Neuropathy in Diabetes

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Michael Rubin and Russell L. Chin

Abstract

Diabetes is the most common cause of sensory polyneuropathy in the United States, and can cause any type of focal, multifocal, or polyneuropathy. Etiology of neuropathy in diabetes continues to be an area of active investigation and is likely multifactorial. Treatment remains, first and foremost, control of blood glucose levels to the best extent possible. Otherwise, treatment is symptomatic in nature. At this time, no agents are available to promote nerve regeneration.

Keywords

Polyneuropathy • Mononeuropathy • Ischemia • Autoimmune • Anticonvulsants • Tricyclic antidepressants

Contents

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Introduction

Approximately 387 million people worldwide have diabetes mellitus (DM) [1]. In the United States, 29.1 million people or 9.3% of the population have DM, including about 208,000 people younger than 20 years [2]. Over half of these individuals will eventually develop neuropathy [3].

DM can affect any nerve, or nerves, in any combination. A clinically useful classification of diabetic neuropathy is shown in Table 1.

Neuropathy is the most common late complication of DM and may lead to significant disability, including painful foot ulceration, Charcot joints, and symptomatic autonomic dysfunction, as well as depression, anxiety, and sleep disorders [4].

Table 1 Classification of diabetic neuropathy

Generalized symmetric polyneuropathies
Acute sensory
Chronic sensorimotor
Autonomic
Focal and multifocal neuropathies
Cranial
Truncal
Focal limb
Proximal motor (amyotrophy)
Coexisting CIDP

(With permission. Taken from Dyck PJ, Albers JW, Andersen H, et al. Diabetes Metab Res Rev 2011;27:620–628)

Definitions

Neuropathy is a nonspecific term implying an abnormality of nerves. It is often used synonymously, and imprecisely, with *polyneuropathy* or *peripheral neuropathy,* the latter two being equivalent. *Polyneuropathy* or *peripheral neuropathy* identifies a predominantly distal, symmetric abnormality of nerves, which usually begins in the feet and gradually ascends. *Mononeuropathy* indicates the presence of an abnormality of a single nerve. *Multiple mononeuropathy* or *mononeuropathy multiplex* describes the presence of an abnormality affecting multiple nerves, usually in a random, asymmetric manner. Note that these terms imply nothing regarding underlying etiology

Pathogenesis of Diabetic Neuropathy

Defining a precise cause for diabetic neuropathy has proven difficult, with evidence suggesting that both metabolic and vascular derangements may be responsible for peripheral nerve disorders in diabetes. Although it is appealing to ascribe focal or multifocal neuropathies to a vascular etiology, and symmetric polyneuropathies to metabolic dysfunction, the associations are likely more complex, with vascular or metabolic dysfunction not restricted to any particular neuropathy. Furthermore, spinal cord involvement occurs early in diabetic peripheral neuropathy (DPN), indicating that the neuropathic process in humans is not confined to the peripheral nerve. This may explain why a variety of therapeutic options attempted in DPN have been unsuccessful [5]. Cerebral injury also occurs, as documented by mild performance deficits on a range of neuropsychological tests compared with nondiabetic control subjects, and may play a role as well [6]. Type 2 DM appears to promote cerebral cortical neuro-degeneration, an effect perhaps driven by tau phosphorylation, through mechanisms yet to be elucidated [7].

Vascular Hypothesis

Traditionally, disease progression in diabetic polyneuropathy (DPN) was characterized by the development of vascular abnormalities, comprising capillary basement membrane thickening and endothelial hyperplasia, with subsequent hypoxia. Improved nerve conduction velocities, using alpha 1-antagonists and renin-angiotensin system inhibitors, were hypothesized to be the result of increased neuronal blood flow.

Recently, however, this hypothesis has been questioned. Neuropathy may not be a "microvascular" complication, after all. Changes in neuronal blood vessels may be the secondary effect of an underlying neuronal and glial disorder associated with neuropathy, rather than the other way around. Recent evidence suggests that diabetic neuropathy selectively targets sensory and autonomic neurons over motor neurons, with little vascular involvement, but with loss of corneal innervation [8] and epidermal innervation [9]. Nerve degeneration in the cornea significantly correlates with thermal thresholds, various measures of pain and pressure, and neurological disability.

Glucose

Hyperglycemia is the major factor in the development of diabetic neuropathy, and, as demonstrated in the Diabetes Control and Complications Trial, intensive therapy effectively delayed the onset and slowed the progression of

diabetic neuropathy, as well as retinopathy and nephropathy, in patients with insulin-dependent DM [10].

In experimental models of diabetes, both microvascular and macrovascular diabetic complications may be somewhat preempted by exogenous insulin therapy, and, even more so, by intranasal insulin [11] or pancreatic islet cell transplantation [12], the latter suggesting that factors other than insulin prevent diabetic complications, possibly C-peptide which is cleaved before insulin signaling occurs [13]. This is further complicated in type 2 diabetes where intensive glucose control does not lower the risk of cardiovascular disease [14]. Some antihyperglycemic agents may have impact on diabetic complications. Metformin, perhaps through to its effects on vitamin B_{12}, has been associated with a worsening of peripheral neuropathy, but appears to have a beneficial effect on macrovascular complications including atherosclerosis and atherothrombosis, ascribed to improvements in dyslipidemia, a reduction in proinflammatory profiles, decreased oxidative and carbonyl stress, and restoration of endothelial function within the vasculature [15].

