Diabetic Neuropathies

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Abstract

Diabetes mellitus is a common condition and diabetics are prone to develop a spectrum of neuropathic complications ranging from symmetric and diffuse to asymmetric and focal neuropathies that may be associated with significant morbidity. Diabetic sensorimotor polyneuropathy is the most common of these complications, occurring in patients with type 1 and 2 diabetes mellitus, as well as in those with prediabetes and glucose intolerance. In this review, the authors discuss the wide variety of neuropathies that can present in the context of diabetes, including the clinical manifestations, diagnostic features, and approach to management.

Keywords
- diabetes
- diabetic neuropathy
- neuropathy
- polyneuropathy

Diabetes mellitus is a global epidemic in developing and developed countries. Presently in the United States over 9% of the population is affected, and the prevalence is nearly 26% for individuals over age 65[1]; by 2050, it is estimated that one in three people will have the condition. In addition, prediabetes affects 37% of Americans over the age of 20; there are an estimated 8.1 million people with undiagnosed diabetes mellitus.[1] On a global scale, it is estimated that the number of people affected by diabetes mellitus will double to 366 million by 2030.[2]

Diabetes mellitus frequently affects the peripheral nervous system and is the most common cause of neuropathy in the world today. Peripheral neuropathy will occur in up to 50% of all patients with diabetes mellitus[3,4] Moreover, a substantial subset of asymptomatic patients may have electrophysiological features of neuropathy.[5]

Though diabetic sensorimotor polyneuropathy (DSP) is the most common manifestation,[6] there are several other neuropathy syndromes that can occur in the context of diabetes mellitus. These include small fiber and autonomic neuropathies, as well as asymmetric and focal processes including mononeuropathies, cranial neuropathies, and radiculoplexus neuropathies (see ►**Table 1**). In this review, we will summarize the clinical features, diagnostic approach, and treatment options for the more commonly encountered syndromes.

Diabetic Sensorimotor Polyneuropathy

Clinical Features

Diabetic sensorimotor polyneuropathy is by far the most common neuromuscular manifestation of diabetes mellitus, affecting approximately 50% of all patients with the disease.[6] This is a length-dependent, sensory-predominant process that most often begins insidiously and progresses slowly. Paresthesias and numbness begin distally in the toes and ascend gradually over time. As sensory symptoms reach the level of the midcalves, they will often emerge in the fingertips. Distal weakness and atrophy lag behind, and will typically develop contemporaneously with the onset of more advanced sensory manifestations. Some patients will also experience pain in the legs and feet.[7] Though a pure autonomic neuropathy exists, some features of dysautonomia may be present in patients with DSP, including erectile dysfunction, orthostatic hypotension, cardiac arrhythmias, changes in sweating, and bowel and bladder disturbances.

The clinical assessment of patients with DSP begins with a complete history. The history should capture the duration of diabetes (as the incidence of DSP increases with disease duration), the severity of hyperglycemic exposure, and whether there are other diabetic complications such as retinopathy and nephropathy. The physical examination

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Table 1 Subtypes of diabetic neuropathy

Symmetric and diffuse
Diabetic sensorimotor polyneuropathy
Small fiber neuropathy
Autonomic neuropathy
Treatment-induced diabetic neuropathy
Diabetic cachexia
Asymmetric and focal
Mononeuropathy -Carpal tunnel syndrome -Ulnar neuropathy at the elbow -Peroneal neuropathy
Diabetic lumbosacral radiculoplexus neuropathy
Diabetic cervical radiculoplexus neuropathy
Thoracic radiculopathy
Cranial neuropathy

may reveal large fiber (vibration, joint position sensation) and small fiber (pain, temperature) sensory deficits in the feet and ankles, and in the hands in more advanced cases. Ankle reflexes may be depressed or unobtainable. Subtle weakness and atrophy may be present in the feet. Monofilament examination in the toes is a useful screening test for DSP[8] and can identify asymptomatic patients at risk for developing DSP.[9]

