

SHORT REPORT

Mononeuritis multiplex in diabetes mellitus: evidence for underlying immune pathogenesis

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Four patients with type 2 diabetes mellitus developed mononeuritis multiplex subacutely. Sural nerve biopsies showed multifocal axonal loss in all patients, with epineurial perivascular inflammation affecting small calibre vessels in three. Three patients improved with immunotherapy. These observations suggest that mononeuritis multiplex in diabetes may be caused by an immune mediated vasculopathy and that it is pathogenetically akin to the more common and better recognised diabetic amyotrophy.

Mononeuritis multiplex is defined as a disorder involving two or more named peripheral nerve trunks and most often occurs in collagen vascular disorders or as a manifestation of non-systemic vasculitis restricted to peripheral nerves.¹ Although diabetes mellitus is commonly mentioned as a cause of mononeuritis multiplex,¹ very few cases have been clearly documented in published reports. Furthermore, the mechanism of the nerve injury is uncertain. We previously reported preliminary findings in two diabetic patients with mononeuritis multiplex suggesting an inflammatory basis.² We now report clinical, electrophysiological, and sural nerve biopsy findings and the treatment outcome in four diabetic patients with mononeuritis multiplex.

CASE REPORTS

Four patients with type 2 diabetes who developed mononeuritis multiplex were evaluated in the neuromuscular clinics at the Universities of Minnesota and Iowa between 1995 and 2001. All patients had undergone detailed medical and neurological examination. None had any systemic autoimmune disorder, malignancy, toxic exposure, or HIV risk factors. Laboratory studies included haemoglobin A1C, erythrocyte sedimentation rate (ESR), anti-nuclear and Sjogren's syndrome antibodies, rheumatoid factor, and serum immune fixation electrophoresis.

Investigations

Nerve conduction and needle electromyographic studies (EMG) were done using conventional techniques. Sural nerve biopsies were undertaken using a standard approach. The specimen was divided into two 2 cm sections. One piece was stretched and fixed in glutaraldehyde/paraformaldehyde and used for plastic embedded sections stained with MAB (methylene blue, azure II, basic fuchsin). The unstretched sample was fixed in 10% formalin and stained with haematoxylin and eosin, and in two cases with immunohistochemical monoclonal stains for T and B lymphocytes.

Treatment

Patients were treated with immunosuppressive agents including intravenous immune globulin, oral prednisone, intravenous pulsed methylprednisolone, and oral chlorambucil.

Description of case 1

A 47 year old man with a four year history of type 2 diabetes, treated with an oral hypoglycaemic agent, had had mild symmetrical numbness in the feet for four years. Eighteen months before our initial evaluation he noted left foot drop with painful onset, which progressed over six months, requiring a brace and the use of a cane. Four months later he developed pain of sudden onset in the right wrist, numbness, and weakness progressing to wasting of the interosseous muscles. Two months later he developed numbness over the dorsum of the left hand and increased weakness in the right hand. After another two months he developed pain and numbness in the left T8 dermatome. He had lost 13.6 kg (30 pounds) over the 18 months but had no other constitutional symptoms.

Examination showed severe weakness and atrophy in the right interossei with normal strength in the abductor digiti minimi, and left foot drop. Sensory examination revealed decreased cutaneous sensation in the distribution of right ulnar, left dorsal ulnar cutaneous, and left superficial peroneal nerves along with mild distal symmetrical loss in the lower extremities. Tendon reflexes were normal including the ankle jerks.

Laboratory evaluation was normal or negative, including antinuclear antibodies, rheumatoid factor, serum immune fixation, ESR, and C reactive protein. HbA1C was 7.0%.

Electrodiagnostic studies

Bilateral sural and left ulnar sensory nerve action potential amplitudes were reduced. Right ulnar motor study recorded from the abductor digiti minimi was normal. With recording over the first dorsal interosseus muscle, however, there was marked reduction in the compound muscle action potential (CMAP) amplitude, suggesting fascicular involvement of the ulnar nerve. Left peroneal CMAP amplitude was markedly reduced, while right peroneal and bilateral tibial CMAP amplitudes were normal. Needle EMG showed profuse fibrillation in the right first dorsal interossei muscle with absent motor unit potentials (MUP). Fibrillations were also seen in left tibialis anterior with large amplitude polyphasic MUP and moderately reduced recruitment.

