

# Guillain-Barré syndrome

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## Abstract

**Guillain-Barré syndrome is an autoimmune disorder encompassing a heterogeneous group of pathological and clinical entities. Antecedent infections are thought to trigger an immune response, which subsequently cross reacts with nerves leading to demyelination or axonal degeneration. Both intravenous immunoglobulin treatment and plasma exchange have been found to be equally beneficial. Several factors are useful in predicting the outcome of these patients.**

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One of the earliest descriptions of what we know today as Guillain-Barré syndrome is found in Landry's report on 10 patients with "ascending paralysis" in 1859.<sup>1</sup> In 1916 Guillain, Barré, and Strohl described two French soldiers with motor weakness, areflexia, and "albuminocytological dissociation" in the cerebrospinal fluid.<sup>2</sup> Subsequently several cases with similar manifestations were reported, and this clinical entity was named after Guillain and Barré. Later, different types of the syndrome with characteristic clinical features were identified. This distinction is possible today on the basis of clinical features, aetiology, and electrophysiological characteristics.

## Epidemiology

The annual incidence of Guillain-Barré syndrome is around 1-3/100 000 population according to epidemiological studies from Europe, USA, and Australia.<sup>3-10</sup> It can occur in any age group. The age specific curve seems to show a bimodal distribution, with peaks in young adults and the elderly.<sup>3 5 8 9 11</sup> Some studies show an increase in incidence with age, especially in the older age group.<sup>4-6 8 10</sup> Males appear to be affected more commonly.<sup>5 6 8-10</sup> There are no consistent geographical variations. However, modest seasonal variations are noted in some series.<sup>8 11</sup> In a cohort study, age adjusted relative risks indicate that the risk for Guillain-Barré syndrome is lower during pregnancy and increases after delivery.<sup>12</sup>

## Clinical features

Symptoms are preceded by an antecedent event in about two thirds of patients.<sup>13 14</sup> Respiratory infections are the commonest, reported in about 40% of cases within one month before the onset of the disease.<sup>13 14</sup> About 20% experience gastroenteritis as the antecedent cause.<sup>13 15</sup>

The commonest manifestation is limb weakness, more proximal than distal. Facial palsy is the commonest type of cranial nerve involve-

ment (in 53%), followed by bulbar weakness, ophthalmoplegia, and tongue weakness.<sup>16</sup> In about half the cases the illness is heralded by sensory symptoms.<sup>17</sup>

Altogether about 80% have sensory symptoms.<sup>16</sup> Pain is a very common symptom, experienced by around 90%, and is often severe.<sup>18</sup> Autonomic dysfunction is seen in about two thirds of the cases, manifesting as either excess or reduced activity of the sympathetic or parasympathetic nervous system.<sup>19</sup> Pulse and blood pressure changes are the commonest manifestations of dysautonomia (box 1).<sup>19 20</sup>

The onset of symptoms can either be acute or subacute. Gradual recovery takes place after a plateau phase. In a large multicentre study, the mean time to reach nadir, improvement, and clinical recovery were 12, 28, and 200 days, respectively.<sup>14</sup> It was also found that 98% of patients achieved the plateau phase by four weeks from the onset. The mean duration of the plateau was found to be 12 days in another study.<sup>17</sup>

### Box 1: Clinical features of Guillain-Barré syndrome

- Motor dysfunction
  - Symmetrical limb weakness: proximal, distal or global
  - Neck muscle weakness
  - Respiratory muscle weakness
  - Cranial nerve palsies: III-VII, IX-XII
  - Areflexia
  - Wasting of limb muscles
- Sensory dysfunction
  - Pain
  - Numbness, paraesthesiae
  - Loss of joint position sense, vibration, touch and pain distally
  - Ataxia (see text)
- Autonomic dysfunction
  - Sinus tachycardia and bradycardia
  - Other cardiac arrhythmias (both tachy and brady)
  - Hypertension and postural hypotension
  - Wide fluctuations of pulse and blood pressure
  - Tonic pupils
  - Hypersalivation
  - Anhydrosis or excessive sweating
  - Urinary sphincter disturbances
  - Constipation
  - Gastric dysmotility
  - Abnormal vasomotor tone causing venous pooling and facial flushing
- Other
  - Papilloedema

