Neuropathies of Medical Diseases
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AANEM 57th Annual Meeting
Québec City, Québec, Canada

AANEM

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American Association of Neuromuscular & Electrodiagnostic Medicine
2621 Superior Drive NW
Rochester, MN  55901

Printed by Johnson Printing Company, Inc.
Neuropathies of Medical Diseases

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Course Description
Many of the common systemic medical disorders, and some of the medications used for those disorders, may cause neuropathy and are discussed in this book. This work focuses on diabetic neuropathies, vasculitic neuropathies and those associated with connective tissue diseases, neuropathies associated with renal failure, gastrointestinal disease and nutritional deficiencies and medication-related neuropathies. The physician will learn up-to-date information on these topics, as well as the current approaches to the diagnosis and management of this important group of neuropathies.

Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:
(1) recognize up-to-date information on the various neuropathies associated with those medical diseases that most commonly produce neuropathy.
(2) incorporate the current approaches to the diagnosis and management of this important group of neuropathies.

Activity Profile
This enduring material activity is a reproduction of the printed materials from a course at the AANEM Annual Meeting (October 6-9, 2010). Physician participation in this activity consists of reading the manuscript(s) in the book and completing the clinical and CME questions.

Release Date: January 10, 2011
Expiration Date: January 10, 2014. Your request to receive AMA PRA Category 1 Credits™ must be submitted on or before the credit expiration date.
Duration/Completion Time: 2 hours

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Dr. Bril is a consultant and speaker for Talecris. She also received research support from Esai Pharmaceuticals and Johnson & Johnson. Any conflict of interest was resolved according to ACCME Standards.

Dr. Donofrio is a consultant for Bristol Myers Squibb. Any conflict of interest was resolved according to ACCME Standards.

All other authors/faculty have nothing to disclose.

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The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
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INTRODUCTION

Peripheral neuropathies can be divided into mononeuropathies, mononeuritis multiplex, and diffuse polyneuropathy. Many etiologies exist for polyneuropathies including diabetes, vitamin deficiencies, uremia, connective tissue disorders, inheritance, and many other causes. Polyneuropathy as an adverse effect from medications is rare, but as the number of medications used to treat medical disorders increases, one must keep in mind the potential link between the patient's neuropathy and his or her medications. Also to be considered is the superimposition of a medication-induced neuropathy in someone with a preexisting neuropathy such as the use of chemotherapeutic agents in patients with an underlying inherited or diabetic neuropathy. Jain et al has estimated the incidence of polyneuropathy from medications or toxins to be 2-4%.37 This discussion will focus on commonly prescribed medications, immunosuppressant agents, and chemotherapeutic drugs that can lead to polyneuropathies as an undesired adverse effect.

MEDICATION-INDUCED NEUROPATHIES

The presentation of patients with drug-related or induced polyneuropathy often does not differ from that of most chronic length-dependent neuropathies except for a few exceptions. The peripheral nervous system reacts to toxins in a limited manner. Spencer and Schaumburg hypothesized that most toxins including medications produce damage in one of four regions of the peripheral nerve: 1) the distal sensory and motor axon (axonopathy), 2) the Schwann cell (demyelinating neuropathy), 3) the dorsal root ganglion (ganglionopathy or neuronopathy), and 4) the anterior horn cell or motor neuron.78 In keeping with this classification, most medication-induced neuropathies can be categorized into one of four groups depending upon the region of the peripheral nervous system where the primary pathologic process occurs (see Table 1). As is true of most classifications, not all drugs fit perfectly into a category and some drugs can cause pathology in more than one category as well as in the central nervous system. Table 1 groups medication-induced neuropathies by the major confirmed or presumed anatomic site of pathology. Several drugs are listed in more than one grouping since the medication can cause an axonopathy or a demyelinating neuropathy. Not all of the medications listed in the Table 1 will be discussed here.

Amiodarone

The most common neurological adverse effects of amiodarone are tremor, optic neuropathy, and peripheral neuropathy.26,54 The polyneuropathy typically begins between 5 and 12 months after amiodarone is first prescribed and is estimated to occur in 6% of patients who are treated for several months or more.12 Unlike most toxic neuropathies, amiodarone gives rise to more than one type of pathological process in the peripheral nerve. The neuropathy may be primarily axon loss, demyelinating, or a combination as reflected in the nerve conduction studies (NCSs).35,86 Nerve biopsy shows severe loss of large and small myelinated fibers as well as unmyelinated fibers.54 Not uncommonly, amiodarone can cause a polyneuropathy that appears strikingly similar to chronic inflammatory demyelinating polyneuropathy (CIDP) in its clinical evolution and the electrodiagnostic (EDX) findings of a multifocal demyelinating polyneuropathy. Sometimes patients may
be treated for CIDP with several immunosuppressant medications before the diagnosis of amiodarone-induced neuropathy is considered. Although a trial period off of amiodarone should be considered to distinguish between the two disorders, often the diagnosis can be made by correlating the onset of the polyneuropathy to the introduction of amiodarone.

### Amitriptyline

Amitriptyline is a tricyclic antidepressant that has become a well-accepted treatment for neuropathic pain. Ironically, amitriptyline has been associated with the development of a peripheral neuropathy in several case reports. Zampollo described a man who developed lower limb paresthesias, distal hypesthesia, and reduced ankle reflexes after taking 150 mg of amitriptyline uninterrupted for 2 years. Motor and sensory amplitudes were reduced, latencies were normal or prolonged, and conduction velocities were slowed, consistent with diffuse axon loss. When amitriptyline was discontinued, symptoms, signs, and the electrophysiologic abnormalities normalized within 3 years. Meadows and colleagues reported a woman who developed an amitriptyline-induced neuropathy and whose symptoms remitted when treated with pyridoxine 500 mg/day. The authors hypothesized that amitriptyline produces a polyneuropathy in the same way as isoniazid, by depleting the availability of pyridoxal phosphate.

### Colchicine

Riggs and colleagues first described a relationship between colchicine and a neuropathy and myopathy in 1986. Their patient had taken large doses of colchicine for 5 years. The neurological examination was consistent with a severe sensory and motor neuropathy and a mild proximal myopathy. The muscle biopsy showed an increase in variability of myofiber size, rounded and atrophic myofibers, muscle fibers containing small vacuoles and subsarcolemmic deposits, and uneven staining of central muscle fibers. After discontinuing colchicine the patient recovered except for persistent gait ataxia and distal hand weakness. In a larger study of 12 patients with colchicine myopathy and neuropathy, Kuncl and colleagues found similar abnormalities on clinical examination. Sural nerve biopsy in one patient identified mild loss of large myelinated axons, degenerating axons, and regenerating axon clusters. Biopsies of proximal muscles showed a distinctive vacuolar myopathy, in which the vacuoles were distributed either centrally or in the region of the subsarcolemma. After discontinuation of colchicine, the patients’ neurologic function returned to normal within 4 weeks except for symptoms and signs of a mild neuropathy. The authors related the colchicine neuropathy and myopathy to renal dysfunction, as the adverse effect only occurred in patients with elevated serum creatinine and who were taking therapeutic doses of colchicine.

### Dapsone

Dapsone is commonly used to treat distinct dermatologic disorders such as dermatitis herpetiformis, pyoderma gangrenosum, acne conglobata, alopecia mucinosa, and leprosy. Several patients have been described who have developed a motor greater than sensory, distal greater than proximal polyneuropathy after taking dapsone. The neuropathy has been found in patients taking dosages ranging from 100 to 600 mg/day for several weeks to 16
years. An atypical feature of the neuropathy is greater involvement of the hands than in the feet. NCSs typically show normal to low normal conduction velocities, normal to prolonged distal latencies, and reduced compound muscle action potential (CMAP) amplitudes. The authors propose that dapsone has its primary effect on the motor soma and axons of the motor neuron.

Marked improvement has occurred in all patients after discontinuation of dapsone. Similar to isoniazid, dapsone is metabolized by acetylation. Slow acetylation of the drug and accumulation of toxic blood and tissue levels has been implicated as the initiating step in the development of the neuropathy.

Disulfiram

Disulfiram has been used since the 1940s as an agent to help the detoxification of chronic alcoholics. Mokri and colleagues reported four patients with a disulfiram-induced motor and sensory symmetric polyneuropathy, varying from mild to severe. Initial symptoms of the neuropathy developed several weeks to 4 months after beginning the disulfiram. NCSs showed absent sensory nerve action potentials (SNAPs), reduced amplitude of CMAPs, and slightly diminished nerve conduction velocities. In one patient, repeat NCSs 1 year later showed partial recovery of the SNAP in the median nerve and normalization of the conduction velocity in the motor fibers of the median and ulnar nerves. The investigators reported a decrease of both large and small myelinated fibers and axon degeneration in the sural nerve biopsy. Rare fulminant cases of disulfiram-induced neuropathy have been reported.

