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CLINICAL REVIEW

Guillain-Barré syndrome

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SOURCES AND SELECTION CRITERIA

I prepared this review by searching Cochrane reviews, Medline, PubMed, and my personal archive of references. I downloaded and assessed all references that dealt with Guillain-Barré syndrome and its subtypes—acute inflammatory demyelinating polyradiculoneuropathy, acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy.

Guillain-Barré syndrome is a peripheral neuropathy that causes acute neuromuscular failure. Misdiagnosis is common and can be fatal because of the high frequency of respiratory failure, which contributes to the 10% mortality seen in prospective studies.[1] Our understanding of the wide spectrum of the disease and its pathogenesis has increased enormously in recent years. Several high quality randomised controlled trials have established the effectiveness of early treatment.

What is the spectrum of Guillain-Barré syndrome?

The clinical spectrum of Guillain-Barré syndrome is varied—at least three different types have been identified. In Europe and North America about 95% of cases are acute inflammatory demyelinating polyradiculoneuropathy and the other 5% are acute axonal motor disorder and acute sensory and motor axonal neuropathy.[2] The frequency of these axonal neuropathies varies throughout the world, and in Asia and South America they make up about 30% of the syndrome.[3] The closely related Miller Fisher syndrome is thought to be an inflammatory neuropathy that affects the cranial nerves to the eye muscles in particular, and it is characterised by ophthalmoplegia, accompanied by areflexia and ataxia but not weakness.[4] Some cases of acute inflammatory demyelinating polyradiculoneuropathy have features of the Miller Fisher syndrome, but with associated weakness.

The incidence of Guillain-Barré syndrome varied from 1.2 per 100 000 to 1.6 per 100 000 in the most recent and carefully conducted European studies.[5,6] The incidence rises with age but is bimodal in some studies,[7] with a minor peak in young adults, and is slightly more common in men.[8] Twelve cases of familial Guillain-Barré syndrome have been described,[9,10] but there is no strong HLA link,[11] although one study suggested a link with a CD1 poly morphism.[12] Recurrence of pure Guillain-Barré syndrome is rare, and patients with a more chronic disease that resembles Guillain-Barré syndrome but takes longer than four weeks to reach its nadir are classified as having subacute or chronic inflammatory demyelinating polyneuropathy. These patients behave differently to those with Guillain-Barré syndrome and often respond to steroids.[13]

Box 1 Differential diagnosis of Guillain-Barré syndrome

- Hypokalaemia
- Polymyositis
- Lead poisoning
- Porphyria
- Transverse myelitis and neuromyelitis optica

What are the clinical features?

All types of Guillain-Barré syndrome present with acute neuropathy, defined as progressive onset of limb weakness that reaches its worst within four weeks. Limb weakness is usually global[14]—both proximal and distal—unlike that of dying back axonopathy, such as neuropathy associated with drug toxins or alcohol, which is usually distal. Sensory loss is variable in acute inflammatory demyelinating polyradiculoneuropathy. Typically there are sensory symptoms but few sensory signs.[14] Reflexes are usually lost early in the illness, although acute motor axonal neuropathy can be associated with retained reflexes or even brisk reflexes.[15] Autonomic signs such as tachycardia, hypertension, or lack of sinus arrhythmia are common.[16] The respiratory system is affected in a third of cases, but this may not be associated with clear dyspnoea, which makes it more difficult to assess.[17] It is essential to measure vital capacity in such cases to anticipate failing respiratory effort.[18] A falling vital capacity is a more useful warning sign of incipient respiratory arrest than blood gases or oxygen saturation, which often remain normal until breathing stops altogether. The cranial nerves are often affected, with facial weakness and bulbar palsy the most common problems, followed by an eye movement disorder. Guillain-Barré syndrome can be confused with diseases

Box 2 Infections that have been linked to Guillain-Barré syndrome

- *Campylobacter jejuni*
- Epstein Barr virus
- Cytomegalovirus
- Mycoplasma
- Human immunodeficiency virus

