Autoimmune inflammatory neuropathy

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Pathological classification

Inflammation of peripheral nerves may be due to autoimmune disease, infection or vasculitis. The nerve fibres are normally protected by a specialised endothelium, positive endoneurial pressure and perineurial barrier. Most cases of inflammatory neuropathy are characterised by endoneurial inflammation and primary demyelination without infection or vasculitis, and are thought to have an autoimmune pathogenesis. Macrophages penetrate the Schwann cell basement membrane, ingest the myelin sheath and denude the axon (Fig 1(a)–(c)). If the inflammation is severe, the axons may undergo 'bystander' degeneration. In rare cases, the autoimmune response is directed against the axon and causes a primary axonal neuropathy (Fig 2). Some organisms, such as Mycobacterium leprae and herpes zoster, have a special ability to grow within Schwann cells or sensory neurons. Vasculitis, particularly Churg-Strauss syndrome and polyarteritis nodosa, may affect peripheral nerves, usually causing acute axonal degeneration, very occasionally demyelination, and producing the clinical picture of multiple mononeuropathy or symmetrical polyneuropathy. Rarely, vasculitis is confined to peripheral nerves. This review focuses on autoimmune inflammatory neuropathy.

There is a temporal spectrum of inflammatory demyelinating polyradiculoneuropathies with similar pathology, from acute through subacute to chronic (Table 1), although there is an unexplained difference in response to steroid treatment. Guillain-Barré syndrome (GBS), the commonest clinical presentation of an autoimmune neuropathy, is now agreed to be a heterogeneous condition incorporating several pathological entities.

Fig 1. Electron micrograph of a sural nerve biopsy from a patient with Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy): (a) a macrophage surrounds a normal myelinated axon; (b) it penetrates and digests the myelin, and (c) strips the axon. (Reproduced, with permission, from Ref 1.)
Guillain-Barré syndrome

Clinical features

The annual incidence of GBS is about two per 100,000 and increases with age. Half the patients eventually make a complete recovery, but many have persistent fatigue, 15% are still unable to walk unaided after a year, and 8% die. A worse outcome is predicted by older age, preceding diarrhoea, severe weakness, and neurophysiologically inexcitable motor nerves. Children usually recover faster and more completely.

Two-thirds of patients have had symptoms of a respiratory or gastrointestinal infection in the preceding two weeks. Campylobacter jejuni (Fig 3), cytomegalovirus, Epstein-Barr virus and Mycoplasma pneumoniae have all been incriminated in case-control studies and may be asymptomatic. A popular, but unproven, hypothesis is that molecular mimicry between the infecting organism and peripheral nerve antigens triggers an autoimmune response. Treatment of the infection does not influence outcome.

The major symptoms are weakness and/or sensory disturbance of upper and/or lower limbs, usually symmetrical, often proximal and distal but not necessarily 'ascending', and progressing for up to four weeks. There may be severe neuropathic or radicular pain. Reflexes are usually absent in affected limbs. There is often involvement of autonomic, cranial and respiratory muscle nerves.

The diagnosis is made from the characteristic history, with flaccid weakness, raised cerebrospinal fluid (CSF) protein with normal white cell count, and exclusion of other (eg toxic) causes (Table 2). Nerve conduction studies may support the diagnosis by showing features of demyelination. Difficulties in diagnosis may be caused by the fact that reflexes, CSF protein and neurophysiology may all be normal, particularly in the first few days of the disease. Most cases of GBS have acute inflammatory demyelinating polyradiculoneuropathy but a small proportion has acute motor (or motor and sensory) axonal neuropathy. In either type, electromyography four weeks later may identify axonal degeneration, indicating a poor outcome. GBS is the most common cause of acute neuromuscular paralysis, but alternative diagnoses should always be considered. Antibodies to ganglioside GM1 are present in up to 25% of cases of Guillain-Barré syndrome follow enteritis due to Campylobacter jejuni, a flagellated Gram-negative bacterium. Antibodies to the lipopolysaccharide in its coat may cross-react with myelin antigens.