Metabolic Hypothesis

One hypothesis suggests that glucose and myoinositol are structurally similar, and myoinositol uptake in diabetic nerves is reduced by hyperglycemia, which in turn impairs membrane-bound Na/K ATPase, resulting in axoglial changes and abnormalities of nerve conduction velocity. In clinical trials, however, myoinositol supplementation was of no benefit.

A popular hypothesis invokes accumulation of polyols, particularly sorbitol, through the aldose reductase pathway. Aldose reductase converts glucose into sorbitol, accumulation of which lowers intracellular myoinositol. Reduced myoinositol is also associated with impaired sodium-potassium ATPase activity, alteration in protein kinase C (PKC) subunits, and slowed nerve conduction velocities. This hypothesis underlies the rationale for using aldose reductase inhibitors to prevent diabetic neuropathy. However, their success has been uninspiring. Sorbinil resulted in only small increases in nerve conduction velocities, and tolrestat had some clinical benefit but the study involved mild diabetic neuropathy [16, 17]. The poor results are not surprising. Study of sural nerve biopsy specimens shows no correlation between sorbitol content and neuropathy [18] and dietary myoinositol replacement resulted in no improvement in neuropathy. In fact, PKC subunits in peripheral nerve are distributed and behave in such a manner as to make it uncertain whether their inhibition is to be encouraged or counteracted [19, 20].

Immune Hypothesis

Evidence supporting an immune pathogenesis is strongest for diabetic autonomic neuropathy. Autonomic ganglia heavily infiltrated by lymphocytes, plasma cells, and macrophages were found at autopsy in five patients with type 1 diabetes and symptomatic autonomic neuropathy. Striking cervical sympathetic ganglia atrophy was reported in another with severe sensory and autonomic neuropathy [21].

Autoimmunity may be involved in diabetic lumbosacral radiculoplexus neuropathy (DLRPN) as well. Pathological study revealed polymorphonuclear small vessel vasculitis affecting epineurial vessels with polymorphonuclear transmural infiltration of postcapillary venules in 4 out of 15 patients. IgM deposits were found in affected vessel walls and endoneurium, and activated complement was seen along small vessel endothelium. Perivasculitis was seen in another six and demonstrated findings suggestive of healed vasculitis [22].

Evidence for an autoimmune basis for the common symmetrical DPN remains sparse.

Mitochondrial Dysfunction

Oxidative stress may target mitochondria, and mitochondrial injury may release cytochrome-c, initiating apoptosis [23]. In support of this mechanism, morphological mitochondrial changes in the form of vacuolization have been reported, but may be artifactual [24].

Altered Protein Synthesis and Axonal Transport

Pathological findings in human DPN support a distal axonopathy of the dying back variety. Such distal degeneration may result from impaired protein synthesis combined with abnormal axonal transport, both of which have been demonstrated in the experimental, streptozocin-treated, diabetic rat model [25].

Insulin Deficiency and Nerve Growth Factor

Nerve growth factor (NGF) is an endogenous protein necessary for small diameter nerve fiber development and survival. Levels of NGF are decreased in animal models of diabetic neuropathy and NGF was felt to play a role, particularly in the development of small fiber, painful, DPN. Nevertheless, multicenter phase III clinical trials showed no significant benefit of NGF in the treatment of DPN, and this avenue of investigation has been halted.

Insulin is itself a potent neuronal growth factor, acting on sensory neuronal and axonal receptors that share signaling cascades with neurotrophin growth factors [26]. Applied near nerves in rats, it reversed sciatic motor velocity slowing, as it did when administered intrathecally, suggesting it has an important role in supporting peripheral nerve [27]. Thus, inadequate insulin dosing may itself play a role in the development of diabetic neuropathy.

Clinical Characteristics of Neuropathy

The most common presenting symptoms of neuropathy are summarized in Table 2. A directed line of questioning is essential to thoroughly investigate the patient's problem, which may include more than one diabetes-related process. It is also important to consider other disease processes that could produce similar presentations, but would merit different therapies (See Table 3).

Table 2 Neuropathic symptoms and signs in diabetes mellitus

Sensory
1. Negative symptoms: numbness, deadness, "cotton wool feeling," "thick," "less sensitive," loss of dexterity, painless injuries, ulcers
2. Positive symptoms: burning, prickling, pain, hypersensitivity to light touch, stabbing, electric shock-like, tearing, tight, band-like
Motor
1. Proximal weakness: difficulty rising from a seated position, difficulty climbing stairs, falls secondary to knees "giving out," difficulty raising arms above the shoulders (as in combing or shampooing hair)
2. Distal weakness: difficulty turning keys or opening jars, impaired fine hand coordination, toe scuffing, tripping, foot slapping

Adapted from Windebank and Feldman [28]

