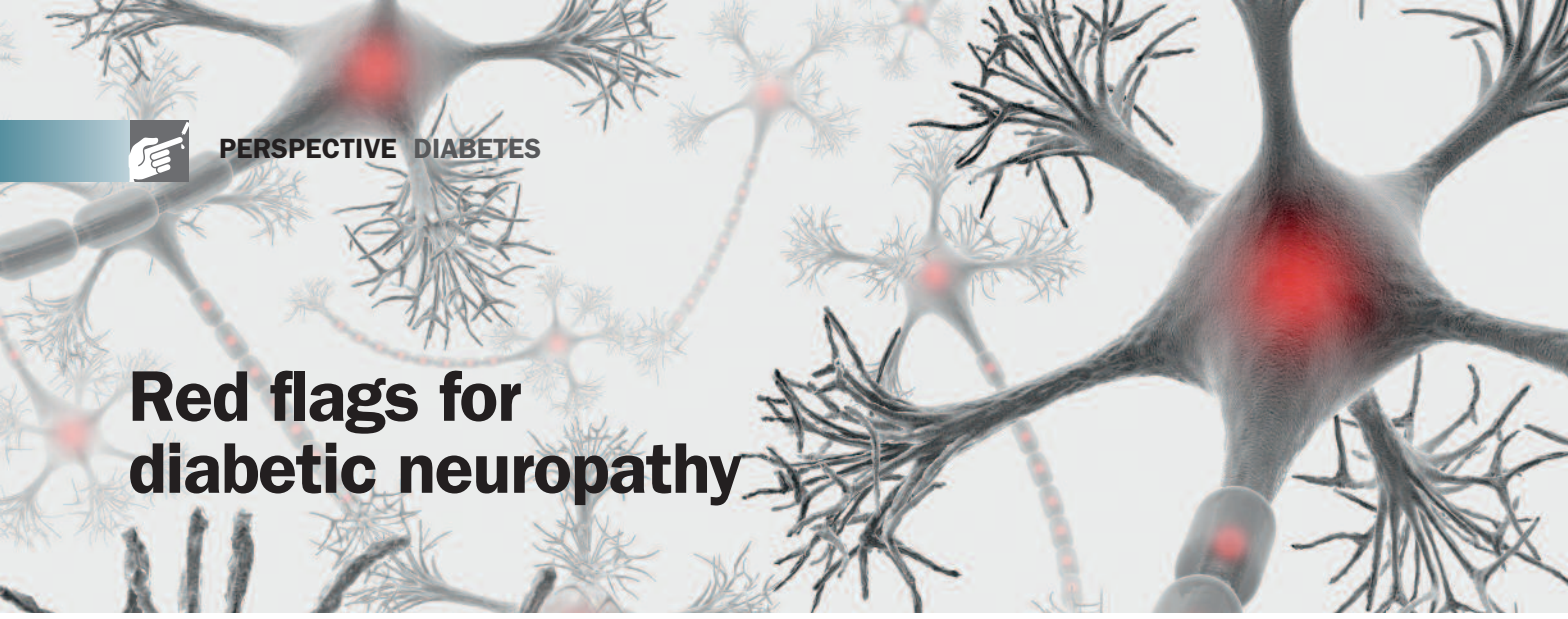

Red flags for diabetic neuropathy

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Atypical progression of neuropathy, relative lack of coexistent retinopathy or neuropathy, failure to achieve adequate control of dysaesthesia and secondary problems associated with diabetic neuropathy are all indicators for urgent patient review and possible referral.

