

Diabetic Neuropathies

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Abstract: Diabetic peripheral neuropathy is a well-known microvascular complication of type 2 diabetes mellitus attributed to chronic hyperglycemia. Tingling paraesthesias, pain and hyperesthesias in the feet occur in newly diagnosed or poorly controlled diabetics and the symptoms resolve with proper glycemic control. The present article focuses on classification of diabetic neuropathy and its management.

EPIDEMIOLOGY

Diabetes mellitus is a pandemic with a prevalence of 8.3% translating into 371 million diabetics worldwide¹. It relates to type 2 diabetes mellitus, which may be asymptomatic in many patients for a prolonged duration, and is diagnosed only with the emergence of complications². Involvement of the nervous system by diabetes was described 150 years ago. With increasing recognition of the variable nature, the classifications of diabetic neuropathy were first suggested in 1893. Almost six decades later, the relationship of neuropathy and duration of diabetes was recognized³.

Diabetic peripheral neuropathy (DPN) is a well-known microvascular complication of type 2 diabetes mellitus attributed to chronic hyperglycemia, and is defined as the presence of peripheral nerve dysfunction in diabetics after exclusion of other causes⁴. This is associated with further infections, foot ulcers and non-traumatic amputations. Estimates of foot infections in type 2 diabetes mellitus range from a lifetime risk of 4 to 7% annually^{5,6}. Neuropathy and neuropathic pain lead to reduced health-related quality of life in patients with type 2 diabetes mellitus and impose a huge economic burden on the patients and healthcare system. Apart from the direct costs involved, DPN can also lead to work absence, change in employment and disability⁷.

Due to differences in defining and testing diabetic neuropathy, and the type of patient populations studied, the results of studies on diabetic neuropathy have been variable. Using a combination of clinical symptoms and signs, quantitative sensory testing, nerve conduction studies and heart rate variability, the prevalence was found to be 54% and 45% in type 1 and 2 diabetes respectively in a population based study⁸. Approximately 11.9 million adults in the United States aged ≥ 40 years have diagnosed diabetes. Of those, 3.9 million (32.7%) have diabetic neuropathy and 1.6 million (13.1%) have co-morbid neuro- and retinopathy⁹.

RISK FACTORS

The most important risk factor for the development of diabetic polyneuropathy is hyperglycaemia. Tight glycaemic control delays the progression of neuropathy in type 1 diabetes while the effect is not similar in type 2 diabetes. Duration of diabetes, age of the subject, hypertension and smoking are important risk factors besides hyperglycaemia. Other factors linked to neuropathy include the patient's height, level of alcohol consumption and high cholesterol and triglyceride levels. The search for candidate genes is ongoing³. The severity of diabetic polyneuropathy is staged as shown in table 1³. The classification of diabetic neuropathies is shown in table 2¹⁰.

NEUROPATHY RELATED TO IMPAIRED GLUCOSE TOLERANCE AND HYPERGLYCAEMIA

An oral glucose tolerance test is an important investigation of patients with a painful "idiopathic" neuropathy as 25-36% of such individuals are likely to have impaired glucose tolerance^{11,12}. However, the fasting blood glucose and glycosylated haemoglobin levels are normal. Skin biopsy in this painful small fibre neuropathy reveals abnormal epidermal innervations. Tingling paraesthesias,

Stage	Features
N0	Diabetic patient; no symptoms/ signs of neuropathy
N1	Asymptomatic; signs of neuropathy (e.g. distal sensory loss \pm absent ankle jerks)
N2	Symptomatic (variety of pain or numbness)
N2a	Less severe
N2b	More severe; weakness of dorsiflexion +
N3	Disabling polyneuropathy (inability to walk due to weakness of sensory ataxia; inability to use hands because of numbness)
	Disabling pain
	Autonomic failure

