The treatment of inflammatory polyneuropathy by plasma exchange

MLP GROSS, NJ LEGG, MC LOCKWOOD, C PALLIS

From the Department of Medicine (Neurology and Nephrology), The Hammersmith Hospital and Royal Postgraduate Medical School, London, UK

SUMMARY Observations are reported on six patients with inflammatory polyneuropathy who were treated by plasma exchange. In four cases the polyneuropathy was acute and in two it was chronic or relapsing. Two acute cases and one chronic relapsing case had plasma exchange during a rapidly progressive phase of the disease, and showed a prompt and substantial recovery of function. The other three patients were exchanged when disease activity had reached a plateau. Only minor degrees of improvement were seen in two of these cases. One patient showed an initial mild deterioration before subsequent recovery. There were no significant side effects. These findings are discussed in relation to the pathogenesis and clinical management of inflammatory polyneuropathy.

Acute inflammatory polyneuropathy, or the Guillain-Barré syndrome, is usually a monophasic illness, but cases with an initially similar presentation may pursue a chronic relapsing or a chronic progressive course. Cell-mediated immunity plays an important part in the pathogenesis of the disorder.^{1,2} Considerable evidence exists, however, both in the clinical context and in the animal model of experimental allergic neuritis, that humoral factors may also be involved.³ Complement-fixing antibodies against nerve tissue have been found in 50% of patients with acute inflammatory polyneuropathy,⁴ and cell-free serum from such patients (and from animals with experimental allergic neuritis) can demyelinate nerve tissue in culture.⁵ IgG and IgM have been demonstrated by immunofluorescence on the surface of nerves in animals with experimental allergic neuritis⁶ and in patients with acute inflammatory polyneuropathy.^{7,8} This IgG appears to be specific.⁹ In one study these antibodies were best demonstrated during progression and early recovery of the disease: they were thought to correlate with disease activity.¹⁰ Circulating immune complexes^{11,12} and immune complex deposition in the kidneys were seen in six consecu-

tive patients with acute inflammatory polyneuropathy.¹³ More recently, serum from animals with experimental allergic neuritis¹⁴ and from patients with acute inflammatory polyneuropathy¹⁵ has been shown to induce demyelination when injected subperineurally into rat sciatic nerve.

The treatment of acute inflammatory polyneuropathy is largely supportive. Steroids have often been given, but their effect is doubtful. A recent controlled trial¹⁶ showed no benefit from prednisone, indeed recovery was significantly less in the treated group. There is also evidence to suggest that steroids may predispose to relapse.¹⁷ Other agents tried (with mixed results) have included methylprednisolone,¹⁸ azathioprine,¹⁹ cyclophosphamide²⁰ and 6-mercaptopurine.²¹ Acute inflammatory polyneuropathy may, however, occur in patients already receiving immunosuppressive therapy for renal transplantation²² or Hodgkin's disease.²³ We first reported the rapid recovery of a single patient with acute inflammatory polyneuropathy following plasma exchange.²⁴ Further single cases (or small groups of patients) have since been reported,²⁵⁻³⁰ many of whom responded favourably. In this communication we describe our experience with six further patients. Four had acute inflammatory polyneuropathy and two had chronic relapsing inflammatory polyneuropathy.

Methods

Plasma exchange Having given informed consent, the

Address for reprint requests: Dr MLP Gross, Department of Neurological Science, Royal Free Hospital, Pond Street, London NW3 2QG, UK.

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patients underwent plasma exchange using a Haemonetics model 30 cell separator (Haemonetics Corporation, Boston, USA). Three of the patients had Scribner arteriovenous shunts which enabled three or four litre exchanges to be carried out in less than two hours. The other three patients had venovenous exchanges, using antecubital veins. Total plasma volume exchanges (55 ml/kg body weight) were carried out, in which plasma protein fraction was used as a substitute. Appropriate concentrations of potassium and calcium were added to the plasma protein fraction. The volumes of plasma exchanged ranged from 12–28 litres, and the exchanges were spaced out over periods ranging from 4 to 10 days.

Neurological assessment Each patient was clinically assessed on the day of admission and daily thereafter. Muscle strength was graded according to the standard 0–5 MRC scale. Vital capacity and tidal volume were estimated frequently, where indicated. Sensory testing (pin-prick, light touch, vibration sense and position sense) was repeatedly carried out, and the state of the reflexes was recorded regularly. In some instances motor activities such as walking were timed.

