Chronic inflammating polyradiculoneu

Richard Hughes
Department of Neuroimmunology,
Guy's, King's and St Thomas'
School of Medicine, Guy's Hospital,
London SE1 1UL, UK; Email: richard.
a.hughes@kcl.ac.uk
Practical Neurology, 2002, **2**,
198–207

INTRODUCTION

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is uncommon but important. It can be disabling but is usually treatable, and probably underdiagnosed. The only population-based studies suggest a prevalence of one or two per 100 000 but these are probably underestimates because of lack of referral or recognition of cases (Lunn *et al.* 1999; McLeod *et al.* 1999). In our population-based study of 46 patients in the south-east of England, 13% required an aid to walk and 54% were receiving medical treatment on the prevalence date (Lunn *et al.* 1999). The natural history of untreated disease is not known but two old large series included 7–35% of patients who eventually became bedridden or died from their disease (Dyck *et al.* 1975; Prineas & McLeod 1976). In a more recent large series, improvement with treatment was only partial, relapses were frequent, and 60% of patients were left with disability or continued to need treatment (Barohn *et al.* 1989).

HISTORY

The concept of CIDP emerged gradually from descriptions of recurrent attacks of steroid responsive demyelinating neuropathy (Austin 1958), was distinguished from the Guillain–Barré syndrome (GBS) (Thomas *et al.* 1969), and then described in increasingly large series (Dyck *et al.* 1975; Prineas & McLeod 1976). Thomas and colleagues pointed out the resemblance of the inflammatory demyelinating lesions in the peripheral nerves to those in chronic experimental autoimmune neuritis (Thomas *et al.* 1969).

CLINICAL PATTERNS

The typical clinical picture is of a chronic, more or less symmetrical, sensory and motor neuropathy with absent tendon reflexes.

natory

uropathy

There are several variants (Table 1). About 85% of patients have sensory symptoms, and purely sensory symptoms occur in 6% (McCombe *et al*. 1987; Oh *et al*. 1992). Most patients have motor symptoms and predominantly motor symptoms occur in 22% (McCombe *et al.* 1987). A pure motor form, multifocal motor neuropathy with conduction block (MMN) (Nobile-Orazio 2001), shows differences in its response to treatment and may be a different entity. A multifocal form with sensory and motor involvement was described by Lewis and Sumner and has now been labelled multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) (Lewis *et al*. 1982; Saperstein *et al*. 2000). The proportion of patients falling into these various groups is not known, but in my own experience symmetrical forms of the disease are the most common and MMN and MAD-SAM each represent about one tenth of patients.

In the typical form of the disease, weakness is usually both proximal and distal, especially in the lower limbs, perhaps because of root involvement. Sensory involvement is usually less marked than motor and affects large more than small fibres. The respiratory muscles are affected in 15%, bulbar muscles in

Table 1 Chronic inflammatory demyelinating neuropathies

Subacute (4–8 weeks progressive phase)
  subacute inflammatory demyelinating polyradiculoneuropathy
Chronic (> 8 weeks progressive phase)
  chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  multifocal motor neuropathy with conduction block (MMN)
  multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)

6–10%, facial muscles in 6–15% and the ocular motor nerves in 4% of cases in the three largest series (Dyck *et al*. 1975; McCombe *et al.* 1987; Barohn *et al.* 1989). The autonomic nervous system is not usually affected, in contrast with GBS. However, the condition is very variable and cranial nerve signs can be prominent and are occasionally presenting features. Sometimes the upper limbs are initially and preferentially affected. Disabling sensory loss may be more marked than weakness. Approximately 20% have painful paraesthesiae, which are sometimes severe. Approximately 3% of patients have a postural tremor, which may be disabling. With advancing disease, wasting occurs, due to superimposed axonal degeneration, and contractures may develop. Rare childhood onset patients have pes cavus and clawing of the toes, although such features would lead to consideration of the diagnosis of Charcot-Marie-Tooth disease. Peripheral nerve thickening may occur in CIDP but less often than in hereditary demyelinating neuropathies. Papilloedema occurs in 1–7% of patients, possibly due to the increased CSF protein.

TIME COURSE

The clinical course of CIDP may be progressive, or relapsing and remitting with each relapse developing slowly over several weeks or sometimes more abruptly as in GBS. In approximately 3% the onset attack is acute, very like GBS, but the patient later shows a relapsing course, which responds to steroids or intravenous immunoglobulin (IVIg) (Mori *et al*. 2002).

We do not really know where GBS ends and CIDP begins. About 10% of patients with GBS have a period of early worsening 2 to 8 weeks after being treated with IVIg (Kleyweg & van der Meché 1991). Most of these patients eventually improve without further relapses and the early worsening may be because the immunotherapy has taken the nadir out of what would have been a monophasic illness. Guillain–Barré syndrome was once defined as having a progressive phase lasting no more than 4 weeks (Asbury 1981). Then, in 1991, an expert committee cleverly insisted on a progressive phase for CIDP of more than 2 months [Ad Hoc Subcommittee of the American Academy of Neurology (AAN) AIDS Task Force 1991]. This left an uncommon but inconvenient group of patients with a progressive phase of 4–8 weeks, which we called subacute (Hughes *et al*. 1992).

