

SENSORIMOTOR PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS

P.A. McCombe*§, A.C. Klestov†, A.E. Tannenbergt‡,
J.B. Chalk*§, M.P. Pender*§

Departments of Neurology* and Rheumatology†, Royal Brisbane Hospital,
Department of Pathology‡, Mater Hospital and Department of Medicine§,
The University of Queensland, Royal Brisbane Hospital, Brisbane

SUMMARY

We describe 3 patients with severe sensorimotor neuropathy complicating rheumatoid arthritis. Two patients had evidence of vasculitis and an axonal neuropathy. These patients were unusual in that the neuropathy occurred early in the course of rheumatoid arthritis. The third patient had a demyelinating neuropathy with a high cerebrospinal fluid protein level, and is a probable example of a chronic inflammatory neuropathy occurring in rheumatoid arthritis. All patients improved or were stabilized with corticosteroid therapy.

Rheumatoid arthritis may be complicated by compression neuropathy, symmetrical sensory neuropathy or mononeuritis multiplex^{1,2,3,4,5,6,7}. Severe neuropathy affecting sensory and motor function is uncommon^{3,7}, is usually associated with rheumatoid vasculitis, commonly has the characteristics of axonal degeneration⁶ and occurs late in the course of rheumatoid arthritis^{4,7}. We report the histories of 3 patients with rheumatoid arthritis and severe sensorimotor neuropathy who differed from the usual clinical pattern.

CASE REPORTS

Case 1

This 73 year old male developed a left foot drop followed by numbness, pain and increasing weakness of the left lower limb. Three weeks later he developed pain in the right anterior thigh and calf and weakness of the right lower limb and was unable to stand

or walk. Two years previously he had developed pain and swelling in the wrists and in the metacarpophalangeal and proximal and distal interphalangeal joints of both hands. A diagnosis of rheumatoid arthritis was made by his local medical officer and he was treated with oral prednisone and ketoprofen, with relief of symptoms. Seven months before the onset of the foot drop he experienced further pain and swelling of the hands, and then symptoms were again successfully treated with corticosteroids. He had continued to take oral prednisone 10 mg/day until the onset of the weakness.

He had ulnar deviation of the fingers, symmetrical thickening of the metacarpophalangeal joints and wasting of the small muscles of both hands. Several splinter haemorrhages were present under the fingernails, and there were vasculitic skin lesions on the lower limbs and rheumatoid nodules on the flexor aspects of both wrists. There was wasting of both quadriceps and bilateral weakness of hip flexion. There was weakness of dorsiflexion and eversion of both feet. The deep tendon reflexes were normal in the upper limbs, but the knee jerks were reduced and the ankle jerks absent. The plantar responses were flexor. There was loss of pain and light touch sensation in a stocking distribution over both lower limbs up to the mid-calf, and bilateral impairment of joint position and vibration sense in the toes.

The erythrocyte sedimentation rate was 82 mm/hour, the platelet count was $498 \times 10^9/l$, the C-reactive protein level was 130 mg/l (normal <5) and testing for rheumatoid factor was positive with a level of 419 IU (nephelometry; normal <40). The antinuclear factor titre was 1:2560. Serum IgG immune complexes were 153 $\mu\text{g/ml}$ (normal less than 118). Serum immunoglobulin and complement levels were normal. Syphilis serology, human immunodeficiency virus screen and hepatitis B screen were negative. The cerebrospinal fluid protein level was 360 mg/l (normal <400 mg/l). X-rays showed subluxation of the first metacarpophalangeal joints and of the interphalangeal joint of the left thumb and a large erosion of the left ulna. Results of peripheral nerve conduction studies (Table 1) were consistent with axonal degeneration. A lumbar myelogram plus computerized tomographic examination was normal. In the muscle biopsy there was a prominent segmental vasculitis seen as a lymphohistiocytic inflammatory infiltrate involving the walls of a small artery, with thrombosis of the lumen of the artery. There was lymphocytic cuffing of a venule in the adjacent adipose tissue. There was fibre grouping, and atrophic fibres were present. In the sural nerve, light microscopy revealed a severe loss of myelinated fibres. There was evidence of vasculitis affecting perineurial arteries, with lymphoid infiltration of the walls of some and eccentric fibrous scarring and thrombosis of others. Teased fibre examination showed evidence of severe axonal degeneration but no evidence of segmental demyelination. Electron microscopy showed loss of small unmyelinated fibres and evidence of axonal degeneration, but no evidence of primary demyelination.

