

## Original articles

## Pathogenesis and treatment of inflammatory demyelinating polyradiculoneuropathy

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### Abstract

*Inflammatory demyelinating polyradiculoneuropathy causes a spectrum of conditions ranging from acute (Guillain-Barré syndrome), through subacute to chronic forms. The pathogenesis of acute forms is related to antibody responses against glycolipid epitopes which mimic bacterial, especially *Campylobacter jejuni*, structures but T cells are also involved. The pathogenesis of chronic forms is poorly understood. Different forms differ in their responses to steroids. Chronic inflammatory demyelinating polyradiculoneuropathy responds to steroids but a variant multifocal motor neuropathy and the acute forms of inflammatory demyelinating polyradiculoneuropathy do not. Acute and chronic forms respond to plasma exchange and intravenous immunoglobulin.*

**Key words :** Guillain-Barré syndrome ; chronic inflammatory demyelinating polyradiculoneuropathy ; pathogenesis ; treatment.

### The oligoclonal spectrum

The concept of a spectrum of several clinical syndromes ranging from acute through subacute to chronic inflammatory neuropathy has gained general acceptance. Dispute about whether to lump patients together or split groups into smaller categories does continue (Katz *et al.*, 2000 ; Saperstein *et al.*, 2000 ; Dyck and Dyck, 2000). This debate can be partially resolved by accepting that the population incidence frequency distribution is not uniform but rather resembles the oligoclonal band pattern in an inflammatory CSF. Similarly the boundaries of the different syndromes which we try to define are not really sharp. Although most patients with Guillain-Barré syndrome (GBS) reach their nadir within two to three weeks, the upper boundary of the progressive phase is only arbitrarily set at four weeks. The actual frequency distribution of onset phases extends beyond this (Gibbels and Giebisch 1992). Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) was defined as having a progressive phase of more than eight

weeks (Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force 1991). To fill the gap in the spectrum we described seven patients with a progressive phase between four and eight weeks (Hughes *et al.* 1992). There are similar overlaps in clinical features. Strictly speaking Fisher syndrome as originally described involved only ophthalmoplegia, ataxia and areflexia with, at most, facial weakness (Fisher, 1956). Patients who present with an initially pure Fisher syndrome often develop generalised weakness. Bulbar weakness is often accepted as part of the syndrome.

### Electrophysiological subtypes

Electrophysiological studies have now made clear that GBS may be caused by a primary axonal neuropathy affecting either the motor, or the motor and sensory fibres, as well as the conventional acute inflammatory demyelinating polyradiculoneuropathy. These patients with axonal neuropathy form a substantial proportion of the total number of patients with GBS in China and are relatively common in central America, India and Japan. In the USA and Europe axonal forms of the disease account for less than 5% of cases (Hadden *et al.*, 1998). Electrophysiological studies have also helped to define a variant of CIDP, multifocal motor neuropathy, which is clinically purely motor and electrophysiologically characterised by multifocal partial conduction block (Parry and Clarke, 1988 ; Van den Bergh *et al.*, 1989). The response of all categories of patients to immunotherapy argues for an important role of inflammatory and probably autoimmune processes in their pathogenesis. A subset of patients amongst those who we currently classify as chronic idiopathic axonal neuropathy (Notermans *et al.*, 1993) will probably turn out to have an autoimmune pathogenesis.

### Pathogenesis

The major thrust in understanding the pathogenesis of inflammatory neuropathy has been the

identification of antibodies to gangliosides that correlate with different clinical patterns of neuropathy (Hughes *et al.*, 1999). While there is agreement about the general principles, detailed examination of the data only gives strong support for the antibody hypothesis in the Fisher syndrome. There is a very close association between antibodies to ganglioside GQ1b and Fisher syndrome. In the other conditions where these antibodies are found, there are clinical features, usually ophthalmoplegia, which form part of Fisher syndrome. There is still some disagreement between laboratories about the details. However sera from patients with Fisher syndrome do contain antibodies probably directed against ganglioside GQ1b that bind to terminal motor nerve fibres and induce conduction block (Buchwald *et al.*, 1995 ; Buchwald *et al.*, 1998 ; Willison and O'Hanlon, 1999). In ordinary GBS antibodies to ganglioside GM1 are found in about 25% of patients with GBS. They occur especially in patients with severe axonal degeneration either as part of pure axonal forms of the disease or as part of the common acute inflammatory demyelinating polyradiculoneuropathy form. Investigations continue to discover whether the best fit with axonal neuropathy is with antibodies to ganglioside GM1 or a related ganglioside such as GD1a, N-acetylgalactosaminyl GD1a, or GM1b (Hughes *et al.*, 1999 ; Yuki *et al.*, 2000). There is a large body of evidence supporting the idea that infection with organisms such as *Campylobacter jejuni* stimulates an immune reaction which cross-reacts with carbohydrate epitopes shared by the organism and myelin or axolemma (Hughes, *et al.*, 1999). Attempts to identify antibodies in chronic inflammatory demyelinating polyradiculoneuropathy have been less successful and in the typical case antibodies to gangliosides or myelin proteins are rarely found (Meléndez-Vásquez *et al.*, 1997). In the subgroup of patients with multifocal motor neuropathy antibodies to ganglioside to GM1 are found, but only in about 50% of patients and their presence does not bear a close relationship to response to treatment (Nobile-Orazio, 1996).