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## Antecedent events

### INFECTIONS

#### *Campylobacter jejuni*

Infections are well established as antecedent events of the Guillain-Barré syndrome. *Campylobacter jejuni* is the commonest pathogen identified. About 20% of patients report a preceding diarrhoeal illness.<sup>15</sup> Studies from the USA and Europe have shown culture or serological evidence of preceding *C jejuni* infection in 26–36% of patients.<sup>15 21–23</sup> This was found in as many as 45% in a Japanese study.<sup>24</sup>

Patients tend to develop acute motor axonal neuropathy or acute motor-sensory axonal neuropathy more often, and acute inflammatory demyelinating polyradiculoneuropathy less often, in association with *C jejuni* (24% *v* 2% and 40% *v* 76%, respectively).<sup>15</sup> This infection also remains the most frequent antecedent infection in the Miller Fisher syndrome (see below).<sup>25</sup> Guillain-Barré syndrome following *C jejuni* infection has been shown to be associated with slower recovery, severe residual disability, and axonal degeneration.<sup>15</sup>

Both the serotype of the organism and host susceptibility seem to play important roles in the pathogenesis. There are several serotypes of *C jejuni*. In Japan, Penner serotype 19 (O:19) is the commonest strain associated with Guillain-Barré syndrome (around 80%); this is a rare strain in sporadic *C jejuni* enteritis.<sup>24 26</sup> However, in the USA and Germany only 29% are positive for O:19.<sup>27</sup> The commonest strain isolated in association with Guillain-Barré syndrome from South Africa is O:41.<sup>28</sup> Serotype O:2 is the commonest strain associated with the Miller Fisher syndrome.<sup>29 30</sup> Based on American data, it has been estimated that the risk of developing Guillain-Barré syndrome following infection with *C jejuni* and O:19 serotype is 1 in 1058 and 1 in 158, respectively.<sup>31</sup>

The pathogenesis of *C jejuni* associated Guillain-Barré syndrome is explained on the basis of a mechanism called “molecular mimicry.” Gangliosides are important surface molecules of the nervous system. According to the concept of molecular mimicry, antibodies formed against ganglioside-like epitopes in the lipopolysaccharide moiety of *C jejuni* cross react with peripheral nerves causing damage. Molecular mimicry was first demonstrated between the lipopolysaccharide of O:49 serotype and GM1 ganglioside of the nervous tissue.<sup>32</sup>

Host susceptibility also seems to be important in determining the outcome following *C jejuni* infection. It was shown that campylobacter isolated from both patients with Guillain-Barré syndrome and those with enteritis contained similar ganglioside-like epitopes, and those who developed Guillain-Barré syndrome had raised titres of antibodies against gangliosides GM1 and GD1a.<sup>33</sup>

#### *Cytomegalovirus*

Cytomegalovirus is the second commonest infection reported. The evidence of preceding cytomegalovirus infection was present in 5% of patients with Guillain-Barré syndrome in a Japanese study<sup>24</sup> and in 11–13% in European

studies.<sup>13 22</sup> In a study from Belgium, it was as high as 22%.<sup>34</sup>

Guillain-Barré syndrome following cytomegalovirus infection appears to be a distinct entity. It is found more commonly in females and young age groups. Affected individuals tend to have a severe course initially, with respiratory difficulties. They often develop cranial nerve palsies (usually bilateral facial palsy) and severe sensory loss.<sup>35</sup>

Reduced sensory nerve action potentials are found more often in this group, but nerve conduction velocity, percentage of conduction blocks, and denervation activity do not differ significantly from other groups. Their recovery is usually delayed.<sup>35</sup> Liver function disturbances may be present in this group. In a prospective study involving 100 patients increased liver enzymes were found in 38, and 10 of them showed evidence of recent cytomegalovirus infection.<sup>36</sup>

The exact pathogenesis is not clear in this group, and molecular mimicry has been proposed as a possible mechanism. Anti-GM2 antibodies are found significantly more often in cytomegalovirus associated Guillain-Barré syndrome than in control cases.<sup>37</sup> A recent report on the occurrence of anti-GM2 antibodies in acute cytomegalovirus infection without neuropathy<sup>38</sup> raises the question of host factors in the pathogenesis.

