Inflammatory Demyelinating Neuropathies and Neuropathies Associated with Monoclonal Gammopathies: Treatment Update

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Summary: This review focuses on recent data regarding inflammatory demyelinating neuropathies and neuropathies associated with monoclonal gammopathies. We describe both acute and chronic inflammatory neuropathies, and we discuss conditions ranging from mostly cell-mediated to antibody-mediated disorders. These diseases are characterized by proximal and distal sensory motor involvement. Treatments are based on immune-modulation and/or immune-suppression. Work-up sequence and therapeutical modes are discussed in the light of recently published data, with a special interest on new treatment modalities. **Key Words:** Inflammation, antibody, immune-modulation, neuropathy, gammopathy.

GUILLAIN-BARRÉ-SYNDROME

The concepts of Guillain-Barré-Syndrome (GBS) have changed over the last decade.[1] The spectrum of GBS ranges from acute inflammatory demyelinating polyneuropathy to pure motor, sensory motor, or bulbar variants, and the Miller-Fisher syndrome.[2] Detailed immunopathological features have been described in GBS: most current investigations are based on the hypothesis of gangliosides mimicry of Campylobacter jejuni lipopolysaccharides in GBS, together with the pathogenic role of different antibodies that interfere with nerve conduction or induce nerve damage in concert with inflammatory cells and their mediators.[3] Recent evidence suggests that GBS mirrors a common clinical phenotype shared by a group of variant forms of the neuropathy. A number of steps helpful in the subclassification of GBS have been proposed.[4]

Motor-sensory GBS

Approximately 75% of GBS in Western countries. Paresthesia is not diagnostic for motor-sensory GBS because it also occurs in patients who have a pure motor form. The cranial nerves, especially facial nerves, are involved in the majority of patients. The myotatic reflexes are usually absent. Autonomic dysfunction is more frequent than in the pure motor form. Cytomegalovirus (CMV) infection occurs in approximately 20% of these patients.

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Pure motor GBS

Approximately 20% of GBS in Western countries. Paresthesias may occur. In the majority of patients, weakness usually begins in the distal muscles of the extremities and the cranial nerves, and respiratory muscles are usually spared. Myotatic reflexes disappear relatively late. Autonomic dysfunction is less frequent. *C. jejuni* infection occurs more frequently in this group (approximately 65%), and anti-ganglioside antibodies against GM1 are found in approximately 40% of patients.

Miller-Fisher variant of GBS

Approximately 3% of GBS in Western countries. Although weakness of the extraocular muscles is the hallmark of this form of GBS, together with ptosis and paralysis of the sphincter pupillae, sometimes there is also weakness of the facial muscles and lower bulbar muscles. Rarely is there involvement of the muscles of the trunk and extremities. Ataxia is present in half the patients, and the myotatic reflexes are usually absent. Anti-immunoglobulin (IgG) antibodies against ganglioside GQ1b are present in approximately 90% of the patients.

IMUNOTHERAPY FOR GUILLAIN-BARRÉ SYNDROME

Further studies are necessary to validate the usefulness of the proposed subclassification with respect to treatment and prognosis. This is particularly important if subgrouping of GBS patients may lead to more individ-

ualized treatment.[5] More advanced age is an adverse prognostic factor, although age did not have a significant influence on the treatment effect in either of the large trials comparing intravenous immunoglobulin (IVIg) with plasma exchange (PE).[6,7] There was also no influence of the presence or absence of sensory deficit on the response to treatment in either of those trials. The occurrence of a previous diarrheal illness had been a significant adverse prognostic factor in some series.[6] It has been suggested that for the IgG anti-GM1-positive subgroup of GBS patients, IVIg therapy may be more efficacious than PE.[8] According to a recent review,[9] the analysis of the results of all the randomized trials confirms that PE hastens recovery and shows that it also improves the outcome at 1 year without a significant effect on mortality or increase in adverse events. Furthermore, the synthesis of the evidence shows that IVIg and PE have similar clinical effects. When the results of two trials were combined, intravenous methylprednisolone did not produce significant long- or short-term benefit. When a correction for prognostic factors was taken into account, a minor synergistic effect on short-term outcome of IVIg combined with intravenous methylprednisolone could not be excluded.[10] The explanation for the lack of more obvious benefits from corticosteroids is unclear, but they might have harmful effects on denervated muscle or inhibit macrophage repair processes.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disorder characterized by progressive or relapsing-remitting course. The clinical hallmark of CIDP is the presence of both proximal and distal, usually symmetric, weakness. The majority of CIDP patients also have sensory involvement (numbness and paresthesia) as well as hypo- or areflexia. In addition to the typical clinical picture, CIDP also includes different variants, such as a form with predominant distal weakness, a pure sensory form, an asymmetric form, and a form with predominant cranial nerve involvement.[11] Differentiation between CIDP and GBS relies on clinical criteria of the time necessary to reach maximum clinical deficit. In GBS, this is less than 4 weeks, and in CIDP it is more than 8 weeks.[12] Electrophysiologically, the disease is characterized by demyelinating features including prolonged distal latency, slowed conduction velocity, delayed or absent F-waves, and partial conduction block.[13] Furthermore, as with GBS, the diagnosis of CIDP is supported by the finding of albuminocytologic dissociation on CSF analysis with elevated protein level and normal white cell count. CIDP is considered to be an autoimmune disease. Consequently, various forms of immunotherapy have been tried in its treatment. Randomized, controlled trials have only focused on short-term effects, but most patients need long-term therapy.