Table 3 Differential diagnosis of diabetic polyneuropathy

Hereditary neuropathies
Hereditary motor and sensory neuropathy (e.g., Charcot–Marie Tooth syndrome)
Hereditary sensory and autonomic neuropathy (e.g., familial dysautonomia)
Acquired neuropathies
Autoimmune processes (e.g., Sjogren's, vasculitis)
Infectious (e.g., Lyme, HIV, syphilis, leprosy)
Demyelinating (e.g., chronic inflammatory demyelinating polyneuropathy)
Toxic (e.g., medication related)
Nutritional disorders (e.g., alcohol, B12 deficiency)
Idiopathic

Modified from Dyck et al. [29]

Diabetic Sensory Polyneuropathy (DSPN)

This, the most common form of diabetic neuropathy, is a length-dependent sensory neuropathy with little in the way of motor weakness [30]. It begins and remains most pronounced in the feet, with a combination of large and small sensory fiber involvement. Clinically, the first signs are a reduction or loss of ankle reflexes, accompanied by decreased or absent vibratory sensation in the toes. This may progress to sensory loss involving multiple modalities including pain, temperature,

position, and vibration, with positive or negative symptomatology. Weakness and atrophy of the small foot muscles and ankle dorsiflexors, with varying degrees of autonomic dysfunction, may follow, but are usually minor. The predominantly distal "stocking and glove" pattern of involvement develops because the distal portions of the longest nerves, being furthest from the nucleus in the dorsal root ganglion or anterior horn cell, are affected first.

The electrodiagnostic findings of DSPN (see section "Electrodiagnostic Features") include slowed nerve conduction velocities and diminished amplitudes – findings that correlate well with clinical abnormalities [9]. Most patients also have an absent sympathetic skin response and many demonstrate a decreased heart rate response to deep breathing and Valsalva maneuver, indicating autonomic nerve involvement [31, 32].

The clinical course of DSPN is characterized by an insidious onset (usually following several years of hyperglycemia), a slow course, and is rarely disabling. Although estimated to occur in 54% of type 1 and 45% of type 2 diabetes, most patients are asymptomatic and painful forms occur in about 11% [6]. DSPN has been found to be strongly associated with concurrent retinopathy and nephropathy. These points may be useful in differentiating DPN from other diabetic neuropathies.

An acute, painful, small fiber polyneuropathy with cachexia and weight loss (also known as "diabetic cachexia") was first described by Ellenberg in 1974 [30]. Its particular clinical hallmarks include mostly men, aged 50–70 years, with a monophasic course, and a lack of association with duration or severity of diabetes, or with other complications of diabetes such as retinopathy or nephropathy.

Diabetic Autonomic Neuropathy (DAN)

The prevalence of autonomic impairment is 54% in type 1 and 73% in type 2 DM [33]. The autonomic nerves may be involved in isolation or in combination with other nerve types.

Table 4 Autonomic symptoms by organ system

Sudomotor: loss of sweating or excessive sweating in defined areas, gustatory sweating, dry skin
Cardiovascular: postural light-headedness, fainting, micturition syncope, cough syncope, exertional syncope
Pupillary: usually asymptomatic, poor dark adaptation, poor tolerance of bright lights
Sexual: impotence, loss of ejaculation, retrograde ejaculation, inability to reach sexual climax
Urinary: urgency, incontinence, dribbling, hesitancy
Gastrointestinal: nausea, vomiting, early satiety, nocturnal diarrhea

Diabetic autonomic neuropathy (DAN) is associated with increased mortality [34]. Although more commonly associated with long-standing diabetes, it may evolve early in the course of disease. DAN presents mainly in the form of cardiac autonomic neuropathy, but may also affect the gastrointestinal, genitourinary, thermoregulatory, and pupillary systems. The cardiovascular hallmark is reduced heart rate variability, with clinical manifestations including light-headedness, orthostatic hypotension, and syncope [35]. Patients with DAN may have complement-fixing autoantibodies to sympathetic and parasympathetic ganglia, but their significance and pathogenic role have yet to be determined. They do not appear to be associated with cardiac dysautonomia [36].

Presenting symptoms vary depending on the organ system involved (see Table 4). Impotence may be an early manifestation of autonomic dysfunction, occurring in 30–60% of male patients. The incidence of gastrointestinal symptoms is reportedly as high as 75% and symptoms of either increased or decreased gastric motility may coexist [37].

A careful history is crucial. Additionally, bedside testing for dry skin, pupillary reactivity, and heart rate and blood pressure variability in the supine and seated positions are simple screening methods for autonomic dysfunction. Sophisticated quantifiable tests for dysautonomia, including sympathetic skin responses, quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat test, sweat imprints, and pupil edge light cycle testing, are beyond the scope of primary care practices. Recently, corneal confocal microscopy has been demonstrated to be a rapid,

Table 5 Management of DAN-related disorders

1. Impotence:
Meds: α2-adrenergic receptor blockers (e.g., yohimbine), sildenafil citrate
Vacuum devices, penile injections or implants
2. Neurogenic bladder:
Intermittent self-catheterization
3. Gastroparesis:
Reduce meal size, limit fats, and high calorie foods
Meds: cisapride, domperidone, erythromycin, metoclopramide
4. Orthostatic hypotension:
Head elevation at night (prevents Na and water loss and supine hypertension)
Compression stockings
Increase salt intake to 10–20 g
Meds: fludrocortisone, midodrine, phenylpropanolamine, NSAID's (inhibit prostaglandins)

noninvasive, sensitive, and specific diagnostic test for DAN [38]. Management of the more common manifestations of DAN is outlined in Table 5.

