

SHORT REPORT

Chronic inflammatory demyelinating polyneuropathy associated with carcinoma

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Abstract

The association of chronic inflammatory demyelinating polyneuropathy (CIDP) and carcinoma has rarely been reported and its relevance is debated. Thirty three consecutive patients with probable or definite CIDP (idiopathic or associated with M protein) were investigated. Three patients with definite CIDP had a concomitant carcinoma. One had an IgM paraprotein. Steroids and intravenous immunoglobulins were effective.

(*J Neurol Neurosurg Psychiatry* 1996;60:188-190)

Keywords: chronic inflammatory demyelinating polyneuropathy; cancer; paraneoplastic neurological syndrome; monoclonal gammopathy

A wide range of peripheral neuropathies have been reported as remote effects of cancer.^{1,2} At present, only subacute sensory or motor neuropathies are well established paraneoplastic syndromes.³ Sensorimotor neuropathies associated with cancer are a heterogeneous group.¹ Among them, primary demyelinating neuropathies have rarely been reported. We describe carcinoma in three patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

Materials and methods

We investigated 33 consecutive patients with probable or definite CIDP using the criteria of the ad hoc Subcommittee of the American Academy of Neurology.⁵ Eighteen had idiopathic CIDP, one systemic lupus erythematosus, 11 IgG or IgM monoclonal gammopathy, and three a carcinoma.

Laboratory studies included chest radiography, biological tests as recommended by the ad hoc committee,⁵ and search for anti-GM1 antibodies. The serum samples of the three patients with a carcinoma were tested by immunofluorescence on rat brain and human nerve with anti-IgG and anti-IgM antisera. Unless specified, results of these studies were negative.

Motor conduction velocities were studied with a surface electrode in the median and ulnar nerves by stimulation at the wrist, elbow,

axilla, and Erb's point and in the peroneal and tibial nerves at the ankle and knee as described by Kimura.⁶ F waves were elicited 10 times for each test by supramaximal stimulation and measured by the minimal latency. The criteria for partial conduction blocks were a > 20% drop in the p amplitude between proximal and distal sites with a < 15% change in duration. Sensory conduction velocities were examined in the median, ulnar, and sural nerves. The limits of normal values were obtained from the laboratory. Electromyography was performed with a concentric needle electrode in the tibialis anterior, extensor digitorum brevis, abductor digiti minimi, and abductor pollicis.

Nerve biopsies were processed to give paraffin, semithin, and ultrathin sections, and for teased fibre examination.⁷

Case reports

PATIENT 1

In January 1992, a 73 year old man complained of progressive paraesthesia and numbness, sometime painful, in all four limbs. His gait became unsteady and his hands clumsy. He was referred after a two month progression. There were proximal and distal deficits in the lower limbs and in the hands corresponding to MRC grade 4. Tendon reflexes were diffusely abolished. Pallaesthesia was diminished below the knees. Identification of objects was difficult in both hands. Pain and temperature perception was normal. The disability score was grade 2 on Winer's scale.⁸ His CSF contained 1 leucocyte/mm³ and 1.27 g/l protein with a normal IgG pattern. The patient received intravenous IgGs (0.4 g/kg/day for four days) and then 0.75 mg/kg/day prednisone with reduction of paraesthesia in the four limbs and improvement of strength to MRC grade 5 and easy identification of objects in the hands within two weeks. Serum carcinoembryonic antigen 19-9 was 4050 µg/l (normal < 3.5 µg/l) and an otherwise asymptomatic pancreatic adenocarcinoma was discovered. Surgery was performed after three months of evolution. A few days later a stroke occurred and the patient was discharged.

