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NEUROPATHIES ASSOCIATED WITH MONOCLONAL GAMMAPATHIES

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ABSTRACT

There is increasing evidence that monoclonal proteins are implicated in the development of peripheral neuropathy. Approximately ten percent of patients with peripheral neuropathy of unknown cause have a monoclonal protein and this rate is significantly higher than prevalence rates of monoclonal protein in comparable segments of the general population. Extensive clinical, electrophysiological and immunopathological evidences indicate that peripheral neuropathy associated with monoclonal protein are heterogeneous, including: 1. the demyelinating, predominantly sensory neuropathies associated with anti-MAG antibodies; 2. the axonal, sensory neuropathies associated with anti-sulfatide and anti-chondroitin sulfate antibodies; 3. the motor neuropathies associated with anti-GM1 antibodies. Patients with chronic polyneuropathies should be evaluated for underlying plasma cell dyscrasia.

Key words: monoclonal gammapathies, neuropathies

The association between neuropathies and monoclonal gammapathies has been realized in the early seventies, but the frequency of such association is still undetermined, due to the polymorphic presentation of the neuropathy and the heterogeneous study populations, frequently small.

Particularly, in recent years, several studies have been dedicated to the definition of the epidemiology and pathogenesis of peripheral neuropathies and monoclonal gammapathies of undetermined significance.

The difficulties in gathering significant epidemiologic data depend on various factors: the high prevalence of monoclonal gammapathies in the elderly population, from a prevalence of 1-2% obtained with less sensitive techniques[1,2] to 7-8% with more sensitive methods,[3] in the vast majority of cases the monoclonal gammapathy is asymptomatic and is detected only by chance.

Chazot and coworkers[4] first described three cases of peripheral neuropathy associated with benign monoclonal gammapathy.

Subsequently, Read et al.[5] reported three additional cases with the same association. Kelly et al.[6] in 1981 reported that a monoclonal gammapathy was present in 10% of the patients with idiopathic peripheral neuropathy in comparison of 2.5% of patients with neuropathy of known etiology. Subsequent studies report a variable prevalence of neuropathy associated with monoclonal gammapathy: from 29% reported by Smith et al.[7] to 46% reported by Nobile-Orazio et al.[9] to 59% of Vrethem et al.,[10] to 71% of Osby et al.[8] The peripheral neuropathy is more frequently associated with IgM monoclonal gammapathy than with IgG or IgA,[10,11] even if IgG monoclonal gammapathy is more common in the general population.[12]

Table 1 reports the etiology of peripheral neuropathies observed at the Istituto Neurologico Mondino during the years 1982-1988: 6.5% of the peripheral neuropathies is associated to a monoclonal gammapathy.

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Pathophysiology

In the last ten years antibodies directed against *self* constituents have been implicated in the pathogenesis of several peripheral neuropathies and motor neuron disease. The principal antibodies involved in these disorders are those directed against the carbohydrate epitopes of certain glycoconjugates. It is believed that the immunoglobulins (Ig), which attack the glucide portion of the myelin-associated glycoprotein (MAG), are responsible for a chronic demyelinating neuropathy. Antibodies that react with the carbohydrate epitope of ganglioside GM1, on the other hand, are associated with a primarily motor neuropathy.

More recently, antibodies binding to a carbohydrate epitope of sulfatide and of chondroitin sulfate C have been associated with a predominantly sensory neuropathy. Furthermore, the presence of monoclonal proteins reactive against certain intermediate filaments have been described in some patients with chronic axonal neuropathy. These antibodies bind to a precise antigenic determinant that may be shared by different glycoconjugated and/or proteins present in the nervous system. The particular topographic distribution of the antigenic target is responsible for determining the different characteristics of the clinical syndrome.

