Neuropathy in diabetes

Solomon Tesfaye

Abstract

Diabetic polyneuropathy affects 30—50% of patients with diabetes mellitus. It encompasses several neuropathic syndromes, the commonest being distal symmetrical polyneuropathy or 'diabetic peripheral neuropathy' (DPN). Risk factors for DPN include poor glycaemic control and drivers of macrovascular disease including hypertension. Strong evidence in humans and animals implicates nerve ischaemia as the cause of DPN. Despite several well-designed recent trials, no novel approved treatment with unequivocal effects on the decline in nerve function in DPN has emerged. Painful DPN affects 15—26% of those with diabetes, produces considerable disability, and is challenging to assess and manage. First-line therapies are tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors (e.g. duloxetine) or anticonvulsants (e.g. pregabalin, gabapentin). Second-line drugs include opioids. Diabetic autonomic neuropathy also results in considerable morbidity, reduced quality of life and increased mortality. It may involve cardiovascular, gastrointestinal, urogenital, pupillomotor, thermoregulatory and sudomotor function. Although counselling and non-pharmacological interventions are of some use, more severely afflicted patients require pharmacological intervention.

Keywords autonomic neuropathy; diabetic neuropathy; diabetic peripheral neuropathy; distal symmetrical polyneuropathy; painful diabetic neuropathy

What's new?

- A major consensus meeting was convened in Toronto in 2009 on the diagnosis and management of diabetic neuropathies and this was published in a summary paper (Tesfaye et al. *Diabetes Care* 2010) and six other papers on all aspects of diabetic neuropathies published in *Diabetes Metabolism Research Reviews* in 2011
- The largest ever combination trial in painful diabetic neuropathy (COMBO-DN study) was published in 2013 (Tesfaye et al. *Pain* 2013)

Epidemiology and risk factors

Diabetic polyneuropathy is one of the commonest complications of diabetes mellitus, but is not one disease entity, as it encompasses several neuropathic syndromes (Figure 1). By far the commonest of these is distal symmetrical polyneuropathy, or 'diabetic peripheral neuropathy' (DPN).

Several clinic- and population-based studies have reported similar prevalence rates for DPN. These are around 30% of all individuals with diabetes, if clinical peripheral neurological examination is used, rising to around 50% if electrophysiological testing is employed.[1] The prevalence increases with increasing duration of diabetes, with about 50% of both type 1 and type 2 patients affected after 25 years, with no gender difference. Other correlates with DPN include increasing age, poor glycaemic control, hypertension, smoking, obesity and hyperlipidaemia.[2]

Classification of diabetic polyneuropathy

Watkins and Edmonds[3] have suggested one classification for diabetic polyneuropathy based on the natural history of the various syndromes, which separates them into three distinct groups (Table 1).

Solomon Tesfaye *MD FRCP is a Consultant Physician and Honorary Professor of Diabetic Medicine, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK. Competing interests: I have received honoraria from Eli Lilly and Pfizer.*

Progressive neuropathies

Diabetic peripheral neuropathy

This is by far the commonest neuropathic syndrome. There is a 'length-related' pattern of sensory loss, with sensory symptoms starting in the toes and extending to involve feet and legs in a stocking distribution. When the disease is severe in the lower limbs there is often upper limb involvement, with similar progression proximally from the fingers. Exceptionally, nerve damage can extend over the entire body including the head and face. Sub-clinical autonomic neuropathy detectable by autonomic function tests is usually present, but overt clinical autonomic neuropathy is less common. Motor manifestations may become manifest only late in the disease course.

The main clinical presentation of DPN is sensory loss, of which the patient may not be aware, or may describe as 'numbness' or a 'dead feeling'. However, some experience progressive, unpleasant sensory symptoms (Figure 2), including tingling (paraesthesiae), burning pain, paroxysmal shooting pains down the legs, lancinating (knife-like or stabbing) pains, contact pain due to clothes and bedclothes (i.e. misperception of non-painful stimuli as painful, known as allodynia), exaggerated perception of a slightly painful stimulus (hyperalgesia), pain on walking, often described as 'walking barefoot on marbles/hot sand', sensations of heat or cold in the feet; a persistent ache in the feet, or cramp-like sensations in the legs. Occasionally, pain can extend to the whole of the legs, in which case upper limb involvement also is usual. There is a wide spectrum of severity of symptoms, ranging from minor tingling in one or two toes to a numb diabetic foot, or severe painful neuropathy refractory to drug therapy.