PATIENT 2

In September 1993, a 73 year old man experienced paraesthesia and loss of strength in his

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Received 19 June 1995
and in revised form
2 October 1995

hands. Symptoms steadily progressed over three months. In October, diarrhoea and abdominal pain appeared and in December a rectosigmoidal adenocarcinoma with a single hepatic metastasis was discovered. Rectosigmoidectomy and partial hepatectomy were performed in January 1994. He was referred in June 1994. There was a diffuse deficit in both hands corresponding to MRC grade 4. Areflexia was also diffuse. Sensory loss was present in both hands for pallesthesia and stereognosis with mild reduction of thermal perception and pain perception. In the lower limbs, pallesthesia and thermal and pain perceptions were normal. The patient had difficulty with arthrokinesthetic sense in his big toes and Romberg's test was positive. The disability score was grade 2. His CSF contained 1 leucocyte per mm³ and 0.90 g/l protein with a normal IgG pattern. Because of chronic supuration in the surgical scar, steroids were not given. However, his neurological status showed considerable improvement. In April 1995, paraesthesia had disappeared. The patient had a better hand grip. Muscle strength was MRC grade 5 in the left hand and 5 in the right hand except for the abductor pollicis which was graded 4+. Stereognosis and pallesthesia were normal in the left hand but remained altered in the right. Romberg's test and lower limb arthrokinesthetic sense were normal. There was no recurrence of the tumour.

PATIENT 3

In June 1993, this 61 year old man complained of motor disability. He was referred in August after a 2.5 month progression. Examination showed severe proximal and distal motor deficit in the four limbs sparing the face and the bulbar musculature. There was no amyotrophy or fasciculation. Areflexia was diffuse and sensory examination was normal. Winer's disability score was grade 4. His CSF contained 1 leucocyte/mm³ and 1.30 g/l protein with a normal IgG pattern. IgM and IgG anti-GM1 antibodies was positive on thin layer chromatography and enzyme linked immunoabsorbent assay (ELISA). Immunofixation electrophoresis showed a faint monoclonal IgM kappa. Serum IgM, IgG, and IgA concentrations and bone marrow aspiration were normal. Anti-MAG antibodies were not seen on ELISA and western blot. The patient

received intravenous IgGs (0.4 mg/kg/day for four days). His neurological status improved to grade 3 of Winer's scale. He relapsed in October but his condition rapidly improved to grade 2 with 1 mg/kg/day prednisone. In November, laboratory tests showed hepatic perturbations and abdominal CT disclosed a hepatic tumour. Biopsy showed a cholangiocarcinoma. Two successive attempts at steroid tapering resulted in rapid deterioration to grade 4. Each time, function was recovered on readministration of prednisone (1 mg/kg/day). Because of a poor cardiorespiratory status, surgery was dismissed. The patient underwent seven alcohol injections into the tumour between March and June 1994. Before this treatment, the disability score was grade 4 on Winer's scale. In June, it was 2 and prednisone has been tapered to 0.3 mg/kg/day without relapse. Azathioprine (2 mg/kg/day) was introduced in June. Abdominal CT showed complete necrosis of the tumour. In November, the disability score was 1. There was only diffuse areflexia. In April 1995, his neurological status was unchanged; however, CT showed a relapse of the tumour.

Results

ELECTROPHYSIOLOGY

Each patient showed several of the following: reduced motor conduction velocities, abnormal F waves, conduction blocks and temporal dispersion in several nerves (table). Sensory conduction velocities were mildly reduced in patients 1 and 2 and slightly in patient 3. In the three patients, electromyography showed reduced interference pattern. Patient 3 had rare fibrillation potentials in the distal part of the lower limbs.

NERVE BIOPSIES

In patient 2, mild perivascular mononuclear cell infiltrates were found in the perineurium. The myelinated fibre density was reduced. There were thin myelin sheaths, onion bulb formations, and rare regenerating clusters. Fourteen per cent of teased myelinated fibres showed demyelination and remyelination and 14% axonal degeneration. In patient 3, there were mononuclear cell infiltrates around endoneurial and perineurial vessels. Density of myelinated fibres was normal. Some myelinated fibres had thin myelin sheaths. Two per-