Anti-MAG antibodies in peripheral demyelinating neuropathies

In roughly half the cases in which peripheral neuropathy is associated with an IgM monoclonal gammapathy, the monoclonal protein shows auto-antibody activity against myelin and, in particular, against MAG. A distal, symmetric neuropathy is usually observed in such patients. The disorder progresses slowly and is predominantly sensory at first, but will also involve the motor component later on. Electrophysiological studies reveal alterations compatible with demyelination or mixed damage resulting from demyelination and axonal degeneration. Affected patients often present a quantitative increase in serum IgM levels, and the protein electrophoresis or immunoelectrophoresis demonstrates a monoclonal immunoglobulin. Such abnormalities may also be absent despite the presence of anti-MAG antibodies.[13] This monoclonal IgM anti-MAG molecule in most cases represents the expression of a *monoclonal gammapathy of undetermined significance* (MGUS), although it is also discovered at times in the course of Waldenström's macroglobulinemia and chronic lymphatic leukemia.[14]

The epitope that the anti-MAG globulin reacts with is also weakly expressed by the glycoprotein Po, which is present in peripheral myelin and is shared by two peripheral nerve glycosphingolipids: glucuronyl paragloboside sulfate (GPGS) and glucuronyl lactosaminyl paragloboside sulfate (GLPGS).[15,16] Pathologic studies[17] on sural nerve biopsies from patients affected with this neuropathy have revealed the presence of segmental demyelination, at times accompanied by axonal degeneration. Direct immunofluorescence (IF) has demonstrated IgM and complement deposits on myelin sheaths, suggesting possible complement mediation in the development of the disease.[18,19]

Electron microscopy investigation has documented a widening of myelin lamellae at the level of the lower density lines, which is considered typical of this form of neuropathy.[20] The anomaly could be the result of anti-MAG antibody cross-reactivity towards glycolipids GPGS and GLPGS or towards glycoprotein Po, which

Table 1. Etiology of peripheral neuropathies observed at the Istituto Neurologico Mondino from 1982 to 1988.

Peripheral neuropathy	*No pats.*	*%*
Genetically determined	31	12.0
Idiopathic inflammatory polyradicoloneuritis (Guillain-Barré)	49	18.8
Diabetic	32	12.3
Toxic (alcohol) and nutritional	58	22.3
Uremic	2	0.8
Paraneoplastic	5	1.9
Idiopathic	66	25.4
Associated to monoclonal gammapathy	17	6.5
Total	260	100.0

is localized for the most part in the compact portion of the myelin. Experimentally, intrasural injection of the sera from patients with anti-MAG antibodies evidenced the binding of these molecules on the surface of the myelin sheaths, leading to demyelination and anomalies of nerve conduction.[21-23] A demyelinating neuropathy was also obtained with systemic transfer of these antibodies into animals.[24]

Anti-GM1 antibodies in peripheral neuropathies and in lower motor neuron disease

IgM monoclonal gammapathy with anti-GM1 activity has been described in patients suffering from lower motor neuron disease or from predominantly motor neuropathy.[25,26] In some cases high anti-GM1 antibody titers were detected in the absence of a monoclonal gammapathy[27,28] and were associated with a multifocal block of motor conduction.[29-32] IgG or IgA anti-GM1 antibodies were reported at high titers in a group of Guillain-Barrè syndrome patients with severe axonal degeneration and less favorable prognosis, at times preceded by enteritis from Campylobacter.[33,34]

Anti-GM1 antibodies are present at low titers (≤1:800) in healthy individuals and in disorders such as multiple sclerosis, Alzheimer's disease and systemic lupus erythematosus.[32] Antibody titers equal to or greater than 1:6400 must be considered more specific for lower motor neuron disease or motor neuropathies with or without conduction block.

Antibodies with anti-GM1 activity are usually class M polyclonal Ig, although they occasionally appear as monoclonal gammapathies. In the majority of patients anti-GM1 globulins react with the disaccharide portion Gal(β1-3)GalNac of GM1, which is also found on gangliosides GD1b and asialo-GM1 (35). These antibodies prove to be specific for GM1 or cross-reactive with GM2 in some cases.

The role of these Ig in the motor neuropathy or motor neuron disease associated with them has not yet been determined. A possible pathogenetic role for them is supported by the distribution of GM1 and Gal(β1-3)GalNac in the nervous system. Several studies have established that human anti-GM1 antibodies bind to the surface of motor neuron but not to that of sensory neurons, thus offering a potential explanation for the predominantly motor involvement of the disease.[36-38] Moreover, histochemical studies with cholera toxin, specific for GM1, and with peanut agglutinin, specific for Gal(β1-3)GalNac, have shown that the target epitopes of the antibodies are highly concentrated at the level of the nodes of Ranvier.[39-41] IgM deposits were found on the nodes of Ranvier in the sural nerve of a woman with anti-GM1 antibodies and multifocal motor conduction block.[42] Intraneural injection of this patient's serum into the rat provoked nerve conduction block.[43] Similarly to what was found in this patient, IgM deposits at the nodes of Ranvier and alterations of nerve conduction were also discovered in rabbits immunized with GM1 or Gal(β1-3)Gal Nac.[44]