Left sural nerve biopsy (fig 1, panels A to C) showed moderate loss of large myelinated fibres with inhomogeneous distribution suggesting multifocal ischaemic nerve injury. There were several areas with perivascular collections of > 50 mononuclear cells (T lymphocytes) surrounding small epineurial blood vessels. There was no fibrinoid necrosis or transmural inflammation.

The patient was treated with oral prednisone 60 mg/day for six weeks, followed by gradual taper over one year. Pain improved within one month of treatment and weakness started improving within six weeks, with nearly complete recovery of motor and sensory deficits and independent ambulation within six months. Prednisone has been discontinued for over two years and the patient remains well.

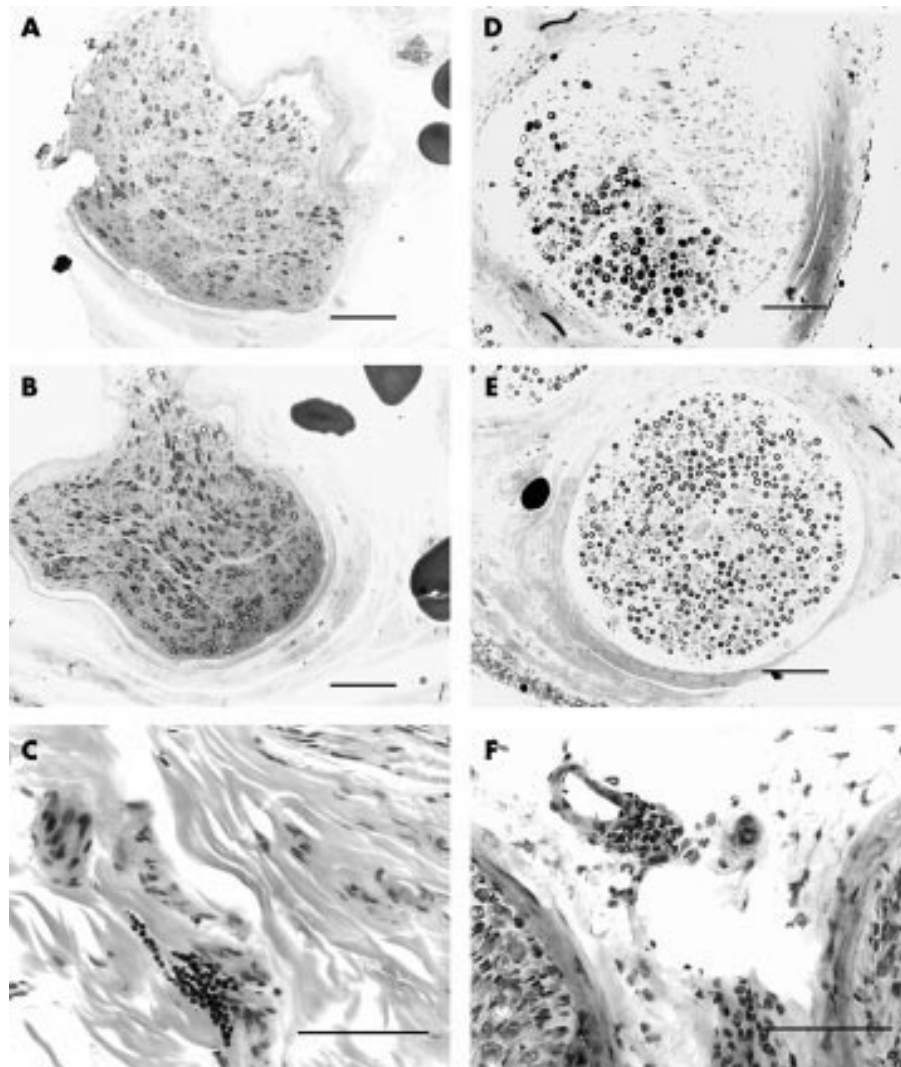


Figure 1 Panels A–C are from patient 1 and panels D–F are from patient 2. Panels A, B, D, and E (methylene blue, azure II, and basic fuschin stain) show moderate loss of large myelinated fibres with variation in fibre density within and between fascicles, which is characteristic of a microangiopathic process. Panels C and F (haematoxylin and eosin stain) show perivascular collections of mononuclear inflammatory cells affecting epineurial vessels, without fibrinoid necrosis or transmural inflammation. (Calibration bar, 100 μ m.)