Diagnosis

Electrodiagnostic testing is central to the diagnosis of DSP as emphasized in recent criteria from the Toronto Expert Panel on Diabetic Neuropathy.[10] Electrodiagnosis in DSP usually reveals evidence of a distal axonopathy. On nerve conduction studies (NCS), the diagnosis of DSP requires abnormalities affecting at least two nerves, one of which must be the sural nerve.[11] Studies performed should include unilateral peroneal, tibial, and median motor responses, sural and median sensory responses, and tibial F-waves. Ulnar motor and sensory responses may also be tested.[12] Unilateral studies are appropriate given the symmetrical nature of the condition.[13]

Parameters from NCS can be used both to diagnose DSP and to identify patients with diabetes mellitus at risk for developing the complication.[14] Electromyography (EMG) can be used to screen for other processes such as lumbosacral radiculopathy. In DSP, EMG may reveal features of denervation in distal muscles that can suggest subtle motor fiber involvement, even without abnormalities on NCSs.[15]

Though the NCS in DSP typically reveal features of axonal degeneration, more pronounced slowing of motor conduction velocities can be observed particularly in type 1 diabetics with poor glycemic control.[16] These DSP patients with features suggestive of demyelination (D-DSP) differ from diabetic patients who are diagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in that their glycemic control is worse and they have less severe neuropathy.[17] Although DSP is the most common type of neuropathy seen in diabetes patients, it is important to consider other syndromes if the clinical phenotype or the electrophysiological profile are suggestive. Chronic inflammatory demyelinating polyradiculoneuropathy may be missed in patients with diabetes, and these individuals can have a positive response to treatment.[18]

Conventional NCSs as described above assess only large fiber function. Sympathetic skin responses (SSR) can be used to assess small fiber disease, though its diagnostic performance appears to be limited in diabetic patients.[19] Other tests that can be used to detect small fiber involvement include skin biopsy with measurement of intraepidermal nerve fiber density,[20] quantitative sweat testing, corneal confocal microscopy,[21–24] and cutaneous axon-mediated flare laser Doppler imaging.[25] More frequently, small fiber neuropathy is diagnosed based on symptoms of neuropathic pain, impaired temperature/pain sensation, and autonomic dysfunction.[26] Of note, owing to the early involvement of small fibers in DSP, there is substantial rationale to pursue the use of these small fiber morphological or functional tests to assess risk for future disease in asymptomatic patients with diabetes.

Treatment

There are currently no established disease-modifying treatments for DSP. Optimized glycemic control is the cornerstone of management, decreasing the incidence of neuropathy in type 1 diabetes[27,28] and yielding some improvement in NCS findings and vibration perception thresholds in type 2 diabetics.

Several therapeutic options exist for the management of neuropathic pain, and a recent evidence-based document provides guidance.[29] Antidepressants including amitriptyline, duloxetine, and venlafaxine may be effective. Among anticonvulsants, pregabalin has the highest level of evidence, though gabapentin and valproic acid may also be utilized (►**Table 2**). Alpha lipoic acid is an antioxidant that has been shown to yield some improvement in neuropathic pain, sensory symptoms, and deficits,[30,31] although some trials have failed to show benefit.

A recent randomized controlled trial of fulranumab, a monoclonal antibody directed against nerve growth factor (NGF), revealed some efficacy in the reduction of daily pain when administered at 10 mg subcutaneously every 4 weeks.[32] This study was terminated early because of a clinical hold placed by the Food and Drug Administration (FDA) due to concern that anti-NGF antibodies could be associated with osteoarthritis or osteonecrosis.