TREATMENT OPTIONS FOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

There are three proven effective treatments available (prednisone, IVIg, and PE) that are useful in more than 60% of patients.[14,15] New open studies indicated possible efficacy for cyclophosphamide, mycophenolate, rituximab, etanercept, cyclosporine, and interferons. Several nonrandomized studies suggest the efficacy of corticosteroids in treating CIDP. Significant improvement after corticosteroids in 65 to 95% of patients has been reported in the two largest retrospective studies on CIDP.[16,17] In most patients, steroids have to be continued for many years with the consequent risks associated with their protracted use.[18] Overall, the best steroid regimen is not known.

Over the years, several uncontrolled trials have suggested the beneficial effect of IVIg in treating CIDP, demonstrating an effect in more than 60% of treated patients.[19,20] However, only a few studies have addressed the long-term efficacy of IVIg in CIDP so far.[21] A retrospective study comparing the long-term efficacy of IVIg and PE, besides confirming the comparable initial response to both therapies, showed a more frequent need for prolonged treatment with IVIg (50%) than PE (30%), a difference that was balanced by the less frequent occurrence of adverse effects after IVIg than PE.[22]

PE has been demonstrated to be effective in CIDP treatment.[23] Eighty percent of patients of both chronic progressive and the relapsing course improved substantially with PE. However, 66% of PE responders relapsed within 7 to 14 days after stopping PE. The PE nonresponders improved with prednisone. One study on two severely affected CIDP patients who became resistant to a great variety of treatments reported that they dramatically improved when the plasma exchange was followed immediately by IVIg.[24] Generally, corticosteroids, IVIg, and PE seem to be equally effective in treating CIDP.[25]

No evidence-based guidelines can be given concerning long-term management, because none of the trials systematically assessed long-term treatment. For patients starting on corticosteroids, a course of up to 12 weeks on their starting dose should be considered before deciding whether there is no treatment response. If there is a response, tapering the dose to a low-maintenance level over 1 or 2 years and eventual withdrawal should be considered. For patients starting on IVIg, observation to discover the occurrence and duration of any response to the first course should be considered before embarking on further treatment. Between 15 and 30% of patients do

not need further treatment. If patients respond to IVIg and then their condition worsens further, repeated doses should be considered.

Immunosuppressive agents are often used together with corticosteroids to reduce the need for IVIg or PE or to treat patients who have not responded to any of these treatments, but there is no evidence-based data on which to base this practice.[26] More research is needed before any recommendation can be made. In the meantime, immunosuppressant treatment may be considered when the response to corticosteroids, IVIg, or PE is inadequate. For refractory CIDP, high-dose cyclophosphamide and autologous blood stem cell transplantation has been proposed.[27]

MULTIFOCAL MOTOR NEUROPATHY

In 1986, Roth et al.[28] described a motor neuropathy with proximal multifocal persistent conduction block. Subsequently, Parry and Clarke[29] (and in a separate report, Pestronk et al.[30]), reported similar patients. Since then, there have been a number of studies describing patients who have multifocal motor neuropathy (MMN) with persistent conduction block. Whether patients who have MMN and patients who have Lewis Sumner syndrome have the same disorder with varying degrees of sensory involvement has been debated.[31,32]