Chronic inflammatory demyelinating polyradiculoneuropathy needs to be considered in any patient with a relapsing neuropathy, any patient with a GBS-like illness and a prolonged onset phase, and in any patient with a chronic neuropathy

DIAGNOSTIC CRITERIA

The AAN committee required the presence of progressive or relapsing weakness of more than one limb attributable to radiculoneuropathy, exclusion of other causes, relatively normal CSF cell count and fulfilment of strict electrophysiological criteria for a probable diagnosis of CIDP (Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force 1991). Definite diagnosis required nerve biopsy evidence of a demyelinating neuropathy. A practical simplification of these criteria is offered in Table 2. It is now appreciated that the AAN neurophysiological criteria were too strict and a recent modification (Table 3) promises to be more sensitive but still adequately specific (Nicolas *et al.* 2002).

DIFFERENTIAL DIAGNOSIS

Chronic inflammatory demyelinating polyradiculoneuropathy needs to be considered in any patient with a relapsing neuropathy, any patient with a GBS-like illness and a prolonged onset phase, and in any patient with a chronic neuropathy. The diagnosis is most likely when there is areflexia, proximal as well as distal motor involvement and greater motor than sensory deficit. The presence of a general medical condition,

Table 2 Diagnostic criteria after the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force 1991

Clinical
    Progressive or relapsing motor and sensory (rarely only motor or sensory) dysfunction of the limbs developing over at least 2 months
    Reduced or absent tendon reflexes
    No alternative cause, e.g. relevant toxin exposure, family history
    No CNS involvement
Neurophysiological
    Neurophysiological studies indicating the presence of multifocal demyelination
CSF
    Cell count < 10/mm3 or > 10/mm3 if HIV positive (protein concentration usually increased, often > 1000 mg/L)
Nerve biopsy
    Unequivocal evidence of demyelination or remyelination (inflammation, onion bulb formation, variation between fascicles)

Table 3 Neurophysiological criteria after Nicolas *et al.* 2002

The nerve conduction studies must show one of the following abnormalities in at least three different nerves.
    Conduction block* or temporal dispersion† in at least three different nerves and abnormal conduction values suggestive of demyelination in at least one nerve
    Conduction block or temporal dispersion in at least two different nerves and abnormal conduction values suggestive of demyelination in at least one other nerve
    Conduction block or temporal dispersion in one nerve and abnormal conduction values suggestive of demyelination in at least two other nerves
    Abnormal conduction values in three nerves
Criteria for abnormal conduction indicating demyelination include:
    maximum motor nerve conduction velocity < 80% of the lower limit of normal if the compound muscle action potential is > 80% of the lower limit of normal and maximum motor nerve conduction velocity < 70% of the lower limit of normal if it is not.

*Conduction block is an amplitude drop of 30% between proximal and distal sites (neurophysiologists argue about this figure which ranges from 20 to 50% by different criteria: the figure is less reliable when the amplitude is small).
†Temporal dispersion is a prolongation of the compound muscle action potential by more than 15%.
For more details consult the original publication or your neurophysiologist who is in the best position to diagnose CIDP.

Table 4 Differential diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy

Guillain–Barré syndrome
Subacute inflammatory demyelinating polyradiculoneuropathy
Multifocal motor neuropathy with conduction block
Charcot-Marie-Tooth disease type 1
Charcot-Marie-Tooth disease type 3 (Dejerine–Sottas syndrome)
Charcot-Marie-Tooth disease type X
Hereditary liability to pressure palsies
Other genetic causes, e.g. Refsum's disease, metachromatic
    leukodystrophy
Paraproteinaemic demyelinating neuropathy
    Solitary plasmacytoma
    Osteosclerotic myeloma
    Waldenstrom's macroglobulinaemia
    Monoclonal gammopathy of undetermined significance:
        IgM paraproteinaemia with antibodies to Myelin Associated
            Glycoprotein (MAG)
        IgM paraproteinaemia without antibodies to MAG
        IgG paraproteinaemia
        IgA paraproteinaemia
Some toxin/drug-induced neuropathies (hexacarbons,
    amiodarone)
Chronic relapsing axonal neuropathy

such as carcinoma, plasma cell dyscrasia, diabetes mellitus or systemic lupus erythematosus, does not preclude a diagnosis of CIDP because all these may be associated or possibly causative illnesses. Fortunately, once the nerve conduction tests have identified a demyelinating rather than an axonal neuropathy, the differential diagnosis becomes much more limited (Table 4).