#### *Other infections*

Associations with Epstein-Barr virus and *Mycoplasma pneumoniae* are more often found in Guillain-Barré syndrome than in control patients (10% and 5%, respectively). Serological evidence of infections with *Haemophilus influenzae*, parainfluenza type 1 virus, influenza A and B viruses, adenovirus, varicella zoster virus, and parvovirus B 19 is not more common than in controls.<sup>13 22</sup>

HIV infection is a well known association with Guillain-Barré syndrome, which can occur during seroconversion.<sup>39</sup> Guillain-Barré syndrome has also been reported following Lyme disease.<sup>40</sup> The numerous other preceding infections that have been cited—such as hepatitis A, B, C, and D, typhoid, and falciparum malaria—are confined to anecdotal case reports.

### VACCINES

Isolated case reports and epidemiological studies have drawn attention to a possible association of Guillain-Barré syndrome with several vaccines including Semple rabies,<sup>41</sup> oral polio,<sup>42 43</sup> influenza,<sup>44 45</sup> measles,<sup>46</sup> measles/mumps/rubella (MMR),<sup>47</sup> tetanus toxoid containing vaccines,<sup>48</sup> and hepatitis B.<sup>49</sup> However, a temporal association between the two events does not necessarily mean there is a cause-effect relation. One needs to evaluate the available epidemiological data to decide whether the alleged association is statistically significant.

During the A/New Jersey influenza (“swine flu”) vaccination programme in 1976–1977 in the USA, increased numbers of cases of Guillain-Barré syndrome were reported. As a result, nationwide surveillance for the syndrome

was initiated and epidemiological studies were conducted to determine the statistical significance of the association. It was shown that the relative risk of Guillain-Barré syndrome following vaccination ranged from 4 to 7.8 over a period of six weeks.<sup>44</sup> Subsequently the Expert Neurology Group of the Centers for Disease Control reassessed the data and found the relative risk to be 7.1. They concluded that there was an increased risk of developing Guillain-Barré syndrome within the first six weeks after vaccination but not beyond that. It was also shown that 8.6 cases of Guillain-Barré syndrome per million vaccinations in Michigan and 9.7 cases per million vaccinations in Minnesota were attributable to vaccination.<sup>50</sup>

However, subsequent studies have not shown such a high relative risk. For the 1978–1979 influenza vaccination campaign, the relative risk of Guillain-Barré syndrome after vaccination was 1.4 and that association was not found to be statistically significant.<sup>51</sup> During the 1979–1980 and 1980–1981 seasons the relative risk was 0.6 and 1.4, respectively.<sup>52</sup> It was 1.1 for the period of 1980–1988, and a temporally related increase in Guillain-Barré syndrome could not be demonstrated.<sup>53</sup> Later a group of researchers found an adjusted relative risk of 1.7 for the 1992–1993 and 1993–1994 seasons. The estimated maximum of the attributable risk was 1.6 cases per million vaccinations.<sup>54</sup> This means that the risk of developing Guillain-Barré syndrome after influenza vaccination is one to two cases per million persons vaccinated. It should also be noted that no cases of vaccine associated Guillain-Barré syndrome were found under the age of 45 in the 1992–1993 and 1993–1994 seasons.<sup>54</sup>

Reviewing the data, the US Advisory Committee on Immunization Practices (ACIP) in their 1999 recommendations concluded: “Among persons who received the swine influenza vaccine in 1976, the rate of Guillain-Barré syndrome that exceeded the background rate was slightly less than 10 cases per million persons vaccinated. Evidence for a causal relationship of Guillain-Barré syndrome with subsequent vaccines prepared from other virus strains is less clear. . . . Even if Guillain-Barré syndrome were a true side effect of vaccination in the years after 1976, the estimated risk of Guillain-Barré syndrome of slightly more than one additional case per million persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination in all age groups. . . . The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death greatly outweigh the possible risks for developing vaccine associated Guillain-Barré syndrome.”<sup>55</sup>

A retrospective study based on hospital records from Finland showed a significantly increased incidence of Guillain-Barré syndrome during a nationwide oral polio vaccination campaign.<sup>45</sup> However, subsequent epidemiological studies from Finland<sup>56</sup> and southern California<sup>57</sup> failed to prove a cause-effect relation between oral polio vaccination and Guillain-Barré syndrome. Furthermore, a large scale study analysing data from Latin America between 1989 and

1991 found no temporal association between the mass oral polio vaccination campaign and Guillain-Barré syndrome.<sup>58</sup>