Painful DPN affects 16—26% of all people with diabetes,[4,5] is characteristically more severe at night, and often prevents sleep.[6] Some patients experience constant tiredness due to sleep deprivation, and others are unable to maintain full employment. Severe painful neuropathy can occasionally cause marked reduction in exercise threshold and interfere with daily activities. Not surprisingly, depressive and anxiety symptoms are frequent.[6]

Importantly, many with DPN have none of the above symptoms, and their first presentation may be with a foot ulcer. This underlines the need for careful foot examination of all individuals with diabetes to identify those at risk of ulceration. The

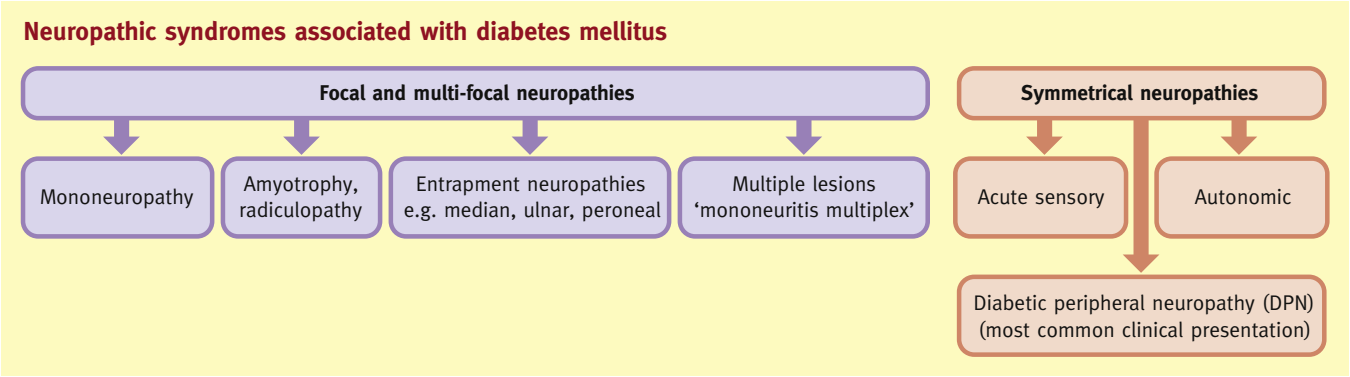

Figure 1

insensate foot is at risk of mechanical and thermal injury, and patients must be warned about these and given appropriate foot care advice.[7] In those with advanced neuropathy, there may be sensory ataxia, causing unsteadiness on walking and even falls, particularly if there is associated visual impairment.

DPN is usually easy to detect clinically. Shoes and socks should be removed and the feet examined at least annually and more often if neuropathy is present. The most common presenting abnormality is reduction or absence of vibration sense in the toes, easily detected using a 128-Hz tuning fork. As the disease progresses, sensory loss involving all sensory modalities appears in a stocking and, sometimes, a glove distribution. In severe sensory loss, proprioception may also be impaired, leading to a positive Romberg's sign. Ankle tendon reflexes are lost, with knee reflexes also reduced or absent in advanced neuropathy.

Muscle strength is usually normal early during the course of the disease, although mild weakness may be found in toe extensors. However, with progressive disease significant generalized muscular wasting ensues, particularly in the small muscles of the hand and feet. Fine movements of fingers are then affected, with difficulty in handling small objects. Wasting of the dorsal interossei is usually due to entrapment of the ulnar nerve at the elbow. Clawing of the toes, increasing plantar and toe pressures, is believed to be due to pulling of long extensor and flexor tendons that is unopposed due to wasting of the small muscles of the foot. This renders metatarsal heads prone to callus formation and ulceration. Deformities such as bunions can form the focus of ulceration, and with more extreme deformities, such as those in Charcot's arthropathy, the risk is further increased. As one of the most common precipitants of foot ulceration is inappropriate footwear, a thorough assessment should also include examination of shoes for poor fit, abnormal wear, internal pressure areas or foreign bodies.

Classification of diabetic polyneuropathy[3]

Progressive neuropathies

- Onset gradual; no recovery
- Associated with increasing diabetes duration and other microvascular complications
- Sensory disturbance predominates; autonomic involvement common
- Includes diabetic peripheral neuropathy, the commonest neuropathy in diabetes, usually with autonomic neuropathy

Reversible neuropathies

- Acute onset; spontaneous recovery
- Often occur at diabetes presentation; not related to diabetes duration or other microvascular complications
- Includes acute painful neuropathies ('acute painful neuropathy of poor glycaemic control' and 'acute painful neuropathy of rapid glycaemic control'), cranial nerve palsies and focal neuropathies such as diabetic amyotrophy

Pressure palsies

- Not specific to diabetes, but occur more frequently in diabetes than in general population. No association with diabetes duration or other microvascular complications
- Include carpal tunnel syndrome

Table 1

Symptoms of diabetic peripheral neuropathy

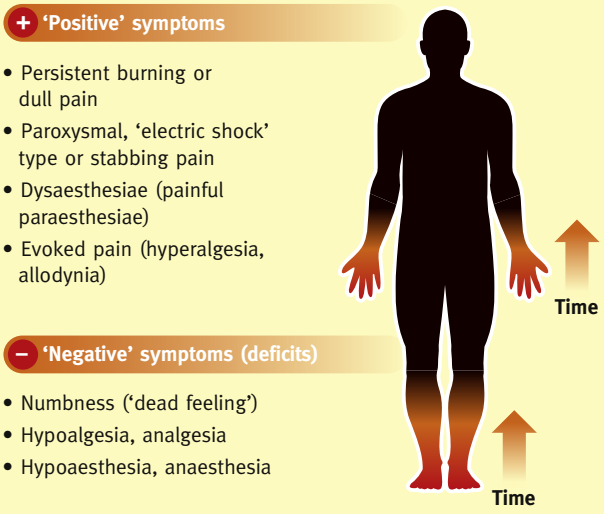

Figure 2