoneuropathy; AMAN = acute motor axonal neuropathy; GBS = Guillain-Barré syndrome

The first descriptions

Landry’s 1859 description of 10 cases of acute ascending paralysis fitted well with the modern concept of Guillain-Barré syndrome (GBS) but necessarily lacked the defining features of tendon areflexia and CSF albuminoctological dissociation (Landry, 1859). Westphal and Erb described examination of the patellar tendon reflex in 1875 and examination of this and other reflexes rapidly entered regular neurological practice (Erb, 1875; Westphal, 1875; Boes, 2014). Quincke (1891) introduced lumbar puncture for the management of hydrocephalus in 1891. These discoveries set the stage for the seminal paper of Guillain, Barré and Strohl in 1916 (Guillain et al., 1916). A meeting of the Inflammatory Neuropathy Consortium of the Peripheral Nerve Society in Glasgow from 21–24 June 2016 (www.pnsociety.com/inflammatory-neuropathy-consortium) celebrated its centenary. A 63-chapter companion book records the centennial reflections of the speakers and others (Willison and Goodfellow, 2016).

The 1916 description by Guillain, Barré and Strohl


On 13 October 1916, during the battle of the Somme, members of the Société de Neurologie serving in the French Army held a meeting where Guillain, Barré and Strohl described two soldiers with weakness of the limbs.

‘The first soldier... of the hussars, 25 years old, arrived at the neurological centre of the Sixth Army because of motor disturbances of the lower and upper limbs on the 20th August 1916. The illness began on 25th July with tingling of the feet and weakness of the lower limbs making him stop walking after 200 to 300 metres. The tingling then spread to the upper limbs and lower part of the face during the following days and he developed weakness in the upper limbs.’

Five days later, examination showed severe generalized weakness more pronounced distally and mild impairment of touch, pain and temperature sensation on his hands. He could only walk a few steps and his gait was unstable. The second soldier... of the infantry, 35 years old, arrived at the same army centre on 5 September 1916 with leg weakness. It began on 28 August after a 15 km walk and spread from his legs to his arms. The next morning he fell over when he shouldered his backpack and could not get up. Examination showed that...
with the upper limbs, especially distally. His head was mostly turned to the left and he had difficulty turning it to the right. He could open and close his mouth but slowly and incompletely’.

Some of these findings are difficult to explain on the basis of a diagnosis of acute neuropathy, especially when we read that the reflexes were difficult to obtain because of ‘l'hypertonie musculaire’. The signs reported suggest that more than peripheral nerve disease was responsible. However, a centenary is not the time to be challenging a diagnosis. Like the first soldier, the second had distal tingling and slight reduction of sensation. Importantly, in both cases the tendon reflexes were absent and the CSF protein concentrations were increased despite a normal cell count. The first soldier could walk for an hour by the time he was discharged 30 days after being seen. The second had improved before being sent for convalescence after 25 days.

Guillain-Barré syndrome did not gain immediate acceptance into the canon and the following year Gordon Holmes was continuing to use Osler’s term ‘Acute Febrile Polyneuritis’ (Holmes, 1917) to describe ‘about twelve’ soldiers with an illness indistinguishable to the modern reader from GBS. Although he used the term febrile, most of the men were seen by Holmes when the disease was well established and they were no longer febrile. The timing of the febrile illness in relation to the onset of weakness is not clearly described except in one in whom the onset occurred ‘a short time’ after relapsing trench fever and another who had had diarrhoea and vomiting ‘within the previous few weeks’. Two of Holmes’ patients died whereas Guillian continued to insist that the course of GBS was benign and death rare, although in his last word on the subject he conceded that it did not confer immortality (Guillain, 1953).

