

THE DIABETIC NEUROPATHIES: TYPES, DIAGNOSIS AND MANAGEMENT

J Gareth Llewelyn

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J Neurol Neurosurg Psychiatry 2003;74(Suppl III):ii15–ii19

Although over the years the considerable breakthroughs made in our understanding of diabetic neuropathy has come from both neurologists and diabetologists, in recent times (in the UK) it is diabetologists that have assumed the main clinical role in diagnosing and managing the most common neuropathy in the western world. It may therefore be that referral of patients with diabetic neuropathy from the diabetic clinic only occurs if there is a neurologist with a particular interest or if help is required regarding a specific issue such as an atypical clinical picture or pain control. This creates a risk that those training in neurology end up with a somewhat skewed view of the spectrum of diabetic neuropathies. The other situation where neurologists come across diabetic neuropathy is when the patient is found to have diabetes in the course of investigating a peripheral neuropathy.

DIAGNOSIS OF DIABETES MELLITUS

Diagnosis of diabetes mellitus (DM) is made on a combination of typical symptoms—weight loss, thirst, weakness and fatigue—with a persistently raised blood glucose (table 1). Glycosuria and raised HbA1c values alone are not used to make the diagnosis of diabetes mellitus.

CLASSIFICATION OF THE DIABETIC NEUROPATHIES

Based on a modification of the classification proposed by PK Thomas, a number of distinct syndromes are identifiable (table 2).

Hyperglycaemic neuropathy

Tingling paraesthesia, pain or hyperaesthesia in the feet have long been described in patients with newly diagnosed DM or those with very poor glycaemic control, this being the phenomenon of hyperglycaemic neuropathy. The symptoms, and slowing of nerve conduction, are rapidly reversed by improving glucose control.

Diabetic symmetric distal polyneuropathy with autonomic neuropathy

This is the most common diabetic neuropathy and it is characterised by a length related distal distribution of sensory and motor symptoms and signs. As autonomic involvement occurs in many patients with diabetic symmetric distal polyneuropathy (DSDP), and forms an important part of the clinical complex, it is best that both are considered together.

It is highly likely that by the time DSDP is diagnosed, the patient with either type 1 or type 2 diabetes will have had a prolonged period (sometimes over years) of abnormal glucose metabolism. This is particularly the case in those with type 2 DM who tend to be “discovered” to be diabetic on presentation with symptoms and signs of a neuropathy. It is also worth remembering that it is usual to find evidence of either retinopathy or nephropathy in any case of DSDP—whether newly diagnosed or long established.

Some patients with DSDP have no symptoms, but the most common complaint is of tingling, buzzing or prickling sensations affecting the feet, which may also feel tight or hot or cold. The symptoms are often, but not exclusively, symmetric in distribution. The patient may complain of numbness or “as if my feet are wrapped up in cotton wool”. The pains in the feet are often worse at night—although this phenomenon is not unique to DSDP.

Clinical signs

The cardinal sign is absent ankle reflexes (table 3). Without this, it is difficult to make a diagnosis of DSDP. Loss of knee reflexes occurs in about two thirds of cases, but loss of any upper limb reflexes occurs in only a quarter of patients with DSDP. Muscle weakness is usually mild and confined to the feet, mainly in the distribution of the common peroneal nerve and more obviously affecting extensor hallucis longus and extensor digitorum brevis compared with dorsiflexion and eversion. Proximal leg weakness can be seen, but this, together with the presence of significant upper limb weakness, should make one suspicious of an alternative diagnosis and only after appropriate investigations are negative can a diagnosis of DSDP be made in these cases.

Correspondence to:
Dr Gareth Llewelyn,
Department of Neurology,
Royal Gwent Hospital,
Newport NP20 2UB, UK;
gareth.llewelyn@gwent.wales.nhs.uk

Table 1 Biochemical diagnosis of diabetes mellitus

Random plasma glucose	>11.1 mmol/l, or
Fasting plasma glucose	>7.8 mmol/l, or
2 hour plasma glucose during GTT*	>11.1 mmol/l

*Glucose tolerance test using 75 g glucose load.

