

Peripheral neuropathy and benign IgG paraproteinaemia

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SUMMARY Three patients with peripheral neuropathy and an associated benign IgG paraproteinaemia are described. No direct immunological evidence for an aetiological role of the paraprotein was found, and the implications of this are discussed.

The association of peripheral neuropathy with paraproteinaemia is well-established and has been described with cryoglobulinaemia (Abramsky *et al.*, 1974; Cream *et al.*, 1974; Reza *et al.*, 1974), primary and secondary amyloidosis (Benson *et al.*, 1975), Waldenström's macroglobulinaemia (Dayan and Lewis, 1966; Iwashita *et al.*, 1974; Propp *et al.*, 1975), multiple myeloma (Victor *et al.*, 1958; Silverstein and Doniger, 1963), and benign IgM paraproteinaemia (Hobbs *et al.*, 1976). Peripheral neuropathy has also been described in association with raised levels of polyclonal immunoglobulins (Whitaker *et al.*, 1973; Hobbs *et al.*, 1976; Iwabuchi *et al.*, 1976), especially IgM. Until the report of Chazot *et al.* (1976) of three patients, there had been no reports of the association between an apparently "benign" IgG monoclonal paraproteinaemia and peripheral neuropathy. There had, however, been case reports of isolated IgG paraproteinaemias associated with various clinical pictures of which peripheral neuropathy was part (Iwashita *et al.*, 1971; Kopp *et al.*, 1973). We report here the results of immunological studies on three patients with peripheral polyneuropathy for which no cause could be found, who also had a "benign" IgG paraproteinaemia.

Case reports

CASE 1 BH (UOH NO. 603218)

A 62 year old housewife was admitted to hospital with a 15 month history of paraesthesiae and numbness, first in the hands, then in the feet, accompanied by difficulty with fine hand movements and increasing difficulty in walking. Three

months before admission the abnormal signs were confined to weakness of the interossei bilaterally and a flaccid left foot drop with a depressed left ankle reflex. On admission, however, she was unable to rise from a chair or to walk. There was severe wasting and weakness of all muscle groups in all limbs, most marked distally, with areflexia but no fasciculation. There was sensory loss of all modalities except pinprick in a glove and stocking distribution.

Electrophysiological studies confirmed the presence of a mixed sensorimotor polyneuropathy, and a sural nerve biopsy showed a mixture of axonal degeneration and demyelination. The following investigations were normal or negative: full blood count (FBC), ESR, blood urea and electrolytes, serum calcium (Ca⁺⁺), liver function tests (LFTs), WR, serum aldolase and creatine phosphokinase (CPK), glucose tolerance test (GTT), serum B₁₂, antinuclear factor (ANF), serum thyroxine (T₄), serum immunoglobulins, bone marrow, urinary porphyrins, ECG, chest, abdominal, and spinal radiographs. The CSF contained one lymphocyte per mm³ and 0.65 g/l of protein of which 0.13 g/l was IgG. The serum protein electrophoretic strip showed a compact band of 0.15 g/l, shown to be IgG λ by immunoelectrophoresis.

The patient was given a short course of steroids, during which she deteriorated. On discharge to her local hospital after eight weeks her legs were nearly paralysed but her arms were slightly stronger though still not useful for feeding. On discharge from the local hospital, 15 months after the onset, she was able to walk with the aid of a walking frame and could dress herself unaided. Twenty-seven months after the onset her only complaint was of paraesthesiae in the hands and

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feet. She was walking unaided and lived alone completely independently. Examination revealed normal power in all limbs except for the small hand muscles. There was no wasting. Arm reflexes were all present though sluggish but both knee and ankle reflexes were absent bilaterally.

