Diagnosis, epidemiology and treatment of inflammatory neuropathies

This article reviews the main diagnostic, epidemiological and therapeutic issues relating to the three main inflammatory neuropathies: Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy and multifocal motor neuropathy. The current knowledge base and recent developments are described.

Inflammatory neuropathies are a treatable cause of morbidity. The three main clinical entities are Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy and multifocal motor neuropathy. The clinical features of these conditions are well defined and allow identification of potential cases. Diagnostic criteria have been established and are of high practical clinical value. Data on the incidence and prevalence of the different sub-types are available in part, although questions remain unanswered because of the heterogeneity of existing data. Effective evidence-based treatments are now available for the three disorders. This article reviews the diagnostic, epidemiological and therapeutic features of these neuropathies, focusing on recent advances and developments.

Diagnosis

Guillain–Barré syndrome is an acute-onset, monophasic, immune-mediated polyradiculoneuropathy, first described by Guillain, Barré and Strohl, in 1916 (Guillain et al, 1916). Guillain–Barré syndrome is characterized by the onset of limb and cranial nerve-innervated muscle weakness associated with diminished or absent reflexes and with sensory loss occurring in a distal pattern.

Table 1. Clinical and biochemical evidence supporting a diagnosis of Guillain–Barré syndrome

Bilateral and flaccid weakness of four limbs
Decreased or absent reflexes
Autonomic dysfunction
Progression of symptoms between 12 hours and 28 days
Monophasic illness pattern with subsequent clinical plateau
Elevated CSF protein
CSF total white cell count <50 cells/μl
No identified alternative diagnosis

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Infections such as *Campylobacter jejuni* enteritis often precede the onset of symptoms. Less common preceding infections include cytomegalovirus, Epstein–Barr virus, and *Mycoplasma pneumoniae*.

Early symptoms can include paraesthesiae affecting the distal extremities. Typically patients have a progressive, relatively symmetrical ascending limb weakness which often begins in the legs and spreads to the arms and bulbar muscles. Involvement of diaphragmatic muscles can lead to neuromuscular respiratory failure. Cranial nerve involvement is common, including facial weakness, ophthalmoplegia and bulbar weakness. Autonomic involvement can cause cardiovascular (lability in blood pressure and heart rate) and gastrointestinal (such as ileus) instability. The life-threatening complications of Guillain–Barré syndrome can result directly from respiratory failure and autonomic failure as well as risk of pneumonia and venous thromboembolism.

Diagnostic criteria for definite Guillain–Barré syndrome are well defined (Asbury and Cornblath, 1990). The clinical diagnosis is supported by a combination of biochemical and electrophysiological findings (*Table 1*). They may not all be evident at initial presentation and careful screening for alternative diagnoses is required (*Table 2*). The clinical nadir for Guillain–Barré syndrome is within 4 weeks (within 2 weeks in most patients), which differentiates it from chronic inflammatory demyelinating polyradiculoneuropathy.

CSF analysis typically shows an elevated protein level with normal white cell count. Rarely CSF protein levels can be normal, particularly if the sample is obtained very early in the course of the illness (Hughes and Cornblath, 2005). The presence of anti-ganglioside antibodies can help differentiate subtypes of Guillain–Barré syndrome: anti-GM1 antibodies are associated with acute motor axonal neuropathy while anti-GQ1b antibodies are associated with Miller–Fisher syndrome.

Electrophysiology is useful diagnostically in distinguishing demyelinating from axonal forms, although this may not be straightforward on initial nerve conduction studies (Uncini et al, 2010). Electrophysiology can show clear demyelinating features with reduction in motor conduction velocities, motor conduction block or temporal dispersion, prolonged distal motor latencies, and prolonged minimum F-wave latencies or absent F-waves

(Van den Bergh and Piéret, 2004). Various combinations of these parameters have been proposed for demyelinating Guillain–Barré syndrome, with very variable sensitivities (Alam et al, 1998). On the other hand, electrophysiology may show absence of all above-mentioned demyelinating characteristics with signs of exclusive axonal dysfunction which may lead to a diagnosis of pure motor or sensory and motor axonal Guillain–Barré syndrome (Ho et al, 1995; Hadden et al, 1998). Magnetic resonance imaging of the lumbar spine may show nerve root thickening and enhancement (Bradley, 1999).

Guillain–Barré syndrome encompasses a spectrum of separate entities:

1. The demyelinating form: acute inflammatory demyelinating polyradiculoneuropathy
2. The axonal forms, including acute motor axonal neuropathy and acute motor and sensory axonal neuropathy
3. Miller–Fisher syndrome.

