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IgG monoclonal paraproteinaemia and peripheral neuropathy

A F Bleasel, S H B Hawke, J D Pollard, J G McLeod

Abstract

Five patients with peripheral neuropathy and benign IgG monoclonal paraproteinaemia are reported, all of whom had a sensorimotor neuropathy with a remitting and relapsing course. The serum paraprotein level did not correlate with the patient's clinical status. Electrophsyiological studies showed marked slowing of conduction velocity and conduction block in four of the patients and mild slowing in the other. Sural nerve biopsies demonstrated a demyelinating neuropathy with inflammatory cell infiltrates in each of the five patients. Three of the patients had evidence of myelin/Schwann cell reactivity on immunofluorescence studies and in all nerves dense expression of major histocompatability complex class I and II molecules was evident within the endoneurium, on invading mononuclear cells, endothelial cells and Schwann cells. All the patients responded to treatment, plasmapheresis being particularly effective. Four patients have achieved prolonged remissions after all treatment had ceased. These five cases of peripheral neuropathy and IgG paraproteinaemia were identical in their clinical, electrophysiological and pathological features to patients with chronic inflammatory demyelinating polyneuropathy.

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The association of benign monoclonal paraproteinaemia or gammopathy (BMG) with peripheral neuropathy is well recognised.[1–3] Neuropathy is more common in patients with IgM BMG than in patients with immunoglobulin subclasses IgG and IgA[2] even though IgG BMG is more common than IgM BMG.[4] Relatively few patients with IgG BMG associated peripheral neuropathy have been reported in whom the clinical and electrophysiological features and pathology have been described. No commonly reported antigenic determinant has been associated with IgG paraproteinaemia.[5] We describe the clinical features, electrophysiological and sural nerve biopsy findings in five patients with IgG BMG and peripheral neuropathy.

Institute of Clinical Neurosciences, Royal Prince Alfred Hospital and Department of Medicine, University of Sydney, Sydney, Australia
A F Bleasel
S H B Hawke
J D Pollard
J McLeod

Correspondence to:
Professor J G McLeod, Institute of Clinical Neurosciences, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia

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Materials and methods

Patients

Of 813 patients referred to our laboratory for sural nerve biopsy between July 1981 and November 1988, 12 were found to have a peripheral neuropathy associated with a monoclonal gammopathy. In these patients a diagnosis of BMG was made as the uninvolved immunoglobulin subclasses were within the normal range, there was no Bence Jones proteinuria, no evidence of plasma cell infiltration, lymphoma or amyloid deposition on bone marrow aspirate and trephine, and no bony lesions were seen on radiological skeletal survey. Other causes of peripheral neuropathy were excluded. Six patients had IgM paraproteins, 5 had IgG paraproteins and 1 patient had an IgA paraprotein. The 5 patients with IgG paraproteinaemia are the subject of this report; some aspects of the treatment of patients 1 and 3 have appeared in previous publications.[6 7]

Electrophysiological studies

Nerve conduction studies were performed in the upper and lower limbs. Motor conduction velocity was measured in the median, ulnar and lateral popliteal nerves when recording compound muscle action potentials with bipolar surface electrodes over the abductor pollicis brevis, abductor digiti minimi and extensor digitorum brevis muscles respectively. The median and ulnar sensory nerve action potentials (SNAP) were recorded at the wrist with bipolar surface electrodes after orthodromic stimulation through ring electrodes of the index and little finger respectively. The sural SNAP was recorded with bipolar surface or subcutaneous needle electrodes in the lower calf following orthodromic stimulation of the nerve at the lateral malleolus. Electromyography was performed in 3 of the patients using concentric needle electrodes placed in the intrinsic muscles of the hand and distal muscles in the lower limbs. The results of the nerve conduction studies were compared with results obtained in a population of 20 men and women without symptoms or signs of neurological disease between the ages of 50–80 years.