CASE 2 GT (UOH NO. 325237)

A chartered accountant, who admitted to smoking at least 30 cigarettes a day, was 43 years old when he was admitted to another hospital in 1960. The history was of 18 months' paraesthesiae and weakness in the hands, and similar symptoms of six months duration in the feet. Increasing limb weakness had precipitated admission when the findings were of marked wasting and weakness of all limbs with areflexia, glove and stocking loss of all sensory modalities, and mild bilateral facial weakness. Investigations included a normal ESR and bone marrow, no LE cells in the blood, and a CSF protein of 1.1 g/l. He made a gradual and nearly complete recovery over the next year, being left with some paraesthesiae in all four extremities.

He remained well until 14 years later when a short nonspecific febrile illness was followed by a very rapidly progressive generalised weakness leading to inability to walk, stand, wash, or even feed himself over the course of three days. There was no difficulty with breathing or swallowing. Neurological examination showed profound weakness without wasting in all limbs with areflexia and glove and stocking loss of all sensory modalities. The following investigations were normal or negative: FBC, ESR, blood urea and electrolytes, Ca⁺⁺, LFTs, WR, ANF, fasting blood sugar, urinary porphyrins, serum immunoglobulins, ECG, chest, skull, and spinal radiographs. The CSF protein was 4.25 g/l and serum immunoelectrophoresis showed an IgG_K paraproteinaemia of 0.7 g/l.

He started to improve spontaneously and three months after the onset was able to walk one mile unaided. Twenty months after the onset he still complained of the original paraesthesiae. There was no weakness or wasting, the right biceps and triceps reflexes were just obtainable but the remaining reflexes remained absent. Vibration sense was absent to the knees and there was subjective blunting to pinprick in a stocking distribution.

CASE 3 WS (UOH NO. 632935)

A 61 year old retired policeman was admitted with a six month history of slowly progressive numbness, paraesthesiae, clumsiness, and weakness, first in the hands then in the feet. There was marked weakness of the small hand muscles and slight

weakness of the wrists and ankles with areflexia and blunting to pinprick and cottonwool in a glove and stocking distribution. Electrophysiological studies confirmed a sensorimotor polyneuropathy, and all haematological and biochemical tests were normal except for protein immunoelectrophoresis which showed an IgG_K paraprotein of 0.5 g/l. The CSF contained two lymphocytes per mm³ and 0.5 g/l of protein. He was discharged but readmitted two months later, being unable to rise from the sitting position and with increasing difficulty in walking. The hands and feet were paralysed with a lesser degree of weakness in the proximal musculature. There was some extension of the glove and stocking sensory loss, and the vital capacity was 3.851.

The following investigations were normal or negative: FBC, ESR, blood urea and electrolytes, Ca⁺⁺, LFTs, fasting blood sugar, bone marrow, LE cells, ANF, Australia antigen, WR, faecal occult blood, ECG, intravenous pyelogram, barium meal, follow-through, and enema, full skeletal survey, liver and spleen scans, and repeated chest radiographs. The CSF protein had risen to 1.14 g/l with four lymphocytes per mm³. Serum electrophoresis at intervals over the next year showed persistence of the IgG_K monoclonal band at approximately 0.5 g/l. Serum immunoglobulins were persistently normal. Sural nerve biopsy showed fibrosis and loss both of axons and myelin.

The neuropathy progressed, necessitating tracheostomy and assisted respiration six weeks after the second admission (nine and a half months after the onset). Prednisolone in high doses produced diabetes mellitus (which regressed after steroid withdrawal) but no improvement in the neuropathy. Azathioprine for one month was also found ineffective. After four weeks on the ventilator he was totally paralysed without a flicker of movement anywhere, except eye movements, bilateral facial paralysis, complete inability to speak, swallow, or breathe and, as far as could be determined, total anaesthesia to all sensory modalities. He was incontinent of urine and faeces, and developed a membranous colitis with diarrhoea and vomiting, a right calf deep venous thrombosis, and recurrent chest infections. Fibreoptic bronchoscopy showed only small amounts of mucopurulent sputum and no suggestion of any neoplasm. At this stage he was so severely ill that he was not expected to survive. Management was confined to general supportive measures only, but after six weeks on a ventilator there was slight movement at hips and shoulders and from this point on there was slow but steady improvement. He was dis-

charged home 10 months after his second admission with normal cranial nerves, useful though reduced power in all limbs symmetrically, areflexia, and glove and stocking loss of all sensory modalities. He continued to improve and when last seen, 16 months after the onset, was walking with two sticks but still had some difficulty rising from the sitting position. The strength in his arms had largely recovered though fine movements of the fingers were awkward. Postural sense was still impaired in his legs, and he complained of pain in both calves.

