Chapter 2
Classification and Clinical Features

Classification

Several classification systems for the neuropathies have been proposed. Some are based on presumed aetiology whereas others refer to topographical features or disease pathogenesis. However, the inter-relationship of aetiology, mechanisms and symptoms is complex and poorly understood, and, as such, this traditional classification is of little use in clinical practice (Fig. 2.1).

Until the underlying pathophysiology of diabetic neuropathies has been elucidated, the most useful systems for practising physicians are those based on clinical manifestations. Three classification systems are presented in Fig. 2.2. This book follows the system used in the 2005 American Diabetes Association statement,[3] which discusses diabetic neuropathies under three headings: sensory neuropathies; focal and multifocal neuropathies; and autonomic neuropathy.

The clinical features associated with each type of neuropathy are discussed in detail on the following pages. Pain terminology, as defined by the International Association for the Study of Pain, is summarised in Fig. 2.3. The definition and classification of symptoms are described in more detail in Chap. 3.

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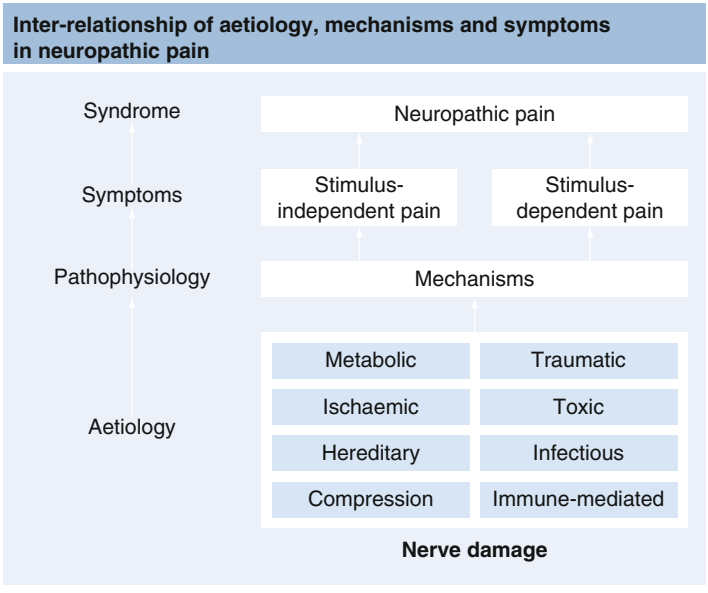

FIGURE 2.1 Inter-relationship of aetiology, mechanisms and symptoms in neuropathic pain (Reproduced with permission from Woolf and Mannion[1])

Sensory Neuropathies

Chronic Sensorimotor Distal Symmetrical Polyneuropathy

Chronic sensorimotor distal symmetrical polyneuropathy (DPN) is the most common form of diabetic neuropathy, being present in more than 10% of patients at the diagnosis of type 2 diabetes.[5] DPN occurs in both type 1 and type 2 diabetes and becomes more common with increasing age and duration of diabetes. In a large population survey, neuropathic symptoms affected 30% of type 1 diabetic patients and 36% and 40% of male and female type 2 diabetic patients,

Three classification systems for diabetic neuropathies

A. Clinical classification of diabetic neuropathies

Polyneuropathy	**Mononeuropathy**
Sensory • Acute sensory • Chronic sensorimotor	Isolated peripheral Mononeuritis multiplex Truncal
Autonomic • Cardiovascular • Gastrointestinal • Genitourinary • Other	
Proximal motor (amyotrophy)	
Truncal	

B. Patterns of neuropathy in diabetes

Length-dependent diabetic polyneuropathy
- Distal symmetrical sensory polyneuropathy
- Large fibre neuropathy
- Painful symmetrical polyneuropathy
- Autonomic neuropathies

Focal and multifocal neuropathies
- Cranial neuropathies
- Limb neuropathies
- Proximal diabetic neuropathy of the lower limbs
- Truncal neuropathies

Non-diabetics neuropathies more common in diabetes
- Pressure palsies
- Acquired inflammatory demyelinating polyneuropathy

C. Classification of diabetic neuropathy

Rapidly reversible
- Hyperglycaemic neuropathy

Generalised symmetrical polyneuropathies
- Sensorimotor (chronic)
- Acute sensory
- Autonomic

Focal and mutifocal neuropathies
- Cranial
- Thoracolumbar radiculoneuropathy
- Focal limb
- Proximal motor (amyotrophy)

Superimposed chronic inflammatory demyelinating neuropathy

FIGURE 2.2 Three classification systems for diabetic neuropathies (Copyright © 2004 American Diabetes Association from Boulton et al.[2] Reproduced with permission from the American Diabetes Association)