Table 2 Classification of the diabetic neuropathies

- ▶ Generalised neuropathy
 - hyperglycaemic neuropathy
 - symmetric distal polyneuropathy with/without autonomic neuropathy
 - acute painful sensory neuropathy variants
- ▶ Focal and multifocal neuropathy
 - cranial neuropathies
 - focal limb neuropathies
 - thoracolumbar radiculoneuropathy
 - lumbosacral radiculoplexus neuropathy (Bruns-Garland syndrome)

Table 3 Clinical assessment in diabetic symmetric distal polyneuropathy (DSDP)

- ▶ Look for any deformity, callus or foot ulcer, infection or fissure
- ▶ Absent ankle reflexes (mandatory)
- ▶ Test all sensory modalities starting at the toes and fingertips (in many diabetic screening clinics, vibration sensation and neurofilament sensitivity are the only modalities tested and this seems to be an effective part of a neuropathy screen)
- ▶ Weakness of small foot muscles (extensor hallucis longus and extensor digitorum brevis)
- ▶ Check resting pulse and blood pressure lying and standing
- ▶ Check peripheral pulses
- ▶ Look for retinopathy
- ▶ Check urine for protein

Sensory disturbance is very common. Vibration sense at the toes is most frequently affected. Pin prick, temperature, and light touch sensations are lost in a sock or stocking distribution, and if there is upper limb sensory loss in a glove distribution, the level of impairment in the legs has to have reached mid thigh. If not, look for another explanation for the upper limb sensory loss. Testing of deep pain sensation can be done by applying pressure over the nail of the big toe with the handle of the patella hammer. Any sensory loss puts the diabetic foot at risk of ulceration. Based on the relative loss of sensory modalities, one can arbitrarily divide the neuropathy into “large fibre type” (predominant loss of vibration, light touch, and joint position senses) and “small fibre type” (predominant loss of pain and temperature), but these subgroups are uncommon and represent both ends of the continuum of DSDP.

In more severe cases, sensory loss can extend to involve the trunk, affecting initially the anterior chest/abdominal wall in a “breastplate” distribution, and may extend laterally around the trunk.

Clinically significant symptomatic autonomic neuropathy is relatively uncommon, but specific autonomic function tests are said to show an abnormality in 97% of patients with DSDP. If there is a prominent autonomic neuropathy but only a very mild DSDP or no distal polyneuropathy in a patient with diabetes, think of another cause for autonomic disturbance.

Table 4 Blood tests in a patient with DSDP

- ▶ B12 and folate values
- ▶ Serum protein electrophoresis
- ▶ ANA/ENA/rheumatoid factor
- ▶ Thyroid function
- ▶ FBC/ESR, U&Es and LFTs

ANA, antinuclear antibody; ENA, extractable nuclear antigen; ESR, erythrocyte sedimentation rate; FBC, full blood count; LFT, liver function test; U&E, urea and electrolytes

What should be considered in a differential diagnosis?

Although diabetes is a common condition, there is the possibility that there may be another cause for the distal neuropathy. Good history taking (alcohol, family history of neuropathy, drug history, etc) and a few basic blood tests (table 4) should be enough to secure the diagnosis of DSDP.

What atypical features might suggest an alternative or additional neuropathy?

(1) *Severe autonomic neuropathy with mild DSDP*: One has to consider amyloid neuropathy which can produce a small fibre neuropathy with spontaneous pains, but where autonomic features are prominent. The clinical features of familial and non-familial amyloidosis will be very similar

(2) *Rapidly progressive motor component*: When there is prominent weakness, the possibility of a superimposed chronic inflammatory demyelinating polyneuropathy (CIDP) has to be considered. There is some evidence that CIDP may be more common in patients with diabetes than in the general population. Nerve conduction studies may be helpful. CSF protein will be elevated in both CIDP and DSPD, but the presence of oligoclonal bands would point to CIDP.

Painful DSDP variants

Although it is not clear whether either of the two syndromes outlined below are distinct entities or simply part of the spectrum of painful DSDP, it is of value to be aware of their existence.

Insulin neuritis

A severe painful sensory neuropathy can be seen in relation to tightening of glucose control. This can be seen when trying to improve glucose control in a patient already established on insulin, or in patients being started on insulin for the first time. The pain is often difficult to control, and as with other painful diabetic neuropathy syndromes, is worse at night. Clinical signs are not uncommonly minimal or even absent. Nerve conduction studies may be normal.

Over a period of up to 12 months, recovery is usual.

