Dysimmune polyneuropathies – new diagnostic and therapeutic insights

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Summary

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Polyneuropathies are systemic diseases of the nervous system that affect peripheral motor, sensory and vegetative autonomous nerve fibres. The prevalence is 2.4% in the general population and 8% in those older than 55 years. Although inflammatory polyneuropathies represent only about 10% of all polyneuropathies, they are important since they are potentially treatable. They encompass the Guillain-Barré syndrome (GBS) and its chronic sibling chronic inflammatory demyelinating polyneuropathy (CIDP), the vasculitides of the peripheral nervous system (VAS) and polyneuropathies that are associated with autoantibodies, e.g. in the context of a paraproteinaemia.

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated neuropathy that causes significant neurological morbidity. Despite the resemblance to the Guillain-Barré syndrome and the observation that immunosuppressive therapies can lead to a clinical improvement the pathogenesis of CIDP is poorly understood. Since CIDP responds to plasmapheresis and intravenous immunoglobulins (IVIG), humoral mechanisms seem to be involved. But so far autoantibodies against various proteins like P0, glycoproteins and glycolipid components such as GM1, LM1, chondroitin sulfate C have only been found in a minority of patients. Most of the mononuclear inflammatory cells in nerve biopsies are macrophages and activated T-lymphocytes. But until now no specific target in human nerves for the T-cell attack could be identified.

An interesting aspect is how T cells cross the blood-nerve barrier. We could show that nerve biopsies of patients with CIDP, systemic and non-systemic vasculitis expressed increased levels of the matrix metalloproteinases MMP-9 and MMP-2. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endoproteinases that are effectors of the extracellular matrix remodelling. This may indicate that MMP-9 derives essentially from blood-derived immune cells where it functions as an effector molecule of extravasation and early interstitial infiltration as common pathogenetic mechanisms of inflammatory neuropathies.

DNA microarray analysis is a powerful tool for simultaneous analysis and comparison of gene products expressed in normal and diseased tissues. We have undertaken gene expression analysis to identify differentially expressed genes in nerve biopsy samples of CIDP patients and compared the results to nerve biopsies of normal nerve and of vasculitic neuropathy. Of special interest were (1) tachykinin precursor 1, which may be involved in pain mediation; (2) stearoyl-CoA desaturase, which may be a marker for remyelination and (3) the allograft inflammatory factor-1, a modulator of immune response during macrophage activation and marker of blood-vessel damage.

Another important aspect of dysimmune polyneuropathies is therapy. The polyneuropathy associated with antibodies to myelin-associated glycoprotein (anti-MAG) is a chronic symmetric sensorimotor demyelinating neuropathy caused by monoclonal IgM against myelin-associated glycoprotein in the context of an IgM paraproteinaemia. Rituximab is a chimeric monoclonal antibody that specifically eliminates normal and malignant B-lymphocytes and B-cell precursors. It is approved to treat B-cell lymphoma in haematology. Rituximab prevents the formation of new antibody-secreting cells and reduces titres of antibodies. We treated in a phase-II, 12-month pilot study 9 patients with anti-MAG neuropathy. There was clinical improvement in 6 of the 9 patients, and

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7 had improved nerve conduction studies by at least 10%. These findings were accompanied by laboratory evidence of reduction of B cells, anti-MAG antibodies and total IgM. IgM levels fell to a median of 58% and anti-MAG antibody titres fell to a median of 38% of the initial values one year after treatment. A follow-up study with the double dose of rituximab in the same patients led to improvement in 4 patients for 2 of them for the first time. In comparison to the baseline before the first treatment with rituximab 375 mg/m^2 4 out of the 7 patients who were retreated improved and all 6 of the patients in whom neurography could be done had significant improvement of nerve conduction velocities. The IgM fell to a median of 38% and the anti-MAG antibody titres fell to a median of 16% of the initial values.

Rituximab was well tolerated which is important since conventional treatments like chlorambucil or interferon-alpha have produced inconsistent or no beneficial effects in placebo-controlled trials and longer follow-up studies, and may even be associated with long-term complications. Recently, a double-blind multicentre study on rituximab in anti-MAG associated polyneuropathy has been started in collaboration with French neuropathy centres.