Pathology

Holmes found that the sciatic nerves of the fatal cases ‘contained some fibres in the early stage of degeneration, their myelin sheaths being broken up into chains of spherical or oval globules, while the calibre of other fibres was irregular and their staining unequal’. During World War II, Haymaker and Kernohan in the US Army Institute of Pathology collected material from 50 autopsies from all theatres of war around the world (Haymaker and Kernohan, 1949). They found that the pathology was confined to the peripheral nerves and, in their limited material, affected in particular the point at which the ventral and dorsal spinal roots fuse. They considered that the earliest change was oedema, followed by swelling and irregularity of the myelin sheaths and axis cylinders and only later lymphocyte and phagocyte infiltration. However, Krücke soon described seven personal cases in which cellular, predominantly lymphocytic, infiltration was the first abnormality, present from the first days of the disease (Krücke, 1955). By this time autoallergy had become a popular cause of disease and experimental encephalitis had been produced by injecting monkeys with rabbit brain. Waksman and Adams (1955, 1956) injected peripheral nerve tissue with Freund’s adjuvant into laboratory animals producing experimental allergic neuritis (EAN) with extensive lymphocytic and histiocytic infiltration of the peripheral nerves, spinal roots and dorsal root ganglia. From the same institution, the Massachusetts General Hospital, Asbury, Arnason and Adams published a collection of 19 autopsies which showed very similar changes associated with demyelination (Asbury et al., 1969). The histological appearances led to GBS being regarded as synonymous with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) (Arnason, 1984). Electron microscope studies in both EAN and in GBS biopsies subsequently showed that demyelination begins with macrophage invasion, digestion and stripping of intact myelin sheaths (Lampert, 1969; Prineas 1972, 1981). This histological similarity led to extensive studies showing that EAN is driven by T cell responses against myelin proteins P2, P0 or PMP22 and potentially exacerbated by antibodies to glycolipids (Kadlubowski and Hughes, 1979; Linnington et al., 1984, 1992; Milner et al., 1987; Hahn et al., 1993; Gabriel et al., 1998). Furthermore, certain mouse strains with defective immunoregulatory genes spontaneously develop autoimmune neuropathy due to T cells reacting against myelin P0 protein (Salomon et al., 2001; Louvet et al., 2009; Su et al., 2012; Meyer zu Horste et al., 2014). These observations showed that T cell responses to myelin proteins can induce inflammatory neuropathy. Nevertheless, attempts to identify antibody or T cell responses to the same antigens in human neuropathies have only rarely been successful and then only in a few patients without any detected relationship to clinical features (Makowska et al., 2008).

Acute motor axonal neuropathy

In 1986, Feasby and colleagues reported five patients, including one autopsy study, with a form of GBS in which the predominant abnormality was axonal degeneration (Feasby et al., 1986). Shortly after, McKhann et al. (1991, 1993) investigated an epidemic of GBS occurring in the summer months in children in Northern China. The neuropathy resembled the conventional form of GBS clinically but was usually predominantly motor and the electrophysiological findings were strikingly different with reduced compound muscle action potentials without conduction slowing implicating an axonal pathology. Subsequent histological studies of autopsy material supported this conclusion and validated the concept of acute motor axonal neuropathy (AMAN) (Griffin et al., 1995). Rather than endoneurial infiltration of T cells and penetration of the myelin sheaths by macrophages to produce demyelination as in AIDP, in these autopsied cases there was invasion of macrophages into the periaxonal space at the paranodes followed by degeneration of the axons while the myelin sheaths remained intact (Griffin et al., 1996).
some particularly severe cases the sensory axons were affected as well, producing acute motor and sensory axonal neuropathy (AMSAN). Investigation of the cause of these conditions has been much more successful than that of AIDP. Deposits of IgG and C3d on the axolemma of the affected axons in AMAN implicated an antibody-mediated mechanism (Hafer-Macko et al., 1996). Antibodies to gangliosides were already known to occur in GBS (Ilvas et al., 1988) and antibodies to ganglioside GM1, GD1a and GalNAc-GD1a were found to be particularly common in AMAN. Yuki and colleagues produced a convincing model replicating the electrophysiological and histological appearances of AMAN by immunizing rabbits with ganglioside GM1 (Susuki et al., 2003). Willison produced a more refined mouse model in which passively transferred monoclonal antibodies to GD1a destroyed the motor nerve terminals (Goodfellow et al., 2005; McGonigal et al., 2010; Willison, 2012). Many of the patients with AMAN in the studies in China had had Campylobacter jejuni infection, which was soon recognized as the commonest precipitant of GBS throughout the world. Strains of Campylobacter associated with GBS carry epitopes in the lipoooligosaccharide in their cell walls, which antibodies to ganglioside GM1 or GD1a recognize (Yuki et al., 1993). A likely cause of AMAN is that a bacterium carrying a ganglioside-like epitope in its cell walls triggers an antibody response that cross-reacts with axolemmal antigens in immunogenetically susceptible subjects. The hypothesis is convincing but lacks an explanation for the breakdown of the blood–nerve barrier to allow the antibodies access to the endoneurium. In very distal intramuscular nerves and in spinal roots, this may not represent a significant barrier.

