Diabetic Neuropathy: Clinical Features, Etiology, and Therapy

David Podwall, MD, and Clifton Gooch, MD

Address
Department of Neurology, Columbia University College of Physicians & Surgeons, 710 West 168th Street, 13th Floor, New York, NY 10032, USA.
E-mail: clg33@columbia.edu

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Diabetes mellitus is a common cause of peripheral nervous system disorders that manifest in a variety of clinical forms, many of which are often misdiagnosed. Over the past two decades, our understanding of the pathophysiology of diabetic nerve injury has improved remarkably through the elucidation of the important roles of the polyol pathway of glucose metabolism, oxidative injury, advanced glycosylation end-products, vascular insufficiency, and other mechanisms. A large number of clinical treatment trials based upon this abundant scientific data have met with limited success, but ongoing and future trials offer promise for more dramatic success in treating this common cause of morbidity and mortality in the diabetic population.

Introduction

Diabetes mellitus is a common disease and continues to be a major source of morbidity and mortality around the globe, despite remarkable advances in our understanding of its pathogenesis and increasingly effective therapies for tight glucose control. It remains the most common cause of peripheral neuropathy in the United States and is second worldwide only to leprosy. Peripheral neuropathy is found by objective testing in 66% of patients with type 1 diabetes mellitus [1]. Diabetic nerve injury can be divided into several clinical syndromes, which may occur in isolation or in varying, overlapping combinations (Table 1). Among the peripheral nervous systems (PNS) syndromes, distal symmetric polyneuropathy is most common, accounting for 54% of neuropathies in patients with type 1 diabetes. Mononeuropathy, specifically carpal tunnel syndrome, is second, affecting 33% of type 1 diabetes patients with PNS dysfunction, followed by visceral autonomic neuropathy in 7% and other diabetic nerve injury in 3%. Objective neuropathy is found in a similar proportion of patients with type 2 diabetes mellitus, at a rate of 59%. Polyneuropathy is also most common in this group, occurring in 45%, followed by carpal tunnel syndrome in 35%, visceral autonomic neuropathy in 5%, and other diabetic nerve injury in 3%. Overall, 10% of all diabetic patients have neurologic injury due to nondiabetic causes, highlighting the importance of careful assessment of neurologic symptoms in diabetic patients presenting with neuropathy. Over the past two decades, our understanding of the pathogenesis of these disorders has advanced considerably, fostering a host of therapeutic trials.

Classification and Clinical Features

Distal symmetric neuropathy

Distal symmetric neuropathy is the most common form of nerve injury in diabetes. Numbness, paresthesias, or both begin insidiously in the feet and gradually ascend; however, dysesthetic pain may be the initial symptom in some patients. Over months to years, the sensory loss typically worsens in both intensity and distribution and eventually affects the hands and arms. This is a particularly important development clinically, as the numb foot significantly increases the chance of unrecognized cutaneous ulceration, which frequently is the first step in the sequence of events leading to tissue necrosis, gangrene, and limb amputation. Sensory loss increases the risk of amputation 1.7-fold in the otherwise healthy diabetic patient, 12-fold in diabetic patients with foot deformity, and 36-fold in diabetic patients having an earlier amputation [2]. Loss of light touch and temperature sensations usually appear early in the course of the disease, whereas loss of proprioceptive sense usually follows and manifests as gait ataxia with increased risks of falls and fractures. Motor nerves are typically involved next, causing distal weakness and atrophy with foot-drop and loss of hand strength. The differential diagnosis of distal, symmetric sensory, or sensorimotor neuropathy is broad, including over 100 potential etiologies; therefore, diabetic patients presenting with neuropathic symptoms must be carefully evaluated for other potential causes of nerve injury. In patients with diabetic neuropathy, new neuropathic symptoms are often erroneously attributed to diabetes rather than correctly diagnosed as common superimposed conditions, such as carpal tunnel syndrome and compressive cervical and lumbosacral radiculopathy. It is important to make the correct diagnosis because these conditions are often treatable.

