Pathophysiology of autoimmune polyneuropathies

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Summary

The most common autoimmune neuropathies include the acute inflammatory polyneuropathy [the Guillain-Barré Syndrome(s)]; chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN) and IgM anti-MAG-antibody mediated paraproteinemic neuropathy. These neuropathies occur when immunologic tolerance to peripheral nerve components (myelin, Schwann cell, axon, and motor or ganglionic neurons) is lost. Based on the immunopathologic similarities with experimental allergic neuritis induced after immunization with nerve proteins, disease transfer experiments with the patients’ serum or with intraneural injections, and immunocytochemical studies on the patients’ nerves, it appears that both cellular and humoral factors, either independently or in concert with each other, play a role in the cause of these neuropathies. Although in some of them there is direct evidence for autoimmune reactivity mediated by specific antibodies or autoreactive T lymphocytes, in others the underlying immune-mediated mechanisms have not been fully elucidated, in spite of good response to immunotherapies. The review highlights the factors associated with breaking the T-cell tolerance, the T-cell activation and costimulatory molecules, the immunoregulatory T-cells and relevant cytokines and the antibodies against peripheral nerve glycolipids or glycoproteins that seem to be of pathogenic relevance. Antigens in the nodal, paranodal and juxtaparanodal regions are discussed as potentially critical targets in explaining conduction failure and rapid recovery. Based on the immunopathologic network believed to play a fundamental role in the pathogenesis of these neuropathies, future therapeutic directions are highlighted using new biological agents against T-cells, cytokines, B-cells, transmigration and transduction molecules.
Autoimmune peripheral neuropathies (APN) occur when immunologic tolerance to peripheral nerve components (myelin, Schwann cell, axon, and motor or ganglionic neurons) is lost [1]. In some of these neuropathies there is evidence for autoimmunity mediated by antibodies or T lymphocytes against peripheral nerve. In others, the underlying immunopathology is unclear but an autoimmune cause is suspected when the neuropathy coexists with another systemic autoimmune diseases, viral infections or circulating antibodies, and responds to immunotherapies. This paper address the prevailing autoimmune phenomena that govern the most common autoimmune neuropathies and highlight the rationale for future immunotherapies based on key molecules involved in the immunopathogenic network.

**Key clinicopathological features of autoimmune peripheral neuropathies relevant to immunopathogenesis**

The most common autoimmune neuropathies include:
- acute inflammatory polyneuropathy (the Guillain-Barré Syndrome(s) [GBS]);
- chronic inflammatory demyelinating polyneuropathy (CIDP) and its variants;
- polyneuropathies associated with IgM monoclonal gammopathies and anti-myelin-associated glycoprotein (MAG) antibodies;
- multifocal motor neuropathy (MMN) with conduction block;
- paraneoplastic neuropathies associated with anti-Hu antibodies.

Although clinically and pathogenetically diverse, the APN share in common an immune process directed against peripheral nerve components mediated by activated T-cells, macrophages, complement or antibodies that work alone or in concert with each other to induce demyelination and a varying degree of axonal loss [1]. In some GBS variants and in anti-MAG neuropathy, the antigenic targets have been identified and the antibodies characterized; in acute inflammatory demyelinating polyneuropathy (AIDP), the most common GBS variant however, as well as in CIDP and MMN, the target antigens remain still elusive.

**Guillain-Barré syndrome**

The GBS is characterized by acute (within 1 week) or subacute (within 3 weeks) ascending motor weakness, areflexia, and mild to moderate sensory abnormalities [1–4]. It is an inflammatory demyelinating polyneuropathy with perivascular and endoneurial inflammatory infiltrates throughout the nerves, roots or plexuses, and segmental demyelination in areas associated with the lymphoid cells and macrophages. Because in GBS the peripheral myelin, the axon or the Schwann cells are the putative target antigens, GBS represents several syndromes based on the degree of involvement of the motor or sensory nerve fibers and the myelin sheath or the axon [1–4]. These syndromes include: the AIDP, where the main target is the myelin and accounts for the majority of GBS patients; the acute, motor axonal neuropathy (AMAN), where the primary pathology is in the axon either due to massive acute demyelination and inflammation, as occurs in experimental allergic neuritis when the animals are immunized with a high dose of myelin antigen [5], or to a primary axonal event mediated by macrophages. A number of these cases have high GM1 antibodies and, as discussed later, report an infection with *Campylobacter jejuni* [2,6]; the acute motor-sensory axonal neuropathy (AMSAN), which is like AMAN but with involvement of the sensory axons; the Miller–Fisher syndrome, characterized by acute onset of ophthalmoplegia, gait ataxia, normal sensation and areflexia [1–4], and it is a distinct variant due to the presence of a unique IgG antibody directed against GQ1b ganglioside [1–3,6,7], and the sensory ataxic GBS, due to involvement of dorsal roots and ganglionic neurons. Because some of these patients have antibodies to GD1b ganglioside they may be forming a continuum with Miller–Fisher syndrome, probably sharing autoantibodies with the same sialic groups [7,8], and the acute pandysautonomic neuropathy where the target antigen is probably in the ganglionic neurons [1].