IASP pain terminology

Pain term	Definition
Allodynia	Pain caused by stimulus that does not usually provoke pain. May be static (produced by single, non-moving stimulus) or dynamic (ie, produced by a moving stimulus)
Analgesia	Absence of pain in response to a painful stimulus that would normally be painful
Central pain	Pain initiated or caused by a primary lesion or dysfunction in the central nervous system
Dysaesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked
Hyperalgesia	Increased pain response to a painful stimulus
Hyperaesthesia	Increased sensitivity to non-painful stimuli (e.g., temperature, touch)
Hyperpathia	Pain syndrome characterised by abnormally painful reaction to a stimulus, especially repetitive stimulation
Hypoalgesia	Reduced pain response to a painful stimulus
Hypoaesthesia	Decreased sensitivity to non painful stimuli (e.g., temperature, touch)
Neuritis	Inflammation of a nerve or nerves
Neurogenic pain	Pain initiated or caused by a primary lesion, dysfunction or transitory perturbation in the peripheralor central nervous system
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system
Neuropathy	A disturbance of function or pathological change in a nerve: in one nerve, mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy
Paraesthesia	An abnormal sensation, whether spontaneous or evoked

Figure 2.3 IASP pain terminology (Adapted with permission from Merskey and Bogduck[4])

respectively.[2,6] However, 10% of men and 12% of women in the non-diabetic population reported similar symptoms.

Around half of patients with DPN experience symptoms, most often burning pain, electrical or stabbing sensations, paraesthesia, hyperaesthesia, and deep aching pain. Neuropathic pain tends to be intermittent and is typically worse at night. Symptoms are most commonly experienced in

the feet and lower limbs but may extend to the hands and fingers in more severe cases.

DPN tends to have an insidious onset and many patients are truly asymptomatic, putting them at risk of foot ulceration and other late sequelae including Charcot's neuroarthropathy and even amputation.[2,7] Often, a neurological deficit is discovered by chance during a routine examination; patients may not volunteer symptoms, but on enquiry admit that their feet feel numb or dead.[3]

Recently, unsteadiness has been recognised as a manifestation of DPN, reflecting disturbed proprioception and possibly abnormal muscle sensory function.[6,8] This unsteadiness has been quantified and may result in repetitive minor trauma or falls, as well as late complications including neuroarthropathy.[8] In most severe cases, with loss of proprioception, patients may demonstrate a positive Romberg's sign.[8]

Examination of the lower limbs usually reveals a symmetrical sensory loss of vibration, pressure, pain and temperature perception (mediated by small and large fibres), and absent ankle reflexes. Sensorimotor neuropathy is often accompanied by autonomic dysfunction, signs of which include a warm or cold foot, sometimes with distended dorsal foot veins (in the absence of obstructive peripheral vascular disease), dry skin and calluses under pressure-bearing areas.[3] Any pronounced motor signs should raise the possibility of a non-diabetic aetiology, especially if asymmetrical.

Acute Sensory Neuropathy

Acute sensory (painful) neuropathy is a rare, distinct variety of the symmetrical polyneuropathies. It is characterised by severe sensory symptoms similar to those associated with DPN but with few neurological signs on examination. Differences between acute sensory and chronic sensorimotor neuropathies are summarised in Fig. 2.4.

The overriding symptom reported by all patients is pain. This may be described as constant burning pain, discomfort

Contrasts between acute sensory and chronic sensorimotor neuropathies

	Acute sensory	Chronic sensorimotor
Mode or onset	Relatively rapid	Gradual, insidious
Symptoms	Severe burning pain, aching: weight loss usual	Burning pain, paraesthesia, numbness, weight loss unusual
Symptom severity	+++	0 to ++
Signs	Mild sensory in some: motor unusual	Stocking and glove sensory loss: absent ankle reflexes
Other diabetic complications	Unusual	Increased prevalence
Electrophysiological investigations	May be normal or minor abnormalities	Abnormalities unusual in motor and sensory nerves
Natural history	Complete recovery within 12 months	Symptoms may persist intermittently for years: at risk of foot ulceration

FIGURE 2.4 Contrasts between acute sensory and chronic sensorimotor neuropathies (Copyright © 2004 American Diabetes Association from Boulton et al.[2] Reproduced with permission from the American Diabetes Association)

(especially in the feet), severe hyperaesthesia, deep aching pain or sudden, sharp, stabbing or electric shock-like sensations in the lower limbs. Symptoms tend to be worse at night and bedclothes may irritate hyperaesthetic skin.

