

Table 1 Motor nerve conduction studies and response to IVIg in patients with multifocal motor neuropathy

Patient	Age at onset (years)	Sex	Duration of disease at first visit (years)	Motor nerve conduction studies			Nerves with possible axonal degeneration (dCMAP)	Response to IVIg (before→after IVIg)			Antiganglioside titres*	
				Total nerves tested	Nerves with CB (% of CB)			Rankin	ULDS	LLDS		
					Definite (AAEM)	Probable (AAEM)	Possible					
1	62	M	11	4	MCN L (56%)		UN R (85%)†, UN L (43%)‡	UN R (2.6) PN R (0.7), PN L (NR), UN R (0.1)	3→2	3→2	1→0	0
2	39	M	9	7	UN L (92%), MN R (61%)	UN R (45%), MN L (58%)‡			2→1	3→2	2→1	GM1 (1/640)
3	30	M	4	8	MN R (76%)		UN R (46%)‡, TN L (50%)†	UN L (2.8)	2→2	3→2	1→0	GD1a (1/5120 IgG)
4	21	F	5	8	UN R (93%), UN L (87%) MN R (60%), MN L (80%), PN L (60%)			RN L (NR), UN L (2.8), MN L (1.5)	3→1	3→2	2→0	0
5	47	F	4	7	MN R (62%)	UN R (42%)	MN L (41%)‡	None	2→1	1→0	2→2	0
6	53	M	19	10	TN R (81%)		UN R (54%)†, UN L (66%)†, MN L (60%)†, RN L (40%)†	MN R (0.2), UN R (1.8), PN R (0.4), TN L (0.1)	2→2	2→2	2→2	0 (IgM M protein)
7	25	F	1	5	MN L (50%)			UN L (0.5)	2→1	2→1	0→0	GM1 (1/640)
8	28	M	4	7	UN R (70%), UN L (99%), MN R (88%), MN L (93%), TN R (64%), PN R (52%)			None	3→3	3→3	2→2	0
9	48	M	3	10	RN R (58%), RN L (93%), UN R (53%), TN L (96%)			PN L (0.8)	2→1	2→0	2→2	0
10	43	M	8	6	MN R (89%)		UN R (39%)	None	2→1	3→2	0→0	0
11	36	M	4	10	MN L (96%)		UN R (61%)†	None	2→0	2→0	0→0	0
12	40	M	0.25	8	UN R (50%)	UN L (46%)		None	2→0	2→0	2→0	GD1a (1/1280)
13	29	M	0.25	6	UN L (52%)			None	2→1	2→1	2→0	0
14	34	M	10	6		MN R (40%)	RN L (36%)	UN L (NR)	2→1	3→2	0→0	0
15	25	F	25	8			MN L (42%)†	UN L (0.6 V)	2→1	2→2	0→0	0 (IgM M protein)
16	24	F	12	10			MN L (39%)	None	2→2	2→2	2→2	0
17	46	M	2	6			UN R (35%)	UN L (2.7), PN R (0.9), PN L (1.3)	2→1	2→0	2→1	GD1a (1/640), GM2 (1/327 680)
18	50	F	10	8			UN L (37%)	UN L (2.7), PN R (0.9), PN L (1.3)	2→1	2→0	2→1	GD1a (1/640), GM2 (1/327 680)
19	35	M	1	6			RN R (40%)†, UN R (34%), MN R (55%)†, MN L (44%)†	None	3→2	3→2	2→0	0
20	53	M	4	9			TN R (65%)†, TN L (43%)	None	1→1	2→1	2→1	GM1 (1/81 980), GD1a (1/10 240)
21	39	F	25	8				PN R (NR), RN L (NR)	3→3	3→3	3→3	0
22	46	F	20	6				UN L (0.5), MN R (NR), MN L (NR)	3→3	3→3	0→0	GM1 (1/640)
23	57	F	16	3				UN R (0.4), UN L (0.6), MN R (NR), MN L (NR)	3→3	3→3	0→0	0
								None	2→2	2→2	0→0	0

*IgM unless otherwise specified; †moderate temporal dispersion; ‡severe temporal dispersion. AAEM, American Association of Electrodiagnostic Medicine criteria; CB, conduction block; dCMAP, distal compound muscle action potential (mV); F, female; IVIg, high dose intravenous immunoglobulin treatment; L, left; LLDS, lower limb disability score; M, male; MCN, musculocutaneous nerve; MN, median nerve; NR, no response; PN, peroneal nerve; R, right; RN, radial nerve; TN, tibialis posterior nerve; ULDS, upper limb disability score; UN, ulnar nerve.

