

## LETTERS TO THE EDITOR

### Multiple sclerosis and hypertrophic demyelinating neuropathy

Exceptionally demyelinating lesions may occur in spinal roots and in peripheral nerves,<sup>1-5</sup> in multiple sclerosis (MS). A patient who satisfied criteria for clinically definite MS also developed hypertrophic demyelinating polyneuropathy identified by sural nerve biopsy.

A 24 year old white male mechanic with no personal or family history of relevant disease was admitted to hospital in June 1985 with diplopia, weak, numb legs and a sensation of oppression radiating girdlewise at the mid-thoracic level. He recovered without treatment within four weeks, but three months later again had numbness on the right side. On this occasion he was treated with adrenocorticotropic hormone (ACTH) and the symptoms disappeared.

In March 1986 he was admitted to our centre with weakness of the legs, accompanied by an urge to urinate. Clinical examination revealed horizontal nystagmus, asymmetrical paraparesis affecting chiefly the left leg, superficial hypoaesthesia on the right side below the level of dermatome T5, profound hypoaesthesia in both legs, enhanced knee reflexes and bilateral Babinski's sign. Examination showed normal CSF and CT scans, brainstem evoked potentials with waves IV and V missing bilaterally and visual evoked potentials with bilaterally increased latencies. ACTH treatment brought about almost complete recovery from leg weakness and profound hypoaesthesia.

He was again admitted to our centre in November 1988 after six weeks of progressive paraparesis with Lhermitte's sign. Examination revealed vertical nystagmus, asymmetrical paraparesis with marked weakness in dorsiflexion of the right foot, absence of the right knee reflex, right and left Achilles tendon reflexes, and bilateral Babinski's sign. T2 weighted MRI showed several areas of increased signal in the periventricular white matter of both cerebral hemispheres. Treatment for two weeks with intravenous methylprednisolone showed a marked improvement. He was sent home, and the following year took 150 mg oral azathioprine a day. During this time he had transitory reduction of visual acuity in the left eye and right hemifacial numbness from which he recovered in less than a week.

In May 1990, after five months without medication, he was admitted to our hospital for the third time with intense tetraparesis preventing eating and locomotion, and hypoaesthesia in both hands and feet. Clinical examination revealed predominantly distal tetraparesis, total lack of osteotendon reflexes and persistent Babinski's sign. No abnormality was detected by blood analyses (serotests were carried out for: syphilis, HIV, HTLV-1, Lyme disease, antinuclear antibodies, antiphospholipid antibodies; determination of B12 vitamin, folic acid, porphyrin metabolism, adrenal function and lead) or by urine tests for metachromatic bodies. HLA-A3 and HLA-B7 were negative. The protein content of CSF was 680 mg/l,

with 100 mg/l of IgG, but the cell count was normal. Visual and brainstem evoked potentials and MRI were similar to those recorded previously. Electroneuromyography revealed slow motor nerve conduction in all four limbs: right median was 41 m/s (normal 50-70), right ulnar 43 m/s (normal 50-70), left tibial 29 m/s (normal 40-60) and an absence of evoked response in the right common peroneal nerve; sensory conduction velocities and action potentials amplitudes were decreased: right median 45 m/s (normal 50-70) and 6.5  $\mu$ V (normal > 8), left sural 32 m/s (normal 50-70) and 2.5  $\mu$ V (normal > 5). A right sural nerve biopsy revealed that some fascicles exhibited slight fibre loss, with early onion bulb formation in occasional fibres, whereas others showed prominent hypertrophic neuropathy with abundant large bulbs and thin myelin sheaths (fig).

Demyelination was confirmed by examination of teased fibres, and a number of fibres with axonal degeneration ovoids were also observed. There was no vasculitis, amyloid or metachromatic material. The patient was treated with intravenous methylprednisolone and subsequently with oral prednisone. In May 1991 he maintained an acceptable condition and led an independent life with 30 mg a day prednisone.

This patient fulfilled the criteria for clinically definite MS. At the same time, histopathological examination of the sural nerve revealed demyelinating neuropathy. Nukada *et al*<sup>6</sup> have described a similar case of hypertrophic neuropathy with no inflammatory infiltrate and with different degrees of affection among the fascicles of the same nerve.

