LETTERS TO THE EDITOR

Chronic progressive motor polyneuropathy after ganglioside treatment

Autoantibodies against ganglioside GM1 are associated with selective motor nerve involvement in motor neuropathy, lower motor neuron syndromes, amyotrophic lateral sclerosis, sensorimotor neuropathies, and acute axonal Guillain-Barré syndrome.^{1,2} On the other hand, gangliosides from bovine brain are used to treat various neurological disorders. Adverse reactions resembling Guillain-Barré syndrome or motoneuron disease with high antibody titres against gangliosides after ganglioside treatment have, however, been reported.^{3,4} In similar cases published recently ganglioside antibodies were not studied.⁵ We present a patient who developed a chronic progressive motor polyneuropathy associated with a high titre of serum ganglioside GM1 antibodies after treatment with gangliosides.

A 39-year-old woman with neither family history of neurological disease nor history of drug abuse or exposure to neurotoxins developed progressive pain and weakness of her right thumb and atrophy of thenar muscle over a period of 14 months and was diagnosed as having carpal tunnel syndrome. After operation, weakness of her right hand persisted. She was given bovine brain gangliosides (Cronassial) intramuscularly every other day for three weeks in a total dose of 80 mg. Ganglioside treatment was discontinued when she started to feel ill. During the next six weeks she developed pain, progressive and ascending weakness and muscle cramps in her legs and later in her hands. She lost 6 kg body weight and had outbreaks of sweat and disturbed sleep. Micturition and bowel function were normal.

On admission, there was symmetrical and distal dominant muscular weakness in all four extremities, more pronounced in the legs. Tendon reflexes could not be elicited and the plantar responses were flexor. Sensory nervous function, mental state, speech, pupil reaction, and cranial nerve functions were intact. There were no fasciculations, and except for right thenar atrophy the bulk of proximal and distal muscles of all four limbs seemed normal. Nerve conduction studies disclosed a decreased compound muscle action potential (CMAP, 2.5 mV) in the right ulnar nerve and a slightly prolonged distal latency (5.0 ms) in the right peroneal nerve, whereas motor nerve conduction velocity was normal.

Electromyographic examination of upper and lower extremity muscles revealed polyphasic potentials (4-6 mV) of prolonged duration and a reduced recruitment pattern during maximal effort, indicative of a neurogenic lesion. Fibrillations in the tibialis anterior muscle were suggestive of axonal damage. Serum creatine kinase activity was slightly raised (91 IU/l). Cerebrospinal fluid protein concentration was increased (134 mg/dl). There were three mononuclear cells/mm³. No oligoclonal bands were found in CSF or in serum. Common causes for polyneuropathy

such as metabolic disorders, nutritional deficits, impairment of liver or renal function, collagenosis, neoplasia, paraproteinemia, and infection (for example, *Campylobacter jejuni* enteritis), and other causes of muscular weakness were ruled out.

The patient was treated with a series of plasma exchanges, leading to a good clinical recovery within one month. During the next two months, however, she again developed symmetrical and distal dominant muscle weakness as well as pronounced atrophy. Nerve conduction studies of the left peroneal nerve revealed a considerably decreased and dispersed CMAP (1.5 mV), a prolonged distal latency (6.0 ms), and normal motor nerve conduction velocity; sensory nerve conduction studies gave normal results; the F-wave response in the left median nerve was absent. The patient responded to daily treatment with 40 mg methylprednisolone and 150 mg azathioprine with a significant stabilisation of muscle strength within four weeks and steroids were tapered during the next seven months. One year after the last steroid medication there was a significant relapse of neuropathic disease that responded again to steroids.