**Neurophysiology**

As sampling peripheral nerve tissue to investigate the underlying pathology is invasive and site-limited, neurophysiological testing is crucially important in distinguishing between the various forms of GBS. Early papers reported markedly slowed nerve conduction velocities and delayed distal motor nerve latencies consistent with demyelination (Bannister and Sears, 1962; Wiederholt et al., 1964; McLeod, 1981). The description of an axonal form of the disease by Feasby and colleagues and the cases of AMAN in China led to attempts to separate the cases of GBS into two groups from the electrophysiological features (Hadden et al., 1998). These attempts have been complicated by the changes that occur as the disease progresses, so that patients who were classified as having demyelinating features at onset are reclassified as axonal 2 weeks later and vice versa. Part of the confusion arises because transient failure of impulse conduction, from whatever cause and at whatever site along the nerve, can either be followed by rapid recovery or lead to distal axonal degeneration. This can lead to confusion when one tries to pigeon hole these rapidly changing findings into either ‘axonal’ or ‘demyelinating’, terms usually reserved for chronic neuropathies. The confusion has led to a call for serial studies to enable a more accurate classification (Uncini and Kuwabara, 2012).

**Other syndromes**

In addition to the typical generalized polyneuropathy seen in AIDP and AMAN or AMSAN, regional variants of GBS have become recognized and some have associations with antibodies to particular gangliosides (Table 1). In the best known of these, the Fisher syndrome of ophthalmoplegia, areflexia and ataxia, named after Charles Miller Fisher (Fisher, 1956), there is convincing evidence for the role of antibodies. Ninety per cent of patients with Fisher syndrome have antibodies to ganglioside GQ1b (Chiba et al., 1992). Ganglioside GQ1b is enriched in human ocular motor nerves and at mouse motor nerve terminals. Application of monoclonal anti-GQ1b antibody and complement to mouse motor nerve terminals caused lysis of both the terminal axon and the perisynaptic Schwann cell (Halstead et al., 2004). As pure Fisher syndrome is relatively benign, post-mortem studies are not available and biopsies of affected parts of the peripheral nervous system are impractical, so that the underlying pathology has not been extensively studied. In one pathological case report, sural biopsy did show lengthening of nodes of Ranvier, myelin splitting and macrophage internodal axonal invasion without any features of segmental demyelination (Miller et al., 2014). GQ1b has been localized by immunohistochemistry with anti-GQ1b antibodies to both paranodal Schwann cell membranes and motor nerve terminals of human extraocular nerves (Chiba et al., 1997; Liu et al., 2009), indicating that both sites may be vulnerable to immune attack. In sensory nerve electrophysiology studies, sensory action potentials have been shown to diminish in amplitude during the acute phase of the illness, and then recover, suggesting reversible conduction failure (Guiloff, 1977; Umaphathi et al., 2012). Ophthalmoplegia does occur in GBS and patients who present with ophthalmoplegia, areflexia and ataxia may go on to develop generalized limb weakness, resulting in a GBS-Fisher overlap syndrome. Furthermore instead of ascending paralysis or generalized weakness occasional patients have descending weakness affecting the face, bulbar muscles and upper limbs. Many forms of frustes and related disorders including Bickerstaff’s encephalitis occur (Al-Din et al., 1982; Odaka et al., 2001; Ito et al., 2008).