symptoms and their duration, type of progression (chronic progressive, stepwise, remitting), number and type of clinically affected motor nerves, predominant distribution of weakness (proximal versus distal, upper versus lower limbs), and presence, severity, and distribution of sensory symptoms and signs. Severity of the neuropathy was scored according to the following scales. (1) The Medical Research Council rating scale measures muscle strength in the 20 most affected muscles of the upper and lower limbs (maximal score of 100). (2) The modified Rankin disability scale¹⁴ scores 0 as no symptoms; 1 as non-disabling symptoms not interfering with lifestyle; 2 as minor disability leading to some restriction of lifestyle but with the patient retaining the ability to look after himself or herself; 3 as moderate disability significantly interfering with lifestyle or preventing fully independent existence; 4 as moderately severe disability preventing independent existence, although with the patient not in need of constant attention day and night; and 5 as total dependence, requiring constant attention day and night. (3) The functional impairment scales for upper and lower limbs¹⁴ score 0 as no symptoms; 1 as upper and lower limb symptoms without functional impairment (normal walk); 2 as some minor difficulties in manual activities or abnormal walking without support; 3 as inability to perform some manual activities or the ability to walk independently with support; 4 as inability to perform manual tasks or the need for help with walking; and 5 as total paralysis or being confined to a wheelchair.

Nerve conduction studies

In all patients nerve conduction studies were performed as reported previously¹⁴ in at least four motor nerves (range 4–10, mean 7.2) and two sensory nerves (range 2–7, mean 4.6) before any treatment and yearly during follow up. Motor CB was classified according to AAEM criteria⁵ as follows: (a) *definite*: presence of at least 50% or 60% reduction of proximal versus distal CMAP amplitude in the nerves of the upper and lower limbs, respectively, with minimal temporal dispersion ($\leq 30\%$ increased CMAP duration); (b) *probable*: presence of either at least 40% or 50% reduction of proximal versus distal CMAP amplitude in the nerves of the upper and lower limbs, respectively, with minimal temporal dispersion (see above) or at least 50% or 60% reduction of proximal versus distal CMAP amplitude in the nerves of the upper and lower limbs, respectively, with moderate temporal dispersion (31% to 60% increased CMAP duration).

In addition we defined *possible* CB as the presence of (a) at least 30% or 40% reduction of proximal versus distal CMAP amplitude in the nerves of the upper and lower limbs, respectively, with minimal temporal dispersion (see above), (b) at least 40% or 50% reduction of proximal versus distal CMAP amplitude in the nerves of the upper and lower limbs, respectively, with moderate temporal dispersion (see above), or (c) at least 50% or 60% reduction of proximal versus distal CMAP amplitude in the nerves of the upper and lower limbs, respectively, with severe temporal dispersion ($> 60\%$ increased CMAP duration).

Finally, *no overt* CB was defined as the presence of a lesser degree of CMAP amplitude reduction or the absence thereof.

In all patients the following electrophysiological parameters were also analysed: (a) the number of motor nerves with other features of demyelination: $> 30\%$ reduction of motor conduction velocities below the lower normal limits and $> 50\%$ increase of F wave and distal latencies above the upper normal limits when the distal CMAP amplitude was $< 80\%$ of the lower normal limits, or $> 20\%$ reduction of motor conduction velocities below the lower limit of normal and $> 20\%$ or $> 25\%$ increase of F wave or distal latencies, respectively, above the upper limit of normal when the distal CMAP amplitude was $> 80\%$ of the lower normal limit¹⁵; (b) the number of

motor nerves with possible signs of axonal degeneration, defined as the presence of 50% or more reduction of distal CMAP amplitude below the lower normal limits (nerves in which no motor response could be elicited were included in this category) associated with a neurogenic pattern on needle electromyography of corresponding muscle; and (c) the number of sensory nerves with reduced amplitudes or delayed latencies of sensory nerve action potentials.

Immunological studies

In all patients anti-GM1, anti-GM2 and anti-GD1a IgG and IgM antibodies were measured by enzyme linked immunosorbent assay (ELISA) before treatment according to a previously reported standard ELISA procedure.¹⁶ In all patients the presence of monoclonal gammopathy was investigated by standard agarose gel serum electrophoresis and characterised by immunofixation. Cerebrospinal fluid was examined in 18 patients for total protein concentration and cell count by standard procedures.