Table 2: Classification of Diabetic Neuropathies

Impaired glucose tolerance and hyperglycaemic neuropathy
Generalized neuropathies
<ul style="list-style-type: none"> • Sensorimotor • Acute Painful (including treatment induced) • Autonomic • Acute motor
Focal and multifocal neuropathies
<ul style="list-style-type: none"> • Cranial • Thoracolumbar • Lumbosacral radiculoplexus (Bruns-Garland syndrome) • Focal limb (entrapment and compression)
Superimposed chronic inflammatory demyelinating neuropathy
Hypoglycaemic neuropathy

pain and hyperesthesias in the feet occur in newly diagnosed or poorly controlled diabetics and the symptoms resolve with proper glycemic control. Transient pain occurring after diabetic ketoacidosis is called hyperglycaemic neuropathy and is potentially reversible with better glycemic control. A characteristic feature of the diabetic nerve to switch to anaerobic glycolysis protects the nerve function from ischemia¹³. However, the reversibility of the neuropathy associated with Impaired Glucose Tolerance (IGT) is not well studied.

DISTAL SYMMETRICAL SENSORI-MOTOR POLYNEUROPATHY

Diabetic symmetrical distal polyneuropathy (DSDP) should be diagnosed in the presence of other complications like nephropathy and retinopathy because of the strong association¹⁰. Sensory symptoms if present may be variable and intermittent. The feet are predominantly affected, and the symptoms can progress proximally. The main symptoms are numbness or a feeling of walking on cotton wool or wearing a thick sock; pain which may be dull, constant and boring or spontaneous sharp, shooting or stabbing in nature; tingling, pins and needles; walking on hot sand; allodynia or cramps in the calves and foot muscles. Though significant distal weakness in the lower limbs is uncommon, there may be wasting of the extensor digitorum brevis. The cornerstone of the clinical diagnosis of DSDP is the absence of ankle reflexes.

Typically, there is loss or impairment of all the sensory modalities in the toes and feet, but the vibration sense is the first to go. Rarely, the pattern is *pseudosyringomyelic* with selective loss of pain and temperature sensations. The sensory loss progresses proximally in the *stocking* distribution, and thereafter to the fingertips. However, the involvement of the whole legs and arms is uncommon but if it occurs, the midline of the front of the chest and abdomen are affected with a *breastplate* pattern of sensory loss. DSDP is invariably present in the presence

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of clinical autonomic abnormalities while in DSDP only half the cases have autonomic neuropathy¹⁴.

ACUTE PAINFUL NEUROPATHY

A relatively rare entity, it is experienced as a severe and unremitting burning pain mainly in the feet after the patient initially loses a lot of weight over a short period of time. There is no muscle weakness and sensory loss maybe minimal; ankle reflexes may be absent or present. Impotence and reactive depression are common. Maintaining a good glycemic control is essential as this will lead to increase in body weight and the pain will subside which may be prolonged up to 10 months and/ or incomplete. Also reported is an acute symmetrical painful neuropathy occurring a few weeks after the diagnosis of diabetes, but not associated with a dramatic weight loss³. Treatment with insulin¹⁵ and oral hypoglycaemic drugs¹⁶ may very rarely trigger acute painful neuropathy. Resolution of the pain may take a year or longer with maintenance of a good glycemic control³.

The physical examination and the nerve conduction studies may be normal or may have mild abnormalities. Nerve biopsy shows evidence of a chronic axonal neuropathy with prominent regenerative activity¹⁷.

DIABETIC MOTOR NEUROPATHY

Muscle weakness as the major feature in diabetic subjects, wherein distal sensory polyneuropathy is predominantly observed, may occur. This situation is important to understand as chronic inflammatory demyelinating neuropathy (CIDP) may coexist and is potentially reversible with immunotherapy. In a diabetic subject with established neuropathy, a rapid progression of neuropathy may be suggestive of superimposed CIDP. A trial of immunotherapy is warranted if there are two or three electrical changes of demyelination on neurophysiological study¹⁸. In addition, changes of the underlying axonal loss will be present.

Protein content maybe elevated in the cerebrospinal fluid (CSF) in diabetic neuropathy but the presence of oligoclonal bands may suggest an ongoing inflammatory process. Positive immune-reactivity for matrix metalloproteinase-9 in sural nerve biopsy may help to identify cases with superimposed CIDP¹⁹. The time course to improvement is similar in diabetic and non-diabetic patients with CIDP; however, the level of functional recovery may be comparatively less in those with diabetes³.