During the following stable period the patient became included in a screening programme for patients with neuropathy. This involved measurement of serum ganglioside GM1 antibodies by enzyme-linked immunosorbent assay.² Titres were determined by serial twofold dilution of test serum in triplicate and were expressed as the mean reciprocal value of the highest serum dilution that gave a positive, specific (above background without ganglioside GM1) absorbance reading. Twenty eight months after ganglioside treatment had ended very high antiganglioside GM1 IgG (200 000) as well as increased IgA (6400) and IgM (3200) titres were detected in serum from the patient in comparison to mean titres in 26 patients with Guillain-Barré syndrome (IgG, 250; IgA, 140; IgM, 100) and in 20 normal, untreated controls (IgG, 200; IgA, 40; IgM, 120). The patient's IgG binding to ganglioside GD1b was 2% of that to ganglioside GM1; no binding to gangliosides GD1a and GT1b was detected. Over the next 15 months ganglioside GM1 antibody titres decreased by 75%. Repeated intravenous immunoglobulin (0.4 g/kg body weight/day for five days) again improved the patient's strength and steadiness. For the first time in three years she was able to run and to climb stairs without the support of her arms.

In conclusion, after treatment with bovine brain gangliosides, our patient developed a slowly progressive axonal form of pure motor polyneuropathy with massive muscle atrophy and distal accentuation, symmetrically affecting all four extremities. As the clinical course and symptoms as well as electrodiagnostic results do not support the diagnosis of a Guillain-Barré syndrome or amyotrophic lateral sclerosis-like disease, this neurological disorder seems to differ from those reported after ganglioside treatment.^{3,4} The immune response in our patient was antiganglioside GM1, similar to the case of Latov *et al.*,³ whereas Yuki *et al.*⁴ found increased antiganglioside GM2. Distinct antibody reactivities against different ganglioside epitopes seem to relate to different types of disease also without ganglioside treatment; ganglioside GM1 specific

antibodies occurred most often in multifocal motor neuropathy and distal dominant lower motor neuron syndromes.¹

Several points argue for the possibility that the ganglioside preparation given may have triggered or contributed to the development of polyneuropathy in our patient: (1) the start of ganglioside treatment was followed within weeks firstly by a severe feeling of illness and then by the onset of neuropathy; (2) remarkably high, antiganglioside GM1 (predominantly IgG) titres were seen around two years later strongly suggesting active immunisation; (3) the patient repeatedly responded to immunomodulatory therapies. Therefore, in support of others,^{3,4} our findings indicate that in some patients there may be a causal link between parenteral ganglioside administration and neurological disease via immune mechanisms. Thus the possible risk involved in the therapeutic use of gangliosides should be carefully considered.

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Hereditary multiple exostosis with spinal cord compression in a 13-year-old boy

Multiple exostosis is one of the most common bone dysplasias. The disorder is characterised by exostosis arising in the metaphysis of the long bones.^{1,2} Growth disturbance or malignant transformation to chondrosarcoma are rare but well recognised.³ Neurological symptoms are rare and are usually caused by direct compression of a peripheral nerve, nerve root or, less often, the spinal cord.

We report the case of an otherwise healthy boy (the second of three children) known to have familial (four generations of affected family members) multiple exostosis. He was examined at the age of 13 years, six months after the onset of a slowly progressive left-sided weakness.

The boy could walk independently and move both arms and legs without difficulties except for heelwalking on the left foot. There was mild left-sided weakness predominantly in the upper limb. He had exaggerated tendon reflexes in the left arm and leg and a left ankle clonus. The Babinski sign was bilaterally extensor. Reduced tactile gnosis in the left palm with compromised two-point discrimination and a reduced contralateral perception of hot and cold below the level of the lesion (indicating a Brown-Sequard syndrome) was detected. There was discrete muscular atrophy of the left lower limb.

CT and MRI of the upper spine showed pronounced compression of the spinal cord at the CII–CIII level by an invading exostosis (figs 1 and 2). Medial laminectomy of CII and CIII with extirpation of the exostosis as well as the posterior arches of CII and CIII was carried out in order to prevent the patient from developing tetraparesis. PAD showed a cartilaginous exostosis. Spasticity was still present two days after the operation but discrimination between hot and cold was normal and the extensor Babinski sign of the right foot had disappeared. The tendon reflexes were exaggerated in the left arm but tactile gnosis was normal. The Babinski sign was still extensor in the left foot. One year after the operation left hand function was not fully restored and reduced muscle mass was noted. At present, two years after the operation, the boy has no significant disability but there is still slight recognisable left-sided weakness.

