

# Advances in the Pathogenesis and Therapy of Inflammatory Neuropathies

The inflammatory neuropathies are a diverse group of peripheral nerve disorders presumed to have an immune mediated pathogenesis. They are characterised pathologically by inflammatory infiltration of the peripheral nerves associated with destruction of myelin and/or axons. The inflammatory neuropathies are typified by the idiopathic demyelinating neuropathies, both chronic and acute, and the closely related neuropathies associated with paraproteinaemia. However, vasculitic, infectious and parainfectious, paraneoplastic neuropathies and more recently diabetic plexopathy<sup>1</sup> are included. Some of these may be thought of as primary disorders of the peripheral nervous system (e.g. Guillain-Barré Syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)) and others secondary to a systemic immune process with subsequent involvement of the peripheral nerves (e.g. the neuropathy associated with vasculitis and the connective tissue diseases). Even some neuropathies with a known inherited pathogenesis (e.g. the hereditary motor and sensory neuropathies (HMSN)) may have an inflammatory element.<sup>2,3</sup>

Increased understanding of the pathogenesis of the inflammatory neuropathies from disease induction to cell damage is informing developments in treatment. These will be the exciting advances of the near future. The acute inflammatory neuropathies are an excellent example of the progress in clinically directed research in this area.

## Guillain-Barré Syndrome

Guillain-Barré Syndrome is the commonest cause of acute neuromuscular paralysis in the developed world. It affects about 2 per 100 000 population per year. It is now recognised that the syndrome is an umbrella term for disease variants including acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy (AMAN), acute motor-sensory axonal neuropathy (AMSAN) and the Miller Fisher syndrome. The mortality of GBS remains about 5-10% despite the almost routine use of intravenous immunoglobulin (IVIg) or plasma exchange (PEX).

The subtypes of GBS are probably specified by the pathogenic mechanisms predominant in any one case and emerging evidence is helping to clarify these. Pathogenic mechanisms may be complicated by geographical and genetic susceptibility factors in populations and the agents to which they are exposed. For instance in Europe and the USA more than 90% of patients have the AIDP sub-type and *Campylobacter jejuni* infection precedes onset of the GBS in 26% of cases.<sup>4</sup> In China and Japan, where AMAN accounts for more than 60% of GBS cases, preceding *C. jejuni* infection may occur in 2/3 of patients<sup>5</sup> and seems to be exclusively associated with AMAN.<sup>6</sup>

*Campylobacter jejuni*, cytomegalovirus, Epstein Barr virus, *Mycoplasma pneumoniae* and more recently unencapsulated *Haemophilus influenzae* are all associated with GBS. All of these organisms have been shown to have ganglioside-like epitopes in their surface coat. Furthermore *Campylobacter jejuni* possesses a very similar protein glycosylation mechanism to eukaryotic cells.<sup>8</sup> Similarity between neural gangliosides and pathogen borne molecules is the basis of molecular mimicry which remains the major theory explaining how an infectious organism can drive an autoimmune response.

The exclusive involvement of B-cells, T-cells, cytokines

or complement in a subtype of inflammatory neuropathy is unlikely. The role of the individual facets of the immune system is becoming increasingly clear.

## Antibodies and B-cells

Antibody targeting of specific neural epitopes is responsible for the pathogenic phenotype of several inflammatory neuropathies, best illustrated by the Miller Fisher Syndrome and its variants, AMAN and possibly multifocal motor neuropathy with conduction block (MMNCB). Limited evidence exists for the pathogenesis of anti-MAG and other chronic neuropathies and remains less convincing for AIDP.