**Chronic inflammatory demyelinating polyneuropathy**

The CIDP is the most common form of chronic APN with prevalence as high as 9/100,000 [9,10]. It is also the most gratifying autoimmune neuropathy because it is treatable in the majority of the cases. It is considered as the chronic counterpart of GBS because it shares with GBS not only various clinical, electrophysiologic, histologic and laboratory features but also a variety of autoimmune components. Like in GBS, the nerve biopsies in CIDP show demyelination and remyelination, along with occasional epineurial or endoneurial T-cells and macrophages either scattered or in small perivascular clusters in the endoneurium [9,11–14]. Electrophysiologically there is demyelination in motor and sensory fibers with slow conduction velocity, prolonged distal motor or sensory latencies, prolonged F wave latencies, and conduction block with dispersion of the compound muscle action potentials. CIDP differs from GBS predominantly by its tempo, mode of evolution, prognosis, and responsiveness to steroids or immunosuppressants [1,9]. In CIDP, like GBS, the demyelination is multifocal affecting spinal roots, plexuses and proximal nerve trunks [11,12,14,15], resulting in a variable clinicopathological picture [9]. According to the distribution of symptoms and signs, the most notable CIDP variants are the asymmetric, unifocal or multifocal motor-sensory form (Lewis–Sumner syndrome); the
pure motor; the pure sensory; the sensory ataxic; and the pure distal [1,9,11,15].

**Multifocal motor neuropathy with conduction block**

MMN has distinct clinical and electrophysiologic criteria, namely, weakness in the distribution of individual motor nerves and multifocal conduction block limited to motor but not sensory nerves [1,16]. In contrast to CIDP, in which sensory conduction block is also present, in MMN the sensory conduction remains normal across the nerve segments that have motor block. The reason for a selective motor involvement is unclear. Differences in the antigenic specificities in the myelin components between the motor and the sensory fibers are suspected because the ceramide composition of gangliosides differs between sensory and motor fibers [1,7]. Although the immunopathology of the disease is unclear, MMN patients respond remarkably well to immunotherapy with IVIg. Up to 50% of patients have high IgM anti-GM1 antibody titers but the pathogenic role of these antibodies in inducing conduction block and muscle weakness, has not been established [1,16].

**IgM-MGUS polyneuropathies with anti-myelin-associated glycoprotein or ganglioside antibodies**

Most of these patients present with a large fiber, demyelinating polyneuropathy that manifests as sensory ataxia [1,17–19]. Others have a sensorimotor polyneuropathy with mixed features of demyelination and axonal loss. Conduction velocity is slow with a rather characteristic prolonged distal motor and sensory latencies. The serum protein electrophoresis shows a monoclonal IgM spike that recognizes myelin components, most often MAG [19], as discussed later. Sural nerve biopsy demonstrates diminished number of myelinated axons with a characteristic splitting of the outer myelin lamellae, linked to the presence of IgM deposits that recognize MAG in the same area of the split myelin sheath [1].

**Immunopathogenesis**

Based on the immunopathologic similarities with experimental allergic neuritis induced after immunization with myelin proteins, disease transfer experiments with the patients’ serum or with intraneural injections, and immunocytochemical studies on the patients’ nerves, it appears that both cellular and humoral factors, either independently or in concert with each other, play a major role in the cause of APN [1].

**Cellular factors**

**Guillain-Barré Syndrome**

The role for a T-cell-mediated process in GBS is mostly derived by analogy to experimental allergic neuritis (EAN), induced by immunizing animals with peripheral nerve myelin, which resembles GBS in both its pathology and its clinical course [1–4]. Animals sensitized to whole human nerve or to various myelin proteins such as Po, P2, and the neutral glycolipid galactocerebroside, develop segmental demyelination with mononuclear cell infiltrates consisting of macrophages and T-cells. In EAN, the T-cells are sensitized against myelin and can passively transfer the disease to healthy animals. In human GBS there are perivascular and endoneurial inflammatory infiltrates throughout the nerves, roots or plexuses and segmental demyelination in areas associated with the lymphoid infiltrates and especially macrophages which are the most dominant cells [1–4]. The macrophages break through the basement membrane of healthy Schwann cells and make direct contact with the outermost myelin lamellae, leading to lysis of the superficial myelin sheath [1–4]. Cytokines and chemokines released by the activated T-cells or complement activation, may increase capillary permeability and facilitate transmigration of additional macrophages. When the demyelination is extensive, it is followed by axonal degeneration [1–5]. The degree and effectiveness of remyelination and axonal regeneration dictate the degree of clinical recovery. Increased levels of IL-2 and soluble IL-2 receptors are noted in the serum during the acute phase of GBS suggesting ongoing T-cell activation [2]. Further, lymphocytes from GBS patients exert myelinotoxic activity when applied to cultures of myelinated axons [1].