The course of GBS is usually acute and monophasic but a small per cent have recurrent disease and in up to 16% of cases of chronic inflammatory demyelination polyradiculo-neuropathy (CIDP) the onset is acute, establishing a spectrum between that disease and AIDP (McCombe et al., 1987; Dionne et al., 2010). The pathogenesis of CIDP is not well understood. Like GBS it is probably heterogeneous. IgG4 antibodies to paranodal proteins contactin and neurofascin 155 occur in a very small percentage of
patients with CIDP and may be pathogenic in this small subgroup (Mathey et al., 2015).

### Diagnosis

A committee of the American National Institute of Neurological and Communicative Disorders and Stroke proposed diagnostic criteria for research that included clinical features of progressive limb weakness and loss of tendon reflexes with supportive CSF and electrodiagnostic features (Asbury et al., 1978). These worked well in clinical practice (Asbury and Cornblath, 1990), but the acceptance of variants and forms frustes complicated the application of such criteria. More recently the Brighton organization published more explicit consensus diagnostic criteria of both GBS and Fisher syndrome for use in epidemiological studies (Sejvar et al., 2011b). These include clinical, neurophysiological and CSF criteria and exclusion of other causes. The possibility of only mild neurophysiological changes and frequently normal CSF, especially in the first week of the illness, complicate the application of these criteria in practice. In a retrospective study of 335 adult Northern European patients collected in clinical trials and observational studies only 61% fulfilled all criteria, but 94% fulfilled the clinical and either neurophysiological or CSF criteria (Fokke et al., 2014). In the absence of a diagnostic biomarker, diagnosis will continue to depend on recognition of the characteristic clinical picture and exclusion of other causes.

### Epidemiology

GBS is usually an uncommon sporadic disease. In a systematic review of studies from North America and Europe, the crude incidence of GBS ranged from 0.81 to 1.89 cases per 100 000 person–years (Sejvar et al., 2011a). The incidence rises with increasing age, being 0.62 cases per 100 000 person–years among 0 to 9 year olds and 2.66 cases per 100 000 person–years among 80 to 89 year olds. It is more common in males than females, the relative risk being 1.78 (95% confidence interval, 1.36–2.33) times greater in males. The reasons for the age and sex distribution are unknown and are not typical of autoimmune disease.

In 1976 there was an epidemic of GBS following the swine flu vaccination programme in the USA in which the eventual conclusion was that the rate of attributable cases had been between 0.49 and 0.59 cases per 100 000 adult vaccinees over the 6 to 8 week period after the vaccine (Langmuir et al., 1984). Since then the occurrence of GBS has become a bellwether of the safety of vaccination programmes. Subsequent influenza vaccines have either not been associated with GBS or the attributable risk has only been ~0.1 additional GBS cases above expected per 100 000 vaccinees. There have been occasional small epidemics of GBS associated with infectious illnesses but the most striking epidemics of GBS so far encountered have been those associated with Zika virus both in French Polynesia in 2013 and 2014 (Cao-Lormeau et al., 2016) and South America in 2015 and 2016 (Dos Santos et al., 2016; Pardo, personal communication). The 42 incident cases from French Polynesia were significantly more likely to have antibodies against Zika virus than contemporary controls admitted to hospital with a non-febrile illness. The neurophysiological features were interpreted to represent AMAN, although review of the published data suggests that many of these cases were in fact AIDP-based on the presence of prolonged distal motor latencies. The AIDP phenotype is similar to the experience with Zika virus-associated GBS in Colombia (Pardo, personal communication). Although antibodies to glycolipids were present in some patients from French Polynesia, there were none of the antibodies to ganglioside GM1 and GD1a previously associated with Campylobacter-associated AMAN, suggesting pathophysiological distinctions between post-Zika GBS in French Polynesia and typical AMAN.