PATHOGENESIS

Although CIDP occurs at any age, it is more common in the middle aged and elderly. It is uncommon in children but has been reported as young as 2 years of age. All reported series have included more men than women, an unusual sex ratio for an autoimmune disease but the same as in GBS. Nevertheless the inflammatory features at *foci* of active disease, and response to immunotherapy, have led to the general acceptance that CIDP is an autoimmune disease. Experimental autoimmune neuritis, which it resembles, can be induced by T cell responses to any of the peripheral nerve myelin proteins P0, P2 or PMP22 (Adam *et al*. 1989; Hughes *et al*. 1999). Recently antibody responses to PMP22 have been found in 49% of patients with CIDP (Gabriel *et al*. 2000) and to P0 in 28% (Yan *et al*. 2001) but these reports have not been confirmed or converted into useful diagnostic tests. Attempts to find antibodies to gangliosides or other peripheral nerve antigens have been unrewarding. In multifocal motor neuropathy with conduction block, antibodies to ganglioside GM1 are present in 30–80% of cases but their role in pathogenesis of that condition is unproved (Nobile-Orazio 2001). Antibodies to gangliosides and other glycoconjugates are present in 10% or less of patients with CIDP (Meléndez-Vásquez *et al*. 1997).

There is not the same relationship between infection and onset or relapse that is seen in GBS. Only one quarter of our series of 40 patients reported an infection preceding the onset of their illness and it is unusual for relapses to have a clear relationship to infection (Meléndez-Vásquez *et al*. 1997). In one case of recurrent GBS, recurrences were preceded by cytomegalovirus exposures and higher titres of antibodies to cytomegalovirus were found in 39 CIDP patients than in 25 controls (Donaghy *et al*. 1989; McCombe *et al*. 1987; McLeod *et al*. 1999). However, we did not find IgM antibodies to cytomegalovirus in any of our 40 patients (Meléndez-Vásquez *et al*. 1997).

INVESTIGATION

See Table 5. There is no diagnostic test that clinches the diagnosis of CIDP. Neurophysiology is the most important investigation, distinguishing axonal from demyelinating neuropathies (Figure 1), and showing a multifocal process rather than the diffuse demyelination characteristic of the hereditary demyelinating neuropathies.

It is customary to send off a battery of blood investigations, which are more useful as a baseline for future treatment and reassuring the faint-hearted than likely to detect a cause. Searching for a paraprotein is important because serum protein electrophoresis reveals a paraprotein in about 10% of cases (Kelly *et al*.

Table 5 Investigation of demyelinating neuropathy

Blood tests
    Full blood picture, ESR
    Renal, liver and thyroid profile
    Fasting glucose, glycosylated haemoglobin
    Serum protein electophoresis
    Serum immunoglobulin levels
Urine
    Glucose
    Bence-Jones protein
CSF
    Cells, protein, immunoglobulin oligoclonal bands
Immunology
    Anti-HIV antibodies
    Antiganglioside antibodies
    Antimyelin associated glycoprotein antibodies
Radiology
    Chest X-ray
    Skeletal survey
Molecular genetic tests
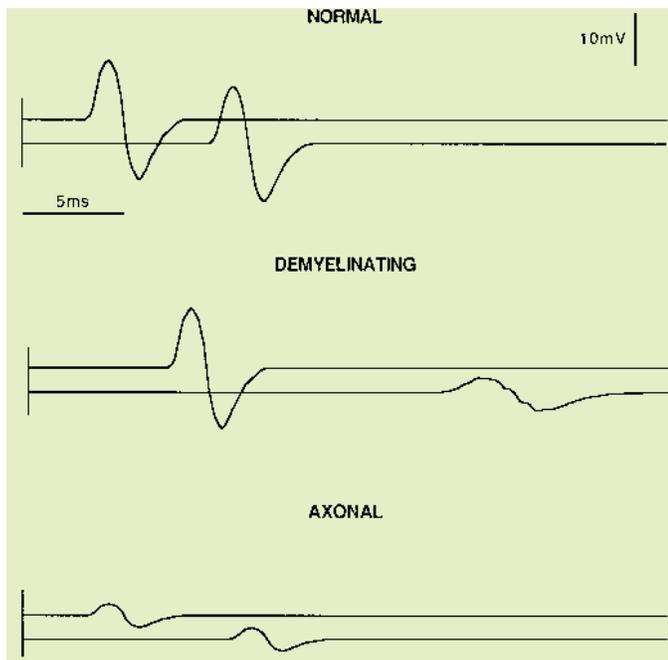   Peripheral myelin protein 22 gene duplication or deletion

Figure 1 This diagram has been reproduced with permission from the BMJ. It was kindly provided by Professor Kerry Mills, and shows the compound muscle action potentials elicited from a muscle such as the abductor pollicis brevis following distal (upper) and proximal (lower of each pair of traces) stimulation.

In the normal nerve the distal motor latency is short and nerve conduction velocity rapid (> 50 m/s).