**Chronic inflammatory demyelinating polyneuropathy**

In CIDP, the cellular component is not as striking as in GBS, but its role is becoming increasingly compelling. Although CIDP is defined as an “inflammatory polyneuropathy”, there are only minimal signs of T-cell infiltrates in the sural nerve biopsies [9,20]. The predominant lymphoid cells are macrophages, found scattered or in clusters around endoneurial vessels [9,12–15]. Macrophages constitute the final effector cells associated with the demyelinating process [21]. They express activation markers, probably induced by specific cytokines released by activated T-cells in situ or in the circulation, [9,11–15,21] penetrate the basement membrane of the Schwann cell, displace the cytoplasm, split the myelin lamellae and result in focal destruction of the myelin sheath (macrophage-mediated demyelination). The macrophages, but also the Schwann cells, play a role in local antigen presentation because they express the costimulatory molecules B7-1, B7-2 while their counter-receptors CTLA-4 and CD28 are expressed on the rare endoneurial CD4+ T-cells [22–24]. The role of B7-1/B7-2 is further supported by the development of a spontaneous autoimmune polyneuropathy with clinical, electrophysiologic and immunopathological features similar to human CIDP, in a strain of non-obese diabetic mice deficient in B7-2 costimulation [25]. Recent data indicate that the few T-cells found in the nerve biopsies of CIDP patients have strong monoclonal and oligoclonal restrictions in their T-cell receptor repertoire [26]. The clonal expansions found in the nerve biopsies overlapped...
with those in the patients’ peripheral blood lymphocytes, implying an antigen-driven, CD8+ T-cell-mediated attack against peripheral nerve components [26].

A higher frequency of Th17-positive cells is also noted in the peripheral blood and CSF while interleukin-17, which augments the induction of costimulatory molecules and enhances chemotaxis of monocytes, is increased in the plasma and the white cells [27]. There is also dysfunction of the immunoregulatory T-cells, which may further enhance the local inflammatory microenvironment and sustain the disease process [9,27–29]. Soluble adhesion molecules, chemokines, cytokines and metalloproteinases are also increased in the patients’ sera, endothelial cells and CSF, and may facilitate lymphoid cell transmigration across the blood-nerve barrier [30–34]. Genes for various inflammatory mediators are upregulated not only in the sural nerve biopsies [35] but also the skin of these patients [36], suggesting that the inflammatory process is not only active locally but also systemically [9].

**Humoral factors: the role of antiganglioside antibodies**

**Guillain-Barré Syndrome**

There is much stronger evidence that circulating serum factors are responsible for GBS. On clinical grounds, this is supported by the beneficial effect of plasmapheresis, that removes not only putative pathogenic antibodies but also other inflammatory mediators relevant to demyelination and conduction block [1,9]. On laboratory grounds it is supported by the variety of autoantibodies detected in the patients’ serum. Serum from the acute phase of GBS can demyelinate rodent dorsal root ganglionic extracts in a complement-dependent manner. Further, GBS serum injected into rat sciatic nerves causes demyelination and conduction block [1–4,6]. Immunocytochemical studies on the peripheral nerves of GBS patients show deposits of IgG, IgM, and membranolytic attack complex, implying complement-fixing IgG antibodies directed against myelinated fibers [1–4]. Further, complement-fixing IgM antibodies against a human peripheral nerve myelin glycolipid that contains carbohydrate epitopes as well as high-titer antibodies against various sulfated or acidic glycosphingolipids are present in several GBS patients [1,2,6–8].

Gangliosides are present in all tissues but they are especially abundant in the nervous system. Their lipid portion lies in the cell membrane, and their signature sugar residues are exposed at the extracellular surface bearing one or more sialic acid molecules, such as one sialic acid ganglioside (GM1), two (GD1a), three (GT1a) or four (GQ1b) [1,2,7,17] (figure 1). Although they do not represent a common “GBS antigen”, different gangliosides appear to be involved in different GBS subtypes [1,2]. Some of them may be of pathogenic relevance because immunization of rabbits with GM1 and GD1b induces acute neuropathy with histological features of AMAN [2,7,8]. Their pathogenicity has been strengthened by an inadvertent experiment in humans who had received ganglioside injections for various maladies and developed AMAN with GM1 antibodies [37]. Additionally, antibodies to GQ1b or GD1a cause conduction block at the motor nerve terminals in a preparation of mouse phrenic nerve [1,2,7,8].