Laboratory investigations The following data were obtained on all patients: full blood count, ESR, clotting screen, fasting blood glucose, VDRL, TPHA, C3, C4, immune complexes, ANF, DNA binding, serum proteins, IgG, IgM, IgA, rheumatoid factor, urea and electrolytes, liver function tests, HBsAg, folic acid, B12, and viral antibodies. CSF examination included cell count, protein, glucose, Gram stain, culture, AFB, IgG, VDRL, and viral antibodies. Chest radiographs, ECGs and nerve conduction studies were also performed.

PATIENTS

Case 1 (HH No 488180) Seven days after a sore throat a 22-year-old woman complained of progressive weakness of the limbs. Examination confirmed the weakness and revealed generalised areflexia and impaired postural sense in both fingers and toes. The CSF contained 1.3 g/l of protein but no cells. Motor conduction velocities were 62 m/s in the left median, 43 m/s in the left ulnar and 30 m/s in the left common peroneal nerve. Median and ulnar terminal latencies were prolonged to about 10 m/s. Sensory nerve action potentials were lost. During her first week in hospital her weakness progressed. She was unable to raise her arms, to lift either heel off the bed against gravity or to flex her neck against resistance. A severe facial diplegia developed, and vital capacity dropped by 75%. At this stage (11 days after the onset of her neurological illness and at a time when her deficit was progressing) she received 3 litre plasma exchanges with plasma protein fraction on four successive days. She improved rapidly after the second exchange, and was able to sit and stand unaided, lift her arms above her head and smile almost normally. After the fourth exchange she could walk unaided and her vital capacity had returned to normal. The sensory deficit responded more slowly, over a period of two weeks. Finally her reflexes returned. Nerve conduction velocities only reverted to normal after six months. All other investigations were normal.

Case 2 (HH No 491934) A 55-year-old man had a diarrhoeal illness followed seven days later by rapidly progressive weakness in all four limbs. The CSF showed no cells and 1.44 g/l of protein. All other investigations were normal. The patient rapidly became tetraplegic and his condition then remained static for the next seven days. Thereafter, respiratory function decreased marginally and he developed a severe facial diplegia. At this stage he already had marked muscle wasting. No motor response could be elicited by stimulating the right median or ulnar nerves, but sensory and mixed nerve action potentials were present with normal latencies and ascending conduction velocities. Seventeen days after the onset of weakness he underwent seven 4 litre plasma exchanges with plasma protein fraction. After the sixth exchange there was an improvement in the strength of his neck muscles, but not in the power of any other muscle group. Further deterioration, however, did not occur. He never required respiratory assistance. Improvement has been very slow and incomplete, over a period of two years.

Case 3 (HH No 500170) A 48-year-old man had an influenza-like illness followed after three weeks by a feeling of pins and needles in the left arm and weakness in both legs which prevented him from running upstairs. Over the next 11 days he suffered progressive deterioration so that he could not lift his legs off the bed. On admission he was unable to sit up from the supine position, the triceps muscles were weak bilaterally, and there was global weakness of the legs. He was areflexic, and vibration sense was impaired below the iliac crests. No further deterioration occurred for seven days, but slight muscle wasting was apparent at this stage. The CSF protein was 5.1 g/l with one white cell per cubic millimetre. Motor conduction velocity in the right lateral popliteal nerve was 34 m/s and the right sural nerve action potential was absent. All other investigations were normal. Nineteen days after the onset of the weakness he underwent—on three occasions—4 litre plasma exchanges with plasma protein fraction. Shortly after the first exchange he felt weaker. Examination revealed increased weakness in the muscles of the forearms and hands. Over the next six days both upper and lower limbs became globally weaker and weakness increased in his abdominal muscles too. His condition then remained static for a week, after which he gradually improved.

