MANAGEMENT OF INFLAMMATORY NEUROPATHIES

Robert D M Hadden, Richard A C Hughes

Inflammatory neuropathies are uncommon but important to diagnose because they are treatable. This review summarises the clinical approach to diagnosis and treatment of Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and related neuropathies which are thought to be caused by direct autoimmune attack on peripheral nerves. Features that suggest that a neuropathy is likely to be inflammatory include loss of reflexes without muscle wasting, elevated cerebrospinal fluid (CSF) protein, positive sensory symptoms such as pain or tingling, asymmetry, and proximal weakness. Nerve conduction studies show features of demyelination, especially motor nerve conduction block and temporal dispersion. Inflammatory neuropathy has been arbitrarily classified according to the time from symptom onset until maximal severity, where “acute” is less than four weeks and “chronic” is more than eight weeks, with a rare intermediate “subacute” group. Assessing the efficacy of potential treatments is difficult because the natural history is variable and may include spontaneous improvement. However, some progress has been made in conducting the randomised trials and systematic reviews as a basis for management decisions.

GUILLAIN-BARRÉ SYNDROME (GBS)

Definition
GBS is a clinically defined syndrome with several underlying pathologies. It affects 1–4 per 100 000 per year, men slightly more often than women. Diagnostic criteria include progressive weakness of two or more limbs reaching a maximum within four weeks, reduced or absent tendon reflexes in the weak limbs, and exclusion of alternative causes (box 1). Some cases may be so mild that medical attention is never sought. Most cases are caused by acute inflammatory demyelinating polyradiculoneuropathy (AIDP), but some are caused by acute motor axonal neuropathy (AMAN) or acute motor and sensory axonal neuropathy (AMSAN). Primary axonal GBS is thought to be caused by an autoimmune attack on axonal antigens, and is common in Asia, but is responsible for less than 5% of GBS cases in Europe and North America. Reflexes are sometimes preserved in AMAN. Rarer variants of GBS are the pharyngo-cervico-brachial pattern, acute oropharyngeal palsy (not to be confused with diphtheria), involvement of the lower but not upper limbs, and a pure motor and a pure sensory form. Acute pandysautonomia and acute sensory neuronopathy may also be related.

Investigations
Cerebrospinal fluid examination is needed largely to exclude alternative diagnoses, such as infectious (for example, Barrella or poliomyelitis) or lymphomatous polyradiculitis. The CSF protein is classically elevated as a result of albumin leakage from the blood, but may be normal within the first week. The CSF leucocyte count is usually normal but the diagnostic criteria allow up to 50 cells/μl. Pleocytosis is more likely in coexistent HIV infection.

GBS is preceded in two thirds of cases by an infection such as Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus or Mycoplasma pneumoniae. The infection is usually cleared before development of neurological symptoms. Identification of serum IgM antibodies to one of these agents demonstrates recent infection but is not clinically useful. Stool culture occasionally isolates C jejuni, but antibiotics probably do not influence outcome (level 4 evidence; box 2). The risk of developing GBS after C jejuni enteritis is less than 1 in 2500.

Serum antibodies to many peripheral nerve antigens have been found in GBS, but the majority of GBS patients have no identified autoantibodies so the pathogenesis of the disease is still debated. The antibodies that are found may also be present in other neurological diseases or occasional normal controls, and may be an epiphenomenon. Nevertheless, some antibodies do correlate with clinical subtypes of GBS (table 1). Their presence does not influence treatment.

Neurophysiology
Nerve conduction studies may help in diagnosis, classification and (to a limited extent) predicting prognosis. Neurophysiology helps to exclude alternative diagnoses such as myositis and

See end of article for authors’ affiliations

Correspondence to:
Dr Robert Hadden, West London Neurosciences Centre, Charing Cross Hospital, Fulham Palace Road, London W6 8RF, UK;
rob.hadden@doctors.org.uk

www.jnnp.com
myasthenia. Neurophysiological abnormalities are often very mild or occasionally normal in early GBS, and do not correlate well with clinical disability. The earliest consequence of acute demyelination is focal axonal conduction block, and it takes several days before slowing of conduction develops. Unfortunately for the purposes of diagnosis, conduction block is most common in the proximal nerve roots at sites that are awkward to test, at distal sites that mimic axonopathy, and at sites of compression, so it is often difficult or impossible to distinguish between axonal and demyelinating GBS in the early stages. Axonal degeneration may occur as a consequence of primary autoimmune attack on the axon or as a bystander phenomenon secondary to a primary attack on the myelin. It becomes evident after a few weeks as muscle wasting and electromyographic features of denervation, which signify a poor outcome. In the early stages, axonal neurophysiology may represent reversible axonal dysfunction rather than degeneration.

