Immunosuppressive Treatment in Multifocal Motor Neuropathy

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We report the results of immunosuppressive treatments of 13 patients with multifocal motor neuropathy and elevated titers of serum antibodies to the GM1 ganglioside. All patients failed to respond to oral prednisone. There was no clinical response in 4 patients treated with plasma exchange. Nine patients received cyclophosphamide, with clinical improvement and fall in antibody titers in 8. In 3 patients, cyclophosphamide was discontinued with ensuing clinical relapse and rise in the titers of serum anti-GM1 antibodies. These patients provide further evidence for the efficacy of cyclophosphamide therapy in patients with multifocal motor neuropathy.

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Lower motor neuron syndromes can be divided into clinical subsets based on the patterns of weakness, electrodiagnostic abnormalities, and serum antiglycolipid antibody activity [1]. One such syndrome, multifocal motor neuropathy (MMN), is characterized by distal, asymmetrical weakness and conduction block on motor but not sensory axons [1–4]. High titers of serum antibodies to GM1 ganglioside are common in this syndrome [1, 2] and in acquired lower motor neuron syndromes in general [1, 5–9].

Individual patient reports suggest that MMN may respond to immunotherapy [2]. Cytotoxic medications such as cyclophosphamide may be useful in producing clinical improvement, that is, an increase in strength [2, 3]. In this study, we report our retrospective experience with the treatment of a series of 13 patients with a diagnosis of MMN. Our results show that prednisone treatment, even in high doses, is not often associated with clinical benefit in patients with MMN. In contrast, improvement in strength commonly occurs within 3 to 6 months after institution of cyclophosphamide therapy. Further, there is usually a correlation between clinical improvement and reduction of titers of anti-GM1 antibodies.

Patients and Methods

Patients

We studied the effects of immunosuppressive therapy in patients with MMN defined by clinical, electrophysiological, and immunological criteria (see Results). The features of 9 of these patients (Patients 1, 2, 6, 7, 9–13) have been outlined previously [1]. Three improved after cyclophosphamide therapy in that study. The patients with MMN reported here are all those examined and treated by us between January 1987 and June 1990.

Electrodiagnostic Studies

Electrodiagnostic studies were performed under standard conditions with attention to maintenance of skin temperature above 32°C. Conduction block in motor nerves was defined as a reduction in the ratio of proximal-to-distal compound muscle action potential (CMAP) amplitude to <0.70 when the ratio of the proximal-to-distal negative peak duration was <1.15 [10–12]. Abnormal temporal dispersion with or without conduction block was considered present when the ratio of proximal-to-negative peak duration was >1.15. Potential sites of nerve entrapment were taken into consideration when evaluating conduction block.

Determination of Serum Antibodies

Antibodies to gangliosides were assayed by enzyme-linked immunosorbent assay (ELISA) methodology as described previously [1]. Briefly, 400 ng of GM1 (Sigma Chemical, St Louis, MO) was adsorbed to wells of ELISA plates before the addition of test serums at dilutions of 1:50 to 1:100,000 for 5 hours at 4°C. Horseradish peroxidase–linked specific goat anti-human IgM or IgG was then added overnight, and color was developed for approximately 30 minutes until a standard positive control reached an optical density (OD) of 1.0 at 450 nm. Serum ODs were determined and titers calculated from a linear range of dilutions. Titers of serum IgM agonist GM1 ganglioside ≥ 350 are more than 4 SDs above the mean value in panels of normal control subjects [13]. A spontaneous fall of more than 60% in titers of IgM

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anti-GM1 antibodies occurs in less than 5% of untreated patients [14].

Quantitation of Motor Function

Strength testing was quantitated using the Medical Research Council (MRC) rating scale. MRC values were determined on each side for the following six muscles: deltoids, biceps, interossei, iliopsoas, quadriceps, and anterior tibialis. A patient was judged improved if strength increased in weak muscles of at least one extremity an average of one or more MRC grades. MRC values were also averaged for each patient, giving a strength index that could be followed over time.