Assessment of response to intravenous immunoglobulin treatment

All patients were treated with intravenous immunoglobulin (IVIg) (Ig Vena, Farma Biagini, now Kedrion, Castelvécchio Pascoli, Italy or Sandoglobulin, Sandoz, Basel, Switzerland) at the initial standard dose of 2 g/kg over four or five consecutive days, followed by periodic maintenance IVIg infusions at a dose of 1–1.2 g/kg over two or three consecutive days at the time of clinical worsening. Response to IVIg treatment was assessed in all patients 8–10 days after each of the initial two or three IVIg courses and classified as follows: (a) consistent, with improvement by at least one point in the Rankin disability or in the upper or lower limb impairment scores, or of at least 20% in the upper or lower limb MRC sumscores; or (b) marginal, with improvement by at least 10% in the upper or lower limb MRC sumscores without changes in disability or impairment scores. Patients were subsequently examined during follow up initially every month then every two to three months before IVIg infusions. To decrease the frequency of IVIg infusions, oral cyclophosphamide was added for 12 patients at some time during the follow up for one to three years at a daily dose of 1.5–2 mg/kg and was subsequently adjusted (range 0.5–3 mg/kg/day) to maintain the white blood cell count between $3 \times 10^9/l$ and $3.5 \times 10^9/l$.¹⁷ One of these patients also received azathioprine and chlorambucil for at least six months each during follow up while another patient with an IgM monoclonal gammopathy had been treated for three years with chlorambucil 2.5–5 mg/day before starting IVIg.

RESULTS

Clinical features

With few exceptions, all patients fulfilled the clinical diagnostic criteria for MMN recently proposed for use in randomised trials.¹⁸ The only exceptions were disease duration at the time of the first visit at three months in two patients (patients 12 and 13, table 1); predominant lower limb involvement in three patients (patients 5, 9, and 17); proportional upper and lower limb impairment in five patients (patients 6, 12, 13, 19, and 20); and mild sensory signs in two patients (patients 8 and 18). None of these findings was deemed sufficient to exclude the clinical diagnosis of MMN.

In 14 of the 23 patients with clinically typical MMN (patients 1–14, table 1), nerve conduction studies found the presence of definite or probable CB according to the AAEM criteria in at least one motor nerve, while six patients (patients 15–20) had a possible CB in at least one motor nerve. In three patients (patients 21–23), no overt CB was detected in the motor nerves examined, although they all had some, usually minor, electrophysiological features consistent with segmental demyelination. In one (patient 21) no motor response was

Table 3 Response to IVIg treatment in patients with multifocal motor neuropathy in relation to the presence and degree of motor CB

	Patients with definite or probable CB (AAEM criteria)	Patients with possible CB	Patients without overt CB
Number of patients treated	14	6	3
Number that consistently improved	12 (86%)	4 (67%)	1 (33%)
In Rankin score	11	3	0
Mean Rankin scores before → after IVIg	2.2→1.2	2.2→1.7	2.7→2.7
In UL impairment score	12	3	0
Mean score before → after IVIg	2.4→1.4	2.3→1.7	2.7→2.7
In LL impairment score	6	3	–
Mean score before → after IVIg	1.3→0.6	1.8→1.2	0→0
By 20% in UL or LL MRC score	5	1	1
Mean UL MRC score before → after IVIg	75.8→87.3	79.5→88.5	57.3→63
Mean LL MRC score before → after IVIg	88.3→95.5	83.3→89.3	96.3→98.7
Number that marginally improved >10% in UL or LL MRC score	1 (7%)	1 (17%)	0

and degree of motor CB. Twelve patients with definite or probable CB (86%) and four patients with possible CB (67%) consistently improved after IVIg treatment, while an additional patient in both groups improved marginally (total patients improved 93% and 83%, respectively). The mean improvement in the Rankin, upper limb impairment, and MRC scores was also higher in patients with definite or probable than in those with possible CB but the difference was not significant. A consistent improvement in the upper limb MRC sumscores (27%) but not in the Rankin and limb impairment scores was observed after IVIg treatment in one patient without overt CB (patient 21). Another patient in this group (patient 22) had only slight improvement (7%) in the upper limb MRC sumscores; nonetheless, she reported a consistent improvement in her upper limb strength. Even though oral cyclophosphamide in some patients reduced the frequency of maintenance IVIg infusions,¹⁷ it did not seem to affect the degree of response to IVIg; however, this aspect was not specifically addressed.