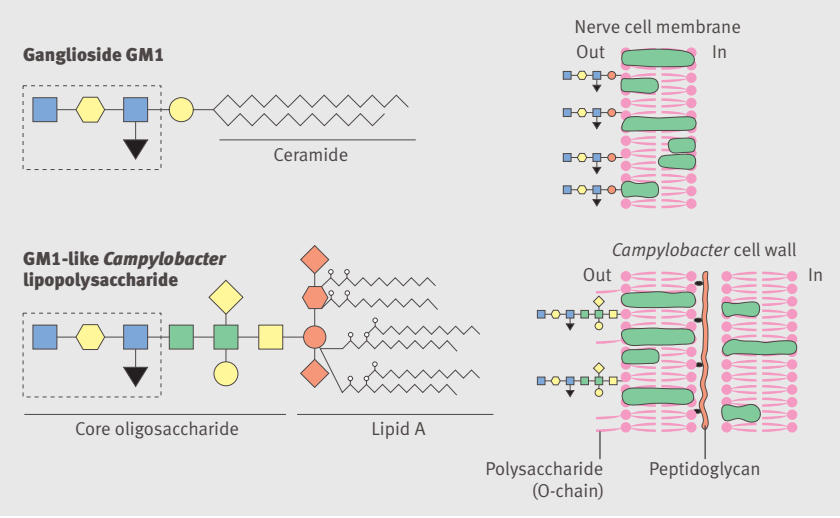

Fig 1 | Structural similarities between ganglioside GM1 in nerve cell membranes and a *Campylobacter jejuni* lipopolysaccharide. Adapted, with permission, from a review by Ang[27]

of the spinal cord, brainstem, or muscle (box 1). About 20% of patients are still ambulatory at the time of diagnosis but some will deteriorate to become bed bound.[19] Occasionally patients with mild disease develop mild distal weakness only.

How can you confirm the clinical diagnosis?

Nerve conduction studies are the most useful confirmatory test and are abnormal in 85% of patients, even early on in the disease.[2] They should be repeated after two weeks if they are normal initially. Typically these show signs of conduction block, prolonged distal latencies, delayed F waves, and sometimes the paradox of a small median sensory action potential with retained sural responses.[20] Motor conduction velocities are usually normal initially but may slow later. Guillain-Barré and Strohl documented the increase in cerebrospinal fluid protein, which is helpful diagnostically but is not specific to Guillain-Barré syndrome.[21] Finding more than 50×10^6 cells/l in cerebrospinal fluid casts extreme doubt on the diagnosis. Some patients produce inappropriate amounts of antidiuretic hormone, and it is good practice to check electrolytes. In appropriate circumstances, measuring concentrations of porphyrins or lead may help diagnose unusual causes of acute neuropathy not caused by Guillain-Barré syndrome (box 1). It may be helpful to measure antiganglioside antibodies, as well as antibodies to *Campylobacter jejuni*.

UNANSWERED QUESTIONS AND FUTURE RESEARCH

- What is the minimum amount of intravenous immunoglobulin needed to accelerate recovery and exactly how does it work?
- What is the value of a second course of intravenous immunoglobulin in patients who do not respond to the first course?
- How useful are prophylactic antibiotics against asymptomatic *Campylobacter jejuni* infection?
- Does physiotherapy speed up recovery?
- Trials are needed of novel treatments such as antiganglioside columns and complement inhibitors

What causes Guillain-Barré syndrome?

Around 75% of patients have a history of preceding infection, usually of the respiratory and gastrointestinal tract.[22] A large number of infections have been linked to the onset of the syndrome, but only a few associations have been established (box 2).

How are nerves damaged?

The syndrome is triggered by infection in three quarters of patients; a third have serological evidence of *C jejuni* infection and a few continue to excrete *C jejuni* in faeces.[23] This association with preceding infection suggested that the altered immunity in the syndrome may result from the infectious organism sharing epitopes with an antigen in peripheral nerve tissue. It has now been established that *C jejuni* lipopolysaccharide shares epitopes with certain gangliosides (fig 1).[24] The closest association between antibodies and the neurological disease is seen with Miller Fisher syndrome, where more than 90% of patients have antibodies against the ganglioside GQ1b,[25] although only a small proportion of these patients have evidence of a preceding *C jejuni* infection. Thus, several different organisms may cross react with peripheral nerve antigens. Evidence that these