Table 1. Diabetic neuropathic syndromes

Distal symmetric neuropathy
Large fiber sensory
Sensorimotor
Small fiber neuropathy
Painful neuropathy
Diabetic neuropathic cachexia
Mononeuropathy: ischemic
Cranial (III, VI, VII)
Radicular (thoracic, lumbosacral)
Peripheral (femoral)
Mononeuropathy: compressive
Carpal tunnel syndrome
Ulnar at the elbow
Peroneal at the fibular head
Regional neuropathic syndromes
Diabetic amyotrophy
Diabetic thoracoabdominal neuropathy
Autonomic neuropathy
Orthostatic hypotension
Cardiac dysrhythmia
Gastrointestinal dysfunction (diarrhea, constipation)
Impotence

Small fiber neuropathy

Distal leg and foot pain resulting from small nerve fiber injury can also be the presenting feature of diabetes. Although loss of pinprick and temperature sensation may occur, painful burning, electric, aching, and stabbing paresthesias are common and may be incapacitating. Fortunately, due to advances in the pharmacotherapy of neuropathic pain, these symptoms can be adequately controlled in most patients. After onset, painful neuropathy may improve spontaneously over months to years in some, but will become chronic in others. The subacute syndrome of diabetic neuropathic cachexia presents with rapid and dramatic weight loss and severe neuropathic pain, and often follows the institution of tight glucose control (*ie*, the initiation of insulin or aggressive increases in oral hypoglycemic therapy). Because paraneoplastic acute painful sensory neuropathy and severe weight loss can also be the initial manifestations of an occult malignancy, patients with these symptoms require extensive evaluations. In contrast to many of the paraneoplastic conditions, diabetic neuropathic cachexia has a good prognosis and most patients regain lost weight concurrent with resolution of their pain within several months after the onset of symptoms.

Mononeuropathy

Diabetic mononeuropathies are caused by both vasculopathy and increased susceptibility to compressive injury. Classically, vascular mononeuropathies occur when arterioles supplying the nerve (vaso nervorum) are occluded. These occlusions are often due to accelerated atherosclerosis, as well as thrombosis and inflammation. Neuronal ischemia is often heralded by an acute, deep aching pain, lasting minutes to hours, either in the vicinity of the nerve or in its dermatome, followed by acute numbness and weakness in the associated dermatomes and myotomes. Diabetic mononeuropathy can affect cranial nerves, nerve roots, or peripheral nerves. Third nerve palsy is the most common cranial diabetic neuropathy and presents with a pupil-sparing oculomotor palsy ("the diabetic third"). Ischemic mononeuropathy can also affect the nerve roots, causing acute symptoms, which, in the cervical and lumbosacral regions, may mimic compressive radiculopathies. Diabetes is a prominent cause of isolated thoracic radiculopathy, which may be confused with the prodrome of herpes zoster. In the arms and legs, peripheral mononeuropathies may occur; acute diabetic femoral mononeuropathy is a prototypic diabetic mononeuropathy.

Compressive mononeuropathies are common neurologic disorders in the general population and are even more prevalent in diabetic patients. Already injured by diabetes, peripheral nerves are prone to other forms of injury and, therefore, are highly susceptible to compressive damage. As mentioned previously, carpal tunnel syndrome has been documented in over 30% of diabetic patients [1]. Although common, carpal tunnel syndrome can cause severe, intractable pain and can result in debilitating hand weakness if allowed to progress; however, conservative therapy is usually quite effective when instituted at an early stage. Unfortunately, complaints of hand numbness, pain, and weakness in diabetic patients are often attributed to neuropathy when carpal tunnel syndrome is the underlying cause. Ulnar mononeuropathy at the elbow and peroneal mononeuropathy at the knee are also frequent in this population and often respond to conservative measures.