Ethambutol

Ethambutol is a medication used with other anti-mycobacterial agents to treat tuberculosis. Optic neuritis is a well-known adverse effect of ethambutol therapy. Tugwell and James described three patients who developed a polyneuropathy 5-9 months after initiation of ethambutol therapy. The timing of the onset of the polyneuropathy was similar to the interval delay for optic neuritis. All patients had features consistent with a sensory greater than motor neuropathy. NCSs showed reduced SNAP amplitudes and slightly prolonged sensory distal latencies. Motor amplitudes were normal and motor conduction velocities were either normal or slightly reduced. All three patients improved when the ethambutol was discontinued. An unpublished series of over 1000 patients taking ethambutol reported 15 patients who complained of numbness in the extremities at some time while taking the medication.

Gold

In 1950, Doyle and Cannon reported the first extensive description of polyneuritis as an adverse reaction to gold therapy. They described a man who developed features of a severe motor and sensory polyneuropathy after receiving a cumulative dose of 900 mg of Myochrysine (450 mg of gold). At the peak of the neuropathy, the patient could not feed himself and complained of paresthesias from the feet to the rib cage. Physical examination revealed findings consistent with a severe motor and sensory polyneuropathy as well as marked incoordination, dysmetria, writhing movements of the hands (athetosis), and gait ataxia. The patient improved rapidly once the gold injections were discontinued. Walsh was the first to describe nerve conduction data in gold neuropathy. He reported his results in a woman who developed a polyneuropathy after receiving a total of 85 mg of gold. The findings were in keeping with a sensory greater than motor axon loss neuropathy. A sural nerve biopsy showed loss of large and small diameter myelinated fibers. Teased fiber preparations demonstrated that most fibers were undergoing active axon degeneration and only rare fibers showed segmental demyelination. Katrak and colleagues reported electrophysiologic and nerve biopsy results in three patients with gold-induced peripheral neuropathy. In one patient, NCSs were normal, whereas, in the other two patients, abnormalities were recorded in almost all nerves tested. Many of the conduction rates (prolonged latencies and slowed conduction velocities) were sufficiently severe to suggest a demyelinating process. Nerve biopsy in two patients showed findings confirming axon degeneration. In all three patients, improvement occurred when the gold therapy was discontinued.

Hydralazine

Hydralazine is a chelating agent and a carbonyl reagent that has been shown to form complexes with sulfhydryl groups. It inhibits enzymes involved in pyridoxine metabolism and it is this capability to inhibit pyridoxine that accounts for the development of peripheral neuropathy in patients who take hydralazine. Although infrequently used for the treatment of hypertension, hydralazine was a mainstay of therapy several decades ago. Kirkendall and Page in 1962 reported two patients who developed symptoms and signs of a polyneuropathy after taking hydralazine for 3-8 months. In one patient, the neuropathy appeared to be primarily sensory. In the other, the neurologic deficits were a left foot drop and pronounced sensory symptoms and signs distally in the legs. In both patients, stopping the hydralazine and adding pyridoxine lead to improvement in symptoms and strength within 2-4 weeks. Raskin and Fishman reported two additional patients with hydralazine-induced polyneuropathy, one who developed symptoms after 7 days and the other after 10 years.

Isoniazid

Isoniazid is a hydrazide of isonicotinic acid. Its major route of metabolism is through acetylation to acetyl isoniazid. Isoniazid has been one of the mainstays of tuberculosis treatment for five decades. Isoniazid is another medication that causes peripheral neuropathy through its effect on pyridoxine metabolism. Studies have shown that a large bimodal variation exists among humans in the metabolism of isoniazid. Patients can be categorized into rapid or slow inactivators of isoniazid and this bimodality is genetically determined.
and colleagues identified a polyneuropathy in six of 17 subjects taking isoniazid, four of whom were slow inactivators of isoniazid. Although the number of patients was small, they proposed the hypothesis that slow inactivators are more predisposed than rapid inactivators to develop polyneuropathy after treatment with isoniazid. Other investigators have shown that metabolism of isoniazid is inherited as an autosomal recessive trait. Slow acetylators are unable to metabolize isoniazid quickly which leads to high blood levels and a greater propensity to develop a toxic neuropathy.

In 1959, Money reported 84 patients with pulmonary tuberculosis who were receiving anti-tuberculous therapy with isoniazid and para-aminosalicylic acid. Polyneuropathy was the most common of the neurological adverse effects. In almost all cases, the neuropathy did not develop until 6 months after the onset of isoniazid therapy. Sensory symptoms and signs were more common than weakness and the lower extremities were more affected than the upper. Most patients improved when prescribed vitamin B supplementation despite the maintenance of isoniazid therapy. Ochoa described the neuropathological findings in nine patients with isoniazid neuropathy. Several months after clearing of the intoxication, improvement was noted in six of the nine patients.

**Lithium**

It is well-known that lithium in toxic doses can cause tremor, but it can also lead to a severe polyneuropathy. Vanhooren and colleagues reported two patients who developed an acute motor and sensory polyneuropathy as a result of lithium intoxication. Both patients initially presented with central nervous system manifestations including coma, hypertonia, conjugate eye deviation, Babinski signs, hemiparesis, and extrapyramidal signs. When consciousness was regained, one patient was found to have proximal weakness and the other flaccid paralysis in the legs and areflexia. Motor NCSs showed reduced CMAP amplitudes and either normal or diminished conduction velocities. In one patient, the sural response was absent. Several months after clearing of the intoxication, improvement was documented in sensory and motor amplitudes. Sural nerve biopsy in one patient identified a moderate loss of myelinated fibers, mild endoneural fibrosis, and scattered vacuolated macrophages in which myelin debris was observed. Both patients improved from lithium intoxication, but incompletely.

**Metronidazole**

Metronidazole is a 5-nitroimidazole antimicrobial used for the treatment of protozoan infections (trichomoniasis, giardiasis, and amoebiasis), as a bactericidal agent in anaerobic infections, and for Crohn's disease. Several authors have reported a sensory neuropathy or neuronopathy in patients receiving metronidazole for the treatment of Crohn's disease. Patients typically complain of paresthesias in the feet and hands. Sensory examination shows a distal gradient loss to small fiber more than large fiber perception in the setting of preserved strength. NCSs show absent to reduced SNAP amplitudes and normal motor conduction studies. Sural nerve biopsy in the patient reported by Bradley and colleagues identified a loss of many myelinated fibers and axonal degeneration in all of the remaining sensory fiber sizes. When metronidazole was discontinued in the three patients reported by Coxon, the sensory neuropathy improved completely in one, partially in another, and remained static in the third.9

**Misonidazole**

Misonidazole is a 2-nitromidazole used as a red blood sensitizer prior to radiation therapy. It is chemically similar to metronidazole. Approximately one-third of patients given misonidazole will develop a neuropathy. Melgaard and colleagues reported eight patients who developed a severe subacute sensory polyneuropathy after treatment with misonidazole for 3-5 weeks. The total dose of misonidazole varied between 17 and 22 gm. All patients except one complained of severe pain and paresthesias in the feet and hands. Strength was rarely affected and deep tendon reflexes were preserved. On sensory testing, touch, pain sensation, vibration, and joint position sense were affected more in the feet than in the hands. Three to 5 months after discontinuation of the misonidazole, four patients were improved, three had died from the underlying carcinoma, and one patient was unchanged. NCSs were consistent with a severe primarily sensory neuropathy.

**Nitrofurantoin**

Nitrofurantoin is a synthetic bacteriostatic antimicrobial. In years past, it was used to treat a wide range of gram positive and gram negative organisms, and currently it is frequently prescribed for urinary tract infections. Several authors described a toxic neuropathy temporally related to the use of nitrofurantoin in 1956. The neuropathy can present as early as 1-2 weeks after initiation of nitrofurantoin therapy. The major manifestations are distal paresthesias, loss of sensory perception in the hands and feet, mild-to-moderate distal weakness, and areflexia. The neuropathy may resolve over time or it may be irreversible. Ellis reported six patients who developed an acute form of nitrofurantoin-induced polyneuropathy. Three of the patients died from complications of the polyneuropathy; the relationship to nitrofurantoin was not recognized and nitrofurantoin was continued until death. The other three patients made partial recoveries. All six patients had renal insufficiency, an observation also noted by Loughridge and other authors. This relationship led to the recommendation that nitrofurantoin be used with caution in patients with renal insufficiency. Craven described five patients who developed a polyneuropathy after receiving treatment with nitrofurantoin. All of the five patients had normal blood urea nitrogen (BUN) levels when the drug was first prescribed, yet all were determined to have mild renal insufficiency at the time the neuropathy developed clinically. Paul and colleagues demonstrated in vitro that nitrofurantoin reversibly inhibits the formation of citrate at the stage of generation of acetyl coenzyme A from pyruvate and coenzyme A. Inhibition should be greater when the blood level
of nitrofurantoin is higher, a condition that exists in renal insufficiency.

