

Guillain-Barré syndrome

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Guillain-Barré syndrome consists of at least four subtypes of acute peripheral neuropathy. Major advances have been made in understanding the mechanisms of some of the subtypes. The histological appearance of the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) subtype resembles experimental autoimmune neuritis, which is predominantly caused by T cells directed against peptides from the myelin proteins P0, P2, and PMP22. The role of T-cell-mediated immunity in AIDP remains unclear and there is evidence for the involvement of antibodies and complement. Strong evidence now exists that axonal subtypes of Guillain-Barré syndrome, acute motor axonal neuropathy (AMAN), and acute motor and sensory axonal neuropathy (AMSAN), are caused by antibodies to gangliosides on the axolemma that target macrophages to invade the axon at the node of Ranvier. About a quarter of patients with Guillain-Barré syndrome have had a recent *Campylobacter jejuni* infection, and axonal forms of the disease are especially common in these people. The lipo-oligosaccharide from the *C jejuni* bacterial wall contains ganglioside-like structures and its injection into rabbits induces a neuropathy that resembles acute motor axonal neuropathy. Antibodies to GM1, GM1b, GD1a, and GalNac-GD1a are in particular implicated in acute motor axonal neuropathy and, with the exception of GalNacGD1a, in acute motor and sensory axonal neuropathy. The Fisher's syndrome subtype is especially associated with antibodies to GQ1b, and similar cross-reactivity with ganglioside structures in the wall of *C jejuni* has been discovered. Anti-GQ1b antibodies have been shown to damage the motor nerve terminal in vitro by a complement-mediated mechanism. Results of international randomised trials have shown equivalent efficacy of both plasma exchange and intravenous immunoglobulin, but not corticosteroids, in hastening recovery from Guillain-Barré syndrome. Further research is needed to discover treatments to prevent 20% of patients from being left with persistent and significant disability.

In 1916, three French neurologists Georges Guillain, Jean-Alexandre Barré, and André Strohl described two soldiers with acute areflexic paralysis followed by recovery. They noted a raised concentration of cerebrospinal fluid (CSF) protein but a normal cell count.^{1,2} During the past 15 years, it has become clear that this clinical picture, now called Guillain-Barré syndrome, can be produced by different pathological subtypes and is related to other less common disorders (table 1).

The most common underlying subtype of the syndrome is acute inflammatory demyelinating polyradiculoneuropathy (AIDP).^{3,4} Another subtype, first clearly described in *The Lancet*, in which the neurological deficit is purely motor, has come to be known as acute motor axonal neuropathy (AMAN).⁵⁻⁷ When sensory fibres are also affected, this axonal subtype is called acute motor and sensory axonal neuropathy (AMSAN).⁸

In North America and Europe, typical patients with Guillain-Barré syndrome usually have AIDP as the underlying subtype, and only about 5% of patients have axonal subtypes of the disease.⁹ Large studies in northern China, Japan, and Central and South America show that axonal forms of the syndrome constitute 30–47% of cases.^{5,6,10,11} AIDP and the two axonal subtypes usually affect all four limbs and can involve the cranial nerves and respiration. Autonomic involvement is common in AIDP, especially in severe cases with respiratory failure, but less common in AMAN.¹² Some cases of acute dysautonomia without involvement of somatic nerves may be inflammatory and possibly autoimmune.

In 1956, C Miller Fisher described a triad of acute ophthalmoplegia, ataxia, and areflexia, now known as Fisher's syndrome, and postulated that this set of features

was a form of Guillain-Barré syndrome.¹³ Patients with Fisher's syndrome may have facial and lower cranial-nerve involvement. Overlap forms of Fisher's syndrome with limb weakness and respiratory involvement are not uncommon. Formes frustes are sometimes encountered with various combinations of ophthalmoplegia, facial palsy, bulbar palsy, and sensory neuropathy.

In this review, we consider the epidemiology, diagnosis, pathogenesis, and treatment of the principal subtypes of Guillain-Barré syndrome.^{14,15}

	Antibodies
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)	Unknown
Acute motor and sensory axonal neuropathy (AMSAN)	GM1, GM1b, GD1a
Acute motor axonal neuropathy (AMAN)	GM1, GM1b, GD1a, GalNac-GD1a
Acute sensory neuronopathy	GD1b
Acute pandysautonomia	
Regional variants	
Fisher's syndrome	GQ1b, GT1a
Oropharyngeal	GT1a
Overlap	
Fisher's syndrome/ Guillain-Barré-syndrome overlap syndrome	GQ1b, GM1, GM1b, GD1a, GalNac-GD1a

Table 1: Classification of Guillain-Barré syndrome and related disorders and typical antiganglioside antibodies, by pathology

Search strategy and selection criteria

For the sections on pathogenesis and diagnosis, we searched MEDLINE and EMBASE in all languages on Nov 4, 2004, and our personal databases, using the search term "Guillain-Barré syndrome". For the sections on treatment, we searched the Cochrane Library and made use of the relevant Cochrane reviews which themselves used the published search strategy and methods for selecting evidence of the Cochrane Neuromuscular Disease Group.

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Epidemiology

Worldwide incidence

The incidence of typical Guillain-Barré syndrome has been reported to be relatively uniform between 0·6 and four cases per 100 000 per year throughout the world,¹⁶ but the most recent and careful population-based studies in Europe consistently report an incidence of 1·2–1·9 per 100 000.^{17–22} Atypical cases such as Fisher's syndrome are much less common and Italian researchers have reported an incidence of 0·1 per 100 000.¹⁸ All reports agree that men are about 1·5 times more likely to be affected than are women. In Europe and North America, the incidence increases steadily with advancing age from less than one per 100 000 in patients younger than 30 years to about four per 100 000 in those older than 75 years.¹⁸ In China, the reported incidence is about the same in children and much less in adults than in adults elsewhere, giving an annual incidence of 0·66 per 100 000 for all ages.²³ On the Caribbean island of Curaçao, incidence rose sharply from 1·62 per 100 000 during the time between 1987 and 1991 to 3·10 per 100 000 between 1992 and 1999.²⁴ Similar studies from other regions report a stable incidence of Guillain-Barré syndrome in successive years.

Most cases are sporadic, but small clusters have been associated with outbreaks of bacterial enteritis caused by contaminated water,²⁵ and summer epidemics occur in northern China, probably caused by *Campylobacter jejuni* infection.^{5,26} In all series, about two-thirds of patients have had an infection within the previous 6 weeks, most commonly a flu-like illness but also gastroenteritis.^{27,28} Often, the responsible organism is not identified, but observational and case-control studies implicate a range of bacteria (including *Mycoplasma pneumoniae*) and viruses as possible triggers for the syndrome (table 2). The infection may elicit an immune response that cross-reacts with axolemmal or Schwann cell antigens, and so damages the peripheral nerves.