In demyelinating neuropathy the distal motor latency is prolonged and nerve conduction velocity markedly slowed to less than 80% of normal. The proximally evoked action potential is reduced in amplitude. The reduction in amplitude may be due partly to conduction block of some nerve fibres and partly to dispersion of the arrival of the individual nerve fibre action potentials at the motor end plate. Nerve conduction velocity is usually uniformly slowed in Charcot-Marie-Tooth disease type 1. Chronic inflammatory demyelinating polyradiculoneuropathy usually shows multifocal abnormalities with partial conduction block.
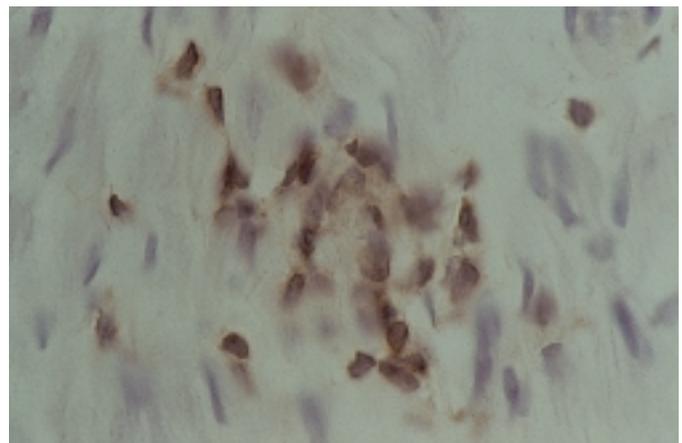
In axonal neuropathy the compound muscle action potential is also reduced but the distal motor latency and nerve conduction velocities are relatively preserved.

1981). The DNA test for the most common cause of Charcot-Marie-Tooth disease, duplication of the peripheral myelin protein 22 gene, occasionally turns up an unexpected case. Immunological tests have been disappointing but searching for antibodies to ganglioside GM1 is part of the ritual.

The CSF is useful because an increased protein concentration is found in almost every case (Barohn *et al.* 1989; Dyck *et al.* 1975). The value is often more than 1000 mg/L and the cell count is normal or nearly normal. As an exception, in CIDP associated with HIV the cell count is commonly raised.

Nerve biopsy is often unhelpful in the diagnosis of CIDP (Molenaar *et al.* 1998) because the sural nerve, which is the one usually biopsied, is a distal sensory nerve and the brunt of the pathology falls on the motor fibres, nerve roots and proximal nerve trunks (Krendel *et al.* 1989; Bouchard *et al.* 1999). The most common abnormalities are loss of axons and ongoing axonal degeneration, which are probably the consequence of proximal inflammatory foci. Epineurial lymphocytic infiltration is quite common but nonspecific and therefore unhelpful. The most specific diagnostic features are endoneurial lymphocytic infiltration and remyelinated, demyelinated or demyelinating nerve fibres, but these are only found in about one quarter of patients (Figure 2). Onion bulbs occur in about one tenth of patients and are the consequence of repeated episodes of de- and re-myelination (Figure 3). They are usually sparse and much less abundant than in Charcot-Marie-Tooth disease Type 1a. With increasing experience I have veered towards avoiding nerve biopsy except when the diagnosis is in doubt.

Figure 2 Transverse fozen section of sural nerve from a patient with CIDP showing a cluster of T cells identified in the endoneurium with an immunoperoxidase labelled monoclonal antibody. Such a finding is highly specific but not very sensitive for the diagnosis.
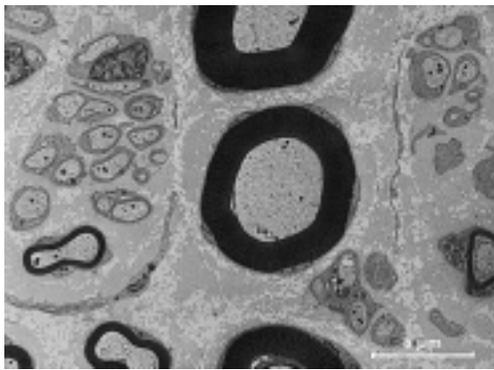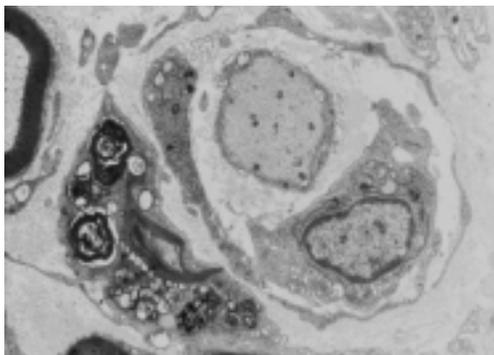
(a)

(b)

(c)

Figure 3 (a) An electron micrograph of a normal myelinated nerve fibre (once belonging to the author). (b) Ongoing macrophage-associated demyelination: an early stage in the formation of an onion bulb from a patient with CIDP. (c) A mature onion bulb consisting of a thinly myelinated axon surrounded by concentric wraps of Schwann cells separated by collagen from the same patient.