Toole and Parrish reviewed the world literature on nitrofurantoin neuropathy in 1973. They noted that most patients experienced the onset of neuropathic symptoms within the first 6 weeks of treatment. The daily dosage prescribed ranged from 100 to 800 mg. Available followup information revealed that nitrofurantoin was stopped, approximately one-third experienced complete resolution of symptoms and signs, one-half had residual disease, and one-sixth remained unchanged.

Nerve conduction findings in nitrofurantoin-induced polyneuropathy are scant. Nerve biopsy showed atrophy of the peripheral nerves.

**Nitrous Oxide**

In 1978, Layzer and colleagues reported three patients, two dentists and a hospital technician, who presented with symptoms of numbness and the sensation of an electric shock passing from the toes to the neck after flexion of the neck. All three patients had a common history of excessive recreational use of nitrous oxide. In the same year, the same author described 15 additional patients with the same condition. He characterized the clinical presentation as a myeloneuropathy because of the combination of peripheral and central nervous system findings. All of his patients were dentists except for one, and all had abused nitrous oxide recreationally, except for two who were exposed to the inhalant professionally. In each case, the patient improved after cessation of the nitrous oxide. Five of the 15 patients continued to have moderate disability 6 weeks to 3 years after discontinuation of nitrous oxide. Because of its similarity to subacute combined degeneration, Layzer speculated that nitrous oxide might interfere with vitamin B12 metabolism. This hypothesis was furthered when Amess and colleagues showed in patients undergoing cardiac bypass surgery that nitrous oxide inhalation produced an identical deoxyuridine suppression test result to that found in patients with vitamin B12 deficiency. Since all of their patients had normal vitamin B12 concentrations, the data suggested that nitrous oxide interferes with vitamin B12 function. In this disorder, NCSs showed normal results in motor nerves and mild slowing of conduction velocities in sensory nerves. Sural nerve biopsy showed a normal number of nerve fibers, varying degrees of myelin ovoid formation, and rare fibers showing focal areas of axon swelling and denuded myelin. Unlike typical subacute combined degeneration, patients with nitrous oxide poisoning do not have a megaloblastic anemia. Magnetic resonance imaging (MRI) scanning of the cervical and thoracic spine may show increase signal in the posterior column, a finding that may be misinterpreted as multiple sclerosis.

The profound effect of nitrous oxide on B12 metabolism raises the awareness to carefully follow patients with pernicious anemia and neuropathy postoperatively when nitrous oxide is used in general anesthesia or, conversely, to encourage anesthesiologists to avoid nitrous oxide in patients with B12 deficiency neuropathy. It also creates concern for the use of nitrous oxide in patients with borderline B12 levels and patients with undiagnosed pernicious anemia or other causes of B12 deficiency. The risk of exposure of nitrous oxide to patients with neuropathy may be far greater than our present appreciation of the problem. Nitrous oxide should be considered in health care professionals who present with a clinical presentation suggestive of subacute combined degeneration and in patients who admit to recreational sniffing of whipped cream dispensers (whippets).

**Phenytoin**

Phenytoin has been commonly prescribed for epilepsy since its introduction in 1938. Lovelace and Horwitz identified 26 of 50 patients taking phenytoin who showed a peripheral neuropathy by clinical examination and electrophysiological study and in whom no other etiology could be found for neuropathy. All patients had absent deep tendon reflexes in the lower extremities. Conduction velocities in the lower extremities ranged from 30 to 40 m/s in most affected patients, and the sensory and motor amplitudes were often low in amplitude, long in duration, and complex. The authors determined that the neuropathy was more likely to occur in patients who had taken phenytoin for more than 10 years. There was no correlation between the dosage of phenytoin and the development of a polyneuropathy.

Shorvon and Reynolds followed 51 patients prospectively for 5 years with epilepsy who were prescribed either phenytoin or carbamazepine monotherapy. None of the patients receiving carbamazepine developed either clinical or electrophysiologic features suggestive of a diffuse polyneuropathy. In the phenytoin group, none who were taking therapeutic doses developed clinical evidence of a neuropathy. In the group of patients taking phenytoin who developed polyneuropathy, review of the medical records uncovered recurrent toxic drug levels and low folic acid levels.

**Pyridoxine**

Pyridoxine is an essential vitamin that has been consumed in large doses by individuals to aid in bodybuilding and has been prescribed as a treatment for premenstrual syndrome, carpal tunnel syndrome, schizophrenia, fibromyalgia, autism, and hyperkinesis. The minimum daily requirement of pyridoxine is 0.6 to 1.3 mg/d. Schaumburg and colleagues reported two patients who began to experience ascending numbness 3 and 11 months after consuming large doses of pyridoxine (2 and 3 g) daily. Neurological examination demonstrated normal strength, loss of ankle reflexes, and a distal gradient loss of vibration, pin prick, temperature, and touch sense. Neither patient improved when the pyridoxine was discontinued and after 1 year of followup. In their patients, motor NCs were normal. Schaumburg and colleagues reported a larger cohort of patients who developed a severe sensory neuropathy after taking from 2 to 6 g of pyridoxine daily for 2 to 40 months. All patients showed profound loss of most sensory modalities and were areflexic. All patients improved when pyridoxine was stopped, and two patients experienced almost complete recovery after 2-3 years of followup. The authors
concluded that vitamin B6 in high doses was probably toxic to the dorsal root ganglia. In 1980, Krinke and associates showed that large doses of pyridoxine produced a sensory neuronopathy in dogs; spinal cord pathology showed widespread neuronal degeneration in the dorsal root ganglia, the sensory nerve fibers in the peripheral nerves, dorsal columns of the spinal cord, and the descending spinal tract of the trigeminal nerves.

Although pyridoxine sensory neuronopathy is most commonly observed in individuals taking large doses of the vitamin, toxicity can be observed in patients taking much smaller doses. Of the 16 patients reported by Parry and Bredesen, three had been taking less than 1 gm/day, and one had taken only 100-200 mg for 3 years. Neuropathy has been reported as developing in patients taking doses as low as 24 mg/day.

**Statins**

The statins are inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that regulates the synthesis of cholesterol. In 1994, Jacobs reported the development of a sensory polyneuropathy in a patient who was treated with lovastatin for 2 years. The patient’s symptoms abated when lovastatin was discontinued, but returned within 2 weeks when pravastatin was substituted for lovastatin. The following year, Ahmad reported two patients who had lovastatin-induced neuropathy.

NCS results were published in four patients with a polyneuropathy caused by simvastatin. CMAP amplitudes were reduced in three of four patients, and all patients had absent or reduced SNAP amplitudes. Motor and sensory conduction velocities were either normal or slightly slowed. The authors proposed that the simvastatin might produce toxicity through an adverse reaction on mitochondrial function. Inhibitors of HMG-CoA reductase, in addition to blocking cholesterol synthesis, also interfere with synthesis of dolichol and ubiquinone. A deficiency of ubiquinone, a key enzyme in the mitochondrial respiratory chain, might interfere with the energy utilization of the neuron and in turn produce a reversible polyneuropathy.

Jeppesen and colleagues reported similar electrophysiologic results to those of Phan in seven patients who developed a polyneuropathy after taking one of the following statin medications: lovastatin, fluvastatin, pravastatin, or simvastatin. Four of their patients had an irreversible neuropathy, a finding that the authors attributed to a longer exposure to the statins (4-7 years compared to 1-2 years).

The polyneuropathy associated with statins is most often sensory or sensorimotor in type. There have been at least two case reports of patients who developed a mononeuritis multiplex after exposure to a statin medication and whose neuropathy improved after withdrawal of the drug and worsened with reintroduction. A patient developed a polyneuropathy resembling Guillain-Barré syndrome (GBS) after use of simvastatin. The neuropathy began 6 months after the medication was prescribed. NCSs showed primarily axon loss features in sensory and motor fibers in the lower limbs. The spinal fluid protein level was 1.18 g/l (normal 0.20-0.45). The patient was treated with intravenous immunoglobulin (IVIg) over 5 days and recovered well over the course of the subsequent year. The authors hypothesized an acute hypersensitivity reaction to the statin lead to the development of a polyneuropathy resembling GBS.

Substitution of one statin that causes a polyneuropathy for another may not prevent the reoccurrence of a drug-induced neuropathy. Ziajka and Wehmeier reported a patient who developed a neuropathy after taking lovastatin and whose symptoms returned when treated with simvastatin, pravastatin, and atorvastatin.

The presence of renal failure and diabetes appears to increase the incidence of neuropathy in patients who take statins.