Key points

- **Neuropathy is often the 'forgotten complication' of diabetes.**
- **Dysaesthesia followed by anaesthesia, autonomic neuropathy and then motor neuropathy is the typical clinical course of peripheral diabetic neuropathy.**
- **Nondiabetic causes of neuropathy should always be considered when a patient with diabetes presents with neuropathic symptoms.**
- **The most important neuropathic red flags prompting review and consideration of referral in patients with diabetes are atypical anatomical patterns of neuropathy, atypical progress of neuropathy and relative lack of other associated microvascular complications.**
- **Other red flags include failure to achieve adequate control of dysaesthesia and secondary problems associated with diabetic neuropathy (especially anaesthetic feet) should also prompt review.**

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Neuropathy is a common and important complication of diabetes but is often the 'forgotten complication' – not investigated, not recognised and not appreciated as important.[1,2] It can affect all body systems and can present in a range of ways in different people and in the same person during their lifetime. This article reviews the natural history of diabetic neuropathy and identifies some red flags that should prompt review of the patient and consideration of referral to a specialist medical or allied health colleague.

'Natural history' of diabetic neuropathy

Disturbed sensations are usually the first symptoms of neuropathy noticed by patients with diabetes. Damage to small diameter afferent sensory nerves responsible for pain and temperature and involved in reflex motor arcs causes loss of or abnormal sensation (anaesthesia or dysaesthesia). Damage to larger fibres involved in reflex motor arcs abolishes tendon reflexes. Neuropathy usually progresses bilaterally and symmetrically from distal areas (supplied by the longest nerves) and presents in the lower limbs long before there is upper limb involvement.

Abnormal sensations are the most disturbing symptom to patients and may limit their activities during the day and their sleep during the night. Early in neuropathy, the loss of sensation is not noted by the patient but may be found as subtle loss of pain and temperature sensations on examination. As neuropathy progresses, anaesthetic symptoms become dominant. This anaesthesia is less disturbing for the patient than is dysaesthesia, but is far more dangerous because of the risk of unnoticed peripheral tissue damage.

Symptoms of autonomic neuropathy usually start with skin dryness but later can be associated with genitourinary, gastrointestinal and cardiovascular problems. When large diameter nerve fibres are affected, vibration, position sense and motor symptoms occur. Muscle atrophy can cause skeletal changes. In the feet, the extensors of the toes are predominantly intrinsic muscles and as these atrophy the preserved toe flexors, which are more proximal, produce clawing of the toes. Weakness may mean the patient can no longer open jars or carry objects in their hands. Various disastrous events can happen, particularly in association with the loss of protective peripheral sensation, with foot problems and falls being responsible for considerable morbidity.

The typical clinical course of the four common syndrome complexes of classical peripheral diabetic neuropathy – dysaesthesia, anaesthesia, autonomic neuropathy and motor neuropathy – may be accelerated or disturbed by superimposed nondiabetic causes of peripheral neuropathy (see box on page 20). The entrapment neuropathy carpal tunnel syndrome, for example, is very common in patients with diabetes. These other causes should always

Nondiabetes-related causes of peripheral neuropathy

- Nutrition – vitamin deficiencies (thiamine, vitamin B_{12} and folic acid, especially with the 'tea and toast' diet of many older people). Excessive alcohol intake can also be associated with thiamine deficiency.
- Medical problems – especially entrapment neuropathies (e.g. carpal tunnel syndrome); less commonly coeliac disease, myeloma, hypothyroidism, paraneoplastic disorders and chronic inflammatory demyelinating polyradiculopathy (rare but important as treatable with immunotherapy).
- Medications – commonly: nitrofurantoin, metronidazole and colchicine; less commonly: sulfasalazine, perhexiline, isoniazid and statins (associated with neuropathy and myopathy).

be considered when a patient first presents and reconsidered periodically as symptoms change and neuropathy progresses.

The classic clinical course of diabetic neuropathy is illustrated by the patient's quotes given in the box on this page.[3-7]

Neuropathic red flags

Neuropathic red flags prompting review and consideration of referral in patients with diabetes include:

- atypical anatomical patterns and atypical progress of neuropathy
- relative lack of other associated microvascular complications (retinopathy, nephropathy)
- failure to achieve adequate control of dysaesthesia
- secondary problems associated with diabetic neuropathy, especially foot problems.