Acute painful neuropathy with severe weight loss

Originally termed “diabetic neuropathic cachexia”, this uncommon condition occurs predominantly in male patients with poorly controlled type 1 diabetes. Females who try to control their diabetes by not eating and become anorexic also develop a similar painful neuropathy. Pronounced weight loss is the key feature. The distal lower limb pain is severe, with burning and tightness of the feet. Depression is not uncommon.

The weight loss is dramatic, and when body weight stabilises—usually after a period of improved glucose control with insulin—the pain begins to abate. It can take up to 12 months for improvement to occur and a further 1–2 years for recovery of body weight back to normal and for the pain to subside completely.

Table 5 When should nerve conduction studies be requested, and a nerve biopsy considered, in a diabetic with a distal polyneuropathy?

When should nerve conduction studies be requested?
(1) When there is a rapid progression of limb weakness (for example, superimposed CIDP)
(2) When there is a family history of neuropathy with clinical features to suggest underlying CMT disease
When should a nerve biopsy be considered?
(1) If there is prominent early autonomic neuropathy (amyloid)
(2) If there is rapid progression of limb weakness (CIDP)
(3) If there is a rapid multifocal clinical pattern (vasculitis—combining the nerve biopsy with a muscle biopsy will increase the yield of diagnosis of vasculitis)

CIDP, chronic inflammatory demyelinating polyneuropathy; CMT, Charcot-Marie-Tooth.

Summary

Development of DSDP is more common with longstanding diabetes, being male and tall. It is usually, if not invariably, associated with retinopathy and/or nephropathy. In a patient with DM who has developed symptoms and signs of a distal polyneuropathy, check the blood tests outlined in table 4, and if these are all normal then the diagnosis of DSDP is secure. Nerve conduction studies add little.

Where there are atypical clinical features further investigations including nerve conduction studies will be required, and one may also consider a nerve (and muscle) biopsy (table 5).

Aetiology

There is still some way to go before being able to put together a unifying hypothesis for the pathogenesis of DSDP. From experimental diabetic neuropathy, a wide range of metabolic changes have been found with some factors interconnecting (table 6). The fact that none of these metabolic derangements has reproduced the pathological changes seen in human DSDP, has promoted the search for a vascular aetiology.

Many questions remain unanswered, particularly those relating to how metabolic changes within the nerve of a diabetic patient might predispose it to vascular injury. When we are closer to finding the answer, the search for more specific effective treatments can begin.

Treatment

Strict glucose control from the time of diagnosis of DM is the most important aspect of treatment. This has been clearly

demonstrated in type 1 DM where tight glycaemic control reduces the risk of developing DSDP by 69% at five years. The same has not yet been shown for type 2 DM, but one might suspect similar outcomes. Once established, DSDP is irreversible and slowly progressive. At this stage, strict glucose control provides no clinically significant improvement from the patient's perspective, despite modest improvement in vibration threshold and nerve conduction studies.

From the research studies that identified metabolic abnormalities, a variety of potential treatments have been investigated—for example, aldose reductase inhibitors, myo-inositol supplementation, α lipoic acid, and administration of nerve growth factor—but none have had sufficient impact on DSDP to be approved as a specific long term treatment. Pancreatic transplantation is of real benefit only in those who have advanced renal failure and could undergo a combined kidney and pancreas transplant, despite studies that have shown that pancreatic transplantation can halt the progression of DSDP.

The treatment of pain associated with DSDP has received considerable attention over the last decade, but this still poses one of the most difficult aspects of management, as there is no single effective treatment. The list of approved drugs is increasing but often based on evidence from short term trials—for example, intravenous α lipoic acid, which has been granted a licence for use in painful DSDP in Germany, but not in the UK.

With such a variety of drugs available the best way to approach the treatment of pain in DSDP is to have a sequence of preferred choice drugs (often dictated by personal experience), and where possible to stick to monotherapy (table 7). Although the use of opiates is often frowned upon, they do have a role where antidepressants and anti-convulsants have failed or provided only modest pain control. Tramadol (up to 400 mg/day) is the best opiate to start with, and in certain circumstances morphine may be required.

FOCAL AND MULTIFOCAL NEUROPATHIES

This group of neuropathies should not be considered in isolation as they often co-exist with DSDP. Their aetiologies are likely to differ, however, with the focal and multifocal neuropathies having a prominent vascular component or a compressive aetiology as opposed to the predominant metabolic component in DSDP.