Histological studies

Sural nerve biopsy was performed at the level of the lateral malleolus to obtain 3–4 cm of nerve which was divided into four equal portions. A piece of nerve was fixed in picric acid saline for 24–36 hours, dehydrated in alcohol, embedded in paraffin wax, and cut transversely in serial sections of 5 μm. The sections were stained with haematoxylin, counterstained with eosin and examined by light

microscopy. A second piece of nerve was fixed for at least 24 hours in 10% buffered formaldehyde (pH 7·0) and then stained for 24 hours in 1% osmium tetroxide. Single fibres were teased from the nerve and examined under the light microscope. A third piece of nerve was fixed in 2·5% phosphate buffered glutaraldehyde at 4°C for a minimum of 3 hours, usually overnight. After washing in buffer the tissue was post-fixed in Dalton's chrome osmium for 90 minutes at 4°C. The tissue was dehydrated in alcohol, passed through acetone and embedded in Spurr's resin. Sections were cut with glass or diamond knives and double stained with uranyl acetate and lead citrate and examined using a Philips 200 or 201 electron microscope.

Immunological studies

Direct immunofluorescence (IF) was performed on a portion of nerve that had been snap frozen in iso-pentane cooled in liquid nitrogen. Cryostat sections of 6 μm were fixed in acetone and then incubated for 30 minutes in a dark moist chamber after application of fluorosceine isothiocyanate (FITC) conjugated antibodies (F(ab)2 portion of goat or rabbit monospecific antiserum) against IgG, IgM, IgA (heavy chain specific), C3 and fibrin. Sections were examined with a Leitz fluorescence microscope. Indirect IF was performed using sections of fresh frozen normal control peripheral nerve incubated with the patient's serum. The sections were then incubated with FITC conjugated antibodies as for direct IF.

Immunohistochemical studies using monoclonal antibodies to T-cell subsets, macrophages and major histocompatability complexes I and II were performed on all nerves as previously described.[8] Evidence of serum anti-myelin activity was also sought in patients 1, 2 and 5 by immunoblot and ELISA. A postmortem preparation of human sciatic nerve myelin, obtained within 12 hours of death, was run on 12·5% sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS PAGE) and the separated proteins transferred electrophoretically to nitrocellulose membranes[9]. After blocking with 2·5% bovine albumin and 0·02% sodium azide in phosphate buffered saline the nitrocellulose was cut into 3 mm strips which were then incubated in the presence of serum from patients or controls overnight. The strips were washed and then incubated with peroxidase conjugated rabbit antihuman IgG, IgM and IgA and the reaction product revealed by dipping the strips into Chloro-1-naphthol H_2O_2 solution. Separate strips after SDS PAGE were stained with Coomassie blue to show separated proteins. For the ELISA assay microtitre plates were coated with purified human myelin and incubated with the test sera. The wells were probed with horseradish peroxidase-anti-IgG, IgM and IgA.

