MANAGEMENT OF INFLAMMATORY NEUROPATHIES

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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 criteria¹ 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).² 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).³ 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, *Borrelia* 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/ μ l. 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*.⁴ 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).⁵ 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

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Box 1: Differential diagnosis of acute flaccid paralysis (after Cornblath²)

1. Acute anterior poliomyelitis
 - caused by poliovirus
 - caused by other neurotropic viruses
2. Acute myelopathy
 - space occupying lesions
 - acute transverse myelitis
3. Peripheral neuropathy (all except GBS usually have axonal neurophysiology)
 - Guillain-Barré syndromes
 - post-rabies vaccine neuropathy
 - diphtheritic neuropathy
 - heavy metals, biological toxins or drug intoxication
 - acute intermittent porphyria (usually pure motor neuropathy)
 - vasculitic neuropathy
 - critical illness neuropathy
 - lymphomatous neuropathy
 - infections (HIV, Borrelia)
4. Disorders of neuromuscular transmission
 - myasthenia gravis
 - biological or industrial toxins—for example, botulism
5. Disorders of muscle
 - hypokalaemia
 - hypophosphataemia
 - inflammatory myopathy
 - acute rhabdomyolysis
 - trichinosis
 - periodic paralyses
6. Functional/non-organic

myasthenia. Neurophysiological abnormalities are often very mild or occasionally normal in early GBS, and do not correlate well with clinical disability.⁶ 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 alone⁷ (fig 1, level 1a evidence). It reduced the median time to regain the ability to walk unaided from 85 to 53 days in one study and from 111 to 70 days in another, and improved long term disability at one year. A large French study showed that for mild GBS (patients able to stand unaided but unable to run) two 1.5 plasma volume exchanges were better than none, for intermediate severity four exchanges were better than two, and for ventilated patients six exchanges were no better than four (level 1b evidence). There were more adverse events with fresh frozen plasma as the replacement fluid than albumin.

Table 1 Antibodies to gangliosides associated with subtypes of acute inflammatory neuropathy

GM1	Pure motor GBS, GBS with preceding <i>Campylobacter jejuni</i> infection
GM1, GM1b, GD1a, GalNAc-GD1a	Axonal GBS
GQ1b, GT1a	GBS with more severe sensory abnormality, ophthalmoparesis or bulbar palsy; Miller Fisher syndrome; Bickerstaff's brainstem encephalitis; or overlapping syndromes
GT1a	Pharyngeocervicobrachial weakness
GBS, Guillain-Barré syndrome.	

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. Immunoabsorption 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, phenylalanine or tryptophan. In small studies, immunoabsorption 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)⁸ 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

Figure 1 Guillain-Barré syndrome. Mean improvement in disability grade four weeks after randomisation to plasma exchange or supportive care. Reproduced from Raphaël *et al* with permission from Update Software.

Box 2: Levels of evidence

- 1a: Meta-analysis of randomised controlled trials
- 1b: Randomised controlled trial
- 2a: Non-randomised controlled trial
- 2b: Quasi-experimental study
- 3: Non-experimental descriptive study
- 4: Expert opinion

ganglioside GM1. If a patient has not improved at all two weeks after treatment then it seems reasonable to try another course of the same or different treatment, especially if neurophysiological conduction block is still present. About 10% of patients experience a temporary clinical relapse a few weeks after initial improvement. This may be because the treatment has worn off before the underlying disease has subsided, and does not necessarily mean the patient will develop CIDP. Most clinicians give a repeat course of the same treatment if the relapse is severe (level 4 evidence).

General supportive management

The most common causes of death in GBS are still respiratory failure, cardiovascular disturbance, and thromboembolism. Outcome is better for patients managed in specialist neurology centres than district general hospitals. The vital capacity is the most useful measure of respiratory muscle weakness, and if this falls below 20 ml/kg (approximately 1500 ml for an average adult) then urgent referral to an intensive care unit should be made. Do not wait for a fall in arterial oxygen saturation or symptoms of breathlessness, which are very late signs indicative of imminent death. Patients with rapid worsening, bulbar weakness or autonomic dysfunction are more likely to need ventilation. Sympathetic and parasympathetic hyper- or hypoactivity may cause cardiac brady- or tachyarrhythmias and rapid fluctuations in blood pressure. Tracheal suctioning risks triggering bradycardia or asystole which can be prevented by hyperoxygenation beforehand. A cardiac pacemaker is rarely needed. All patients should have continuous ECG monitoring until they are clinically improving and the tracheostomy is removed. Low dose subcutaneous heparin is recommended for prophylaxis of venous thromboembolism. Neuropathic and radicular pain are common, and have traditionally been treated with conventional analgesics, amitriptyline or carbamazepine. A recent placebo controlled trial has provided strong evidence for the efficacy of gabapentin 500 mg twice daily. Physiotherapy is useful to avoid contractures and aid mobilisation. Many patients become depressed.