A diagnosis of peripheral sensorimotor neuropathy secondary to rheumatoid vasculitis was made, and he was treated with prednisone 75 mg/day for 2 weeks. Azathioprine 150 mg/day was then added and the steroid dose was gradually reduced. This treatment produced improvement in his pain but no improvement in his weakness or wasting. The

C-reactive protein level fell to 6 mg/l and the ESR fell to 50 mm/hour. After 2 months, when the prednisone dose had been reduced to 50 mg/day, he developed increased weakness. The C-reactive protein level had risen to 165 mg/l. He was treated with methotrexate 10 mg twice weekly for 3 weeks. His course was then complicated by secondary infections which cleared after treatment with antibiotics and withdrawal of methotrexate. His condition is stable at the time of writing but he continues to have weakness of the lower limbs and is maintained on prednisone and azathioprine.

Table 1 Nerve conduction studies

	Controls	Case 1	Case 2	Case 3
<i>Motor Conduction</i>				
<i>Median Nerve</i>				
Terminal latency (msec)	2.6-4.0	4.5	3.2	7.3
Compound muscle action potential (mV)	5.0-20.0	10.0	6.0	1.0
Conduction velocity (m/sec)	50.0-65.0	47.9	-	45.0
<i>Ulnar Nerve</i>				
Terminal latency (msec)	2.0-3.1	4.3	3.0	5.9
Compound muscle action potential (mV)	7.0-16.0	5.0	5.0	2.0
Conduction velocity (m/sec)	50.0-66.0	59.7	48.0	35.5
<i>Lateral Popliteal Nerve</i>				
Terminal latency (msec)	2.9-5.6			10.2
Compound muscle action potential (mV)	2.5-14.0	No Response	No Response	<0.2
Conduction velocity (m/sec)	41.0-56.0			22.5
<i>Sensory Conduction</i>				
<i>Median Nerve</i>				
Sensory action potential (μ V)	10.0-50.0	Absent	10.0	Absent
<i>Ulnar Nerve</i>				
Sensory action potential (μ V)	5.0-44.0	Absent	8.0	Absent

Case 2

This 63 year old woman presented in December 1986 with 7 days of difficulty in walking. She noticed inability to dorsiflex the right foot and 6 days later inability to

dorsiflex the left foot. For one month she had also had numbness of both feet, particularly on the lateral aspects, and of the fingers. For 4 months she had experienced pain and stiffness of the fingers, wrists, elbows, shoulders, knees, ankles, feet and temporomandibular joints which responded poorly to treatment with non-steroidal anti-inflammatory drugs. In December 1985 she had experienced an episode of pancreatitis secondary to gallstone obstruction, and had undergone cholecystectomy in January 1986. One month before the onset of the presenting neuropathic symptoms she had been found to be diabetic.

There was swelling and tenderness of the shoulder, wrist, proximal and distal interphalangeal, knee and ankle joints bilaterally. There was wasting of the quadriceps and the intrinsic muscles of the hands. Both hands also had features of flexor tenosynovitis. There were no rheumatoid nodules. There was weakness of all muscle groups, but the weakness was worse distally and there was bilateral absence of ankle dorsiflexion. The deep tendon reflexes were normal in the upper limbs, but the knee jerks were reduced and the ankle jerks absent. There was reduction in perception of all modalities of sensation over the fingers of the right upper limb in the distribution of the ulnar nerve and over the feet up to the ankles, with additional sensory loss over the lateral aspects of the legs.