Keywords: dysimmune neuropathies; CIDP; vasculitic neuropathy; anti-MAG associated neuropathy; rituximab

Introduction

Polyneuropathies are systemic diseases of the nervous system that affect peripheral motor, sensory and vegetative autonomous nerve fibres. The prevalence is 2.4% in the general population and 8% in those older than 55 years [1]. Although dysimmune polyneuropathies represent only about 10% of all polyneuropathies, they are important since they are potentially treatable. They encompass the Guillain-Barré syndrome (GBS) and its chronic sibling chronic inflammatory demyelinating polyneuropathy (CIDP), the vasculitides of the peripheral nervous system (VAS) and polyneuropathies that are associated with autoantibodies, e.g. in the context of paraproteinaemia.

Guillain-Barré syndrome – molecular mimicry and anti-GM1 antibodies

GBS is an acute inflammatory polyneuropathy with various clinical, electrophysiological and pathological subtypes. In the United States, Europe and Australia the predominant form is acute inflammatory demyelinating polyneuropathy (AIDP). Less frequent are cases of severe axonal Guillain-Barré syndrome. Reports from China describe patients with a picture suggesting predominantly motor axonal involvement, termed "acute motor axonal neuropathy" (AMAN) [2, 3]. The most important pathogenetic mechanism in Guillain-Barré syndrome is probably molecular mimicry, e.g. after infections with *C. jejuni*. In the molecular mimicry concept it is thought that an antibody response launched against *C. jejuni* is inadvertently directed to peripheral nerve because of epitopes shared between the lipopolysacharide fraction of *C. jejuni* and glycolipid antigen on the myelin sheaths and the axolemma [4]. Anti-GM1 antibodies are directed against gangliosides, a class of complex glycosphingolipids containing sialic acid. Gangliosides are present in neural tissues, especially at synapses [5]. Antecedent *C. jejuni* infection was found in 23% of GBS patients in comparison to CMV infection in 8% and EBV infection in 4% [6, 7]. The subgroup of GBS patients with *C. jejuni* infection are more likely to have antibodies to ganglioside GM1 and are more likely to have neurophysiologic criteria of axonal neuropathy and pure motor Guillain-Barré syndrome [6–9].

We have described a patient who developed after hepatitis A vaccination with concomitant diarrhoea a variant of Guillain-Barré syndrome, an acute motor axonal neuropathy (AMAN) in combination with an acute disseminated encephalomyelitis (ADEM). His complement fixation of *C. jejuni* was positive and he had high titres of IgG anti-GM1 antibodies. AMAN, an acute flaccid paralysis without clinical or electrophysiological involvement of sensory nerves, has been described among children and young adults in northern China [10]. Most cases have antecedent infection with *C. jejuni* and many display antibodies directed against GM1 ganglioside-like epitopes [11, 12]. ADEM is a monophasic syndrome occurring in the context of an infection, immunisation or vaccination. Its pathological characteristics are perivascular inflammation, oedema and demyelination in the central nervous system [13–15]. Our patient fulfilled the diagnostic criteria for both ADEM and AMAN. To our knowledge, this combination of ADEM and AMAN has not previously been described. In our case we postulate that the immunological attack must have been directed against two different antigens, possibly because of a double immunogenic stimulation with both *C. jejuni* and the hepatitis A vaccine [16].

Chronic inflammatory demyelinating polyneuropathy – effector molecules of inflammation, migration and remyelination

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated neuropathy that causes significant neurological morbidity. The characteristic clinical picture is one of slowly progressive weakness and sensory loss, which usually affects proximal and distal muscles, absent tendon reflexes, features of demyelination in nerve conduction studies, elevated protein in the cerebrospinal fluid. Abnormalities on sural nerve biopsy consist in segmental demyelination accompanied by thinly myelinated fibres with Schwann-cell proliferation (onion bulbs), myelin breakdown with ovoids and interstitial infiltrations with inflammatory cells, mostly lymphocytes and macrophages [17–20]. There is no marker for this disease but the diagnosis is based on criteria that take into account the clinical presentation, electroneurography, the analysis of the cerebrospinal fluid (CSF) and the nerve biopsy [21–23].

The resemblance to the Guillain-Barré syndrome and the observation that immunosuppressive therapies can lead to a clinical improvement led to the assumption that CIDP is an immune-mediated disease [24–27].

Humoral pathogenetic mechanisms as well as cell-mediated immunity are discussed in CIDP. Since CIDP responds to plasmapheresis and intravenous immunoglobulins (IVIG), humoral mechanisms seem to be involved. But so far autoantibodies against various proteins like P0, glycoproteins and glycolipid components such as GM1, LM1, chondroitin sulfate C have only been found in a minority of patients, with the exception of the IgM paraproteinaemic polyneuropathy [27].