There has been some concern that certain immunisations might trigger Guillain-Barré syndrome in susceptible individuals. This fear arose because of a slightly increased incidence of the syndrome after "swine flu" vaccines were given in the USA in 1976.^{30–32} Other influenza vaccines have not been associated with the same risk, and there has been a steady decline in the number of cases of Guillain-Barré syndrome associated with influenza vaccine in the USA between 1990 and 2003.³³ A retrospective case study of the combined 1992–93 and 1993–94 vaccine campaigns in the USA identified a

	Netherlands 1987–96 (n=476) ²⁹	North America and Europe 1993–95 (n=383) ²⁹
<i>C jejuni</i>	32	23
Cytomegalovirus	18	8
Epstein-Barr virus	7	2
<i>M pneumoniae</i>	9	Not tested

Table 2: Preceding infections detected serologically in two large series of patients with Guillain-Barré syndrome

Panel 1: Differential diagnosis of acute flaccid paralysis

Brainstem stroke

Brainstem encephalitis

Acute anterior poliomyelitis

- Caused by poliovirus
- Caused by other neurotropic viruses

Acute myelopathy

- Space-occupying lesions
- Acute transverse myelitis

Peripheral neuropathy

- Guillain-Barré syndromes
- Post-rabies vaccine neuropathy
- Diphtheritic neuropathy
- Heavy metals, biological toxins or drug intoxication
- Acute intermittent porphyria
- Vasculitic neuropathy
- Critical illness neuropathy
- Lymphomatous neuropathy

Disorders of neuromuscular transmission

- Myasthenia gravis
- Biological or industrial toxins

Disorders of muscle

- Hypokalaemia
- Hypophosphataemia
- Inflammatory myopathy
- Acute rhabdomyolysis
- Trichinosis
- Periodic paralyses

marginally significant, very small increase in the risk of Guillain-Barré syndrome, equivalent to about one case per million vaccinees above background incidence.³⁴ Despite many individual case reports, other conventional vaccines have not been associated with a significant risk.³⁵ However, rabies vaccine that contains brain material is followed by Guillain-Barré syndrome in about one in 1000 cases.³⁶

Diagnosis

The diagnosis of Guillain-Barré syndrome itself is usually not difficult for the neurologist, but can be challenging for the doctor of first contact who may not have seen a case since medical school. Established diagnostic criteria exist and have stood the test of time.³⁷ Most patients will have an acute neuropathy reaching a peak in under 4 weeks, weakness, hyporeflexia or areflexia, and raised protein concentrations in CSF. However, the rapid development of inexplicable weakness in a patient recovering from a febrile illness may be mistaken for a psychological complaint at first. The differential diagnosis is wide (panel 1)³⁸ and depends first on the clinician recognising that the problem is an

acute peripheral neuropathy and not a brainstem, spinal cord, or conus lesion.

In patients without sensory involvement, disorders such as poliomyelitis, myasthenia gravis, electrolyte disturbance, botulism, or acute myopathy need to be considered. Hypokalaemia is a commonly missed alternative diagnosis. Once the diagnosis of an acute peripheral neuropathy is established, Guillain-Barré syndrome is the most common, but not the only, cause. The clinician should consider alternative causes such as diphtheria, vasculitis, porphyria, tick paralysis, and toxic neuropathy while examining the patient and taking their history.

Rare cases of acute transient sensory neuropathy may be AIDP, with only the sensory nerves or roots being affected; but this condition needs to be distinguished from acute sensory neuronopathy. The differential diagnosis of Fisher's syndrome includes an acute brainstem lesion, especially brainstem encephalitis.

In Guillain-Barré syndrome, the onset phase has been arbitrarily defined as lasting for up to 4 weeks.³⁷ Differentiation between subacute and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), in which the onset phase lasts 4–8 weeks^{39,40} or more than 8 weeks,⁴¹ respectively, may only be able to be done retrospectively. Difficulties in classification arise when patients have recurrent attacks of Guillain-Barré syndrome: such cases overlap with CIDP.^{42,43} Between 8% and 16% of patients presenting with a Guillain-Barré-like illness have one or more episodes of worsening after initial improvement. In one study,⁴⁴ patients who deteriorated more than 9 weeks after the onset of their neuropathy or who had more than two treatment-related fluctuations were more likely to develop CIDP.

Neurophysiological testing

Neurophysiological studies play a very important role in diagnosis, subtype classification, and confirmation that the disease is a peripheral neuropathy (panel 2).^{9,45} Sufficient information is required: usually, this would include data from at least three sensory nerves, at least three motor nerves with multisite stimulation and F waves, and bilateral tibial H-reflexes. In some cases, information from a smaller number of nerves may suffice. With this neurophysiological information, individual patients can be classified into one of the three subtypes of Guillain-Barré syndrome: AIDP, AMSAN, or AMAN (panel 2).^{9,45} However, unlike the clinical diagnostic criteria, which have been agreed on, there is no consensus on neurophysiological criteria for classification.^{9,46–49} Most clinicians rely primarily on motor conduction studies to identify demyelination, with additional detail coming from sensory conduction studies, which is useful for differentiation between AMAN and AMSAN.

Three large studies initially described the early electrodiagnostic findings in AIDP,^{50–53} which have been confirmed in later studies.^{9,54,55} In studies from the USA, Australia, and western Europe, early electrodiagnostic studies were abnormal in more than 85% of patients, with most showing evidence of demyelination. Up to 13% of studies were normal, but few remained normal with serial repetition.⁹ Motor conduction studies were abnormal earliest, with sensory conduction studies abnormal slightly later. The probability of finding an abnormal study indicating demyelination was increased as more nerves were studied and if late responses, F waves, and H-reflexes, were included.^{51,56} Early abnormalities included prolonged distal and F-wave latencies and reduced conduction velocities. With multisite—including proximal—

Panel 2: Neurophysiological criteria for AIDP, AMSAN, and AMAN

AIDP

At least one of the following in each of at least two nerves, or at least two of the following in one nerve if all others inexcitable and dCMAP > 10% LLN:

- Motor conduction velocity < 90% LLN (85% if dCMAP < 50% LLN)
- Distal motor latency > 110% ULN (> 120% if dCMAP < 100% LLN)
- pCMAP/dCMAP ratio < 0.5 and dCMAP > 20% LLN
- F-response latency > 120% ULN

AMSAN*

None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10% LLN
Sensory action potential amplitudes < LLN

AMAN*

None of the features of AIDP except one demyelinating feature allowed in one nerve if dCMAP < 10% LLN
Sensory action potential amplitudes normal

Inexcitable

dCMAP absent in all nerves or present in only one nerve with dCMAP < 10% LLN

dCMAP=compound muscle action potential amplitude after distal stimulation; pCMAP=compound muscle action potential amplitude after proximal stimulation; LLN=lower limit of normal. ULN=upper limit of normal. *In the original definitions the difference between AMSAN and AMAN proposed here is implied but not stipulated.