Methods

The serum immunoglobulin levels were measured by radial immunodiffusion (using standard Hoechst Partigen plates for IgG, A, and M). The paraproteins were detected by routine serum electrophoresis on cellulose acetate, and identified by agarose gel immunoelectrophoresis. The paraprotein was quantified by staining the strips with nigrosine and scanning them in a Joyce-Loebl double beam integrating densitometer, using the value for total globulins found by subtraction of the albumin concentration from the total serum protein measured by the Autotechnion (SMA 12/60).

Serum from each patient was stored, and all were tested in a batch against postmortem mixed sensorimotor nerves. Three necropsy cases with no clinical evidence of nerve damage before death were chosen. Portions of brachial plexus, median nerve, and femoral nerve were selected. These were frozen in liquid nitrogen, and 10 longitudinal and transverse sections cut in a cryostat. They were then exposed for 10 minutes either to phosphate buffered saline or serum from each case of neuropathy with paraproteinaemia. They were then washed three times in phosphate buffered saline after which fluorescein conjugated anti-immunoglobulin G, A, or M was added, left for 10 minutes, and then washed in phosphate buffered saline.

The sections were mounted in glycerine and examined in a Leitz incident light microscope with a mercury HBO 200 ultraviolet source. The method was adapted from the routine used for detecting antibasement membrane immunoglobulin in pemphigoid or anti-intercellular substance antibody in pemphigus.

Results

The immunoglobulin results are given in the Table.

Table Immunoglobulin results on the three patients studied

Patient	IgG g/l	IgA g/l	IgM g/l	Paraprotein type and level (g/l)
Normal range	7.2-19.0	0.8-5.0	0.5-2.0	
BH	17.7	1.3	0.6	G λ 0.15
GT	14.4	0.9	0.8	G κ 0.7
WS	8.9	2.3	1.1	G κ 0.5

In each patient the paraprotein was below 1.0 g/l, and in none has it increased over a period of two years. In none was light chain or immunoglobulin detectable in urine concentrated fiftyfold. In all three, bone marrow aspiration and skeletal radiological surveys were within normal limits. None was anaemic or had a raised blood urea or raised serum calcium. In these respects the three patients fall into the category of benign paraproteinaemia. No autoantibody binding to peripheral nerve was demonstrable in the necropsy specimens. Neither could immunoglobulin from the patients' sera be shown to bind to nerves taken from necropsy cases.

It was felt unreasonable to take nerve biopsies from the patients simply to look for autoantibody, possibly bound to their own nerve: BH and WS had had routine nerve biopsies fixed in formalin for diagnosis which were unsuitable for subsequent immunofluorescence.

Discussion

Three patients are described in whom a severe remitting peripheral neuropathy was associated with a single abnormal finding—an IgG paraproteinaemia without evidence of myeloma, collagen disorder, sarcoidosis, or malignancy. Attempts to show specific binding of the paraprotein to homologous undamaged nervous tissue were not successful, and the nature of this association remains in doubt.

Clinically there were no distinguishing features of the neuropathy, although all three patients progressed within a relatively short period to severe disability, and all recovered to complete independence. One of them (case 2) was reminiscent of the relapsing case described by Contamin *et al.* (1976), his two relapses separated by 14 years. The most striking clinical course was, however, exhibited by case 3 who progressed to the most extraordinary degree of severity such that a carcinomatous aetiology seemed the most likely and recovery was thought highly improbable.