Selective Patient Reports

Patient 6

A 63-year-old woman presented in 1985 with a 10-year history of progressive weakness. Bilateral thumb weakness was followed 5 years later by left finger extensor weakness, which progressed slowly to involve intrinsic hand muscles bilaterally. Neurological examination revealed asymmetrical atrophy and weakness in the upper extremities with greater involvement distally. Lower extremity strength was normal. Deep tendon reflexes were preserved. Sensory examination was normal. She was treated for 3 years with oral prednisone, up to 60 mg per day, but weakness progressed to include lower extremities and she became areflexic. Nine therapeutic plasma exchanges and intravenous methylprednisone (1 gm × 3 treatments) did not interrupt her decline. By the end of 1987, she was quadriplegic and was begun on intravenous cyclophosphamide (3 gm/M^2), followed 1 month later by oral cyclophosphamide (2 mg/kg/day). Within 4 months she began to regain strength, and after 6 months was ambulatory and had full use of her hands, at which time cyclophosphamide was discontinued. She remained stable for 1 year, but then noticed the return of thumb weakness. Oral cyclophosphamide (2 mg/kg/day) was restarted and within 1 month her strength returned.

Serum and urine immunofixation patterns and cerebrospinal fluid protein were normal. A sural nerve biopsy was normal. IgM anti-GM1 titer was 480 units before cyclophosphamide therapy and fell to 0 units over 15 months. As the antibody titer rose to 195 units, she had an exacerbation, and as the titer fell to 68 units with treatment, she went into remission. Sensory nerve conduction studies were normal. Motor nerve conduction studies showed conduction block with varying degrees of abnormal temporal dispersion (Fig 1).

Patient 5

A 35-year-old man presented with 1.5 years of weakness first affecting the grip of his right hand, then weakness of his right arm and left leg. He had no sensory complaints. Neurological examination revealed atrophy and weakness of the right hand and left leg. Reflexes were present and normal in the left arm and left knee, but decreased in the right arm and were absent at the left ankle. Sensory examination was normal. The patient was begun on prednisone, 60 mg per day for 3 months, but his weakness progressed. Intravenous cyclophosphamide (3 gm/M^2), followed by oral cyclophosphamide (2 mg/kg/day), was started. Improvement in strength occurred by 6 weeks and he has returned to work. His neurological examination has remained normal while he takes oral cyclophosphamide.

Serum and urine immunofixation patterns and cerebrospinal fluid protein were normal. Sural nerve biopsy was normal. IgM GM1 ganglioside titer was 398 units before cyclophosphamide therapy and fell to 50 units over 4 months. Sensory nerve conduction studies were normal. Motor nerve conduction studies showed conduction block.

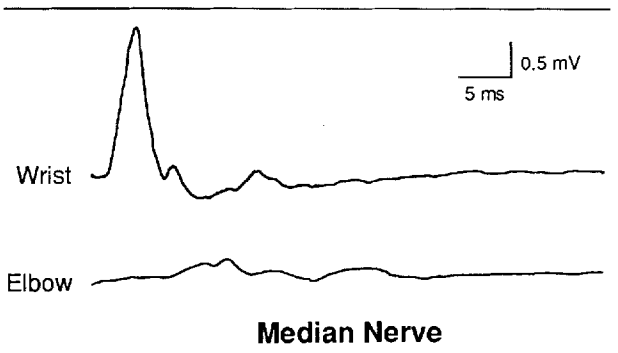

Fig 1. Median motor conduction study of Patient 6, demonstrating partial conduction block. The area of the median nerve response on elbow stimulation is <30% of the response on wrist stimulation.

Results

The clinical and electrophysiological profiles of the 13 patients are presented in Table 1. There were 9 men and 4 women, ages 30 to 66 years. All 13 patients had asymmetrical weakness, with prominent upper extremity involvement and a normal sensory examination. Reflexes were normal in 6 patients, decreased in 4 patients, and absent in 3 patients. Duration of symptoms ranged from 1 to 20 years. Eight patients had normal motor nerve conduction velocities, and 5 had mild slowing. All 13 patients had normal sensory-evoked amplitudes and conduction velocities. The striking finding in each patient was prominent multifocal motor conduction block with varying degrees of abnormal temporal dispersion, especially in the upper extremities (see Fig 1). Serum anti-GM1 antibody titers were high (≥350) in each of the patients.