Table 6 Pathogenesis of diabetic symmetric distal polyneuropathy (DSDP)

► Metabolic	<p>Hyperglycaemia leads to overactivity of polyol pathway (via aldose reductase), with secondary depletion of myo-inositol which reduces the concentration of phosphoinositides, leading to low concentrations of diacylglycerol which serves as a second messenger for stimulation of Na-K ATPase. The resulting depletion of Na-K ATPase has been proposed to lead to axonal degeneration and demyelination</p> <p>Advanced glycosylation of endproducts. May lead among other changes to an increase in low density lipoproteins thereby promoting smooth muscle proliferation and atheromatous change in endoneurial vessels</p> <p>Reduced concentration of nerve growth factors. In particular NGF, insulin-like growth factors (IGF-1 and IGF-2), ciliary neurotrophic factor, and glial derived neurotrophic factor</p> <p>Increased oxidative stress. This leads to increased lipid peroxidation. Antioxidants such as α lipoic acid may help</p> <p>Altered fatty acid metabolism. Prostaglandin precursors (especially γ linolenic acid and PGE₁) are depleted. PGE₁ is a vasodilator with antiplatelet activity and it also inhibits collagen deposition and plays a role in regulating tissue Na-K ATPase</p>
► Vascular	<p>Basement membrane reduplication in vasa nervorum</p> <p>Reduced endoneurial blood flow</p> <p>Reduced endoneurial oxygen tension</p>

Table 7 Treatment of painful DSDP

A. For localised pain (for example, dorsum of foot)	Capsaicin cream (0.075%) applied four times/day (maximum 6–8 weeks)	
B. For generalised distal pain		Dose (mg/day)
	Gabapentin	600–3600
	Carbamazepine	100–800
	Amitriptyline	10–150
	Nortriptyline	10–150
	Imipramine	10–150
C. For those whose pain is resistant to the above drugs consider:	Mexiletene	
	SSRI (citalopram or paroxetine)	
	Other anticonvulsants (lamotrigine, topiramate)	
	Opioids: tramadol, pethidine/morphine	
	Spinal cord stimulator	
D. Alternative	Opsite dressing (applied to painful areas)	
	Acupuncture	
	Pain psychologist/counsellor	

SSRI, selective serotonin reuptake inhibitor.

Cranial neuropathies

The sixth nerve palsy associated with diabetes occurs in older patients and does not pose a great diagnostic dilemma. Onset is abrupt and usually painless. Full recovery occurs in the vast majority over 3–5 months. Detailed investigations are rarely required.

A third nerve palsy is not as common as a sixth nerve palsy, but again tends to be seen in patients over the age of 50 years, most of whom have evidence of a DSDP. In 50% of cases the onset is associated with retro-orbital pain, which may persist for several days. The key feature is that the palsy spares the pupil, possibly because the pupillomotor fibres of the IIIrd nerve are located on the outer layers of the fascicle, and ischaemia tends to affect the centre of the fascicle.

Although it is only rarely that a pupil sparing IIIrd nerve palsy arises from a posterior communicating artery aneurysm, as this possibility exists, imaging (magnetic resonance/computed tomographic angiography) is recommended. In diabetic IIIrd nerve palsy imaging is usually normal, although it has been postulated that small mesencephalic infarcts may be an alternative explanation. No specific treatment is required other than prismatic help with diplopia as the ptosis recovers. Complete resolution normally occurs over 3–6 months.

Limb mononeuropathies

Diabetic nerves seem to be more susceptible to compression injury, although exactly why this is the case is not well understood. The treatment of entrapment neuropathy (carpal tunnel syndrome, ulnar neuropathy or common peroneal neuropathy) should follow the same management guidelines as in a non-diabetic patient (see Fuller, p ii20). If the nerve compression is symptomatically troublesome, and especially if there is associated muscle weakness, decompression is needed. The results of decompressive surgery are not as good as in non-diabetic patients.

Diabetic truncal radiculoneuropathy

This is a phenomenon seen in both type 1 and type 2 diabetics, usually in middle or old age. The cardinal features are outlined in table 8. The diagnosis is made on clinical grounds, but evidence of denervation can be found in abdominal wall or intercostal or paraspinal muscles in the region where the pain

Table 8 Diabetic truncal radiculoneuropathy: clinical features

- ▶ Pain over a focal area on the chest and/or abdomen. Usually unilateral, the pain often burning in quality, and in a variety of distributions reflecting nerve root or intercostal nerve trunk involvement
- ▶ Focal contact hyperaesthesiae in the same area as the pain
- ▶ Focal anterior abdominal wall weakness may be evident
- ▶ Associated weight loss in some cases may be profound
- ▶ Good prognosis with spontaneous recovery over several months

and/or sensory loss has occurred. The abrupt onset and spontaneous recovery suggests a vascular aetiology, but an “inflammatory” aetiology cannot be excluded as it can coexist with diabetic lumbosacral radiculoplexus neuropathy (see below).