Atypical anatomical pattern and progression

The typical anatomical pattern of diabetic neuropathy is symmetrical and progression is typically:

- from distal to proximal
- from lower to upper limb (the 'glove and stocking' pattern)[3]
- from functions related to finer nerve fibres (pain, temperature and autonomic function) to those related to thicker, more myelinated fibres (vibration and position sense, and motor function)
- from asymptomatic but detectable to profound and associated with clinical problems.

Although diabetes can be associated with other forms of neuropathy (e.g. mononeuropathies affecting cranial nerves, spinal roots, sensory motor nerve or multiple nerve roots), atypical anatomical patterns and progression – i.e. asymmetrical, proximal to distal progression, upper limb or truncal involvement before lower limbs affected – suggest other causes (see the box on this page).[4]

Nerve root damage caused by lumbar spine or disc disease is a common confounder of diabetic neuropathy as it occurs in patients of the same age group as those with type 2 diabetes. However, it has a radicular, unilateral and more proximal distribution. In the past, neuropathy was often present when patients were first diagnosed with type 2 diabetes because the diabetes had typically remained undiagnosed for five to 10 years before becoming symptomatic. Sometimes diabetes was only suspected and detected when symptomatic neuropathy occurred. This situation is far less common now, when diabetes is detected earlier because of increased awareness and the widespread use of multiple biochemical analyses, including blood glucose level estimation and oral glucose

Diabetic neuropathy – an illustration of the clinical course

The clinical course of diabetic neuropathy is illustrated by Annie's quotes, below.

Annie, who has had type 2 diabetes for five years:

'At night armies of ants march up and down my legs. Sometimes the ants decide to burn instead and my legs feel like they're on fire.'

Six years later:

'I feel like I walk on cotton wool. Sometimes my feet are like slabs of wood and just slap down on the ground.'

In response to your suggestions about footcare:

'I use special soap and moisturiser and still my skin is dry and cracked and itches like mad. I just can't stop scratching, and of course that makes things much worse.'

After 15 years of diabetes:

'I checked the water temperature before I got in but when I sat down in the bath it was boiling hot. I jumped out but I had terrible scalds on my feet and lower legs.'

Two years later:

'My feet have become so ugly. My toes are like claws and the tops are red and callused from rubbing on my shoes.'

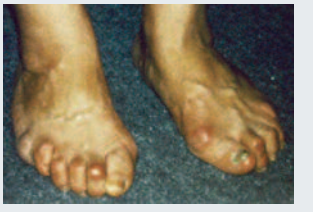

Figure. Clawed toes.

After extensive laser therapy for retinopathy had impaired her peripheral and night vision and neuropathy had impaired her position sense, leaving her dependent on her vestibular system for balance in dim light:

'I don't know what happened that night. I walked into the house and the next thing I knew I was on the floor and so unsteady I couldn't stand up.'

After developing a foot ulcer – Annie was lucky she avoided a below-knee amputation:

'It all started on Tuesday when I wore my new shoes on a tour of the Botanic Gardens. I noted blisters on both feet that night but on Thursday my left foot was red and swollen and there was pus coming from a new sore on the sole. I got a fever on Saturday and my doctor sent me to hospital.'

tolerance testing. Lifestyle intervention and tight glycaemic control at this earlier stage of diabetes may result in nerve fibre regeneration.[8]

The ageing process itself is associated with progressive neuronal drop-out, and the combination of increasing patient age and increasing duration of diabetes accelerates this process. This combination increases the rate of detectable neuropathy much more than the rate of severe and clinically significant neuropathy, perhaps reflecting the mortality associated with severe neuropathy, especially autonomic neuropathy.[9] Even so, anaesthetic diabetic neuropathy is uncommon in the early years of diagnosis and progresses in severity over years and decades.

Thus the presence of typical 'diabetic' neuropathy at or within a few years of diagnosis of type 2 diabetes or its rapid progression over months rather than years suggests the neuropathy has causes other than diabetes.[4] Similarly, loss of vibration and position sense or motor function occurring before or at the same time as abnormal sensation and autonomic function suggests other causes. Specialist assessment and investigation may help to define or exclude nondiabetic causes of symmetrical, peripheral progressive neuropathy.