Most of the mononuclear inflammatory cells in nerve biopsies are macrophages and activated T-lymphocytes [28]. Analysis of T-cell subsets shows that there are more cytotoxic/suppressor $CD8^+$ cells than $CD4^+$ cells. These findings are similar to the animal model of experimental autoimmune neuritis (EAN) where cytotoxic T-lymphocytes are thought to be pathogenetic. But until now no specific target in human nerves for the T-cell attack could be identified. Likewise no dominant T-cell receptor Vβ utilisation could be found which is an argument against clonally expanded T cells [29]. Gammadelta T cells that react to nonprotein antigens like autologous glycolipids have been demonstrated in nerve biopsies of inflammatory polyneuropathy [30, 31]. MHC class II molecules and the MHC-like molecule CD1a have recently been demonstrated in macrophages in sural nerve biopsies of CIDP patients, which indicates that macrophages serve as antigen presenting cells [32]. They also may phagocyte myelin debris and secrete inflammatory effector molecules [33]. The presence of macrophages in clusters around endoneurial vessels in sural nerve biopsies helps to distinguish them from hereditary demyelinating neuropathy [34].

Matrix metalloproteinases MMP-9 and MMP-2

An interesting aspect is how T cells cross the blood-nerve barrier. We could show that nerve biopsies of patients with CIDP, systemic and non-systemic vasculitis expressed increased levels of the matrix metalloproteinases MMP-9 and MMP-2. Matrix metalloproteinases are a family of zinc-dependent endoproteinases that are effectors of the extracellular matrix remodelling. They are subdivided into collagenases, gelatinases, stromelysins, matrilysins, membrane-type metalloproteinases and metalloelastase, according to their substrate affinity for different types of extracellular matrix (ECM) components.

MMP-2 and MMP-9 belong to the gelatinases that are involved in the breakdown of the blood-brain and blood-nerve barrier in various neuroinflammatory diseases [35, 36]. Several matrix metalloproteinases are up-regulated in brain tissue and cerebrospinal fluid from multiple sclerosis and its animal model "experimental autoimmune encephalomyelitis" (EAE) [37–44]. In the peripheral nervous system up-regulation of gelatinases has been found in nerve biopsy specimens from patients with Guillain-Barré syndrome, CIDP and non-systemic vasculitic neuropathy (NSVN) [45].

We compared the expression of MMP-2 and MMP-9, and their cellular source in nerve biopsy samples from secondary (i.e. due to an underlying disease such as panarteritis nodosa or rheumatoid arthritis) vasculitic neuropathy (SVN), CIDP and non-inflammatory neuropathies (NINs) [46]. Congruent with earlier results [45] MMP-2 was diffusely expressed in endothelial cells and perineurial stroma in the normal nerve biopsy specimens and nerve sections from CIDP. In contrast, secondary vasculitic neuropathy showed spotty up-regulation of MMP-2 in stromal cells of the endo- and epineurium as compared to CIDP and non-inflammatory neuropathy. Moreover, up-regulation of MMP-2 in nerve tissue seems to be a common feature between secondary vasculitic neuropathy and non-systemic vasculitic neuropathy [45]. In contrast, MMP-2 is not transcriptionally up-re-

gulated in nerve tissue from Guillain-Barré syndrome [35], CIDP or its corresponding animal model experimental autoimmune neuritis [47].

The role of MMP-2 in inflammatory processes is not fully understood. In vitro assays have shown that MMP-2 mediates the migration of T cells across a blood-brain-barrier model [48, 49]. The promoter regions of other matrix metalloproteinases contain the activator protein 1 (AP-1) transcription factor, which binds to specific DNA sequences in gene promoters thereby affecting transcription. MMP-2 does not contain this modulatory sequence which speaks in favour of a constitutive expression [50]. Since we found expression in the perineurium and the endothelium of blood vessels also in non-inflammatory polyneuropathies, MMP-2 may play a role as housekeeping gene for physiological tissue turnover. Its up-regulation in CIDP and vasculitic neuropathy, however, indicates an additional function in the pathogenesis of inflammation.