The combination of central and peripheral demyelination has previously been reported.<sup>2,3</sup> In 1987 Rubin *et al*<sup>3</sup> described two cases very similar to our patient, referring to them as cases of combined central and peripheral myelinopathy. CNS demyelination of the kind associated with MS has also been found in Guillain-Barré syndrome.<sup>1,4,5</sup> CNS myelin plaques like those produced by MS were observed, together with the demyelination and inflammatory infiltration of spinal roots, such as found in the postmortem examination of another patient with idiopathic acute demyelinating polyradiculoneuropathy.<sup>7</sup>

The chronology of our patient's case history suggests that the first bouts of symptoms were caused by CNS myelin lesions, but that the peripheral nervous system has been most affected in the past two years. The observed hypertrophic demyelinating neuropathy is quite different from neuropathies caused by compression or nutritional prob-

lems, and also from the subclinical neuropathies revealed by electrophysiological examination in a larger number of patients with MS.<sup>8,9</sup> It resembles chronic idiopathic demyelinating polyneuropathy, which can evolve either progressively or in recurrent bouts but generally responds well to corticotherapy. It has also been associated with subclinical signs of CNS white matter involvement on MRI.<sup>10,11</sup>

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### Chlorambucil fails to improve patients with motor neuropathies and antibodies to gangliosides

Evidence that an autoimmune mechanism may play a role in the pathogenesis of motor neuron syndromes has been emphasised by the presence of anti-gangliosides antibodies in some of these patients.<sup>1,2</sup> Recent data suggest that "high" levels of serum anti-GM1 antibodies are commonly found in some patients with a predominantly motor neuropathy that can mimic a motor neuron disease: the interest in identifying patients with such antibodies and progressive motor neuron syndromes lies in the fact that they may improve following immunotherapy.<sup>3</sup> We report three patients with multifocal motor neuropathy and serum antibodies to gangliosides. Immunosuppressive treatment with

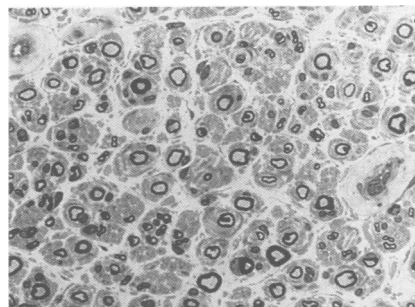


Figure Sural nerve biopsy, loss of myelinated fibres, thin myelin sheaths and presence of abundant onion bulbs (1 $\mu$ m toluidine blue stained,  $\times$  400).

Table Physiological and therapeutic response profile

Patients	Motor conduction studies			Anti-GM1 Titres before/after therapy	Manual Muscle Score before/after therapy	Simplified Barthel Index before/after therapy
	Velocity	Temporal dispersion	Conduction block			
1	NV	NV	M (0.6), U (0.4), P (0.5)	103/120	50/35	50/35
2	NV	NV	R (0), T (0.5), P (0.4)	630/612	135/140	55/55
3	NV	NV	NV	132/164	150/140	78/78

NV = at or within 15 % normal values.

U = ulnar, R = radial, M = median, T = tibial, P = peroneal.

Values in brackets are the ratios proximal/distal motor action potential area.

oral chlorambucil resulted in no significant improvement.

All patients had weakness and wasting, with electrophysiological evidence of denervation-reinnervation in one or more extremities that was not attributable to focal nerve or roots lesions. No upper motor neuron signs (bulbar dysfunction, spasticity, brisk reflexes) or cranial nerve dysfunction were seen. No patient had sensory signs or electrophysiological evidence of a peripheral neuropathy involving sensory fibres. Laboratory, enzyme and biochemical, including serum immunoelectrophoresis, CSF and neuroimaging studies were carried out to exclude other conditions which may cause motor neuron signs.<sup>3</sup>

Patient 1 was a 62 year old woman with asymmetrical tetraparesis who had progressive weakness, suggestive of a left sciatic neuropathy, for six years. She experienced cramps and fasciculations, right sciatic neuropathy for two years, and radial and median neuropathies for one year. The progression was not slowed by prednisone 1.5 mg/kg per day for five weeks. Examination revealed asymmetrical generalised weakness and muscle wasting, distal in the upper extremities (grade 3 to 4+) and distal greater than proximal in the lower extremities (grade 0 to 4). The tendon reflexes were decreased or absent. She was then given oral chlorambucil 0.15 mg/kg per day over a period of six months, without modifying the progression of the disability.

Patient 2 was a 67 year old man who had progressive weakness with wasting and cramps involving the right upper limb for four years. Two surgical explorations of the radial nerve were carried out, without evidence of entrapment. Six months before admission he developed cramps and weakness of his right lower limb. Examination revealed multifocal weakness, wasting and fasciculations in the distribution of the right ulnar, radial and axillary, left radial and right sciatic nerves. Reflexes were decreased or absent. The symptoms and signs were not modified by prednisone, 1.5 mg/kg per day for two months. He was then given oral chlorambucil 0.15 mg/kg per day for six months, without modifying the symptoms.