IMMUNOTHERAPY

Steroids

Because of the inflammatory and presumed autoimmune nature of CIDP, steroids should be beneficial. This expectation is borne out by the experience of experts in the field and the conclusions of the only randomised trial (Dyck *et al.* 1982). However the significance of the beneficial result reported in that trial was lost when the results were re-analysed according to the intention-to-treat principle and with pessimistic imputations about the fate of the patients who were lost to follow-up (Mehndiratta & Hughes 2001). Nevertheless, the overwhelming conclusion from case series and nonsystematic reviews is that steroids are beneficial and it is probably inappropriate and unethical to consider further trials comparing steroids with placebo. The serious adverse effects of steroid treatment, including obesity, hypertension, diabetes mellitus, osteoporosis and cataracts, have led to continuing searches for alternative treatments.
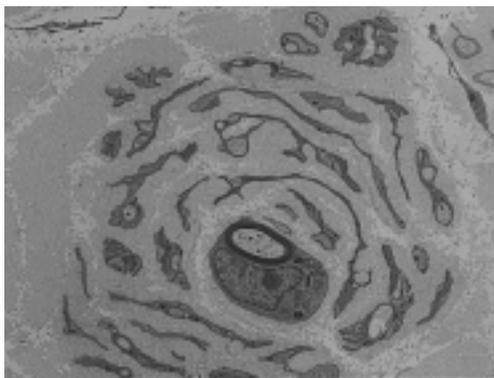
In the absence of evidence to guide dosage, my practice is to start oral prednisolone 1.5 mg/kg (maximum 120 mg) on alternate days. Bisphosphonate prophylaxis for osteoporosis must be started at the same time because the process of steroid-induced bone resorption begins immediately. The risks of hyperkalaemia,
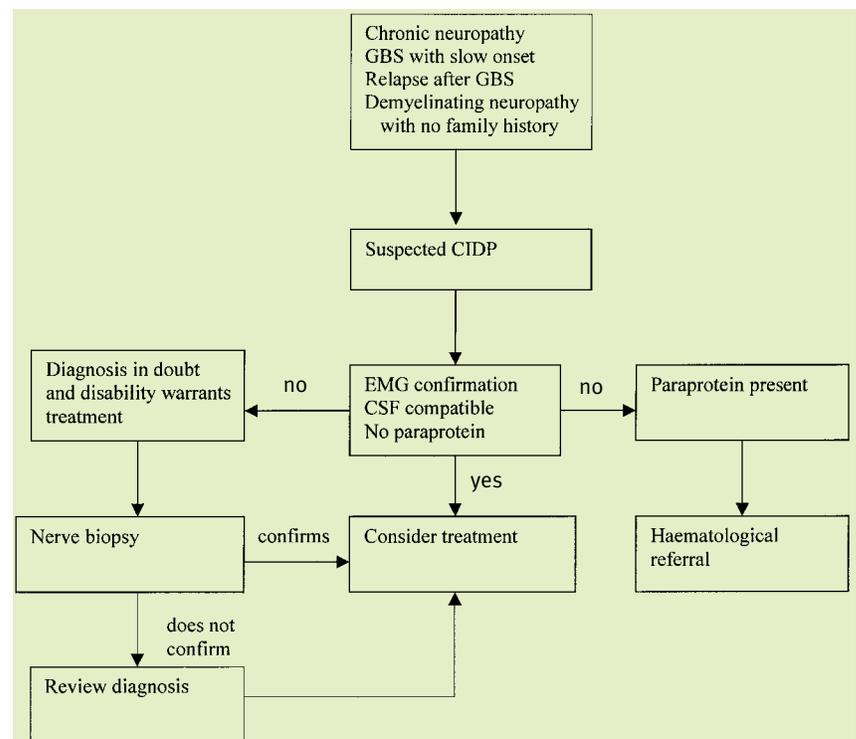
hyperglycaemia and hypertension merit appropriate monitoring. Subsequent dosage depends on the response. I try to hold this initial dose for at least 2 and if possible 4 weeks. Once there is an adequate response I reduce the dose by 10 mg every 2 weeks, down to 40 mg on alternate days, then by 5 mg on alternate days every 2 weeks down to 20 mg, then by 2.5 mg on alternate days every 2 weeks until as low a dose as possible has been achieved. Most patients require a dose in the region of 10–25 mg on alternate days to maintain remission. This regimen is based on the protocols reported by others and personal experience. Good evidence to confirm the hypothesis that alternate day dosing reduces adrenopituitary axis suppression and the proposal that it does not cause steroid myopathy would be welcome.

Plasma exchange

Two small but high quality trials both showed benefit from plasma exchange (PE). Dyck and colleagues at the Mayo clinic undertook a double blind trial in 29 patients comparing twice weekly PE or sham exchange for three weeks. They showed significantly greater improvement in clinical impairments and motor nerve conduction (Dyck *et al.* 1986). Hahn and colleagues in London, Ontario, undertook a crossover trial comparing PE with sham exchange in 18 treatment-naïve patients of whom 16 completed the crossover period. Patients received four exchanges in the first week, three in the second, two in the third and one in the fourth. There were significant improvements in impairment, disability, grip strength and proximal compound muscle action potential amplitude with PE that were not seen with sham exchange (Hahn *et al.* 1996a). A Cochrane review is in progress and is likely to conclude that PE produces short-term improvement (Mehndiratta 2001, pers. comm.). In order to maintain improvement, PE has to be repeated at variable intervals, but often as little as 4 weeks,

with IVIg the likelihood of improvement after three or four weeks was 2.47 times greater (95% confidence interval 1.02–6.01) than with placebo

which is inconvenient and eventually gives rise to difficulties with venous access.