Serum urea, creatinine, electrolytes and thyroid function tests were normal. The blood glucose level was 13.6 mmol/l, and the glycosylated haemoglobin level was 12.4 (normal <6.5). Serum B12 and folate levels were normal. The creatine kinase level was 240 u/l (normal range 20-140 u/l). The ESR was 80 mm/hour at the onset of the neuropathy and the platelet count was $636 \times 10^9/l$. The C-reactive protein level was 216 mg/l (normal <5 mg/l), rheumatoid factor was present with a titre of 1:256 (Rose-Waaler) and the antinuclear factor titre was 1:160. Serum immunoglobulin and complement levels were normal. Hepatitis B surface antigen was not present. The CSF protein level was 260 mg/l (normal <400 mg/l). X-rays of the hands showed generalized osteoporosis and early juxta-articular erosions of the proximal phalanges of the left 5th and the right 2nd digits. Nerve conduction studies were consistent with axonal degeneration (Table 1). In the muscle biopsy there was evidence of type II muscle fibre atrophy, but no evidence of acute or chronic denervation or of polymyositis. One artery showed perivascular cuffing with a sparse mononuclear cell infiltrate that also focally invaded the arterial wall, which was thickened. A sural nerve biopsy showed extensive loss of myelinated fibres. There was a focal sparse lymphocytic vasculitis involving the small vessels of the perineurium. Skin biopsy showed a focal sparse lymphocytic vasculitis involving a small vessel near the sweat glands and several vessels of the superficial dermal plexus.

The patient was treated with insulin. However, her neurological problems became worse and she developed a vasculitic rash over the lower limbs, with the sudden onset of pain and numbness of the right thumb and weakness in the upper limbs. She also developed pain in the posterior thighs. Because of the progression of the neuropathy at the time of the development of vasculitic lesions, a diagnosis of rheumatoid vasculitis causing neuropathy was made. She was treated with 4 pulses of 1 or 2 g intravenous

methylprednisolone over 2 weeks and oral cyclophosphamide 100 mg/day for one week and then cyclophosphamide 150 mg/day for 2 weeks. The neurological signs stabilized and the pain settled dramatically. After this initial therapy, oral prednisone 75 mg/day was commenced and the cyclophosphamide dose was reduced. The ESR fell to 40 mm/hr. She has since been taking low dose (5 - 10 mg) prednisone daily and has become mobile and independent, although she continues to have symptoms and signs of neuropathy.

Case 3

This 72 year old female developed paraesthesiae in the feet and legs, pains in the legs and feet, lower limb weakness, loss of balance and difficulty in walking. She was admitted to hospital 2 weeks after the onset of symptoms and continued to deteriorate for another 4 to 6 weeks. She had a past history of rheumatoid arthritis which commenced at the age of 35 years and affected her hands, wrists, elbows, shoulders, neck, ankles, feet and hips. She had been treated at different times with non-steroidal anti-inflammatory drugs, gold injections and corticosteroids. She was not being treated with corticosteroids at the onset of the neuropathy, but was taking phenylbutazone and naproxen.

She had ulnar deviation of the fingers and swelling of the metacarpophalangeal joints. There was pain on movement of the neck, hands, wrists, knees and feet. There was deformity of the toes, and synovial thickening of the knees. There was no evidence of cutaneous vasculitis. Cranial nerve examination was normal. There was weakness of the lower limbs but in the upper limbs power was normal except for difficulties associated with the rheumatoid hand deformities. The upper limb reflexes were normal but the knee and ankle jerks were absent. There was impairment of all modalities of sensation in a stocking distribution up to the knees. In the upper limbs, sensation was normal. Romberg's sign was positive. She continued to deteriorate after admission to hospital, the weakness and sensory disturbance spreading to the upper limbs.

Serum urea, electrolytes, liver function tests and thyroid function tests were normal. Serum complement and immunoglobulin levels were normal. Serum electro-phoresis suggested an acute phase reaction. The ESR was 64 mm/h at the onset of the neuropathy. The platelet count was $321 \times 10^9/l$. Rheumatoid factor was present with a titre of 1:40 (Rose-Waaler). Testing for anti-nuclear factor was negative. The results of nerve conduction studies are shown in Table 1 and were consistent with primary demyelination. The CSF protein was 990 mg/l.

She was given oral prednisone 80 mg on alternate days and had a gradual reduction in pain and improvement in strength. The steroid dose was gradually tapered. About 6 months after the onset of neuropathy, when she was receiving prednisone 10 mg on alternate days, there was clinical and biochemical evidence of an increase in the activity of the rheumatoid arthritis. This responded to increasing the dose of steroids, and later to treatment with penicillamine. Six years after the onset of the first episode of neuropathy she became weaker and had increased pain in the lower limbs. The CSF

protein was 2,400 mg/l. She improved with an increased dose of prednisone and since then has been steroid dependent, with continuing evidence of peripheral neuropathy.