Diabetic Radiculoplexus Neuropathy

This group of asymmetric, non-length-dependent neuropathies may be divided into three subtypes: lumbosacral radiculoplexus neuropathy (DLRPN), thoracic radiculoneuropathy (DTRN), and cervical radiculoplexus neuropathy (DCRPN).

Diabetic Lumbosacral Radiculoplexus Neuropathy (DLRPN)

DLRPN (also known as diabetic amyotrophy, Bruns-Garland syndrome, femoral or femoral-sciatic neuropathy, proximal motor neuropathy, or proximal diabetic neuropathy) is the most common of these asymmetric neuropathies. It consists of a syndrome of subacutely evolving, painful, usually asymmetric, proximal weakness that tends to affect males over 50 with type 2 DM. Its development is usually unrelated to glycemic control or duration of DM. The patient initially complains of unilateral deep, aching pain localized to the anterior thigh with occasional involvement of the buttock and lumbar musculature. Pain is typically worse at night, and not increased with straight leg raising, mechanical movement, coughing, or sneezing. The pain is followed by ipsilateral weakness and atrophy of the pelvic girdle and thigh musculature, resulting in weakness of hip flexion and knee extension, and depressed or absent knee reflex. It may evolve into a widespread, bilateral paralytic disorder and may be associated with weight loss of 4.5 kg or more. The syndrome is monophasic, with spontaneous, slow, and often incomplete recovery [39]. The pain resolves before motor improvement. Although motor predominant, there is unequivocal evidence that autonomic and sensory nerves are also involved, and there may be a coexisting distal polyneuropathy.

The histopathological findings include ischemic injury and microvasculitis [40, 41]. The cerebrospinal fluid protein is usually elevated, supporting an inflammatory process targeting areas of weakness of the blood-nerve barrier [42]. Patients with nondiabetic LRPN have similar clinical and pathological findings, further supporting an inflammatory etiology rather than one related to hyperglycemia [41].

There is no proven course-altering treatment for DLRPN. Glycemic control, physiotherapy, and pain control are recommended. Intravenous immunoglobulins have been reported to be beneficial based on anecdotal evidence [43, 44], but are generally reserved for patients with severe, bilateral, progressive deficits [39]. Intravenous methylprednisolone has been recommended as a therapy for patients in the subacute phase, given its role as a first-line agent for other forms of microvasculitis. It may have a role in reducing the pain, but not the disability associated with this condition [45].

Diabetic Thoracic Radiculoneuropathy (DTRN) and Diabetic Cervical Radiculoplexus Neuropathy (DCRPN)

DTRN (also known as truncal radiculopathy) is characterized by the acute onset of unilateral, aching, or burning pain in a band-like distribution, affecting the lower thoracic or abdominal wall in older men. Patients with both type 1 and type 2 DM are susceptible. The pain is worse at night and may be associated with hypersensitivity to

touch and profound weight loss [46]. Focal motor weakness, though rare, may occur and result in localized bulging of the abdominal wall resembling a hernia [47].

Similar to DLRPN, DTRN is not related to the duration or severity of diabetes, is not associated with retinopathy or nephropathy (as seen with DPN), and is suspected to be secondary to a vasculitic process resulting in ischemic injury [48]. The syndrome also has a relatively acute onset and monophasic course with remission over 6–18 months.

It is important to exclude visceral pathology, including myocardial infarction and dissecting abdominal aortic aneurysm. A history of trauma may suggest rib fracture or chest wall muscle strain. Herpes zoster (shingles) in elderly, immunocompromised patients and the rare occurrence of thoracic intervertebral disk herniation should also be considered.

Electrophysiological findings include the presence of denervation potentials in the intercostal, anterior abdominal, and paraspinal muscles at the affected level. Coexisting polyneuropathy is also common [47].

Management of these patients usually involves only supportive care. Steroids or immunosuppressive treatments have not proven effective.

Diabetic cervical radiculoplexus neuropathy (DCRPN) has been reported to occur preceding, concurrent with, or following the lumbosacral syndrome [49]. It may also occur in isolation in a diabetic patient, but when it does, given it being uncommon, more extensive workup would be appropriate, including imaging studies of the brachial plexus, spinal fluid examination, and possibly nerve biopsy to exclude true vasculitis.

Cranial Neuropathy

Cranial neuropathies, particularly affecting the oculomotor (III), but also the abducens (IV), trochlear (VI), and facial (VII) nerves, can occur suddenly in patients with DM.