Besides Campylobacter and Zika virus, the other principal infections established as occurring before GBS more often than chance are cytomegalovirus, Mycoplasma pneumoniae, Epstein-Barr virus, Haemophilus influenzae and hepatitis E (Willison et al., 2016). There is a long list of case reports and small case series implicating other agents of which herpes zoster and HIV are particularly plausible candidates. The fundamental question remains whether these all produce the disease by eliciting an antibody response against an antigen in the infective agent cell wall, as in the likely Campylobacter mechanism, or in the host membrane that a virus may collect in its envelope during budding, or in some other way.

The ongoing International Guillain-Barré syndrome Outcome Study (IGOS) has collected more than 1300 of its target 1500 patients from centres in 18 countries in North America, Europe and Australasia. The interim results confirm that the clinical picture is different in different parts of the world. The usual sensory and motor form of the disease is the commonest in most countries but in Bangladesh a pure motor form is the most common (van den Berg for the IGOS consortium, 2016). As the study

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Table 1 Guillain-Barré syndrome subtypes, related disorders and associated antiganglioside antibodies

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Associated antiganglioside antibodies</th>
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<tbody>
<tr>
<td>AIDP</td>
<td>None</td>
</tr>
<tr>
<td>AMSAN</td>
<td>GM1, GM1b, GD1a</td>
</tr>
<tr>
<td>AMAN</td>
<td>GM1, GM1b, GD1a, GalNac-GD1a</td>
</tr>
<tr>
<td>Acute sensory neuropathy</td>
<td>GD1b</td>
</tr>
<tr>
<td>Fisher syndrome</td>
<td>GQ1b, GT1a</td>
</tr>
<tr>
<td>Fisher/GBS overlap syndrome</td>
<td>GQ1b, GM1, GM1b, GD1a, GalNac-GD1a</td>
</tr>
<tr>
<td>Cervico-brachial-oropharyngeal syndrome</td>
<td>GT1a</td>
</tr>
</tbody>
</table>

AMSAN = acute motor and sensory axonal neuropathy.
continues it should be possible to correlate this observation with neurophysiological subtypes, knowledge of the antecedent events and serum biomarkers and so shed further light on the pathogenesis.

Clinical course and treatment

The usual course of the disease is progression continuing for 1 to 28 days, a plateau phase of several days or even weeks and then gradual recovery, sometimes complete but often not. Increasingly sophisticated prognostic scores have been derived from natural history studies or data from patients participating in treatment trials. One of these allows prediction of the ability to walk after 6 months from the age, presence of a preceding diarrhoeal illness and a GBS disability grade score: older age, preceding diarrhoea and worse disability all predict a worse prognosis (van Koningsveld et al., 2007). Another allows prediction of the need for ventilation from the time to hospital admission, presence of facial or bulbar weakness and strength measured with the Medical Research Council sum score (the sum of the scores of 12 muscle groups) (Walgaard et al., 2010).

Guillain, Barré and Strohl treated their first patient with rest, massage and strychnine. Since then, supportive care, occupational and physical therapy, and artificial ventilation have been the mainstays of treatment. Plasma exchange or intravenous immunoglobulin, but not corticosteroids, have been shown to hasten recovery (Hughes et al., 2007). Despite these treatments improvement is often slow and incomplete, and patients continue to suffer from pain and fatigue. In the Netherlands only ~3% of patients with GBS enrolled in clinical trials or observational studies between 1986 and 2008 died, but the mortality has been closer to 10% in countries without excellent intensive care facilities (van den Berg et al., 2013). In the mouse models of AMAN and Fisher syndrome, complement fixing antibodies and complement fixation are critical for pathogenesis, and complement blockade is highly effective as treatment (Willison et al., 2008). It is greatly hoped that ongoing trials of complement blockade with the complement blocking drug eculizumab added to the usual intravenous immunoglobulin regime will improve the outcome from GBS.

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References


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