Intravenous immunoglobulin

Vermeulen *et al.* showed that first plasma and then intravenous immunoglobulin (IVIg) infusion appeared to benefit patients with CIDP (Vermeulen *et al.* 1985). This observation has been confirmed in three randomised trials (Hahn *et al.* 1996b; Thompson *et al.* 1996; Mendell *et al.* 2001) but not in a fourth (Vermeulen *et al.* 1993). The evidence from these trials has been summarized in a meta-analysis, which concluded that with IVIg the likelihood of improvement after three or four weeks was 2.47 times greater (95% confidence interval 1.02–6.01) than with placebo (Van Schaik *et al.* 2002). Unfortunately the treatment effect commonly lasts only 4 weeks and seldom more than 12, so that treatment, which costs about £2500 (and rising) for a standard 2.0 g/kg course, has to be repeated.

A further trial did not find a significant difference between the short-term effects of IVIg and PE (Dyck *et al.* 1994). Finally, our own trial did not detect any significant difference between the short-term benefits from IVIg and oral prednisolone (Hughes *et al.* 2001a).

Advice about the use of IVIg is available in a recent article in *Practical Neurology* (Pritchard & Hughes 2001).

Choice of initial treatment

In my recent review I concluded that the comparative trials were short-term,

'but the long-term comparative trials needed to decide which of these treatments is superior seem unlikely to be performed. About two thirds of patients respond to each treatment. Steroids may be preferred because they are much less expensive and more convenient. If patients do not respond or require unreasonably high or prolonged doses they may respond to IVIg. Plasma exchange is more inconvenient and invasive and now

Both pure motor CIDP and MMN may be made worse by steroids, which should be avoided

usually only considered as a third option' (Hughes 2002).

In patients with pure motor CIDP, steroids may cause worsening and IVIg is more likely to be effective (see below).

Immunosuppressive drugs

Because of the disadvantages of steroids, IVIg and PE, cytotoxic drugs and immunomodulatory treatments have been tried (van den Bergh 2001). One small trial failed to show benefit from azathioprine (Dyck *et al.* 1985) and another from beta interferon (Hadden *et al.* 1999). However these trials were too small or too short to conclude that these agents are ineffective. There have only been anecdotal reports or small series describing benefit with cyclophosphamide, cyclosporin and mycophenolate but no randomised trials (Hughes *et al.* 2001b). Despite the absence of evidence, immunosuppressive drugs are often used in treatment-resistant cases. The most common is probably azathioprine but the better safety profile of methotrexate in rheumatoid arthritis and dermatomyositis suggests that this be considered as an alternative. Oral or intravenous cyclophosphamide and cyclosporin each have their protagonists. There is a need for trials to determine whether any of these treatments are beneficial. In the meantime I recommend adding azathioprine for severely affected patients who respond inadequately to the primary treatments, prednisolone, IVIg or PE. To reduce the 10% risk of adverse effects and intolerance, I measure the thiopurine methyl transferase enzyme level in the blood before starting the drug and then gradually increase the dose to 2.5 mg/kg, but more slowly and to half this dose or less if the enzyme levels are low.

SPECIAL SITUATIONS

Pure motor CIDP and MMN

Both pure motor CIDP and MMN may be made worse by steroids, which should be avoided (Donaghy *et al.* 1994; Umapathi *et al.* 2002). Plasma exchange is also unlikely to help. By contrast, IVIg is often dramatically and rapidly effective, experience that is supported by three small trials (Van den Berg *et al.* 1995; Federico *et al.* 2000; Léger *et al.* 2000). Unfortunately the improvement is short-lived and not invariable and disability progresses slowly despite repeated treatment. Many different immunosuppressive drugs, principally cyclophosphamide, have been tried but the Cochrane review did not identify any randomised trials. The evidence from nonrandomised studies is inadequate to conclude whether any particular immunosuppressive agent is effective (Umapathi *et al.* 2002).

Paraproteinaemic demyelinating neuropathy

The peripheral neuropathy associated with a paraprotein may resemble the different forms of CIDP and respond to the same treatments. However, the management of these patients has been reviewed elsewhere and involves special considerations beyond the scope of this review (Hughes 2002).

GENERAL TREATMENTS

Because immunotherapy takes time to work and is often only partially effective, measures to deal with the symptoms of CIDP are also needed. Amitriptyline, gabapentin and carbamazepine are all worth trying for neuropathic pain. A physiotherapist will help with gait and balance retraining and is the best person to supervise judicious use of foot drop splints, sticks, crutches

or frames. Dealing with the fatigue and other consequences of a chronic, disabling and unpredictable disease may be aided by the excellent support provided by the CIDP network of the GBS Support Group (see patient information below)

CONCLUSIONS
Chronic inflammatory demyelinating polyradiculoneuropathies are a set of progressive or relapsing, often disabling diseases that are potentially treatable.

Although progress has been made in defining some effective treatments, patients are often left with significant disability and existing treatments can have unacceptable adverse effects.

More research is needed to investigate the possible benefits of existing treatments, especially immunosuppressive agents, and to identify new less toxic regimens.