The risk of developing Guillain-Barré syndrome following tetanus toxoid containing vaccines was evaluated using data from two large scale epidemiological studies. It was found that fewer cases of Guillain-Barré syndrome were seen after vaccination than expected by chance alone. The authors concluded that there was no association of public health significance.<sup>59</sup>

The reported associations of Guillain-Barré syndrome with measles vaccine<sup>46</sup> and MMR vaccine<sup>47</sup> are mostly confined to anecdotal case records. A large scale study from South America, based on over 2000 children with Guillain-Barré syndrome after mass measles vaccination campaign in 1992 and 1993, failed to establish a statistically significant causal relation.<sup>60</sup>

Guillain-Barré syndrome has been reported after hepatitis B vaccination.<sup>49</sup> A postmarketing surveillance study for neurological adverse events following hepatitis B vaccination reported nine cases among an estimated 850 000 recipients of the vaccine. The study did not show any conclusive epidemiological association between neurological adverse events and the vaccine.<sup>61</sup> Another epidemiological study drew similar conclusions.<sup>62</sup>

#### ANECDOTAL ASSOCIATIONS

Several associations and triggering factors have been reported, mostly in the form of individual case reports. These include surgery, epidural anaesthesia, renal transplantation, bone marrow transplantation, systemic lupus erythematosus, sarcoidosis, lymphoma, and snake bite. The statistical significance of these relations is unclear and they could even be chance associations. A prospective study examining antecedent events for the syndrome found that immunisation, insect bites, and animal contacts were equally common in both index and control groups.<sup>13</sup> Several drugs have also been implicated as triggering factors. A case-control study showed that patients with Guillain-Barré syndrome had used antimotility drugs and penicillins more often, and oral contraceptives less often.<sup>63</sup> However, a review of published reports on drug associated Guillain-Barré syndrome concluded that a definite cause-effect relation could not be established with the available data.<sup>64</sup>

#### Clinicopathological types

##### ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the commonest type of Guillain-Barré syndrome.<sup>15</sup> Necropsy studies have shown lymphocytic infiltration of the peripheral nerves and macrophage mediated segmental demyelination.<sup>65 66</sup> Infiltration with T cells in the endoneurium has been demonstrated during the early phase.<sup>66</sup> Axonal loss may also occur, especially in severe cases as a secondary event. These pathological changes seem to be mediated by both humoral and cellular

immunity in variable degrees. Characteristic electrophysiological features reflect segmental demyelination. Subsequent remyelination is associated with recovery.

#### ACUTE MOTOR AXONAL NEUROPATHY

During summer epidemics of Guillain-Barré syndrome in northern China in 1991 and 1992, a majority of patients was found to have a pure motor axonal form of neuropathy, and the term “acute motor axonal neuropathy” (AMAN) was coined. Around 55–65% of the patients belonged to this category, of whom 76% were seropositive for *C jejuni*, compared with 42% in AIDP cases.<sup>67</sup> Among sporadic cases of Guillain-Barré syndrome, about 10–20% are of AMAN type.<sup>23</sup> Antiganglioside antibodies anti-GM1, GD1a, and GD1b are found in this group.

Electrophysiologically, compound muscle action potential amplitudes are reduced but motor distal latencies, motor conduction velocities, sensory nerve action potentials, and F waves are within the normal range.<sup>68</sup> Necropsy studies have shown Wallerian-like degeneration of motor axons exclusively.<sup>67, 68</sup> The earliest pathological changes are lengthening of the nodes of Ranvier, distortion of the paranodal myelin, and dissection of the axon from the adaxonal Schwann cell plasmalemma by extending macrophage processes.<sup>69</sup> These early nodal and periaxonal changes may be reversible, which probably explains the rapid recovery in some cases.

Tendon reflexes could either be preserved<sup>70</sup> or exaggerated,<sup>71</sup> the latter particularly in AMAN cases. Hyperreflexia is seen in about one third of patients, usually during the early recovery phase and occasionally in the acute phase. This finding is significantly associated with the presence of anti-GM1 antibodies and less severe disease.<sup>71</sup>

AMAN is characterised by rapidly progressive weakness, often with respiratory failure and usually good recovery.<sup>68</sup>