Diabetic polyneuropathy is mainly sensory in type and asymmetrical in distribution. Asymmetrical distribution with or without prominent muscle weakness or wasting warrants evaluation of an alternative cause of neuropathy. There is a loss of both small as well as large fibres in diabetic neuropathy. Hence, in case of dominant vibration, joint position sensation loss with relative sparing of pain and temperature sensation (i.e. large fibre neuropathy), the possibility of M paraproteinemic neuropathy or a sensory ganglionopathy must be kept. Similarly, amyloidosis or hereditary sensory and autonomic neuropathy should be considered in those with a small fibre neuropathy with or without autonomic neuropathy.

AUTONOMIC NEUROPATHY

The reported prevalence of diabetic autonomic neuropathy (DAN) varies widely depending on different criteria used to define autonomic dysfunction, different type and number of tests performed, the use of age-related normative values, the presence or absence of signs and symptoms of autonomic neuropathy, and different patient cohorts studied³.

A meta-analysis of adult patients including 15 studies from 1966 to 2001 reported prevalence rates of DAN between 1 and 90%²⁰, while Dimitropoulos reported a prevalence of cardiac autonomic neuropathy (CAN) that varies between 1 and 90% in patients with type 1 diabetes and 20–70% in patients with type 2 diabetes²¹. On the other hand, in a community-based population study, the prevalence of autonomic neuropathy, defined by one or more abnormal heart rate variability test results was 16.7%²².

In 1992, Ziegler et al. in a multicenter study reported that the prevalence of CAN in type 1 diabetes and type 2 diabetes patients was 25.3 and 34.3%, respectively (more than two of six abnormal autonomic function tests). Using more strict criteria (abnormalities in at least three of six autonomic function tests), the prevalence of CAN was 16.8% for patients with type 1 and 22.1% for individual with type 2 diabetes²³.

The various clinical manifestations associated with diabetic autonomic neuropathy are enumerated in table 3. Although the overwhelming evidence shows that the prevalence of cardiac autonomic neuropathy increases with the duration of diabetes,

one study showed no change in autonomic function test results in adults with type 1 diabetes over a 9-year follow up²⁴. Cardiac mortality and the syndrome of *sudden death at night* in diabetics is thought to be due to the predisposition to arrhythmias secondary to hypoglycaemia in those with autonomic neuropathy. Also, ventricular tachycardia is associated with reduced heart rate variability. Autonomic neuropathy may contribute to the development of nephropathy and is considered as a risk factor for stroke after 10 years²⁵. There is also documented increased anesthetic-induced cardiorespiratory arrests and perioperative cardiac instability³.

Erectile dysfunction (ED) is more common in men with diabetes. Dependent on the selected population, age, type and duration of diabetes, the prevalence of diabetic ED varies from 32 to 90%. In 12-30% of men ED is the first sign of diabetes, diagnosed later²⁶.

Table 3: Clinical Manifestations Associated With Diabetic Autonomic Neuropathy

Cardiovascular	<ul style="list-style-type: none"> Increased heart rate Impaired cardiac function Painless myocardial infarction Orthostatic hypotension
Gastrointestinal	<ul style="list-style-type: none"> Abnormal esophageal motility Gastroparesis Diarrhea and constipation
Urogenital	<ul style="list-style-type: none"> Erectile dysfunction Impaired testicular pain Retrograde ejaculation
Sudomotor function	<ul style="list-style-type: none"> Anhidrosis Gustatory sweating
Respiratory	<ul style="list-style-type: none"> Sleep Apnea
Pupillary function	<ul style="list-style-type: none"> Small unreactive pupil

Table 4: Risk factors for foot ulcers

Polyneuropathy (somatic ± autonomic)
Presence of or history of an ulcer
Altered peripheral circulation-ischemia or abnormally high blood flow
Foot deformity (clawing of toes, wasting of small foot muscle, high arches, flat feet, Charcot joint)
Callus
Peripheral edema