### Disease modifying treatment

Plasma exchange (PE) was the first disease modifying therapy proven to be superior to supportive treatment alone (fig 1, level 1a evidence). It reduced the median time to regain the ability to walk unaided from 111 to 70 days in another, and improved long term ability to walk unaided from 85 to 53 days in one study and was more effective in subtypes of GBS, and we recommend that all subtypes are treated similarly, although the results from small subgroups suggest that IVIg might be better than PE for patients with axonal GBS, motor GBS or antibodies to antigens associated with axonopathy.

Plasma exchange is more dangerous in patients with coagulopathy, unstable blood pressure or uncontrolled sepsis.

Variations of plasma exchange have been developed to try to improve safety. Immunoadsorption selectively removes immunoglobulin without requiring administration of foreign blood products, thereby avoiding risks of infection and allergic reaction, and may be done with columns containing staphylococcal protein A, phylalalanine or tryptophan. In small studies, immunoadsorption and double filtration plasmapheresis showed no significant difference in outcome compared with PE (level 2b evidence). A small trial of CSF filtration also showed no difference from PE. However, none of these studies were large enough to prove equivalence and use of these alternative treatments is not warranted outside clinical trials.

Intravenous immunoglobulin (IVIg) has become the treatment of choice for GBS in most countries. Although it has not been adequately tested against placebo in a randomised trial, it has similar short and long term efficacy to PE (fig 2, level 1a evidence) and avoids adverse effects related to hypotension and the requirement for a large venous catheter. It costs about the same as PE in the UK. The conventional dose is 0.4 g/kg/day for five days. In a trial of 39 patients requiring ventilation, six days of 0.4 g/kg/day was more effective than three days (level 1b evidence). Combined PE and IVIg was not significantly better than either alone in one trial.

Corticosteroids, surprisingly, worsen the long term outcome in GBS when given alone (level 1a evidence), perhaps because any beneficial effect is balanced by a detrimental effect on denervated muscle. However, a recent Dutch trial suggests the combination of intravenous methylprednisolone (500 mg/day for five days) followed by IVIg hastens recovery slightly more than IVIg alone. The use of corticosteroids will need to be re-evaluated when the trial has been published and the results incorporated into the systematic review.

### Situations for which evidence is lacking

Most published trials excluded children, patients with very mild GBS, and those seen more than two weeks after onset. There is therefore no evidence for treatment in these groups. The expected benefit needs to be considered against the risk of adverse effects and cost. Mildly affected patients usually recover well without treatment, though one third have residual symptoms at six months. The response to treatment is generally less in patients treated later, but we usually treat patients presenting beyond two weeks if they are still deteriorating (level 4 evidence). None of the trials was statistically designed to prove whether different treatments were more effective in subtypes of GBS, and we recommend that all subtypes are treated similarly, although the results from small subgroups suggest that IVIg might be better than PE for patients with axonal GBS, motor GBS or antibodies to antigens associated with axonopathy.
are still unable to walk unaided. Factors associated with poor outcome are older age, preceding diarrhoeal illness, more severe weakness, rapid onset, electrically inexcitable nerves, and muscle wasting. Chronic fatigue is common even in those who recover normal muscle power. Even after between three and six years, over one third still have lifestyle alterations, and half have residual muscle aches and cramps (related to sensory deficit).

**Miller Fisher and related syndromes**

Miller Fisher syndrome (MFS) is clinically defined by acute ataxia, ophthalmoplegia, and areflexia. Facial weakness and pupillary abnormalities are common. The index cases had no limb weakness. There is some inconsistency in published studies as to whether cases with limb weakness should be called MFS or Miller Fisher/Guillain-Barré overlap syndrome (our preference). The frequency of MFS is about 1–5% of GBS, but higher in Asia. There are no randomised trials of treatment in MFS, but outcome is almost always good even without treatment, and probably only those with limb weakness require treatment as for GBS. In a recent series of 50 patients with MFS, almost all were completely asymptomatic at six months, whether or not they had received plasma exchange.

Bickerstaff’s brainstem encephalitis differs from MFS in having altered consciousness, extensor plantar responses, and CSF pleocytosis. Wernicke’s encephalopathy is an important differential diagnosis. There are no trials of treatment but spontaneous recovery is usual, so that it is difficult to assess reports of benefit from PE or IVIg.

**CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)**

**Clinical presentation**

The time course of CIDP may be relapsing–remitting, chronic progressive, monophasic or have a GBS-like onset. Motor and sensory nerves are usually involved. Several variants are now being recognised (box 3). Most of the inflammation occurs in the proximal roots. Symptoms are primarily caused by conduction block resulting from demyelination, which generally responds well to treatment. The degree of block of conduction may also be increased by physical factors such as temperature, ischaemia, and exercise, which can explain rapid fluctuations in symptoms. After some years of disease there is a gradual accumulation of axonal degeneration, clinically evident as wasted muscles, which is generally irreversible. In the later stages disability is caused by a combination of axonal degeneration and demyelination, and responsiveness to treatment gradually decreases. Half of all patients suffer temporary severe disability and 13% have a long term requirement for aids to walk. Factors associated with a better prognosis are younger age, relapsing–remitting course, and absence of axonal damage.
Corticosteroids were the first accepted treatment but entered clinical practice without today’s high standards of evidence. Immunosuppressive agents, initially azathioprine, are mostly used in patients who have failed to respond to the above treatments. Their effects have probably not been fairly tested, as these patients often have significant axonal degeneration. Azathioprine is a broad spectrum immunosuppressive agent and may have a steroid sparing action. Several small case series suggested improvement with 3 mg/kg daily but the effect onset may be delayed by 3–12 months (level 3 evidence). The only randomised trial showed no major effect at 2 mg/kg (courses of similar cost) or between IVlg and oral prednisolone.

In summary, prednisolone, IVlg and PE are probably equally effective in the short term, and have not been compared in the long term, so the choice depends mainly on cost, adverse effects, and personal preference. We usually recommend starting treatment with oral prednisolone in patients for whom there are no contraindications (obesity, hypertension, diabetes, ulcer history). If it is not effective we use IVlg, followed by PE. In pure motor CIDP we start with IVlg. Immunosuppressive agents, initially azathioprine, are mostly used in patients who have failed to respond to the above treatments. Their effects have probably not been fairly tested, as these patients often have significant axonal degeneration.

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Blood was efficacious in two sham controlled randomised trials (level 1b evidence). One trial used PE twice weekly for three weeks, and the other used four exchanges in the first week, three in the second, two in the third, and one in the fourth. To maintain improvement PE has to be repeated at intervals as short as four as weeks. Its usefulness is limited by its inconvenience, venous access problems, requirement for hospital attendance and specially trained staff, and adverse events. Complications, usually from the use of a central venous catheter, were reported in one series in 17% of 381 procedures and one was fatal.

IVlg appeared efficacious in three of four randomised trials and the efficacy was supported by a meta-analysis (fig 3, level 1a evidence). Unfortunately its benefit lasts only 2–12 weeks, so that treatment has to be repeated and is very expensive. Approximately two thirds of patients respond, of whom one third improve and need no further treatment and two thirds require repeated courses. The initial dose should be 0.4 g/kg daily for five days (smaller doses were less effective), but maintenance doses can usually be reduced to 0.4–2.0 g/kg in total and given over 1–2 days. Crossover trials have shown no significant short term difference between IVlg and PE (courses of similar cost) or between IVlg and oral prednisolone.

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Cyclophosphamide is an alkylating agent, which predominantly depletes B lymphocytes. Intravenous cyclophosphamide in pulses of 1 g/m² monthly for up to six months induced notable improvement in 12 of 15 patients in one series. It is probably effective (level 3 evidence) but risks serious side effects on the bladder, marrow, and gonads. Oral cyclophosphamide 2 mg/kg is a simpler alternative with fewer short term side effects.

Cyclosporin A particularly inhibits T lymphocyte proliferation. In the largest series, all 14 patients improved either in disability or in relapse rate (level 3 evidence). Over half had adverse effects, including nephrotoxicity, hypertension, nausea, oedema, and hirsutism, so lower doses are now recommended, starting at 3–7 mg/kg daily and maintenance at 2–3 mg/kg.

Interferons are naturally occurring cytokines. Beta interferon 1a (Rebif) downregulates inflammatory responses and was beneficial in some small series at 44 µg subcutaneously three times weekly for about six months. The one randomised trial showed no benefit, but used only 22 µg three times weekly for three months in patients resistant to other treatments. Alpha interferon upregulates immune responses, and has been reported occasionally to cause CIDP and other autoimmune diseases. Nevertheless, it may be beneficial in CIDP, and 15 of 26 patients improved with alpha interferon 2a 2-3 MIU subcutaneously three times weekly for six weeks. Both interferons are very expensive but usually have only minor adverse effects.

There are a few reports of the efficacy in CIDP of methotrexate, tacrolimus (FK506), mycophenolate, etanercept, and autologous stem cell transplantation.

