Painful legs in people with diabetes: Painful diabetic neuropathy until proven otherwise, or is it?

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Article points

1. Patients with diabetes will commonly present with pain in the leg(s).
2. Painful diabetic neuropathy is a common cause of lower-limb pain in this population, but alternative causes should be investigated for as part of a careful differential diagnosis.

Key words

- Diabetic neuropathy
- Differential diagnosis
- Neuropathic pain

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Patients with diabetes will commonly present with pain in the leg(s). While it is easy to attribute this to painful diabetic neuropathy, alternative causes should be sought. This should be based on a careful history and relevant investigations, as the management for each of the differentials is different.

Diabetic peripheral neuropathy (DPN) is a length-dependent process and its sensory manifestations are most pronounced in the lower limbs and, in more severe cases, in the fingers and hands. Painful diabetic neuropathy occurs in approximately 20% of people with diabetes and they will typically describe symmetrical pain, paraesthaesia, hyperaesthesia, deep aching, burning, sharp stabbing sensation, and allodynia (pain due to non-painful factors, such as touch), which tend to be worse at night (Veves et al, 2008). They will also describe discomfort to the point that they cannot tolerate bed sheets covering their feet.

The risk of painful neuropathy is significantly greater among those with type 2 diabetes, women, and people of south Asian origin (Abbott et al, 2011). However, many patients may experience "negative" symptoms, such as numbness, unsteadiness (Allet et al 2009) due to disturbed proprioception, and reduced muscle strength and size (Andersen, 2012). Pain, unsteadiness, and reduced activities of daily living have been associated with depressive symptoms (Vileikyte et al, 2009). Severe weakness warrants urgent investigations to exclude non-diabetic neuropathy, especially chronic inflammatory demyelinating polyneuropathy (CIDP), which has been suggested to occur more frequently among people with diabetes in some (Sharma et al, 2002; Casellini and Vinik, 2007) but not all (Laughlin et al, 2009) studies. Of course other neuropathies such as Guillain Barre syndrome should be identified from the clinical history of an acute onset rapidly ascending neuropathy with weakness (Gonzalez-Suarez et al, 2013).

Equally, many people with DPN may have no symptoms, however, the absence of symptoms must never be interpreted as absence of neuropathy. Indeed on examination, there is usually a symmetrical sensory loss to touch, pain, and temperature in a stocking distribution, and knee and ankle reflexes may be reduced or absent. In the most severe cases, a loss of proprioception together with a positive Romberg's sign may be observed.

As DPN is often accompanied by distal sympathetic autonomic dysfunction, examination may reveal warm, dry skin (in the absence of peripheral vascular disease). Small-muscle wasting in the feet and hands may be seen in more advanced cases. Indeed, the "at risk" foot for neuropathic ulceration might also have a high arch (pes cavus) and clawing of the toes.

Neuropathy evaluation

The 10-g monofilament is commonly employed due to its low cost and ease of use for identifying the neuropathic deficit in the lower limbs. It has been accepted as the test of choice in primary care, yet it has major limitations in terms of specificity (Miranda-Palma et al, 2005). A screening test that has such a low specificity even for advanced disease, together with its limited medical therapies (Malik et al, 2013), and variations in access to vascular interventions (Goodney et al, 2013), may well explain the huge variation and continuing burden of lower-limb amputation (Homan et al, 2012). Furthermore, a normal 10-g monofilament test should not be used to reassure the patient that they have no neuropathy; in particular, it cannot rule out painful neuropathy

due to small fibre damage, as this test – at best – only detects advanced, large fibre neuropathy.

A number of simple neuropathy screening questionnaires/examinations are available, such as the Michigan Neuropathy Screening Instrument (Herman et al, 2012) and the neuropathy symptom score (Abbott et al, 2010), which enable quantification of both positive and negative symptoms. The use of composite scores to assess clinical signs may be helpful in identifying the patient with DPN.

