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References


Chronic Relapsing Axonal Neuropathy: A First Case Report

Elisabeth Chroni, MD,* Susan M. Hall, DSc,† and Richard A. C. Hughes, FRCP*

A relapsing and remitting axonal polyneuropathy developed in a woman at age 47. Serial electrophysiological studies showed that the amplitudes of compound muscle action potentials and sensory action potentials were reduced but conduction velocities were only mildly slowed. F wave latencies were normal and there was no evidence of conduction block. Two sural nerve biopsy specimens showed changes supportive of axonal neuropathy. Repeated responses to prednisolone alone and later prednisolone and azathioprine suggested that inflammatory, possibly autoimmune, processes were important in this case of chronic relapsing axonal neuropathy.


Idiopathic chronic axonal polyneuropathy is usually insidiously progressive [1]. We report a woman with a

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chronic relapsing disorder responsive to immunosuppressive treatment that clinically resembled chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), in whom repeated nerve conduction studies and two nerve biopsy specimens suggested an underlying axonal polyneuropathy. It has been suggested that an acute axonal neuropathy can be reversible and mimic Guillain-Barré syndrome (GBS) [2]. We propose that a chronic relapsing axonal neuropathy (CRAN) may resemble CIDP.

**Patient History**

In June 1985 a 50-year-old woman was referred for complaints of progressively impaired sensation in the limbs, trunk, and face for 3 years and muscle weakness of the limbs for 2 years. Over the same period the patient had gradually lost 10 kg. She had had a laminectomy in 1975 for left sciatica and a hysterectomy in 1979 for fibroids. There was no history of exposure to drugs or neurotoxins or of abuse of alcohol. Her sister had had an acute episode of paralysis in her 20s, and a hysterectomy in 1777 for fibroids. There was no history of exposure to drugs or neurotoxins or of abuse of alcohol. Her sister had had an acute episode of paralysis in her 20s, and a hysterectomy in 1777 for fibroids. There was no history of exposure to drugs or neurotoxins or of abuse of alcohol.

Neurological examination revealed mild bilateral facial weakness and impairment of taste. The other cranial nerves were normal. There was mild wasting of intrinsic hand muscles, global weakness of the upper extremities (grade 5 to 4 on the Medical Research Council scale), and slight weakness of hallux dorsiflexion and hip flexion (grade 5 – 4). Except for the left ankle jerk the tendon reflexes were present and the plantar responses were flexor. There was subjective impairment of pain perception in the four limbs but light touch and temperature sensation were normal. Vibration and joint position sense were normal except for in the left hallux. Coordination was normal. Findings on general examination were unremarkable.

Results of the following laboratory tests were either normal or negative: full blood cell count; erythrocyte sedimentation rate; renal and liver function; serum protein electrophoresis; creatine kinase, rheumatoid factor, thyroxine, vitamin B₁₂, and folate acid concentrations; urine porphobilinogen level; and chest x-ray and barium meal studies. Antinuclear antibodies showed a diffuse pattern at 1:160 but all other autoantibody titers including anti-DNA and antinuclear protein were negative. The cerebrospinal fluid (CSF) was acellular with 150 (normal, 100–400) mg of protein/liter.

Motor conduction studies of median, ulnar, peroneal, and tibial nerves demonstrated a reduction in the size of the compound muscle action potentials (CMAPs); velocities were either normal or slowed proportional to the reduction of CMAP amplitudes. There was no evidence of conduction block in any of the nerves. In all tested nerves, F wave minimum latency, F chronodispersion, and F persistence were normal. The sensory-evoked potentials (SAPs) were of low amplitude with normal conduction. In follow-up studies the amplitudes of the SAPs gradually fell while those of the CMAPs fluctuated. Motor and sensory conduction velocities remained either normal or slightly slowed (Table). The needle electromyographic examination of distal and proximal muscles in the upper and lower limbs showed evidence of denervation and reinnervation.

Sural nerve biopsies were performed in 1985 (on the left) and in 1988 (on the right). Both specimens were examined by light and electron microscopy and showed a mild reduction in myelinated fibers, many regenerating clusters, and occasional fibers undergoing wallerian degeneration. In 1988 teased preparations showed that 40% of 81 fibers had short internodes (< 400 μm) and inappropriately thin myelin sheaths, consistent with regeneration following axonal degeneration. There was no evidence of inflammation or segmental demyelination. After the initial evaluation, the condition slowly continued to deteriorate for another year, despite treatment with prednisolone, 100 mg, on alternate days for 5

### Serial Nerve Conduction Studies

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<td><strong>Motor</strong></td>
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<td>Median N</td>
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<td>Amp (mV)*</td>
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<td>46</td>
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<td>FLmin (msec)</td>
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<td>0.6</td>
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<td>D lat (msec)</td>
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*Distal/proximal amplitude of the CMAP is provided when available.