We also need to use the strategies of the Cochrane Collaboration to synthesize what evidence there is from randomised trials as the basis for treatment guidelines.

PATIENT INFORMATION
- Guillain–Barré Syndrome Support Group (www.gbs.org.uk). Information and support to people with Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy and related conditions.
- Peripheral Neuropathy Trust (www.neuropathy-trust.org). Information about all forms of neuropathy, especially chronic idiopathic axonal neuropathy.

ACKNOWLEDGEMENTS
This article is based on the Cochrane systematic reviews that have been quoted and on my contribution to the Festschrift for Professor PK Thomas (Hughes 2002).

REFERENCES
Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force (1991) Research criteria for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). *Neurology*, **41**, 617–8.

Adam AM, Atkinson PF, Hall SM, Hughes RAC & Taylor WA (1989) Chronic experimental allergic neuritis in Lewis rat. *Neuropathy and Applied Neurobiology*, **15**, 249–64.

Asbury AK (1981) Diagnostic considerations in Guillain–Barré syndrome. *Annals of Neurology*, **9**, 1–5.

Austin JH (1958) Recurrent polyneuropathies and their corticosteroid treatment. *Brain*, **81**, 157–92.

Barohn RJ, Kissel JT, Warmolts JR & Mendell JR (1989) Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. *Archives of Neurology*, **46**, 878–84.

van den Bergh P (2001) Intravenous immunoglobulin (IVIG) in the treatment of chronic demyelinating polyradiculoneuropathy. *Acta Neurologica Belgica*, **101**, 147–51.

Bouchard C, Lacroix C & Planté V *et al.* (1999) Clinicopathologic findings and prognosis of chronic inflammatory demyelinating polyneuropathy. *Neurology*, **52**, 498–503.

Donaghy M, Gray JA & Squier W *et al.* (1989) Recurrent Guillain–Barré syndrome after multiple exposures to cytomegalovirus. *American Journal of Medicine*, **87**, 339–41.

Donaghy M, Mills KR & Boniface SJ *et al.* (1994) Pure motor demyelinating neuropathy: Deterioration after steroid treatment and improvement with intravenous immunoglobulin. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**, 778–83.

Dyck PJ, Daube J & O'Brien P *et al.* (1986) Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. *New England Journal of Medicine*, **314**, 461–5.

Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H & Groover RV (1975) Chronic inflammatory polyradiculoneuropathy. *Mayo Clinic Proceedings*, **50**, 621–51.

Dyck PJ, Litchy WJ & Kratz KM *et al.* (1994) A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. *Annals of Neurology*, **36**, 838–45.

Dyck PJ, O'Brien PC & Oviatt KF *et al.* (1982) Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Annals of Neurology*, **11**, 136–41.

Dyck PJ, O'Brien P, Swanson C, Low P & Daube J (1985) Combined azathioprine and prednisone in chronic inflammatory demyelinating polyneuropathy. *Neurology*, **35**, 1173–6.

Federico P, Zochodne DW, Hahn AF, Brown WF & Feasby TE (2000) Multifocal motor neuropathy improved by IVIg: randomized, double-blind, placebo-controlled study. *Neurology*, **55**, 1256–62.

Gabriel CM, Gregson NA & Hughes RAC (2000) Anti-PMP22 antibodies in patients with inflammatory neuropathy. *Journal of Neuroimmunology*, **104**, 139–46.

Hadden RD, Sharrack B, Bensa S, Soudain SE & Hughes RA (1999) Randomized trial of interferon beta-1a in chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology*, **53**, 57–61.

Hahn AF, Bolton CF & Pillay N *et al.* (1996a) Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy (CIDP): a double-blind, sham-controlled, cross-over study. *Brain*, **119**, 1055–66.

Hahn AF, Bolton CF, Zochodne D & Feasby TE (1996b) Intravenous immunoglobulin treatment (IVIg) in chronic inflammatory demyelinating polyneuropathy (CIDP): a double-blind placebo-controlled cross-over study. *Brain*, **119**, 1067–78.

Hughes RAC (2002) Systematic reviews of treatment for

inflammatory demyelinating neuropathy. *Journal of Anatomy*, **200**, 331–339.

Hughes R, Sanders E, Hall S, Atkinson P, Colchester A & Payan J (1992) Subacute idiopathic demyelinating polyradiculoneuropathy. *Archives of Neurology*, **49**, 612–6.

Hughes RAC, Gregson NA, Hadden RDM & Smith KJ (1999) Pathogenesis of Guillain–Barré syndrome. *Journal of Neuroimmunology*, **100**, 74–97.

Hughes RAC, Bensa S & Willison HJ *et al.* (2001a) Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Annals of Neurology*, **50**, 195–201.

Hughes RAC, Swan AV & van Doorn PA (2001b) Cytotoxic drugs and interferons for chronic inflammatory demyelinating polyradiculoneuropathy (Protocol for a Cochrane Review). *The Cochrane Library Issue 4*, Oxford, Update Software.

Kelly JJ, Kyle RA, O'Brien PC & Dyck PJ (1981) The prevalence of monoclonal gammopathy in peripheral neuropathy. *Neurology*, **31**, 1480–3.