Fisher Syndrome (ataxia, ophthalmoplegia and areflexia)<sup>9</sup> is associated with serum IgG antibodies to the ganglioside GQ1b (see Figure 1) in 90% of cases. These antibodies may cross-react with similar gangliosides, commonly GT1a, which may extend the phenotype to bulbar muscles. Ganglioside GQ1b is found in greatest concentration in cranial nerves II, III, IV and VI.<sup>10</sup> In an *ex vivo* model these antibodies bind to nerve at the nodes of Ranvier and the neuromuscular junction where they fix complement (see below), disrupt cell structure and cause neuromuscular conduction failure similar to the spider venom  $\alpha$ -latrotoxin.<sup>11</sup>

The AMAN variant of GBS is associated with antibodies to GM1, GD1a, GalNAc-GD1a and GD1b. Although unusual in the western hemisphere, AMAN accounts for the majority of GBS patients in China. It is often more clinically devastating than AIDP but can be followed by remarkable recovery. A complement-dependent antibody-mediated attack has been demonstrated in the motor nerves and roots. Some monoclonal IgG anti-GD1a antibodies specifically bind motor nerves (see Figure 2) giving explanation to the motor phenotype. An animal model of IgG anti-GD1a neuropathy has recently been described<sup>12</sup> in which an axonal neuropathy was induced by implanting mouse anti-GD1a producing hybridomas to host mice. This strengthens the evidence for the pathogenesis of anti-GD1a antibodies in AMAN.



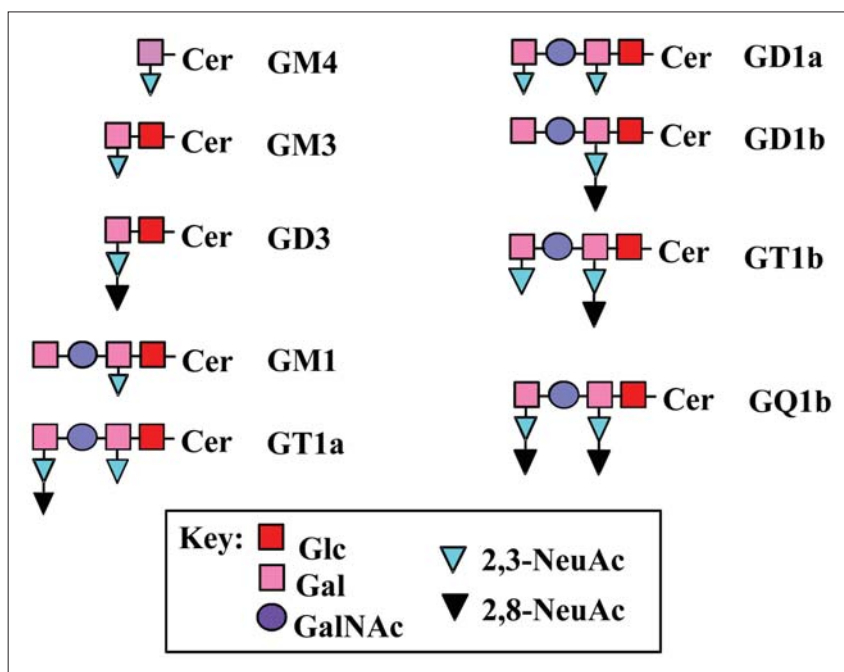
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Figure 1: Structures of the common complex gangliosides found in peripheral nerves. All are derived from a common backbone. Structural similarities are apparent explaining cross-reactivities of serum anti-ganglioside antibodies.

Cer = ceramide, Glc = glucose,  
Gal = galactose,  
GalNAc = N-acetylgalactosamine,  
2,3-NeuAc = 2,3-linked  
N-acetylneuraminic acid (sialic acid),  
2,8-NeuAc = 2,8-linked  
N-acetylneuraminic acid



## T-cells

Experimental autoimmune neuritis (EAN) is a T-cell mediated disease and is the prototypic animal model for inflammatory neuropathy. The endoneurium is infiltrated with lymphocytes under the guidance of leucocyte and endothelial adhesion molecules and chemokines and their receptors.<sup>13</sup> Myelin is stripped by activated macrophages which, at least early on, are endogenous. However the role of T-lymphocytes in GBS remains elusive. Chemokines and receptors have been shown to be upregulated in human specimens and T-cells are certainly activated and present in damaged nerve. Of four T-cell lines isolated from GBS patient nerve specimens two had  $\gamma\delta$ -T-cell receptors illustrating the importance of the immune reaction to non-protein antigens.<sup>14</sup> Proof of the specific role of the T-cell in GBS pathogenesis although not far away is still lacking.