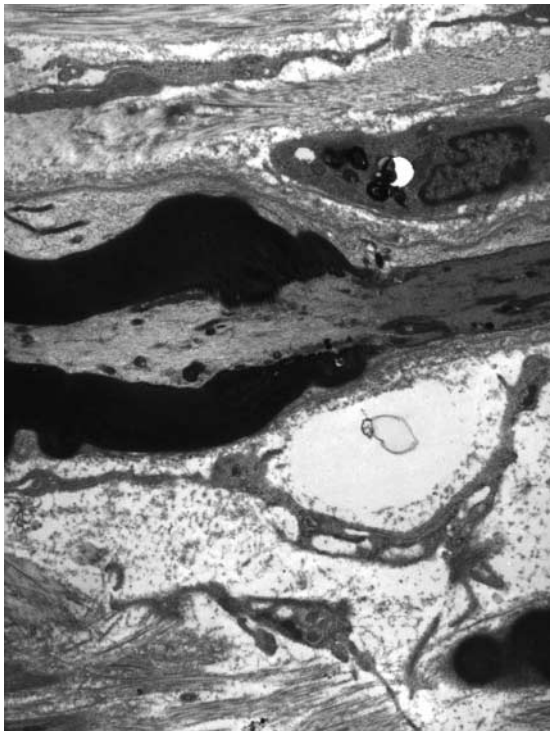

Fig 2 | Electron microscopy of a nerve biopsy specimen from a patient with Guillain-Barré syndrome associated with HIV infection showing a macrophage apparently stripping myelin from a denuded axon. Reproduced, with permission, from the book by Hughes[14]

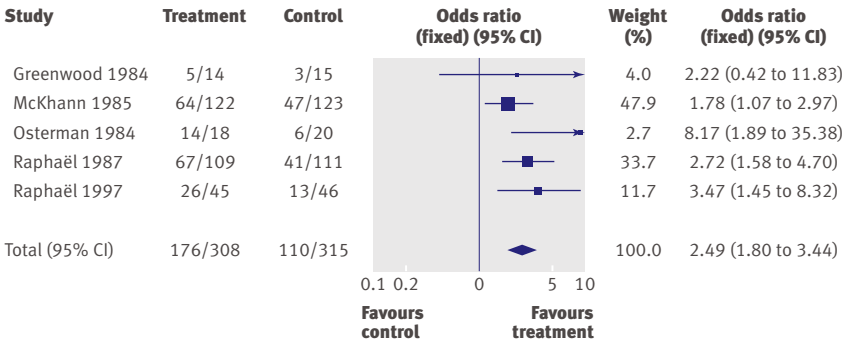

Fig 3 | Forest plot of plasma exchange compared with supportive treatment in Guillain-Barré syndrome. Proportion of patients who improved one grade at 4 weeks. Adapted, with permission, from a Cochrane review[34]

antibodies are responsible for the clinical signs of Miller Fisher syndrome comes from studies in which anti-GQ1b antibody and monoclonal antibody raised against GQ1b block conduction in a mouse hemidiaphragm preparation.[26]

Antiganglioside antibody is present in the serum of many patients with acute motor axonal neuropathy,[28] and this together with the pathology suggests that antibodies fix complement, which attracts macrophages and leads to axonal damage (fig 2).[29] Many of these antibodies are of the IgG1 or IgG3 subtype, which usually need T cell help; however, no convincing T cell immunity has been established. Unusual T cells such as those with a γδ receptor have been cultured from peripheral nerve biopsy specimens,[30] but their relation to the development of the neuropathy is uncertain. In addition, histological examination at autopsy of nerves from patients with acute motor and sensory axonal neuropathy supports antibody mediated damage to the axon, as does a rabbit model of acute motor axonal neuropathy.

Many unanswered questions remain about the relation between antiganglioside antibody and Guillain-Barré syndrome. Acute inflammatory demyelinating polyradiculoneuropathy is the most common form of the syndrome in Europe and North America, yet

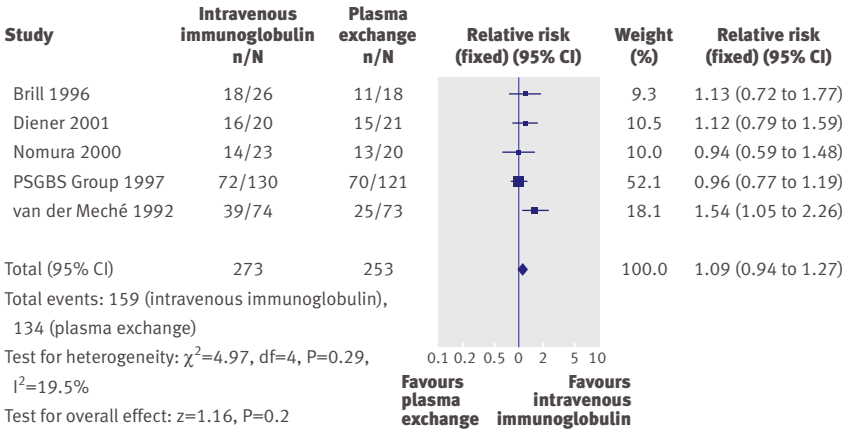

Fig 4 | Forest plot of intravenous immunoglobulin compared with plasma exchange in Guillain-Barré syndrome. Change in disability grade at 4 weeks. Adapted, with permission, from a Cochrane review[35]

