Human immunoglobulin for diabetic amyotrophy—a promising prospect?

A E Courtney, G V McDonnell, V H Patterson

Abstract

Diabetic neuropathies are universally recognised and cause significant morbidity. At present improving glycaemic control is the only recognised treatment. A man with type 2 diabetes presented with disabling asymmetric lower limb proximal neuropathy. Rapid clinical, functional, and electrical improvement followed treatment with intravenous immunoglobulin. The aetiology of diabetic amyotrophy remains controversial but there is evidence for an immune mediated process and this case suggests a role for immunoglobulin in the management of this debilitating condition.

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Case report

A 63 year old former labourer presented with a five month history of progressive proximal leg weakness and weight loss. Previously well, his walking distance had been unrestricted and he had been riding a bicycle. A steady decline led to mobilisation with a Zimmer frame and great difficulty climbing stairs. He complained of a painful burning sensation in his left shin and numbness of the left leg. There had been a 12 kg weight loss in four months. Diabetes mellitus had been diagnosed six months previously and dietary treatment initiated.

On examination he was pale and thin (body mass index 20) with quadriiceps wasting and fasciculation. Tone was normal, power (Medical Research Council scoring) was reduced: left hip flexion, 4+; right hip flexion, 3; left knee flexion and extension, 4. Both knee jerks were absent but both ankle jerks were present. Plantar responses were bilaterally flexor. Below the left knee light touch sensation was diminished and vibration sensation was absent.

Investigations revealed a raised glycated haemoglobin of 9.7% (standardised to Diabetes Control and Complications Trial, normal <7%), and creatine kinase was less than 20 U/l. Full blood picture, liver function tests, and urea and electrolytes were normal. Nerve conduction velocities were generally slowed: median and ulnar nerves 40 m/s (normal >50 m/s) and lateral popliteal 24 m/s (normal >40 m/s). Responses were of low amplitude but there was no evidence of conduction block. Electromyography was mildly abnormal with neurogenic type changes, particularly in the lower limbs. Muscle histology revealed variation in fibre diameter with occasional fibre degeneration, and scattered angulation. Although there was no evidence of vasculitis, a macrophage reaction was noted in the interstitium and in relation to the degenerating fibres. The overall findings were consistent with denervation.

The patient was treated with intravenous human immunoglobulin (IVIg), 2 g/kg of body weight in divided doses over five days. A basal bolus insulin regimen was started to improve glycaemic control. After three days of IVIg there was significant subjective and objective improvement in lower limb function. By the time of discharge after one week, there was full power in all muscle groups and knee reflexes had returned. The only remaining sensory abnormality was of absent vibration sense at the left great toe. Nerve conduction velocities had significantly improved: median and ulnar nerves 50 m/s, lateral popliteal 32 m/s. The patient was discharged on insulin, glycaemic control also having improved.

Discussion

Clinically significant neuropathy is well described in diabetes mellitus and can take a variety of forms, autonomic and somatic systems both being affected (Box 1). Although in the published literature some authors reserve the title of diabetic amyotrophy for a unilateral weakness of acute onset, it is generally accepted to include those with subacute onset of bilateral (if asymmetrical) lower limb weakness and atrophy. The typical patient is middle aged or older with type 2 diabetes and symptoms of weakness, followed by wasting of proximal lower limb muscle and reduced or absent reflexes, often accompanied by pain and weight loss. Although initial

Box 1: Types of diabetic neuropathies

Symmetric
- Distal symmetric polyneuropathy.
- Autonomic neuropathy.
- Transient distal sensory neuropathy.
- Diabetic neuropathic cachexia (rare).

Asymmetric
- Diabetic amyotrophy (proximal diabetic neuropathy, diabetic lumbosacral radiculoplexopathy).
- Cranial neuropathy.
- Truncal radiculopathy.
- Isolated mononeuropathy.
Human immunoglobulin for diabetic amyotrophy

symptomatology is typically unilateral, by the time of clinical assessment there is usually evidence of bilateral involvement, the latency to involvement of the second leg ranging from three days to eight months. The onset with severe pain in the back, hip, or thigh frequently leads to a misdiagnosis of a compressive lumbosacral radiculopathy. Sensory symptoms are not a prominent feature but it is recognised that a peripheral sensory neuropathy can coexist. The natural course is self-limiting, with slow and sometimes incomplete recovery. Cases have been documented in which there has been worsening for 18 months. The onset with bilateral involvement of the second leg ranging from three days to eight months. The onset with bilateral involvement of the second leg ranging from three days to eight months. The onset with bilateral involvement of the second leg ranging from three days to eight months. The onset with bilateral involvement of the second leg ranging from three days to eight months.

