Q J Med 2012; **105**:1119–1123
doi:10.1093/qjmed/hcr166 Advance Access Publication 14 September 2011

Case report

QJM

Elevated cerebrospinal fluid protein in diabetic lumbosacral radiculoplexus neuropathy

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An 86-year-old ex-sailor with Type 2 diabetes was admitted in September 2010, with a 3-year history of weakness and pain in his legs, ataxia, recurrent falls, significant difficulties in walking and getting up, intermittent paraesthesia in his feet with strong jerks in the lower limbs and unintentional weight loss of 4 stones over the last few years. He was an ex-smoker and had previous history of chronic pancreatitis, Stage 3 chronic kidney disease, right shoulder pain with impingement syndrome, bilateral Dupuytren's contracture, right carpal tunnel release operation, bilateral cataracts surgery and early dry macular degeneration. He underwent left hemicolectomy for Dukes' B adenocarcinoma of the splenic flexure with no distal metastases. His medication included Metformin and Creon.

Three years earlier, he was investigated in the neurology clinic, with similar complaints of falls and ataxia. He had stopped drinking excessive amounts of alcohol by 2006. Previous investigations revealed normal or negative results including haematinics, erythrocyte sedimentation rate, autoantibody screening, antineutrophilic cytoplasmic antigen (ANCA: c and p), serum immunoglobulins, paraneoplastic antibodies (negative for HU, YO, RI, MA, TA and TR), blood and cerebrospinal fluid (CSF) treponemal antibodies, HIV 1 and 2 antibodies, coeliac disease screening, rheumatoid factor, complement and prostatic specific antigen. CSF showed normal cytology, glucose and no oligoclonal bands were detected; CSF protein was high at 2.84 g/l while CSF serology for Lyme disease was negative. Previous Computerized tomogram (CT) of abdomen and pelvis was consistent with calcified chronic pancreatitis. Previous nerve conduction study/Electromyography (NCS/EMG) showed axonal sensory and motor generalized neuropathy; repeat study in 2008 showing extensive polyradiculoneuropathy, with prolonged F wave latences in the upper limbs, some degree of demyelination in the nerve roots but no electrophysiological evidence of distal demyelination at this stage. He was initially treated in 2007–08 with diazepam, baclofen and clonazepam as an inpatient for jerky leg movements. By 2010, this gentleman was becoming more and more caravan-bound. Unfortunately, he collapsed and was readmitted in September 2010 and was found to be generally hyporeflexic on examination with equivocal planter responses, bilateral leg wasting, diffuse dimunition of light touch sensation in the glove and stocking distribution, fasciculations and reduced vibration sensation in the lower limbs; sense of coordination was normal and sitting balance was reasonably good. There were no signs to suggest cerebellar involvement. The visual fields and speech were normal. Investigations revealed neutrophilic leucocytosis with raised C-reactive protein, 76.3 mg/l (NR: 1–5) with negative or normal urine culture, haematinics, renal, liver, bone, throid with good glycaemic control (HbA1c: 6.7%, 50 mmol/l). Tumour markers, creatine kinase and blood lead level were normal; serum and urine electrophoresis revealed no abnormal bands with normal CXR. Magnetic resonance

imaging (MRI) showed generally diffuse degenerative changes in the whole spine, small disc protrusions at C3/4, C4/5 and C5/6 levels indenting the thecal sac, moderate degree of canal stenosis at L2/3, L3/4 and L4/5 level with no intrinsic or extrinsic cord compression. CSF revealed very high protein (4.74 g/l) with normal cytology, glucose and culture; CSF oligoclonal bands were weakly positive in inflammatory pattern. NCS/EMG on this occasion revealed evidence of mixed axonal and demyelinating polyneuropathy; sensory nerve action potentials were of reduced amplitude in the upper limbs and absent in the lower limbs with distal motor latencies mildly prolonged and F wave latencies in the demyelinating range in the upper limbs, motor conduction velocity in the demyelinating range in the left median nerve suggesting peripheral nerve demyelination. Concentric needle EMG sampling showed evidence of chronic partial denervation with reinervation in all the muscles in the lower limbs with scanty positive sharp waves, fibrillation potentials in the right tibialis anterior, increased insertional activity in the medial gastrocnemius muscles with chronic denervation changes in the quadriceps muscle, consistent with a diagnosis of polyradiculoneuropathy (Figures 1–4). Clinical features, raised CSF protein along with EMG/NCS led to the diagnosis of diabetic polyradiculoneuropathy; he was commenced on steroids (prednisolone 60 mg per day) on a reducing dose regimen and a repeat lumbar puncture was planned after 6 weeks. He was also commenced on insulin, Lansoprazole and weekly Alendronate. His CRP returned to normal after commencing steroids. He was referred to the physiotherapists before his discharge and was subsequently readmitted 6 weeks later in October 2010 for repeat lumbar puncture which showed a significant reduction in CSF protein (0.75 g/l) with normal glucose, cytology and culture while continuing on steroids. This gentleman was also seen in the neurosurgical clinic and was offered C4/5 intralaminal decompression procedure, however, he elected for conservative management. Post discharge, he was followed up in December 2010 when he was feeling much better on steroids with no further weight loss and was using a frame in the house for walking and had noticed improved posture balance as he was standing up much longer in the kitchen with legs feeling much stronger and no recent falls.