TIPS FOR THE NON-SPECIALIST

- Guillain-Barré syndrome should be considered in any patient developing rapidly progressive limb weakness
- Absent reflexes are a "red flag" for Guillain-Barré syndrome in patients with rapidly progressive weakness
- Patients with suspected Guillain-Barré syndrome should be referred to hospital as an emergency
- A history of weakness preceded by respiratory or gastrointestinal tract infection suggests Guillain-Barré syndrome

relatively few affected patients have antibody to gangliosides. Experimental allergic neuritis in rats and mice seems to be predominantly a cell mediated disease, but no convincing evidence of T cell immunity to protein antigens exists for the human disease. Complex biochemical association of lipids can influence the available antigenic determinants, however,[31] and the role of combinations of protein and lipid antigens remains to be determined, as does the role of lipid immunity.

How do you treat Guillain-Barré syndrome?

Mortality in Guillain-Barré syndrome dropped dramatically with the advent of intensive care and safe ventilation, and it is now about 10%.[1] Clinical studies document infections, pulmonary emboli, and cardiac rhythm disturbances as the major causes of death.[19] Mildly affected patients who remain capable of walking unaided and are stable for more than two weeks are unlikely to progress and can be managed as outpatients. Most patients need emergency admission to hospital, where they can be carefully monitored. A multidisciplinary consensus group has recommended subcutaneous heparin and graduated stockings to prevent deep venous thrombosis and pulmonary emboli.[32] Pain management is not easy, but gabapentin and carbamazepine may help. Narcotic analgesics may occasionally be needed.[32] The timely institution of mechanical ventilation is important. Studies of patients who needed ventilation suggest that those with a vital capacity of less than 20 ml/kg are most at risk.[33] A Cochrane review has shown that plasma exchange is better than supportive treatment (fig 3).[34] In five randomised but unblinded clinical trials of 623 patients, plasma exchange reduced the proportion of patients needing ventilation from 27% to 14% (relative risk 0.53, 95% confidence interval 0.39 to 0.74, P=0.001). Similarly, the time taken to recover walking with an aid was significantly shortened in two trials (30 *v* 44 days, P<0.01). Although intravenous immunoglobulin has not been tested against supportive treatment alone, a Cochrane analysis of three trials indicated that such treatment was equivalent to plasma exchange.[35] Two of these trials were combined in a meta-analysis of 398 patients, and change of disability (fig 4), time to walk unaided, and proportion of patients unable to walk at one year were not significantly different

SUMMARY POINTS

Guillain-Barré syndrome is a rare but important disease that can lead to life threatening respiratory failure

Structural similarities between a triggering infectious organism and peripheral nerve tissue are important in its pathogenesis

Treatment consists of rapid administration of intravenous immunoglobulin or plasma exchange, which shortens the time to recovery

Around 10% of patients die from respiratory failure, pulmonary emboli, or infection

Around 20% of patients have residual disability, with weakness or persistent sensory disturbance

between the two groups. Since these trials, intravenous immunoglobulin has become the standard treatment for the syndrome because it can be given rapidly and has fewer side effects than plasma exchange. The standard regimen of 0.4 g/kg body weight each day for five consecutive days is well tolerated, but side effects include dermatitis and much more rarely renal impairment and hyperviscosity effects, including strokes.

Unusually for a disease that is thought to have an immunological aetiology, steroids are ineffective. Possible explanations are that the immunological process that damages nerves has already stopped by the time steroids begin to take effect or that steroids interfere with nerve repair. The mechanism of action of intravenous immunoglobulin is uncertain and probably multifactorial, including the provision of anti-idiotype antibodies, blockade of Fc receptors, and interference with complement activation. Increased catabolism of antibodies may also play a part.

Data from plasma exchange trials indicate that treatment is still beneficial for four weeks after the first symptoms appear and that it is more effective if given as early as possible after onset. Trial data largely apply to patients given intravenous immunoglobulin within two weeks, although some benefit may extend for up to four weeks. No trials have looked at the possible benefit of further courses of immunoglobulin, which are often given if patients fail to improve or deteriorate after the initial treatment.

Can we predict outcome after treatment?

Population based studies suggest that the outcome is worse in older patients, in patients in whom the deficit and peak were severe, in patients with electrophysiological or clinical evidence of extensive axonal damage,[19 36] and in patients who were previously infected with *C jejuni*. Immunotherapy with intravenous immunoglobulin or plasma exchange does not seem to reduce the proportion (15-20%) of patients who sustain permanent neurological deficit and are unable to work at 12 months.

What new treatments can we expect?