Some physicians have challenged the relationship between statins and the development of polyneuropathy. Others recognize the relationship to be low risk and acknowledge that long-term exposure increases the chances for the neuropathy. One paper estimated the incidence of statin-induced neuropathy to be approximately 1 case per 10,000 patients taking statins; another manuscript estimated 60 cases per 100,000. The Netherlands Pharmacovigilance Center in 2006 reported 17 patients who developed neuropathy associated with the use of statins and worsening of a pre-existing polyneuropathy in two other patients. The polyneuropathies were associated with the prescription of simvastatin, atorvastatin, pravastatin, and rosvastatin. The time to onset of the polyneuropathy after taking the statin ranged from 1 day to 6 years. Eight of the patients did not note the onset of their neuropathy symptoms for 2 years or more. Approximately half of the patients experienced partial to complete recovery when the drug was stopped. The report concluded that long-term exposure to statins increases the risk for polyneuropathy and this will take on greater importance as more patients worldwide are prescribed statins. Another study from Denmark reported a four to 14 fold increased risk for developing an idiopathic polyneuropathy in patients taking a statin medication compared to nonusers.

**Thalidomide**

Thalidomide was initially manufactured as a sedative and hypnotic. In 1961 it was withdrawn from use because of teratogenesis and propensity to cause phocomelia in neonates. Thalidomide is now undergoing resurgence as an effective treatment for several dermatological conditions and has a role in the treatment of multiple myeloma, human immunodeficiency virus (HIV) infection, and rheumatologic disorders.

Thalidomide was first described as causing a sensory and motor polyneuropathy in the early 1960s. The neuropathy is often associated with erythema of the hands and brittle fingernails. The incidence of neuropathy varies greatly from one report to another with some authors reporting a neuropathy in up to 100% of patients exposed to thalidomide. The occurrence of neuropathy is
probably related to the cumulative dose of thalidomide and a total
dose of 20 g is considered threatening. 10

Women and the elderly are most prone to developing the neu-
ropathy and it appears to be more common in patients who are
slow drug acetylators. Most patients complain of paresthesias,
hypesthesias, and leg cramps, greater distally than proximally
and more in the legs than in the upper extremities. 62 Coasting
(further progression of the neuropathy after the medication is
stopped) is commonly observed for a month when thalidomide is
discontinued. Small fiber modalities are often more affected than
large fiber. Nerve conduction results are consistent with a sensory
polyneuropathy. 47

Complete recovery is the rule in approximately 25% of patients,
whereas 30% improve partially and 45% do not recover. 62

**Antiretroviral Medications**

Antiretroviral medications are categorized as nucleoside reverse
transcriptase inhibitors (NRTIs), non-nucleoside reverse tran-
scriptase inhibitors, protease inhibitors, fusion inhibitors,
chemokine co-receptor antagonists, and integrase inhibitors.
Peripheral neuropathy is associated with the use of the following
NRTIs: didanosine (ddl), zalcitabine (ddC), and stavudine (d4T),
fialuridine (FIAU), and lamivudine (3TC). 68, 77 All three agents
cause a polyneuropathy that is sensory greater than motor. The
neuropathy typically presents 6 to 8 weeks after starting treatment
and manifests as burning, paresthesia, and pain in the calves. 68
Signs on neurologic examination are commonly loss of small
and large fiber sensory functions and absent ankle reflexes. 77 The
neuropathies are clinically indistinguishable from those of HIV-
associated distal sensory neuropathy, yet the acute or subacute
onset and rapid progression paralleling the use of the NRTIs give
a strong clue to the cause of the neuropathy as a toxic reaction to
the NRTIs. The toxic neuropathies are dose dependent and, in
the case of ddC, coasting may occur. In one study of ddC, all pa-
tients who received high dose (0.12-0.24 mg/kg/day) developed
a distal sensory polyneuropathy. 5 Because of the common toxic-
ity of neuropathy after treatment with the NRTIs, lower doses are
often used to initiate therapy. Even low doses of ddL, ddC,
and d4T may cause a neuropathy in patients with pre-existing
subclinical neuropathy, inherited neuropathies, older patients,
and those with poor nutrition. Usually clinical improvement is
observed 1 month after the discontinuation of the NRTI.

The incidence of neuropathy may increase substantially if the
NRTIs are used in a therapeutic regimen with hydroxyurea, a
drug which itself is neurotoxic. 59 The mechanism of neurotoxicity
from the NRTIs is unknown, but may relate to its inhibition of
mitochondrial DNA gamma polymerase.

---

**PERIPHERAL NEUROPATHIES ASSOCIATED WITH
CHEMOTHERAPEUTIC AGENTS**

Several of the commonly prescribed chemotherapeutic agents can
cause polyneuropathy and they are listed in Table 2. They include:
the vinca alkaloids, the platinum agents, the taxanes, suramin, cy-
tosine arabinoside (Ara-C), etoposide, and ifosfamide.

**Table 2 Peripheral neuropathy chemotherapeutic agents**

<table>
<thead>
<tr>
<th>Vinca alkaloids</th>
<th>Vincristine</th>
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<tbody>
<tr>
<td></td>
<td>Vinblastine</td>
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<td></td>
<td>Vindesine</td>
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<td></td>
<td>Vinorebine</td>
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<tr>
<td>Platinin agents</td>
<td>Cisplatin</td>
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<tr>
<td></td>
<td>Carboplatin</td>
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<td></td>
<td>Oxaliplatin</td>
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<tr>
<td>Taxanes</td>
<td>Paclitaxel</td>
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<td></td>
<td>Docetaxel</td>
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<td></td>
<td>Suramin</td>
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<tr>
<td></td>
<td>Cytosine arabinoside (Ara-C)</td>
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<tr>
<td></td>
<td>Etoposide (VP-16)</td>
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<tr>
<td></td>
<td>Efosfamide</td>
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<td></td>
<td>Bortezomib</td>
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</table>

**Vinca Alkaloids**

The term vinca alkaloid is derived from the extraction of the
agent from the periwinkle plant. The vinca alkaloids consist of
vincristine, vinblastine, vindesine, and vinorelbine. In a rank
order of toxicity, vincristine is the most toxic and the develop-
ment of neuropathy is widely recognized by oncologists and neu-
rologists. 15 Some authors estimate that it occurs to some extent
in most patients who receive the drug. 68 Vincristine causes a
dose-dependent sensory greater than motor and autonomic poly-
neuropathy. The neuropathy typically presents with paresthesia of
the feet and hands and loss of ankle reflexes. Distal weakness may
be present on examination but is clinically significant much less
often. Unlike other chemotherapeutic agents, vincristine gives rise
to an autonomic neuropathy which may manifest as abdominal
pain, constipation, and sometimes an ileus. 15 Fortunately, the
neuropathy induced by vincristine is usually reversible once the
chemotherapy is stopped and complete recovery occurs in about
80% of patients, but the recovery may not be attained for 2 years.33 Coasting may occur for several weeks to months after vincristine is discontinued. NCSs confirm the findings expected in an axon loss sensory greater than motor neuropathy. Vincristine must be avoided in patients with pre-existing inherited neuropathies as the resulting cumulative neuropathy can be devastating and relatively permanent.

Vinorelbine is less toxic than vincristine, causing a distal sensory neuropathy in 20-30% of patients treated.15 The neuropathy is severe in few patients.

**Platinum Agents**

The platinum chemotherapeutic agents consist of cisplatin, carboplatin, and oxaliplatin and each share structural and toxicity properties. Cisplatin was the first agent developed and is used to treat ovarian, testicular, lung, bladder, head and neck, and germ cell tumors. It primarily causes a polyneuropathy by toxicity at the site of the dorsal root ganglion and thus causes a gangliononeuropathy which affects the large more than small sensory fibers. This pathology predicts the deficits found on examinations such as ataxia, loss of vibration and joint position sense more than pain and cold perception, areflexia, as well as a Lhermitte's sign.11 Pain and weakness are not common. The neuronopathy commonly is manifested when the total dose exceeds 300 mg/m² and occurs in almost all patients when the total dose is greater than 600 mg/m². Symptoms of the neuronopathy may not be noticed until 8 weeks after treatment is stopped.57 Coasting may be experienced for up to 6 months. NCSs show markedly reduced or absent SNAPs and preserved motor nerve conduction function.

Carboplatin has similar antitumor activity to cisplatin. It is more myelosuppressive than cisplatin and much less neuropathic as a neuropathy is observed in only 6% of patients exposed to the chemotherapeutic agent and is usually mild.9 Oxaliplatin is structurally similar to cisplatin and is used to treat metastatic colorectal cancer.