In contrast, MMP-9 was up-regulated in CIDP and secondary vasculitic neuropathy to a similar extent. MMP-9 expression in individual nerve tissue specimen was highest in the epineurium and specifically around blood vessels in both neuropathies, and double-labelling experiments have identified T cells as the predominant cellular source of MMP-9. This may indicate that MMP-9 derives essentially from blood-derived immune cells where it functions as an effector molecule of extravasation and early interstitial infiltration as common pathogenetic mechanisms of inflammatory neuropathies. The inverse correlation of MMP-9 expression and the distance to blood vessels suggest that MMP-9 is down-regulated in the course of interstitial migration. Given the important role of matrix metalloproteinases in the pathogenesis of inflammation, their specific inhibition may offer a new strategy in treatment of inflammatory polyneuropathies. The beneficial effect of IFN-β on the course of multiple sclerosis is believed to result, among other factors, from its suppressive effect on MMP-9 [51]. However, IFN-β has been shown to be ineffective in a randomised double-blind study in advanced CIDP which may be explained by the fact that inflammation subsides at this chronic stage and, therefore, the disease becomes unresponsive to any form of immunomodulatory treatment [52]. Specific metalloproteinase inhibitors are another group of candidate compounds for the treatment of inflammatory neuropathies, but so far their disappointing results in other disease areas, mainly oncology, have prevented their use in inflammatory neuropathies. More selective compounds, targeting specifically gelatinases and their use in early disease phase, may be necessary to consider MMP-inhibitors as novel therapeutic approach in the future [53].

From a diagnostic point of view endoneurial MMP-9 expression may be a helpful additional parameter in the differential diagnosis between CIDP in association with diabetes mellitus and diabetic neuropathy [54] and between CIDP and hereditary demyelinating polyneuropathies [34].

Gene expression studies

DNA microarray analysis is a powerful tool for simultaneous analysis and comparison of gene products expressed in normal and diseased tissues [55–57]. We have undertaken gene expression analysis to identify differentially expressed genes in nerve biopsy samples of CIDP patients, which might serve as markers for the disease or participate in pathogenesis [58]. Results in 8 archived shock-frozen CIDP nerves were compared to those in 3 normal nerves (NN) or 3 nerves affected by vasculitis (VAS), as controls. Hierarchical clustering analysis demonstrated distinct gene-expression patterns distinguishing these disease groups. The technique is feasible, although small amounts of RNA have to be amplified. The differentially expressed genes are mostly involved in immunity and signal transduction. In the following we highlight genes that seem to us to be of special interest in CIDP and vasculitis.

Stearoyl CoA desaturase (SCD)

SCD is up-regulated in CIDP versus normal nerve and in CIDP versus vasculitis. It is a rate limiting enzyme in the biosynthesis of monounsaturated fatty acids that are present in myelin and a target in leptin signalling [59–61]. It regulates the synthesis of oleic acid, a major fatty acid in peripheral nervous system myelin. In the rat sciatic nerve the SCD mRNA declines during wallerian degeneration and rises again as regenerating axons recontact Schwann cells. In addition, the specific and total SCD activities measured in sciatic nerves of trembler mice, an animal model of dysmyelination, were 15 and 17% of normal values [62]. This enzyme might have a role in the remyelination process and neonatal myelin development.

Allograft inflammatory factor 1 (AIF-1)

AIF-1 is both up-regulated in CIDP and VAS as compared to normal nerves. This gene was originally cloned from activated macrophages in human and rat atherosclerotic allogenic heart grafts

undergoing chronic transplant rejection [63]. It is encoded within the HLA class III genomic region and inducible by proinflammatory cytokines like IFN-γ, IL-1β or TNF-α. AIF-1 is a modulator of immune response during macrophage activation and important for their survival and migration activity [64, 65]. However, AIF-1 is also expressed in activated T-lymphocytes [66] and interestingly AIF-1 mRNA and protein were observed in medial vascular smooth muscle cells in immunologic and mechanical models of arterial injury [67]. It is constitutively expressed in the brain by a subset of microglial cells and increased there in the context of focal human brain infarctions, human and rat traumatic brain injury, human gliomas, but also in rat autoimmune encephalomyelitis and uveitis [68–71]. It is therefore an example of a gene that is elevated in inflammatory nerve disease and may be an interesting candidate for inflammatory mechanisms concerning the extravasation of macrophages and lymphocytes from blood vessels.