Panel 3: Investigations for Guillain-Barré syndrome

Studies related to establishing the diagnosis

Electrodiagnostic studies: a minimum study could include three sensory nerves (conduction velocity and amplitude), three motor nerves (distal latency, amplitude, and conduction velocity) with F waves and bilateral tibial H-reflexes

Cerebrospinal fluid examination: a minimum study could include glucose, protein, cell count, and bacterial culture

Studies to be done in special circumstances

Urine porphobilinogen and delta-aminolaevulinic acid concentrations

Antinuclear factor

HIV testing in at risk subjects

Drug and toxin screen

Studies related to general medical care

Urine analysis

Complete blood count

Erythrocyte sedimentation rate

Biochemical screening

Coagulation studies

ECG

Chest radiograph

Pulmonary function tests

Studies related to understanding causation

Stool culture and serology for *C jejuni*

Stool culture for poliovirus in pure motor syndromes

Acute and convalescent serology for cytomegalovirus, Epstein-Barr virus and *M pneumoniae* as a minimum

Antibodies to gangliosides GM1, GD1a, and GQ1b

stimulation, partial motor-conduction block was also an early, major electrophysiological abnormality and was distributed in the distal terminals, proximal segments, and common compression sites.⁵⁷⁻⁵⁹ More features of axonal degeneration developed over time, including both reduced evoked amplitudes and abnormal electromyography.⁹ This pattern can complicate classification of individual patients; the later a study is done the more likely it is that axon loss will have occurred, thus subtype classification becomes difficult.

For sensory conduction, the sural sensory action potential (SAP) is frequently normal in Guillain-Barré syndrome, while the median SAP is abnormal: the so-called "normal sural-abnormal median pattern".^{52,60}

Criteria for an abnormal study may not always be met, especially in patients with mild or early forms of the syndrome, when neurophysiological abnormalities can be minor. In other patients, definitive assignment to a subtype of Guillain-Barré syndrome may be impossible. Such classification difficulties arise when motor nerves are inexcitable. Then, it is not possible to determine whether the absence of recordable action potentials is due to complete conduction block from demyelination or to axonal degeneration or dysfunction. While this differentiation may be made by nerve biopsy, such an

investigation is rarely necessary except as a research procedure.^{61,62} There is no particular best time to do nerve conduction studies, although they should be done as soon as possible after presentation and the studies should be repeated after 1 or 2 weeks if the initial studies are non-diagnostic or do not allow adequate neurophysiological classification. Electromyography to assess axon loss could be useful in assisting with prognosis.

Investigations

In addition to neurophysiological testing, a lumbar puncture procedure is traditional and almost always appropriate. A raised CSF protein concentration is present in about 80% of patients, but CSF protein content is more likely to be normal during the first days of the illness.^{10,14} CSF should be analysed before treatment with intravenous immunoglobulin (IVIg), which can cause aseptic meningitis. Other investigations may be needed to exclude causes of similar illnesses or to identify infections or diseases that may be associated with Guillain-Barré syndrome (panel 3).

Pathogenesis

Pathological studies

AIDP

The classic pathological picture of Guillain-Barré syndrome is of multifocal mononuclear cell infiltration throughout the peripheral nervous system in which the distribution of inflammation corresponds to the clinical deficit.³ Macrophages invade the myelin sheaths and denude the axons. For the most part, macrophages seem to invade intact myelin sheaths (figure 1), as occurs in experimental autoimmune neuritis.^{4,63,64} According to one hypothesis, the activated macrophages are targeted to antigens on the surface of Schwann cells or the myelin sheath by activated T lymphocytes, which are major actors in experimental autoimmune neuritis. The initial invasion of the Schwann cell basement membrane is a consequence of matrix metalloproteinases, toxic nitric oxide radicals, and other mediators released by activated macrophages.^{65,66} According to an alternative, but not mutually exclusive hypothesis, the initial event is the binding of antibodies to the surface of the Schwann cell, fixation of complement, probable damage to the Schwann cell, and vesicular dissolution of myelin in advance of cell invasion. Evidence for this theory comes from autopsy material early in the course of the disease.⁶⁷ In severe lesions, the axons are also damaged probably as a secondary or "bystander" consequence of the toxic enzymes and radicals released by the immune mediated inflammatory response directed against the myelin.

AMAN

In AMAN, the pathological process is different.^{68,69} Probably targeted by their Fc-receptor-mediated binding of antibodies directed against ganglioside antigens on

the axolemma, macrophages invade the nodes of Ranvier where they insert between the axon and the surrounding Schwann cell axolemma, leaving the myelin sheath intact (figure 2). In severe cases, the axons are damaged in the ventral root, which may cause severe degeneration of the whole axon. However, patients with AMAN usually reach their nadir quicker and recover as fast as those with AIDP.⁷⁰ This rapid decline and subsequent recovery may be because in AMAN the pathological process blocks conduction but does not sever the axon, or perhaps because any degeneration which does occur is very distal.^{71,72}

AMSAN

The pathology in AMSAN resembles that in AMAN, with the same pattern of macrophage invasion of the perinodal space. However, with AMSAN, the dorsal, as well as the ventral, roots are affected. There is the same paucity of lymphocytic inflammation consistent with an antibody-mediated pathogenesis.⁸

Fisher's syndrome

The pathology of the pure form of Fisher's syndrome is not clear: since it is a benign condition, uncomplicated cases do not come to autopsy, and the affected parts of the nervous system cannot be biopsied. One case with relatively little weakness had inflammation and demyelination in the spinal roots.⁷³ The primary electrophysiological finding in Fisher's syndrome is an abnormality of sensory conduction. Sensory nerve action-potential amplitudes initially fall and then return to normal along with clinical improvement. The time course of these changes is consistent with sensory peripheral nerve demyelination or conduction failure along the axon, not axonal loss followed by regeneration.^{74,75} In most patients with the clinical picture of Fisher's syndrome, only the peripheral nervous system is affected, but some patients do have additional brain stem lesions. In others with a similar clinical picture but with the additional features of drowsiness and extensor plantar responses, the underlying problem is brain stem encephalitis (also known as Bickerstaff's encephalitis).⁷⁶