Anti-sulfatide antibodies in inflammatory polyradiculoneuritis and in sensory neuropathies

Sulfatides are the most abundant sphingolipid acids present in the myelin sheath and are constituted by a galactocerebroside sulfate, generally in position 3. These compounds have been demonstrated on the surface of oligodendroglia,[45] of Schwann cells,[46] of dorsal root ganglion (DRG) neurons,[47] of ependymal cells and in the interpeduncolar nucleus.[48] Recently, high titers of anti-sulfatide Ig have been described in patients with inflammatory polyradiculoneuritis[49,50] and with predominantly sensory neuropathy.[47,51] These antibodies had been previously documented in multiple sclerosis, idiopathic thrombocytopenic purpura and active chronic hepatitis. It should be kept in mind that antibody titers up to 1:3200 may be found even in healthy individuals.

The anti-sulfatide antibodies present in polyradiculoneuritis are of the IgG type, and it has been hypothesized that they could represent the result of an alteration in the immune situation with a consequent increase in the production of antibodies belonging to the normal immune repertoire, which might be correlated to exposure to myelin antigens, or to cross reactivity with glycolipids of the viral capsid in the case of a previous infectious episode.

In sensory neuropathies characterized by painful paresthesia and reduced thermal and superficial tactile sensitivity, with normal electrophysiological parameters, the anti-sulfatide antibodies may be both IgG and IgM. Neurophysiological and morphological investigations demonstrated that axonal damage was the mechanism responsible for these alterations.[47,51,52] Since anti-sulfatide Ig bind to surface antigens on DRG neurons, it is possible that this may be where they exert their pathogenic effect, i.e. at the site where the blood-nerve barrier is most permeable.[53]

Furthermore, it should be kept in mind that sulfatides form an integral part of the binding sites of certain extracellular adhesion molecules[54] and of endorphin receptors;[55] therefore anti-sulfatide antibodies could interfere with or alter molecular interactions. Moreover, studies have shown that such antibodies may be directed against different epitopes[52] and are able to cross-react with other glycoconjugates.[56] This might explain the differences in immunohistochemical reactivity obtained so far among various anti-sulfatide antibodies.[57,58]

Anti-chondroitin sulfate C antibodies and sensory neuropathies

Chondroitin sulfate C is a glycosaminoglycan composed of hexosamine and non-nitrogenous carbohydrate joined by glycosidic bonds, which is present in neuronal and axonal membranes, in the endoneurium, but not in myelin.[59] Anti-chondroitin sulfate C serum antibodies were first described in two patients with epidermolysis and chronic sensory neuropathy associated with a monoclonal IgM peak.[60] Since then 5 more cases have been reported in patients showing the same antibody reactivity associated with chronic sensory neuropathy and monoclonal IgM peak;[61-63] however, none of these latter patients exhibited cutaneous alterations.

Morphological examination of the sural nerve demonstrated that axonal degeneration was the main cause of nerve damage in all these cases, while immunohistochemical studies revealed the presence of IgM in the endoneurium of three out of 7, and of IgM in the Schmidt-Lanterman incisures of one patient. In all probability differences in antigen conformation, density and accessibility, as well as in antibody affinity explain the discrepancies found so far in the results. In addition, it has been reported that antibody reactivity towards chondroitin sulfate C in patients with chronic sensory neuropathy is not necessarily associated with a monoclonal gammapathy, and that in 66% of these cases there is a cross-reactivity with sulfatides.[52] Thus, it is likely that the antibodies are directed against epitopes containing galactose-6-sulfate in these latter patients.

Anti-intermediate filament antibodies and neuropathies

In some patients with chronic sensorimotor neuropathies associated with a monoclonal gammapathy, the monoclonal protein reacts with certain intermediate filaments, in particular vimentin and desmin,[64] and with the neurofilaments.[65,66] Furthermore, monoclonal protein reactivity against both neurofilaments and a surface antigen expressed by a neuroblastoma cell line was described in a patient suffering from motor neuron disease.[67]

Monoclonal proteins are directed against different epitopes, some of which are unphosphorylated and located in the core of the protein, and others are phosphorylated and situated in the C-terminal.[66] Morphologic studies have revealed the presence of axonal degeneration with precocious alterations in neurofilament structure and distribution. Moreover, in some patients it was possible to document the presence of the monoclonal protein within the axon.