The commonest form in the western world is acute inflammatory demyelinating polyradiculoneuropathy, which is characterized electrophysiologically by focal demyelination of motor and sensory peripheral nerves and roots. The axonal subtype, in particular acute motor axonal neuropathy, is more common in Asia (Ogawara et al, 2000). There is no evidence of a poorer prognosis in axonal forms, some of which recover very rapidly and completely via reversible conduction failure (Uncini et al, 2010). Miller–Fisher syndrome is a well-documented but rare variant of Guillain–Barré syndrome which comprises a triad of ataxia, areflexia and ophthalmoplegia. Overlap between Guillain–Barré syndrome and Miller–Fisher syndrome can occur (Mori et al, 2012).

Table 2. Common mimics of Guillain–Barré syndrome

Spinal cord compression
Botulism
Myelitis
Myasthenia gravis
Cord infarction
Organophosphate poisoning
Poliomyelitis
Dermatomyositis or polymyositis
Chronic inflammatory demyelinating polyradiculoneuropathy
Hypokalaemia or hyperkalaemia
Cauda equina compression
Carcinomatous meningitis
Paraneoplastic neuropathy
Brainstem encephalitis
Tick paralysis
Hypophosphataemia
Heavy metal poisoning
Vasculitic neuropathy
Critical illness neuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy is an autoimmune acquired symmetrical demyelinating neuropathy, typically affecting motor more than sensory function. Large fibre sensory modalities are more involved than small fibre functions. Chronic inflammatory demyelinating polyradiculoneuropathy shares a number of clinical and laboratory features with Guillain–Barré syndrome. Clinical examination findings are of proximal and distal limb weakness with diminished or absent reflexes. There is preferential loss of large fibre modalities, vibration sense and joint position sense, often associated with positive sensory symptoms. The disease course varies: it can present acutely or with slow progression over several months, and in monophasic, progressive and relapsing-remitting forms. Cranial nerve involvement is unusual, and this may help to differentiate chronic inflammatory demyelinating polyradiculoneuropathy from Guillain–Barré syndrome (Dionne et al, 2010). Chronic inflammatory demyelinating polyradiculoneuropathy can present in a purely motor form, or in a pure sensory form where ataxia is the leading complaint. There are multifocal variants – MADSAM (multifocal asymmetrical demyelinating sensory and motor neuropathy) or 'Lewis–Sumner syndrome' – which are well documented (Lewis et al, 1982). The latter can present with exclusive upper limb involvement and resemble multifocal motor neuropathy, the differentiating element being the sensory involvement in Lewis–Sumner syndrome (Rajabally and Chavada, 2009).

Several diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy have been proposed. Recently more sensitive ones have become available. Mandatory clinical features for typical chronic inflammatory demyelinating polyradiculoneuropathy include symptoms for more than 8 weeks, proximal and distal weakness in the four limbs, hyporeflexia or areflexia and sensory involvement predominantly of large fibre function. Electrophysiology remains a key diagnostic tool in chronic inflammatory demyelinating polyradiculoneuropathy. Demonstration of heterogeneously distributed demyelination is required for the electrodiagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (Vallat et al, 2010). Demyelinating abnormalities of similar parameters to those for Guillain–Barré syndrome (Van den Bergh and Piéret, 2004) occur in a patchy distribution and there have been multiple electrophysiological criteria proposed consisting of combinations of abnormalities of these parameters. More recent ones (Hughes et al, 2006) have demonstrated high sensitivity and specificity in several centres (Rajabally et al, 2009a). It remains unknown whether truly axonal forms of chronic inflammatory demyelinating polyradiculoneuropathy do exist and very few cases have been described (Uncini et al, 1996). Although this is beyond

the focus of this review, it is possible that lack of sufficiently extensive electrophysiological testing, in particular of multiple nerves, proximal nerve segments and underuse of more recently identified parameters like distal duration of the motor action potential (Rajabally et al, 2012) may account for these so-called 'axonal' forms of chronic inflammatory demyelinating polyradiculoneuropathy. Histology may also confirm the inflammatory demyelinating nature of electrophysiologically axonal-looking forms (Vallat et al, 2003).

The diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy is supported by further laboratory investigations. CSF protein is elevated in most patients. The white cell count is typically less than 10 cells/mm^3 (Vallat et al, 2010). Magnetic resonance imaging of the spine can demonstrate enlargement and/or contrast enhancement of the roots, lumbosacral and brachial plexi. In carefully selected cases of persistent diagnostic uncertainty, a nerve biopsy can add supportive evidence. Histopathological analysis, which needs to be performed in an adequately experienced neuropathology laboratory specializing in peripheral nerve histology, typically reveals endoneurial oedema, macrophage-associated demyelination, remyelination, 'onion bulb' formation (a characteristic cross-sectional appearance of demyelination affecting myelinated nerve fibres) and endoneurial mononuclear cell infiltration (Hughes et al, 2006). However, absence of such features does not exclude the diagnosis and should not result in withholding treatment.