Motor nerve conduction studies

Limit of normal		Median				Ulnar				Peroneal				Tibial			
		MCV > 50 m/s	Amp > 4 mV	DL < 5 ms	FWL < 31 ms	MCV > 50 m/s	Amp > 4.5 mV	DL > 4 ms	FWL < 31 ms	MCV > 40 m/s	Amp > 4 mV	DL > 6.5 ms	FWL < 58 ms	MCV > 40 m/s	Amp > 4 mV	DL > 6.5 ms	FWL < 58 ms
Patient 1	R	40	3.6*	5.4	38.2	32	4.1*	5.1	42	46	0.9*	6.3	NO	35	0.7*	7.5	NO
Patient 2	R	29	3.2*	5.1	43	36	5.4*††	3.2	35.9	38	1.1	4.3	55	30	0.7*	6.2	71
	L	36	3.1**	5	NO	45	5.8	3.2	33.5	38	0.5	6.2	NO	28.6	0.8*	6.8	80
Patient 3	R		ND				ND		34.5		5	1.8	NO	31	6.5†	7.3	80
	L	55	4.8	4.8	32.3	43	5.1†	3.3	NO	33	1.6*	4.8	56.7	35	5.4†	8	65

MCV = motor conduction velocities (between the elbow and wrist for the median and ulnar nerves and between the knee and the ankle for the tibial and peroneal nerves); amp = amplitude of the muscle action potential on wrist or ankle stimulation; DL = distal latency; FWL = F wave latency on wrist or ankle stimulation; R = right; L = left; ND = not done; NO = not obtainable.

*Dispersion of the muscle action potential after stimulation at elbow or wrist and knee or ankle.

**Proximal dispersion of the muscle action potential.

†Conduction block between elbow and wrist or knee and ankle.

††Proximal conduction block.

cent of teased fibres were demyelinated and 2% underwent axonal degeneration. Nerve biopsy was not performed in patient 1.

Discussion

The peripheral neuropathy of these three patients shared many features with CIDP. All of the patients showed a sensorimotor neuropathy affecting the four limbs with diffuse areflexia, progressing for at least two months. Their CSF contained high concentrations of protein and the studies of motor conduction velocities showed a demyelinating pattern. All of these are major criteria for the diagnosis of CIDP.⁵ When tested in two patients, intravenous IgGs and steroids were effective therapeutic agents. Although non-specific, response to these treatment are another characteristic of CIDP.⁹ Nerve biopsies showed mononuclear cell infiltrates and a mixture of demyelination, remyelination, and axonal degeneration. Similar lesions can be found in the nerves of patients with CIDP.^{9,10} Finally, the presence of anti-GM1 antibodies in one of our patients conforms to the finding that these antibodies can be detected in patients with CIDP.¹¹

It is interesting that CIDP preceded the discovery of adenocarcinoma by a few months. The association of cancer and primary demyelinating neuropathy has seldom been studied. Guillain-Barré syndrome occurs with Hodgkin's disease¹² but rarely with carcinoma.² The association of chronic demyelinating neuropathies and lymphoma is rare.¹³ Chronic or relapsing demyelinating neuropathies occurring with carcinomas were first described by Croft *et al* in 1967⁴ and occasional cases have been reported since that could have corresponded to CIDP.² More recently, three patients similar to ours have been reported.^{14,15} In all these patients, the neuropathy usually occurred in a close temporal relation with the cancer and some patients, as our patients 2 and 3, improved after treatment of the tumour.^{14,16} However, a spontaneous remission of CIDP cannot be ruled out.

As cancer is common, it is difficult to determine whether the association of carcinoma and CIDP is a coincidence or depends on a paraneoplastic process. In our series, three out of 33 patients referred for the diagnosis of dysimmune demyelinating neuropathy had a carcinoma. As few patients were studied, bias is possible. Some studies suggest that carcinomas can express antigens shared with

Schwann cells^{17,18} and that patients with tumours can produce antibodies reacting with these cells.¹⁹ Interestingly, immunotherapy with melanoma cell preparations has been reported to induce demyelinating neuropathy.²⁰ Thus it is not unlikely that a neuropathy similar to CIDP can result from an autoimmune process induced by tumours.

We thank Dr C Caudie, Laboratoire de Biologie, Hôpital Neurologique, Lyon, for measuring anti-GM1 antibodies and E A Derrington for correcting the English.

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