The significance of autoantibodies directed against axonal proteins requires further study. It has been shown that Ig with anti-neural activity penetrate the axon by endocytosis and are then transported to the cell body through retrograde axonal flow.[68] Therefore it is possible that these molecules transported inside the axon are able to bind to the target antigen and exert their pathogenic effect.

Clinical aspects

The neuropathies associated with monoclonal gammapathy are generally characterized by sen-

sory and motor symptoms with insidious onset and slow progression. The clinical diagnosis is based on the presence of motor deficit with amyotrophy, reduction or lack of deep reflexes, decrease of superficial and deep sensitivity.

The beginning of the symptoms has been characterized, for most of the patients, by sensory troubles at the distal level of the limbs, particularly the lower limbs: paresthesias are expressed with tingling, prickling, sensation of electric shock and belt. Some forms of sensory neuropathy are characterized only by paresthesias and torpor, other types are extremely painful, described by the patient as burning, piercing or cushing; these sensations can be rising in response to tactile stimuli. These sensitive deficits, more frequent at the hands and feet, are usually distributed as a *sock* or *glove*. The deep sensory troubles are characterized by the loss of vibratory sensitivity and sense of position, so the patients can present an ataxic walking.

The distribution of the motor deficit is characteristic: usually the muscles of the feet and legs are primarily and most heavily affected, and only subsequently, and less heavily, those of hands and forearm are involved. The atrophy of the affected muscles progresses slowly in several months and its intensity is proportional to the number of damaged nervous fibers. Atrophy is a consequence of disuse, particularly in demyelinating neuropathy; of disuse and denervation in conditions which interrupt the axon. Reduction or loss of tendon reflexes, even in absence of motor deficit, frequently represent the first sign of a still clinically occult neuropathy. Sometimes the patient report muscular ticks and cramps, in the first instance the involved muscles show jerking, trembling or undulatory movements. Strain increases the involuntary activity and there is reduction in efficiency that the patients feel as a sense of heaviness and rigidity.

The clinical picture of neuropathies associated with IgM gammapathy is rather uniform, both in cases with anti-MAG activity and in cases without antibody activity: about 80% of the patients are male in the age range of 40-75 years, the neuropathy is usually sensory-motor, with preponderance of sensory symptoms, while the motor disturbances are less severe and of late onset.[69] Characteristics of this form are ataxia (sensory) and postural tremor, that is not always present and of uncertain origin.[71] The cranial nerve and the vegetative system are characteristically spared.[72]

Patients with IgG gammapathy present a mixed sensory-motor neuropathy; the motor deficits are more severe and frequently at distal level of the limbs, while ataxia and tremors are absent. Sometimes involvement of the autonomous nerve system may be associated.[71]

Polyneuropathies associated with IgA gammapathy are uncommon and have been reported anecdotically. At present, is not possible to define a specific clinical pattern, although very low progression, cramps and jerking, sometimes simulating a motoneural form, may be associated.[73]

Table 2 reports the clinical characteristics of the patients with peripheral neuropathy and monoclonal gammapathy observed at the Istituto Neurologico Mondino during the years 1982-1988, while Table 3 shows the most important diagnostic investigations performed.

Diagnostic investigations

The management of a patient with monoclonal gammapathy and neuropathy requires the combined expertise of the hematologist and of the neurologist. The former should define the nature of the monoclonal gammapathy. Although this can be seldomly malignant, i.e. multiple myeloma or Waldenström's macroglobulinemia, usually the clone is indolent, like in patients with MGUS. There is presently a consensus[74] to simplify the approach to these patients as follows: if the monoclonal immunoglobulin concentration is less than 20 g/L if it is an IgG, or less than 10 g/L if it is IgA or IgM, no Bence Jones proteinuria, normal blood count and chemistry, and no bone pain, then the bone marrow examination and bone x-ray survey is unnecessary. This simplified approach would reduce both the economic and, most importantly, the psychologic costs to the patient, without compromising his/her care.

Table 2. Clinical aspects of patients with polyneuropathy and monoclonal gammapathies observed at the Istituto Neurologico Mondino.