Relative lack of other microvascular complications

The defining complications of diabetes are microvascular: the triad of retinopathy, neuropathy and nephropathy. Indeed the levels of glycaemia for a diagnosis of diabetes were established as those levels at or above which retinopathy occurred. The general diabetes risk factors for complications (i.e. the medical ABCS for complication risk – high A_{1c} levels, high blood pressure, high total cholesterol levels and smoking) apply, but hyperglycaemia is necessary for the development of all three microvascular complications.

Generally, the microvascular complications occur in parallel, although retinopathy is more often detected than the others, probably because the microvascular circulation is readily available for inspection (by ophthalmoscopy). The presence and level of severity of one microvascular complication without the coexistence and similar level of severity of the others suggests a cause or contributor other than diabetes. This is particularly true for neuropathy and nephropathy if diabetic retinopathy is absent or at a very different level. Such discrepancies should prompt review and consideration of referral of the patient to a neurologist or endocrinologist.

Failure to control neuropathic pain

Painful diabetic neuropathy is notoriously difficult to control. Generally, both local and systemic interventions, as listed in the box on this page, succeed in relieving only half of the discomfort and only in half of the treated population.[4]

Clinical trials of single agents have been of limited value in establishing treatment algorithms because they are usually small trials of short duration, with different patient populations, medication dosages and assessment criteria, and also industry-sponsored.[10] Combination therapies have been shown to have modest benefits over single therapies but may be associated with significant adverse effects. Moreover, the pain syndrome itself may become more complicated with time, with the development of secondary components affecting the spinal cord, brain and psyche.

A safe approach is to try the local measures and then, if pain continues to disturb the patient's quality of life, to consider adding one of the systemic agents to the regimen. If further measures are needed, consider referring the patient, ideally to a multidisciplinary pain clinic or to a pain management specialist who has access to psychological or psychiatric colleagues.

Associated secondary problems

The common secondary problems associated with diabetic neuropathy are related to loss of sensation, autonomic neuropathy, motor neuropathy and the psychological and social problems associated with disabilities and limitations in physical, social and emotional life. Each may prompt team care planning to organise referral, future care and ongoing monitoring.

Sensory neuropathy

Anaesthetic feet

A podiatrist can advise and support patients with anaesthetic feet and should be actively involved in ongoing management if patients have one of the other major diabetic foot risk factors (the podiatric ABCS of foot risk – anaesthesia, poor blood supply, inadequate foot care, abnormal foot structure).[11] Appropriate footwear, foot care,

Intervention options for painful neuropathy

Local measures

- Film dressing – wrapping the foot reduces sensory stimulation and dysaesthesia.
- Capsaicin 0.075% cream three to four times per day – depletes skin substance P, a neuropeptide involved in pain perception. Most effective if applied after a shower/bath, especially at night. Patients should be advised to wear gloves during the application and wash hands afterwards to avoid contaminating other body surfaces (e.g. mouth, eyes).
- Transcutaneous electrical nerve stimulation – may reduce central appreciation of the abnormal nerve impulses.

Systemic measures

- Antidepressants – low-dose tricyclics such as amitriptyline, 10 to 150 mg at night, are traditional; the selective serotonin and noradrenaline reuptake inhibitor duloxetine (indicated for diabetic peripheral neuropathic pain) and selective serotonin reuptake inhibitors (off-label use) may also be effective.
- Nerve stabilisers – anticonvulsants can be effective, particularly gabapentin (indicated for neuropathic pain) 900 to 3600 mg/day; in severe cases, a combination of gabapentin and up to 20 mg/day of oxycodone (indicated for moderate-to-severe pain) should be trialled; pregabalin (indicated for neuropathic pain) may also be used.

ongoing monitoring and action plans for prompt recognition and response to problems such as ulcers may prevent a disastrous event, for example, amputation (see Annie's story in the box on page 20).