Regional neuropathic syndromes

Diabetes can also selectively damage a group of nerves in a specific region. The best known of these regional syndromes is diabetic amyotrophy. Diabetic amyotrophy is most common in patients with adult-onset diabetes and typically begins with subacute proximal leg aching followed by proximal leg weakness. Although it may start unilaterally, the amyotrophy usually evolves into a bilateral syndrome and may progress in a stepwise fashion over weeks to months and may be accompanied by significant weight loss. Leg weakness remains most severe in the femoral and obturator nerve distributions, with some involvement of the knee flexor compartment. Electrophysiologic studies reveal denervation in the proximal myotomes, often with lumbosacral nerve root involvement at multiple levels as well, but without evidence of mechanical compression by imaging studies. Weakness usually plateaus over weeks, then gradually improves within 12 to 36 months in most patients [3•]. The differential diagnosis is broad and includes upper lumbosacral polyradiculopathy due to spinal stenosis, chronic inflammatory demyelinating polyneuropathy, and inflammatory myopathy. Another regional syndrome is diabetic thoracoabdominal neuropathy, in which multiple thoracic nerve roots produce a syndrome of thoracic and abdominal pain, often accompanied by

Table 2. Possible etiologies of diabetic neuropathies

Polyol pathway activation
Excess sorbitol and fructose
Decreased myoinositol
Increased aldose reductase activity
Decreased NADPH
Decreased reduced glutathione
Decreased nitric oxide synthetase and nitric oxide
Advanced glycosylation end-products
Intra- and extraneural deposition
Hydrogen peroxide formation
Increased low-density lipoproteins
Vascular insufficiency
Accelerated atherosclerosis of the vaso nervorum
Decreased nitric oxide with impaired vasodilation
Decreased γ-linolenic acid with decreased vasodilation and platelet inhibition
Neurotrophic factors
Nerve growth factor deficiency
Insulin deficiency
Neuronal membrane ion channel dysfunction
Excessive voltage gated calcium channel activation
Sodium channel dysfunction

abdominal muscle weakness. The initial pain of this syndrome may mimic cardiac ischemia or malignancy. A variant may disproportionately involve the lumbosacral nerve roots subacutely, overlapping with diabetic amyotrophy.

Autonomic neuropathy

Autonomic neuropathy is also common, affecting nearly 50% of diabetic patients. Although autonomic symptoms may be mild, the potential for life-threatening cardiac dysfunction is significant. Cardiac disease due to silent cardiac ischemia and cardiac arrhythmia is one of the most common causes of death in diabetic patients, accounting for 25% of fatalities over a 10-year period in one study, and is also an independent risk factor for stroke not only due to advanced atherosclerosis, but also because of dysregulation of vascular tone and serum glucose and other factors [4]. Orthostatic hypotension is another common autonomic symptom in this group and can cause syncope with severe falls, fractures, and head injuries. Gastrointestinal dysfunction is another common problem, and dysmotility may provoke severe, intermittent diarrhea as well as troublesome constipation [5]. Genitourinary dysfunction, manifesting as impotence, was the most common autonomic symptom among men (40% affected) in the Rochester Diabetic Neuropathy Cohort [1].

Etiology and Pathogenesis

The metabolic consequences of chronic insulin deficiency and hyperglycemia in the peripheral nerve are highly complex, but great strides in our understanding of these phenomena have been achieved over the past decade. Vascular insufficiency is another major contributor and often works in tandem with metabolic insult to accelerate neuropathic injury in diabetes. Many of the most studied factors are detailed in Table 2.

The polyol pathway and oxidative injury

With chronic hyperglycemia, glucose readily diffuses into the cytosol [6]. Excess intracellular glucose is processed, in part, through the polyol pathway, producing sorbitol and fructose through a series of reactions catalyzed by aldose reductase [7]. The excess fructose and sorbitol decreases expression of the sodium/myoinositol co-transporter, which reduces cellular uptake of myoinositol. Decreased levels of intracellular myoinositol then lower levels of its metabolite phosphoinositide. Consequently, the phosphoinositide signaling pathway is impaired, which, in turn, interferes with activation of the transmembrane sodium pump and decreases nerve sodium/potassium ATPase activity [8]. As a result, nerve conduction is slowed, and with chronic exposure, membrane breakdown ensues.