#### ACUTE MOTOR SENSORY AXONAL NEUROPATHY

The evidence of axonal degeneration in Guillain-Barré syndrome has been reported by some investigators in the past. In 1984, Brown and Feasby reported that the very low M response amplitudes that can occur because of axonal degeneration in Guillain-Barré syndrome were correlated with subsequent denervation of muscles and a poor clinical outcome.<sup>72</sup> In 1986, Feasby *et al* published observations on seven patients who had a very acute and severe illness with motor and sensory dysfunction, characterised by marked muscle wasting and poor recovery. Electrophysiology showed inexcitable motor nerves and evidence of sensory and motor axonal dysfunction. Necropsy in one of the cases showed features of axonal degeneration with no demyelination or inflammation. They concluded that the features suggested a new clinicopathological entity.<sup>73</sup> Later studies from northern China identified this group as having acute motor sensory axonal neuropathy (AMSAN).<sup>65</sup> Re-

ports from northern China also showed that AMSAN could follow *C jejuni* infection.<sup>74</sup>

Necropsy studies have shown Wallerian-like degeneration of sensory and motor fibres, with little demyelination or lymphocytic infiltration. Numerous macrophages in the periaxonal and intra-axonal spaces have also been demonstrated.<sup>65, 74</sup> Such periaxonal macrophages are found in both AMAN and AMSAN, and probably indicate the presence of an important epitope in the axolemma or periaxonal space.<sup>65</sup>

In AMSAN the disease course is typically fulminant, generally with slow and incomplete recovery. This group probably has the most severe form of immune mediated axonal damage in Guillain-Barré syndrome.

#### MILLER FISHER SYNDROME

In 1956, Fisher described three patients with ataxia, areflexia, and ophthalmoplegia (internal and external)—the classical triad of signs in the Miller Fisher syndrome.<sup>75</sup> Mild limb weakness, ptosis, facial palsy and bulbar palsy may also occur in Miller Fisher syndrome.<sup>75–76</sup> This entity accounts for about 5% of patients with Guillain-Barré syndrome.<sup>77</sup>

Miller Fisher syndrome has been shown to be associated with preceding infections with two *C jejuni* strains, Penner serotype 2 and Lior serotype 4.<sup>29</sup> Almost all patients have IgG autoantibodies against ganglioside GQ1b,<sup>78</sup> which plays a key role in the pathogenesis.

Anti-GQ1b antibodies were found to immunostain the paranodal region of the third, fourth, and sixth cranial nerves. It was also shown that the oculomotor nerve contained the highest concentration of GQ1b gangliosides.<sup>78</sup> It is possible that antibody mediated damage takes place in the paranodal region owing to the presence of GQ1b epitopes, and resultant conduction block is the most likely mechanism of ophthalmoplegia. Further evidence for the importance of anti-GQ1b antibody in the pathogenesis of ophthalmoplegia is provided by its presence in non-Miller Fisher Guillain-Barré syndrome with ophthalmoplegia, and its absence in Guillain-Barré syndrome without ophthalmoplegia.<sup>78</sup> The same study showed evidence of immunostaining with anti-GQ1b antibodies in dorsal root ganglia. Antibody mediated damage at that level could be the explanation for areflexia.

Motor weakness of the limbs may also be seen in some patients. Serum containing anti-GQ1b from patients with Miller Fisher syndrome has been found to interfere with neuromuscular transmission,<sup>79</sup> which could be the mechanism responsible for muscle weakness.

The pathogenesis of ataxia has been a focus of debate. Both peripheral and central mechanisms have been proposed. Some workers have suggested a peripheral mechanism, as a result of abnormalities of joint position sense and muscle spindle proprioception.<sup>80</sup> However, Fisher himself noted that ataxia was out of proportion to the degree of sensory loss.<sup>75</sup> Ataxia of central origin has been proposed, based on findings from magnetic resonance imaging (MRI) and electrophysiological tests.<sup>81</sup> Strong evidence for a central mechanism was

provided by a study which showed selective immunocytochemical staining of the cerebellar molecular layer with IgG anti-GQ1b antibodies.<sup>82</sup>

Neuropathological studies are scanty in Miller Fisher syndrome, as it is a rare disorder. One necropsy study showed features of demyelination and inflammation in the third and sixth cranial nerves, spinal ganglia, and peripheral nerves. Those features were not associated with signs of axonal damage or neurogenic atrophy, and the central nervous system was also normal histologically.<sup>83</sup>