Although there are a number of reasons to consider MMN to be a variant of CIDP, it appears to be a distinct clinical entity with a different therapeutical strategy. The pathognomonic feature of this condition is the presence of multiple focal motor nerve conduction blocks and high titer of IgM anti-GM1 antibodies in up to 85% of MMN patients.[33,34] However, neither the presence of anti-GM1 antibodies nor conduction block is necessary to diagnose MMN. Thus, the presence of anti-ganglioside antibodies and conduction blocks is supportive but not essential to the diagnosis.[35] The presence of high-titer anti-GM1-antibodies and clinical improvement after IVIg therapy strongly suggests that the disease has an immunological background. However, the relationship of anti-GM1 to pathogenesis is uncertain. As MMN is a potentially treatable disorder, its differentiation from lower motor neuron disorders is important.[30] Repeated administration of IVIg has become the gold standard of treatment for MMN. Several studies have demonstrated the efficacy of IVIg in MMN, including a few placebo-controlled, double-blind trials.[36,37] Lack of improvement after one, or at most two treatments should be considered as a treatment failure. However, even with intensive IVIg therapy some patients had progression of neurologic deficits.[38] In addition, a proportion of patients does not respond to IVIg at the outset[39] or requires progressively more frequent doses to maintain remission. However, the response to increasing the IVIg dose or frequency tends to decline after several years.[40,41] Previous studies have suggested that response to treatment is no different between MMN patients with or without conduction block.[42] Deciding whether to treat patients with MMN without electrodiagnostic evidence of demyelination may be difficult. However, there are data suggesting that criteria requiring strict evidence of conduction blocks may lead to underdiagnosis of this potentially treatable neuropathy.[43] High titers of serum IgM anti-GM1 antibodies are a useful indicator that an MMN may be immune-mediated and treatable. Van den Berg-Vos et al.[38] studied 37 consecutive patients with clinically typical MMN and demonstrated that anti-GM1 antibodies were found more often in patients who respond to IVIg therapy. Older age at onset, a greater number of affected limb regions, and a creatine kinase level greater than 180 U/L were significantly found more often in IVIg nonresponders. Furthermore, the lack of amyotrophy has also been suggested as a factor that predicts a good response to IVIg therapy.

There are no randomized controlled trials to indicate whether immunosuppressive agents are beneficial in MMN.[44] However, a number of uncontrolled studies and case studies have reported on the use of immunosuppressive treatments as a primary therapy for MMN. In contrast to CIDP, there is a lack of efficacy of corticosteroids treatment.[45,46] Moreover, some patients may even worsen with corticosteroids treatment.[47] Cyclophosphamide given intravenously at high doses, followed by an oral cyclophosphamide as maintenance therapy, was the first treatment reported as effective in MMN, with more than 70% of patients showing clinical improvement.[30,48] Although its efficacy may even be comparable with IVIg, cyclophosphamide is now rarely used to treat MMN because of its side effects, some of which, such as tumor production, are delayed by a number of years. In addition, a number of various uncontrolled studies also suggest a moderate beneficial effect of immunosuppressive treatments as adjunctive or second-line therapy to improve the response to and therefore reduce the need for frequent IVIg infusions.[17,39]

It was recently reported that mycophenolate mofetil did not have a significant-sparing effect on IVIg.[49] Rituximab was reported to permit to delay by 1-week IVIg infusion in one patient increasingly less responsive to IVIg.[41] Unfortunately, in the absence of controlled trials a nonsystematic review of case studies and one's own experiences can only provide limited support for the beneficial effects of immunosuppressive agents for the treatment of MMN.[50]

NEUROPATHY WITH IGM MONOCLONAL GAMMOPATHY AND OTHER DYSGLOBULINAEMIC NEUROPATHIES

The detection of a monoclonal immunoglobulin in serum or urine usually raises concerns about the size of the underlying B-cell-derived clone, and possibly systemic effects caused by its expansion.[51] However, a small clone can synthesize a very toxic protein, producing devastating systemic damage and protean clinical presentations. The monoclonal protein can aggregate and deposit systemically as occurs in monoclonal cryoglobulinemia. Alternatively, some monoclonal proteins possess antibody activity toward autoantigens and cause peripheral neuropathies. Other humoral mediators may contribute to neuropathy in variant disorders, such as the polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. The clone synthesizing the noxious monoclonal proteins is often small, and sensitive techniques may be required to detect these immunoglobulins. Although the treatment of these conditions is not optimal, significant advances have been made (Table 1).