Overview of clinical features and investigations in the four cases

Three of our four patients were women. Patients were 47 to 72 years of age, and the duration of diabetes was one to four years. All patients had type 2 diabetes mellitus; three were treated with oral hypoglycaemic agents and one (patient 2) with insulin. All presented with mononeuropathy multiplex evolving in a stepwise manner over 16 to 18 months (table 1). All patients reported moderate to severe pain in the region of the affected nerves. They all had motor and sensory deficits in the distribution of the affected nerves in addition to mild distal symmetrical sensory loss in the feet. Ulnar and peroneal nerves were affected in all the patients. Three patients had weight loss of 6.8 to 13.6 kg (15 to 30 pounds). Two patients had a raised ESR (54 and 70 mm/h) with no other clinical or serological evidence of a systemic autoimmune disorder. HbA1C was mildly raised in all patients (6.4% to 7.0%).

Electrodiagnostic studies

Electrodiagnostic studies showed reduced or absent sensory and motor responses in the distribution of the affected nerves, indicating axonal degeneration in all patients. No patient showed focal slowing of conduction velocity or segmental temporal dispersion of responses across potential sites of

compression. One patient had a more than 50% amplitude decrement in the ulnar nerve in the mid-forearm at the time of the initial study. A repeat study 10 days later showed that the distal amplitude had fallen, indicating that this was non-continuity conduction block, probably caused by an acute ischaemic lesion. Sural sensory potentials were absent in two and reduced in two (to 1.8 and 3 μ V).

Sural nerve biopsies showed multifocal loss of axons in all four patients (fig 1). Three had perivascular collections of mononuclear inflammatory cells (T lymphocytes) surrounding small calibre epineurial blood vessels, consisting of > 50 lymphocytes (fig 1C) in one, and smaller collections of 20 to 50 lymphocytes in two (fig 1F). None showed fibrinoid necrosis or transmural inflammation.

One patient had complete resolution of weakness and sensory loss within six months of treatment with prednisone. One continued to deteriorate in spite of prednisone and intravenous immune globulin, though her condition eventually improved spontaneously two years after presentation. One patient improved with intravenous pulsed methylprednisolone, 500 mg weekly for 12 weeks; she relapsed with increasing pain and weakness four weeks later, with subsequent improvement with a second course, along with oral chlorambucil. One patient improved over three months

Table 1 Clinical features and treatment outcome

Case	Age/sex	Duration of DM	Progression of MM (months)	Weight loss (kg)	Involved nerves	Functional limitations	Pain	Treatment	Follow up (months)	Pain	Functional status
1	47/M	4 years	18	13.6	R ulnar, L peroneal, L dorsal ulnar cutaneous, L T8	Brace and cane	Severe	Prednisone	24	Resolved within one month	Normal: independent walking
2	55/F	4 years	18	11.4	L>R peroneal, L ulnar	Wheelchair	Severe	Prednisone, IVIG	12	No change	No response: wheelchair
3	72/F	1 year	16	6.8	L>R peroneal	Walker	Moderate	IVM, chlorambucil	6	Improved in two months	Improved: ambulation, cane
4	61/F	3 years	16	None	R>L peroneal, L femoral	Brace and cane	Moderate	IVM, chlorambucil	6	Improved in two months	Improved: ambulation, brace, and cane

DM, diabetes mellitus; F, female; IVIG, intravenous immunoglobulin; IVM, intravenous pulse methylprednisolone 500 mg weekly for 12 weeks; L, left; M, male; MM, mononeuritis multiplex; R, right.

with intravenous pulsed methylprednisolone followed by oral chlorambucil. Pain improved remarkably in these three patients within one to two months of the treatment. There was no change in the distal symmetrical sensory neuropathy in the feet following treatment in any of the four patients.