Experimental autoimmune neuritis

The pathology of AIDP closely resembles that of experimental autoimmune neuritis induced in animals by immunisation with peripheral nerve myelin. The predominant mechanism is a CD4 T-cell mediated response against one of the myelin proteins P2, P0, or PMP22.⁷⁷⁻⁷⁹ The hypothesis is that because of a loss of regulation⁸⁰ activated T cells cross the blood-nerve barrier, encountering a cross-reactive antigen in the endoneurium. The activated T cells then release cytokines and activate macrophages, which are the effector cells invading the myelin sheaths and inducing demyelination (figure 3).⁶⁶

Immunity to myelin protein antigens

T cells are clearly involved in the pathogenesis of AIDP since they are abundant in early lesions. Circulating activated T cells and serum soluble IL-2 receptor concentrations are increased in the acute stage³⁵ and oligoclonal

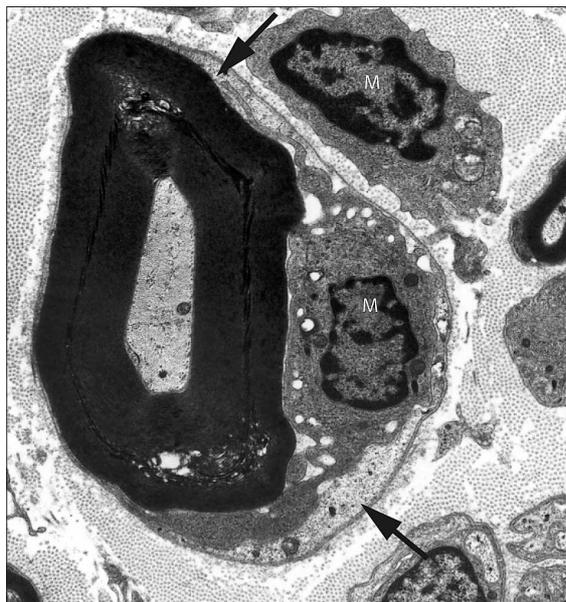


Figure 1: Nerve fibre from patient with AIDP

Electron micrograph shows a macrophage (M) has invaded Schwann cell basement membrane and stripped the abaxonal Schwann cell cytoplasm (arrows). Reproduced from reference 14, with permission from Springer Science and Business Media.

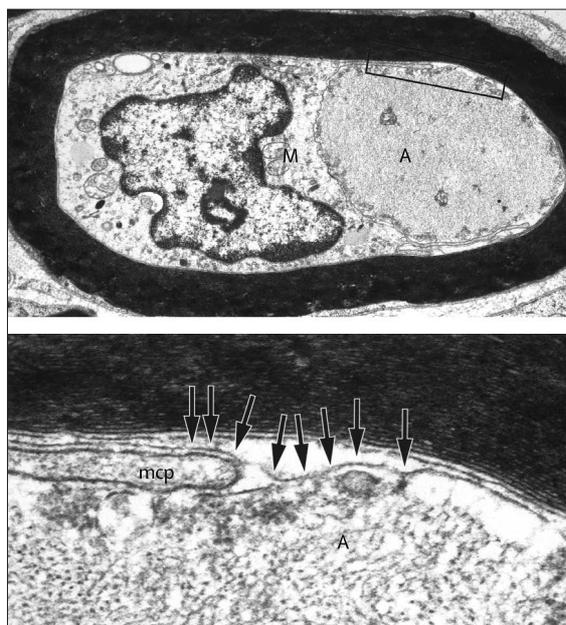


Figure 2: Nerve fibre from patient with AMAN

Lower panel is enlargement of box in upper panel. Electron micrograph shows macrophage (M) that has invaded the periaxonal space and axolemma (arrows) surrounding the axon (A). mcp=macrophage process. Reproduced from reference 68, with permission from Springer Science and Business Media.

expansion of V β and V δ gene usage occurs.⁸¹ This increase is likely to be caused by impairment of T-cell regulation. The occasional occurrence of Guillain-Barré syndrome in

patients with suppressed immune function caused by AIDS, or immunosuppression after organ transplantation is difficult to explain but might be the result of a simultaneous loss of regulatory mechanisms, possibly associated with cytomegalovirus infection.⁸² The antigenic targets of the activated T cells are not clear. There is only limited evidence of T-cell responses to the antigens which will induce experimental autoimmune neuritis.^{35,83-87} Although there are some reports of antibodies to P0 or PMP22, there are also contradictory reports and more research is needed.^{87,88}

Induction of experimental disease with glycolipids

Models of human peripheral neuropathy can be induced in rabbits by immunisation with glycolipids. Immunisation with galactocerebroside induces a demyelinating neuropathy and antibodies to galactocerebroside induce demyelination after intraneural injection.³⁵ However, antibodies to galactocerebroside—which can be detected readily with a complement fixation test—are rarely found in any of the Guillain-Barré syndrome subtypes except sometimes in association with *M pneumoniae* infection.^{89,90}

Particular interest has recently focused on gangliosides, which are glycosphingolipids whose lipid portions lie in the cell membrane and have their signature sugar residues exposed at the extracellular surface bearing one (ganglioside GM1), two (GD1), or more sialic acid molecules attached to one or more of the sugar residues (figure 4). Gangliosides are present in all tissues but are especially abundant in the nervous system. Immunisation of rabbits with two of the relatively minor glycolipids does induce disease. Immunisation with GD1b induces acute sensory neuronopathy mimicking a human disease in which antibodies to this ganglioside are often found.⁹¹

Immunisation with ganglioside GM1 induces an acute peripheral neuropathy for which results of histological analysis are similar to AMAN.^{92,93} This experiment was unwittingly repeated in humans when the injection of gangliosides became popular for the treatment of various conditions such as sciatica and stroke. A small number of cases of Guillain-Barré syndrome were reported in recipients of these injections. In one series, six patients with the AMAN subtype of Guillain-Barré syndrome all had antibodies to ganglioside GM1, whereas people who had received gangliosides without ill effects had none.⁹⁴ Systemic injection of antibodies to gangliosides does not induce disease; however, a mild mixed axonal-demyelinating neuropathy was induced in mice with a hybridoma secreting antibodies reactive with both GD1a and GT1b.⁹⁵ The different results might be explained by breakdown of the blood-nerve barrier in the hybridoma-bearing mice.