Capsaicin cream therapy applied to painful areas can be of modest benefit.[33] An open-label study revealed that use of lidocaine patches can improve pain and quality of life, and may allow tapering of other analgesic medications.[34]

Diabetic Autonomic Neuropathy

The prevalence of diabetic autonomic neuropathy (DAN) increases with age and duration of diabetes mellitus, and

Table 2 Symptomatic treatment for neuropathic pain in diabetic neuropathy

Level and recommendation	Treatment	Dose
Level A, recommended	Pregabalin	300–600 mg/d
Level B, recommended	Gabapentin	900–3600 mg/d
	Sodium valproate	500–1200 mg/d
	Venlafaxine	75–225 mg/d
	Duloxetine	60–120 mg/d
	Amitriptyline	25–100 mg/d
	Dextromethorphan	400 mg/d
	Morphine sulfate	Up to 120 mg/d
	Tramadol	210 mg/d
	Oxycodone	Mean: 37 mg/d Max: 120 mg/d
	Capsaicin	0.075% 4 times daily
	Isosorbide dinitrate spray	
	Electrical stimulation	Percutaneous electrical nerve stimulation 3–4 times/wk
Level B, not recommended	Oxcarbazepine	
	Lamotrigine	
	Lacosamide	
	Clonidine	
	Pentoxifylline	
	Mexiletine	
	Magnetic field treatment	
	Low-intensity laser treatment	
	Reiki therapy	

Source: Adapted with permission from Bril V, England J, Franklin GM, et al. Evidence-Based Guideline: Treatment of Painful Diabetic Neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2011;76:1758–1765.

with worsening glycemic control.[35,36] Though DAN can occur in isolation, more commonly it is accompanied by a sensory neuropathy. Autonomic dysfunction occurs frequently in diabetes, and may be seen in over 30% of patients.[35]

Diabetic autonomic neuropathy can affect the cardiovascular, gastrointestinal, genitourinary, and sudomotor systems. The symptomatic features of cardiovascular involvement include resting tachycardia, orthostatic hypotension (defined as a postural drop in systolic or diastolic blood pressure over 20 mm Hg or 10 mm Hg, respectively), poor exercise tolerance, and myocardial infarction. Risk of mortality is increased in patients with cardiac autonomic involvement.[37] Gastrointestinal symptoms may include gastroparesis (early satiety), constipation, and diarrhea. Urinary dysfunction may begin with impaired bladder sensation and decreased frequency of urination. This may be followed by more frequent urinary tract infections and incontinence. Sexual dysfunction, including erectile dysfunction in men, is also a common feature of autonomic involvement.[38] Sudomotor dysfunction can result in sweating abnormalities, including reduced sweating in distal limbs with increased sweating centrally.

Tests of autonomic function can be useful in DAN, as abnormalities may be detected even in asymptomatic individuals. Cardiovascular functioning can be assessed with variability in heart rate to deep breathing and both heart rate and blood pressure responses to the Valsalva maneuver and tilt. The Quantitative Sudomotor Axon Reflex Test (QSART) provides an index of sudomotor function by measuring distal limb sweat response to iontophoresed acetylcholine. The sympathetic skin response (SSR) can also be used to indicate the presence of DSP,[19] and absence of the SSR is seen more frequently in diabetic patients with symptoms of autonomic dysfunction.[39]

As with most other diabetic complications, optimized glycemic control can be important in the prevention and treatment in DAN. Intensive glycemic control can delay onset and progression of abnormalities on autonomic testing.[27,40] Nonpharmacological treatment for orthostatic hypotension due to DAN may include use of compression stockings and gradual transition from supine to standing positions. The α-agonist midodrine can be effective in the treatment of neurogenic orthostatic hypotension,[41] and the mineralocorticoid fludrocortisone can also be of benefit.[42] Both agents

can worsen supine hypertension, and potential negative effects on other cardiac comorbidities (such as congestive heart failure) must be considered. Symptoms of gastroparesis may respond to smaller, more frequent meals, and treatment with prokinetic agents such as metoclopramide and domperidone. Patients with erectile dysfunction, once hypoandrogenism has been evaluated and managed, may be initially treated with oral phosphodiesterase type 5 inhibitors (such as sildenafil). See ►**Table 3** for a summary of treatment options for DAN.