**Taxanes**

The taxanes consist of paclitaxel and docetaxel, the latter a semisynthetic analogue of paclitaxel. They are used primarily to treat solid tumors, particularly breast and ovarian cancers. The major toxicity of paclitaxel is myelosuppression, but it becomes neurotoxic when used with granulocyte colony stimulating factor. The risk of neuropathy increases when high infusion rates are used and when incorporated with other neurotoxic agents such as cisplatin. The polyneuropathy of paclitaxel is primarily sensory in nature.15 Its severity depends on the cumulative dose and dose intensity per cycle.15 A large number of patients develop a polyneuropathy when doses of 135 to 200 mg/m² every 3 weeks are prescribed.84 The neuropathy typically will develop after the third to seventh cycle, but can arise within days of the first infusion. Neuropathy invariably develops when doses larger than 250 mg/m² are used in single doses.84 As would be expected in a sensory polyneuropathy, the initial symptoms are numbness, paresthesia, and pain in the feet and ankles. In severe cases, the hands become numb and ataxia may arise. Severe neuropathy often develops when the cumulative dose exceeds 1500 mg/m² and in patients with preexisting diabetes, alcoholic neuropathy, and inherited neuropathies.15 When paclitaxel is stopped, the neuropathy may progress for up to 4 weeks. The neuropathy resolves in mild cases, but up to 40% of patients are left with permanent sensory symptoms in the toes and feet and some may have weakness below the knees and ataxia. Electrophysiologic testing shows findings that are consistent with a sensory greater than motor axon loss polyneuropathy. The mechanism of toxicity is probably interference with axonal transport due to the accumulation of disassembled microtubules in the dorsal root ganglion, axons, and Schwann cells.68 Some evidence exists that alpha-lipoic acid diminishes the symptoms of paclitaxel-induced neuropathy.30

Because of its semisynthetic relationship to paclitaxel, docetaxel-induced neuropathy shares many of the clinical characteristics of paclitaxel. Fortunately, when used in typical dosing, a clinically significant neuropathy is less common than after receiving paclitaxel.15 Slightly less than 50% of patients who receive docetaxel will develop a neuropathy. Severe neuropathy is not common, but it tends to occur when cumulative doses of greater than 600 mg/m² are prescribed.17 Similar to paclitaxel, it presents with numbness in the feet and hands after the third to fifth treatment. When docetaxel is stopped, coasting may take place for several months. Fortunately, most patients improve or are left with mild residual sensory symptoms. Approximately 5% of patients exposed to docetaxel will develop a proximal myopathy superimposed on the distal neuropathy.

**Suramin**

Suramin is a hexasulfonated naphthylurea used to treat prostate cancer, adrenocortical, ovarian, and renal cell carcinoma, malignant thymomas, and non-Hodgkins lymphoma. Suramin toxicity causes two types of neuropathy: 1) a length-dependent, sensory greater than motor axon loss neuropathy, and 2) a subacute motor greater than sensory demyelinating neuropathy resembling CIDP or a prolonged case of GBS.13 Suramin has an unusually long half life of 40 to 50 days which contributes to its neurotoxicity. The incidence of neuropathy ranges from 25 to 90% and neurotoxicity appears to be dependent on the peak suramin blood level rather than the cumulative dose.15 The length-dependent sensory greater than motor neuropathy is the more common neuropathy observed after treatment with suramin and is slowly reversible in most patients, once chemotherapy is stopped. The motor demyelinating polyneuropathy is observed in about 10% of patients and may not occur until 1-5 months after suramin is first used as a treatment. Like CIDP and GBS, patients can become bedridden from the polyneuropathy and may require ventilatory support. The cerebrospinal fluid (CSF) protein is elevated, furthering the resemblance to CIDP and GBS. Most patients improve over 3-6 months. Plasma exchange can be useful to enhance recovery time.
Cytosine Arabinoside

Acute cerebellar dysfunction is one of the most recognized toxicities of high dose Ara-C. Toxicity to Ara-C has been described as causing several types of peripheral nervous system toxicities including a pure sensory polyneuropathy, an acute motor and sensory neuropathy similar to GBS, and bilateral brachial plexopathy.\(^{15}\) Fortunately, toxicity to Ara-C is rare. The neuropathy may begin within hours to 3 weeks after the Ara-C treatment is initiated.

Etoposide

Etoposide (VP-16) is a semisynthetic derivative of podophyllotoxin and is used to treat a wide variety of neoplasms that include lymphoma, leukemia, testicular, and small cell carcinoma of the lung. The polyneuropathy that develops after treatment with etoposide is primarily sensory and is most likely related to the effect of the drug on the dorsal root ganglion.\(^{25}\) The polyneuropathy from etoposide develops in up to 10% of patients receiving the drug; it tends to resolve completely once therapy is discontinued.

Efosfamide

Efosfamide is used to treat lymphomas, testicular and cervical carcinomas, sarcomas, and lung cancers. A neuropathy occurs in about 4% of patients who receive the chemotherapy and is typically sensory in manifestation.\(^{15}\) Symptoms begin within 10 days to 2 weeks after the drug is prescribed and the symptoms resolve within 2 weeks of stopping the drug.\(^{64}\)

Bortezomib

Bortezomib is a chemotherapeutic agent used primarily to treat multiple myeloma that is refractory to other agents. It is a member of the proteasome inhibitors. It causes a length dependent painful primarily sensory polyneuropathy in 37 to 47% of patients who receive the drug.\(^{20,40}\)

**NEUROPATHIES FROM IMMUNOSUPPRESSANT AGENTS**

Tacrolimus

Tacrolimus is an immunosuppressant that interferes with T-cell function and is primarily prescribed to prevent rejection after solid organ transplantation. Central nervous system toxicity in the form of headaches, encephalopathy, behavioral changes, seizures, and headache are more common than the rare neuropathies. The best classified neuropathy after tacrolimus therapy is a chronic demyelinating polyneuropathy that resembles CIDP or a more asymmetric form that begins about 2-10 weeks after initiation of therapy with the agent.\(^{15}\) Similarities to CIDP include areflexia, greater involvement of large than small fibers, and an elevated spinal fluid protein. The nerve conduction abnormalities also resemble CIDP as patients have slowed conduction velocities, prolonged distal latencies, reduced CMAPs, and temporal dispersion of proximal CMAP amplitudes. Patients have improved after receiving IVIg and plasma exchange suggesting that the pathogenesis of this neuropathy is autoimmune and inflammatory.

Another presentation of a tacrolimus-induced polyneuropathy is an acute predominantly motor axon loss neuropathy that begins 1-2 weeks after the drug is prescribed, suggestive of GBS.\(^{15}\) The polyneuropathy can be devastating, producing facial weakness and quadripareisis. Most patients improve once tacrolimus is stopped.

A similar drug-induced polyneuropathy has been described in patients receiving cyclosporin, beginning 1-8 weeks after treatment is started.\(^{15}\)

Leflunomide

Leflunomide is a new immunosuppressant agent used to treat rheumatoid arthritis. Leflunomide is an isoxazole derivative and is structurally unrelated to other immunomodulatory drugs. It is a known inhibitor of the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), a key enzyme in the synthesis pathway of the pyrimidine ribonucleotide uridine monophosphate (rUMP) synthesis. It causes a painful sensory greater than motor axon loss polyneuropathy usually arising 3-6 months after therapy is begun. In a series of 113 patients treated with leflunomide in a rheumatology clinic in France, Martin and colleagues reported the development of a neuropathy in 10% of patients.\(^{52}\) The patients who developed neuropathy were older than those who did not have a neuropathy (69 versus 54 years), were more often diabetic, and more commonly undergoing treated with potentially neurotoxic drugs.

**Tumor Necrosis Factor-α Antagonists**

Tumor necrosis factor-α (TNF-α) antagonists are used to treat patients with refractory autoimmune disorders including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn’s disease, and ulcerative colitis. The agents work at several levels of inflammation and immunogenesis to block or reduce damage at the vascular endothelium, blood nerve barrier, and to prevent access of immunoglobulins, cytokines, complement, macrophages, nitrogen oxide metabolites, and proteases to the sites of pathology.\(^{39}\) Three TNF-α antagonists are presently marketed: infliximab, etanercept, and adalimumab.\(^{39}\)

Several presentations of peripheral neuropathy have been reported as adverse effects in patients receiving TNF-α antagonists.\(^{28}\) Those vary in manifestation from GBS to CIDP, Fisher syndrome, multifocal motor neuropathy, mononeuropathy simplex or multiplex, and an axonal sensory or sensorimotor polyneuropathy.\(^{39}\) The timing and dosing of TNF-α antagonists has varied greatly in each patient for each condition. In some patients, the neuropathy developed within 8 hours of the first dose and in others after 2 years. Many
patients improve once the TNF-α is stopped and treatment with corticosteroids, IVig, or plasma exchange may not be necessary. The pathogenesis of TNF-α antagonist-induced neuropathy has been hypothesized as resulting from enhanced T-cell proliferation and cytokine production when the TNF-α antagonist modifies the antigen-presenting cell function, T-cell receptor signaling, and decreasing apoptosis of auto-reactive T cells. 39

SUMMARY

Many medications have been implicated in causing polyneuropathy and the list grows each year. Medications can induce neuropathy by acting on the peripheral axon, the anterior horn cell, the dorsal root ganglion, or the Schwann cell. In addition to commonly prescribed medications, neuropathy can represent toxicity from chemotherapeutic agents, antiretroviral therapy of HIV, and most recently from prescription of the immunosuppressants and TNF-α antagonists. Recognition of this type of neuropathy will require a good knowledge of the neurologic literature, a high clinical suspicion, and review of the patient’s present and prior therapy when no other cause for neuropathy is evident.