Although there is some controversy, results of most in-vivo and ex-vivo studies have failed to show any effect of antibodies to GM1 on nerve conduction.⁹⁶⁻⁹⁸ That there was no effect could be explained by the need for prolonged application of the antibody to its epitope to exert its effect. However, some researchers⁹⁹⁻¹⁰¹ have shown that

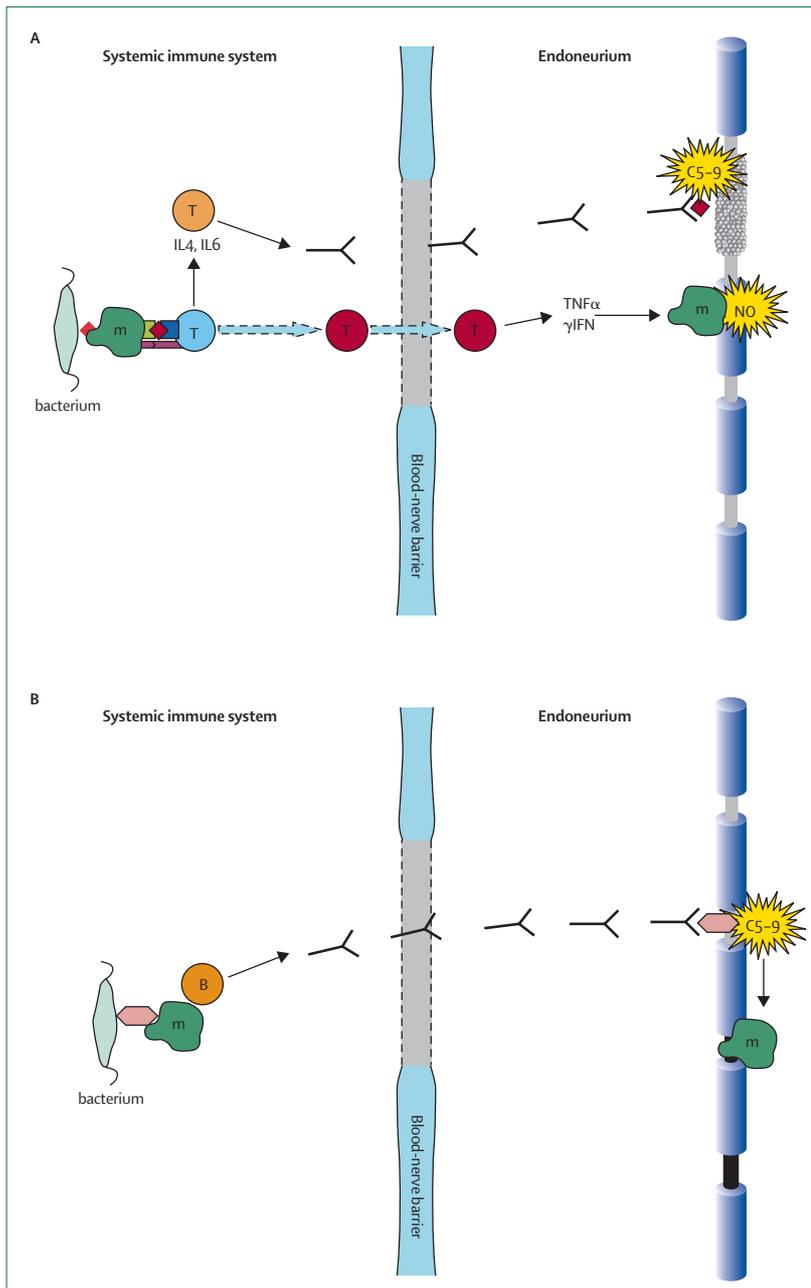


Figure 3: Immune mechanisms in (A) AIDP, and (B) AMAN, AMSAN, and Fisher's syndrome

(A) A bacterial protein epitope is presented by a macrophage to a T cell. The T cell is activated, penetrates the endothelium, recognises a cross-reactive antigen and, in the lower section, releases cytokines that activate endoneurial macrophages. These release enzymes and toxic nitric oxide (NO) radicals and so ultimately invade compact myelin. In the upper section, the activated T cell releases cytokines that help the B cell to produce antibodies that cross a damaged blood-nerve barrier and engage unidentified cross-reactive epitopes on the abaxonal Schwann cell surface, fix complement, damage the Schwann cell, and so produce vesicular dissolution of myelin. (B) A bacterial ganglioside-like epitope stimulates B cells to induce antibodies that opsonise cross-reactive axolemmal antigens, fix complement and target macrophages to invade the periaxonal space, and block conduction or cause axonal degeneration. In Fisher's syndrome, the perisynaptic Schwann cell at the motor nerve terminal is also targeted.

antibodies to GQ1b cause initial massive excitation and eventual conduction block at the GQ1b-rich motor-nerve terminals in the mouse phrenic nerve-diaphragm preparation. Most recently, both monoclonal mouse antibodies to GD1a and serum from a patient with AMAN containing antibodies to GD1a were shown to cause excitation and eventual conduction block of motor axons in the same preparation from mice over-expressing GD1a.¹⁰² In this model, the terminal motor axons were damaged but the perisynaptic Schwann cells were preserved. Likewise, antibodies to GalNAc-GD1a from a patient with AMAN and rabbit antibodies to the same glycolipid reacted with motor neurons and motor nerve terminals and blocked neuromuscular transmission in mouse spinal cord muscle co-culture.¹⁰³

Antibodies to gangliosides may participate in activating the immune system directly. Sera that contain high titres of anti-GM1 antibodies have the capacity to react with Fcγ receptors and, thus, activate neutrophils *in vitro*.¹⁰⁴ Although neutrophils have not been described in early Guillain-Barré syndrome lesions, they are present in the earliest lesions in rat experimental autoimmune neuritis.^{105,106} Opsonisation of antigens on the abaxonal Schwann cell surface or axolemma is a possible mechanism for macrophages to target antigens in AIDP and a likely mechanism in AMAN or AMSAN (figure 4).

Immunity to myelin glycolipids

By contrast with the dearth of information about immunity to myelin proteins in Guillain-Barré syndrome, many observations point to the importance of antibodies to gangliosides especially in AMAN and Fisher's syndrome.^{107,108} The AMAN subtype of Guillain-Barré syndrome is associated with antibodies to ganglioside GM1 in 64% of patients, GM1b in 66%, GD1a in 45%, and GalNAc-GD1a in 33%. Similar associations have been found for AMSAN, which is less common than AMAN. The AIDP subtype is not commonly associated with any of these antibodies.¹⁰⁹

The closest association is between Fisher's syndrome and antibodies to ganglioside GQ1b. Antibodies to this ganglioside are present in more than 90% of patients and are absent in other forms of inflammatory neuropathy except for an overlap syndrome in which Guillain-Barré syndrome is associated with ophthalmoplegia, formes frustes of Fisher's syndrome consisting of ophthalmoparesis or ataxia alone, or the related condition of Bickerstaff's encephalitis. Many patients with antibodies to GQ1b also have antibodies to the closely related GT1a. In rare cases, patients with a bulbar variant of Guillain-Barré syndrome have antibodies to ganglioside GT1a alone. These associations alone make a strong case for the importance of antibodies in the pathogenesis of these subtypes related to Fisher's syndrome of Guillain-Barré syndrome. However, the associations are approximate and not absolute. For instance, antibodies reacting with GD1a are associated not only with AMAN but also with formes

frustes of Fisher's syndrome with ataxia, or ataxia and facial palsy without ophthalmoplegia with little or no weakness.¹¹⁰