Treatment-Induced Neuropathy

A proportion of patients who undergo rapid glycemic control will experience a treatment-induced neuropathy (also known as insulin neuritis). Though this has previously been considered a relatively rare entity, a recent, large retrospective review revealed that 10% of patients with diabetic neuropathy experienced this treatment complication.[43] This condition occurs in type 1 and 2 diabetes mellitus, and can be associated with both insulin and oral hypoglycemic medications.

Treatment-induced neuropathy of diabetes (TIND) is a small-fiber neuropathy that typically manifests as severe pain and/or autonomic dysfunction within 8 weeks of significant glycemic control. Neuropathic burning and lancinating pain most typically develops in a distal symmetric pattern, though the proximal limbs and trunk can also be involved. The pain may be more severe and difficult to treat as compared with that seen in DSP. Allodynia and hyperalgesia may also be present. Orthostatic syncope and presyncope are the most common autonomic symptoms, though erectile dysfunction and gastrointestinal symptoms may also be present.[44] Pain and autonomic symptoms usually improve with time. There appears to be a correlation between the magnitude of glycemic control (as measured by the decrease in hemoglobin A1c), and the severity of neuropathic pain and autonomic dysfunction.[43]

Diabetic cachexia is a rare disorder that can also occur soon after rapid glycemic control. Patients experience severe neuropathic pain associated with marked weight loss and sensorimotor polyneuropathy. Symptoms typically improve over a matter of months.[45]

Diabetic Radiculoplexus Neuropathies

Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) has also been known as diabetic amyotrophy and Bruns-Garland syndrome.[46] Most patients have type 2 diabetes mellitus; in some, DLRPN is the presenting feature.[47] Patients are typically over the age of 50 and are more often male. Patients with DLRPN often have better glycemic control and fewer diabetic complications as compared with patients with DSP.[48]

Diabetic lumbosacral radiculoplexus neuropathy usually presents acutely with severe pain in the lower back, hip, and proximal leg. Patients may initially be diagnosed with lumbosacral radiculopathy. Within days or weeks, weakness and atrophy develop in the proximal muscles of the hip and thigh, and at times in the lower leg and ankle. Knee-extension weakness can be a dominant finding and may give the impression of a femoral neuropathy. Although motor findings predominate, proximal and distal sensory loss also develops in the majority of patients. There may be significant weight loss associated with this condition; some patients also have autonomic involvement.

Though the syndrome begins asymmetrically, some degree of contralateral leg weakness will occur in the vast majority of patients at a median time of approximately 3 months after onset. Progression of weakness can continue for up to 18 months.[46] This is a monophasic syndrome and patients typically do improve, though recovery is often incomplete. Pain may persist. Though proximal weakness tends to improve earlier and more completely, many patients are left with a persistent foot drop.

Involvement is not always limited to the legs. Up to one third of patients experience upper limb involvement. This may take the form of a mononeuropathy (focal ulnar or median neuropathy) or less commonly a more extensive cervical radiculoplexus neuropathy.[47–49] Patients with cervical radiculoplexus neuropathy experience severe pain followed by weakness, atrophy, and numbness in one arm. Contralateral arm involvement can occur in 35% of patients.

Table 3 Treatment options for autonomic neuropathy

Autonomic symptoms	Treatment
Orthostatic hypotension	Nonpharmacologic measures: -Elastic stockings -Increased salt intake -Gradual changes in posture
	Fludrocortisone 0.1 mg po daily (starting dose)
	Midodrine 10mg po tid
Gastroparesis	Smaller, more frequent meals
	Metoclopramide 5 mg po tid (starting dose)
	Domperidone 10 mg po tid
Erectile dysfunction	Sildenafil 50 mg once daily, 1 hour before intercourse

Abbreviations: po, by mouth; tid, 3 times daily.

Isolated thoracic root involvement can also occur in patients with DLRPN.[6] Affected patients present with neuropathic pain, numbness, and paresthesias in the chest or abdomen.[50] Some patients experience symptoms spanning multiple dermatomes. Electromyography can reveal features of active denervation in the thoracic paraspinal, abdominal, and intercostal muscles.

