CASE REPORTS

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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Keywords: diabetes mellitus; neuropathy; immunoglobulin

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 quadriceps 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 limbs 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.
symptomatology is typically unilateral, by the
time of clinical assessment there is usually evi-
dence of bilateral involvement, the latency to
involvement of the second leg ranging from
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 coex-
st. 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.

Although neuropathies are frequent sequelae of
diabetes, amyotrophy in itself is relatively
uncommon and its pathogenesis remains un-
certain. The assumption of ischaemic aeti-
ology has been increasingly challenged over the
past decade by evidence, direct and implied,
supporting an inflammatory basis. Nerve
biopsy specimens of the intermediate cutane-
ous nerve of the thigh in cases similar to this
one have demonstrated an inflammatory vascu-
lopathy 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 cer-
ebrospinal fluid protein concentrations are
similar to chronic inflammatory demyelinating
polynuropathy (CIDP). It is debatable as to
whether CIDP is simply more common in
patients with diabetes than in the general
population, or whether demyelination contrib-
utes to the separate entity of proximal motor
polyneuropathy as a secondary event.

The clinical response to immunomodulatory
treatment demonstrated in this case provides
further corroboration evidence. Although stud-
ies 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
denent 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 amyotro-
phy, 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 dem-
onstrated 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 rap-
idly reverse diabetic peripheral neuropathy.
The Diabetes Control and Complications Trial
has indicated that intensive treatment mark-
edly delays the presentation of clinically
significant polyneuropathy. Others have previ-
ously demonstrated improvements in motor
conduction velocity and vibration perception
threshold in diabetic neuropathy treated with
other immunomodulatory therapies. Continuous
subcutaneous insulin infusion (CSII). A further study of 18 insulin depend-
ent patients demonstrated a mean improve-
ment 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 demyelina-
tion, then it is reasonable that immunomodula-
tion will produce a favourable response. There
is strong evidence suggesting that IVIg is ben-
eficial in CIDP. As the biological effects in
vivo have yet to be fully elicited, the mecha-
nisms underlying recovery remain equivocal.
One theory suggests IVIg may have anti-
idiotypic antibodies that have regulatory effects
on antibody production and lymphocyte activ-
ity. Alternatively, blockade of macrophage Fc
receptors by IVIg may modulate their autoag-
gressive activities, or IVIg may act as a receptor
for activated complement components pre-
venting their binding to myelin proteins. The
down-regulation and neutralisation of cytokine
production by IVIg is another feasible mech-
anism of action.

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

A randomised control trial is required to
determine if intravenous immunoglobulin
should be standard first line treatment for dia-
betic 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 asymmetri-
cal 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.
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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