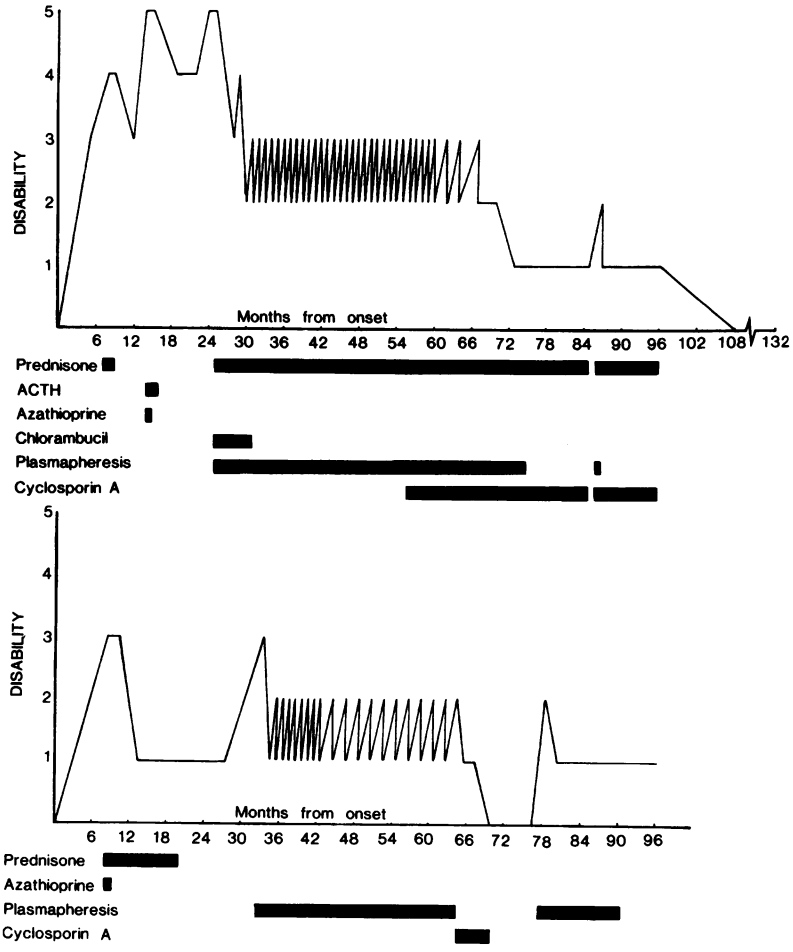

Figure 1 Clinical course of patients 1 and 3 represented by disability scores during follow up. Disability scores: 0, normal; 1, signs but no symptoms or vice versa; 2, mild motor and/or sensory symptoms with signs; 3, moderately disabled by motor and sensory symptoms including ataxia; 4, requiring assistance with eating or dressing, or using a walking aid and 5, not ambulant.[10] Individual therapies are indicated below each graph. The periods of dependence upon plasmapheresis are represented by the sawtooth sections of the graph.

Results

The mean age of the patients at the onset of symptoms was 53·4 years (range 43–73 years). A summary of the clinical course and treatment of patients 1 and 3 is shown in fig 1. Patient 5 had had an upper respiratory infection some weeks before the onset of neurological symptoms but an antecedent illness or vaccination was not reported in the others. The earliest symptoms were sensory in each patient with symmetrical distal limb paraesthesiae and numbness which ascended over weeks or months. Only patient 5 had painful sensory symptoms. Peak disability was reached from 9 to 20 months after the onset of symptoms. There was considerable variation in the degree of motor involvement within the group. Patient 3 had a predominantly sensory neuropathy while weakness developed 7–18 months after the onset of sensory symptoms in the other four patients. Patients 1, 4 and 5 had severe weakness and were bedbound at some time during their illness although none of the patients had significant respiratory muscle weakness. None of the patients had tremor. Cranial nerves were affected in two patients; facial paraesthesiae was reported in patient 3 and orofacial paraesthesiae and vocal cord paresis noted in patient 5. CSF examination revealed variable elevation of protein, 0·5–1·5 g/L (normal range 0·15–0·45 g/L), without

pleocytosis in all patients. The initial serum paraprotein levels were 1·9–9·0 g/l for patients 1, 2, 3 and 5 with IgG κ, and 1·0 g/l for patient 4 with IgG λ.

All patients relapsed after initially responding to treatment some after their treatment was stopped and others whilst continuing treatment. Reintroduction or intensification of treatment always produced another remission and four of the patients have achieved prolonged remissions requiring no therapy. Prednisone, with or without azathioprine, has generally been used as first line treatment but has required supplementation except in one of the patients (patient 2). Azathioprine produced intolerable nausea in patient 1 and hepatitis in patient 3. All patients responded to plasmapheresis and in both patients 3 and 5 plasmapheresis was the sole treatment for 32 months. Patients 1, 3 and 4 were dependent upon plasmapheresis; these patients developed symptoms between treatments and improved promptly following exchange. This dependence was abolished by the introduction of cyclosporin A in patients 1 and 3.

Electrophysiological studies

The results of electrophysiological studies are shown in table 1. Marked slowing of motor conduction velocities was present in 4 of 5 patients. The slowing was associated with conduction block and dispersion of the compound muscle action potentials. Sensory conduction was abnormal in every patient. Sural SNAPs were absent in patients 2, 4 and 5 at presentation but were not performed in patients 1 and 3. EMG studies in patients 1, 3 and 5, with gross slowing of motor conduction, revealed minor spontaneous activity in distal limb muscles in patients 3 and 5. In addition there were reduced interference patterns in the muscles sampled and scattered large amplitude polyphasic motor units (patients 1 and 3). These EMG findings indicated that there was chronic partial denervation, consistent with secondary axonal loss in a primary demyelinating neuropathy. The motor conduction velocities of patients 1 and 4 improved following treatment, matching the clinical improvement. Such a correlation between improved clinical state and nerve conduction was not seen in patients 2, 3 and 5, there being apparent worsening or no change on motor conduction velocities despite improvement in their clinical state. Patient 3 showed some improvement in motor conduction velocity later in the course of her neuropathy.