The diagnosis of DLRPN is based mainly on clinical suspicion and electrophysiological testing. Nerve conduction studies reveal asymmetrically attenuated or unobtainable motor and sensory responses in the lower limbs, with relatively mild slowing of conduction velocity. Electromyography reveals active denervation and neurogenic motor unit potential remodeling with a pattern of reduced recruitment in muscles spanning the territory of multiple nerve roots and peripheral nerve trunks. Fibrillation potentials are present in lumbosacral paraspinal muscles in the majority of patients. More diffuse findings to suggest DSP may also be present. Though not routinely done, nerve biopsy can reveal multifocal axonal loss with features of a microvasculitis.[47] Imaging of the lumbosacral plexus and/or spine is useful to exclude structural/compressive causes.

Practice varies when it comes to management of DLRPN. There are reports of some patients improving with a variety of immunomodulatory therapies, including plasma-exchange, intravenous (IV) immunoglobulin, and corticosteroids.[51–53] However, a recent Cochrane review on the topic found no randomized control trial evidence to support immunomodulatory treatment of DRLPN.[54] One randomized control trial of IV methylprednisolone in DLRPN (presented as an abstract) did not show significant benefit for impairment as measured by the Neuropathy Impairment Score.[55] Neuropathic pain may respond to immune-based therapies,[52,55,56] and can also be treated with tricyclic antidepressants and anticonvulsant agents.

Mononeuropathies

Compressive mononeuropathies occur with a higher frequency in patients with diabetes mellitus as compared with the general population. Median neuropathy at the wrist is likely the most common and though symptomatic carpal tunnel syndrome occurs in less than 10%, electrophysiological features are present in approximately one quarter of patients.[6] Other common nerve compression sites that may be more vulnerable in diabetic patients include the ulnar nerve at the elbow, the peroneal nerve at the fibular head, and the lateral femoral cutaneous nerve at the inguinal ligament.

Electrodiagnosis of carpal tunnel syndrome can be more difficult in patients with DSP, due to pre-existent underlying injury to the median nerve. In fact, electrophysiological changes at the carpal tunnel may reflect the underlying severity of DSP and not exclusively the presence of carpal tunnel syndrome.[57] Electrophysiological parameters cannot separate those diabetic patients with clinical carpal tunnel syndrome from those who are asymptomatic. Segmental median nerve sensory studies and comparative sensory studies can increase accuracy of diagnosis.[58]

Cranial Neuropathies

Patients with diabetes mellitus can develop neuropathy affecting the third, fourth, sixth, or seventh cranial nerves. Oculomotor neuropathy is the most common manifestation. The presentation is usually that of a noncompressive, fascicular oculomotor neuropathy. Patients have unilateral ptosis and limitation of supraduction, infraduction, and adduction with sparing of the pupillary light response. Some patients will also experience retro-orbital pain.

Summary

Neuropathy is a very common complication of diabetes mellitus. Diabetic sensorimotor polyneuropathy is the most prevalent type of diabetic neuropathy and is characterized by the gradual onset of sensory manifestations, pain, and in more severe cases weakness, in a length-dependent manner. Optimized glycemic control and treatment for neuropathic pain are the mainstays of management. Diabetic autonomic neuropathy can affect cardiovascular, gastrointestinal, genitourinary, and sudomotor systems. Treatment-induced neuropathy of diabetes is characterized by severe pain and autonomic dysfunction shortly after the restoration of significant glycemic control; symptoms usually resolve spontaneously. There are also numerous focal and multifocal neuropathies. Diabetic lumbosacral radiculoplexus neuropathy is usually heralded by severe pain in the lower back and proximal leg, followed by weakness, atrophy and sensory symptoms proximally, and at times distally, in the leg. Patients with diabetes mellitus may also experience focal mononeuropathies and cranial neuropathies. Knowledge of the spectrum of diabetic neuropathies is essential to allow early recognition and initiation of treatment for these common complications of diabetes mellitus.

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