Patient 3 was a 37 year old man who experienced left hand clumsiness, progressive weakness and wasting with cramps of his forearm for two years. Examination revealed that left deltoid, biceps and triceps (MRC grade 4), wrist extensors and flexors (MRC grade 3), finger extensors and flexors and intrinsic hand muscles (MRC grade 0) were weak and amyotrophic, with active fasciculations throughout. Tendon reflexes were absent in the left upper limb. He was treated with chlorambucil, 0.15 mg/kg per day for 6 months, without improvement.

Strength testing was quantified using a manual muscle test score, based on the Medical Research Council scale. Flexion and

extension at the ankle, wrist, elbow, hip, knee, and shoulder abduction were tested bilaterally. The patient's ability to perform motor activities of daily living skills was rated using a simplified Barthel index. Motor function was tested at the start of oral chlorambucil and at one, three and six months apiece.

The presence of anti-GM1 antibodies in sera was measured before and after treatment by ELISA using purified ganglioside antigens, as previously reported:<sup>1</sup> titres greater than or equal to 100 units were considered as "high" in our laboratory.

Multisegmental motor nerve conduction studies were performed with percutaneous supramaximal stimulation while recording the compound muscle action potential with TECA 4 mm disc electrodes. Determination of conduction block and temporal dispersion was made based upon the criteria of Feasby *et al.* F-wave latencies from at least 10 responses were recorded following stimulation at the wrist or ankle. Using surface electrodes, sensory nerve action potentials were recorded orthodromically. Needle examination was performed using standard DISA concentric electrodes.

The physiological and therapeutic profiles of the 3 patients are presented in the table. All patients showed evidence of a multifocal neuropathy involving motor fibres but sparing of sensory axons. This was shown as asymmetrical and variable conduction block along motor axons in patients 1 and 2, prolongation of F-wave latencies and reduction of the CMAPs amplitude. Axonal loss was found in all patients, was prominent in patient 1, as shown by denervation potentials at rest, and voluntary motor unit potentials indicative of chronic denervation-reinnervation.

Relative strength and simplified Barthel index measurements were not improved and both parameters declined or were stabilised over time. By ELISA assay, the levels of anti-GM1 measured after treatment with chlorambucil were not modified.

Treatment was well tolerated, without haematological side effects but patients 1 and 2 developed transient haemorrhagic cystitis.

Our study was designed to assess the efficacy of chlorambucil in the treatment of multifocal motor neuropathy syndrome presenting as a progressive, multisegmental weakness with wasting, fasciculations and cramps and anti-GM1 antibodies. Our patients were similar to several previously reported cases of selective motor neuropathy, with or without electrophysiological evidence of conduction block.<sup>2,5</sup> Recent data have suggested that antibody responses to gangliosides are probably T-cells independent responses of B cells and that prednisone is ineffective in suppressing antibodies.<sup>2,5</sup> Cyclophosphamide has been shown to be effective but in view of the danger of serious toxicity, therapy with this agent is limited.<sup>5</sup>

We therefore elected to use chlorambucil, an immunosuppressive drug with some B cell specificity but with fewer side effects.

Clearly, our results demonstrate that chlorambucil is not an alternative drug that can be recommended. Chlorambucil lacked a therapeutic effect as judged in the absence of improvement in the manual muscle test score and simplified Barthel index. Moreover, chlorambucil did not reduce significantly the titre of anti-GM1 antibodies. The duration of therapy seems to have been sufficient in our cases, because improvement in strength began within two to five months in the reported improved patients.<sup>5</sup>

In summary, we feel that the use of chlorambucil is not effective in patients with lower motor syndrome and anti-GM1 antibodies. Whether other regimes of immunosuppression other than cyclophosphamide or the administration of parenteral immunoglobulins that have been shown to be effective in other neuropathies, such as chronic inflammatory demyelinating polyneuropathy should be used, remains to be investigated.

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#### Unilateral vestibular paralysis as the sole manifestation of mumps

A 36 year old man noted sudden rotational vertigo with nausea, vomiting and postural imbalance. The next day clinical and electro-oculographic findings confirmed a left vestibular paralysis. There was spontaneous horizontal-rotatory (counterclockwise) nystagmus to the right enhanced by Frenzel's lenses and increasing on gaze to the right. Stance and gait were unsteady with a tendency to fall to the left. The left horizontal semicircular canal was unresponsive to stimulation with warm (44°C) and cold (30°C) water. The audiogram was normal.