Multifocal motor neuropathy is characterized by slowly progressive muscle weakness over many months to years without sensory loss. Fasciculations may also be seen. Atrophy is typically absent or mild although it can progress with the disease. This is thought to be related to the underlying pathophysiology of the disorder with conduction block rather than neuronal loss as happens in contrast in anterior horn cell disease. The weakness is asymmetric and develops more prominently in the arms than the legs. Wrist drop, weakness of grip and foot drop are common presenting symptoms (Van Asseldonk and Franssen, 2005). The presentation can mimic motor neurone disease although pyramidal tract signs should not be found in multifocal motor neuropathy. *Table 3* lists clinical features (mandatory and supportive). Cranial and diaphragmatic weaknesses are extremely infrequent.

Table 3. Clinical diagnostic criteria for multifocal motor neuropathy

Clinical features	Slow or stepwise focal progressive limb weakness*
	Asymmetrical pattern*
	At least two motor nerves involved*
	Symptoms for more than 1 month*
	More pronounced upper limb symptoms
	Reduced or absent reflexes in affected limb
	Cramps and fasciculations in affected limb
	Response to immunomodulatory therapy
Absent features	Marked sensory impairment†
	Cranial nerve involvement†
	Upper motor neurone signs†
	Marked bulbar involvement†
	Diffuse symmetric presentation†

* mandatory criteria; † exclusion criteria. From Joint Task Force of the European Federation of Neurological Societies and Peripheral Nerve Society (2010)

The key electrophysiological feature is conduction block detected on motor nerve conduction studies and the lack of sensory nerve conduction abnormalities. A 'definite' conduction block is defined by at least 50% area reduction of the compound muscle action potential whatever the nerve segment length, with a degree of proximal dispersion of the compound muscle action potential not exceeding 30%. A 'probable' conduction block occurs when at least 30% area reduction is observed, with <30% dispersion or alternatively when a 50% area reduction is found but with >30% of compound muscle action potential dispersion. According to most recent guidelines, electrophysiological evidence of definite or probable conduction block should be found in at least one nerve, although some forms of multifocal motor neuropathy do not display conduction block on routine nerve conduction studies (Joint Task Force of the European Federation of Neurological Societies/Peripheral Nerve Society, 2010). These cases may require more extensive as well as more sophisticated electrophysiological techniques for block detection. In a remainder, no blocks may be found although whether these cases should be denied a trial of treatment is highly debatable. Anti-GM1 has been strongly associated with multifocal motor neuropathy, with cohort studies reporting between 20% and 85% of patients being seropositive (Cats et al, 2010a). Anti-GM1 antibody positivity correlates with worse function and prognosis in multifocal motor neuropathy (Cats et al, 2010a). CSF protein levels are typically normal or slightly elevated, unlike in chronic inflammatory demyelinating polyradiculoneuropathy or Guillain–Barré syndrome. Magnetic resonance imaging demonstrates T2 high signal in the brachial plexus corresponding with symptom distribution in multifocal motor neuropathy (Van Es et al, 2007). This can help differentiate multifocal motor neuropathy from motor neurone disease in which magnetic resonance imaging is normal.

Epidemiology

More is known about Guillain–Barré syndrome than the other inflammatory neuropathies, probably because its rapidly progressive course often requires hospital admission. McGrogan et al (2009) conducted the first systematic review on the subject including 63 articles published between 1980 and 2008. Their best estimate of the incidence worldwide was between 1.1 and 1.8/100 000/year. They found similar rates of Guillain–Barré syndrome in North America and Europe. Antecedent infection within

4 weeks of symptom onset was present in up to 70% of reported cases, most commonly enteric, particularly caused by *C. jejuni*. There was no clear seasonal variability. Interestingly there had been a fall of incidence between the 1980s and 1990s. Sejvar at al (2011) re-examined the data to publish a systematic review and meta-analysis of age-related Guillain–Barré syndrome incidence. Their reported crude incidence ranged from 0.81–1.89 cases/100 000/year. An exponential rise in incidence of Guillain–Barré syndrome with age was found, but with increasing confidence intervals. They reported a male preponderance with a ratio of 1.78:1.