Trials of immunotherapy in Guillain-Barré syndrome are difficult to organise, complex, and expensive. Most patients are now treated in local units rather than large neurological centres. This compounds the difficulties of organising clinical trials with enough patients to show that new treatments are effective. Theoretically, complement inhibitors should be effective in many patients but have yet to be tried in clinical trials. Affinity columns that remove antiganglioside antibodies might be more effective than conventional plasma exchange. Trophic factors and sodium channel blockade offer possible neuroprotection for damaged axons and might reduce the proportion of patients left with disability. Antibiotics against *C jejuni* might confer some benefit for the minority of patients who secrete *C jejuni* in faeces for some weeks after diagnosis.

ADDITIONAL EDUCATIONAL RESOURCES

- Guillain-Barré Syndrome Support Group (www.gbs.org.uk)—Provides free information leaflets for doctors and patients
- Neuromuscular Disease Centre (http://neuromuscular.wustl.edu)—Provides detailed information on the clinical features and investigation of Guillain-Barré syndrome

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When I use a word

Tom Swifties

Edward Stratemeyer, a children's writer, was the American equivalent of the creator of Billy Bunter, Charles Hamilton (1876–1961), also known as Frank Richards, Hilda Richards, Owen Conquest, Ralph Redway, and two dozen other pseudonyms.

Stratemeyer was born in Elizabeth, New Jersey, in 1862 but in 1890 moved to Newark, where he died in 1930. From 1899 onwards he produced several series of children's books, featuring characters such as the Rover Boys (published under the name of Arthur M Winfield), the Bobbsey Twins (as Laura Lee Hope), the Hardy Boys (as Franklin W Dixon), Nancy Drew (as Carolyn Keene), and Tom Swift (as Victor Appleton). Now Charles Hamilton wrote every word that appeared under his numerous pseudonyms (an estimated lifetime's output of 100 million words). But Stratemeyer, a skilful entrepreneur, engaged others to develop his ideas, in a collaboration he established in 1914, the Stratemeyer Literary Syndicate. The group included Howard R Garis, who also created the character Uncle Wiggily for the Newark *Evening News*, and Stratemeyer's daughter Harriet Stratemeyer Adams, who continued his work after his death.

The syndicate disliked using the word "said" on its own, or even at all. In one striking but typical sequence that I picked at random from a Hardy Boys novel, *The Mark on the Door* (1934, written by Leslie McFarlane), the consecutive verbs are shouted, cried, declared, declared (again), inquired, admitted, replied, cried, remarked, asked, returned, and suggested. Often, the verbs were qualified by adverbs or adjectives: "cried angrily," "asked, interested," "observed significantly," "asked sharply," "considered briefly," and "said bitterly" are examples, all taken from the first chapter of the same book. This habit was particularly prominent in the Tom Swift stories.

It wasn't long before someone parodied the method and produced the form of pun that has come to be known as a Tom Swifty, a succinct form of the Wellerism (of which more another time). In the Circe episode of *Ulysses* (1922) James Joyce included three primitive examples:

A MILLIONAIRESS: (*Richly*) Isn't he simply wonderful?
A NOBLEWOMAN: (*Nobly*) All that man has seen!
A FEMINIST: (*Masculinely*) And done!

But more subtle varieties are possible. My favourite is "I do like reading D H Lawrence," admitted the lady chattily.

David Crystal, in *The Cambridge Encyclopedia of the English Language*, classified Tom Swifties into three types, according to the part of speech that carries the pun, and I have added a fourth, although some take the view that only the adverbial ones are true Swifties. Here they are, with some medical examples that I have for the most part adapted from published examples.

1. Adverbial Swifties (the most common form)

"I'm afraid you've got osteopetrosis," said the doctor stonily.
"I'm in the RAF Medical Corps," said Tom paradoxically.
"Give it parenterally," said the anaesthetist in vain.

2. Verbal Swifties

"I'm dying," the patient croaked.
"It's alopecia," Tom bawled.
"Not too much water, please," said the pharmacologist, concentrating.

3. Adjectival Swifties

"He died intestate," said the gastroenterologist.
"That was a rash diagnosis," said the dermatologist.
"I'm schizoid," said Tom, being frank.

4. Substantive Swifties

"I'm a homoeopathist," said the dilutee.
"I've no alternative," said the allopath.

What Crystal calls the "do it" variant of the adverbial type has sexual connotations. "Prescribers do it three times a day after meals," "Pharmacists do it formulaically," and "Clinical pharmacologists do it interactively."

Finally, Tom Swifties have been used in psychological research. One group concluded that "a social setting is a required but not a sufficient condition for a pun to evoke a groan."

"Cobblers" you say? Well that could be the *last* word on the subject.

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