Oculomotor palsy occurs acutely, over several hours, and is marked by pain and ipsilateral headache associated with diplopia and ptosis, with pupillary sparing. Examination is noteworthy for ophthalmoparesis, usually with pupillary sparing, because the pupillomotor fibers travel circumferentially along the surface of the optic nerve and retain their vascular supply in this otherwise diabetic microinfarctive process [50, 51]. The pupil may be involved in up to 18% but this should prompt a search for a compressive lesion such as an aneurysm or tumor. Prognosis is generally excellent with recovery within days to a few months [42, 52].

Facial neuropathy (VII), or Bell's palsy, may have an increased association with DM and may have a slower recovery rate when compared to nondiabetic patients [53].

Entrapment and Compression Neuropathy

Patients with diabetes are at greater risk for external compression or entrapment neuropathy, particularly of the median, ulnar, radial, and peroneal nerves. The reasons for this, however, are unclear [54, 55].

The most commonly associated mononeuropathy is carpal tunnel syndrome (CTS), with a prevalence in the general population of 3.8% versus 15–33% in patients with diabetes.

More frequent in women than men, CTS initially presents with sensory symptoms in a median nerve distribution (particularly digits I–III) and sometimes all five fingers. The patient may develop a "pins and needles" sensation or a deep aching pain in the forearm. This may be followed by weakness and wasting of the thenar muscles. Treatment includes wrist splints, anti-inflammatory medication, and steroid injections, with carpal tunnel surgical release reserved for severe cases. Improvement following surgical release may be less substantial than in nondiabetic patients [56].

Ulnar neuropathy at the elbow is the second most common mononeuropathy associated with DM. Symptoms include pain and paresthesiae in the fourth and fifth fingers, often accompanied by pain or tenderness along the medial aspect of the elbow. Weakness and atrophy of ulnar-innervated muscles, particularly the interossei, are common. Nerve conduction studies confirm the diagnosis. Treatment includes anti-inflammatory medication

and avoidance of elbow bending. Surgery is offered for progressive cases.

Peroneal neuropathy is the most common compressive neuropathy of the lower extremity. Involvement at the fibular head results in foot drop, and weakness of foot eversion (but not inversion). Numbness over the dorsolateral foot and lower leg may also be seen. Most cases improve spontaneously with conservative management [57].

Sciatic, lateral femoral cutaneous neuropathy (meralgia paresthetica), radial, and obturator neuropathies have been reported with diabetes; however, a causal relationship is difficult to prove.

Electrodiagnostic Features

Standard nerve conduction studies (NCS) allow the physician to directly measure *large* fiber motor and sensory nerve function. These fibers are involved in position and vibration sensation, deep tendon reflex function, and muscle strength. *Small* diameter fibers, which convey pain and temperature sensation and autonomic function, are not routinely studied, though they may be assessed by skin punch biopsy. Thus, in diabetes where large fiber nerve function is often impaired, NCS are ideally suited to define the extent and severity of disease.

Motor and sensory nerves are tested individually with NCS but the underlying principle for each is similar. A nerve is stimulated at one or more sites along its course and a recording is made at a second site. If a motor nerve is being studied, the recording electrode is placed over a muscle that the nerve supplies. Sensory nerves, unlike motor nerves, have no end organ from which a recording can easily be made; both the recording and stimulating electrodes are placed over the nerve at some distance apart (Figs. 1 and 2).

Electromyography (EMG) complements NCS in the study of peripheral nerve function. Indeed, NCS and EMG are often performed in tandem and referred together as "an EMG" – as in "get an EMG." Specifically, EMG is the study of the electrical activity of muscle, performed by means of a needle electrode inserted directly into the muscle. Together with NCS, EMG can distinguish neuropathy from myopathy, localize neuropathic disorders, and quantify and provide prognostic information for nerve and muscle disorders.

Electrophysiological findings in diabetes are well described. When large diameter nerve fibers are affected in diabetic polyneuropathy, NCS reveal decreased evoked response amplitudes of both motor and sensory nerve fibers with mild

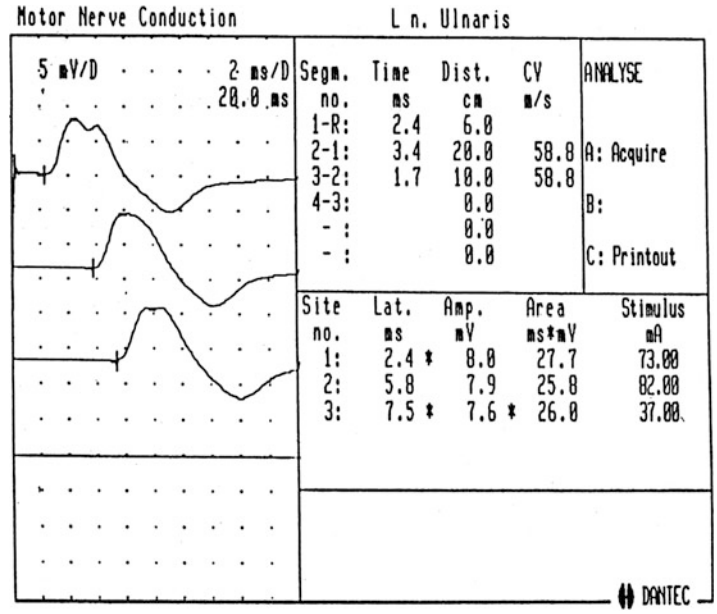

Fig. 1 Normal ulnar motor nerve conduction studies are shown above, with normal amplitude (Amp), conduction velocity (CV), and latencies (Lat). Note amplitude sensitivity is set at 5 mV/D