In addition to producing sorbitol and fructose with potentially deleterious direct effects, activation of the polyol pathway requires aldose reductase. Activation of aldose reductase depletes its cofactor, NADPH, with further negative consequences for the nerve. Because NADPH is also a cofactor for nitric oxide synthetase (NOS) and for glutathione reductase, decreased levels of NADPH lead to lower levels of nitric oxide and reduced glutathione, a buffer against oxidative reactions. Lack of nitric oxide may inhibit vascular relaxation, which can cause neuronal ischemia, and decreases levels of reduced glutathione, which increases susceptibility to neuronal oxidative injury [8]. Signs of augmented oxidative injury have been well documented in diabetic neuropathy, and increases in reactive oxidative species have been demonstrated following both excessive activation of the polyol pathway and excessive glycation in diabetic patients [8]. The tight regulation of free transition metals is also compromised by diabetes, leading to the formation of reactive oxidative species by auto-oxidation and the Fenton reaction [10,11]. Aldose reductase inhibitors protect both neuronal structure and function in numerous rodent models, including both the diabetic BioBred/Worchester (BB/W) rat and in rats with streptozotocin (STZ)-induced diabetes [11,12]. Although there is considerable evidence supporting these hypotheses, some recent data suggest a more complex pathophysiology for neuronal injury during polyol pathway activation [6,13,14].

Nitric oxide deficiency

Nitric oxide is the product of NOS, which uses NADPH as a cofactor. In the blood vessel wall, nitric oxide activates guanylate cyclase, causing smooth muscle relaxation and vasodilation. As NADPH levels fall with excessive polyol pathway activity, nitric oxide levels also fall, limiting vascular dilation and potentiating neuronal ischemia. NOS may also be inhibited by the superoxide anion formation documented in diabetes. In animal models, nitric oxide deficiency is

potent enough to counteract the beneficial effects of vasoactive agents, aldose reductase inhibitors, antioxidants, and aminoguanidine on nerve function [11].

Advanced glycosylation end-products

Chronic intracellular hyperglycemia ultimately helps create the family of glycating agents known as advanced glycosylation end-products (AGEs), which deposit within and around the peripheral nerve. Although numerous intra- and extracellular neuronal proteins may be affected, glycation of neurofilaments or neurotubules has been well documented and may interfere with axonal transport and other functions [5]. A measure of excessive hemoglobin glycosylation (HbA_{1C}) also correlates with peripheral nerve dysfunction (*ie*, lowered motor nerve conduction velocities), as well as autonomic nervous system injury (*ie*, lowered Valsalva ratios) [15]. AGEs may also activate NADPH oxidase, contributing to hydrogen peroxide formation and further oxidative stress [16].

Vascular insufficiency

There is abundant evidence for neuronal ischemia and infarction in diabetes, both in humans and in animal models. Microelectrode polarography first demonstrated reduced sural nerve endoneurial oxygen tension, and reduced endoneurial blood flow (EBF) has been demonstrated in vivo in the diabetic sural nerve [11,17]. Diabetic neuropathy also correlates with loss of the peripheral nerve vasculature in animal models. Numerous pathologic changes appear in nerve biopsies taken from human and animal subjects with diabetes, including capillary basement membrane thickening, endothelial cell hyperplasia, and neuronal ischemia and infarction [11]. Abnormalities in endoneurial capillaries are more severe than in the epineurium, skin, and muscle, possibly due to intraneural neurovascular interactions [17,18]. In diabetic patients, peripheral vascular disease can also exacerbate neuropathy, an effect that may be partially reversed by surgical revascularization [19], whereas gene transfer of plasmid DNA encoding vascular endothelial growth factor may reverse the destruction of the vasa nevorum and restore peripheral nerve function in rats with STZ-induced diabetes [20]. Electrophysiologic assays, somewhat less sensitive for early neuronal ischemia, show failure of the normal increase in nerve conduction velocity with exercise, suggesting possible failure of increased EBF [21].