Other symptoms of acute sensory neuropathy include severe weight loss, depression and, in men, erectile dysfunction.[2] Clinical examination is usually relatively normal, with allodynia on sensory testing, a normal motor examination and, occasionally, reduced ankle reflexes.

Acute sensory neuropathy tends to follow periods of poor metabolic control (e.g. ketoacidosis) or a sudden change in glycaemic status (e.g. insulin neuritis), including an improvement in glycaemic control induced by oral hypoglycaemic agents. It has also been associated with weight loss and eating disorders.[9]

The natural history of acute sensory neuropathy is very different from DPN: its onset is acute or subacute but symptoms improve gradually with stabilisation of glycaemic control, and typically resolve in less than 1 year.[10]

The Effects of Painful Neuropathic Symptoms on Negative Affect and Quality of Life

As noted above, the symptoms of the sensory neuropathies (both acute and chronic) vary from the extremely painful at one end of the spectrum to the painless at the other. The painful symptoms, especially the burning discomfort, electrical sensations and other uncomfortable but very difficult to describe sensory experiences, frequently cause severe physical and mental dysfunction as well as sleep disturbance,[11,12] thereby negatively impacting on individuals' quality of life. The increasingly recognised symptom of neuropathic unsteadiness as a consequence of impaired proprioception can also be incapacitating.[12,13] Whereas most studies, including the recent German Diabetic Microvascular Complications Study,[14] have demonstrated that symptomatic neuropathy markedly diminishes patients' quality of life, such studies have invariably used generic instruments to assess health-related quality of life.[15] As the content of such instruments is imposed by the investigators and did not emerge from patients affected by neuropathic pain and other somatic experiences of neuropathy, the findings from these studies left a gap between painful neuropathy, as abstractly defined, and the patient's experience of pain, which is essential for framing effective interventions. In view of the more recent observation that only 65% of a community-based diabetes population with painful diabetic neuropathy had ever received treatment for their symptoms despite almost all reporting pain to their physician,[16] the adverse effect on quality of life is likely to be even greater than previously reported. In an attempt to overcome these shortcomings, several questionnaires have recently been developed to assess quality of life from the perspective of an individual affected by diabetic neuropathy. One such measure, a neuropathy and foot ulcer-specific quality of life scale, the NeuroQoL,[17] is increasingly being used in trials of new agents for the treatment of painful neuropathy in which quality-of-life measurement is an integral part of the assessment of efficacy.

Mounting evidence suggests that neuropathic symptoms are a source of severe emotional distress. As an example, a cross-sectional study examined the relationship between neuropathy severity and depression symptoms, and demonstrated that neuropathic symptoms, including pain and unsteadiness, were independently associated with depressive symptomatology.[11] Moreover, this association was partially explained by two sets of psychosocial factors: (1) perceptions of symptom unpredictability and the lack of treatment control; and (2) restrictions in daily activities and diminished self-worth due to inability to perform family roles. The longitudinal findings of this investigation were largely consistent with cross-sectional observations and demonstrated that more severe neuropathy at baseline assessment was associated with worsening depressive symptoms over time. Furthermore, a decline in neuropathy-related physical and psychosocial functioning over time contributed to further increments in depressive symptoms. While neuropathic pain contributed to depression, unsteadiness and its psychosocial consequences dominated this relationship over time.[13] By contrast, neuropathic pain appears to have an enduring association with anxiety, as demonstrated by the same research group.[13] In analyses that simultaneously examined predictors of anxiety and depression, both baseline and change in neuropathic pain predicted increases in anxiety over time. Taken together these studies indicate that, in patients with recent increases in pain, clinicians should monitor levels of both anxiety and depression. However, anxiety should be monitored in patients even in the absence of recent increases in pain.

In view of these findings we propose that clinicians should monitor dynamics of affect and select treatment based on the predominant type of emotion, especially as commonly used medications for symptomatic neuropathy are potent mood modulators with distinct class effects on anxiety and depression. Moreover, when making the diagnosis of painful diabetic neuropathy it is important to give a full explanation of the symptoms, their causes and their treatment to the patient. Reassurance that there are no

sinister underlying disorders such as malignant disease, and that the symptoms are eminently treatable and may resolve in due course, is an important part of the initial management of the patient with painful neuropathy. In contrast to the effect of painful symptoms on affect, it has also been clearly demonstrated that negative symptoms such as unsteadiness, and its consequent effects on activities of daily living, may be associated with depressive symptomatology.[11] Practitioners should therefore be aware that such negative symptoms may contribute to depressive affect that might also require treatment. Interestingly, neither the presence nor the past history of diabetic foot ulceration was predictive of depressive symptoms in these reports. A recent study assessed whether depressive symptoms are implicated in the development of diabetic foot ulceration among patients at high biological foot ulcer risk.[18] In this report, depression and foot self-care had important relationships with foot ulcer risk in those patients with no prior foot ulceration but not among those who had previously had a foot ulcer. This suggests that prevention efforts that address psychological and behavioural factors may have greater efficacy in patients who have not yet reached the highest level of biological risk. Addressing depression only in patients already presenting with foot ulcers may therefore be 'too little, too late'.[18]