DISCUSSION

All 3 patients fulfilled the criteria for the diagnosis of rheumatoid arthritis⁸ and had evidence of disease activity at the onset of their neuropathy, which in all cases was of a severe sensorimotor type. The first 2 patients had cutaneous vasculitis and mononeuritis multiplex with additional symmetrical neuropathy. In these patients the duration of rheumatoid arthritis before the onset of neuropathy was brief (4 months to 2 years). This contrasts with the observations of Chamberlain and Bruckner⁴ that patients had a mean duration of rheumatoid arthritis of 9.9 years before the onset of severe sensorimotor neuropathy and with the view of Conn⁷ that sensori-motor neuropathy develops in patients with longstanding rheumatoid arthritis. Patient 2 also had a history of diabetes mellitus which had developed after pancreatitis 12 months previously. However, the simultaneous occurrence of new neuropathic lesions and vasculitic skin lesions, the muscle, nerve and skin biopsy evidence of vasculitis, the biochemical evidence of active rheumatoid arthritis and the beneficial response to immunosuppression strongly suggest that rheumatoid arthritis was the cause of the neuropathy. These 2 patients are similar to those described by Vollertsen *et al.*⁹ in a survey of rheumatoid vasculitis. In our patients the biopsies showed evidence of vasculitis and axonal degeneration such as described by Conn *et al.*⁶ in rheumatoid neuropathy. Beckett and Dinn¹⁰ also found axonal degeneration and arterial occlusion in their 2 patients with clinical rheumatoid neuropathy. Van Lis and Jennekens¹¹ and Conn *et al.*⁶ have found immunoglobulin and complement deposition in the nerves of patients with rheumatoid neuropathy. In our patients the neuropathy was progressive until treated with aggressive immunosuppression. Beneficial effects of azathioprine in rheumatoid neuropathy have also been reported by Chamberlain and Bruckner⁴ and Conn⁷ recommended aggressive treatment of rheumatoid sensorimotor neuropathy. We confirm that early aggressive treatment of vasculitic neuropathy associated with rheumatoid arthritis is beneficial and may prevent involvement of other areas of the peripheral nervous system.

In Case 3, rheumatoid arthritis had been present for 35 years before the onset of neuropathy. There was no evidence of cutaneous vasculitis but laboratory tests indicated that the rheumatoid arthritis was active, although less so than in Cases 1 & 2. The CSF protein was increased, and the electro-physiological abnormalities were consistent with primary demyelination. These features, and

the clinical history of response to steroids and relapse with steroid withdrawal, are typical of an inflammatory demyelinating polyneuropathy such as chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP). It is difficult to decide whether this was a chance relationship or whether the rheumatoid arthritis had influenced the development of neuropathy. There is a report of a patient with rheumatoid arthritis developing an acute inflammatory demyelinating polyradiculo-neuropathy¹², and studies of chronic inflammatory demyelinating polyradiculo-neuropathy have found that some patients have associated autoimmune diseases^{12,13}. There are also reports of chronic demyelinating neuropathy developing in patients with other rheumatological diseases such as systemic lupus erythematosus or Sjögren's syndrome^{14,15}. In the sural nerves taken from rheumatoid arthritis patients without clinical or electrophysiological evidence of neuropathy there was segmental demyelination⁹. Conn and Dyck¹⁶ argued that, in rheumatoid arthritis, arterial occlusion causes ischaemic axonal degeneration and secondary demyelination. However, in our patient there was evidence of a primary demyelinating neuropathy. In the presence of active rheumatoid arthritis, it seems possible that the development of the neuropathy may have been directly or indirectly related to the rheumatoid arthritis. One mechanism by which rheumatoid arthritis could cause demyelinating neuropathy is that of 'vasculomyelinopathy'¹⁷ where it is proposed that immune complex deposition in blood vessels may lead to the entry of inflammatory cells into the neural parenchyma, with resultant primary demyelination. Another explanation is that rheumatoid arthritis may be associated with a disturbance in immunoregulation which predisposes to the development of an inflammatory neuropathy. Thus, while it is not certain that the neuropathy in this patient was related to the rheumatoid arthritis, similar associations may be found with other autoimmune diseases, and there are possible mechanisms by which this can occur.