With immunhistochemical studies we could demonstrate, at the protein level, an increased expression of AIF-1 in peripheral neuropathy compared to normal nerve and in particular, in vasculitic neuropathy and CIDP compared to non-inflammatory neuropathy, confirming our previous gene expression study. As previously shown in other diseases, we demonstrate for the first time in human peripheral neuropathy that the AIF-1 expressing cells are activated macrophages and T-lymphocytes. In vasculitic neuropathy and CIDP we found an increased number of small calibre vessels compared to non-inflammatory axonal neuropathy. This is probably a reaction against the hypoxia and tissue damage induced by the inflammation. In our specimens the thickness of the vessel walls was increased in vasculitic neuropathy compared to non-inflammatory controls and CIDP. By colocalisation studies we demonstrate that vascular smooth muscle cells express AIF-1 in peripheral neuropathy, and in particular in the vessel walls of vasculitic neuropathy nerves.

The increased thickening of the vessel walls occurring in vasculitic nerves and the separation and numerical increase of epineurial smooth muscle cells, can lead to the hypothesis that the narrowing and occlusion of the vessel lumen (and consequent ischaemia) is due not only to the infiltration of inflammatory cells but also to a proliferation of vascular smooth muscle cells [72].

Tachykinin precursor 1 (TAC 1)

TAC 1 is the most up-regulated gene in CIDP versus normal nerve with a fold change of 27.8. The tachykinins are a family of amidated neuropeptides. TAC 1 encodes a precursor containing both substance P and neurokinin A. Tachykinins play a role as excitatory neurotransmitters, and release of tachykinins from primary afferent pain-sensing receptors is required to produce moderate to intense pain [73, 74]. Substance P has a well-characterised function as neurotransmitter, but plays also a major role in modulating inflammatory and immune response and is present in sensory nerves, but also in human monocytes, macrophages and lymphocytes as well as in many other tissues [74–77]. Substance P stimulates human peripheral blood monocytes to produce cytokines [78]. In 6 out of 8 of our CIDP patients pain was present and it might well be that this pain is mediated via tachykinins.

This was the first study to use the microarray technology in human sural nerve biopsies. Up-regulated genes might provide clues to pathogenesis of inflammatory nerve diseases and need to be further explored by studies on the protein level.

Anti-MAG associated polyneuropathy – new therapeutic strategies

The polyneuropathy associated with antibodies to myelin-associated glycoprotein (anti-MAG) is a chronic symmetric sensorimotor demyelinating neuropathy caused by monoclonal IgM against myelin-associated glycoprotein in the context of an IgM paraproteinaemia [79]. In approximately half of the patients with IgM monoclonal gammopathy the monoclonal antibody reacts with the myelin-associated glycoprotein (MAG) [80]. The antibodies are thought to cause neuropathy by complement fixation [81], disruption of myelin compaction [82] or selective loss of MAG from peripheral nerve myelin [83]. Patients with anti-MAG antibody-associated polyneuropathy typically present with a distal and symmetric predominantly sensory neuropathy. It usually begins with numbness and paraesthesia in the feet, with an unsteady gait and rarely with weakness. In time, patients can become severely debilitated, and in advanced cases there can be profound weakness, sensory loss and gait ataxia.

Therapy in patients with neuropathy and IgM monoclonal gammopathy is directed at reducing the antibody concentration, blocking the effector mechanisms and depleting the monoclonal B cells. Therapy in specific cases depends on the neurological presentation and presence of malignancy. Although there is no correlation between antibody titre and severity of the neuropathy [84], the IgM

concentration or titres, when followed serially, may correlate with the clinical status of individual cases [80, 85, 86]. When aiming to reduce the monoclonal antibody concentration, a reduction of 50% or more for a period of at least 3 months has been suggested to constitute an adequate trial [80]. Therapeutic agents include chlorambucil, plasmapheresis or intravenous gammaglobulins (IV Ig) or interferon-α [87–89]. However, such treatment modalities have produced inconsistent or no beneficial effects in placebo-controlled trials and longer follow-up studies, and may even be associated with long-term complications [90].

Rituximab is a chimeric monoclonal antibody that specifically binds to the CD20 antigen on normal and malignant B-lymphocytes. It induces antibody-dependent cell- and complement-mediated cytotoxicity in these cells. It is approved to treat B-cell lymphoma and reduces peripheral B-lymphocyte counts by almost 90% within 3 days [91]. It prevents the formation of new antibody-secreting cells and reduces titres of antibodies. A few case reports of rituximab therapy in anti-MAG and other antibody-related polyneuropathies have shown encouraging results [92, 93].