IgG antibodies that react with GM1, GD1a, GalNAc-GD1a and GM1b are found in 80% of cases with the axonal forms of GBS (AMAN and AMSAN). In the common AIDP subtype, however,
these antibodies are not frequent and in this subtype the main antigenic target remains still elusive. Among the gangliosides, the one that clearly correlates with a specific clinical syndrome is the GQ1b [1,2,8]. Anti-GQ1b antibodies of IgG class appear specifically associated with the Miller–Fisher variant of GBS because they are present in more than 90% of the patients. In contrast, anti-GQ1b antibodies of the IgM class may be found in patients with IgM paraproteinemic polyneuropathies [1,17], as discussed later. Anti-GQ1b IgG antibodies are also found in postinfectious ophthalmoplegias as well as in GBS patients with ophthalmoplegia, but not in GBS patients without ophthalmoplegia or in other autoimmune conditions [1]. Of interest, anti-GQ1b antibody immunostains the paranodal regions of oculomotor nerves III, IV, and VI, suggesting that damage to these regions blocks impulse generation at the nodes of Ranvier, resulting in a conduction block that is characteristic for GBS. Many patients with antibodies to GQ1b also have antibodies to GD1a [1,2,8].

The reasons for different clinical syndromes in connection with specific gangliosides remains unclear, but distribution, accessibility and density or configuration of ganglioside at different sites may be critical factors [1,2,17]. For example, there is more GM1 in ventral than in dorsal roots, hence the predominantly motor neuropathy seen with GM1 antibodies; there is also more GQ1b in the oculomotor muscles, which explains the eye involvement in Miller–Fisher syndrome. How these antibodies induce disease remains still unclear. Current evidence however suggests that antibodies against different acidic glycolipids or sulfatides may be triggered by different viral or bacterial antecedent factors [1,2]. Molecular mimicry between epitopes of viral proteins (which may trigger disease) and myelin components could result in sensitization of cross-reactive T-cells that could mediate the demyelinating process, as discussed below. The activated T-cells may then stimulate B-cells to produce specific antibodies directed against myelin components, or may recruit macrophages as effector cells [1]. A combination of cellular and humoral factors therefore seems to participate in the cause of the disease [1,2]. Circulating cytokines triggered by the initiating event (virus, bacteria) could also upregulate intercellular adhesion molecule (ICAM)-1 expression on the endothelial cells and facilitate the entrance of activated T-cells or antibodies to the endoneurial parenchyma. It is relevant, therefore, that ICAM-1 has been found to be increased in GBS patients [34].

Chronic inflammatory demyelinating polyneuropathy

Humoral factors also play a major role in CIDP as indirectly supported by the beneficial effect of plasmapheresis that removes putative pathogenic antibodies or other inflammatory mediators relevant to demyelination [1,9]. In contrast to GBS however, where some antibodies are implicated in the axonal and ataxic variants, no specific antibody has yet been identified as the causative factor in CIDP. Antibodies to glycolipids LM1, GM1, or GD1b are seen in some patients, but less frequently than in GBS although more frequently than the controls [38,39]. Passive transfer experiments have demonstrated that serum IgG can induce conduction block in rat nerve [40,41]; the 28 kDa myelin protein Po was identified as a putative antigen in up to 20% of the patients [40,41]. Complement-fixing IgG and IgM deposits are found on the patient’s myelin sheath [42] and a band, probably IgG, is detected in the CSF of these patients [43]. Of interest, albeit of unclear clinical relevance, is the observation that B-cells from CIDP patients exhibit reduced expression of FcγRIB, an inhibitory receptor that prevents B-cells from entering the germinal centers to become IgG-positive plasma cells [44]. An immunopathogenetic scheme summarizing the proposed role of T-cells, cytokines, B-cells and autoantibodies is presented in figure 2.