We have described subacute sensorimotor neuropathy with mononeuritis multiplex in 2 patients with active rheumatoid arthritis and vasculitis. These patients developed neuropathy within a short period of the onset of rheumatoid arthritis and obtained benefit from immunosuppressive treatment. In the third patient there was a relapsing sensorimotor neuropathy with primary demyelination but no clinical evidence of vasculitis. This patient also responded well to corticosteroids.

ACKNOWLEDGEMENTS

Dr PA McCombe holds an NHMRC R Douglas Wright New Investigator Award and Dr JB Chalk is an NHMRC Postgraduate Medical Scholar.

REFERENCES

1. Hart FD and Goldin JR. Rheumatoid neuropathy. *British Medical Journal* 1960; 1:1594-1600.
2. Steinberg VL. Neuropathy in rheumatoid disease. *British Medical Journal* 1960; 1:1600-1603.
3. Good AF, Christopher RP, Koepke GH, Bender LF and Tarter ME. Peripheral neuropathy associated with rheumatoid arthritis: A clinical and electrodiagnostic study of 70 consecutive rheumatoid arthritis patients. *Annals of Internal Medicine* 1965; 63:87-99.
4. Chamberlain MA and Bruckner FE. Rheumatoid neuropathy : clinical and electrophysiological features. *Annals of Rheumatic Disease* 1970; 29:609-616.
5. Weller RO, Bruckner FE and Chamberlain MA. Rheumatoid neuropathy. A histological and electrophysiological study. *Journal of Neurology, Neurosurgery and Psychiatry* 1970; 33:592-604.
6. Conn DL, McDuffie FC and Dyck PJ. Immunopathologic study of sural nerves in rheumatoid arthritis. *Arthritis and Rheumatism* 1972; 15:135-143.
7. Conn DL. Rheumatoid neuropathy. In: Utsinger PD, Zvaifler NJ, Ehrlich GE (eds). *Rheumatoid Arthritis*. Philadelphia, Lippincott 1985; pp 365-378.
8. Arnett FC . Revised criteria for the classification of rheumatoid arthritis. *Bulletin of Rheumatic Disease* 1989; 38:1-6.
9. Vollertsen RS, Conn DL, Ballard DJ, Ilstrup DM, Kazmar RE and Silverfield JC. Rheumatoid vasculitis : survival and associated risk factors. *Medicine* 1986; 65:365-375.
10. Beckett VL and Dinn JJ. Segmental demyelination in rheumatoid arthritis. *Quarterly Journal of Medicine* 1972; 41:71-80.
11. Van Lis JMJ and Jennekens FGI. Immunofluorescence studies in a case of rheumatoid neuropathy. *Journal of the Neurological Sciences* 1977; 33:313-321.
12. Korn-Lubetzki I and Abramsky O. Acute and chronic demyelinating inflammatory polyradiculoneuropathy. Association with autoimmune disease and lymphocyte response to human neurotogenic protein. *Archives of Neurology* 1986; 43:604-608.
13. McCombe PA, Pollard JD and McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical and electrophysiological features of 92 cases. *Brain* 1987; 110:1617-1630.
14. Rechthand E, Cornblath DR, Stern BJ and Myerhoff JO. Chronic demyelinating polyneuropathy in systemic lupus erythematosus. *Neurology* 1984; 34:1375-1377.
15. Gross M. Chronic relapsing inflammatory polyneuropathy complicating sicca syndrome. *Journal of Neurology Neurosurgery and Psychiatry* 1987; 50:939-940.
16. Conn DL and Dyck PJ. Angiopathic neuropathy in connective tissue diseases. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R (eds): *Peripheral Neuropathy*. Philadelphia, Saunders, 1984 pp 2027-2043.
17. Reik L. Disseminated vasculomyelinopathy: an immune complex disease. *Annals of Neurology* 1980; 7:291-296.