Seven key studies provide the data for what is known about chronic inflammatory demyelinating polyradiculoneuropathy, mainly retrospective analyses from 1982 to 2008. The reported prevalence varies from 1–8.9/100 000 (Laughlin et al, 2009; Rajabally et al, 2009b). The cause of this heterogeneity is likely multifactorial. Estimates of prevalence have been higher in more recent studies, with diagnostic criteria used representing the most important issue. The reported incidence again varies widely between 0.15–1.6/100 000/year, likely for similar reasons.

Clinical characteristics in most studies show that the relapsing-remitting variant of chronic inflammatory demyelinating polyradiculoneuropathy is most common – about 50% of cases in most studies. However, reporting bias in studies relying on physician reporting may have favoured this form of the disease as they are more likely to have remained under follow up.

A male preponderance was shown in every study, although gender ratios varied between 1.3 and 2.8:1. As for Guillain–Barré syndrome, the reasons for this are not clear, especially given the female preponderance in other autoimmune neurological conditions. Similarly to Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy is more common in the older population which also has no definite explanation.

There are different diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy. The most commonly used are the Ad Hoc Subcommittee of the American Academy of Neurology AIDS Taskforce (1991) chronic inflammatory demyelinating polyradiculoneuropathy electrophysiological criteria. These were designed to be highly specific for selecting a more standardized patient population for recruitment into clinical trials. However, their sensitivity has been questioned (Van den Bergh and Piéret, 2004; Rajabally et al, 2005) and from multicentre analyses, it appears that only 40–50% of patients with a diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy meet these stringent criteria (Rajabally et al, 2009a). In view of this, the European Federation of Neurological Societies/Peripheral Nerve Society criteria of 2006, updated in 2010, appear more appropriate for epidemiological studies to give more accurate estimates. These criteria suggest a chronic inflammatory demyelinating polyradiculoneuropathy prevalence rate of around 5/100 000.

There is little known about the epidemiology of multifocal motor neuropathy, mainly because of its relative rarity. To the authors' knowledge there are no studies specifically on this subject. Nobile-Orazio et al (2005) estimated the prevalence of multifocal motor neuropathy to lie between 1 and 2/100 000, comparable to that of chronic inflammatory demyelinating polyradiculoneuropathy. In the authors' experience this is likely to be an overestimate as chronic inflammatory demyelinating polyradiculoneuropathy appears significantly more common in clinical practice. Cats et al (2010b) published the results of their nationwide survey of features of multifocal motor neuropathy in the Netherlands, looking at their findings of 88 patients with this diagnosis in 2007 (according to Statistics Netherlands, the population was 16.4 million as of 1 January 2008, giving a prevalence rate of about 0.5/100 000). The authors have anecdotally found a comparable rate in their region. Similarly to Guillain–Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy, and again for unknown reasons, multifocal motor neuropathy affects predominantly males. In the Dutch study, 64 of the 88 patients were men (gender ratio 2.66:1). Median age at symptom onset was 40 years (range 22–66 years).

Treatment

The treatment of Guillain–Barré syndrome is divided into immunomodulatory intervention and supportive care. The natural history of this condition is monophasic with improvement expected without treatment. However, early therapy can hasten recovery and reduce disability.

Plasma exchange and intravenous immunoglobulins are both effective, with no proven benefit for one over the other (Raphaël et al, 2002; Hughes et al, 2010a). Four plasma exchanges are required for moderate or severe cases, while mild cases need only two (French Cooperative Study Group on Plasma Exchange in Guillain-Barré Syndrome, 1997). Intravenous immunoglobulin is usually given at 2 g/kg over 2 or 5 days, and is usually preferred in clinical practice because of its greater availability and convenience. Corticosteroid treatment is ineffective (Hughes et al, 2010b). No other immune therapies are of benefit although a Cochrane review indicated that a Chinese herbal agent, Tripterygium polyglycoside, may have some effect (Hughes et al, 2011). This requires further study. Overall Guillain–Barré syndrome patients have a favourable outcome with recovery over weeks to months, and >80% of patients able to walk unaided at 6 months. However, about 20% will have persistent disability after 1 year and mortality within the first year remains at about 4–5%, despite treatment.

The mainstay of supportive care is monitoring for respiratory complications, autonomic complications and venous thromboembolism prophylaxis. Monitoring the forced vital capacity and arterial blood gas analysis is extremely important to decide if and when ventilatory support is required. Practical considerations such as technique and

facial weakness affecting lip-seal must be taken into account. Cardiovascular complications of labile blood pressure and arrhythmia must be monitored. Gastrointestinal immotility can cause significant morbidity and attention must be paid to bowel care. Drug and/or mechanical prophylaxis for venous thromboembolism is essential.