Table 1. Classification of autoimmune inflammatory neuropathy.

| Phase | Definition |
|-------|------------|
| Acute (< 4 weeks progressive phase): | - Guillain-Barré syndrome (GBS): acute inflammatory demyelinating polyradiculoneuropathy | - acute motor axonal neuropathy | - acute motor and sensory axonal neuropathy |
|      | - Fisher syndrome | - Fisher/GBS overlap syndrome | - acute sensory neuronopathy |
| Subacute (4–8 weeks progressive phase): | - subacute inflammatory demyelinating polyradiculoneuropathy |
| Chronic (> 8 weeks progressive phase): | - chronic inflammatory demyelinating polyradiculoneuropathy | - multifocal motor neuropathy with conduction block | - paraproteinaemic demyelinating neuropathy | - chronic relapsing axonal neuropathy |
Table 2. Causes of acute peripheral neuropathy.

Inflammatory:
- Guillain-Barré syndrome
- vasculitis: Churg-Strauss syndrome, polyarteritis nodosa, systemic lupus erythematosus
- infections: diphtheria, HIV, Lyme borreliosis, poliomyelitis
- sarcoidosis

Toxins:
- alcohol
- drugs: gold, isoniazid, nitrofurantoin, taxol, vincristine
- heavy metals (arsenic, lead, thallium), hexacarbons, organophosphates

Metabolic:
- diabetes mellitus, porphyria, tyrosinaemia

Critical illness polyneuropathy

Nutritional deficiencies:
- thiamine

Lymphoma

In about a quarter of patients with GBS, which is not sufficiently common to help with diagnosis (Fig 4). Antibodies to ganglioside GQ1b are a sensitive and specific diagnostic test for the uncommon Fisher syndrome, consisting of ophthalmoplegia, ataxia and tendon areflexia without limb weakness, which overlaps with, and may develop into, full-blown GBS.

Treatment

General management of GBS requires alertness to the possibilities of cardiac arrhythmia (Fig 5), respiratory failure or thromboembolism, as well as to the intensive care required by any paralysed patient. As with any complex rare condition, there is a trend for patients transferred to a specialist neurological centre to have a better outcome. Resistant pain may require non-steroidal anti-inflammatory drugs, amitriptyline, carbamazepine or even opiates.

Several large randomised controlled trials have shown that plasma exchange improves the rate and extent of recovery in GBS. However, intravenous immunoglobulin (IV Ig) (0.4 g/kg/day for five days) is currently preferred; it is equally beneficial, safer, and more convenient. Treatment should be started as soon as possible. There is no evidence to indicate whether treatment started after the first two weeks is helpful. Our practice is to treat patients who are still worsening at that time, but not those who are improving. We also re-treat the 10% of patients who suffer an early relapse, and are setting up a randomised controlled trial of a second course of Ig for patients still bed-bound two weeks after the first course. The less common varieties of acute neuropathy are empirically treated in a similar way. Adverse effects of Ig include headache, fever, nausea, eczema, aseptic meningitis, thrombosis and renal failure, with a theoretical risk of blood-borne infection. Anaphylaxis is a rare, but real hazard, especially in patients with IgA deficiency. Corticosteroids are no better than placebo — a surprising observation, possibly explained by an adverse effect on denervated muscle.

Chronic inflammatory neuropathies

Clinical features

Chronic inflammatory neuropathies are distinguished from other chronic neuropathies by reduced or absent reflexes.

Fig 4. Schematic representation of gangliosides GM1 and GQ1b. These membrane-bound glycolipids are widely distributed throughout the body. Autoantibodies to these and other gangliosides are found in many inflammatory neuropathies, and can assist in diagnosis.
raised CSF protein, usually demyelinating neurophysiology and the lack of a family history (Table 3). Despite being treatable, they are underdiagnosed.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is heterogeneous, with a relapsing-remitting, monophasic or progressive course, and a prevalence of at least one per 100,000. Symptoms commonly include weakness and/or numbness, pain and ataxia. It is rarely severe enough to require ventilatory support, but half of all patients suffer temporary severe disability and 13% become permanently dependent.

Paraproteinaemic neuropathies account for 10% of demyelinating neuropathies, and are more common in the elderly. The paraprotein is usually a monoclonal gammopathy of undetermined significance of any immunoglobulin (Ig) subclass, and the associated clinical picture is heterogeneous. One relatively homogeneous subgroup consists of the syndrome of IgM (usually k) paraprotein, antibodies to myelin-associated glycoprotein, a very slowly progressive, predominantly sensory demyelinating neuropathy, and a postural tremor. Patients with IgG paraproteins commonly resemble patients with CIDP, though a few have axonal neurophysiology. Patients with IgG and IgA paraproteins may have a plasmacytoma or solitary myeloma; this should always be considered, especially in treatment resistant cases.