In diabetic patients, AGEs also increase low-density lipoprotein (LDL), which promotes the proliferation of blood vessel smooth muscle and atherosclerotic change, whereas decreasing levels of nitric oxide restrict compensatory vasodilatation. Acting together, these factors can decrease EBF to a critical threshold, resulting in neuronal ischemia and infarction. In rats with STZ-induced diabetes, EBF was decreased compared with control animals and improved with aldose reductase inhibition [8]; decreasing LDL with statin treatment increased nerve conduction velocity and blood flow in diabetic rats [22].

The metabolism of the omega (n)-6 essential fatty acids (which have an important role in circulation and thrombosis) is compromised in diabetes, possibly due to oxidative disruption. Oxidative injury may also contribute more directly to vascular injury, as peroxidation and hydroxyl radicals cause endothelial damage. Both human and animal studies have demonstrated defective conversion of the n-6 essential fatty acid linoleic acid to γ-linolenic acid, a precursor of arachidonic acid. Arachidonic acid is essential for the production of prostacyclin, a potent vasodilator and platelet inhibitor [23]. In rodent models, γ-linolenic acid in the form of primrose oil can prevent the reduction in nerve conduction velocity induced by diabetes [24], perhaps through restoration of normal prostacyclin levels within the vaso nervorum [11].

Growth factors and insulin deficiency

The neurotrophic factors comprise a group of endogenous proteins essential to the health and survival of certain populations of neurons. These growth factors have different biologic properties and are important for the maintenance of nerve structure and function, as well as repair following injury. Nerve growth factor (NGF), the first factor discovered, is trophic primarily for small sensory and sympathetic fibers. Low levels of both NGF and another neurotrophic factor, insulin-derived growth factor 1 (IGF-1), have been clearly correlated with the severity of nerve injury in patients and animals with diabetic neuropathy [25]. Under normal conditions, neurotrophic factors are rapidly produced in response to acute nerve damage, but after sciatic nerve crush in animal models of diabetic neuropathy (*ie*, BB/W rats), peak expression of both IGF-1 and NGF is delayed significantly. Inadequate timely expression of NGF may reduce macrophage recruitment and Schwann cell proliferation, impairing nerve regeneration in diabetic neuropathy [26]. Furthermore, insulin itself has neurotrophic properties, and its deficiency may also more directly limit recovery from nerve injury.

Neuronal membrane ion channel dysfunction

Diabetes may adversely affect the health of the neuronal membrane as well as the structure and function of its ion channels. Aberrant calcium channel activity plays a critical role in cellular injury and death in a wide variety of organ systems and is the subject of intensive investigation in a host of neurologic and other diseases. Increased voltage-dependent calcium activity, possibly due to impairment of the inhibitory G-protein calcium channel complex, has been demonstrated in diabetic nerve injury [27], and treatment of BB/W diabetic animals with aldose reductase inhibitors normalizes calcium influx and nerve conduction velocity despite persistent hyperglycemia [28]. The role of membrane ion channel dysfunction in diabetes is only now beginning to be explored in greater depth, but emerging evidence suggests a number of different channel types become dysfunctional in the course of the disease, perhaps accounting not only for nerve injury, but

also for active symptoms. Sodium channel dysfunction, in particular, appears to have an important role in the genesis of neuropathic pain in some patients, and changes in sodium channel subunit expression correlate with signs of neuropathic pain in animal models [29].