The most consistent and conspicuous finding on electrophysiological evaluation is reduced or absent sensory nerve action potentials.<sup>80 84 85</sup> Motor and sensory nerve conduction velocities are either normal or minimally slowed. When slowed, the conduction velocity improves with clinical recovery.<sup>85</sup> The tibial H reflex is usually absent. On needle electromyography, denervation changes are absent in limb muscles.<sup>80 84 85</sup>

#### OTHER VARIANTS

Several other variants of Guillain-Barré syndrome have been described. This group includes pure sensory, pure dysautonomic, pharyngeal-brachial-cervical, and paraparetic variants.<sup>86 87</sup> These account for about 10% of cases of the syndrome.<sup>86</sup>

The sensory variant is characterised by symmetrical sensory loss, areflexia, and mild or no weakness. Cerebrospinal fluid analysis and electrophysiological tests are compatible with Guillain-Barré syndrome.<sup>88 89</sup> A necropsy study showed demyelination, with mononuclear cell infiltration of nerves and posterior roots.<sup>89</sup>

It is not uncommon to find features of dysautonomia in Guillain-Barré syndrome. Rarely autonomic neuropathy may be the presenting feature.<sup>90 91</sup> Clinical features vary, and cardiovascular involvement appears to be the commonest manifestation. Plasma cortisol and catecholamines were found to be raised in patients with dysautonomia presenting as hypertension and tachycardia.<sup>92</sup> Electrocardiographic abnormalities such as ST depression, T inversion, tall T waves, and prolonged QTc interval are seen in about one third of cases.<sup>19</sup> Lymphocytic infiltration of autonomic ganglia and perivascular lymphocytic infiltration in the hypothalamus and brain stem were evident in a necropsy study.<sup>93</sup>

Wide fluctuations in pulse and blood pressure have been found in fatal cases of dysautonomia.<sup>16 93</sup> In a series of 100 patients, 31% of deaths were caused by cardiac arrhythmias, probably secondary to autonomic dysfunction.<sup>20</sup> It was shown that reduced RR interval variation on electrocardiography was a good predictor of the subsequent development of serious arrhythmias. Wide fluctuations of pulse and blood pressure, systolic hypertension, and the requirement for mechanical ventilation were other predictors.<sup>20</sup> Vagal overactivity, as shown by abnormal sensitivity to externally applied eyeball pressure, is considered to be a useful bedside test of increased risk of developing serious bradyarrhythmias.<sup>94</sup>

#### Investigations and diagnosis

Diagnostic criteria for Guillain-Barré syndrome have been laid down, based on clinical, laboratory, and electrophysiological features.<sup>95</sup> Progressive motor weakness and areflexia are prime requirements for diagnosis. Cerebrospinal fluid analysis is the only laboratory criterion. However, other laboratory tests provide corroborative evidence for diagnosis and are useful in the management (box 2). In CSF, an elevated or rising protein level on serial lumbar punctures and 10 or fewer mononuclear cells/mm<sup>3</sup> strongly support the diagnosis. CSF protein level may be normal during the first week. In one of the studies 12% of patients were found to have > 5 cells/μl in the CSF.<sup>16</sup> The presence of more than 50 mononuclear cells raises doubts about the diagnosis. CSF pleocytosis is well recognised in HIV associated Guillain-Barré syndrome.<sup>96</sup> Electrophysiological features differ according to the clinicopathological type (box 3).<sup>15 68 95</sup>

Magnetic resonance imaging can be useful in diagnosis, especially when the electrophysiological findings are equivocal. It is a sensitive but unfortunately non-specific test. Spinal nerve root enhancement with gadolinium on

#### Box 2: Investigations

- Cerebrospinal fluid
- Antiganglioside antibodies
- Stool culture for *C jejuni*
- Antibodies to *C jejuni*, cytomegalovirus, EBV, HSV, HIV, *M pneumoniae*
- Biochemical screening: urea, electrolytes, liver enzymes
- Full blood count
- Erythrocyte sedimentation rate
- ECG
- Autonomic function tests
- Electrophysiology

#### Box 3: Electrophysiological features

- AIDP
  - Reduced conduction velocity
  - Conduction block or abnormal temporal dispersion
  - Prolonged terminal latency
  - Absent F wave or prolonged F wave latency
- AMAN
  - Absent or reduced compound muscle action potential (CMAP) amplitude
  - Normal motor terminal latency and conduction velocity
  - Normal sensory nerve action potential (SNAP)
- AMSAN
  - Absent or reduced SNAP amplitude
  - Absent or reduced CMAP amplitude
  - Normal motor terminal latency and conduction velocity