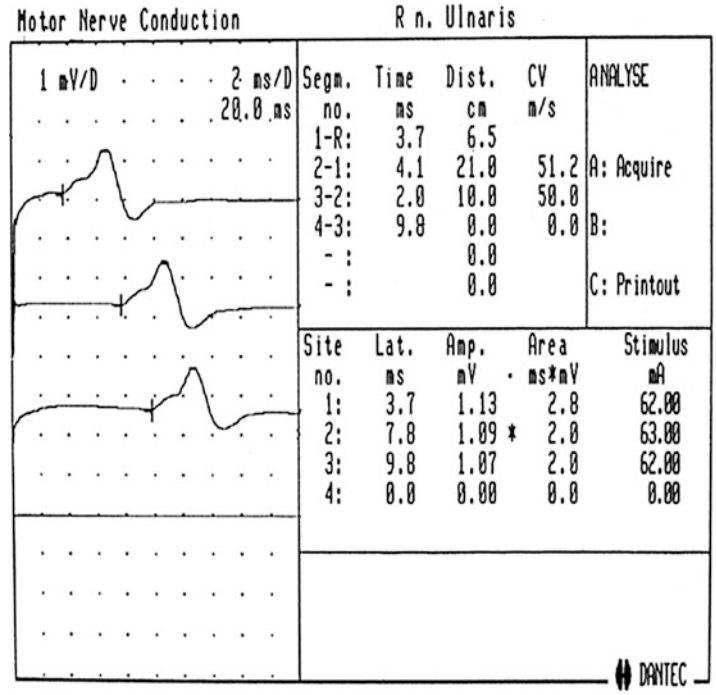

Fig. 2 Abnormal ulnar motor nerve conduction studies are shown above, as may be seen with axonal neuropathy. The amplitudes are decreased, whereas normal velocities are retained. Note, sensitivity of amplitudes measurements is set at 1 mV/D

conduction velocity slowing. As previously discussed, standard NCS are often normal in purely small fiber neuropathy nature, as these smaller fibers are not measurable by these routine studies. Computers (CASE IV systems) can evaluate small diameter nerve fiber function and, when warranted, patients may be referred to centers where this is available. In most instances, however, this will not be necessary.

As a general rule, electrophysiological deficits, when present, should be symmetrical in the context of a polyneuropathy. If the clinical problem is asymmetrical, the NCS will reflect this as well. For example, NCS in peroneal neuropathy at the fibular head causing unilateral foot drop will show abnormalities limited to the peroneal branch of the sciatic nerve, sparing of the tibial nerve, and slowing of peroneal conduction velocity across the fibular head but not in the distal calf. Similarly, ulnar neuropathy at the elbow or median neuropathy at the wrist (carpal tunnel syndrome) will demonstrate slowing localized to the elbow or wrist, respectively. EMG textbooks should be consulted for details in any specific case [57, 58].

Other Investigations

In the setting of sensory symptoms and normal electrodiagnostic studies, a skin punch biopsy can be performed to investigate for a small fiber neuropathy. In this study, a 3-mm diameter circular "punch" biopsy is obtained from the surface skin of the lateral ankle and proximal thigh. The specimens are immunostained with antibodies against markers expressed by peripheral nerve fibers (such as protein gene product 9.5) and the density of epidermal nerve fibers is determined (Figs. 3 and 4).

Qualitative information (such as the orientation of the nerve fibers or the presence of inflammatory cells or congophilic material) may also be useful. Serial biopsies from the same region have been used in research studies to monitor for interval changes or treatment response [59].

Corneal confocal microscopy is a promising, noninvasive technique that assesses small nerve pathology in vivo [60].

Magnetic resonance (MR) neurography is a novel, high-resolution, noninvasive technique that permits the detection, localization, and quantification of early diabetic neuropathy [61]. Its

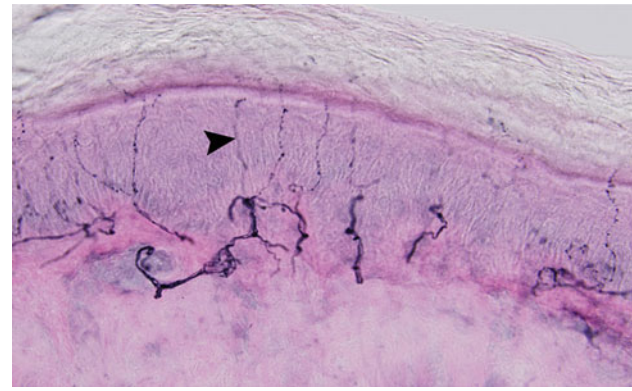

Fig. 3 Diagnosing small fiber neuropathy. This image demonstrates skin with normal nerve fiber density. The Epidermal Nerve Fiber Density (ENFD) analysis is performed by counting the number of epidermal fibers that cross the basement membrane (Image provided as a courtesy of Therapath, LLC)