The modified Neuropathy Disability Score (NDS) comprises a score of one each for touch, pain, and temperature, and two for absent ankle reflexes for each limb, giving a total score our of ten (Abbott et al, 2002). Patients can be graded according to NDS as follows: <3, no neuropathy; 3–5, mild neuropathy; 6–8, moderate neuropathy; 9–10, severe neuropathy.

Signs and symptoms of DPN are highly variable and reproducible diagnosis of DPN based on bed-side techniques is problematic (Dyck et al, 2010a). Nerve conduction (NC) studies provide definitive diagnosis of DPN (Tesfaye et al, 2010a), based on reproducibility, and apparent sensitivity and specificity (Dyck et al, 2010b). However, NC studies only assess large myelinated fibres and – of course – small fibre damage precedes large fibre damage (Quattrini et al, 2007; Umapathi et al, 2007; Løseth et al, 2008). Furthermore, small fibres are central to pain, tissue blood flow, and sweating, which are all key factors in the genesis of foot ulceration. Therefore, there is a compelling argument to include measures of small fibre dysfunction and damage in any definition of DPN (Tesfaye et al, 2010b).

While abnormalities in heat pain thresholds reflect small fibre dysfunction and can be assessed using CASE IV, thermoaesthesiometer, and Medoc instruments (Chao et al, 2007), a careful study of 59 people with diabetes and with and without symptomatic neuropathy showed that warm perception thresholds did not differentiate between those with and without symptoms (Løseth et al, 2008). Similarly, in a study of 191 people with diabetes no difference in heat pain thresholds between those with and without painful neuropathy was found (Sorensen et al, 2006). As a result, the most recent NeuPSIG consensus statement holds that quantitative sensory testing should not be used to aid in the diagnosis of painful neuropathy (Backonja et al, 2013).

Alternative methods for assessing small fibre damage include the Neuropad, a simple indicator pad test that detects sudomotor, and hence small fibre, dysfunction (Quattrini et al, 2008; Pananas et al, 2013), skin biopsy for quantifying intraepidermal nerve fibre density (Quattrini et al, 2007) or indeed the rapid, non-invasive ophthalmic technique of corneal confocal microscopy, which can quantify small fibre damage (Quattrini et al, 2007; Tavakoli et al, 2010).

Other diabetic neuropathies

A number of other manifestations of diabetes, which may present with pain in the lower limbs, require a precise history and careful targeted assessment. *Table 1* provides a list of conditions that present as as pain in the legs of people with diabetes.

Insulin neuritis

Insulin neuritis is characterised by severe, unremitting, symmetrical pain, which can develop when glycaemic control is abruptly improved (HbA_{1c} improvements of 2–5 percentage points over 2–3 months) with insulin or oral hypoglycaemic agents (Gibbons and Freeman, 2010). The underlying pathophysiology is nerve ischaemia due to arterio-venous shunting (Tesfaye et al, 1996). Treatment – contrary to the dogma of loosening glycaemic control – is actually to maintain optimal glycaemic control, mange the patients symptoms, and reassure them that the pain will resolve over 12–18 months (Gibbons and Freeman, 2010).

Page points

1. A number of simple neuropathy screening questionnaires/examinations are available and enable quantification of both positive and negative symptoms.
2. Signs and symptoms of diabetic peripheral neuropathy (DPN) are highly variable and reproducible diagnosis of DPN based on bed-side techniques is problematic.
3. A number of other manifestations of diabetes, which may present with pain in the lower limbs, require a precise history and careful targeted assessment.

Table 1. Differential diagnostic list of conditions presenting as pain in the legs of people with diabetes.

	Symmetrical	Sensory loss	Distal	Pain	Weakness
Diabetic peripheral neuropathy	+	+	+	+	
Insulin neuritis	+	+	+	++	
Diabetic amyotrophy				++	++
Diabetic myonecrosis				++	+
Other neuropathies					
CIPN	+	+	+	+	
Lambert–Eaton syndrome	+				+
Sciatica		+		+	+
Meralgia paraesthetica		+		+	
Morton's neuroma		+	+	+	

CIPN, chemotherapy induced peripheral neuropathy.