All patients were treated with high-dose oral prednisone, many for extended periods, with no clinical response. In the 4 patients treated with only prednisone (Patients 1–4) there was no consistent change in anti-

Table 1. Clinical and Physiological Profile

Patient	Age (yr)/Sex	Duration of Symptoms (yr)	Motor Distribution[a]	Tendon Reflexes	Motor Conduction Studies	
					Velocity	Nerves with Block
1	69/M	3	UE > LE	+[a]	± slow	U
2	62/M	5	UE	+	WNL	U + M
3	47/M	2	UE > LE	0	slow M, otherwise WNL	U + M
4	66/F	8	UE + LE	0	WNL	U + M
5	35/M	1	UE + LE	+[a]	WNL	U + M
6	63/F	10	UE > LE	+[a]	± slow	U + M
7	55/M	3	UE > LE	+[b]	WNL	U
8	48/F	5	UE > LE	+	slow M, otherwise WNL	U + M
9	30/M	3	UE (left only)	+	slow U, otherwise WNL	U + M
10	43/F	1	UE	+	± slow	U + M
11	51/M	1	UE	+	± slow	U + M
12	61/M	20	UE > LE	0	WNL	multifocal
13	32/M	3	UE + LE	+[a]	± slow	U + M

[a]Absent ankle reflexes.
[b]Reduced in areas of severe weakness in arms.

UE = upper extremity; LE = lower extremity; WNL = within normal limits; U = ulnar; M = median; ± slow = two or more motor nerve conduction velocities at or within 10% of the lower limits of normal.

GM1 antibody titers. Titers increased in 2 patients and decreased in the 2 others. Four patients received plasma exchange without clinical benefit.

Nine patients received intravenous and follow-up oral cyclophosphamide treatment [2], with the major side effects of mild leukopenia and alopecia. Eight showed clinical improvement of at least one full grade on the MRC scale during the first 2 to 5 months of treatment. This was usually paralleled by reduced serum GM1 antibody titers, which decreased to an average of 67% of initial levels (Table 2). The percent change in titer, and not the absolute level of titer, correlated with changes in clinical course. Three patients relapsed after cyclophosphamide treatment was stopped. In all, anti-GM1 titers had risen toward pretreatment values. Two of these patients were retreated with cyclophosphamide with subsequent improvement in strength.

Sequential electrophysiological studies were performed on Patient 6. The progression of weakness was related to a progressive decline in the CMAP amplitude. The proximal/distal amplitude ratio was a poor predictor of strength because a disproportionate increase in the distal amplitude could result in a decreased ratio at a time that both amplitudes and strength were increasing (Fig 2).

Discussion

In this study, we followed the clinical status of 13 patients with MMN who were treated with immunosuppressive therapy. Our results suggest that prednisone is rarely an effective treatment for this syndrome. None of our patients with MMN improved during periods of treatment with prednisone alone. The 4 patients who were never treated with a cytotoxic medication all showed slow, continued progression during the 1 to 3 years of observation. The pattern of prednisone resistance of MMN is consistent with most reports of patients with asymmetrical motor neuropathy and motor conduction block [2, 3].

In contrast to the lack of response to prednisone, cyclophosphamide treatment was associated with improved strength in 8 of 9 patients with MMN. Improvement began in the 8 patients after 2 to 5 months of treatment. The eventual degree of increased strength in these patients was at least one MRC grade. One patient (Patient 6), who was initially quadriplegic, improved to normal strength in most muscle groups. In some patients, maintenance of immunosuppressive medications appeared necessary for continued control of the disease process. Three patients developed recurrent weakness 6 to 12 months after cyclophosphamide treatment was discontinued. Two of these patients were restarted on cyclophosphamide with improvement of strength. Treatment with cytotoxic medications has also been reported effective in other patients with lower motor neuron syndromes and high titers of anti-GM1 antibodies [1, 15, 16].

These experiences suggest that cyclophosphamide treatment may be effective in inducing and maintaining

Table 2. Therapeutic Response Profile

Patient	Prednisone[b]	Change in MRC Scale[a]		Anti-GM1 Titers			
		Plasma Exchange	Cytotoxic Medication	Pre-Therapy	During Therapy	% Reduction	Relapse
1	0 (60 × 4 mo)	−	−	114,250	60,800	47	. . .
2	0 (60 × 3 mo)	−	−	582	486	16	. . .
3	−1 (60 × 6 wk)	−	−	14,360	19,040	−33	. . .
4	0 (50 × 1 yr)	−	−	370	720	−94	. . .
5	0 (60 × 3 mo)	−	+1	398	50	87	. . .
6	−1 (30 × 3 yr)	0	+3	458	0	100	198
7	0 (60 × 4 mo)	−	+1	204,500	56,080	73	. . .
8	0 (80 × 4 mo)	−	+1	2,205	2,048	7	. . .
9	0 (80 × 5 mo)	−	+2	1,490	102	93	606
10	−1 (100 × 6 mo)	0	+2	3,880	908	76	. . .
11	0 (100 × 4 mo)	0	+2	1,535	395	74	996
12	0 (80 × 6 mo)	0	0	13,693	9,600	30	. . .
13	0 (60 × 2 mo)	−	+1	1,570	−	−	. . .