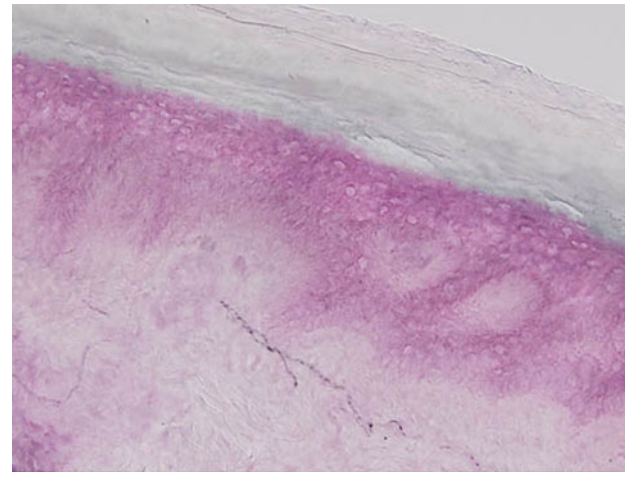

Fig. 4 Abnormal image of epidermal nerve fiber density (Courtesy of Therapath Neuropathology)

clinical role in the diagnosis and management of DPN is promising.

Treatment

The twin goals of treatment are to (1) halt or slow progression of the neuropathy by targeting the underlying pathophysiological mechanisms (Table 6) and (2) manage the clinical symptoms (Table 7).

Management of Underlying Pathogenic Mechanisms

Intensive glycemic control has been shown to slow the progression of DPN in patients with type 1 DM; however, the results in patients with type 2 DM have been variable with intensive therapy resulting in either having partial or no effect. The DCCT showed a 50% reduction in the prevalence rates for clinical or electrophysiological evidence of neuropathy in patients treated with intensive insulin therapy [10]. Pancreatic transplantation resulting in euglycemia has been associated with a gradual improvement of diabetic polyneuropathy [62].

Lifestyle modification with changes in diet, exercise, and weight resulted in cutaneous reinnervation (as determined by serial skin biopsies) and improved pain in one study of 32 patients with prediabetic neuropathy [63].

Alpha-lipoic acid has been shown to diminish oxidative stress, and has been studied in intravenous (600 mg/day for 5 weeks) and oral form (600–2400 mg daily). Recently, a dose of 600 mg daily has been determined to be beneficial and well tolerated, although these results have not been duplicated [64].

Table 6 Management aimed at underlying pathogenic mechanisms

Lifestyle intervention (diet, exercise, weight loss) – Found to result in improved pain and cutaneous innervations in patients with pre-diabetic neuropathy
Glycemic control – Found to reduce clinical and electrophysiologic evidence of neuropathy (particularly in Type 1 DM)
Aldose reductase inhibitors – Found to diminish the reduction in motor nerve conduction velocity. Fidarestat and ranirestat in clinical trials. Epalrestat marketed in Japan. Clinical benefits unclear at this time
Alpha-lipoic acid – Possible effect in reducing somatic and autonomic neuropathies. Dose of 600 mg daily is effective and well tolerated
Gamma-linoleic acid (or evening primrose oil) – An important constituent of membrane phospholipids. Under investigation. One study found benefit at 480 mg daily
Aminoguanidine – Inhibits formation of advanced glycosylation end products. Human trials discontinued secondary to toxicity
Human intravenous immunoglobulin – Anecdotal reports of effectiveness in diabetic neuropathy associated with autoimmunity, e.g., DLRPN
Steroids (methylprednisolone) – May help pain, but not disability in DLRPN
Neurotrophic therapy – Initial positive effects of recombinant human nerve growth factor in sensory neuropathy not borne out in two large multicenter studies

There is a lack of agreement about the benefits of other treatments that target underlying pathogenic mechanisms. Despite disappointing results to date, there is ongoing interest in the use of aldose reductase inhibitors to prevent excessive sorbitol flux in the nerve. Fidarestat and ranirestat are under investigation [65], and epalrestat is available in Japan. Ruboxistaurin mesylate has been used as a PKC beta inhibitor in phase II studies with some benefit noted in a subset of patients with less severe DPN [66]. Gamma-linolenic acid may have some benefit at a dose of 480 mg/day [67]. Nerve growth factor (NGF) trials have concluded that NGF offers no benefit on any end point.

As discussed, intravenous methylprednisolone may improve pain symptoms, but not disability in DLRPN [45], and there are only anecdotal reports of benefit with intravenous immunoglobulin [44].

Management of Neuropathy Symptoms

Current medical management of neuropathic pain includes antidepressants, anticonvulsant medications, opioids, and topical agents. Currently, only duloxetine and pregabalin have FDA approval for management of diabetic neuropathy pain. Careful consideration of comorbidities or risk factors should be given when selecting a therapeutic agent. The treatments are summarized in Table 7 [68–71].