FOCAL AND MULTIFOCAL NEUROPATHIES

This group of neuropathies often coexists with the distal sensory polyneuropathies. Isolated neuropathies of the extraocular muscles and the facial nerve occur at an increased rate in the diabetics. Onset of the VIth cranial nerve palsy is usually abrupt and usually painless. Full recovery occurs in the majority over 3 to 5 months. Though, the IIIrd cranial nerve palsy is also abrupt in onset but is associated with retro-orbital pain for a few days. Complete resolution occurs in 3 to 6 months. There is sparing of the pupillary function in two-third cases as the pupillomotor fibres are located on the outer layer of the IIIrd nerve and the ischemia tends to affect the centre of the nerve. If the pupil is involved, CT/MR angiogram should be carried out to exclude posterior communicating artery aneurysm. Diabetes is a risk factor in Bell's palsy but does not adversely affect the recovery³. The only clinical variation in Bell's palsy is the apparent lower incidence of taste sensation in diabetics as compared to non-diabetics²⁷.

TRUNCAL RADICULONEUROPATHY

This is encountered in type 1 as well as type 2 diabetic usually in the middle or old age and more common in men than women. The onset is abrupt usually with burning pain over a focal area of chest or abdomen and contact of clothes with the skin may be unpleasant. Focal anterior abdominal wall weakness and occasionally profound weight loss may be associated. Spontaneous recovery occurs over several months but uncommonly, truncal radiculoneuropathy can recur³.

Lumbosacral radiculoplexus neuropathy or Bruns-Garland syndrome occurs more commonly in men with type 2 diabetes in middle to late life. The onset is marked by severe aching pain felt proximally in one or both legs or in the lower back which may worsen at night. Over a few days to several weeks, lower limb weakness becomes the main feature. Knee and ankle jerks may be hypoactive and sensations are usually intact. The weakness may slowly progress to generalized lower limb paresis (diabetic paraplegia). This syndrome is caused by ischemic nerve injury secondary to microvasculitis rather than a diffuse microangiopathy^{3,28}. Compression neuropathies namely, carpal tunnel syndrome occur more commonly

in diabetics.

HYPOGLYCEMIC NEUROPATHY

This entity is relatively poorly recognized but is known to occur in patients with insulinoma with neuropsychiatric problems²⁹. The neuropathy is usually sensorimotor, the motor component predominates with arms more affected than the legs and wasting of small muscles of the hand. Recovery occurs with removal of the insulinoma.

An important part of the assessment of any patient with neuropathy is the inspection of the feet as 15% patients with diabetes will develop foot ulceration at sometime³. Neuropathy and ischemia place the diabetic foot at risk and identification of the foot at risk is important³. Table 4 shows the risk factors for foot ulcers in diabetes.

Peripheral nerve biopsy has no role in the diagnosis of diabetic polyneuropathy and should be considered if there is suspicion of an alternative or additional factor responsible for the neuropathy (like vasculitis). The main pathological features in diabetic polyneuropathy include loss of myelinated (diffuse or patchy loss) and unmyelinated fibres, clustering of regenerating fibres, thickening of endoneurial blood vessels and increased durability and rigidity of Schwann cell basal laminae.

TREATMENT OF DIABETIC NEUROPATHY

Good control of diabetes over time is the key to treating diabetic neuropathy. Also, foot care is an important step in preventing complications of neuropathy. Maintaining healthy habits regular medical check ups, controlling blood pressure, exercising regularly, not smoking, and limiting or avoiding alcohol are important preventive measures. Further treatment depends on the specific type of diabetic neuropathy along with the symptoms. NSAIDs, antidepressants (amitriptyline, imipramine) and antiepileptics (pregabalin, gabapentin) are often used to reduce pain from diabetic neuropathy. Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake. Dysesthetic pain can be relieved with capsaicin cream or lignocaine gel applied locally.

Prokinetic agents namely metoclopramide are useful in diabetic gastroparesis; polyethylene glycol maybe used in constipation. Fludrocortisone is useful for postural hypotension. Bethanechol hydrochloride is used for selective stimulation of the bladder to produce contraction to initiate micturition and empty the bladder in patients who have bladder hypocontractility. Complementary therapies such as acupuncture and biofeedback may play a contributory role in alleviating the manifestations of diabetic neuropathy³⁰.

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