Mononeuritis multiplex in a patient with macroglobulinaemia

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SYNOPSIS A case is described of a 73 year old male with Waldenström's macroglobulinaemia and hyperviscosity in association with neurological abnormalities, the Bing-Neel syndrome. The relationship of the clinical features to changes in serum viscosity and the response to therapy with plasmapheresis and chlorambucil are discussed.

In 1944 Waldenström described a condition characterized by excessive production of macroglobulin. Earlier, the association of hyperglobulinaemia with neurological abnormalities had been recognized (Bing and Neel, 1936; Bing *et al.*, 1937) and a further report (Bichel *et al.*, 1950) referred to a similar case with large amounts of macroglobulin in the serum. The combination of neurological features and macroglobulinaemia has since been referred to as the 'Bing-Neel' syndrome. We describe the first case of mononeuritis multiplex, with both cranial and peripheral nerve involvement, in a patient with this syndrome.

CASE REPORT

A 73 year old male was admitted in June 1973 with a four week history of pain and altered sensation in his right hand. Apart from tiredness he was otherwise symptom-free. On examination his blood pressure was 220/130 mmHg and he showed fundal changes of arteriovenous nipping, flame-shaped haemorrhages, and soft exudates; venous dilatation was noted but there were no microaneurysms or new vessel formation. Liver and spleen were clinically enlarged but there was no palpable lymphadenopathy. Sensation was impaired over the distribution of the right ulnar nerve and there was weakness and wasting of the intrinsic muscles in the right hand. No other neurological abnormality was noted.

Haemoglobin concentration was 10.9 g/dl (normocytic, normochromic picture), WBC $8.3 \times 10^9/l$ (31% neutrophils, 67% lymphocytes, and 2% monocytes, some of the lymphocytes being atypical), and platelet count $215 \times 10^9/l$. ESR was 123 mm in the first hour (Westergren). Serum total protein was raised at 127 g/l (albumin 33 g/l) and electrophoresis showed a discrete band in the gamma-globulin region. Serum immunoglobulins were IgG 222 Iu/ml (normal 73–207), IgA 11 Iu/ml (normal 46–289), and IgM 23 500 Iu/ml (normal 47–372). Free kappa chains were detected in the serum and kappa chains were also present in the urine. The bone marrow smear was infiltrated with 60% atypical lymphocytes, some with periodic-acid-Schiff-positive inclusions in the nucleus. Serum relative viscosity at room temperature (22°C) was 5.9 (normal 1.4–2.1). Cryoglobulins were not present and there was no detectable change in serum relative viscosity with temperature (4°C and 37°C). Radiological skeletal survey, including views of the thoracic inlet, cervical and dorsal spine, was normal. Distal motor latency (wrist to abductor digiti minimi) was prolonged in the right ulnar nerve (5.0 ms) and normal in the left ulnar nerve (3.2 ms). Maximal motor conduction velocities were normal in ulnar and median nerves (right ulnar nerve, forearm segment 66.0 m/s; trans-sulcal segment, 57.5 m/s; right median nerve, elbow to wrist, 54.4 m/s; left ulnar nerve, forearm segment, 54.3 m/s; trans-sulcal segment 56.4 m/s; left median nerve, elbow to wrist 55.6 m/s). An EEG showed paroxysms of generalized theta activity suggestive of subcortical involvement (Fig. 1). Blood urea and plasma electrolytes, serum uric acid, liver function tests, and serum calcium, phosphate, and alkaline phosphatase were all normal. An ECG showed changes

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FIG. 1 *Electroencephalogram of patient before plasmapheresis (A) showing generalized slow-wave disturbance, and one year after treatment (B) with return of the tracing to normal. Montage: parietal, alternate right and left.*

of left ventricular hypertrophy and there was evidence of cardiomegaly on the chest radiograph. A diagnosis of Waldenström's macroglobulinaemia with hyperviscosity was made and he was commenced on therapy with chlorambucil 2 mg four times daily. The hypertension was controlled with debrisoquine and chlorthalidone.

A few days after admission he became confused and disorientated. Plasmapheresis, removing 1 l of plasma over two days, resulted in a fall of serum relative viscosity to 3.5 with a marked improvement in his confusional state. As the haemoglobin concentration had fallen to 8.2 g/dl, he was transfused with four units of packed red cells. Plasmapheresis was repeated every four weeks to maintain the reduction in the serum relative viscosity (Fig. 2) and, in addition, he continued on chlorambucil 2 mg twice daily. In December 1973 he developed sudden onset of hoarseness and examination revealed a complete left vocal cord paralysis with mild left hypoglossal nerve palsy. There had been no improvement in his right ulnar neuropathy and he had now developed symptoms suggesting left ulnar nerve involvement. Distal motor latencies were prolonged in both ulnar nerves (right 5.4 ms; left 4.9 ms) and there was marked slowing of maximal motor conduction velocities in all segments of the right ulnar nerve (forearm segment, 46.8 m/s; trans-sulcal