DISCUSSION

The clinical spectrum of multifocal neuropathies in diabetes includes diabetic amyotrophy, truncal neuropathies, cranial neuropathies, mononeuropathies, and mononeuritis multiplex.³ Mononeuritis multiplex differs from diabetic amyotrophy in that it has slower stepwise progression, distal extremity involvement, and sensory-motor multifocal abnormalities, whereas diabetic amyotrophy progresses more rapidly and has predominantly proximal, almost exclusively motor, involvement.⁴ Peroneal and ulnar nerves were involved in all our patients as well as in most of the previously reported cases⁵⁻⁸ and these nerves seem to be particularly susceptible. Pain and weight loss are common in both disorders.

We do not believe that these were compressive neuropathies as the characteristic features of focal nerve compression—namely, conduction slowing and temporal dispersion—were lacking. Rather, these patients had multifocal axon loss presumably secondary to nerve ischaemia. This may explain the presence of severe pain which is common with ischaemic nerve injuries.

Mononeuritis multiplex most often occurs in collagen vascular disorders or as a manifestation of non-systemic vasculitis restricted to peripheral nerves.¹ Although diabetes is often included among the causes of this disorder,¹ we have found only five clearly documented cases affecting the extremity nerves in diabetic patients in English language reports.⁵⁻⁸ The prevalence of true mononeuritis multiplex in diabetes is unknown and it is possible that the condition is underrecognised. There have been no large series of cases, and some that have been reported as having mononeuropathy multiplex in fact had diabetic amyotrophy. Biopsy findings were reported in three of the above five patients with mononeuritis multiplex and showed multifocal axon loss and perineuritis.^{7,8} Immunotherapy (plasma exchange and prednisone in one, intravenous immune globulin in one, and prednisone in one) were given in these three patients and two improved.^{7,8}

All four of our patients showed inhomogeneous fibre loss and three had perivascular inflammatory infiltrates consisting of > 50 or > 20 T lymphocytes, suggesting that an immune mediated vasculopathy was the underlying cause of their neuropathy. Scattered mononuclear cells are a non-specific finding and can be seen in diabetes; however, perivascular collections of lymphocytes, especially of more than 10 to 20 cells,

are usually interpreted as evidence of an inflammatory condition. We therefore treated our patients with immunosuppressive agents and one made a nearly complete recovery, while two improved to a lesser extent. We also noted marked improvement in pain in these patients with treatment. One patient failed to respond to treatment initially, but had eventual improvement over a two year period. The natural history of mononeuritis multiplex in diabetes is unknown and our numbers are small, but we feel there was probably a true therapeutic response in the three patients, as in each of them the disease had continued to progress until the treatment was started. Likewise marked improvement in pain suggests a therapeutic response. These patients also had mild distal symmetrical sensory loss in the feet, which probably reflected the more common length dependent, predominantly sensory polyneuropathy in diabetes, which remained unchanged following the immune treatment.

There is increasing evidence that diabetic amyotrophy is caused by ischaemic nerve injury secondary to microvasculitis rather than diabetic microangiopathy.⁹ Furthermore it appears that diabetic amyotrophy may be amenable to immunotherapy.¹⁰ Our findings suggest that mononeuritis multiplex occurring in diabetes may have a similar pathogenesis and that these patients can show a favourable response to immunosuppressive treatment. We recommend that patients with diabetes who develop mononeuritis multiplex should undergo nerve biopsy to look for inflammatory changes. Immune modulating treatments should be considered even in the absence of inflammatory changes, especially in patients who have progressive neuropathy. A larger study is required to explore the pathophysiology, natural history, and possible treatment options for patients with mononeuritis multiplex in diabetes.

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NEUROLOGICAL PICTURE.....