We treated in a phase-II, 12-month pilot study 9 patients with anti-MAG neuropathy who were resistant to other therapies with rituximab 375 mg/m^2 [94]. There was clinical improvement in 6 of the 9 patients, and 7 had improved nerve conduction studies by at least 10%. These findings were accompanied by laboratory evidence of reduction of B cells, anti-MAG antibodies and total IgM. IgM levels fell to a median of 58% and anti-MAG antibody titres fell to a median of 38% of the initial values one year after treatment. Since not all patients improved clinically and the anti-MAG antibodies were not completely removed, we gave rituximab in a double dose (750 mg/m^2 instead of 375 mg/m^2) to see whether additional clinical improvement might be achieved. The higher dose of rituximab was also well tolerated. One patient died suddenly after month 7 at the age of 80 years. He had tolerated the rituximab applications without immediate side effects and the cause was probably unrelated to rituximab. Four out of the remaining 7 patients improved by at least 2 points on the neurological disability score (NDS). Two had not responded to the lower dosage. One progressed on the NDS by 2 points while remaining stable with neurography and 2 remained stable. The nerve conduction velocity improved in 2 patients by at least 10%. One patient did not consent to control neurography at month 12 and the remaining 4 patients had stable motor nerve conduction velocities. Anti-MAG antibody titres were reduced to a median of 59% and IgM concentrations to a median of 74% compared to baseline (start of high-dose treatment). IgG levels did not fall below the normal range in all 7 patients. In comparison to the baseline before the first treatment with rituximab 375 mg/m^2 4 out of the 7 patients improved and all 6 of the patients in whom neurography could be done had significant improvement of nerve conduction velocities. The IgM fell to a median of 38% and the anti-MAG antibody titres to a median of 16% of the initial values [95]. These results are comparable with another study where patients who had either motor neuropathy with IgM anti-ganglioside antibodies or anti-MAG associated polyneuropathy were treated with rituximab in comparison to an untreated control group [96]. Moreover, our results are confirmed by objective electrophysiological measurements. Improvement of motor nerve conduction velocity in a demyelinating polyneuropathy may be a sensitive marker for ongoing remyelination. However, motor nerve conduction velocity does not correlate with strength, and axonal regeneration most likely occurs much later than remyelination of surviving fibres. All our patients had quite severe axonal involvement on electroneurography and could have responded with a delay to the first rituximab treatment. Therefore, placebo-controlled studies in the early stages of disease with different dose regimens and long-term follow-up are necessary.

Conclusion

The most important results and conclusions of the above-discussed studies can be summarised as follows:

1. AMAN and ADEM can occur together. In our case the immunological attack must have been directed against two different antigens, possibly because of a double immunogenic stimulation with both *C. jejuni* and the hepatitis A vaccine.
2. MMP-2 and MMP-9 are overexpressed in nerve biopsy samples of patients with CIDP, non-systemic vasculitic neuropathy and systemic secondary vasculitic neuropathy in comparison to non-inflammatory controls. MMP-2 may play a role as house-keeping gene for physiological tissue turnover and have an additional function in the pathogenesis of inflammation. MMP-9 functions as an effector molecule of extravasation and early interstitial infiltration as common pathogenetic mechanisms of inflammatory neuropathies.
3. Gene expression studies with DNA microarray technology in sural nerve biopsies of CIDP and

vasculitic nerve are feasible, although small amounts of RNA have to be amplified. The differentially expressed genes are mostly involved in immunity and signal transduction. Of special interest are (1) tachykinin precursor 1, which may be involved in pain mediation; (2) stearoyl-CoA desaturase, which may be a marker for remyelination and (3) the allograft inflammatory factor-1, a modulator of immune response during macrophage activation and marker of blood vessel damage. These results need to be further explored by immunohistochemical studies.

4. Our improved understanding of the pathogenic immune mechanisms in dysimmune neuropathies has allowed the development of specifically tailored immunosuppressive treatment. Rituximab, for example, is an antibody that eliminates specifically B cells and B-cell precursors. Two phase-II pilot studies have shown that it is a safe and promising new drug in the treatment of anti-MAG associated polyneuropathy. Placebo-controlled studies in the early stages of disease with different dose regimens and long-term follow-up are warranted.

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