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Diabetic Neuropathy

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DEFINITION

Diabetic neuropathy can be defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes. The neuropathies in diabetes are grouped as focal or generalized as shown in Table 1. Diabetic sensorimotor polyneuropathy (DSP) is the most common of the neuropathies and is the focus of this discussion.

THE PROBLEM

DSP is the most common complication of diabetes with an exceptionally high incidence and is observed in up to 50% of people with type 2 diabetes when evaluated using objective tests such as nerve conduction studies (NCSs). Currently in the developed world, 1 in 20 people have diabetes and as the prevalence of diabetes is increasing with the aging population and unhealthy lifestyles, both in the developing and developed worlds, the burden in health care costs is huge. The economic costs of diabetes in 2007 in the United States were estimated to be $174 billion, with $116 billion in excess medical expenditures and $58 billion in reduced national productivity. One in five of every healthcare dollars in the United States is spent caring for someone with diabetes and 50% of the total cost is due to hospitalizations. Up to 70% of all leg amputations happen to people with diabetes. As many as 26% of patients with diabetes have painful diabetic neuropathy. As many as 13% of patients have never reported their symptoms to their physician, and 39% have never received treatment whether symptoms are reported, or not. In addition to neuropathy in diabetes, it is known that patients with prediabetes or impaired glucose tolerance have increased rates of neuropathy and these patients have a 2-3 fold

Table 1: Classification of diabetic neuropathy

<table>
<thead>
<tr>
<th>Asymmetrical neuropathies</th>
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<tbody>
<tr>
<td>Upper limb mononeuropathies</td>
</tr>
<tr>
<td>Median neuropathy</td>
</tr>
<tr>
<td>Ulnar neuropathy</td>
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<tr>
<td>Brachial plexus neuropathy</td>
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<tr>
<td>Cranial nerve neuropathies</td>
</tr>
<tr>
<td>Lower limb mononeuropathies</td>
</tr>
<tr>
<td>Diabetic lumbosacral plexoradiculopolyneuropathy</td>
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<tr>
<td>Truncal radiculopathy</td>
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<table>
<thead>
<tr>
<th>Symmetrical neuropathies</th>
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<tbody>
<tr>
<td>Diabetic sensorimotor polyneuropathy</td>
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<tr>
<td>Small-fiber diabetic painful neuropathy with weight loss</td>
</tr>
<tr>
<td>Diabetic pandysautonomia</td>
</tr>
<tr>
<td>Hypoglycemic polyneuropathy</td>
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</tbody>
</table>
increase in neuropathic pain compared to reference subjects. Therefore, DSP is a gigantic global problem and there is no treatment to reverse the disorder.

MAKING THE DIAGNOSIS

The gold standard of diagnosis is a combination of symptoms, signs, and abnormal NCSs. This combination provides the most reliable diagnosis and selection of patients for research studies and should be employed consistently (See Table 2). At a recent consensus meeting on diabetic neuropathy held in Toronto, October 2009, there was agreement with the definition above; i.e. that a confirmed diagnosis of DSP requires symptoms, signs, and abnormal NCSs. A probable diagnosis would encompass patients with symptoms and signs, but no confirmatory NCSs, and a possible diagnosis would be either symptoms or signs alone, without nerve conduction testing. Confirmation of the diagnosis requires NCSs. Subclinical DSP would be those with abnormal NCSs, but no symptoms or signs. Quantitative sensory threshold (QST) testing is not as reliable as NCSs and cannot be depended upon to confirm the presence of DSP. Testing of large fiber sensation (e.g., vibration perception thresholds) is generally more reliable than testing small fiber sensation (e.g., thermal perception thresholds), but even testing large fibers with different devices and test paradigms does not improve the reliability of QST.

Table 2 Diagnosis of diabetic sensorimotor polyneuropathy

<table>
<thead>
<tr>
<th>Neuro-pathic symptoms*</th>
<th>Decreased or absent ankle reflexes**</th>
<th>Decreased distal sensation</th>
<th>Distal muscle weakness or atrophy</th>
<th>Nerve conduction studies</th>
<th>Ordinal likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Abnormal</td>
<td>++++</td>
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<tr>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Abnormal</td>
<td>++++</td>
<td></td>
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<tr>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
<td>Abnormal</td>
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<td></td>
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<tr>
<td>Present‡</td>
<td>Absent</td>
<td>Absent‡</td>
<td>Normal‡</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Present§</td>
<td>Present§</td>
<td>Present§</td>
<td>Normal§</td>
<td>–</td>
<td></td>
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</tbody>
</table>

*Neuropathic symptoms include numbness, altered sensation, or pain in the feet. For clinical research studies enrollment should be limited to cases above the bold horizontal line (i.e., ++++).

**Ankle reflexes may be decreased in normal individuals older than 65 to 70 years.

†This phenotype is common in “small-fiber” sensory polyneuropathy. Determination of intraepithelial nerve fiber density in skin biopsy may be useful to confirm the diagnosis.

§This phenotype in the presence of normal nerve conduction studies (NCSs) is not a distal symmetric polyneuropathy. It is included here to emphasize the importance of including NCSs as part of the case definition for clinical research studies.

DSP begins with a long, subclinical period whose identification and management is challenging (See Fig. 1). Early identification is important as this most likely provides the best opportunity for effective intervention, but simple screening tests for DSP, such as the monofilament examination, are not being performed routinely despite published guidelines. Recently, attention has been focused on the early detection of DSP by measurement of small fibers based on the assumption that diabetes damages the small fibers first. Detection of small fiber neuropathy is challenging. Objective tests such as sympathetic skin responses (SSRs) and cooling detection thresholds (CDTs) are unreliable. Repeatability of SSRs and CDTs are high, and correlations with small fiber symptoms and/or signs are low. The current gold standard is intra-epidermal nerve fiber density (IENFD) measurement obtained by skin punch biopsy (See Fig. 2). A recent report of the American Academy of Neurology (AAN) concluded that IENFD using protein gene product 9.5 (PGP 9.5) immunohistochemistry is a validated, reproducible marker of small fiber sensory pathology and possibly useful to identify DSP (Class III). Because this is an invasive method and not widely available, it is unlikely to be used for diagnosis of small fiber neuropathy in general practice. Other methods to assess small fibers are being investigated for reliability in DSP, namely corneal confocal microscopy and laser Doppler flare imaging techniques.

Corneal confocal microscopy (CCM) measures small nerve fibers in Bowman’s layer of the cornea. These are small Aδ and C fibers arising from the trigeminal nerve (V1) and sharing features with distal small nerve fibers. CCM is a valid way to detect the presence and measure severity of DSP. Corneal confocal microscopy and laser Doppler flare imaging techniques. Other methods to assess small fibers are being investigated for reliability in DSP, namely corneal confocal microscopy and laser Doppler flare imaging techniques. Autonomic neuropathy is also a small fiber neuropathy, but will not be discussed further.

Corneal confocal microscopy (CCM) measures small nerve fibers in Bowman’s layer of the cornea. These are small Aδ and C fibers arising from the trigeminal nerve (V1) and sharing features with distal small nerve fibers. CCM is a valid way to detect the presence and measure severity of DSP. CCM also has shown early nerve regeneration following pancreatic transplant. This promising methodology requires more investigation to be sure that it is.
a valid method to assess and monitor DSP, but this examination could become part of the annual screening tests for patients with diabetes in the future.

The other novel method is laser Doppler imaging (LDI) flare in response to heat stimuli, a flare response due to the axon reflex (See Table 3). Compared to the effects of an eutectic mixture of local anesthetics (EMLA) on the heat-evoked flare and the acetylcholine-evoked flare demonstrate that the LDI flare is due to the axon reflex (See Fig. 3). In a preliminary study of 62 patients, LDI flare was more sensitive than quantitative thermal thresholds to show small fiber abnormality (See Table 3). However, all small fiber test methods were complimentary and none was highly sensitive for small fiber disease including IENFD.