Driving

An occupational therapist can assess the driving capacity of patients with anaesthetic feet. If foot pedals cannot be operated, patients can drive a car with automatic transmission that has been fitted with hand-operated controls for accelerating and braking.

Falls

Patients who have neuropathic impairment of position sense are prone to falls, especially those in whom laser therapy for retinopathy has compromised night vision. These patients may be helped by simple living aids, co-ordinated by a domiciliary care service, a falls clinic or an occupational therapist.

Autonomic neuropathy

Dry skin and mucous membranes

The local pharmacist can advise patients on the use of special nonsoap skin cleansers and intensive moisturisers as well as other preparations, such as artificial tears and saliva, night ophthalmic creams and non-nutritive chewing gums to stimulate salivary flow.

Cardiovascular symptoms

A hypertension specialist may be able to help in the management of the difficult case of profound daytime postural hypotension associated with nocturnal hypertension (revealed by 24-hour ambulatory blood pressure monitoring). An anaesthetist should be forewarned about a patient who has autonomic neuropathy because of their increased risk of arrhythmias during induction and anaesthesia.

Gastrointestinal symptoms

The gut can be affected by autonomic neuropathy at all levels, with nausea, vomiting, delayed gastric emptying, diarrhoea, constipation and faecal incontinence. Referral of affected patients to a gastroenterologist may be helpful. An incontinence adviser can recommend strategies to reduce rectal urgency and faecal leakage as well give advice about pads and underwear to use to improve comfort and lessen embarrassment.

Genitourinary symptoms

Erectile dysfunction is more common in men aged over 50 years and is greatly increased in men with diabetes (about half of men aged 50 with diabetes have erectile dysfunction). Management strategies include the use of phosphodiesterase-5 inhibitors, intrapenile vasodilating injections, vacuum devices to induce erection and penile implants. A sexual health counsellor can support the man and his partner in their efforts to deal with the problem.

A nephrologist or urogynaecologist can help with the urinary problems associated with bladder dysfunction (hydronephrosis, infection and overflow incontinence), and an incontinence adviser can provide practical advice to minimise urinary incontinence and help patients cope with any urinary leaks.

Motor neuropathy

Motor neuropathy usually occurs later than sensory and autonomic neuropathies in patients with diabetes, and is associated with long-term hyperglycaemia. Early occurrence suggests an alternative cause.[4]

Foot deformity

A structural foot problem is usually associated with profound anaesthesia and patients can benefit from podiatric advice, particularly regarding foot care and footwear.

Weakness

A physiotherapist can advise on measures to increase and maintain strength and mobility, and an occupational therapist can provide living aids to increase a person's capacity to live with their disabilities.

Psychological and social problems

Not surprisingly, diabetic neuropathy and its associated clinical syndromes are associated with considerable psychological and social problems, especially anxiety, depression, insomnia and social isolation. Patients may need to be prescribed specific medications (e.g. anxiolytics, antidepressants, hypnotics) and referred for specialist psychological or psychiatric counselling and/or cognitive behavioural therapy. Involvement of the partner and other family members in such cases may also be advisable, considering that they too will be affected by the patient's symptoms, disability, and psychological and social problems.

Conclusion

Neuropathy is common in patients with diabetes and is often overlooked. Nondiabetic causes of neuropathy should, however, be considered when a patient with diabetes first presents with neuropathic symptoms. Throughout the clinical course of diabetic neuropathy (dysaesthesia, anaesthesia, autonomic neuropathy and then motor neuropathy), patients should be monitored for the neuropathic red flags, which should prompt further review and, when appropriate, referral to appropriate specialists and allied health care professionals. These red flags are atypical anatomical pattern of neuropathy, atypical progression of neuropathy, relative lack of coexistent retinopathy or nephropathy, failure to achieve adequate control of dysaesthesia and secondary problems associated with diabetic neuropathy. Careful monitoring of patients with diabetic neuropathy can help prevent disastrous events and improve quality of life. **ET**

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A list of references is available on request to the editorial office.

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