[a] −1 indicates loss of at least one MRC grade; 0, no change in MRC grade; +1 indicates improvement by 1 MRC grade, +2 by 2 MRC grades, and +3 by 3 MRC grades.
[b] Average dose of prednisone given on a daily basis.

MRC = Medical Research Council. (−) Indicates patient did not receive therapy or anti-GM1 titer was not measured.

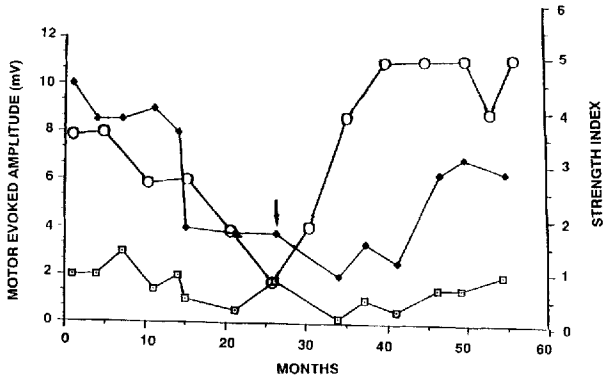

Fig 2. Relationship of changes in distal and proximal ulnar nerve motor-evoked amplitude and functional status during immunosuppressive therapy in Patient 6. Arrow *indicates initiation of cyclophosphamide treatment.* (—◆—) = *Distal ulnar motor-evoked amplitude;* (—□—) = *proximal ulnar motor-evoked amplitude;* (—○—) = *average MRC strength index.*

clinical remission of MMN. Spontaneous improvement is rare in patients with motor neuron disorders or motor neuropathies that are progressive for more than 1 year [1]. The percentage of patients in our study who improved after cyclophosphamide treatment, 88% (8 of 9 patients), is significantly greater ($p < 0.001$) than the 0% response to prednisone in the same patients. Overall, the clinical course was paralleled by changes in anti-GM1 antibody titers. These titers showed no consistent change during treatment with prednisone. Titers were reduced, however, by an average of 67% after cyclophosphamide therapy [14]. Most patients began to improve during the period when antibody titers fell below one-half of their initial levels. All 4 patients with improvement in strength of two or more MRC grades had a reduction in their anti-GM1 antibody titers of 70% or more. Measurement of anti-GM1 antibody titers is probably useful, not only for diagnosing MMN, but also for monitoring necessary and sufficient treatment during a trial of cyclophosphamide.

Our results provide more evidence that MMN is an immune-mediated process. The disorder differs, however, from typical chronic inflammatory demyelinating polyneuropathy (CIDP) [17, 18]. Patients with predominantly motor forms of CIDP [19, 20] usually have symmetrical weakness that involves proximal muscles early in the course of the disease. Although nerve conduction studies in patients with CIDP may show evidence of conduction block, there is often evidence of more diffuse demyelination of both motor and sensory axons. Changes in CIDP that occur in only a minority of patients with MMN include slowing (<70% of normal) of conduction velocities and prolonged distal latencies. A further difference between MMN and CIDP lies in their serum antibody reactivity. High titers of IgM anti-GM1 antibodies are common in patients with MMN, but rare in patients with CIDP [1]. A final contrast between the two disorders is their response to treatment. As has been reported for the overall population of patients with CIDP, those with motor CIDP usually demonstrate increased strength within a few months after treatment with

prednisone. This is clearly not the case for patients with MMN.

In summary, our results provide further support for the effectiveness of cyclophosphamide therapy in patients with MMN. Controlled trials would be useful to confirm this conclusion. Even if cyclophosphamide is efficacious, however, its toxicity limits the benefit:risk ratio, especially in patients with only mild disability. Trials of other medications with fewer side effects are also necessary.

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