MRI is a non-specific feature seen in inflammatory conditions and caused by disruption of the blood–nerve barrier. Selective anterior root enhancement appears to be strongly suggestive of Guillain-Barré syndrome.<sup>97</sup> A study showed that 83% of patients had enhancement of the cauda equina nerve roots.<sup>98</sup> Prominent nerve root enhancement was found to correlate with pain, disability grade, and time for recovery.<sup>98</sup>

#### SPECIFIC TREATMENT

##### *Plasma exchange*

In 1978, Brettle *et al* first drew attention to the improved outcome in a patient with Guillain-Barré syndrome following plasma exchange.<sup>99</sup> Subsequently the efficacy of plasma exchange was established by large multicentre trials.<sup>100–101</sup> Plasma exchange beginning within the first two weeks of the illness reduced the period of hospital stay, the duration of mechanical ventilation, and the time to reach ambulation.<sup>100</sup>

In the North American trial, patients were subjected to a plasma exchange amounting to 200–250 ml/kg body weight over 7–14 days.<sup>100</sup> There has been no consensus over the optimal number of exchanges in patients with different grades of disability. The French Cooperative Group on Plasma Exchange in Guillain-Barré Syndrome recommends two exchanges in mild cases and four in moderate or severe cases, based on their randomised trial involving over 500 patients.<sup>102</sup>

The complications of plasma exchange include hypotension, septicaemia, hypocalcaemia, and abnormal clotting.<sup>103</sup> It could particularly be hazardous in haemodynamically unstable patients.

##### *Intravenous immunoglobulin*

Intravenous immunoglobulin is used in the treatment of several immunologically mediated disorders. It is supposed to act through several mechanisms including anti-idiotypic suppression of autoantibodies. The benefits of intravenous immunoglobulin in Guillain-Barré syndrome were first reported by Kleyweg *et al* in 1988.<sup>104</sup>

A large, multicentre, randomised trial compared plasma exchange, intravenous immunoglobulin, and combination treatment of plasma exchange followed by intravenous immunoglobulin. Patients were randomised to three groups to receive plasma exchange (five exchanges of 50 ml/kg body weight each, completed within 13 days), intravenous immunoglobulin (0.4 g/kg body weight for five days), or combined treatment. In the final analysis, there was no significant difference in efficacy between plasma exchange and intravenous immunoglobulin, as reflected by the major outcome criterion (mean disability grade improvement after four weeks) and secondary outcome measures (time to unaided walking, time to permanent discontinuation of artificial ventilation, and average rate of recovery over 48 weeks). No significant advantage in combined treatment was evident.<sup>105</sup>

Based on these results it was concluded that intravenous immunoglobulin treatment may be preferable to plasma exchange when started

within two weeks in severely affected adults with no contraindications to intravenous immunoglobulin, because it was more convenient, equally effective, and of comparable overall cost.<sup>103</sup> A retrospective multicentre study found that intravenous immunoglobulin accelerated recovery in children with Guillain-Barré syndrome who were unable to walk.<sup>105</sup>

Two reports published in 1993 drew attention to relapses following intravenous immunoglobulin treatment.<sup>106–107</sup> Those observations were based on 15 and seven patients, respectively. A subsequent study involving 172 patients (16 with relapses and 156 without) found that treatment related fluctuations occurred in about 10% of patients and there was no significant difference between those who were treated with plasma exchange and intravenous immunoglobulin alone or in combination with intravenous methylprednisolone.<sup>108</sup> Such relapses are usually treated with another treatment cycle. It was also shown that those who had fluctuations generally took a longer time to reach the nadir and tended to have a protracted disease course. Relapses did not occur in patients with acute motor neuropathy, predominant distal weakness, anti-GM1 antibodies, and preceding gastrointestinal illness. This observation is unlikely to be related to *C jejuni* infection, which was found in equal proportions in patients who relapsed and those who did not.<sup>108</sup>

Intravenous immunoglobulin currently remains the preferred choice in treating Guillain-Barré syndrome. It is a reasonably safe form of treatment, though its side effects and contraindications should be borne in mind (box 4).