### EXCLUDING OTHER CAUSES OF NEUROPATHY

For axonal polyneuropathy, a recent AAN publication suggested that the most helpful diagnostic tests for distal symmetric polyneuropathy are the blood glucose, serum B12, and serum immuno electrophoresis (SIEP). Therefore, in patients with diabetes, serum B12 and SIEP tests should be performed. In addition, an A1C test to assess recent glycemic control is also advisable. Other etiologies to consider are uremia, ethanol abuse, familial neuropathy, toxic neuropathy, and paraneoplasia. One of the most important differential diagnosis is chronic inflammatory demyelinating neuropathy, particularly the variants such as the...
pure sensory variant. Finally, genetic neuropathies should be considered if the phenotype is typical for this form of peripheral nerve disease.

**TREATMENT**

**Disease Modification**

**Glycemic Control**

The only specific disease-modifying treatment for DSP is strict glycemic control maintained indefinitely. Improved metabolic control includes attention to blood pressure, lipids, smoking history, and BMI. The benefits of intensive control for DSP are better defined in Type 1 than in Type 2 diabetes patients. Still, intensive control is the only treatment that may stabilize DSP in Type 1 or Type 2 patients. Even kidney–pancreas transplant stabilizes disease without any significant reversal years after surgery. Optimal levels of A1C are under debate given the results of the ACCORD study and the American Diabetes Association has published a statement concerning target A1C levels in different diabetes patients, generally < 7%. It seems clear that intensive control lowers the risk of neuropathy.

**Reversal of Diabetic Sensorimotor Polyneuropathy**

Other disease-modifying treatments have so far failed to reverse or stabilize DSP or have had unacceptable side effect profiles (See Table 4). These include aldose reductase inhibitors, protein...

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**Table 4** Disease modifying treatment for diabetic sensorimotor polyneuropathy

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Compound</th>
<th>Aim of treatment</th>
<th>Status of randomized clinical trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyol pathway ↑</td>
<td>Aldose reductase inhibitors</td>
<td>Nerve sorbitol ↓</td>
<td>Withdrawn (adverse events)</td>
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<tr>
<td>Sorbitol</td>
<td></td>
<td></td>
<td>Withdrawn (adverse events)</td>
</tr>
<tr>
<td>Tolrestat</td>
<td></td>
<td></td>
<td>Ineffective</td>
</tr>
<tr>
<td>Ponalrestat</td>
<td></td>
<td></td>
<td>Withdrawn (marginal effects)</td>
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<tr>
<td>Zopolrestat</td>
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<td>Withdrawn (adverse events)</td>
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<tr>
<td>Zenarestat</td>
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<td>Withdrawn (adverse events)</td>
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<tr>
<td>Lidorestat</td>
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<td>Effective in phase II trials</td>
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<td>Fiderastat</td>
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<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td>Epalrestat</td>
<td></td>
<td></td>
<td>Marked in Japan</td>
</tr>
<tr>
<td>myo-Inositol ↑</td>
<td>myo-Inositol</td>
<td>Nerve myo-inositol ↑</td>
<td>Equivocal</td>
</tr>
<tr>
<td>γ-Linolenic acid synthesis ↓</td>
<td>γ-Linolenic acid</td>
<td>Essential fatty acids metabolism↑</td>
<td>Withdrawn (effective: deficits)</td>
</tr>
<tr>
<td>Oxidative stress ↑</td>
<td>α-Lipoic acid</td>
<td>Oxygen free radicals ↓</td>
<td>Effective in randomized clinical trials</td>
</tr>
<tr>
<td></td>
<td>Vitamin E</td>
<td>Oxygen free radicals ↓</td>
<td>(studies ongoing)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effective in one randomized clinical trial</td>
</tr>
<tr>
<td>Nerve hypoxia ↑</td>
<td>Vasodilators</td>
<td>Nerve blood flow ↑</td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitors</td>
<td></td>
<td>Effective in phase II trial</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin analogs</td>
<td></td>
<td>Phase III trial ongoing</td>
</tr>
<tr>
<td></td>
<td>PhVEGF165 gene transfer</td>
<td>Angiogenesis ↑</td>
<td>Phase III trial ongoing</td>
</tr>
<tr>
<td>Protein kinase C ↑</td>
<td>Protein kinase C Β inhibitor</td>
<td>Nerve blood flow ↑</td>
<td>Effective in phase II trials</td>
</tr>
<tr>
<td>(ruboxistaurin)</td>
<td></td>
<td></td>
<td>Ineffective</td>
</tr>
<tr>
<td>C-peptide ↓</td>
<td>C-peptide</td>
<td>Nerve blood flow ↑</td>
<td>Effective in phase II trials</td>
</tr>
<tr>
<td>Neurotrophism ↓</td>
<td>Nerve growth factor (NGF)</td>
<td>Nerve regeneration, growth ↑</td>
<td>Ineffective</td>
</tr>
<tr>
<td></td>
<td>BDNF</td>
<td>Nerve regeneration, growth ↑</td>
<td>Ineffective</td>
</tr>
<tr>
<td>Long-chain fatty acid</td>
<td>Acetyl-L-carnitine</td>
<td>Long-chain fatty acid accumulation ↓</td>
<td>Ineffective</td>
</tr>
<tr>
<td>metabolism ↓</td>
<td></td>
<td></td>
<td>Ineffective</td>
</tr>
<tr>
<td>Nonenzymatic glycation ↑</td>
<td>Aminoguanidine</td>
<td>Advanced glycation end product accumulation ↓</td>
<td>Withdrawn</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme, BDNF= brain-derived neurotrophic factor
kinase C (PKC) inhibitors, nerve growth factors, acetyl-l-carnitine, antioxidants, vitamins, and others. Some novel treatments are still under investigation and there remains optimism that a disease-modifying agent will be proven effective in the future. There is an ongoing multicenter study of ranirestat based on phase 2 and 2/3 studies showing changes in electrophysiology. It has been difficult to show efficacy for various reasons: lack of efficacy of the intervention, good glucose control, good diabetes care (lipids, blood pressure, etc), better than usual treatment during the trial, advanced neuropathy, insensitive endpoints, and insufficient power and duration of the studies. In fact, there is a lack of effective treatment for all types of axonal polyneuropathies. Any novel treatment that enhances neural regeneration and function would be a huge step forward in the field of neuromuscular disorders.

### Symptom Control

Control of painful symptoms in patients with DSP can be attempted in a number of ways. An evidence-based practice parameter on the treatment of painful diabetic neuropathy (PDN) is being written by the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM), the AAN, and the American Academy of Physical Medicine and Rehabilitation (AAPMR) and will be published soon. There are various guidelines on treatment of neuropathic pain and PDN, and a sample treatment guideline is shown in Table 5. Figure 4 outlines the current drug treatments and Table 6 shows a proposed treatment algorithm for PDN. Nonpharmacological interventions such as electrical stimulation, acupuncture, exercise therapy, biofeedback, spinal stimulation, magnets, and laser treatments are used by many patients even though the evidence for efficacy is not always clear.

The successful management of patients with PDN combines the science and art of medicine without a “cookbook” approach that would provide a single recipe for all patients. In fact, patients with neuropathic pain are often refractory to commonly used interventions or suffer such adverse reactions that the treatment must be withdrawn. Other elements that contribute to neuropathic pain, such as comorbid depression, are often not addressed and yet will affect the outcome of treatment. Finally, as treatment of neuropathic pain can be difficult, physicians are urged to avoid the “ostrich” approach of ignoring this debilitating problem in the hope that it will disappear. Quality of life (QOL) studies have shown that patients with neuropathic pain suffer chronically and significantly, and it is the physician’s role to try to alleviate this distress and improve the patient’s ability to function and their overall QOL. Most patients with neuropathic pain do not obtain complete relief of pain with any medication and it is important to advise patients concerning realistic expectations on the outcome of their therapy. Responders are generally considered to be those patients who experience a 30-50% reduction in pain (not complete analgesia). Many of the drugs discussed here have modest effect sizes for pain relief as reported in various studies, and only 50-70% of study patients respond to treatment as shown by Figure 5 showing the numbers needed to treat for different classes of drugs. In the clinic, with less precision in patient selection,

### Table 5 Oral Medications for the Management of Neuropathic Pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial Dose</th>
<th>Titration</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclic Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10 mg QHS</td>
<td>Increase weekly by 10 mg/day to max of 150 mg/day</td>
<td>Dry mouth, Blurry vision, Constipation, Urinary retention, Dizziness, Drowsiness, Weight gain</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>300 mg TID</td>
<td>Increase weekly by 300 mg/day to maximum of 3600 mg/day</td>
<td>Dizziness, Somnolence, Ataxia, Fatigue, Peripheral Edema, Weight Gain</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>75 mg BID</td>
<td>Increase weekly by 150 mg/day to maximum of 300 mg BID</td>
<td>Dizziness, Somnolence, Weight gain, Peripheral Edema</td>
</tr>
<tr>
<td><strong>Opioid Analgesics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>10 mg BID</td>
<td>Increase every 3 days by 10 mg to maximum of 60 mg BID</td>
<td>Constipation, Nausea, Somnolence</td>
</tr>
</tbody>
</table>

Adapted from evidence-based guidelines for the treatment of diabetic neuropathy. Evidence-based guidelines list drugs that have received regulatory approval at the time of publication. Duloxetine was approved later and now would be recommended for use.