CLASSIFICATION OF THE MONOCLONAL GAMMOPATHIES

Monoclonal gammopathies are a group of disorders characterized by proliferation of one or a limited number of clones of plasma cells or their B-cell precursors, associated with a production of excessive quantities of monoclonal immunoglobulins of the immunoglobulin (Ig) (IgG, IgA, IgM, IgD, or IgE) isotype, or their constituent heavy or light chains. A circulating monoclonal immunoglobulin is found in approximately 10% of patients with peripheral neuropathies of otherwise unknown cause, as compared with 1% of the general adult population.[52] However, prevalence in normals increases with age, reaching 3% in subjects that are 50 years or older.[53]

THERAPY OF ANTI-MYELIN-ASSOCIATED GLYCOPROTEIN POLYNEUROPATHY

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.[53] A few case reports of rituximab therapy in anti-myelin-associated glycoprotein (anti-MAG) and other antibody-related polyneuropathies have shown encouraging results.[54] There are also reports, however, on clinical worsening in two cases of anti-MAG-associated polyneuropathy.[55,56] In a phase II, 12-month pilot study, nine patients with anti-MAG neuropathy who were resistant to other therapies were treated with rituximab 375 mg/m^2.[57] This study demonstrated clinical improvement in six of the nine patients by at least 2 points on the neurological disability score, and seven had improved nerve conduction studies by at least 10%. There was laboratory evidence of reduction of B cells, anti-MAG antibodies, and total IgM. The treatment was well tolerated and no serious side effects were observed. The effect of rituximab lasts approximately 6 to 9 months and repeated therapy is probably necessary to maintain response. It is unclear, however, whether there should be a schedule for administration or whether rituximab re-treatment should depend on clinical status, IgM, or anti-MAG antibody titer increase.[58] Placebo-controlled, double-blind studies in the early stages of the disease, with clinical and electrophysiological long-term follow-up are currently underway. Fludarabine has also been proposed as a possible treatment for patients with IgM monoclonal gammopathy of unknown significance paraproteinaemic neuropathy.[59]

Table 1. *Characteristics of Polyneuropathy According to Immunoglobin Type*

Plasma Cell Disorder	Type of Neuropathy	Treatment
Multiple myeloma	Sensorimotor or multiple mononeuritis	Cytotoxic agents, steroids, thalidomid bortozomib PBSCT
Waldenström's macroglobulinemia	Sensorimotor or multiple mononeuritis	Fludarabin, rituximab
Osteosclerotic myeloma/POEMS	Sensorimotor proximal und distal, CIDP like	Single: radiation, resection multiple: melphalan-steroids, PBSCT
AL amyloidosis	Sensorimotor, axonal, dysautonomia, painful	Melphalan-prednisone PBSCT
MAG-positive IgM MGUS	Sensorimotor, distal, demyelinating	Rituximab, fludarabin
Cryoglobulinemia	Sensorimotor or multiple mononeuritis, painful	Steroids, plasmapheresis, INF-α if HCV associated

AL = amyloid light chain; CIDP = chronic inflammatory demyelinating polyneuropathy; HCV = hepatitis C virus; IgM = immunoglobulin M; INF = interferon; MAG = myelin-associated glycoprotein; MGUS = monoclonal gammopathy of unknown significance; POEMS = polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; PBSCT = peripheral blood stem cell transplantation.

SENSORY ATAXIC NEUROPATHY OR CHRONIC ATAXIC NEUROPATHY, OPHTHALMOPLEGIA, M PROTEIN, AGGLUTINATION, AND DISIALOSYL ANTIBODIES ASSOCIATED WITH ANTI-DISIALOSYL GANGLIOSIDE ANTIBODIES

Monoclonal IgM anti-disialosyl ganglioside antibodies are typically associated with an ataxic sensory neuropathy, sometimes presenting with chronic ataxic neuropathy, ophthalmoplegia, M protein, agglutination, and disialosyl antibodies (CANOMAD). In this syndrome, the IgMs react with the disialosyl epitope that is shared by the ganglioside GD1b, GQ1b, GT1c, and GD3. This form of sensory ataxic neuropathy (SAN), occasionally with ophthalmoplegia or bulbar signs affects large sensory fibers and is characterized by distal paresthesia, numbness, prominent ataxia, areflexia, and mild or no limb weakness. The neuropathy is usually chronic and slowly progressive, but can also have a relapsing course. Clinical electrophysiology and nerve biopsy show both demyelinating and axonal features. A partial response to IVIg and other treatments has been reported in some cases.[60,61]

In contrast to the chronic neuropathy, which is associated with IgM auto-antibodies, IgG antibodies to disialosyl epitopes (including GD1b and GQ1b) are associated with the Miller-Fisher syndrome or acute ataxic neuropathy with ophthalmoplegia.[62] Anti-GD1b antibodies have been reported to bind to the surface of sensory ganglion neurons, as well as to paranodal myelin in ventral and dorsal roots,[60,63] and anti-GQ1b antibodies bind to human oculomotor, trochlear, and abducens nerve,[64] consistent with the clinical syndrome. Immunization with GD1b has been reported to induce an ataxic sensory neuropathy in rabbits.[65]