Pts	Sex	Age yrs	MC	MC conc. g/L	Type of neuropathy
1	M	77	IgGκ	11.2	S-M polyneuropathy (M>S)
2	M	59	IgGκ	17.8	S-M polyneuropathy (M>S)
3	F	49	IgGκ	13.9	S-M polyneuropathy (M=S)
4	M	69	IgGκ	9.7	S-M polyneuropathy (S>M)
5	F	54	IgGκ	8.5	S-M polyneuropathy (M=S)
6*	M	67	IgGκ	21.9	S-M polyneuropathy (M=S)
7	M	35	IgGκ	11.2	S-M polyneuropathy (M>S)
8	M	68	IgGλ	23.1	S-M polyneuropathy (S>M)
9	F	50	IgGλ	28	S-M polyneuropathy (M>S)
10	M	65	IgGλ	21	S-M polyneuropathy (S>M)
11	F	60	IgGλ	15.1	S-M polyneuropathy (M=S)
12	M	40	IgGλ	13.1	S-M polyneuropathy (M>S)
13	F	63	IgMκ	10	S-M polyneuropathy (S>M)
14	M	59	IgMκ	12.9	S-M polyneuropathy (S>M)
15	F	75	IgMλ	19.9	M polyneuropathy
16	M	70	IgMλ	21	S-M polyneuropathy (S>M)
17	M	51	IgAλ	8.2	S-M polyneuropathy (S>M)

*Patient suffering from miastenia gravis since 1976.
S-M: sensory motor; M: motor; S>M: mainly sensor; M>S: mainly motor.

Table 3. Investigations performed on patients with polyneuropathy and monoclonal gammapathies observed at the Istituto Neurologico Mondino.

Pts	Alb	CSF mg/dL	IgG	MNCV	SNCV	Type of neuropathy
1		np		++	+	normal
2	50.3		12.1	+++	+++	demyelinating
3	59.4		11.2	+++	++	demyelinating
4		np		++	++	np
5	37.2		4.3	++	++	axonal
6	16.6		6.2	+	+	axonal
7	14.9		4.7	+	+	np
8	43		22.9	++	+	axonal
9	109		29.3	++	+	axonal
10		np		+	+	axonal
11		np		++	++	np
12	51.4		8.4	++	++	axonal
13	26.1		4.1	++	++	axonal
14		np		++	++	np
15	40.2		5.4	++	++	axonal
16	46.8		4.92	+++	+++	demyelinating
17	224		58.4	++	++	axonal

MNCV: motor nerve conduction velocity; SNCV: sensory nerve conduction velocity.
+ slowing ≤ 25%
++ slowing 25 to 60%
+++ slowing ≥ 60%
np: not performed

The patients who do not fulfill these criteria will undergo a complete set of investigations comprising bone marrow biopsy, skeletal x-ray (if the monoclonal immunoglobulin is IgG or IgA) or abdominal CT (if IgM). Since AL amyloidosis can be a cause of neuropathy, the patients should be routinely screened for amyloid deposits using the innocuous technique of the subcutaneous fat aspiration.[75] The neurologist, after a careful physical examination, would propose the following studies:

1. electrodiagnostic studies are always required for the diagnosis of peripheral neuropathy. The abnormalities frequently consist of demyelination or mixed changes of both demyelination and axonal degeneration. Motor nerve conduction velocity is typically reduced below the lower limit of normal by 20% or more. Sensory nerve action potentials are consistently reduced in amplitude or unobtainable. Nerve conduction abnormalities tend to be more severe in IgM neuropathies than in neuropathies associated with other immunoglobulin classes.[11] Electrodiagnostic studies are also useful for showing subclinical nerve injury and for monitoring the disease;
2. cerebral spinal fluid (CSF) examination. CSF protein levels in excess of 45 mg/dL are found in most cases, and concentrations above 100 mg/dL are common;
3. the study of the specificity of the monoclonal immunoglobulin for nerve tissue components, performed in specialized laboratories, is necessary for the diagnosis and is relevant for a correct therapeutic strategy;
4. nerve biopsy (sural) may be a useful tool to demonstrate the possible deposits of monoclonal IgM along myelin sheets in patients with anti-MAG antibodies. However, in consideration of the permanent sequelae of nerve biopsy, this procedure should be avoid-

ed when possible. If it is really crucial for the diagnosis, it is mandatory to have the biopsy examined in a specialized center.