There are some differences in the distribution of individual gangliosides which have been invoked to explain the distribution of lesions in Guillain-Barré syndrome subtypes. Thus, there is more ganglioside GM1 in ventral than in dorsal roots, more GQ1b in the ocular motor nerves than in the spinal roots, and more GT1a in the lower than the upper cranial nerves.¹¹¹

The relation between ganglioside distribution and the site of lesions in neuropathies associated with the corresponding antibody is not strict. For instance antibodies to GalNAc-GD1a react with the inner myelin sheath and axolemma of ventral root fibres and also intramuscular nerves but also with small-diameter dorsal root fibres.¹¹⁰ However, a more important factor than the crude anatomical distribution is the density or configuration of gangliosides at different sites. For instance, a specific monoclonal antibody recognises GD1a in the large myelinated nerve fibres of the rodent ventral root, but not in the dorsal root, although it can be detected in both by biochemical methods.¹¹² Another important factor is the accessibility of the ganglioside to the immune system. There is as much GQ1b in the optic nerves, where it may be protected by the blood-brain barrier, since the optic nerves are not affected in Fisher's syndrome despite the presence of antibodies to GQ1b.¹¹¹

Despite the success in identifying antibodies in AMAN, AMSAN, and Fisher's syndrome, no glycolipid antibody has been consistently discovered in a substantial proportion of patients with AIDP. The question, therefore, arises: is AIDP also caused by an unidentified anti-ganglioside antibody? Or is it due to an antibody to a protein or glycoprotein expressed at the Schwann cell surface or perhaps the result of cell-mediated immunity? In this argument about the role of antibodies in AIDP, the

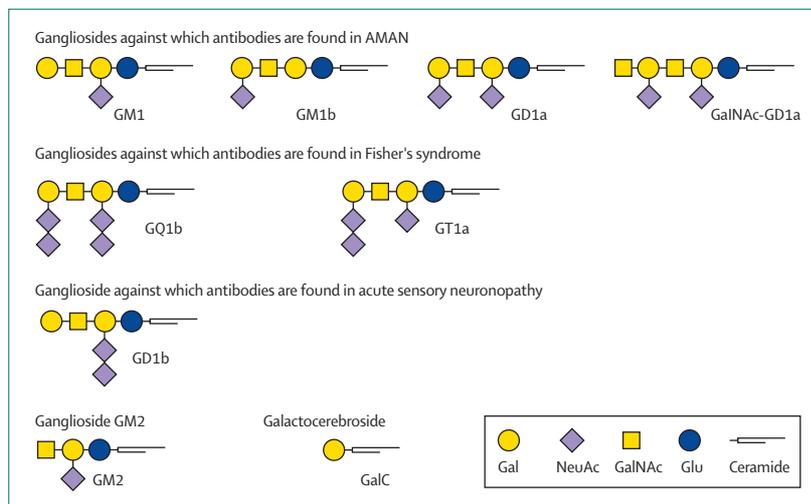


Figure 4: Structures of gangliosides and galactocerebroside and Guillain-Barré syndrome subtype associations. Adapted from reference 107, with permission of Oxford University Press.

fact that detection of antibodies to gangliosides is profoundly affected by the assay system should be kept in mind. In a Japanese study,¹¹³ 32 of 121 patients had antibodies to GM1 only, and 12 more had antibodies to a combination of GM1 and phosphatidic acid.

An unresolved problem is why the antibodies to ganglioside discovered in AMAN and Fisher's syndrome should almost invariably belong to the IgG1 or IgG3 subclasses, which are conventionally thought to require T-helper cell involvement to enable class switching from IgM. Conventional T cells are thought not to be able to respond to glycolipids. The possibility that $\gamma\delta$ T cells, which do have the capacity to respond to glycolipids, are involved has begun to be explored. Such cells have been identified in the peripheral nerves of patients with Guillain-Barré syndrome but are not specific, since they are also present in patients with vasculitic neuropathy.^{114,115} In the single study so far, no significant perturbations of circulating $\gamma\delta$ T cells have been discovered.¹¹⁶

Cross-reactivity between microbial and neural antigens

During the past 10 years, it has become clear that infections can induce antibodies that cross-react with neural antigens and lead to inflammatory neuropathy. In particular, there is convincing evidence for the association between *C jejuni* infection and Guillain-Barré syndrome being caused by cross-reactivity between epitopes in the lipo-oligosaccharide in the bacterial wall and gangliosides.¹¹⁷ *C jejuni* infection may be followed by any subtype of Guillain-Barré syndrome including Fisher's syndrome.¹¹⁸ However, following *C jejuni* infection, axonal degeneration is more likely to occur. In a Japanese study,¹¹⁹ all of 22 patients with preceding *C jejuni* infection had AMAN. The strains of *C jejuni* that precipitate AMAN tend to be different from those that commonly cause enteritis. Furthermore, they are more likely to have the genes for enzymes that synthesise sialic acid structures in the bacterial wall, mimicking gangliosides GM1 and GD1a, or GQ1b.^{120,121} Injection of these strains into mice induced ganglioside antibodies, whereas injection of strains from which the sialic acid synthase genes had been knocked out did not. Furthermore, injection of either GM1 or *C jejuni* lipo-oligosaccharide into rabbits induced GM1 antibodies and a peripheral neuropathy with all the histological hallmarks of human AMAN.^{93,122}

The strains of *C jejuni* that induce Fisher's syndrome often bear epitopes that resemble GQ1b, GT1a, or GD3.^{123,124} Monoclonal antibodies raised against these epitopes on the lipo-oligosaccharide of *C jejuni* stained the motor nerve terminals and induced massive release of acetylcholine and then conduction block in a mouse phrenic nerve-diaphragm preparation.¹²⁵ This event was associated with complement-mediated destruction of the motor nerve terminal and the overlying perisynaptic Schwann cell.^{101,126} This model establishes cross-reactivity between *C jejuni* lipo-oligosaccharides and epitopes on axons or Schwann cells as a likely mechanism to explain

the pathogenesis of Fisher's syndrome associated with *C jejuni* infection. However, there must be other ways in which these antibodies arise, since only a small proportion of patients with Fisher's syndrome have antecedent *C jejuni* infection. There is also evidence of the presence of GM1 and GQ1b-like epitopes in the bacterial wall of *Haemophilus influenzae* which could account for the occurrence of Guillain-Barré syndrome or Fisher's syndrome following infection with that organism.^{124,127,128}