Target antigens in the nodal and paranodal regions: antibodies beyond gangliosides

Although the target antigens in CIDP and the AIDP remain still elusive, recent studies suggest that molecules within the nodal regions of the non-compact myelin and the Schwann cell/axonal interactions, rather than the compact myelin, may be targets of an immune attack [45]. This is a very attractive hypothesis of clinical relevance because it explains best the rapid recovery we see clinically in CIDP and MMN patients, often noticeable within days after plasmapheresis or IVIg, and the fast worsening, over days, towards the end of treatment effects; this cannot be explained on the basis of remyelination or demyelination but rather by a functional, minute-to-minute, blockade induced by humoral factors against nodal molecules associated with saltatory conduction [9]. Electron microscopy studies have now revealed multiple alterations in the nodal and paranodal regions in the Schwann cells of CIDP nerves compared to disease control nerves [46]. The distribution of KCNQ2, a potassium channel subunit present in nodal regions was diminished in CIDP nerves, while paranodin, known as Caspr, an axonal membrane glycoprotein highly enriched at paranodes, was more widespread in CIDP than controls extending along the axon in internodes [46]. Similar alterations were observed in the demyelinated sciatic nerves of mice that also had increased levels of paranodin/Caspr and increased density of ankyrin G clusters [46]. In a related study in EAN mice, disruption of sodium channel clusters at the nodes of Ranvier was associated with loss of the adhesion molecules gliomedin and neurofascin, preceding the loss of sodium channels and paranodal demyelination, and accompanied by antibodies to gliomedin and neurofascin [47]. Collectively, adhesion molecules in the nodal, paranodal or juxtaparanodal regions, as depicted in figure 3, may be target antigens in AIDP, CIDP and MMN. Some of the putative antigenic proteins within these regions
**Candidate antigens in the nodal, paranodal and juxtaparanodal regions of the myelinated fiber**

Gangliocytin 1, Na+ channel, Ankyrin G, Neurofascin 186 are the most common putative antigens in the nodal region; Neurofascin 155, Caspar 1 and contactin 1 in the paranodal; and contactin 2, Caspar 2 and K+ channel in the juxtaparanodal region. Additional ones (see text) include gliomedin, connexin, NCAM, cadherin and others.

In CIDP, KCNQ2, a K+ channel subunit, is diminished; Caspar 1, is more widespread extending to internodal regions; the nodal Na+ channel clusters are disrupted; antibodies to several proteins have been observed; polymorphisms in the Contactin 2 (TAG-1) have been associated with response to IVIg.
include: neurofascins, gliomedin, contactins, such as Transient Axonal Glycoprotein-1 (TAG-1) or Caspr, connexin, NCAM, cadherin, anykin, and others [45] (figure 3). Immune responses against such molecules may change the fine structure at the nodes and induce conduction failure, which would explain the rapid recovery seen after therapy [45].

A number of laboratories, including ours, are actively searching for an immune attack against such target antigens. In one study, 43% of patients with GBS and 30% of patients with CIDP showed IgG fixation at the nodes of Ranvier in an in vitro system; in eight of these patients IgG antibodies recognized the native extracellular domain of neurofascin NF186, gliomedin, or contactin [48]. In two other studies, high-titer antibodies to neurofascin have been observed in some patients with CIDP and AIDP but not in controls [49,50]. Although these antibodies were detected in a small number of patients, there is evidence that they may be pathogenic [50]. Polymorphisms in the TAG-1 molecule have been also noted in CIDP and it was suggested that TAG-1 may be a target antigen [51]. Testing for TAG-1 antibodies in more than 15 CIDP patients using a cell-based assay in our laboratory, was however negative [52]. Further, testing for reactivity to Caspar 2 which is localized in the juxtaparanodal region (figure 3), also failed to detect antibodies against this target antigen in up to 20 CIDP patients, based on a very sensitive cell-based assay we have established [53].