Early attempts (Osuntokun *et al.*, 1966) to define a possible immunological factor in chronic poly-

neuropathy failed to demonstrate antibody to nerve in the sera of 37 patients with chronic polyneuropathy, although none had any immunological disturbance. More recently, Hobbs *et al.* (1976) have shown that IgM from patients with "benign" IgM paraproteinaemias and a peripheral neuropathy binds to homologous undamaged peripheral nerves but that "such binding has not been found with all IgM paraproteins studied nor in any of over 100 IgG and IgA myeloma proteins tested." Chazot *et al.* (1974), looking at "malignant" paraproteinaemias, showed that autologous specific binding to peripheral nerves can be demonstrated in IgG and IgA myelomas, and in Waldenström's (IgM) macroglobulinaemia in patients who also have peripheral neuropathy. The two patients with Waldenström's disease without peripheral neuropathy did not show this phenomenon. Of their "malignant" paraproteins, only the myeloma IgG was shown to bind to homologous peripheral nerves, possibly already damaged, taken from a patient with alcoholic peripheral neuropathy. Chazot *et al.* (1976) confirmed their earlier findings and extended them to include four patients with "benign" paraproteinaemias (three IgG and one IgM) and peripheral neuropathy whose paraproteins showed autologous specific binding. Only one homologous experiment is mentioned when again it was found that a purified myeloma IgG would bind to a nerve biopsied from a patient with alcoholic peripheral neuropathy. Contamin *et al.* (1976) described a patient with a chronic relapsing steroid sensitive polyneuropathy over a 19 year period associated with a "benign" IgG paraprotein which did not progress to overt myeloma.

From the limited data available it seems that binding of a patient's own paraprotein, benign or malignant, to his own abnormal peripheral nerves can be demonstrated in some cases. The affinity of "benign" paraproteins for homologous normal peripheral nerve has been shown only for some IgM paraproteins but not for IgG paraproteins. The significance of "malignant" paraprotein binding to homologous peripheral nerve is unclear (Chazot *et al.*, 1974, 1976; Hobbs *et al.*, 1976), possibly because the former workers used already damaged nerves while the latter used normal nerves.

There are a number of possible explanations for the association described here, one of which is that the two phenomena are unrelated. The incidence of "benign" paraproteinaemia varies from 0.1% in 10 000 blood donors aged 26–60 years, through 3% in both the general population and inmates of old peoples' homes (aged over 60

years), to 19% in 99 people aged over 90 years; while a survey of 748 hospital inpatients aged over 70 years yielded a figure of 7.5% (see Kohn (1976) for references). Obscure peripheral neuropathy is not uncommon and one might expect these to occur together rather more frequently than is the case. In this department in 1976 over 100 inpatients (of whom eight had aetiologically undiagnosed peripheral neuropathy) had protein strips of which only four showed paraproteins (one proven myeloma, one discoid lupus, one sarcoidosis (a diffuse gamma band), and one undiagnosed patient with a marked excess of lymphocytes in the bone marrow. A survey of 238 undiagnosed paraproteinaemias over the last five years in the United Oxford Hospitals did not reveal one with an associated peripheral neuropathy.

A possibility that cannot be excluded on the basis of these and the reported experiments is that the patients' nerves possess a particular antigen not present in undamaged postmortem nerves, and that specific antibody is not detected by the technique employed. Alternatively, both the peripheral nerve damage and the paraprotein may be parallel manifestations of another primary process. For example, the Epstein Barr virus induces monoclonal immunoglobulin production in Burkitt's lymphoma cells while in infectious mononucleosis it may be associated with a peripheral neuropathy.

In our three patients the evidence for a direct aetiological action of the paraprotein in the production of their peripheral neuropathy is not forthcoming, although it is difficult to believe that they are not related. Possibly a collaborative study with a sufficiently large sample of patients could identify a common factor.

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