Kleyweg RP & van der Meché FGA (1991) Treatment related fluctuations in Guillain–Barré syndrome after high-dose immunoglobulins or plasma-exchange. *Journal of Neurological Neurosurg Psychiatry*, **54**, 957–60.

Krendel DA, Parks HP, Anthony DC, St. Clair MB & Graham DG (1989) Sural nerve biopsy in chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve*, **12**, 257–64.

Léger J-M, Chassande B, Musset L, Meininger V, Bouche P & Baumann N (2000) Intravenous imunoglobulin in the treatment of multifocal motor neuropathy with persistent conduction blocks: a randomized double-blind placebo controlled study. *Brain*, **124**, 145–53.

Lewis RA, Sumner AJ, Brown MJ & Asbury AK (1982) Multifocal demyelinating neuropathy with persistent conduction block. *Neurology*, **32**, 958–64.

Lunn MPT, Manji H, Choudhary PP, Hughes RAC & Thomas PK (1999) Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. *Journal of Neurology, Neurosurgery and Psychiatry*, **66**, 677–80.

McCombe PA, Pollard JD & McLeod JG (1987) Chronic inflammatory demyelinating polyradiculoneuropathy. *Brain*, **110**, 1617–30.

McLeod JG, Pollard JD, Macaskill P, Mohamed A, Spring P & Kurana V (1999) Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. *Annals of Neurology*, **46**, 910–2.

Mehndiratta MM & Hughes RAC (2001) Corticosteroids for Chronic Inflammatory Demyelinating-polyradiculoneuropathy (Cochrane Review). *The Cochrane Library 3*, Oxford, Update Software.

Meléndez-Vásquez C, Redford J & Choudhary PP *et al.* (1997) Immunological investigation of chronic inflammatory demyelinating polyradiculoneuropathy. *Journal of Neuroimmunology*, **73**, 124–34.

Mendell JR, Barohn RJ & Freimer ML *et al.* (2001) Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. *Neurology*, **56**, 445–9.

Molenaar DS, Vermeulen M & de Haan R (1998) Diagnostic value of sural nerve biopsy in chronic inflammatory demyelinating polyneuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **64**, 84–9.

Mori K, Hattori N & Sugiura M *et al.* (2002) Chronic inflammatory demyelinating polyneuropathy presenting with features of GBS. *Neurology*, **58**, 979–82.

Nicolas G, Maisonobe T, Le Forestier N, Léger J-M, Bouche P & INCAT Group (2002) Proposed revised electrophysiological criteria for chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve*, **25**, 26–30.

Nobile-Orazio E (2001) Multifocal motor neuropathy. *Journal of Neuroimmunology*, **115**, 4–18.

Oh SJ, Joy JL & Kuruoglu R (1992) 'Chronic sensory demyelinating neuropathy': Chronic inflammatory demyelinating polyneuropathy presenting as a pure sensory neuropathy. *Journal of Neurology, Neurosurgery and Psychiatry*, **55**, 677–80.

Prineas JW & McLeod JG (1976) Chronic relapsing polyneuritis. *Journal of Neurological Science*, **27**, 427–58.

Pritchard J & Hughes RAC (2001) Intravenous immunoglobulin – how to use it. *Practical Neurology*, **1**, 93–8.

Saperstein DS, Amato AA & Wolfe GI *et al.* (2000) Multifocal acquired demyelinating motor and sensory motor neuropathy: the Lewis–Sumner syndrome. *Muscle Nerve*, **22**, 560–6.

Thomas PK, Lascelles RG, Hallpike JF & Hewer RL (1969) Recurrent and chronic relapsing Guillain-Barré polyneuritis. *Brain*, **92**, 589–606.

Thompson N, Choudhary P, Hughes R & Quinlivan R (1996) A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. *Journal of Neurology*, **243**, 280–5.

Umapathi T, Léger J-M, Nobile-Orazio E & Hughes RAC (2002) Immunosuppressants for treating multifocal motor neuropathy (Cochrane review). *The Cochrane Library 2*, Oxford, Update Software.

Van den Berg LH, Kerkhoff H & Oey PL *et al.* (1995) Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. *Journal of Neurological Neurosurg Psychiatry*, **59**, 248–52.

Van Schaik IS, Winer JB, de Haan R & Vermeulen M (2002) Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy (Cochrane Review). *The Cochrane Library Issue 2*, Oxford, Update Software.

Vermeulen M, van der Meché FGA, Speelman JD, Weber A & Busch HFM (1985) Plasma and gamma-globulin infusion in chronic inflammatory polyneuropathy. *Journal of the Neurological Sciences*, **70**, 317–26.

Vermeulen M, van Doorn PA, Brand A, Strengers PFW, Jennekens FGI & Busch HFM (1993) Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. *Journal of Neurology, Neurosurgery and Psychiatry*, **56**, 36–9.

Yan WX, Archelos JJ, Hartung HP & Pollard JD (2001) P0 protein is a target antigen in chronic inflammatory demyelinating polyradiculoneuropathy. *Annals of Neurology*, **50**, 286–92.