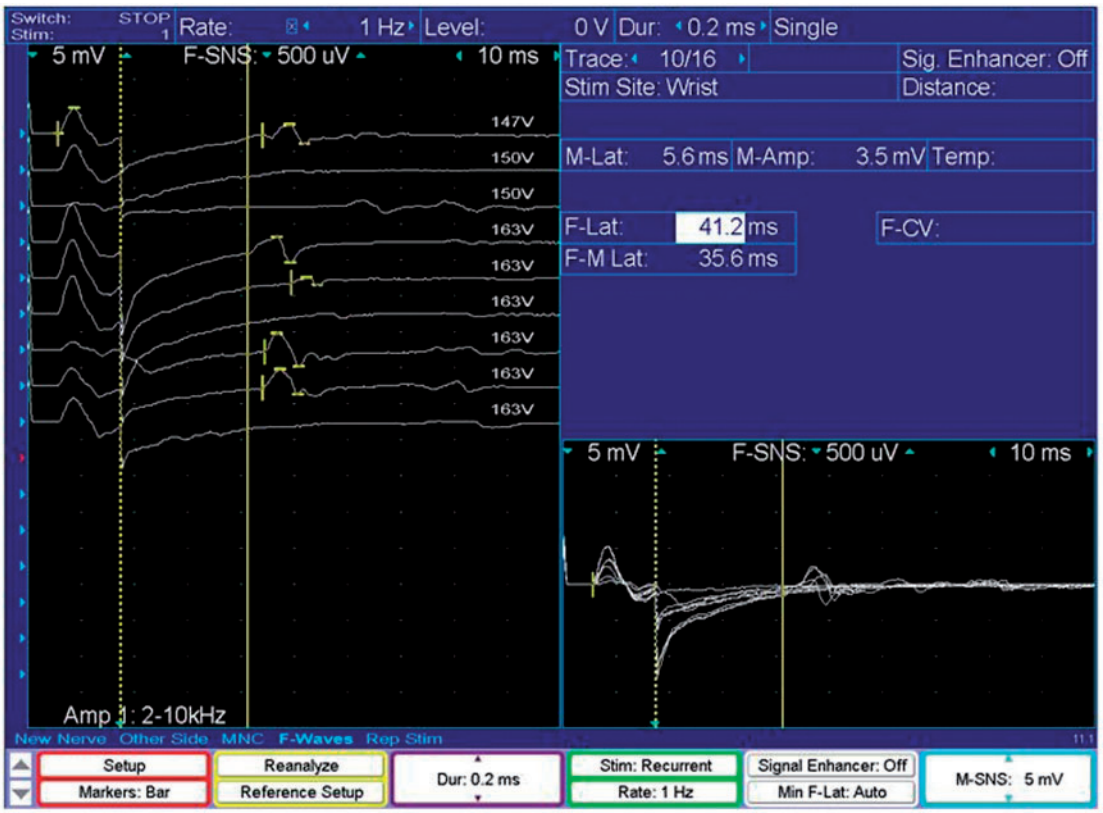

Figure 1. Mixed demyelinating and axonal neuropathy with the prolonged F-wave latency (41.2 ms) in the demyelinating range in the right median nerve.