Multifocal motor neuropathy with conduction block is an uncommon demyelinating motor neuropathy, presenting with progressive patchy asymmetrical weakness beginning in the upper limbs, often with cramps and sometimes minor sensory symptoms. Clinical misdiagnosis as motor neuron disease is possible because of the predominant motor phenotype and occurrence of fasciculations. Antibodies to ganglioside GM1 are present in most cases, but are neither sensitive nor specific.

Neurophysiological examination is essential for the identification of a demyelinating neuropathy (Fig 6).
In CIDP there is slowed nerve conduction, especially in motor nerves and there may be multifocal conduction block. In chronic and severe cases, the superimposition of axonal degeneration may make the distinction from axonal neuropathy difficult. In IgM paraproteinaemic demyelinating neuropathy with anti-myelin-associated glycoprotein antibodies, the slowing of nerve conduction is more distal than proximal and there is no conduction block. In multifocal motor neuropathy with conduction block, there are multiple persistent sites of motor conduction block, but sensory conduction remains normal in the same nerve segments. In contrast, inherited demyelinating neuropathies have uniform slowing without conduction block.

Sural nerve biopsy is indicated only if the diagnosis remains uncertain. It often shows only non-specific changes and may cause unpleasant dysesthesiae. Its greatest use is in the identification of vasculitis.

**Treatment**

**Chronic inflammatory demyelinating polyradiculoneuropathy.** Immuno-modulatory therapy is usually merited in CIDP except in very mild cases. Oral prednisolone (120 mg on alternate days, reducing over 3 months)\(^{12}\), intravenous Ig (0.4 mg/kg/day for 5 days)\(^{13}\) and plasma exchange (10 exchanges over 4 weeks)\(^{14}\) have all been shown to be efficacious in short-term randomised controlled trials (Ig and plasma exchange have equivalent efficacy). Sensory symptoms generally improve less than motor. Azathioprine, cyclophosphamide, cyclosporin A and interferon-α2a have been reported to be effective in some patients, but have not been tested in randomised controlled trials. Our current recommendation for initial therapy in CIDP is either Ig or prednisolone (with consideration of osteoporosis prophylaxis). A trial comparing these two is ongoing. Combination therapy is often necessary as the disease progresses. If treatment fails, the diagnosis should be re-evaluated and a paraprotein re-sought.

**Paraproteinaemic demyelinating neuropathy** has a slightly different treatment response profile\(^{15}\), in that Ig benefits some patients\(^{16}\) but steroids are generally ineffective. Plasma exchange sometimes gives at least short-term benefit, especially in patients with an IgA or IgG paraprotein\(^{16}\). A bone marrow examination or radiological skeletal survey sometimes uncovers a primary plasma cell disorder or solitary myeloma, treatment of which may improve the neuropathy (Fig 7). Cyclophosphamide, melphalan, azathioprine, chlorambucil, fludarabine and interferon-α have been used, but sound evidence is lacking\(^{17}\).

**Multifocal motor neuropathy with conduction block.** Two-thirds of these cases respond to intravenous Ig, but treatment usually needs to be repeated monthly (which is expensive). Steroids have no effect, and may even worsen the disease. Oral or intravenous cyclophosphamide is often used to try to sustain the response, but evidence of efficacy is lacking.

**Fig 6.** Action potentials recorded from the thenar muscle after stimulation of the median nerve at the wrist. Neurophysiological examination is important in the diagnosis of a neuropathy. In axonal neuropathy the major abnormality is a reduced amplitude, whereas in demyelinating neuropathy the response is disproportionately delayed and dispersed.