## Complement

Complement has been visualised in biopsy specimens from inflammatory neuropathies for more than 30 years. It is only recently that the role of complement has been more clearly defined in an *ex vivo* model.<sup>11</sup> Pore-forming membrane attack complex was visualised at the neuromuscular junction in conjunction with GQ1b antibodies and correlated to structural neurofilament disruption at the nerve terminal. This was worsened in mice lacking the complement regulating molecule CD59. Complement is a key weapon delivering antibody directed damage to the target.

## Treatment

The long awaited trial of intravenous methyl prednisolone and IVIG in the treatment of GBS has now been published<sup>15</sup> and provoked some controversy. In a pilot study this combination seemed to be more effective than IVIG alone. In the randomised controlled trial of 233 patients a positive effect of steroids just reached statistical significance on the primary but none of the secondary outcome measures. The biological significance of this effect is negligible. Since previous trials, and a Cochrane meta-analysis, have shown steroids to be at best ineffective, and in some cases harmful, there is no indication for their use in GBS.

The effectiveness of other immunotherapy for GBS is supported by good evidence.<sup>16</sup> Two to five sessions of PEX

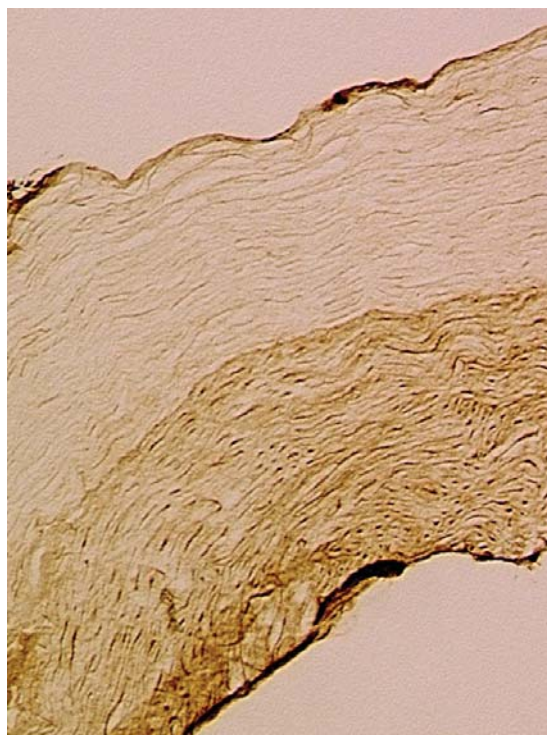


Figure 2: Fresh frozen unfixed nerve root stained with monoclonal IgG monospecific anti-GD1a antibody. Axons of the motor root (below) stain much more strongly than those in the sensory root (above).

hastens recovery in non-ambulant patients preferably started within two weeks of disease onset. Intravenous immunoglobulin is as effective as PEX and is still probably the intervention of choice. The concern about possible contamination of IVIG with prions means that written informed consent is essential before administration. The drive to search for new, more effective and safer therapies is stronger than ever.

Increased understanding of disease mechanisms is informing the development of new treatment. Complement inhibitors are already available and clinical trials in the treatment of GBS are being planned. Specific, targeted immunoadsorption of pathogenic anti-ganglioside antibodies by glycoforms conjugated within haemofilters is being developed for possible clinical use.<sup>17</sup> As T-cell mechanisms become better understood appropriate inhibitors may be developed. The choice of therapy may then be less simple but potentially more effective.


**Additional web content**  
[www.acnr.co.uk](http://www.acnr.co.uk)  
 See [www.acnr.co.uk](http://www.acnr.co.uk) for a case report on Atypical Guillain-Barré Syndrome

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