Chronic inflammatory demyelinating polyradiculoneuropathy responds to immunotherapy in 60–80% of cases (Vallat et al, 2010). Oral steroid therapy with prednisolone is the commonest regimen used with equivalence of continuous *vs* pulse therapy with high-dose dexamethasone demonstrated (van Schaik et al, 2010). Side effects were comparable in both groups although sleeplessness and Cushing's face were more common with prednisolone. Patients with the motor predominant form can experience deterioration or lack of response with steroids which may therefore need to be avoided in such cases (Donaghy et al, 1994; Rajabally et al, 2008).

There is good evidence for the use of intravenous immunoglobulin improving chronic inflammatory demyelinating polyradiculoneuropathy in the short term (Eftimov et al, 2009). Longer-term effectiveness is now confirmed as well (Hughes et al, 2008). Intravenous immunoglobulin is often the first-choice agent as the risk of side effects from long-term steroid therapy remains a concern particularly in older patients where chronic inflammatory demyelinating polyradiculoneuropathy is more common. Repeated courses of treatment at regular intervals may be necessary to prevent relapses and reduce disability, again tailored to the individual. There is evidence for use of plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy, which appears equivalent to that of intravenous immunoglobulin (Mehndiratta et al, 2004). However, plasma exchange is often only tried in refractory cases, or in case of serious contraindication to intravenous immunoglobulin, mainly as a result of difficulty of access to this treatment at many institutions. No other treatments have been shown to be of benefit and although various immunosuppressants have been, and are still, used, this is not based on trial evidence. Methotrexate has been used in an international multicentre randomized controlled trial in an attempt to reduce steroid or intravenous immunoglobulin use (RMC Trial Group, 2009). The outcome of this trial was negative.

The treatment of multifocal motor neuropathy is well established – double-blind placebo-controlled trials support the efficacy of intravenous immunoglobulin (Eftimov and Van Schaik, 2011). Repeat intravenous immunoglobulin infusions are the mainstay of treatment as, in direct contrast to chronic inflammatory demyelinating polyradiculoneuropathy, steroid and plasma exchange therapy are ineffective and may even lead to clinical worsening in multifocal motor neuropathy. Over 90% of multifocal motor neuropathy patients respond to intravenous immunoglobulin according to a retrospective analysis of the largest series reported to date (Cats et al, 2010b). Subcutaneous administration of immunoglobulins is an option for some multifocal motor neuropathy patients although timing, frequency and local adverse effects may be limiting factors (Eftimov and Van Schaik, 2011). Other immune-based therapies have been used in multifocal motor neuropathy but not in randomized controlled trials except for mycophenolate mofetil, which failed to show an effect (Piepers et al, 2007). A retrospective review of several open-label studies revealed that cyclophosphamide was effective in 70% of patients (Eftimov and Van Schaik, 2011) but long-term use is associated with significant adverse side effects, and some patients did not receive intravenous immunoglobulin which may well have been effective. Rituximab, although considered potentially useful as for other immune-mediated neuropathies, failed to be effective in an open-label study of 10 patients (Chaudhry and Cornblath, 2010).

KEY POINTS

- Inflammatory neuropathies consist mainly of Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy.
- The diagnosis of inflammatory neuropathies is clinical, with widely accepted criteria.
- Electrophysiology is essential for diagnostic evaluation of all inflammatory neuropathies.
- Guillain–Barré syndrome has an incidence of about 1–2/100 000 per year; chronic inflammatory demyelinating polyneuropathy has a reported prevalence between 1 and 8/100 000, although a likely estimate would be of around 5/ 100 000 using recent established diagnostic criteria; and multifocal motor neuropathy has a likely low prevalence of about 0.5/100 000.
- In most cases, inflammatory neuropathies are treatable effectively with immunomodulatory therapies.

Conclusions

Inflammatory neuropathies including Guillain–Barré syndrome, chronic inflammatory demyelinating polyradiculoneuropathy and multifocal motor neuropathy are an important group of readily recognizable and treatable neurological disorders. A high index of suspicion is required by hospital clinicians including non-neurologists, given the diverse presentations and increased prevalence with age, particularly in the case of Guillain–Barré syndrome which may be acutely life-threatening, and also chronic inflammatory demyelinating polyradiculoneuropathy. Adequate investigations are required, as well as appropriate interpretation of these, which may not always be straightforward. Specialist neurological, neurophysiological and neurorehabilitation input is essential for accurate diagnosis and optimal management of this potentially challenging group of patients. **BJHM**

Conflict of interest: none.

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