NEUROPATHY WITH MYELOMAS

Although less frequent, neuropathy is estimated to occur in 1 to 13% of patients with all myelomas.[66] It is, however, the neuropathy associated with osteosclerotic myeloma that occurs in 50% of patients and has been the subject of recent studies.[67]

OSTEOSCLEROTIC MYELOMA AND THE POEMS SYNDROME

Osteosclerotic myeloma is a more indolent disease than other forms of multiple myeloma. Affected patients are younger, most commonly presenting in their 50s, but ranging in age from their 30s to their 60s. Neuropathy is frequently the presenting syndrome that leads to diagnosis. Initial symptoms consist of distal (bothersome but not painful) paresthesia in the feet, which spread proximally, followed by weakness. Cranial nerve and autonomic involvement can occur, but are uncommon. The weakness is frequently distal, but can involve proximal muscles and be severe. Electrodiagnostic studies frequently reveal evidence for demyelination and axonal degeneration, similar to CIDP.[68] CSF protein is usually elevated without pleocytosis. Nerve biopsy studies typically reveal a mixture of demyelination, remyelination, and axonal degeneration.[69] Osteosclerotic lesions are a defining feature, and at least one-third of the patients have multiple lesions. While skeletal survey was the method of choice for detecting the bone lesions, it has been replaced by bone computed tomographic scan or MRI, the latter being even more sensitive.[70] Lesions usually involve the spine, pelvic bones, or ribs. A computed tomographic-directed biopsy of a lesion is usually needed to confirm the diagnosis.

Many patients with osteosclerotic myeloma have features of the POEMS syndrome. These include hepatosplenomegaly, lymphadenopathy, edema, gynecomastia, ascites, pleural effusions, hyperpigmentation, hypertrichosis, thickened skin, papilledema, clubbing, thrombocytosis, polycythemia, and various endocrinopathies, including hyperglycemia, hypothyroidism, hypogonadism, and low-serum estrogen or testosterone.[66] However, patients with features of the POEMS syndrome can also present with nonsclerotic myeloma or with Castleman's disease.[71] The cause of these associated abnormalities is unknown, but increased levels of vascular endothelial growth factor and other cytokines have been found in these patients that may have contributed to their clinical presentations.[72,73]

THERAPY AND PROGNOSIS

Selecting the appropriate therapies for the underlying disorder and the best management of the neuropathy requires a multidisciplinary approach.[74] With localized disease, surgery of isolated plasmacytomas or irradiation[75] have been successful. High-dose chemotherapy with autologous peripheral blood stem cell rescue for patients with widespread osteosclerotic lesions is currently the method of choice.[76,77] Polyneuropathy usually improves 3 to 6 months post-therapy, sometimes even later.

The 5-year survival in patients with osteosclerotic myeloma or the POEMS syndrome is about 60%.[71]

NEUROPATHY AND CRYOGLOBULINEMIA

Infection of the hepatitis C virus is the main cause of mixed cryoglobulinemia vasculitis.

The neuropathy in patients with cryoglobulinemia is believed to be caused by vasculitis due to occlusion of

the vaso nervosum by the cryoprecipitates and is associated with such systemic manifestations as purpura, Raynaud's phenomenon, or renal disease. Patients typically present with mononeuritis multiplex, but also with distal symmetric sensory or sensorimotor neuropathy, without systemic disease. In one study, up to 11% of referred patients with neuropathy were found to have cryoglobulinemia.[78] Aggressive antiviral therapy with Peg-interferon-alpha and ribavirin should be considered as induction therapy for hepatitis C virus-mixed cryoglobulinemia vasculitis with mild to moderate disease severity and activity. Rituximab and Peg-interferon-alpha have also been combined, because it appears to also be logical to target both the viral trigger and B-cells.[79] Cryoglobulinemic neuropathy can also respond to therapy with high-dose corticosteroids and plasmapheresis.[80,81]

CONCLUSION

The spectrum of inflammatory demyelinating neuropathies and neuropathies associated with monoclonal gammopathies is a clinical heterogeneous group of polyneuropathies. As distinct syndromes are recognized, often requiring a multidisciplinary work up, therapeutic options are expanding. While therapies with corticosteroids, IVIg, or PE are well established, more data are needed for new treatments, such as selective B-cell ablation.

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