Amp = amplitude; D lat = distal latency; M-CV = motor conduction velocity estimated by the CMAPs; FLmin = F wave minimum latency; CV = conduction velocity; blank = not measured; CMAP = compound motor action potential.
months. Later the disease pursued a chronic relapsing course, responding to the immunosuppressive drugs prednisolone and azathioprine (Fig). Significant reduction and eventual withdrawal of steroids resulted, within 3 to 4 months, in relapses in which the sensory and motor deficits increased. Each time improvement occurred 1 to 4 months after the reestablishment of high doses of prednisolone. At the time of writing, the condition was stable with azathioprine alone following withdrawal of steroids 4 months previously. During the 9-year follow-up, sensory impairment developed in a glove-and-stocking distribution. The muscle power was consistently more reduced in the upper than the lower limbs, being as low as grade 3 in the small hand muscles. The tendon reflexes became diminished or absent. On the last review in February 1994 there was mild bilateral facial and upper limb weakness but normal strength in the legs. She was hypesthetic to pinprick and light touch below the mid forearms, the right knee, and the left hip. Two-point discrimination was severely affected in the fingers and soles of both feet. Vibration sense was impaired at the big toes but joint position sense was normal. Coordination was normal.

Discussion

Our patient's illness superficially resembles CIDP. The initial symptoms evolved gradually over a period of more than 2 months. There was proximal and distal muscle weakness affecting all four limbs symmetrically as well as facial weakness, and the tendon reflexes were either absent or diminished. Superficial and proprioceptive sensations were impaired in a glove-and-stocking distribution. Extensive investigations did not reveal any concurrent illnesses such as cancer, diabetes, or monoclonal gammopathy. Treatment with steroids and azathioprine was beneficial and relapses of the disease occurred when steroid therapy was severely reduced or withdrawn. However, the electrophysiological and pathological hallmarks of CIDP [3–5] were missing. Although CIDP is considered to be a primary demyelinating neuropathy, electrophysiological or pathological evidence of axonal pathology is often present but considered to be secondary or superimposed [6–8]. We consider that the results of serial electrophysiological and pathological studies in our patient and the normal CSF protein level argue for a primary axonal neuropathy.

The idea that an axonal neuropathy can remit derives support from the presentation of children in China with "acute motor axonal neuropathy," an illness clinically indistinguishable from GBS, which eventually re-

Disease progress over a representative period of 3 years assessed by Medical Research Council (MRC) sum score in relation to treatment. MRC sum score is the summation of MRC scores of the following muscle groups: shoulder abductors, elbow flexors, wrist extensors, first dorsal interossei, hip flexors, knee extensors, and ankle dorsiflexors.
mits [2]. If remission from acute axonopathy can occur once, it is reasonable to propose that an axonopathy can pursue a relapsing-remitting course. Our patient with chronic, relapsing, axonal corticosteroid-dependent polyneuropathy that clinically resembled CIDP appears to have the chronic equivalent of acute axonal neuropathy.

We found one report in which a similar idea was proposed: The authors considered that their 6 patients with chronic progressive and/or relapsing polyneuropathy (2 with acute and 4 with subacute onset) had an axonal rather than demyelinating pathogenesis [9]. However, the pathological findings in their patients included 10 to 20% of fibers that were remyelinated and segmental remyelination was depicted. Furthermore, the electrophysiological findings included severely slowed conduction in at least one nerve segment in each patient.

We preferred to use the designation "CRAN" rather than "axonal CIDP" since despite the clinical resemblance to CIDP, there was no laboratory evidence indicating a common pathophysiological mechanism. The efficacy of immunosuppressive treatment suggests an immune pathogenesis in which the axon rather than the myelin is the target of autoimmune reaction.

The favorable response to treatment in our patient tentatively suggests that a trial of immunosuppressive treatment should be considered for patients with chronic idiopathic axonal neuropathy. It is difficult to identify features that might predict a treatment response but the presence of facial weakness and predominant upper limb involvement in our patient might be useful indicators.

References

Neuroprotective Effects of Gangliosides May Involve Inhibition of Nitric Oxide Synthase

Ted M. Dawson, MD, PhD,‡ Kenneth Hung, BS,† Valina L. Dawson, PhD,‡ Joseph P. Steiner, PhD,‡ and Solomon H. Snyder, MD‡§

Gangliosides are polar, sugar-containing lipids that are major constituents of neuronal membranes. Gangliosides are neuroprotective in animal models of neurotoxicity and may also be useful in patients with clinical conditions such as spinal cord injury. We show that a series of gangliosides inhibit nitric oxide synthase activity by binding calmodulin. The prevention of glutamate neurotoxicity in cortical cultures by gangliosides closely parallels their potencies in binding calmodulin and inhibiting nitric oxide synthase. Neuroprotective effects of gangliosides may arise from blockade of nitric oxide formation.


Gangliosides block glutamate neurotoxicity in neuronal cultures as well as in intact animals [1]. They reduce neuronal damage following middle cerebral artery ligation and prevent neurotoxicity in rodents and monkeys following treatment with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which selectively destroys dopamine neurons [2–4]. Clinical efficacy of gangliosides has been demonstrated in spinal cord injury [3–5] and beneficial effects may occur in vascular stroke and subarachnoid hemorrhage [2]. Re-

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