Case 4 (RFH No BD 2282) A 42-year-old woman with polycystic kidney disease underwent nephrectomy in 1967. In February 1980 a huge, infected, remaining kidney was removed. She was left with a large open draining abdominal wound. She became septicaemic, and required intensive antibiotic therapy, as well as haemodialysis. Ten days following surgery she developed an acute areflexic paralysis involving all limbs and the respiratory muscles. There were no abnormalities referable to the cranial nerves. She deteriorated over 72 hours, becoming tetraplegic and unable to lift her head from the bed; her vital capacity fell to 0.3 litres with a pO_2 of 8.6 kp on 35% oxygen. The CSF contained 1.2 g/l of protein, and no cells. It was not possible, at this stage, to perform nerve conduction studies. In anticipation of ventilatory failure she received plasma exchange concurrently with her haemodialysis;³¹ 4 litre

exchanges with plasma protein fraction (3 litres) and fresh frozen plasma (1 litre) were carried out on five occasions. After the second exchange there was a prompt and substantial response, with marked improvement in ventilatory function, limb strength and postural sense. After the fifth exchange both biceps reflexes returned. Seven days following plasma exchange she had normal power, but there was still residual impairment of tactile sense. At this stage, motor conduction velocities were normal but F waves were absent. All other investigations were normal. Two weeks later, when fully recovered from her neuropathy, she died of overwhelming septicaemia. Limited necropsy examination of her right ulnar nerve showed no evidence of demyelination or cellular infiltration.

Case 5 (HH No 373673) A 31-year-old foreman builder had a 13 year history of chronic relapsing inflammatory polyneuropathy. This was associated with mild relapsing glomerulonephritis, with C3 and IgG deposition in the glomeruli shown by immunofluorescence of renal biopsy material. During his paretic attacks the CSF protein was always elevated (up to 2.6 g/l). Initially each relapse was treated with steroids: clinical recovery began after some two weeks and was complete after about two months. However both prednisolone (60 mg/day) and ACTH (80 units/day) proved ineffective for a relapse in 1977, and were therefore discontinued. He was given azathioprine (100 mg/day) with a slow but satisfactory response, and the drug was stopped in August 1978. In December 1978 there was a slow, progressive clinical relapse. He developed tingling in the fingers and toes with loss of tactile and pain sense over the hands and feet. He became areflexic and vibration sense was lost below the level of the iliac crests. Position sense was grossly impaired, both proximally and distally. Power was diminished in all limbs and his gait was unsteady, preventing him from working. Conduction velocity in the right median nerve was 44 m/s and the terminal latency was 9 ms. No drugs were given, but between February 19 and February 22 1979 he underwent 4 litre plasma exchanges with plasma protein fraction on four occasions. After the second exchange there was some improvement of gait. After the fourth exchange he noted a marked decrease in numbness and tingling. The tactile deficit rapidly receded so that four days after the last exchange sensation was impaired only over the distal 2 cm of the fingers and toes. Both knee jerks and the right triceps jerk returned. Postural sense improved rapidly and was judged as normal six days after the last exchange. Improvement was more rapid than on any of the occasions when steroids, ACTH or azathioprine had been used. He has remained well and, 36 months later, is symptom free.

Case 6 (RFH No BC 5665) A 47-year-old man had an 8 year history of refractory anaemia, lymphadenopathy, arthralgia, intermittent fever and hepatosplenomegaly. An episode of mesenteric venous thrombosis required bowel resection in 1977. He had mild diabetes, controlled by diet, and beta thalassaemia trait. The blood picture and bone marrow findings were compatible with myelofibrosis, and a platelet count of 8000/cmm was associated with antiplatelet antibodies. Antinuclear factor was positive and DNA binding was constantly negative. Hepatitis B surface

antigen was positive as was the DNA polymerase. He had received steroids in 1976 and cytotoxic drugs (including vincristine) in 1977. He underwent splenectomy in 1978. In February 1980 he developed a progressive, symmetrical distal, sensorimotor polyneuropathy. The weakness and sensory loss progressed over six weeks and he became areflexic. His condition remained stable for a month, and he then deteriorated further over a period of two weeks, until he was unable to get up from the sitting posture and needed a stick to walk. Examination of the CSF (in May 1980) showed a protein of 1.6 g/l but no cells. His disability progressed still further over the next few weeks despite the use of prednisolone (60 mg/day), azathioprine (100 mg/day) and a three day course of cyclosporin (20 mg/kg/day). Nerve conduction studies showed reduced motor conduction velocities. His neurological state had remained static for at least a week when his immunosuppressive therapy was stopped and he was given 4 litre plasma exchanges (with 3 litres plasma protein fraction and 1 litre fresh frozen plasma) on five occasions. After the fifth exchange there was slight improvement in power and position sense and walking without a stick again became possible. The improvement was only maintained for a few days. A further relapse occurred three weeks after the last exchange.