Multiple cartilaginous exostosis has variable expression. Eighty percent of cases have been diagnosed before the age of 10 years. The exostosis continues to grow until puberty and generally becomes apparent before the age of 30. Occasionally neurological deficits appear and when the spine is involved the complications can be serious. A cervical location of the exostosis dominates among the reported cases.^{3–5} We have found 17 published cases similar to the present one. The 15 who underwent surgery improved but only four recovered completely.⁶ The potential danger of the condition is illustrated by the fact that two patients died before operation. Altogether 14 patients had symptoms indicating spinal cord compression and 12 of these had symptoms from both the spinal cord and roots. The reported case serves to show that spinal cord compression may occur in hereditary multiple exostosis in adolescence and that early signs of spinal cord and root compression warrant a full radiological examination with the aim of performing surgery. CT is useful in revealing the origin

Figure 1 CT revealing the exostosis emerging from the left aspect of the inner vertebral arch (CII–CIII).

Figure 2 MRI depicting the spinal cord and the location of the compression.

and extent of the problem but is not optimal, whereas MRI is superior in visualising spinal cord compression.

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Bilateral tarsal tunnel syndrome

A 52-year-old female school teacher with a positive history of hypertension presented with "sensation of heat" in distal parts of both soles for the past four months. This paraesthesia was accompanied in both feet by "electrical shocks" extending from the plantar arch to the tip of all toes and by occasional nocturnal numbness. No foot trauma, no precipitating factor, or relation to exertion or walking were reported. The patient had been helping herself by bathing her legs in cold water for 10 to 15 minutes, drying, and applying softening cream. This reportedly resulted in a complete relief of symptoms for about four hours.

On examination there were no signs of wasting or weakness of the small foot muscles. There was hypoaesthesia to pin-prick in the region of the medial and lateral plantar nerves. Tinel's sign was positive on the medial aspect of both ankles. General neurological state was normal. No abnormality of ankles and feet could be detected radiologically. Electrophysiological evaluation of both posterior tibial nerves showed a prolonged distal motor latency (6.6 ms) on the right and normal latency (4.9 ms) on the left side (normal distal motor latency range from the ankle to the abductor hallucis is 2.9–5.3 ms). There was no right medial plantar sensory action potential, whereas the amplitude of the left one was 0.3 μ V (normal 0.3–3.7 μ V) and sensory conduction velocity was mildly decreased (32 m/s; normal 35–48 m/s). Denervation activity in both abductor hallucis muscles was recorded by concentric needle electromyography. Thus clinical and neurophysiological findings indicated a diagnosis of bilateral tarsal tunnel syndrome.

Relief of symptoms was achieved after infiltration of 2% xylocaine behind the right medial malleolus.

The patient underwent two separate surgical procedures: firstly, an S-shaped incision was made behind the right medial malleolus to expose the posterior tibial nerve. The right posterior tibial nerve was compressed by an arcade of small branches of the tibial posterior artery, which were cut with bipolar coagulation. A 3 cm long segment of the posterior tibial nerve, thickened and firm on palpation, was separated from the epineurium under a microscope. Surgery on the other leg followed one week later when considerable relief of symptoms was confirmed on the operated leg. The left posterior tibial nerve was thickened and firm on palpation in a length of about 2 cm. In a microscopic surgical procedure, epineurectomy, proximal and distal explorations were performed. No further abnormality that could have been the cause of the nerve compression was found. After both surgical procedures there was a complete relief of symptoms.

Tarsal tunnel syndrome characterised by entrapment of the posterior tibial nerve beneath the flexor retinaculum was first reported by Lam and Keck.^{1,2} Tarsal tunnel syndrome after an acute proximal process not affecting the ankle is rare. The role of ischaemia or traumatic proximal nerve damage causing greater susceptibility of the posterior tibial nerve has been discussed.^{3,4} Some other causes for tarsal tunnel syndrome have also been considered.⁵ To our knowledge, no other case of bilateral tarsal tunnel syndrome has yet been reported.

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