Interest in antibodies has deflected attention from T cell responses in the pathogenesis of inflammatory demyelinating polyradiculoneuropathy, probably inappropriately. Experimental autoimmune neuritis is an accurate model of the neurophysiological and pathological features of human inflammatory demyelinating polyradiculoneuropathy. It is clearly a primarily T cell mediated disease which can be induced by immunisation with P0, P2 and, now, PMP22 myelin proteins (Gabriel *et al.*, 1998). It can certainly be enhanced by the co-administration of anti-myelin or anti-galactocerebroside antibodies with T cell lines against P2 so that antibody can obviously play a role as well. It is likely that activated T cells open the blood nerve barrier and initiate the cascade of

inflammatory events that result in demyelination. The antibodies to gangliosides in GBS and Fisher syndrome belong to the IgG1 subclass which require T cell help for their production. Further attempts to explore the role of T cell responses to myelin proteins should be rewarding.

## Treatment

Despite our incomplete understanding of its pathogenesis, immunotherapy has been shown empirically to be effective in inflammatory demyelinating polyradiculoneuropathy, although there are some surprises. The greatest surprise is that steroids do not have a beneficial effect in GBS. A recent Cochrane systematic review confirmed the impression from randomised studies and narrative reviews that steroids are not effective in GBS (Hughes and van der Meché, 1999). Steroids are also not helpful in multifocal motor neuropathy and sometimes even cause worsening (Nobile-Orazio, 1996). By contrast steroids do seem to help in most cases of CIDP and this impression has been confirmed by a randomised trial comparing oral prednisone for 12 weeks with no treatment (Dyck *et al.*, 1982).

Plasma exchange has been shown to be beneficial in GBS in four large trials. These have established that plasma exchange hastens recovery, shortens the time on the ventilator, and reduces the amount of residual weakness compared with no treatment (Raphael *et al.*, 2000). Plasma exchange has also been shown to be beneficial in CIDP in a randomised trial (Hahn *et al.*, 1996a). Plasma exchange has not been shown to be beneficial in multifocal motor neuropathy, but a randomised trial has not been done.

Following the establishment of plasma exchange as the gold standard treatment for GBS, two large and some smaller trials have shown that intravenous immunoglobulin has equivalent efficacy (Hughes *et al.*, 2000). The addition of intravenous immunoglobulin to plasma exchange did not confer significant extra benefit (Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group., 1997). Unfortunately these treatments still leave 20% of patients dead or disabled a year later. A trial to establish whether a second immunoglobulin dose two weeks after the start of the first will improve this outcome is being planned (Cornblath, D., personal communication). Intravenous immunoglobulin has been shown in two of three randomised trials to be superior to placebo in CIDP (van Doorn *et al.*, 1990 ; Vermeulen *et al.*, 1993). (Hahn *et al.*, 1996b) and in a fourth to be equivalent to plasma exchange (Dyck *et al.*, 1994). Intravenous immunoglobulin has been shown in two randomised trials to be superior to placebo in multifocal motor neuropathy and is now regarded

as the treatment of choice (Azulay *et al.* 1994, Azulay *et al.*, 1997, van den Berg *et al.*, 1995).

Unfortunately, both plasma exchange and intravenous immunoglobulin are expensive, inconvenient and only effective in the short term. A continued search for non-toxic immunosuppressive agents for inflammatory neuropathies has embraced azathioprine, cyclophosphamide, cyclosporin, beta interferon and more recently mycophenolate mofetil. None have been rigorously demonstrated to be beneficial. A determined multicentre effort to construct systematic reviews of the evidence under the auspices of the Cochrane collaboration would be worthwhile as the basis for clinical practice and planning future trials. The Cochrane Neuromuscular Disease Review Group would welcome help with this task from Belgian neurologists. Interested readers should contact the author.

### Conclusions

The past decade has seen major advances in our understanding and treatment of the different forms of inflammatory demyelinating polyradiculoneuropathy but there are still important gaps in our knowledge. Imaginative research, collaborative efforts to collect information about treatment, such as the Cochrane Collaboration, and opportunities to conduct multicentre treatment trials under the auspices of the European Commission offer tremendous possibilities for faster advance in the future.

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