segment, 36.5 m/s). In the left ulnar nerve there was significant slowing in the trans-sulcal segment (41.4 m/s), with normal conduction velocity in the forearm segment (57.2 m/s). Serum relative viscosity at this stage was 3.0 and his serum total protein and IgM levels were falling satisfactorily (Fig. 2). However, because of his clinical deterioration it was decided to increase the frequency of plasmapheresis to every two weeks. He remained well till March 1974 when he presented with a left drop-shoulder due to paralysis of the left trapezius muscle. He now had complete bilateral ulnar nerve palsies (Fig. 3) but he had recovered normal function in his left vocal cord and left hypoglossal nerve. Hepatosplenomegaly was no longer present, his retinopathy had receded, and his hypertension was controlled on chlorthalidone alone. He has continued over 18 months on maintenance therapy with chlorambucil and undergoes plasmapheresis every two weeks when 800 ml plasma is removed and volume replacement given with 0.9% saline.

The patient remains well with no new features and complete recovery of the left trapezius muscle, though clinical evidence of bilateral ulnar neuropathy persists. Distal motor latencies remain prolonged in both ulnar nerves (right 5.8 ms; left 5.2 ms) but although maximal motor conduction velocity in the left ulnar nerve is unchanged (forearm

FIG. 2 Frequency of plasmapheresis is shown together with response in serum total protein (g/l), serum IgM (Iu/ml), and serum relative viscosity.

FIG. 3 Bilateral ulnar nerve palsies with wasting of the dorsal interossei and 'main en griffe'.

segment 52.0 m/s; trans-sulcal segment, 36.3 m/s) the velocity in the right ulnar nerve has improved to within normal limits (forearm segment, 57.8 m/s; trans-sulcal segment, 51.3 m/s). The serum albumin has risen to within the normal range (latest value 42 g/l) despite continuing plasmapheresis but IgG

and IgA levels are both depressed (latest values 35 Iu/ml and 17 Iu/ml respectively). Blood indices have been satisfactory throughout this period and serum total protein and IgM levels have continued to fall towards normal. Bone marrow smear is now within normal limits. Serum relative viscosity has

been maintained between 2.0 and 2.3. The EEG is now normal, with complete resolution of previous changes (Fig. 1).

DISCUSSION

The clinical picture of nervous system involvement in Waldenström's macroglobulinaemia is referred to as the Bing-Neel syndrome and Logothetis *et al.* (1960) found this in up to 25% of patients. Central nervous system features may take the form of a focal brain syndrome, possibly associated with epilepsy, and usually secondary to haemorrhage or thrombosis. Alternatively, a diffuse encephalopathy can occur, with headache, mental changes, and impaired conscious level, the so-called 'coma paraproteinaemicum' described by Wuhrmann (1956). Solomon (1965) has shown that the related EEG disturbance—namely, a slow, diffuse dysrhythmia—may be reversed by effective treatment, as occurred in our patient. The commonest peripheral manifestation is a symmetrical polyneuropathy of sensorimotor type, usually occurring late in the disease (McCallister *et al.*, 1967). Cranial neuropathies consisting of progressive deafness or facial palsy have been reported by Waldenström (1948) and Tischendorf and Hartmann (1950). Glenchur *et al.* (1958) described a case of pure motor neuropathy, with wasting of the intrinsic muscles in both hands. However, the combination of multiple cranial and peripheral neuropathies as in our present case has not been described in Waldenström's macroglobulinaemia.

Solomon (1965) and Fahey *et al.* (1965) have postulated a direct relationship between hyperviscosity due to macroglobulinaemia and neurological involvement. The level of serum viscosity at which symptoms occur is extremely variable but the 'symptomatic threshold' is thought to lie between 6.0 and 7.0. In our patient the serum viscosity at the time of presentation was 5.9 and his symptomatic threshold appeared to be as low as 3.0 (Fig. 2). Although the IBM continuous flow blood cell separator has been shown to be the most effective way of removing the abnormal protein (Powles *et al.*, 1971), this technology is not yet available in our centre and plasmapheresis was therefore carried out at monthly

intervals. When the patient developed new neurological features the interval between each plasmapheresis was reduced to two weeks. Some patients undergo complete remission if plasmapheresis is combined with continuous chlorambucil (McCallister *et al.*, 1967). On this regimen our patient has remained free of new symptoms for almost 18 months, with a serum relative viscosity maintained below 3.0, a marked fall in serum IgM levels, and reversal of the bone marrow to normal. His cranial neuropathies have undergone complete resolution and, although there is no clinical recovery of ulnar nerve function, conduction velocity has improved in the motor fibres of the right ulnar nerve, which Payan (1970) suggests may be the first indication of functional recovery.

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