Although neuropathies are frequent sequelae of diabetes, amyotrophy in itself is relatively uncommon and its pathogenesis remains uncertain. The assumption of ischaemic aetiology has been increasingly challenged over the past decade by evidence, direct and implied, supporting an inflammatory basis. Nerve biopsy specimens of the intermediate cutaneous nerve of the thigh in cases similar to this one have demonstrated an inflammatory vasculopathy in severe cases. While there are no publications of similar studies to demonstrate vasculitis in the motor nerves, it is suggestive of an immune mediated process.

The other topical theory is demyelination. Electrophysiological studies can be supportive of this, and the clinical features and raised cerebrospinal fluid protein concentrations are similar to chronic inflammatory demyelinating polyneuropathy (CIDP). It is debatable as to whether CIDP is simply more common in patients with diabetes than in the general population, or whether demyelination contributes to the separate entity of proximal motor polyneuropathy as a secondary event.

The clinical response to immunomodulatory treatment demonstrated in this case provides further corroborative evidence. Although studies have generally involved small numbers of patients with a variety of neuropathies and treatment has often been given in combination with other immunomodulatory drugs, there are now several reports in the literature of a reversal in deficits in response to intravenous immunoglobulin. In one retrospective study, three of four patients treated with IVIg at a dosage of 0.4 g/kg twice weekly for several months had improvement in muscle strength and reduced neuropathic pain. Other patients in that centre, treated with plasma exchange or corticosteroids, had a gradual improvement over many months. However 59% of the untreated group also improved, although this was not statistically significant and was not evident until at least six months. A separate study involving 15 patients with “multifocal axonal inflammatory vasculopathy”, most of whom would fit the description of diabetic amyotrophy, reported early benefits beginning during treatment with IVIg given over five days. The third study treated five patients with “proximal diabetic neuropathy” with IVIg and all were reported to have improved.

The electrophysiological improvement demonstrated in our patient is not unique and it might be argued that it could be due to better glycaemic control. To date, tight glycaemic control remains unproved in its efficacy to rapidly reverse diabetic peripheral neuropathy. The Diabetes Control and Complications Trial has indicated that intensive treatment markedly delays the presentation of clinically significant polyneuropathy. Others have previously demonstrated improvements in motor conduction velocity and vibration perception threshold in diabetic neuropathy treated with continuous subcutaneous insulin infusion (CSII). A further study of 18 insulin dependent patients demonstrated a mean improvement in median, ulnar and peroneal motor nerve conduction of 2.5 m/s following 12 months of CSII. However we believe that the more acute and much larger improvement seen in this case is a function of IVIg rather than tighter glycaemic control.

If the underlying pathogenesis of diabetic motor neuropathy is an interplay between immune mediated vasculitis and demyelination, then it is reasonable that immunosuppression will produce a favourable response. There is strong evidence suggesting that IVIg is beneficial in CIDP. As the biological effects in vivo have yet to be fully elicited, the mechanisms underlying recovery remain equivocal. One theory suggests IVIg may have anti-idiotypic antibodies that have regulatory effects on antibody production and lymphocyte activity. Alternatively, blockade of macrophage Fc receptors by IVIg may modulate their autogressive activities, or IVIg may act as a receptor for activated complement components preventing their binding to myelin proteins. The down-regulation and neutralisation of cytokine production by IVIg is another feasible mechanism of action.

Any treatment producing a rapid resolution of symptoms and functional improvement in patients with diabetic amyotrophy would reduce the significant morbidity associated with the condition. In this case there was a dramatic improvement subjectively and objectively, both on clinical examination and electrophysiologically.

A randomised control trial is required to determine if intravenous immunoglobulin should be standard first line treatment for diabetic amyotrophy. For illustrative purposes only, assuming 60% of patients given IVIg

Learning points

- Neuropathies are a common complication of diabetes mellitus.
- Type 2 diabetics may develop asymmetrical lower limb proximal motor neuropathy, known as diabetic amyotrophy.
- Recent evidence suggests that the pathogenesis is immune mediated damage with superimposed demyelination.
- Immunosuppression, for example with intravenous immunoglobulin, has been beneficial in some cases.
- More evidence is required before this therapy can be advocated as standard treatment.

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demonstrate improvement in motor conduction velocity of 5 m/s compared with 30% on standard therapy, 80 subjects would detect this difference with a power of 0.8 and alpha value of 0.05. As most centres will see no more than a handful of cases annually, a multicentre collaboration will be necessary.

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