**Triggering events: molecular mimicry between *Campylobacter jejuni* or other microbial agents with gangliosides**

The triggering events that break tolerance in GBS and CIDP patients and lead to disease development remain unclear. Molecular mimicry between epitopes of viral proteins (which trigger the disease) and myelin components may result in sensitization of cross-reactive T-cells that could mediate the demyelinating process [1,9]. In CIDP infections have been implicated but never proven. In contrast, two-thirds of patients with GBS give a history of a flu-like illness or acute dysenteric episodes that precede the development of GBS by 1–3 weeks [1,2]. Among the implicated viruses are cytomegalovirus, Epstein–Barr virus (EBV), herpes, hepatitis A and HIV. Among bacteria, infection with *Mycoplasma pneumoniae* and, most importantly, *C. jejuni*, are the main culprits for certain GBS subsets [1,2]. *Campylobacter* contains glycoconjugates that share epitopes with the peripheral myelin [1,2]. The strain of *C. jejuni* associated with AMAN (Penner D: 19 Serogroup) is different from those causing common enteritis and more likely to have the genes for enzymes that synthesize sialic acid in the bacterial wall mimicking ganglioside GM1, GD1a or GQ1b [1,2,7,8,54]. *Campylobacter* is detected in up to 30% of patients with AMAN and 20% of patients with Miller–Fisher syndrome. Bacterial isolates from AMAN bear GM1-like or GD1a-like lipo-oligosaccharide, while those from patients with Miller–Fisher syndrome have lipo-oligosaccharides mimicking GQ1b [2], and figure 2. Infection by *C. jejuni* carrying GM1-like or GD1a-like lipo-oligosaccharide induces antibodies to GM1 or anti-GD1a, which are expressed in motor nerves resulting clinically in AMAN [2]. On the other hand, infection by *C. jejuni* bearing GQ1b-mimicking lipo-oligosaccharide elicits the generation of anti-GQ1b antibodies, which, by binding to GQ1b expressed in the oculomotor nerves and muscle spindles, may cause the Miller–Fisher syndrome [2]. Cross-reactivity therefore between epitopes in the lipo-oligosaccharide of the bacterial wall and the gangliosides on the peripheral nerve is the best examples of molecular mimicry that trigger disease. This concept is further supported experimentally, as injection of lipo-oligosaccharides extracted from *C. jejuni* into rabbits induce an acute neuropathy with GM1 antibodies, identical to AMAN [1,2,54], while immunization of mice with these lipo-oligosaccharides generate a monoclonal antibody that reacts with GM1, binds to human peripheral nerve and blocks muscle action potentials in muscle-spinal cord co-culture [1]. Because *C. jejuni* is a common cause of a diarrheal illness worldwide, and diarrhea has been an antecedent event in up to 50% of GBS patients, it is the responsible factor that triggers disease in some patients. Isolation of *Campylobacter* from stools early in acute GBS varies from 44% to 88% of patients, and IgG or IgM *Campylobacter*-specific antibody titers are seen in a higher percentage (36%) of GBS patients than in controls (10%). Molecular mimicry may not be limited to *C. jejuni* because GM1 and GQ1b epitopes are also found in the bacteria wall of *Hemophilus influenzae*, which is also a triggering factor in GBS. GBS triggered by CMV infection has been also associated with the presence of IgM anti-GM2 antibodies. Another potential factor for molecular mimicry is *Mycoplasma pneumoniae*, which precedes GBS in 5% of cases and is known to stimulate antibodies against human carbohydrate antigens, including galactocerebroside, the main glycolipid antigen in the peripheral nerve [1,2,54]. Molecular mimicry may play a role in some patients with melanoma because several carbohydrate epitopes, such as GM3, GM2, GD3, are shared by melanin and melanoma cells [55–57], thereby explaining the reported higher incidence of CIDP in patients with melanoma or after vaccination with melanoma lysates [56].

**IgM anti-myelin-associated glycoprotein or sulfoglucuronyl glycosphingolipid (SGPG) antibodies in IgM-MGUS neuropathy**

IgM-MGUS is the most common demyelinating polyneuropathy among paraproteinemic patients [58]. Sera from approximately 50% of these patients react with myelin-associated glycoprotein (MAG), a 100-kDa glycoprotein of the central and peripheral nerve myelin, as well as other glycoproteins or glycolipids that share antigenic determinants with MAG.
The antigenic determinant resides in the carbohydrate component of the MAG molecule [59]. The anti-MAG IgM paraproteins co-react with an acidic glycolipid in the ganglioside fraction of the human peripheral nerve, identified as a SGPG [60–62]. In contrast to MAG, which is mostly present in the CNS, SGPG is found only in the peripheral nerves. More than half of the IgM paraproteins recognize MAG and SGPG, and 75% of the rest recognize ganglioside antigens, indicating that acidic glycolipids are the most common antigenic epitopes [1,61]. Because anti-MAG-reacting sera always recognize the SGPG glycolipid, the assay has been often performed using SGPG as antigen instead of purified human MAG [1]. It is preferable, however, to use MAG as the target antigen rather than SGPG, because the IgM binds to MAG 10–100 times more strongly than to SGPG and low-affinity anti-MAG antibodies can be missed if SGPG is used as the antigen. The sera of some IgM-MGUS patients with sensory ataxia that do not react with MAG, recognize various gangliosides, most commonly those that contain either a disialosyl moiety, such as GD1b, GQ1b, GT1b, the GalNAc-GM1b and GalNAc-GD1a, or two gangliosides that share epitopes with GM2 and GM1, or a combination of GM2 and GM1, GM1 and GD1b [1,17,63].