IMMUNISATIONS AND RELAPSE

Immunisations stimulate the immune system and rarely trigger autoimmune disease. GBS is a rare complication of modern influenza vaccine affecting one in a million recipients. In a retrospective survey, the risk of relapse following immunisation after GBS or CIDP was low but not absent. For GBS the risk of relapse severe enough to require treatment was at most 1.2%. Accordingly the GBS Support Group Medical Advisory Board recommends avoiding immunisations during the first year after the disease onset, and balancing the risks and benefits of immunisation for each patient on an individual basis. The same applies to CIDP in which the use of tetanus toxoid causes particular concern. It seems sensible to avoid immunisations that are not specifically necessary, though the risk–benefit ratio may be more favourable in patients on immunosuppressive therapy.

MULTIFOCAL MOTOR NEUROPATHY WITH CONDUCTION BLOCK

Multifocal motor neuropathy with conduction block (MMN) is a rare slowly progressive motor neuropathy which is related to or a variant of CIDP. There are sometimes minor sensory symptoms but not signs. It usually affects predominantly the upper limbs in an asymmetrical fashion. It can be confused clinically with motor neurone disease because of the cramps and fasciculations. About 50% have IgM antibodies to ganglioside GM1. Diagnosis depends on the demonstration of short focal areas of partial motor conduction block caused by demyelination at sites not vulnerable to entrapment. Sensory conduction is normal across the same segments. Even if no definite conduction block is found in an otherwise typical case, a trial of treatment may be indicated.

IVIg gave rapid dramatic benefit in three small randomised trials, and is the only proven effective treatment (level 1b evidence). About 20% of otherwise typical patients do not respond. Unfortunately, IVIg usually needs to be repeated frequently, every 4–12 weeks, and despite its use the weakness continues to increase. Response may be better in patients with more conduction blocks and antiganglioside GM1 antibodies, and worse in those with older age, widespread weakness, and high creatine kinase. There is insufficient evidence to support any particular second line treatment, but cyclophosphamide is often used. Steroids often cause the disease to worsen, by an unknown mechanism, and should be avoided. Plasma exchange usually has no effect.

PARAPROTEINAEMIC DEMYELINATING NEUROPATHY

About 10% of patients with an acquired demyelinating neuropathy have a paraprotein. When a paraprotein is detected, the patient should be investigated with a skeletal survey looking for an isolated plasmacytoma that may be surgically excised, and a bone marrow biopsy looking for myeloma, etc. Treatment of the cause of the paraprotein may improve the neuropathy. Most paraproteins are monoclonal gammopathies of uncertain significance (MGUS), and not usually treated, but the paraprotein concentration should be monitored regularly looking for a rapid rise that may herald malignant transformation. Paraproteinaemic demyelinating neuropathy is a heterogeneous group of conditions. The following may be distinguished.

(1) The best defined and most common syndrome is a slowly progressive, predominantly sensory neuropathy associated with IgM paraprotein, in which the paraprotein is a monoclonal antibody to myelin associated glycoprotein (MAG). Electron microscopy shows characteristic widely spaced myelin. There is often a postural tremor. The disease usually progresses slowly over years and is rarely disabling. Nerve conduction studies usually show uniform symmetrical conduction slowing and with notably prolonged distal motor latencies. Treatment is difficult. Mild slowly progressive disease is best left untreated. In more severe cases, IVIg has a
transient beneficial effect (level 1b evidence). Fludarabine and rituximab have seemed effective in small series of severely affected patients.

(2) Chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialoganglioside antibodies (CANOMAD) is a rare paraproteinaemic neuropathy similar to chronic MFS, which may respond to IVIg.

(3) The POEMS syndrome of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes is occasionally identified. It may be associated with myeloma, usually osteosclerotic, and Castleman’s disease. Steroids, azathioprine, melphalan, and cyclophosphamide have all been used empirically and there is no evidence on which to select any of these treatments.

(4) Neuropathy with an IgA or IgG paraprotein may resemble CIDP and respond to the same treatments. Rarely there is an underlying solitary myeloma and treatment of this can be curative. Since a paraprotein is not always evident at presentation it is worth repeating serum protein electrophoresis in treatment resistant CIDP. Other possible treatments include chlorambucil, fludarabine, and rituximab.

General management of chronic neuropathy

General management includes foot care, appropriate shoes or boots, ankle and wrist splints, weight reduction, physiotherapy, occupational therapy, and counselling. Fatigue is common but there is no evidence whether antidepressants or exercise programmes help. Autonomic involvement is not uncommon in CIDP or after GBS, and erectile impotence may respond to sildenafil. There are excellent patient support groups for GBS and CIDP based in the USA (http://www.guillain-barre.com/) and the UK (http://www.gbs.org.uk).

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