Tricyclic antidepressants (TCAs) are effective in selected populations, but are less well tolerated and not appropriate for patients with cardiac morbidities. Selective serotonin reuptake inhibitors (SSRIs), such as citalopram and paroxetine, have limited effectiveness, while selective serotonin norepinephrine reuptake inhibitors (SSNRIs), such as duloxetine, have been shown to be helpful.

Gabapentin is at least equally effective as TCAs and is often a first-line treatment given its safer side effect profile. Pregabalin is a more specific alpha-2-gamma ligand with a higher binding affinity and simpler dose titration schedule when compared with gabapentin. There is limited data on the role of carbamazepine for diabetic neuropathy pain and its derivative oxcarbazepine has shown only marginal and inconsistent results. Lamotrigine and topiramate have also produced mixed results, and are not considered first-line therapy.

Opioids have a limited role in diabetic neuropathy pain management. One study found benefit with controlled-release oxycodone versus placebo in a 6-week trial [72]. A role for combination therapy with morphine and gabapentin has also been suggested [73].

Topical creams including capsaicin and lidocaine may be tried but patients find them difficult to use and only a small number respond. Transcutaneous electrical nerve stimulation (TENS) is occasionally helpful, and high-frequency muscle stimulation (HFMS) have been investigated mostly in uncontrolled studies. Frequency-modulated electromagnetic nerve stimulation (FREMS) resulted in pain reduction when compared to placebo stimulation [74]. Magnet therapy was reportedly beneficial but this was not

Table 7 Treatment options for painful diabetic neuropathy

Agent	Daily dosage	Side effects/remarks
Antidepressants		
1. Tricyclics		
Amitriptyline Nortriptyline	25–150 mg 25–150 mg	Dry mouth, urinary retention, sedation, somnolence, postural hypotension
2. SNRIs		
Duloxetine Venlafaxine	60–120 mg 150–225 mg	Nausea, dizziness
3. SSRIs		
Citalopram Paroxetine	40 mg 40 mg	Nausea, vomiting; studied in small series; less effective than TCAs
Anticonvulsants		
1. Gabapentin	300–3600 mg (divided in 3–4 doses)	NB: renally metabolized; must make adjustment
2. Pregabalin	300–600 mg (divided in 2–3 doses)	Dizziness, somnolence, peripheral edema
3. Valproate 4. Carbamazepine	250-1500 mg (divided in 2–3 doses) 200–600 mg	
5. Oxcarbazepine	1200–1800 mg (600–900 mg bid)	Light-headedness, nausea
6. Topiramate	Titrate from 25 mg up to 400 mg.	Diarrhea, weight loss, somnolence
	Typical dose ~100 mg	
7. Lamotrigine 8. Zonisamide 9. Phenytoin	200–400 mg 100–600 mg at bedtime 200–400 mg at bedtime	Rash, headache; must titrate slowly. Inconsistent benefit
Opioids		
Tramadol (weak opioid)	≤400 mg	Inhibits uptake of monoamines; has low-affinity binding to mu-opioid receptors
Controlled release oxycodone	10–100 mg (average 40 mg/day)	Constipation, cognitive dysfunction
Other agents		
Mexiletine	75–225 mg tid, slow titration	Gastrointestinal distress; Class 1B – antiarrhythmic agent; cardiology clearance required
Topical treatment		
1. Capsaicin cream 2. Lidocaine 2.5 %	Capsaicin 0.075 % applied qid Apply over intact skin	Inhibits substance P uptake at sensory endings

SSRI selective serotonin reuptake inhibitors
SSNRI selective serotonin norepinephrine reuptake inhibitors

borne out in a large multicenter trial [75]. Exercise therapy needs further validation in controlled trials [76].

Conclusion

The neuropathic complications of diabetes are varied in clinical presentation, presumed pathogenesis, and treatment response. The most frequent complication is a distal, symmetric sensorimotor polyneuropathy, which is usually chronic and progressive. Metabolic derangements are believed to be the cause of this neuropathy, and tight glycemic control has been shown to slow progression, particularly in type 1 DM. The asymmetric neuropathies affect individual nerves (e.g., cranial neuropathies, intercostal or entrapment neuropathies) or groups of nerves in close proximity to each other (e.g., radiculoplexus neuropathies). They typically have a monophasic course with spontaneous improvement and

histopathological findings of ischemic injury and microvasculitis, implicating an immune-mediated etiology.

There is a compelling need for well-designed research into novel and tolerable methods of halting disease progression and treating neuropathic symptoms, which range from numbness to severe pain.

Internet Resources

1. www.aan.com – Homepage of the American Academy of Neurology; features helpful practice advisories for the treatment of most neurological conditions.
2. www.mayohealth.org – Of interest to your patients for general health advice and reviews of neurological conditions.
3. www.ninds.nih.gov/healinfo/nindspub.htm – NINDS site, brief disease description, synopsis and information about NINDS research.
4. www.foundationforpn.org – Homepage of the Foundation for Peripheral Neuropathy.
5. www.theacpa.org – Homepage of the American Chronic Pain Association.
6. www.neuroland.com – A good page from Baylor College of Medicine for review of neurological diseases; also has a site for patients with links to patient help sources and foundations.
7. www.neuroguide.com – A helpful guide to general neuroscience with numerous links to neurology sites

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