Diagnosis

Diabetic neuropathy remains a clinical diagnosis and a diagnosis of exclusion, as no single test can definitively prove that a neuropathy is due to diabetic injury. As with other neuromuscular diseases, the history and physical examination are paramount. Symptomatic patterns conforming to one of the known syndromes of diabetic neuropathy are a helpful start, and physical examination should demonstrate signs of dermatomal sensory loss or motor weakness consistent with the particular variety of diabetic neuropathy suspected from the history. It is critically important to be aware of overlapping patterns of nerve injury in this population, as the diabetic neuropathic syndromes are not exclusive and frequently occur in combination. Because hundreds of other potential mimics can be the sole or concurrent cause of neuropathic symptoms in a diabetic patient, at least one careful evaluation for other potential causes of neuropathy is warranted at the onset of symptom and should include, at a minimum, electrodiagnostic evaluation and a series of serum studies (including serum glucose, preferably fasting, and a measurement of glycosylated hemoglobin) [30]. If these standard glucose measures are normal or borderline, a 3-hour glucose tolerance test may be useful for the detection of early diabetes presenting with neuropathy. One recent study found abnormal glucose metabolism in 65% of patients with new painful sensory neuropathy, many of whom had impaired glucose tolerance as the sole diagnostic abnormality on serum testing [31•,32,33•].

Electromyography and nerve conduction studies not only provide valuable supportive information for the diagnosis of diabetic neuropathy while helping to exclude mimics, but are also extremely valuable for identifying superimposed focal neuropathic processes such as carpal tunnel syndrome and lumbosacral radiculopathy. These disorders are exceedingly common in the diabetic population and are often easily treatable [1]. Furthermore, other entities, such as cholesterol-lowering agent myopathy, may be more readily distinguished by electrodiagnosis than other methods. Distal symmetric diabetic neuropathy is primarily an axonal disorder, and decreased amplitudes on nerve conduction studies support more pronounced axonal than demyelinating injury in most early cases [34]. Slowing of nerve conduction velocity, a common marker of demyelination, often ensues; therefore, patients often have both axonal and demyelinative features by the time of their presentation. Electrophysiologic abnormalities and clinical manifestations often worsen over time, whereas in those diabetic neuropathic syndromes demonstrating spontaneous clinical improvement, electrophysiologic parameters usually also improve [35].

Routine electrodiagnostic testing assays only the large myelinated sensory and motor nerves, so evaluation of suspected small fiber dysfunction requires special techniques, such as quantitative sensory testing. A more recent method, currently available in only a few specialized centers, is the quantitation of small fiber density in the epidermis of skin biopsies taken from the proximal and distal legs. This technique appears to be highly sensitive to early small fiber neuropathy and may also have a role in clinical trials [36]. As autonomic nervous system function is mediated largely through small nerve fibers, autonomic nervous system injury may sometimes accompany nociceptive small nerve fiber injury. Consequently, mild abnormalities may be present on autonomic nervous system testing, even in the absence of frank autonomic symptoms. Many autonomic batteries are available, and may include assessment of RR interval, Valsalva maneuver, tilt-table testing, sympathetic skin response, thermoregulatory sweat test, silastic sweat imprint testing, and quantitative sudomotor axon reflex test [37].

Therapy

Glycemic control

Despite decades of experimental trials, tight glycemic control remains the best method for preventing and treating the diabetic neuropathies. Dramatic reductions in the incidence of neuropathy have been documented in numerous trials, with one prospective study demonstrating a 69% decrease of the neuropathy in a primary prevention cohort [15,35]. Unfortunately, intensive control is less likely to reverse established injury, particularly in distal symmetric diabetic neuropathy. However, it may slow or stop progression of nerve injury. The possibility of longer-term benefits cannot be discounted, though little data are available to address this issue.

Aldose reductase inhibitors

Because of the many deleterious consequences of excessive activation of aldose reductase during activation of the polyol pathway, inhibition of aldose reductase is an attractive strategy for pharmacologic intervention. Unfortunately, over 20 therapeutic trials of different aldose reductase inhibitors have been performed over the past 20 years, with largely negative results. A meta-analysis of trials performed through 1996 revealed only one very modest benefit: improvement of nerve conduction velocity by 1 m/s after 6 to 13 months of therapy [38]. However, a more recent double-blind, placebo-controlled phase II study of yet another aldose reductase inhibitor, fidarestat, demonstrated improvement in all assayed subjective symptoms and in five of eight electrophysiologic measures, with no improvement in the placebo group [39•]. Phase III trials of this compound are in progress.