When Guillain-Barré syndrome follows cytomegalovirus infection, antibodies against GM2 are common. Such antibodies bind to fibroblasts infected with cytomegalovirus, providing a possible example of cross-reactivity between viral induced glycolipid antigens and a myelin antigen.¹²⁹ However, some patients with cytomegalovirus-associated Guillain-Barré syndrome do not have antibodies to GM2, and these antibodies are not uncommon after cytomegalovirus infection in the absence of Guillain-Barré syndrome, casting doubt on the postulated causative link between cytomegalovirus, GM2, and the syndrome.⁹⁰

Infection with *M pneumoniae* precedes about 5% of cases of Guillain-Barré syndrome and is known to stimulate antibodies against human carbohydrate antigens including galactocerebroside, which is the principal glycolipid antigen of peripheral and CNS myelin.¹⁴ Cross-reactivity with galactocerebroside after *M pneumoniae* infection has been thought to be important in inducing AIDP. However, in a recent study of patients who had Guillain-Barré syndrome after an *M pneumoniae* infection, AMAN was more common than AIDP. In one such patient, antibodies to GM1 cross-reacted with the same epitopes as the antibodies to galactocerebroside antibodies, and antibodies to galactocerebroside were identified in patients who did not develop Guillain-Barré syndrome.⁹⁰ Thus, whether antibodies to galactocerebroside induce disease in human beings is unclear.

Human immunosusceptibility genes as contributory factors

Reports of Guillain-Barré syndrome occurring in more than one family member are rare.¹³⁰⁻¹³⁴ Most investigations have failed to reveal any association between HLA class I or class II antigens, even when the analysis was confined to homogeneous subgroups such as those who developed Guillain-Barré syndrome after swine-flu vaccine.¹³⁵ There was a significant association with HLA DQB1*03 in British *C jejuni* associated Guillain-Barré syndrome,¹³² but this link was not noted in Dutch or Japanese studies.^{131,133,136} Most recently in northern Chinese patients with AIDP, strong positive associations were found with particular DQ β and DQ β positional residues, and a weak negative association with another DQ β residue.¹³⁴ The residues implicated are important in peptide binding and T-cell recognition and are involved in the pathogenesis of autoimmune diseases including insulin dependent diabetes mellitus. No association between AMAN and any

MHC class II alleles was noted in the same study, supporting the view that AMAN has a different pathogenetic mechanism from AIDP.

Attempts to identify other immunogenetic susceptibility factors have mostly been unsuccessful. There was no association with functional polymorphisms of the CD14 lipopolysaccharide receptor or of Toll-like receptor 4, which might be implicated in susceptibility to *C jejuni*, in a cohort of 242 patients with Guillain-Barré syndrome.¹³⁷ Despite initial positive reports, a meta-analysis of all the published data showed no association between FcγR polymorphisms and the occurrence of Guillain-Barré syndrome in 345 western European patients, except that FcγRIIIb-NA2 predisposed people to severe disease.¹³⁸ The relevance of this finding is unclear since FcγRIIIb is only expressed on neutrophils, which are not known to be involved in the pathogenesis of any form of Guillain-Barré syndrome. However, there was a significantly higher frequency of TNFα2 allele in Japanese patients with *C jejuni* infection and Guillain-Barré syndrome than in controls, which is consistent with T cells having an important role.¹³⁹

Clinical course

In typical cases, the first symptoms are pain, numbness, paraesthesia, or weakness in the limbs. The weakness may initially be proximal, distal, or a combination of both. Numbness and paraesthesia usually affect the extremities and spread proximally. In children, pain may be a prominent presenting symptom. The facial nerves are often affected and less often the bulbar and ocular motor nerves. In 25% of cases, weakness of the respiratory muscles requires artificial ventilation. Autonomic involvement is common and causes urine retention, ileus, sinus tachycardia, hypertension, cardiac arrhythmia, and postural hypotension. In severe cases, muscles become wasted after about 2 weeks. The disease reaches its nadir by 2 weeks in most cases and in 4 weeks in nearly all. After a variable plateau phase, recovery begins with return of proximal, followed by distal, strength over weeks or months. Between 4% and 15% of patients die, and up to 20% are disabled after a year despite modern treatment.^{17,140} Even in those who recover well, residual weakness and loss of motor units can usually be detected on clinical and electrophysiological examination and could explain the fatigue that is a common problem.^{141,142}

Prognosis

From the many case series, and especially from population-based studies that have investigated possible prognostic factors, the most consistent finding has been that the outlook is worse in elderly patients.^{9,19,140} In children, recovery is more rapid and more likely to be complete; death is exceptional.^{143,144} In adults and children, severity of disease at nadir, expressed as being

bedbound or requiring artificial ventilation, has usually been identified as an adverse prognostic factor.¹⁴⁰

Patients with a rapid onset phase are more likely to do badly. Patients who can still walk at 14 days are likely to improve with or without treatment but may be left with some residual disability.^{20,145} In some studies, low amplitude motor responses, and in particular, absent motor responses, and axonal involvement shown by initial electromyography are also related to a poorer outcome, probably in the context of AIDP.^{9,19,140}

Most patients with AMAN make a good recovery: 14% of a series of 44 patients were unable to walk independently after 6 months but all eventually recovered this ability.¹⁴⁶ In several studies, patients with a previous diarrhoeal illness or *C jejuni* infection have had more severe disease and a delayed recovery than have other patients.¹⁴⁰ The presence of cytomegalovirus has also been shown to predict delayed recovery and Epstein-Barr virus infection has been associated with milder forms of the syndrome.²⁰

General treatment

Excellent multidisciplinary care is needed to prevent and manage the potentially fatal complications of the disease, and the methods have been the subject of a consensus report.¹⁴⁷ Respiratory failure occurs in 25% of patients and is more likely in cases with rapid progression, bulbar palsy, upper limb involvement, and autonomic dysfunction. Regular monitoring, including measurement of vital capacity, and early transfer to an intensive therapy unit for prophylactic intubation are essential. All patients with severe disease should be monitored for possible cardiac arrhythmia. In non-ambulant adult patients, subcutaneous heparin and graduated compression stockings should be used to prevent deep vein thrombosis. Wide fluctuations of pulse rate and blood pressure occur in severe cases and can herald serious and sustained autonomic failure. Other complications requiring careful management include pain, urinary retention, and ileus.¹⁴⁸

A multidisciplinary rehabilitation programme is as important as immunotherapy, and the occupational and physical therapy methods used reflect individual experience and institutional practice with little research based evidence.^{141,149–151} Persistent fatigue is a common problem, perhaps due to permanent loss of axons,^{142,152} and may respond to an exercise programme.¹⁵³

Although there is no convincing evidence that immunisations in current use cause Guillain-Barré syndrome, slight concern remains that some vaccines—possibly tetanus toxoid—might give rise to the syndrome. In view of this concern, the risks and benefits of immunisation merit individual review.^{34,147,154}

Many patients benefit from joining a patient support organisation such as The GBS/CIDP Foundation International in the USA and the Guillain-Barré Syndrome Support Group in the UK. Both provide patient orientated information websites and leaflets.