Focal and Multifocal Neuropathies

Mononeuropathies

Focal and multifocal neuropathies typically affect older patients with type 2 diabetes.[19] Mononeuropathies, encompassing both entrapment neuropathies and focal limb neuropathies, indicate the greater susceptibility of diabetic nerves to compression.

The median nerve is most commonly affected, giving rise to carpal tunnel syndrome. This can be demonstrated electrophysiologically in 20–30% of diabetic patients and

accounts for 5.8% of all diabetic neuropathies.[20] Symptoms include painful paraesthesia of the fingers, which may progress to a deep-seated ache radiating up the forearm or, very rarely, the whole arm. This occurs primarily at night but may be precipitated during the day by repetitive wrist flexion and extension.[2]

The second most common entrapment neuropathy, accounting for 2.1% of all diabetic neuropathies, results from ulnar nerve compression. It may develop as a result of deformity at the elbow joint secondary to fracture and is often associated with alcoholism. Typical symptoms include painful paraesthesia in the fourth and fifth digits associated with hypothenar and interosseous muscle wasting.[19,20]

Radial neuropathy is rare (0.6%). It presents with the characteristic motor deficit of wrist drop, occasionally accompanied by paraesthesia in the dermatomes supplied by the superficial radial nerve. Causes include humeral fracture, blunt trauma and external compression.[19,20]

Common peroneal neuropathy is the most common of all lower limb mononeuropathies. Involvement of the motor fibres in the common peroneal nerve results in weakness of the dorsiflexors and 'foot drop', whereas loss of the motor supply to the tibialis anterior muscle also leads to weakness in eversion. The resulting sensory deficit is not usually accompanied by pain or paraesthesia. Diabetes is responsible for just 10–12% of cases of peroneal neuropathy; more significant causes include external compression during anaesthesia and inappropriately placed plasters following lower-limb fractures. Once the external pressure has been relieved, most motor deficits will resolve within 3–6 months.[2]

Compression of the lateral femoral cutaneous nerve is uncommon and results in pain, paraesthesia and sensory loss in the lateral aspect of the thigh (known as meralgia paraesthetica). Obesity is the most common cause, followed by trauma due to external nerve injury. Most cases resolve spontaneously.[2]

Cranial Neuropathies

Cranial neuropathies are extremely rare (0.05% of all diabetic neuropathies) and affect older individuals with a long duration of diabetes.[21] They primarily involve cranial nerves III, IV, VI and VII. They are thought to occur due to a microvascular infarct and typically resolve spontaneously over several months, although around 25% of patients will suffer a recurrence.[2]

The classic presentation of oculomotor nerve palsy is acute-onset diplopia with ptosis and pupillary sparing associated with ipsilateral headache.

Pupillary sparing function is normal in 14–18% of patients, however, and the underlying pathology of the condition is not well understood.

Facial neuropathy, or Bell's palsy, typically presents with acute-onset unilateral weakness of facial muscles, widening of the palpebral fissure and secondary corneal irritation. This may be accompanied by taste disturbances and hyperacusis.

Very rarely, other cranial nerves may be affected in patients with diabetes. These include trigeminal neuralgia, hearing loss (cranial nerve VIII), vagal nerve involvement and vocal fold paralysis attributed to recurrent laryngeal nerve involvement.

Diabetic Amyotrophy

Diabetic amyotrophy (proximal motor neuropathy) most commonly affects male type 2 diabetes patients aged 50–60 years and presents with severe pain, uni- or bilateral muscle weakness, and atrophy in the proximal thigh muscles.

Factors that contribute to the development of diabetic amyotrophy are poorly understood but may include ischaemia. The disease develops rapidly at first but then progresses more slowly over several months, indicating a combination of both vascular and metabolic factors.[2] An immune-mediated

epineurial microvasculitis can present in a similar way and should be considered in the differential diagnosis – it can be demonstrated by nerve biopsy.