Histological and immunological studies

Sural nerve biopsies were performed 10–22 months after the onset of symptoms and demonstrated demyelination in each patient. There was no evidence of arteritis. Transverse semi-thin nerve sections, stained with toluidine blue and examined by light microscopy showed varying degrees of reduction in the density of myelinated fibres, from normal fibre density to severe fibre loss. The endoneurial spaces were expanded. Many axons with inappropriately thin myelin sheaths were found among the remaining fibres and Schwann cell proliferation giving rise to "onion bulb" formation was seen in 3 of the biopsies (table 2). Electron microscopy confirmed the presence of demyelinating neuropathy. In addition to the changes found in the semi-thin sections, large axons devoid of myelin were seen in association with mononuclear cells and macrophage mediated active demyelination (fig 2). Teased fibre preparations revealed segmental demyelination in 35-85% of fibres (table 2); myelin ovoids indicating axonal degeneration were present in 3 of the biopsies in 20% or less of fibres.

Positive IF was found in four patients (table 2). Direct and indirect IF demonstrated IgG deposition on Schwann cells and myelin in patient 1. Both direct and indirect IF demonstrated IgG binding to myelin sheaths and blood vessels in patient 5. Patients 2, 3 and 4 had no IgG deposition. Fibrinogen breakdown products (FBP) and C_3 were deposited on blood vessels and the perineurium with direct IF in patient 2. Direct IF showed deposition of FBP on blood vessels in patient 4 and indirect IF demonstrated strongly positive staining for C3 on myelin sheaths, a positive result confirmed with three separate serum samples. In none of the 3 patient's sera tested (patients 1, 3 and 5) was there evidence of binding to myelin by either ELISA or immunoblot. Immunohistochemical studies showed the presence of both $CD4^+$ and $CD8^+$ T cells within nerve, but macrophage/monocytes were the dominant infiltrating cell. Dense expression of MHC class I and II molecules was evident within the endoneurium, particularly

Table 1 Electrophysiological studies

Patient			Duration symptoms	Disability score	Motor conduction						Sensory conduction			
					Median		Ulnar		C. Peroneal		Median		Ulnar	
					Latency	Velocity	Latency	Velocity	Latency	Velocity	Amp	Latency	Amp	Latency
			months		ms	m/s	ms	m/s	ms	m/s	μV	ms	μV	ms
1	M/43	Initial	23	5	9·8	11	10·2	11	Absent	Absent	Absent		Absent	
		Review	46	3	6·4	29	5·6	31	15·5	34	2	5·1	4	4.8
2	F/47	Initial	7	2	5·0	47	4·4	42	7·6	36	6	2·8	Absent	
		Review	3	2	4·4	38	Not done	Not done	Not done	Not done	6	4·3	Not done	
3	F/52	Initial	12	2	5·5	26	4·6	28	8·5	35	Absent		Absent	
		Review	71	0	6·6	20	4·7	23	19·5	10	Absent		Absent	
		Review	88	1	4·3	28	4·5	37	11·0	13	Absent		Absent	
4	M/52	Initial	15	5	7·8	15	16·5	13	22·1	9	Absent		Absent	
		Review	25	2	6·8	21	8·4	26	6·0	25	Absent		Absent	
5	F/73	Initial	13	3	11·3	20	8·0	17	16·0	21	Absent		Absent	
		Review	21	2	7·8	21	6·2	24	17·6	20	Absent		Absent	
Controls, Mean (SD)					3·8 (0·8)	52·2 (4·1)	2·9 (0·7)	53·2 (2·5)	5·1 (1·3)	44·1 (4·9)	11·5 (3·9)	3·4 (0·6)	8·7 (3·7)	2.9 (0·4)

Table 2 Summary of the sural nerve biopsy findings

Patient	Light microscopy	Teased fibres	Direct IF	Indirect IF
1	Moderate to severe loss of myelinated fibres of all diameters, endoneurial oedema, "onion bulbs"	55% SD, 20% AD*	IgG; myelin sheaths and Schwann cells	IgG myelin sheath and Schwann cells
2	Normal density of myelinated fibres, thinly myelinated and occasional demyelinated fibres	55% SD, 10% AD	FBP and C_3; blood vessels and perineurium	Not performed
3	Mild to moderate loss of myelinated fibres of all diameters, thinly myelinated fibres and "onion bulbs"	40% SD, No AD	Negative	Not performed
4	Mild loss of myelinated fibres, cluster formations, thinly myelinated and occasional demyelinated fibres	35% SD, 15% AD	FBP; blood vessels and perineurium	C_3 myelin sheath
5	Moderate loss of myelinated fibres, especially large diameter fibres, "onion bulbs"	85% SD, No AD	IgG: myelin sheaths and blood vessels	IgG myelin sheaths and blood vessels

*SD; segmental degeneration, AD; axonal degeneration, FBP; fibrogen breakdown products.

within areas of cellular infiltrates, on invading mononuclear cells, endothelial cells and Schwann cells.