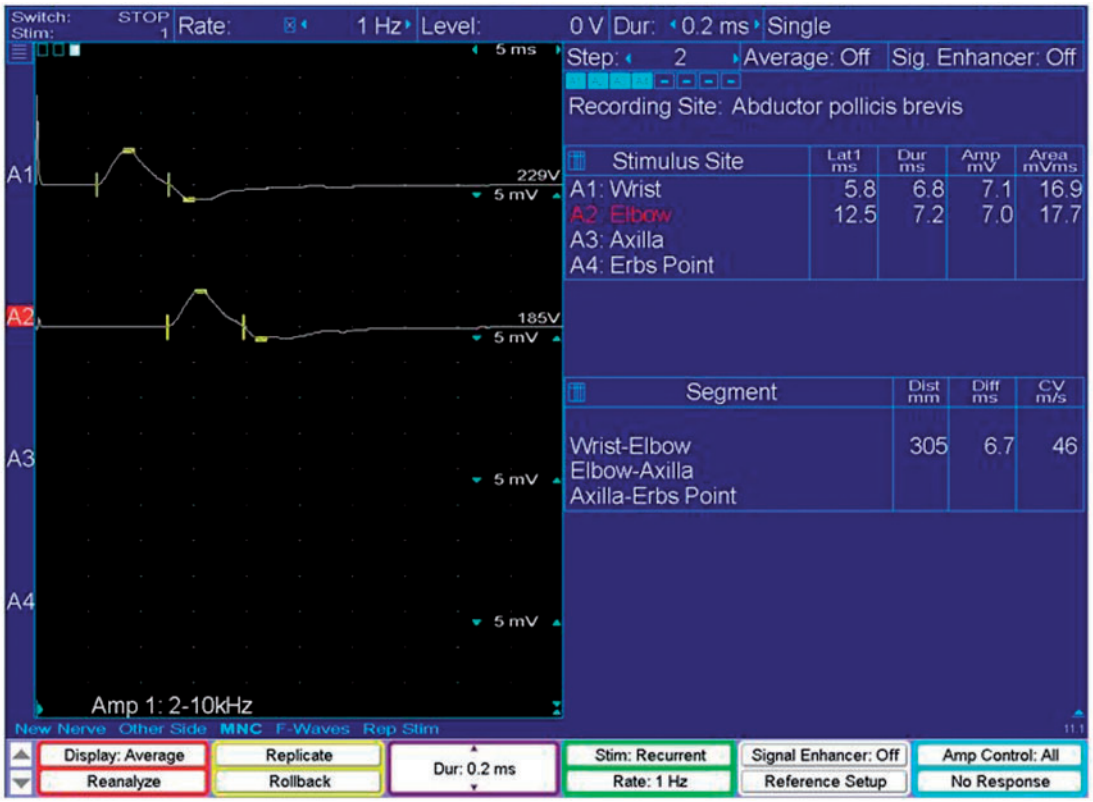

Figure 2. Mixed demyelinating and axonal neuropathy with prolonged motor latency and mildly reduced motor conduction velocity in the right median nerve.