Coccidioidomycosis of the brain, mimicking en plaque meningioma

A 38 year old woman, originally from the Pacific Islands with a history of residence in south western United States, presented with new onset severe headaches. Past medical history included disseminated coccidioidomycosis involving cervical lymph nodes two years earlier, which was incompletely treated with oral fluconazole because of non-compliance. Serum complement fixation coccidioides titres had risen from 1:8 to 1:32. MRI demonstrated multiple isointense, dural based lesions that uniformly enhanced upon contrast administration. These were located over the right parieto-occipital convexity (fig 1a) as well as on the tentorium at the left occipital pole (fig 1b). These lesions were consistent in appearance with en plaque meningiomas. Given the patient's history, however, the possibility of chronic dural inflammation from coccidioidomycosis of the CNS was also considered. The patient was started on high dose fluconazole (800 mg) therapy and

followed with serial MRIs. Despite improvement in the patient's headaches, follow up MRI showed minimal change in lesion size. The patient underwent a left occipital craniotomy and biopsy for definitive diagnosis three months after reinitiating fluconazole. Intraoperatively, numerous bosselated, firm, dural based lesions were noted pushing into the surface of the brain. Pathological evaluation of the biopsy revealed granulomatous inflammation consistent with smoldering coccidioidomycosis (fig 1c).

Coccidioidomycosis is an endemic fungus of south western United States.¹ Infection results from inhalation of windborne arthrospores and characteristically manifests with pulmonary symptoms. An infrequent complication of coccidioidomycosis is dissemination beyond the lung and hilar lymph nodes to bone, skin, subcutaneous tissue, and joints.² In addition, infection may spread to the CNS, typically causing chronic

meningitis.³ Our case illustrates an exceedingly rare example of CNS coccidioidomycosis resulting in dural based mass lesions resembling meningiomas. The treatment for this condition remains controversial. Patients who fail oral fluconazole therapy may be candidates for intravenous amphotericin B and surgical debulking. The roles of experimental therapies such as caspofungin or variconazole remain undefined in the treatment of coccidioidomycosis CNS mass lesions.

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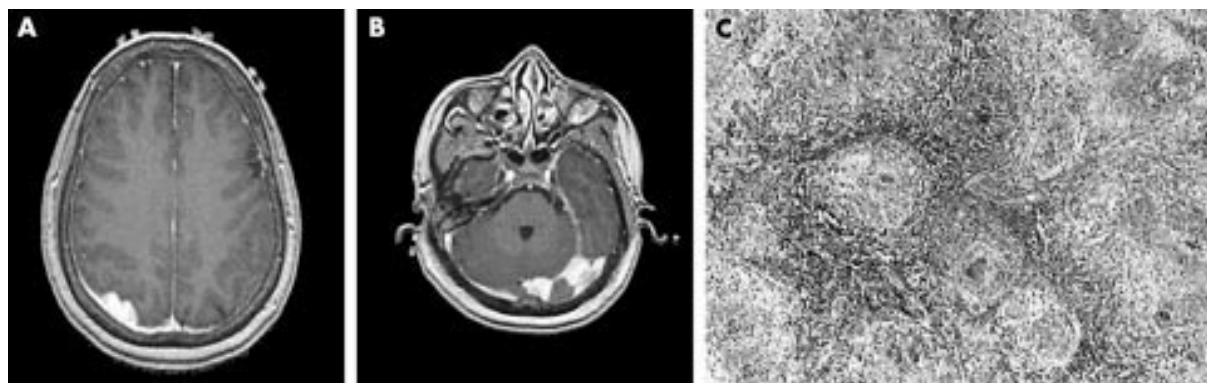


Figure 1 (A) Gadolinium enhanced MRI demonstrating an enhancing dural lesion over the right parieto-occipital convexity. (B) Gadolinium enhanced MRI demonstrating an enhancing dural lesion along the left tentorium near the transverse sinus. (C) Microscopic appearance of the dural biopsy. The specimen shows confluent granulomata of various sizes, some of which demonstrate centrally necrotic foci, and multinucleated giant cells. The larger granulomata display hyalinisation (haematoxylin and eosin stain; original magnification $\times 50$).