Paraprotein levels

Serial paraprotein levels were determined in patients 1,2,3 and 5. In patients 1, 3 and 5 high paraprotein levels were associated with low disability scores. This may be explained by an apparent increase in the paraprotein level over time in these patients despite remission of the neuropathy. However, there was no statistically significant relationship between paraprotein level and disability score or duration of symptoms for any of the patients (Student's *t* test).

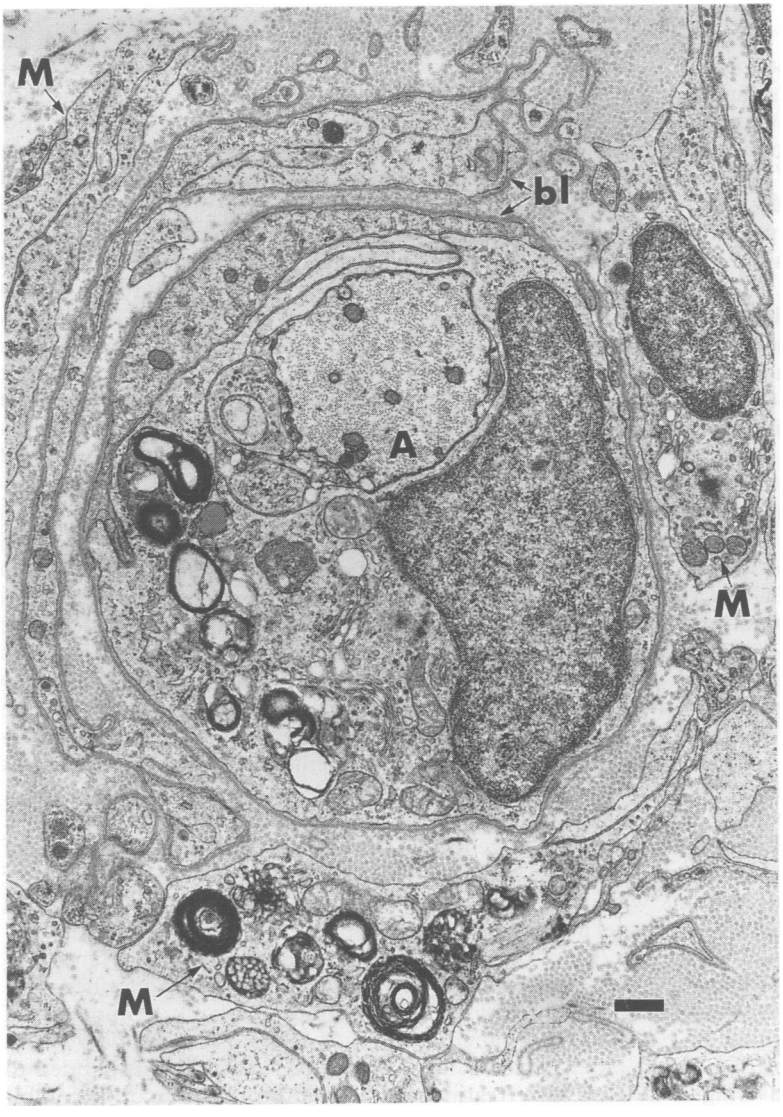

Figure 2 Electron micrograph of sural nerve from patient 3 showing typical macrophage mediated demyelination. An axon (A), has been demyelinated by a macrophage containing myelin debris. Other mononuclear cells (M) (without basal lamina) are in close proximity. Basal lamina (bl) of Schwann cell cytoplasm surrounds the engulfed axon and external to this another Schwann cell cytoplasmic process indicates early "onion bulb" formation. Bar = 1 μm.