Page points

1. Diabetic amyotrophy typically occurs in middle aged and older people with type 2 diabetes and presents as severe unilateral thigh pain and muscle wasting.
2. Central to the correct diagnosis of diabetic peripheral neuropathy (DPN) is the exclusion – or indeed diagnosis – of other treatable causes of neuropathy.
3. Chemotherapy induced peripheral neuropathy (CIPN) is an increasingly frequent problem and is difficult to differentiate from DPN.

Diabetic amyotrophy

Diabetic amyotrophy typically occurs in middle aged and older people with type 2 diabetes. It presents as severe unilateral thigh pain and muscle wasting. Diagnosis requires an accurate and detailed clinical history and neurologic examination, combined with targeted proximal needle electromyography to identify proximal denervation (Laughlin and Dyck, 2013) and biopsy of the intermediate cutaneous of the thigh for pathological proof of vasculitis (Tracy et al, 2009).

Diabetic amyotrophy justifies immunosuppressive therapy, which achieves impressive remission rates – as opposed to the previous non-evidence based approach of improving glycaemic control (Collins et al, 2010). A painless variant of diabetic lumbosacral plexopathy associated with proximal muscle wasting has recently been described (Garces-Sanchez et al, 2011).

Diabetic myonecrosis

Acute onset proximal or distal muscle pain with tenderness and swelling and a raised erythrocyte sedimentation rate and creatine kinase may suggest diabetic myonecrosis (Iyer et al, 2011). This is a rare manifestation, which can occur in patients with poorly controlled diabetes. Arterial and venous imaging will be normal, but a computerised tomography (CT) or magnetic resonance imaging (MRI) will reveal an irregular, enhancing, space-occupying lesion of the affected muscle, and a muscle biopsy will show myonecrosis and proliferative myositis (Bhasin and Ghobrial, 2013). Treatment is supportive, with pain relief and improved glycaemic control.

Other neuropathic conditions

Differential diagnosis

Central to the correct diagnosis of DPN is the exclusion – or indeed diagnosis – of other treatable causes of neuropathy (Boulton, 2007). Again, clinical history is key as it may point to a super-added, non-diabetic cause of peripheral neuropathy. This includes a positive family history of neuropathy (Adams et al, 2012; e.g. hereditary motor and sensory neuropathies, amyloid, etc), exposure to toxins (e.g. insecticides, solvents, etc), infection (Kokotis et al, 2013; e.g. human immunodeficiency virus, etc), medication side-effects (Tan et al 2012; e.g. metronidazole, nitrofurantoin, etc), other systemic disease (e.g. sarcoidosis, systemic lupus erythematosus, etc), predominant motor involvement (e.g. chronic inflammatory demyelinating polyneuropathy), rapid progression (e.g. Guillian Barre), and asymmetry (e.g. radiculopathy). Hence, further recommended investigations include thyroid function tests, serum B12, antinuclear antibodies, serum angiotensin-converting enzyme, estimated glomerular filtration rate, and imaging to exclude a radiculopathy or paraneoplastic neuropathy (Hughes, 2002; Boulton, 2007; Graus and Dalmau, 2013).

Chemotherapy induced peripheral neuropathy

Chemotherapy induced peripheral neuropathy (CIPN) is an increasingly frequent problem and is difficult to differentiate from DPN as it is typically a sensory, length-dependent neuropathy – but, of course, occurs after receiving chemotherapy (Grisold et al, 2012).

A wide range of compounds can cause CIPN, including the platin compounds, vinka alkaloids, taxanes, bortezomib, and thalidomide. Recently, a variety of CIPN assessments and scales have been shown to have good reliability and validity, including the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), the Total Neuropathy Score clinical version (TNSc), the modified Inflammatory Neuropathy Cause and Treatment (INCAT) group sensory sumscore (mISS), the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, and CIPN20 quality-of-life measures (Cavaletti et al, 2013).