Neurotrophic growth factors

Neurotrophic growth factors have also been tested in diabetic neuropathy. Unfortunately, NGF1 not only promotes neuronal growth, but also the activity of substance P, an impor-

tant mediator of cutaneous algesia. As NGF1 is an injectable compound, it is not surprising that dosage strength in phase I studies was limited by injection site hyperalgesia. After a successful phase II study, a large, multicenter phase III analysis randomized over 1000 patients to either recombinant human NGF or placebo for 2 years. Unfortunately, all of the primary endpoints failed to improve in this study. Post-study analysis suggested several potential factors that might have contributed to these negative results, including failure of symptomatic progression in the placebo group, subtherapeutic dosing (limited due to injection site hyperalgesia), and the enrollment of an older patient population with advanced neuropathy [40]. Regardless of the reasons for failure, however, the negative findings of this major and costly study have strongly discouraged further investigation of the neurotrophic factors in the treatment of diabetic neuropathy for the present.

γ-Linolenic acid

γ-Linolenic acid demonstrated clinical and electrophysiologic benefit in a multicenter trial after 1 year of treatment [41]. Despite these results, no further trials have been performed and γ-linolenic acid has not found its way into clinical practice [42••].

α-Lipoic acid

α-Lipoic acid (thioctic acid) is a naturally occurring free radical scavenger and transition metal chelator that has been approved for use in diabetic neuropathy in Germany since the 1960s [43]. Treatment with this potent antioxidant prevents the development of neuronal and neurovascular injury in models of diabetic neuropathy as measured by nerve conduction velocity, nerve blood flow measures, and glutathione levels [44]. Several randomized, controlled trials demonstrated symptomatic benefit in Europe, with possible reduction in objective neuropathic deficits and improvements in cardiac autonomic neuropathy [42••]. The Neurological Assessment of Thioctic Acid in Neuropathy (NATHAN and NATHAN II) trials have been designed to rigorously evaluate the efficacy and safety of this compound over several years, and the results of these studies should be forthcoming shortly.

Immunotherapy

There is some evidence that diabetic lumbosacral radiculoplexopathy includes an inflammatory component, although it is unclear whether this inflammation has a primary role (*eg*, vascular occlusion due to microvascultis) or is an epiphenomenon and is the consequence of the normal immunologic response to neuronal injury due to other factors. Based upon the former possibility, steroids and high-dose intravenous immunoglobulin were used in a few small studies. Although the possibility of more rapid recovery following these interventions has been reported, the variable natural history of this condition and the small numbers of patients in these trials render interpretation of the findings difficult [3•].

Conclusions

Many drugs have been tested for the treatment of diabetic neuropathy over the past 20 years. Nevertheless, meta-analysis of the randomized, controlled treatment trials in diabetic neuropathy from 1981 to 1992 found most did not have sufficient statistical power to detect a clinically meaningful difference [45]. Years of effort and considerable funding have been expended to define clinical valid and reproducible endpoints for diabetic neuropathy trials with good success. Furthermore, sample sizes and treatment durations required to demonstrate a clinically meaningful effect with these measures have been clearly calculated [46]. Future studies should be carefully designed with these parameters in mind to avoid costly and repetitive trials lacking the power to answer the salient therapeutic questions. The more recent NATHAN and NATHAN II trials of α-lipoic acid are better designed and should provide models for future treatment trials in diabetic neuropathy. In the meantime, the paramount importance of aggressive glucose control should be emphasized to all diabetic patients and their primary care providers, not only to prevent neuropathy, but also to avoid other serious end-organ complications. Patients who fail to respond to hypoglycemics quickly should be referred to an experienced diabetologist for optimal management.

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