##### *Corticosteroids*

Steroid treatment in Guillain-Barré syndrome has yielded disappointing results. A double blind, placebo controlled, multicentre trial looked into this issue. Two hundred and forty two patients were randomised to receive either high dose intravenous methylprednisolone

#### **Box 4: Intravenous immunoglobulin treatment**

- Contraindications
  - Selective IgA deficiency
  - Anaphylaxis following previous intravenous immunoglobulin infusion
- Relative contraindications
  - Severe congestive cardiac failure
  - Renal insufficiency
- Adverse effects
  - Malaise, myalgia, fever, chills
  - Vasomotor symptoms, headache
  - Nausea, vomiting
  - Transient increase in liver enzymes
  - Renal tubular necrosis, acute renal failure
  - Aseptic meningitis
  - Hypercoagulable state
  - Anaphylaxis
  - Rashes
  - Encephalopathy

Table 1 Outcome data of Guillain-Barré syndrome in different series

| Reference | No of patients | Duration of follow up | Recovered (%) | Residual deficits (%) | Death (%) |
|-----------|----------------|-----------------------|---------------|-----------------------|-----------|
| 3         | 79             | 1 year                | 62            | 30                    | 8         |
| 14        | 297            | 309 d (mean)          | 71            | 16                    | 11        |
| 16        | 100            | 1 year                | 67            | 20                    | 13        |

(500 mg daily for five days within two weeks of onset) or placebo. The results did not show any significant difference in outcome between the two groups.<sup>109</sup>

However, a pilot study suggested that combined treatment with intravenous methylprednisolone (0.5 g/d) and intravenous immunoglobulin (0.4 g/kg body weight/d) for five days was more beneficial than intravenous immunoglobulin alone.<sup>110</sup>

### Outcome and prognosis

The outcome and prognosis of Guillain-Barré syndrome depend on several factors. Generally by one year about two thirds have made a complete recovery. Ventilatory support is needed in about a quarter of the patients.<sup>3</sup> At one year 18% are unable to run, 9% are unable to walk unaided, and 4% are either bed bound or ventilator dependent.<sup>3</sup> In a prospective study, 36% started to improve during the first week and 85% showed improvement within four weeks.<sup>14</sup> The death rate varies among different series, ranging up to 13% (table 1). It was found to be around 5% in an intensive care setting.<sup>111</sup> The deaths seem to occur more often in the older age group.<sup>3 14</sup> About 25% of deaths occur during the first week and about 50% during the first month.<sup>14</sup> Cardiac arrest as a result of autonomic dysfunction is the commonest cause of death and accounts for about 20–30% of deaths.<sup>14 16</sup> Other causes of death include chest infection, pulmonary embolism, and respiratory failure.<sup>14 16</sup>

The prognosis is influenced by several factors such as the aetiology, clinical features, electrophysiology, and biochemistry (box 5).<sup>14–16 103 112–115</sup> The Italian Guillain-Barré Study Group found that the presence of electrophysiological features of axonopathy adversely affected the chance of recovery.<sup>14</sup> Other workers did not find such a predictive value.<sup>112 116</sup> However, it should be noted that the initial finding of inexcitable nerves<sup>116</sup> and reduced compound muscle action potentials<sup>103 114</sup> were reported to be associated with poor prognosis.

Certain biochemical markers are useful in predicting the outcome. Increased levels of neurone specific enolase and S-100b protein in the CSF have been found to be associated with a longer duration of illness.<sup>115</sup> A longer lasting increase in IgM anti-GM1 predicts slow recovery. However, the absolute antibody level does not seem to correlate with either the length of recovery or the clinical disability at its nadir.<sup>113</sup>

Guillain-Barré syndrome patients are best managed in tertiary care centres where facilities and expertise are available. Despite modern intensive care facilities and immunomodulatory treatment, about 20–30% patients are still left with residual deficits after one year.

### Box 5: Factors associated with poor outcome

- Aetiology
  - Previous gastrointestinal infection
  - C jejuni* infection
  - Cytomegalovirus
- Clinical features
  - Older age
  - Shorter latency to nadir
  - Longer time to clinical improvement
  - Need for mechanical ventilation
  - Greater disability and disease severity
- Electrophysiology
  - Absent or reduced CMAP (mean distal CMAP amplitude <20% of the lower limit of normal)
  - Inexcitable nerves
- Biochemical markers
  - Anti-GM1 antibodies
  - Neurone specific enolase and S-100b proteins in CSF

Finding strategies to enhance their recovery is a major challenge.

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