**Fig 7.** Axial computed tomography of the pelvis of a 45-year-old man referred with ‘treatment resistant chronic inflammatory demyelinating polyradiculo-neuropathy’. Serum protein electrophoresis revealed an immunoglobulin G paraprotein. The destructive lesion in the right sacrum was a solitary myeloma. His neuropathy improved after radiotherapy. Serum electrophoresis should be done in the investigation of any chronic neuropathy.
In all these chronic neuropathies, a significant but unknown proportion of patients eventually becomes less responsive to treatment as secondary axonal degeneration gradually accumulates. A multidisciplinary approach to foot care, orthoses, physiotherapy and environmental aids then becomes particularly important. An excellent patient support group is available.

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References

1 Hughes RAC. Guillain-Barré syndrome. London: Springer–Verlag, 1990.
2 Hahn AF. Guillain-Barré syndrome (review). Lancet 1998;352:635–41.
3 Rees JH, Thompson RD, Smeeton NC, Hughes RAC. Epidemiological study of Guillain-Barré syndrome in south east England. J Neurol Neurosurg Psychiatry 1998;64:74–7.
4 Hadden RDM, Cornblath DR, Hughes RAC, Zielasek J, et al. Electrophysiological classification of Guillain-Barré syndrome: clinical associations and outcome. Ann Neurol 1998;44:780–8.
5 Hughes RAC. Management of acute neuromuscular paralysis. J R Coll Physicians Lond 1998;32:254–9.
6 The Guillain-Barré Syndrome Study Group. Plasmapheresis and acute Guillain-Barré syndrome. Neurology 1985;35:1096–104.
7 Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome. Lancet 1997;349:225–30.
8 Hughes RAC, Van der Meché FGA. Corticosteroid treatment for Guillain-Barré syndrome (Cochrane Review). In: The Cochrane Library, Issue 2, 1999. Oxford: Update Software.
9 Lunn MPT, Mantle H, Choudhary PP, Hughes RAC, Thomas PK. Chronic inflammatory demyelinating polyradiculoneuropathy: a prevalence study in south east England. J Neurol Neurosurg Psychiatry 1999;66:677–80.
10 Ropper AH, Gorson KC. Neuropathies associated with paraproteinemia (review). N Engl J Med 1998;338:1601–7.
11 Blessels GJ, Franssen H, Van den Berg LH, Gibson A, et al. Multifocal motor neuropathy (review). J Neurol 1997;244:143–52.
12 Dyck PJ, O'Brien PC, Ovbiagele KF, Diniapoli RP, et al. Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. Ann Neurol 1982;11:136–41.
13 Hahn AF, Bolton CF, Pillay N, Chalk C, et al. Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy – a double-blind, sham-controlled, cross-over study. Brain 1996;119:1055–66.
14 Hahn AF, Bolton CF, Zochodne D, Feasby TE. Intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy – a double-blind, placebo-controlled, cross-over study. Brain 1996;119:1067–77.
15 Dalakas MC, Quarles RH, Farrer RG, Dambrosia J, et al. A controlled study of intravenous immunoglobulin in demyelinating neuropathy with IgG gammopathy. Ann Neurol 1996;40:792–5.
16 Dyck PJ, Low PA, Windebank AJ, Jadeleigh SS, et al. Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance. N Engl J Med 1991;325:1482–6.
17 Mariette X, Chastang C, Clavelou P, Louboutin JP, et al. A randomised clinical trial comparing interferon-α and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM. J Neurol Neurosurg Psychiatry 1997;63:28–34.
18 The Guillain-Barré Syndrome Support Group of the UK, Lincolnshire County Council Offices, Eastgate, Sleaford, Lincolnshire, NG34 7EB. Tel/fax: 01529 304 615. www.gbs.org.uk.

Key Points

Autoimmune inflammatory neuropathy is a spectrum of disorders:

► acute and chronic
► focal and generalised
► demyelinating and axonal

Guillain-Barré syndrome:

► reflexes, cerebrospinal fluid and neurophysiology may be normal in the early stages
► adverse prognostic factors: older age, preceding diarrhoea, severe weakness, inexcitable nerves
► treat with intravenous immunoglobulin

Chronic demyelinating neuropathy:

► check for a paraprotein
► IgMκ paraprotein with antibodies to myelin-associated glycoprotein is associated with a benign, predominantly sensory neuropathy
► treat chronic inflammatory demyelinating polyradiculoneuropathy initially with prednisolone or intravenous immunoglobulin
► treat multifocal motor neuropathy with conduction block with intravenous immunoglobulin