See
<http://www.gbsfi.com/>
 and
<http://www.gbs.org.uk/>

Immunotherapy

Plasma exchange became accepted as the gold standard treatment for Guillain-Barré syndrome almost 20 years ago. Evidence to support this practice has accumulated from six trials, but not all studies provided all the outcome measures of interest. Most used a 7-point Guillain-Barré syndrome disability grade scale. In four trials, including 585 participants with available data, plasma exchange increased the improvement after 4 weeks by an average of 0.89 grades (95% CI 0.63–1.14). In five trials with 623 participants, plasma exchange almost halved the proportion of patients requiring ventilation after 4 weeks from 27% to 14% (relative risk [RR] 0.53 [95% CI 0.39–0.74]; $p=0.0001$). In four trials with 204 participants, plasma exchange increased the proportion of patients who recovered full strength within a year from 55% to 68% (RR 1.24 [1.07–1.45]).¹⁵⁵ Treatment with plasma exchange was beneficial during the first 4 weeks, but the benefit was greatest when treatment was given early.^{156,157} The usual regimen is a total exchange of about five plasma volumes during 1–2 weeks. For patients with moderate disease, there was no difference in outcome between those who received four 1.5 plasma volume exchanges and those who received six exchanges.¹⁵⁸ The costs associated with plasma exchange are more than recovered by savings made in avoiding intensive care and hospital stay.¹⁵⁹

Since a randomised controlled trial showed that IVIg has similar efficacy to plasma exchange,¹⁶⁰ IVIg has replaced plasma exchange as the preferred treatment for severe Guillain-Barré syndrome in most hospitals because of its greater convenience. In the Cochrane review of IVIg with an additional four trials that included a total of 536 participants, there was no difference between the two treatments in the improvement in disability after 4 weeks (weighted mean difference 0.02 [95% CI 0.25 to –0.20]; more improvement with IVIg than plasma exchange). There was also no significant difference between the two treatments with respect to duration of mechanical ventilation, death, or residual disability.¹⁶¹ The regimen almost always used has been 0.4 g/kg per day for 5 days. Trials of combining treatments, giving IVIg after either plasma exchange or immunoabsorption have failed to show extra benefit compared with either alone.¹⁶¹ The mechanism of action of IVIg is probably multifactorial, possibly involving blockade of Fc receptors, provision of anti-idiotypic antibodies, interference with complement activation, and T-cell regulation.¹⁶²

An American Academy of Neurology practice parameter recommended either plasma exchange or IVIg for the treatment of patients with Guillain-Barré syndrome who have lost the ability to walk, but questions about best practice remain.¹⁶³ The available evidence is mostly for adult patients. Does immunotherapy help children? Severely affected children are usually treated with IVIg because of its greater convenience and the small amount of evidence available supports this practice.¹⁶⁴ Does immunotherapy help mildly affected patients who can still

walk? One trial with 91 participants showed that plasma exchange is beneficial for these patients, but IVIg has not been tested in this population. Is treatment effective if it is started more than 2 weeks after disease onset? The North American trial¹⁵⁶ showed that plasma exchange is effective during the first 4 weeks. Trials of IVIg have included patients within 2 weeks of disease onset, but the effect of IVIg after 2 weeks remains untested. The most important question of all is how should patients be treated who have still not shown any signs of recovery 2 weeks or more after their first treatment? A series of seven cases suggests that a second course of IVIg might be effective,¹⁶⁵ but a randomised controlled trial is sorely needed to provide more support for this observation.

The balance of evidence from six trials with 587 participants is that corticosteroids are ineffective.¹⁶⁶ Improvement has most commonly been measured by assessing change on the 7-point Guillain-Barré syndrome disability scale. In four trials of oral corticosteroids with a total of 120 participants, there was significantly less improvement after 4 weeks with corticosteroids than without (weighted mean difference 0.82 of a disability grade less improvement [95% CI 0.17–1.47]).¹⁶⁶ In two trials with a combined total of 467 participants, there was a non-significant trend towards more benefit from intravenous corticosteroids (weighted mean difference 0.17 of a disability grade more improvement after 4 weeks than with placebo [95% CI –0.06 to 0.39]).¹⁶⁶ Likewise, there was also no significant improvement in patients treated with corticosteroids for other important outcomes including time to recovery of unaided walking, time to discontinue ventilation in the subgroup who need ventilation, death, and disability after 1 year. In one trial, however, there was a non-significant trend toward more rapid improvement when intravenous methylprednisolone 500 mg daily for 5 days was added to IVIg.¹⁶⁷ This effect became significant in a post-hoc analysis after correction for prognostic factors including age and initial disability. The lack of a more obvious effect of corticosteroids is difficult to explain in an inflammatory disease, especially since such treatment is beneficial in the related condition of chronic inflammatory demyelinating polyradiculoneuropathy. Possible explanations for the lack of effect could be that corticosteroids adversely affect the recovery process by inhibiting macrophage clearance of myelin debris and so hamper remyelination or aggravate the damage of denervated muscle fibres.^{168,169}

Although the past 13 years have seen the emergence of treatments that at least shorten the duration of Guillain-Barré syndrome, 20% of patients are left disabled, and persistent symptoms short of severe disability are common in the remainder. Better treatments are needed. It seems unlikely that repeating IVIg treatment will be adequate and further research is needed to identify the key mechanisms at work in the different subtypes of the disease. Complement-mediated mechanisms have been invoked in all subtypes and drugs that inhibit the

complement cascade should be considered. In those patients with detectable antibodies against gangliosides, a novel approach is to absorb the antibodies on a column that has a specific affinity for the individual ganglioside.¹⁷⁰

There is a temptation to borrow drugs that have been shown to be beneficial in multiple sclerosis for the treatment of Guillain-Barré syndrome. A small trial showed that interferon beta-1a would be safe in patients with Guillain-Barré syndrome, but the sample size was too small to detect anything other than a very large effect.¹⁷¹ If T cells were shown to be of prime importance in AIDP then drugs which interdict T-cell cytokines or prevent the passage of T cells into the endoneurium should be considered, dependent on their safety record. Protection of the axons by sodium channel blockade was a successful strategy in experimental autoimmune neuritis and should be considered for Guillain-Barré syndrome.¹⁷² A pilot trial of brain-derived neurotrophic factor in Guillain-Barré syndrome was discontinued when the company undertaking the research withdrew the drug from development,¹⁷³ but other trophic factors or combinations of trophic factors may be worth pursuing.

Conflict of interest statement

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