In terms of assessment, the focus at present is on defining symptoms and neurological deficits in relation to their impact on quality of life, with little emphasis on quantifying neurological deficits apart from neurophysiology, which may be normal in CIPN, due to small fibre damage. Alternative objective techniques that can quantify small fibre damage in CIPN include intraepidermal nerve fiber density in skin biopsies (Lauria et al, 2012) and corneal innervation (Ferrari et al, 2013), which can be assessed by noninvasive corneal confocal microscopy (Ferrari et al, 2010).

In a recent Cochrane review (Albers et al, 2011) it was concluded that there is no good evidence for a number of chemoprotective agents (e.g. acetylcysteine, amifostine, calcium and magnesium,

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diethyldithiocarbamate, glutathione, Org 2766, oxycarbazepine, or Vitamin E) in preventing or limiting the neurotoxicity of platin drugs.

Lambert-Eaton myasthenic syndrome

The very rare Lambert-Eaton myasthenic syndrome should also be considered, especially when the neurologic pattern is that of symmetric, proximal weakness without reflex or sensory abnormalities. Typically, nerve conduction studies may be normal, but there is a decremental response on low-frequency repetitive stimulation and facilitation, only on high-frequency repetitive stimulation. Antineuronal nuclear antibody type 1 (anti-Hu) and P/Q-type calcium channel antibodies can confirm the diagnosis and warrant an initial chest CT, which if negative, should be followed by whole-body positron-emission tomography scan to identify the malignancy (Conwell et al, 2013).

Sciatica

Lumbar radiculopathy (sciatica) can and has been attributed to painful diabetic neuropathy. However, it is characterised by acute onset, proximal lower back/gluteal discomfort, and leg weakness, typically with shooting pain down one leg, which may or may not extend below the knee. The underlying aetiology is compression of the sciatic nerve root/s (L3-5, S1-3) by a herniated or protruding vertebral disc. Lasègue's sign (i.e. a straight leg raising) is accepted as the gold standard test for sciatica and is considered positive if pain in the distribution of the sciatic nerve is reproduced after passive flexion of the straight leg to at least 45 degrees.

It should be noted that, while this test is positive in approximately 90% of people with sciatica, it can be positive in approximately 75% of patients without sciatica. A recent study of 45 people with typical sciatica and a herniated lumbar disc on MRI showed that Lasègue's sign had a sensitivity of 22.2% and specificity of 95.2%, while Cecin's or "X" sign (worsening of pain on flexion of the lumbar spine while simultaneously performing the Valsalva maneuver) had a sensitivity of 73.3% with a specificity of 95.2% (Cecin et al, 2010). While MRI may confirm disc herniation and nerve root compression, a recent study found that MRI performed at 1-year follow-up in people who had been treated for sciatica and lumbar disc herniation could not distinguish between those with and without a favourable outcome (el Barzouhi et al, 2013).

Meralgia paraesthetica

A less common but easily misdiagnosed condition is that of meralgia paraesthetica (MP), which presents in obese people and, therefore, more commonly in people with type 2 diabetes. It presents with unilateral pain, tingling, hyperaesthesia, and numbness on the antero-lateral aspect of the thigh without muscle wasting and is due to compression of the lateral cutaneous nerve of the thigh (LCNT) as it passes underneath the inguinal ligament. A recent ultrasound study has shown a sensitivity and specificity of 95% for diagnosing MP based on a significant increase in the size of the LCNT (Suh et al, 2013).

Morton's neuroma

Morton's neuroma is characterised by pain and or numbness in the 2nd/3rd or 3rd/4th inter-metatarsal spaces, which is exacerbated with compression of the transverse arch and relieved following removal of footwear. Quantitative sensory testing shows hypo- or hyper-aesthesia (Quiding et al, 2013). It is caused by a benign neuroma of the inter-metatarsal plantar nerve, which can be diagnosed with ultrasound or MRI (Gregg et al, 2008). Treatment is with orthotics, local corticosteroid injections or neurectomy.

Conclusion

Diabetes disposes people to a number of painful syndromes of the lower limbs. In such cases, it is important that the clinician undertakes a thorough differential diagnosis. ■

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