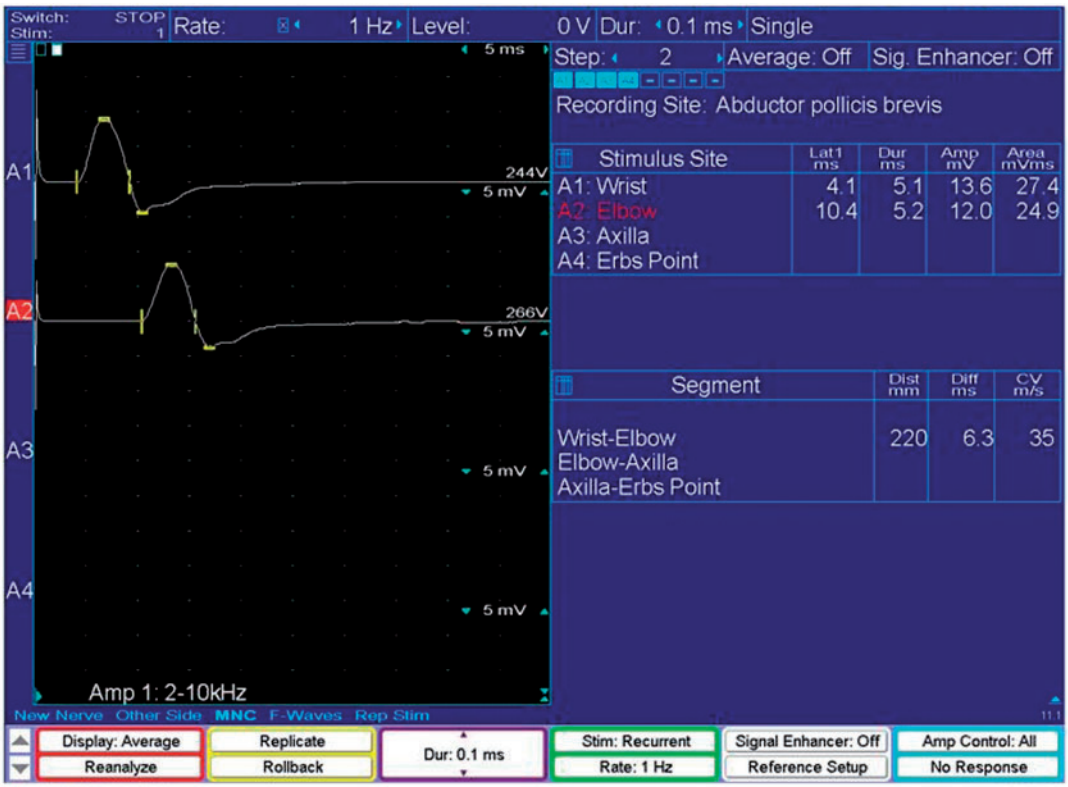

Figure 3. Mixed demyelinating and axonal neuropathy with left median nerve's motor conduction velocity of 35 ms.

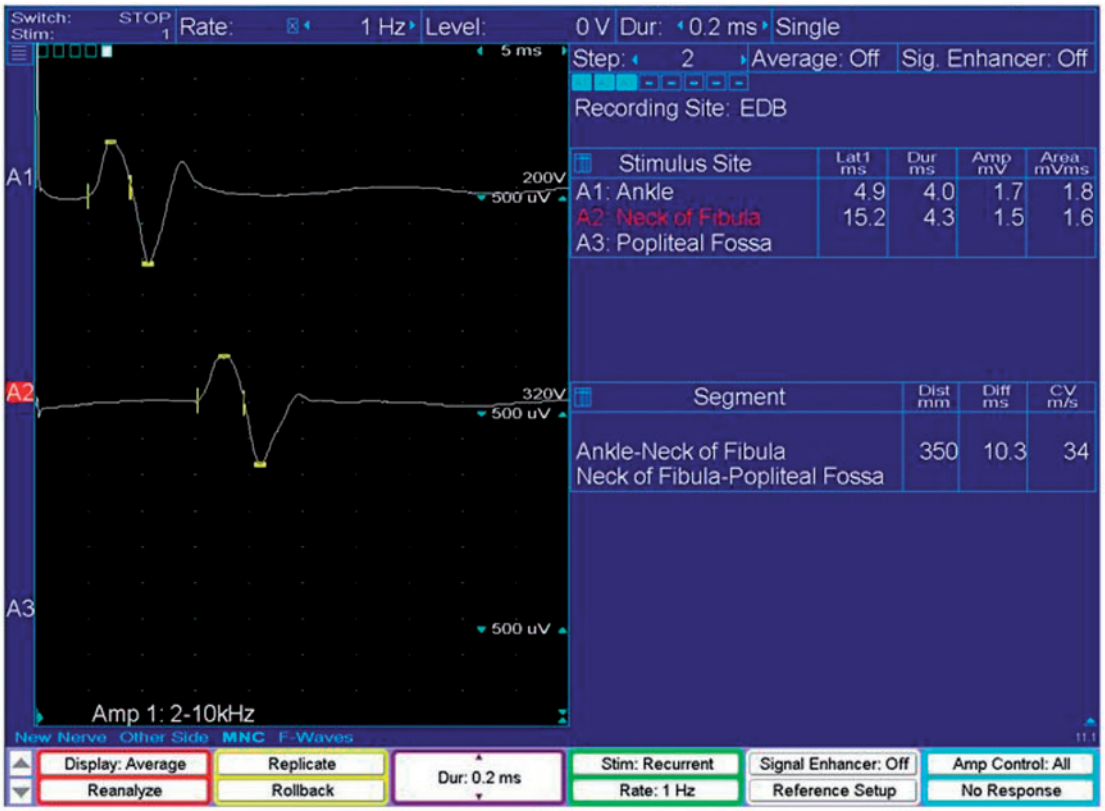

Figure 4. Mixed demyelinating and axonal neuropathy. Right common peroneal nerve showing normal distal motor latency with motor conduction velocity in the axonal neuropathy range.