Treatment

There are some epidemiological and immunopathological evidence that M-proteins are implicated in the development of peripheral neuropathy. Because neuropathies associated with MGUS have a chronic progressive course for many years and may significantly interfere with activities of daily living, specific therapy is needed. Despite some uncertainties about causal linkage between the M-protein peak in the serum and the associated neuropathy, therapy is directed at lowering the M-protein concentration. The decision when to treat depends on the severity of the neuropathy. Data in the literature suggest to separate the neuropathies associated with MGUS into those with IgM M-protein with anti-MAG reactivity and those associated with IgG and IgA M-protein. The last ones in fact better respond to immunosuppressive therapy. Therapeutic modalities utilized to date include plasmapheresis, high dose intravenous immunoglobulin, corticosteroids and chemotherapy alone or in various combinations. Effect of treatment is followed by measurement of serum M-protein and by the clinical evaluation of the neuropathy.

The effectiveness of plasmapheresis was confirmed in a prospective randomized controlled study and this has actually to be considered the first choice treatment.[76]

Thirty-nine patients received either plasma exchange twice weekly for three weeks or sham plasma exchange in a double blind trial. Plasma exchange was performed with an intermittent-flow cell separator or a continuous-flow device, twice weekly for three weeks. The average volume exchanged was 49 mL per kilogram of body weight. Improvement was seen in all treated patients and those with IgG or IgA MGUS had a better response to plasma exchange than those with IgM MGUS. Since this difference was not due to greater removal of IgG and IgA than of IgM by plasmapheresis, we think possible that the different response was due to the different antibody affinity.

In our practice the subsequent intervals of plasma exchange are dictated by the individual clinical response and it depends on the volume of plasma exchanged, the synthetic rate of the monoclonal antibody and the intravascular component of the M-protein. In patients with IgG, IgA or IgM gammapathy without anti-MAG reactivity, and in patients in which plasmapheresis may not be performed, it should be considered the opportunity to start steroid therapy. A daily single high dose of prednisone (80 to 100 mg) is recommended for 4 to 6 weeks. If an initial response is achieved at that time, the even day dosage is reduced by 10 mg every week for 10 weeks to obtain a gradual change to alternate-day therapy (100 mg every other day). Finally, when major improvement has occurred, this dose is gradually reduced to a maintenance dose. Patients may respond to prednisone alone,[71] or prednisone in combination with other immunosuppressive agents[77] but only a minority of patients with IgM gammapathy respond to treatment.[71] In patients with IgM gammapathy it is likely that a more aggressive immunosuppressive therapy is necessary aimed at lowering the M-protein concentration by at least 50%. Kelly et al.[78] reported that 9 of 10 patients with peripheral neuropathy and IgM M-protein responded to prednisone, cyclophosphamide, chlorambucil, azathioprine or plasmapheresis. A combination of intermittent plasmapheresis and high dose prednisone plus either chlorambucil (0.1 to 0.2 mg/kg/d) or cyclophosphamide (2 mg/kg/d) has been suggested in patients with neuropathy associated with IgM gammapathy.[70] In refractory cases high dose intravenous immunoglobulin infusions hold promise for improvement. Cook et al.[79] reported a favorable response in 2 patients with neuropathy and IgM gammapathy previously unsuccessfully treated with prednisone or plasma exchange. Both patients received 2 g/kg body weight divided respectively in 3 and 5 consecutive days. Eight days after the completion of the first infusion both patients noted increased strength and this improvement lasted respectively 3 and 7 weeks. Thereafter patients have been treated at 3 to 7 week inter-

vals with further clinical improvement. More recently Hoang-Xuan et al.[80] reported the results of an open trial on the effectiveness of high dose intravenous immunoglobulins (0.4 g/kg/day for 5 consecutive days) in 16 patients with various immune-mediated neuropathies. Four of the six patients with chronic demyelinating neuropathy showed a dramatic improvement; symptomatic relief was noticed in three of the four patients with chronic neuropathy associated with IgM gammapathy; improvement of the motor function was observed in three patients with purely motor neuropathy, while the treatment was ineffective in three patients with severe axonopathy. Despite these encouraging results, prospective randomized trials are needed to determine the impact of intravenous high dose immunoglobulin on neuropathies associated with monoclonal gammapathy.

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