Discussion

All patients had chronic symmetrical sensorimotor neuropathies of gradual onset with slowing of motor conduction velocities or conduction block or both. Histological studies demonstrated the presence of a primary demyelinating neuropathy in each case with perineural oedema, mononuclear cell infiltrates, segmental demyelination and evidence of remyelination. Immunohistochemical studies confirmed the presence of $CD4^+$ and $CD8^+$ T cells, macrophage/monocytes and MHC class I and II molecule expression, typical or inflammatory neuropathy.[8] In terms of the clinical features, CSF findings, electrophysiological studies and nerve pathology these patients fulfil the diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP); however, the accepted diagnostic criteria exclude patients with BMG.[11 12]

Table 3 summarises the cases of IgG BMG and peripheral neuropathy reported in the literature. Individual clinical details are available in less than half of these cases and in only a few are clinical details, electrophysiological studies and nerve biopsy findings all provided. Males outnumber females and kappa subtypes predominate as in our own series. The mean age at onset of symptoms in the reports summarised in table 3 was 57·3 years and in our patients it was 53·4 years; these findings support the contention of Yeung *et al.*[3] Paraproteinaemic neuropathy tends to occur in older age groups. Most of the patients have had a chronic progressive sensorimotor neuropathy; severe weakness with inability to walk or need for ventilation is more common amongst the IgG BMG neuropathy patients than amongst those with IgM BMG and peripheral neuropathy.[15 17 23 26] In contrast to the cases described by Yeung *et al*,[3] none of our patients had tremor. Remitting and relapsing clinical courses have been described.[2 3 14 15] Peripheral nerve biopsy has most commonly demonstrated a demyelinating neuropathy although mixed axonal degeneration and demyelination have been found in many of the

Table 3 Summary of the reported cases of IgG benign monoclonal gammopathy and peripheral neuropathy

Reference	*Number*	*M/F of cases*	*Age*	*Pathology*	*IF*	*Course and response to treatment*
Chazot, 1976[13]	3	2/1	60–74	"Sclerose endoneural"	positive	No details
Contamin, 1976[14]	1	M	53	Demyelination	—	Relapsing and remitting, steroid responsive
Read, 1978[15]	3	2/1	42–61	Mixture of axonal degeneration and demyelination	negative	Gradual spontaneous improvement
Kahn, 1980[4]	4	—	—	Demyelination in 2 patients	—	No details
Kelly, 1981[16]	9	—	—	No biopsy results	—	No details
Sewell, 1981[17]	1	M	53	Demyelination	positive	No details
Dalakas, 1981[18]	7	—	36–76	Not all patients biopsied, reduction in the numbers of large myelin sheaths	3/7 positive	4/4 patients responsive to immunosuppressive treatment
Ohnishi, 1981[19]	1	F	63	Mixed demyelination and AD	—	No details
Bosch, 1982[20]	1	F	57	Demyelination	positive	Responsive to treatment, plasmapheresis and immunosuppresive agents
Osby, 1982[21]	9	5/4	43–69	No biopsy results	—	No details
Powell, 1984[22]	3	2/1	39–61	Demyelination 2 patients, axonal degeneration in 1, micrangiopathy	—	No details
Sherman, 1984[23]	2	2/0	52, 72	Demyelination in 1 patient, mixed axonal degeneration and demyelination in the other		Responsive to plasmapheresis
Dalakas, 1984[24]	1	—	43	No biopsy results	—	No details
Johansen, 1985[25]	1	F	45	No demyelination, no other details	Negative	No details
Hafler, 1986[26]	3	3/0	35–61	No biopsy results	—	No details
Smith, 1987[27]	2	2/0	47, 64	Mixed axonal degeneration and demylination in 1 patient	—	1 patient responsive to plasmapheresis, the other unresponsive to immunosuppresion
Nemni, 1990[28]	1	F	73	Axonal degeneration	positive	No details
Gosselin, 1991[2]	24	—	58·8	No biopsy results	—	Predominantly slowly progressive, no treatment details
Yeung, 1991[3]	11	6/5	46–74	AD in 2/6, Mixed AD and demyelination in 4/6	6/6 negative	8 chronic progressive, 3 relapsing remiting 4/5 steroid responsive
Current series	5	2/3	43–73	Demyelination	4/5 positive	5/5 relapsing and remitting, responsive to immunosuppresion or plasmapheresis

patients[3 14 15 17 20 22 23 27] and purely axonal degeneration in three patients.[3 28] Positive IF has been reported in less than a third of the nerve biopsies examined with IF; IgG binding to peripheral nerve was found in all but one of the positive cases.[3 13 15 17 18 20 25]