Discussion

Diabetic lumbosacral plexus neuropathy is associated with weight loss, often beginning focally or asymmetrically in the thigh or leg but usually progressive to involve initially the unaffected segment and the contra-lateral side.[1] This condition could present with motor symptoms, distal weakness, imbalance, rarely proximal motor weakness such as amyotrophy and is more common in older people. The demyelinating polyneuropathy is electrophysiologically indistinguishable from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with similar histological features, however, is distinct from the more common axonal polyneuropathy reported in diabetic patients.

Several types of painful neuropathies are common in diabetes mellitus, including symmetrical sensory motor polyneuropathy, single or multiple mononeuropathy, autonomic neuropathy, truncal radiculopathy, plexopathy and proximal motor neuropathy. Pathological studies of diabetic nerves have shown segmental demyelination in addition to axonal loss, vasculopathy and inflammatory infiltrates.[2] Peripheral sensory motor demyelinating neuropathy indistinguishable from CIDP has been reported in literature in both Type 1 and Type 2 diabetes. It represents a clinical picture of predominantly motors symmetric weakness, proximal and distal, associated with hyporeflexia or areflexia and a relapsing or a chronic progressive course. In one study CIDP was found to be 11 times higher in diabetic than in non-diabetic patients.[2] Both CIDP and the non-diabetic lumbosacral radiculoplexus neuropathy (LSRPN) can cause prolonged morbidity due to pain, paralysis, autonomic involvement and sensory loss, most likely secondary to ischaemic injury and microvasculitis. Main pathophysiological mechanisms proposed for diabetic neuropathy are ischaemic nerve injury and microvasculitis (microangiopathy) with an autoimmune component. A reasonable working hypothesis is that multifocal demyelination develops in ischaemic nerve trunks. The subacute progression or progressive symmetric or asymmetric motor or sensory deficit despite optimal diabetes control and unusually high CSF protein level in diabetic neuropathy should alert the clinician to the possibility of an underlying treatable demyelinating peripheral neuropathy, masquerading as diabetic neuropathy.[3] In one study, patients with diabetic CIDP treated with weekly intravenous

methylprednisolone showed marked improvement of the neurological symptoms and signs. Nerve biopsy can sometimes clinch the diagnosis where loss of myelinated fibres, small amount of onion bulbs and thickening of the basement membrane of arterioles with predominant demyelination has been reported.[4]

The following diagnostic criteria have been suggested in one study:[5]

1. proximal weakness of subacute evolution (during a period of 1–3 months)
2. bilateral involvement or unilateral weakness, followed by involvement of the opposite limb within 2 months
3. reduced or absent knee tendon reflexes
4. increased CSF protein concentration
5. progression for at least 2 months and
6. electrophysiological evidence of polyradiculoneuropathy.

Immunotherapy including intravenous immunoglobulins has been found to be effective in some patients with several types of diabetic neuropathy. There is evidence to suggest that treatment might be more effective than no treatment. In one study, immunomodulatory treatment resulted in more rapid improvement, beginning in less than 1 month while untreated patients had no improvement for at least 6 months. A patient with inflammatory neuropathy and raised CSF protein when treated with methylprednisolone and immunoglobulins, rapidly induced a striking improvement of his neurological condition.[6] Another patient with diabetic amyotrophy and raised CSF protein responded to therapy with methylprednisolone and beneficial effects were reported, pain subsiding immediately after starting the therapy and motor strength gradually improved.[7] The main role for attempted treatment with immunomodulatory therapy is to speed recovery, diminish painful neuropathy and possibly limit the burden of deficits. Treatment should be for patients who have severe bilateral progressive deficits, unable to walk or having rapid progression of their condition with or without severe neuropathic pain for which therapeutic intervention can sometimes provide rapid and dramatic relief. Treatment with steroids in patients as in ours necessitates daily dosing and adjustment of insulin dose. Patients who receive intravenous immunoglobulin or plasma exchange will usually need treatment for at least 3 months. Separation of immune-mediated, demyelinating polyneuropathy in diabetic patients from axonal polyneuropathy is important because the former responds to immunomodulatory treatment as reported in our patient.

Conflict of interest: None declared.

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