There is strong evidence that the MAG/SGPG antibodies are related to the cause of the neuropathy because of the following reasons [1]:

- IgM and complement are deposited on the myelinated fibers on the patient’s sural nerve biopsy [64] suggesting that activated complement may be needed for the induction of demyelination;
- the IgM recognizes neural cell adhesion molecules and co-localizes with MAG on the areas of the split myelin lamellae, suggesting involvement in myelin disadhesion [65]. Skin biopsies from these patients have also confirmed the presence of IgM, complement C3d, and MAG deposition on the dermal myelinated fibers and the concurrent loss of nerve fibers [65];
- injection of serum from patients with IgM anti-MAG/SGPG paraprotein supplemented with fresh complement into feline peripheral nerve causes complement-dependent demyelination and conduction block within 2–9 days of the injection [66]. The IgM injected intraneurally localizes to the outer layer of the myelin sheath;
- systemic transfusion of anti-MAG IgM paraproteins produces segmental demyelination in chickens [67], with deposition of IgM on to the outer lamellae of the myelin along with splitting of the myelin lamellae, similar to that observed in the human neuropathy.

New specific therapies as relate to the immunopathogenesis of autoimmune peripheral neuropathies

APN are clinically important because they are potentially treatable with various immunosuppressive, immunomodulating, or chemotherapeutic agents. In GBS, intravenous immunoglobulin (IVIg) and plasma exchange are equally effective based on randomized trials but a number of patients do not adequately respond and are left with significant disability [68]. There is also convincing data from randomized controlled trials that corticosteroids, IVIg, and plasma exchange exert short- or long-term meaningful clinical improvement in about two-thirds of the patients with CIDP [9,69,70]. About one-third of CIDP patients however are refractory or not sufficiently responsive to the aforementioned therapies [9]. In addition, there is a need for steroid and IVIg-sparing agents to diminish the long-term steroid-related side effects and reduce the high cost of IVIg. In MMN the only convincingly effective therapy is IVIg but, as with CIDP, a number of patients do not adequately respond, while those who do respond require IVIg infusions on very frequent, almost monthly, intervals at a significant cost to the patients and insurance carriers. The anti-MAG antibody patients are refractory to available therapies [1,71] with only a small portion of them responding to Rituximab [72]. The immunosuppressants such as azathioprine, cyclosporine, mycophenolate, or cyclophosphamide are variably used as steroid-sparing agents [73]; but their efficacy is overall disappointing. β-interferon and methotrexate offer no benefit in CIDP based on controlled trials [9,74,75]. Accordingly, there is a need for more effective and specific therapies for all APN cases.

The involvement of activated lymphocytes, cytokines, complement, and adhesion or transmigration molecules in their pathogenesis, as depicted in figure 2, justifies pursuing new biological agents, that target specific molecules connected with all the stages of the aforementioned immunopathology, from the early T- and B-cell activation process to the final induction of cytotoxicity, as recently discussed [9,76,77]. These drugs are promising and may be considered as future therapeutic options, provided they are tested in control trials and carefully controlled for some rare but catastrophic side effects such as PML or severe bone marrow suppression. The following agents, already on the market for other autoimmune disorders, target a series of relevant molecules associated with the immunopathology of APN, as depicted in figure 4.

T-cell intracellular signaling pathways

They include:

- the monoclonal antibody Alemtuzumab (CAMPATH), directed against the CD52 molecule, that causes long-lasting lymphocyte depletion. Alemtuzumab has been very effective in multiple sclerosis with almost 70% reduction of relapses and disability prevention and has been promising in CIDP [9,76,77] where a controlled trial has now began;
- the monoclonal antibody Daclizumab that binds to CD25 (IL-2 receptor antagonist) and inhibits T-cell proliferation. The drug is well tolerated, has been approved for one form of...
leukemia, and has been very promising in patients with Multiple Sclerosis in two clinical trials.

- the compound Tofacitinib, an oral Janus Kinase inhibitor, inhibits interleukin-2-dependent differentiation of type 2 and type 17 helper T-cells and attenuates signaling by proinflammatory cytokines, such as interleukin-6 and interferon-γ. Blockade of the Janus kinases results in suppression of both T- and B-cells while maintaining regulatory T-cell function. The drug has been effective in ulcerative colitis and rheumatoid arthritis [77,78].

**B-cells and B-cell trophic factors**

These include:

- Belimumab (Benlysta), a human monoclonal antibody against B-lymphocyte stimulator (Blys) that has been approved for lupus;
- rituximab, a chimeric monoclonal antibody directed against CD20, a membrane-associated phosphoprotein present on B-cells resulting in peripheral B-cell depletion [76–79];
- ocrelizumab, the humanized version of rituximab;
- ofatumumab (Arzera) that targets different CD20 epitopes. Rituximab, at a dose of 2 grams given intravenously in two infusions 15 days apart or 375 mg/m² in four weekly infusions, is a promising agent; up to 50% of the treated patients with CIDP seem to improve after 2–12 months [80]. Controlled studies are needed.