Diabetic Truncal Radiculoneuropathy

Truncal radiculoneuropathy affects middle-aged and elderly patients with diabetes and shows a predilection for men. The key symptom is pain, which is acute in onset but evolves over several months. Pain is typically described as aching or burning, may be superimposed with lancinating stabs and is worse at night in association with cutaneous hyperaesthesia.

The distribution of pain is girdle like over the lower thoracic or abdominal wall and is usually unilateral. Rarely, truncal radiculoneuropathy can result in motor weakness with bulging of the abdominal wall; symptoms may also be accompanied by profound weight loss.

Findings on neurological examination vary from no abnormalities to sensory loss and hyperaesthesia in a complete dermatomal pattern; sometimes just the ventral and dorsal rami are involved. Symptoms generally resolve within 4–6 months.

Again, the pathogenesis of diabetic truncal radiculoneuropathy is not well understood. The acute onset of symptoms suggests a vascular cause, whereas its occurrence in patients with poorer glycaemic control indicates a metabolic basis.[2]

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) should be considered when an unusually severe, predominantly motor neuropathy and progressive polyneuropathy develop in a diabetic patient. This diagnosis is often overlooked and the patient simply labelled as having diabetic amyotrophy or polyneuropathy, which, unlike CIDP, has no specific treatment.

By contrast, progressive symmetric or asymmetrical motor deficits, progressive sensory neuropathy in spite of optimal glycaemic control, together with typical electrophysiological findings and an unusually high cerebrospinal fluid protein level all suggest the possibility of an underlying treatable demyelinating neuropathy.[22]

Autonomic Neuropathy

Diabetic autonomic neuropathy[23] is a serious and common complication of diabetes that results in significant morbidity and mortality. A variation of the peripheral diabetic polyneuropathies, diabetic autonomic neuropathy can involve the entire autonomic nervous system. It may be either clinically evident or subclinical, and is manifested by dysfunction of one or more organ systems (e.g. cardiovascular, gastrointestinal, genitourinary, sudomotor, ocular).[24]

Most often, diabetic autonomic neuropathy is a system-wide disorder affecting all parts of the autonomic nervous system. Clinical symptoms generally do not arise until long after the onset of diabetes. However, subclinical autonomic dysfunction can occur within a year of diagnosis in type 2 diabetes and within 2 years in type 1 diabetes.[25]

Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, exercise intolerance, orthostatic hypertension, constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction and impaired neurovascular function.[2]

Because of its association with a variety of adverse outcomes, including death, cardiovascular autonomic neuropathy (CAN) is the most clinically important and well-studied form of diabetic autonomic neuropathy. It results from damage to the nerve fibres that innervate the heart and blood vessels, and results in abnormalities in heart rate control and vascular dynamics. The earliest indicator of CAN is reduced heart rate variation; later manifestations include silent myocardial ischaemia and sudden death (Figs. 2.5 and 2.6).[25]

Clinical features of autonomic neuropathies

Cardiovascular
- Resting tachycardia
- Orthostatic hypotension
- Silent myocardial infarction, congestive heart failure and sudden death

Gastrointestinal
- Gastroparesis
- Diarrhoea, constipation

Genitourinary
- Bladder dysfunction
- Erectile dysfunction

Peripheral
- Gustatory sweating
- Pulpillary abnormalities

Metabolic
- Hypoglycaemia unawareness, hypoglycaemia unresponsiveness

FIGURE 2.5 Clinical features of autonomic neuropathies (Reproduced with permission from Vinik et al.[26])

Association between CAN and mortality in diabetic patients: pooled data from 15 studies

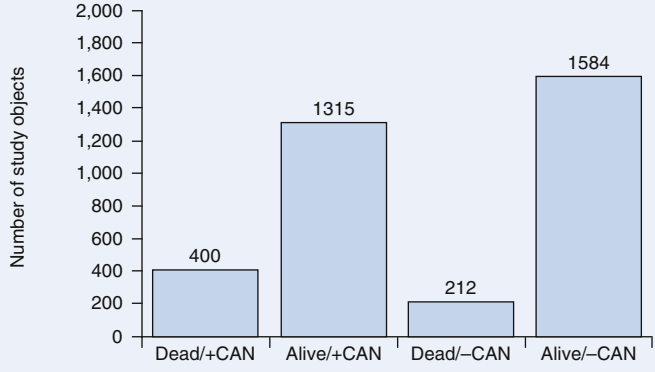

FIGURE 2.6 Association between CAN and mortality in diabetic patients: pooled data from 15 studies. CAN, cardiovascular autonomic neuropathy; +CAN, CAN present; –CAN, no CAN found (Copyright © 2003 American Diabetes Association from Vinik et al.[24] Reproduced with permission from the American Diabetes Association)

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