Discussion

Of these six patients with inflammatory polyneuropathy, four had acute and two had the chronic relapsing form of the disease. Three of the six cases were deteriorating neurologically at the time of the plasma exchanges. All of these cases improved rapidly. They were the three youngest patients in our series and they had the least muscle wasting. The three in whom response was slower already had marked wasting before plasma exchange was initiated. It is probable that cases 1, 2 and 4 would have required ventilation, but this was avoided in all three instances. Within seven days of the final exchange cases 1 and 4 had improved very substantially. Cases 2 and 6 improved only slightly (in case 6 this was sufficient, nevertheless, for the patient to walk unaided instead of needing a stick). Case 3 showed no signs of improvement one week after the last exchange. Case 6 relapsed after completion of a course of exchanges. His hepatitis B status prevented further management along these lines.

It is difficult to assess the effects of treatment in a disorder such as acute inflammatory polyneuropathy. Most cases recover spontaneously. However in our patients the rate of improvement following the exchanges suggested a therapeutic effect. Case 5 had had a number of earlier relapses treated with either prednisone, ACTH or azathioprine. Clinical improvement on these regimes had never started before two weeks and had never been

complete before two months. With plasma exchange improvement was almost immediate, and has been sustained. Case 4 developed acute inflammatory polyneuritis whilst being successfully haemodialysed. The absence of F waves confirmed the radicular nature of her neuropathy and made it unlikely that uraemia was responsible. Case 6 improved with plasma exchange whereas prednisone and azathioprine had had no effect. Other reported cases have also shown a rapid recovery.^{27 30 32 33} Rail and others³⁴ reported improvement of nerve conduction with return of F waves in a case of acute inflammatory polyneuropathy one hour after plasma exchange. We do not have nerve conduction data on the acute effects of plasma exchange. In general improvements in nerve conduction were less striking than the clinical progress.

Clinical recovery was in general too rapid to be explained by remyelination, and it appears more likely that some factor producing a readily reversible conduction block was being removed. This factor could still be antibody, for transient myelin damage with rapid recovery can be produced in vitro by anti-myelin antibody in the absence of complement.³⁵ Other substances could also be responsible: plasma exchange with plasma protein fraction not only depletes immunoglobulin but also cell secretion factors, immune complexes, mediators of inflammation (including acute phase proteins for example, complement, fibrinogen) and antigen. There are also biochemical effects and probably effects due to temperature, although these are reduced by adding potassium and calcium to the replacement fluids and warming the water bath. Measurement of serum calcium and potassium levels before and after plasma exchange showed no significant change. Acute inflammatory polyneuropathy seems in most cases to be a "single shot" disease, and reversal of the acute process, spontaneously or by plasma exchange, usually leads to complete recovery without relapse. However in chronic relapsing cases the benefits of plasma exchange in an individual relapse may be transient, and immunosuppressive drugs may be needed as well.³³ This may reflect a different pathogenesis, as suggested by their HLA association³⁶ which is not seen in the acute disease.³⁷

Our cases and others reported in the literature suggest that plasma exchange has a place in the treatment of inflammatory polyneuropathy, and also suggests which patients are most likely to benefit. Patients with a chronic relapsing disease appear to respond well, and among acute cases the best results are probably obtained in young patients, in those whose disease is at an early stage and still progressing, and in those without severe muscle wasting. In addition we suggest that plasma exchange should be

tried in any patient whose ventilation is failing, before mechanical assistance is necessary. These are of course preliminary criteria, and others will doubtless be found in the future. Clarification is needed not only concerning the most suitable patients but also concerning the technique and particularly the total volume of plasma to be exchanged. We have aimed for 55 ml/kg exchanges on four consecutive days, which is more than is usually employed. However, this volume may still not be sufficient to remove a tightly bound tissue factor, even though 60% of total IgG would be lost.³⁸ Further studies of this aspect of treatment, as well as more extensive experience of its clinical use, will be needed before the role of plasma exchange in the management of acute inflammatory polyneuropathy can be fully assessed.

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