Evidence of myelin/Schwann cell reactivity was found in 3 of our 5 patients by immunofluorescence; IgG deposition was found on myelin or Schwann cells in 2 patients, and in the third patient C_3 binding was observed on the patient's own nerve and on normal nerve when it was incubated in the patient's serum. This last finding was repeated on many occasions and became negative only when the patient was in remission. The finding of complement deposition without antibody may indicate undetectable amounts of antibody binding to the nerve and it is of interest as Koski[29 30] has consistently found evidence of complement fixing antibodies in all cases of Guillain-Barré syndrome and some cases of CIDP. Complement binding to peripheral nerve in CIDP has been previously reported[31 32] and Hays *et al*[31] have described complement deposition without antibody. Each of our three patients was exquisitely sensitive to plasmapheresis and the response to treatment would be consistent with a pathological role for antibody in these cases. Anti-myelin activity was not detected by ELISA or radioimmunoassay in the sera of our patients with IgG BMG and polyneuropathy nor in those previously reported patients when it has been sought.[25 26] A possible explanation for the discrepancy between the results of immunofluoresence studies and those of ELISA and immunoblot assays may be that for the latter 2 assay systems delipidated antigen is used in most laboratories. In nerve sections, however, other epitopes including those on lipid and lipoprotein structures will be present.

While the peripheral neuropathies associated with BMG are a heterogeneous group [1] those cases associated with IgM BMG whose paraproteins have anti-myelin associated glycoprotein (MAG) reactivity[33 34] demonstrate considerable clinical and morphological uniformity.[35 36] Gosselin, Kyle and Dyck[2] have recently reported the clinical and electrophysiological findings in a large series of patients with BMG and neuropathy and found that the type and severity of the neuropathy associated with IgM BMG did not differ significantly between patients with MAG positivity and those without. Evidence of a pathogenetic role for serum paraproteins in the development of polyneuropathy is strongest in those patients with IgM paraproteins and anti-MAG activity. In these patients the M proteins have specific antimyelin activity[33 35] and bind to a carbohydrate moeity common to certain glycoprotein and glycolipid components of peripheral nerve.[37] Despite much controversy the evidence now supports a pathogenetic role for serum paraproteins in MAG associated peripheral neuropathy.

Patients with polyneuropathy and IgG BMG may respond to prednisone alone[3 14 26] or prednisone in combination with other immunosuppressive agents.[18 20 24] Response to plasmapheresis alone or in combination with prednisone and other immunosuppressive agents has been reported in a small number of patients.[3 20 23 26 27] Response to treatment of patients with IgM BMG, anti-MAG reactivity and polyneuropathy has been variable, immunosuppressive treatment resulting in improvement in some [9 23 33 38 39] but not others.[26 40] Yeung *et al*[3] found that only a minority of patients with IgM BMG and neuropathy, with or without anti-MAG reactivity, responded to treatment with prednisone alone or in combination with other immunosuppressive agents.

In peripheral neuropathies associated with IgM paraproteins, some authors have found an association between clinical response and paraprotein levels, and have emphasised the need

to lower paraprotein levels by treatment.[23 38] There was certainly no evidence of paraprotein levels falling with remission of the neuropathy in our patients with IgG paraprotein, in fact the level tended to increase in 3 of the patients. Nevertheless, there may not necessarily be a strict relationship between serum levels of paraproteins and the intraneural level. The latter will depend upon other factors such as the permeability of the blood-nerve barrier. Inflammatory lesions involving the production of vasoactive amines and cytokines may considerably increase the permeability and allow more antibody access to myelinated fibres. Persistence of motor conduction velocity slowing despite clinical improvement is not surprising as conduction velocity measures the fastest conducting fibres and is not a good measure of the function of the whole nerve. Serial measurement of the amplitude of the CMAP may correlate better with recovery of motor function.

Our patients and many of the cases of IgG BMG associated polyneuropathy reported previously are clinically heterogeneous, and they display the electrophysiological, pathological and treatment responsive features of CIDP. The distinction between such cases of chronic demyelinating polyneuropathy and CIDP on the basis of an associated IgG BMG may well be artificial.[41]

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