**Complement**

A monoclonal antibody against C5 (Eculizumab) inhibits C5 and blocks its cleavage and subsequent generation of proinflammatory molecules along with the terminal formation of membranolytic attack complex [76,77]. This agent, approved for paroxysmal hemoglobinuria is of interest in CIDP where complement is activated and deposited on the nerves. This drug was effective in an EAN model, showed some promise in a small uncontrolled trial in MMN patients, and was effective in a controlled study in human myasthenia gravis [76,77].

**Cytokines and cytokine receptors**

These include:
MC Dalakas

- Tocilizumab, an IL6 receptor antagonist, which is promising in SLE and is relevant to APN because IL6 affects the induction of Tregs to pathogenic Th1 cells;
- Brodalumab and Inekizumab, both monoclonal antibodies directed against IL17, which have been recently shown to be effective in psoriasis;
- Ustekinumab, a human monoclonal antibody against the p40 subunit of IL12/1L-23, which has shown effectiveness in psoriatic arthritis and has been approved for plaque psoriasis [77,78].

**Cell adhesion and T-cell migration**

Natalizumab, approved for multiple sclerosis and Crohn’s disease, prevents adhesion and transmigration of T-cells by binding to α4β1 integrin (VLA4) on leucocytes. Because it affects both T- and B-cells, is a reasonable drug to consider for experimental trials in APN, even though it was ineffective in one CIDP case [81]. More appropriate however may be the drug Fingolimod, an anti-T-cell migration agent that traps lymphocytes in the lymphoid organs. The drug approved for multiple sclerosis, is now tested in an ongoing CIDP trial.

**Biomarkers of response to therapies**

Some GBS patients do not respond to therapies and in others the benefit is shown in retrospect when the ongoing immune process is arrested by plamapheresis or IVIg. Similarly, some CIDP patients respond only to steroids, while others, especially with pure motor disease, not only fail to respond but may even worsen with steroids; others respond only to plamapheresis or IVIg but the response is variable [9] Biomarkers predicting the response to IVIg or other therapies from the outset are therefore needed [82]. Based on pharmacokinetics in 174 patients with GBS treated with IVIg [83], patients with a lower increase in serum IgG (DeltalgG) recovered significantly more slowly, and fewer reached the ability to walk unaided at six months; a low DeltalgG was independently associated with poor outcome. If confirmed, this would suggest that patients might benefit from a higher dosage or second course of IVIg early in the disease course. Whether the serum IgG level plays also a role in CIDP remains to be determined. Among the potential biomarkers currently explored in CIDP, the most promising ones seem to be transient axonal glycoprotein-1 (TAG-1), an adhesion molecule involved in axonal maintenance, and the inhibitory FcγRIIB on B-cells [44,51]. An analysis with single nucleotide polymorphisms and haplotype studies in 100 Japanese patients, revealed an association between IVIG responsiveness and polymorphism in TAG-1 [51]. This finding, the first to show that response to IVIg may be genetically determined, needs validation with a larger number of patients of different ethnic groups and genetic backgrounds. The inhibitory FcγRIIB on B-cells transduce inhibitory signals and prevent their transformation into IgG-producing plasma cells [44]. Patients with CIDP were found to have lower FcγRIIB on naive B-cells and failed to upregulate or maintain FcγRIIB as the disease progressed. Of interest, FcγRIIB protein expression was upregulated on monocytes and B-cells after clinically effective IVIg therapy, suggesting that the effect of IVIg on FcγRIIB may be a factor predicting those patients more likely to respond to IVIg. This work should be however confirmed by testing more specimens and performing careful clinical correlations. Other exploratory markers of disease activity include:

- defective Fas-mediated T-cell apoptosis;
- pSTAT 1, 3 and T-bet;
- levels of GFAP and TTR;
- or gene transcripts on skin biopsies [82].

Sera from active CIDP patients have the potential to inhibit axonal growth and enhance axonal degeneration by activation of the Rho-kinase pathway [84]; if confirmed, this may serve as a potential biomarker of monitoring the effectiveness of therapies.

**Disclosure of interest:** the author has received honoraria for lectures or consultancies serving in steering committees for: Talecris/Grifols, Octapharma, Baxter and Novartis.

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Please cite this article in press as: Marinos C. Dalakas, Pathophysiology of autoimmune polyneuropathies, Presse Med (2013), http://dx.doi.org/10.1016/j.lpm.2013.01.058.