Outcome

After one year, about 5% of GBS patients have died and 15% 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.

Figure 2 Guillain-Barré syndrome. Mean improvement in disability grade four weeks after randomisation to plasma exchange (PE) or intravenous immunoglobulin (IVIg). Reproduced from Hughes *et al*⁸ with permission from Update Software.

Box 3: Variants of chronic inflammatory demyelinating polyradiculoneuropathy

- ▶ Symmetrical sensory and motor CIPD
- ▶ Sensory CIPD
- ▶ Motor CIPD
- ▶ Multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy
- ▶ Multifocal motor neuropathy

Diagnosis and investigation

The diagnosis is made on the basis of nerve conduction studies. Conduction slowing and prolonged distal motor latencies occur in both CIPD and hereditary demyelinating neuropathy, but CIPD is distinguished by the presence of motor conduction block, temporal dispersion, and asymmetric involvement, indicating a multifocal process. F-responses are delayed and often absent. Such abnormalities should be present in at least three nerves to meet diagnostic criteria. Some nerves may appear to be normal or to have axonal neurophysiology, so the diagnosis may be missed if too few nerves are tested and proximal conduction block is not specifically sought. A nerve biopsy is sometimes diagnostic, but not necessary and now not routinely done. Most patients with CIPD have axonal degeneration without demyelination on sural nerve biopsy. Serum protein electrophoresis should be done initially and annually thereafter, because the development of a paraprotein may indicate an alternative diagnosis and treatment (see later). Measurement of serum autoantibodies is not usually helpful. The CSF protein is raised in at least 80% of patients. A minority of patients has evidence of coexistent asymptomatic CNS demyelination on magnetic resonance imaging or evoked potential examination.

Immune modulating treatment

Corticosteroids were the first accepted treatment but entered clinical practice without today's high standards of evidence. Corticosteroids induce at least short term improvement in 65–95% of patients (level 1a and 4 evidence). There are many regimens. We prefer oral prednisolone 1.5 mg/kg on alternate days in a single morning dose with careful review and dose adjustment at two weekly intervals for 12 weeks, when a judgement needs to be made about whether to continue or switch to IVIg. Improvement begins after 1–4 weeks (but occasionally months), and reaches a plateau at about six months. Occasional patients deteriorate on steroids by an unknown mechanism, especially those with pure motor forms of CIPD or with multifocal motor neuropathy with conduction block. Prednisolone is cheap but has serious long term adverse effects. Osteoporosis prophylaxis should be started at the same time.

Plasma exchange 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 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.

IVIg appeared efficacious in three of four randomised trials and the efficacy was supported by a meta-analysis (fig 3, level 1a evidence).⁹ 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 IVIg and PE (courses of similar cost) or between IVIg and oral prednisolone.

In summary, prednisolone, IVIg 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 IVIg, followed by PE. In pure motor CIPD we start with IVIg. 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 for nine months, but was underpowered. Side effects include nausea, diarrhoea, rash, leucopenia, altered liver function (requiring long term blood monitoring), infection, and a theoretical risk of neoplasia. Azathioprine is metabolised by thiopurine methyl transferase and 10% of the population are heterozygotes and 0.3% homozygotes for its deficiency. Measurement of enzyme values identifies the heterozygotes, whose dose should be halved, and homozygotes, who should probably not be given the drug. It should not be used with allopurinol.

Figure 3 Chronic inflammatory demyelinating polyradiculoneuropathy. Relative rate of improvement 2–6 weeks after randomisation to intravenous immunoglobulin (IVIg) or placebo. Reproduced from van Schaik *et al*⁷ with permission from Update Software.

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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) down regulates 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 IgMκ 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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