Management involves controlling the pain; topical capsaicin is useful if the affected area is small and well localised. Full recovery over a period of months is usual.

Diabetic lumbosacral radiculoplexus neuropathy (Bruns-Garland syndrome)

Previously termed diabetic amyotrophy, this clinical entity has had a variety of other names. The most recent attempt to define the condition is somewhat of a mouthful for everyday clinical use, and it may be simpler to use the eponym “Bruns-Garland syndrome” (after Bruns who initially described the syndrome in 1890, and Garland who rediscovered it and coined the term “amyotrophy”). It is most common in older patients with type 2 DM and is rarely encountered in those with type 1 DM.

The clinical features are outlined in table 9. The evolution of symptoms can be quite variable, and may progress to generalised lower limb paresis (“diabetic paraplegia”). A clinically indistinguishable syndrome occurs in patients without diabetes.

The main differential diagnosis to consider is that of an infiltrative pelvic malignancy, particularly when there is profound weight loss and unilateral weakness. A similar picture can be seen as a complication of radiotherapy. If there is no pain associated with progressive asymmetric leg weakness, the diagnosis is more likely to be CIDP.

Table 9 Diabetic lumbosacral radiculoplexus neuropathy (Bruns-Garland syndrome): clinical features and investigations

Clinical features	
▶ Males more frequently affected than females	
▶ Pain:	Severe, affecting lower back, buttocks or anterior thighs, burning and aching in quality; worse at night
▶ Weakness:	Follows pain within a matter of a few days to several weeks and usually unilateral at onset. Later may be bilateral but asymmetric. Mainly proximal, but not uncommon for distal muscles to be involved May slowly progress over several weeks
▶ Weight loss:	May be dramatic (>10–20 kg)
▶ Prognosis is reasonable: recovery is heralded by stabilisation of body weight and resolution of pain. Muscle strength improves slowly over many months, but a number of patients never regain normal lower limb strength	
Investigations	
▶ EMG/NCS:	Denervation changes in paraspinal, proximal and distal leg muscles There is often an associated DSDP Lower limb f wave latencies may be more prolonged than usually seen in DSDP
▶ CSF examination	Protein value often raised Only helps if the clinical picture is unusual
▶ Nerve biopsy	Rarely helps management Microvasculitis and endoneurial mononuclear cell infiltration found in the intermediate cutaneous nerve of the thigh and also in the sural nerve

CSF, cerebrospinal fluid; DSDP, diabetic symmetric distal polyneuropathy; EMG, electromyogram; NCS, nerve conduction study.

Suggested investigations are outlined (table 9). Neurophysiology is helpful, but CSF examination and nerve biopsy should only be considered if an alternative diagnosis is considered. Examination of nerve biopsies has shown evidence of microvasculitis and endoneurial inflammatory infiltration but these findings do not influence management. It is uncertain whether these inflammatory changes are primary or secondary phenomena to possible ischaemic injury.

There does appear to be a rarer brachial radiculoplexus neuropathy, reported in association with the Bruns-Garland syndrome in diabetic patients.

Treatment is centred initially around pain control (table 8). This can be difficult and often requires opiates. Physiotherapy and orthotic assessments are helpful in selected, often more severely affected cases. Although the suspected pathogenic mechanism is inflammatory change in the nerve or epineurial vessels, it is not established whether immunosuppression (steroids or intravenous immunoglobulin) has any role to play in the treatment of a syndrome, which eventually spontaneously recovers, albeit that this may be incomplete in a number of patients.

COMMENT

The diabetic neuropathies are common and remain a major source of morbidity. Optimal treatment at this time requires good control of blood sugar, managing symptoms, and fastidious attention to foot care. The disappointing lack of benefit of other treatments may be related to the fact that most were trialled in patients with established neuropathy. It is probable that future pharmacological treatments for the more common DSDP will have to be directed at early neuropathy. This may provide the impetus to rekindle the neurologist's interest and involvement in the diagnosis and management of diabetic neuropathy.

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