DISCUSSION

Since the original descriptions of MMN,^{19,20} more than 300 patients with the disease have been reported on.³ In almost all these patients the presence of CB was considered a “conditio sine qua non” for the diagnosis of MMN despite some disagreements among authors on the degree of CB considered to be required for MMN. Therefore, the AAEM has proposed a set of criteria for the definition of definite and probable CB.⁵ Application of these relatively stringent criteria is probably useful for the inclusion of patients in treatment trials but it risks underestimation of the presence of CB in the early phases of the disease. This was clearly exemplified by one of our patients (patient 8), who initially presented with a 24% reduction of proximal versus distal CMAP amplitude without temporal dispersion in the right ulnar and median nerves. Two years later, as the patient became more severely affected, this increased to 70% and 88%, respectively.⁹ In other patients typical CB may decrease or even disappear in some nerves after several years of the disease because of a progressive reduction of the distal CMAP amplitude,¹² which may reflect either secondary axonal degeneration or the appearance of unrecognised very distal CB. These early or late features of CB, together with possible but often not observed very proximal or very distal CB, have been invoked as a possible explanation for the absence of CB in some patients with clinically typical MMN.^{10,11} Indirectly this hypothesis was supported in some of these patients by the same anti-GM1 antibody reactivity and response to immune therapies, particularly IVIg, as was observed in MMN.^{1,14,16,21–25} Therefore, some authors have questioned whether the presence of CB should be considered

a mandatory criteria for the diagnosis of MMN for patients with otherwise typical clinical presentation.^{10,11} In some of these patients “without” CB, a lesser degree of amplitude reduction than those required by the current diagnostic criteria were present, while in others no evidence of CB was found.^{10,11}

In this study we studied the clinical and immunological features and the response to immune therapy in relation to the presence and degree of motor CB in 23 patients with the typical clinical presentation of MMN. Fourteen of these patients had definite or probable CB according to AAEM criteria, six had possible CB defined as a 10% lesser degree of CMAP reduction than that required by AAEM for probable CB, and three had no evidence of CB according to these criteria. In accordance with a recently reported series of MMN patients with variable degrees of CB,¹² patients with possible CB were clinically and immunologically indistinguishable from those with probable or definite CB in terms of age of onset, progression, distribution and severity of limb weakness, and frequency of antiganglioside antibodies. In addition in our study over 80% of patients in both groups responded to IVIg, although improvement tended to be less pronounced and less frequent in patients with possible than in those with probable or definite CB, possibly reflecting their longer disease duration at the time of the initial treatment.¹³ On the other hand, patients without CB had a similar frequency of antiganglioside antibodies but, at the time of our first evaluation, they were older, had a longer duration and greater severity of the disease, and had more frequent signs of possible axonal impairment than patients with CB. While the latter difference may theoretically explain their less frequent and less intense response to IVIg, the limited number of patients in this group does not permit drawing definite conclusions. Similar findings were recently reported in a prospective study of 37 patients with a lower motor neurone disorder and electrophysiological evidence of CB or other features compatible with segmental demyelination.¹³ Although the inclusion criteria in that study did not specify a multineuropathic distribution of the motor deficits, thus possibly explaining why almost 20% of patients proved to have motor neurone disease at follow up, 70% of patients with definite or probable CB according to AAEM criteria responded to IVIg (84% in our series) compared with 50% of those without CB (56% in our series). These figures varied in relation to applied criteria of defined CB. Still, a variable proportion of patients not fulfilling any of these criteria responded to IVIg, while among patients with CB, lack of response to IVIg was often associated with long disease duration. The results of that and of the present study lend support to the opinion^{10–12} that the failure to fulfil the criteria for definite or probable CB proposed by the AAEM, in a patient with otherwise clinically typical MMN, should not preclude this

diagnosis and consequently a treatment trial with IVIg. In addition the consistent improvement after IVIg observed in one of our patients without CB and the subjective improvement reported by another patient suggested that multineuropathic presentation of a lower motor neurone disorder should alert the investigator to a potentially treatable motor neuropathy despite the absence of CB, particularly in patients with a long disease duration.

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