### Figure 4 Outline of pharmacological treatment of neuropathic pain.

ACD = anticonvulsant drug, ADD = antidepressant drug
the response rate is less and the withdrawal from treatment due to adverse effects is greater so the effectiveness of any treatment is less than expected from the results of published studies. Finally, few comparison studies have been performed to compare efficacy of different treatments.

**CONCLUSION**

DSP is common, underdiagnosed, and undertreated. Physicians need to be aware of the need to screen for DSP and to intervene early in the disease process to try to avoid progression to severe morbidity. Disease modification remains an unmet clinical need.


Vasculitic Neuropathies and Neuropathies Associated With Connective Tissue Diseases

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VASCULITIC NEUROPATHIES

The various forms of vasculitis make up a heterogeneous group of disorders that can affect different organ systems and different blood vessel calibers. Many forms of vasculitis share the common feature of frequently affecting the peripheral nervous system. The purpose of this review is to bring the electrodiagnostic (EDX) physician up-to-date on the causes of and treatment approaches for the most common forms of vasculitic neuropathy.5

CLASSIFICATION OF VASCULITIC NEUROPATHIES

The classification of the vasculitides has become increasingly sophisticated over the past half-century.38 For the EDX physician, it is helpful to conceptualize the classification in terms of 1) clinical characteristics (e.g., systemic or nonsystemic, chronic or acute, monophasic) and 2) histopathologic features (nerve large arteriole vasculitis or nerve microvasculitis).5,59 This construct has limitations because any binary classification scheme of vasculitis necessitates dividing what is likely actually a continuum. Concerning classification based on vessel size, the marked overlap in vessel size involvement amongst the various vasculitides must also be considered. Nonetheless, we believe classification based on clinical and histopathologic features has merit because it allows for a characterization of an individual’s vasculitic neuropathy that provides information about prognosis and provides a blueprint for treatment and other management.

From a clinical standpoint, vasculitis of nerve needs to at least be thought of as being systemic or nonsystemic.3,5 The systemic vasculitides are commonly divided into primary systemic vasculitis, in which there is no known cause, and secondary systemic vasculitis, in which a virus, drug, or connective tissue disease is responsible for vessel wall inflammation.53 Vasculitides are further classified by the kind and size of blood vessels involved, organ involvement, disease associations, underlying mechanisms, and sometimes autoantibody profiles.65 The primary systemic vasculitides most likely to cause vasculitic neuropathy include polyarteritis nodosa, Wegener’s granulomatosis, Churg-Strauss syndrome, and microscopic polyangiitis (MPA).38,53,74 Of these, MPA is perhaps the one that most commonly causes vasculitic neuropathy.74 Secondary causes of systemic vasculitis involving peripheral nerves include connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, and Sjögren’s syndrome.57,62,72 Mixed, type II cryoglobulinemic vasculitis associated with hepatitis C infection is another secondary form of vasculitis. Other viruses associated with vasculitis are human immunodeficiency virus (HIV) and cytomegalovirus (CMV). Sarcoïdosis affecting nerve may also cause an angiitis.8 Vasculitis that appears confined to the nerve and muscle has classically been termed nonsystemic vasculitic neuropathy (NSVN).8,9,11,15,70

An important distinction between systemic vasculitic neuropathy (SVN) and NSVN is that NSVN is usually not fatal, whereas untreated SVN is often fatal.15 Early on it may be difficult to dis-
tistinguish NSVN from SVN; approximately 10% of cases of what initially appears to be NSVN ultimately become SVN.8,63 Thus, the evaluation in the early phase for what appears to be NSVN should be no different than that for SVN. Some investigators suggest, however, that NSVN is simply part of a continuum in the spectrum of SVN. In favor of this view is the demonstration of clinicopathologic and pathologic similarities between NSVN and MPA. On the other hand, NSVN and MPA differ in age of onset, severity, and presence of protoplasmic-staining antineutrophil cytoplasmic antibodies (p-ANCA) (which is absent in NSVN).70

From the vantage point of peripheral nerve histopathology, vasculitis of nerve is organized into two groups: nerve large arteriole vasculitis and nerve microvasculitis.5,16 The separation is based on differences in the size of vessels involved, associated diseases, and course and treatment considerations. It must again be acknowledged again that classification based on vessel size is limited by the known overlap of vessel involvement in vasculitis.65 Large arteriole vasculitis of nerve has involvement of small arteries, large arterioles, and some smaller vessels.16 In large arteriole SVN, pathologic changes are typically found in epineural and perineural vessels 75-200 μm in diameter.15,33 It is important to remember that almost all nerve vessels are small vessels and so nerve “large arteriole” vasculitis is still a “small vessel” vasculitis, but the nerve vessels involved—although small—are larger than those in “nerve microvasculitis.” Nerve large arteriole vasculitis is usually associated with rheumatoid arthritis, polyarteritis nodosa, Churg-Strauss syndrome, or Wegener’s granulomatosis. Nerve microvasculitis is less well defined but involves a different spectrum of vessels—the smallest arterioles, microvessels and venules vessels, and not the large arterioles. The vessels involved in microvasculitis are usually smaller arterioles (i.e., < 40 μm), microvessels, and venules. Nerve microvasculitis occurs in NSVN, microscopic polyangiitis, immune sensorimotor polyneuropathies sometimes associated with sicca, classical Sjögren’s syndrome, and virus-associated neuropathies (some cases of HIV, cytomegalic, hepatitis C, and perhaps others).

It is also thought that many autoimmune (monophasic or relapsing) plexopathies (more accurately, radiculoplexus neuropathies) should also be classified as nerve microvasculitides. These include diabetic lumbosacral radiculoplexus neuropathy (DLRPN, also known as diabetic amyotrophy), non-diabetic LRPN and immune and inherited brachial plexus neuropathies (BPNs) (also called neuralgic amyotrophy and hereditary neuralgic amyotrophy). Histopathologic study of LRPN has demonstrated features suggesting nerve microvasculitis. The pathology of BPN (e.g., cervical radiculoplexus neuropathy [RPN]) has not been as well studied as LRPN but nerve microvasculitis has been demonstrated in some cases.17,20,69 With respect to clinical classification, radiculoplexus neuropathy (RPN) does not fit neatly into the “systemic versus nonsystemic” scheme. RPN probably shares more features in common with NSVN: vessel involvement appears to be primarily confined to nerves and does not seem to involve other organs (although the unexplained weight loss in RPN indicates at least some effects outside of the peripheral nervous system), vessels involved in NSVN and RPN are similar in size, and NSVN and RPN are not fatal disorders. But RPN differs from NSVN in the distribution of nerve involvement and by being monophasic. This unique temporal profile places the focus of RPN (and BPN) treatment on acute intervention rather than on relapse prevention.

**CLINICAL AND DIAGNOSTIC FEATURES OF VASCULITIC NEUROPATHY**

Patients who develop vasculitic neuropathy tend to be over the age of 50 years.41,47 The typical clinical features of vasculitic neuropathy are acute to subacute onset of painful sensory or sensorimotor deficits.43,67 The most common presentations are of an asymmetric polyneuropathy or multiple mononeuropathies (often overlapping).13,15,27,28,32,33,44,47,61,64,68 Commonly, the progression of mononeuropathies is so rapid that on presentation the deficits appear confluent. For this reason, it is imperative that the patient is queried in detail about the clinical course of the initial and all subsequent deficits. Most SVN and NSVN patients experience their initial symptoms in the lower extremities, typically the peroneal or tibial divisions of the sciatic nerve, but any nerve can be affected first. A distal, symmetric polyneuropathy is much less common but vasculitic neuropathy may infrequently present this. Accompanying constitutional symptoms may include myalgias, arthralgias, weight loss, respiratory symptoms, hematuria, abdominal pain, rash, or night sweats. These systemic symptoms may infrequently be minimal or absent early.3 Table 1 lists the clinical characteristics of six common forms of systemic vasculitic neuropathy.

EDX studies often reveal characteristic vasculitic neuropathy findings, including acute-to-subacute axonal loss of sensory and motor nerve fibers, often in a patchy, multifocal, or asymmetric pattern.77 In contrast, studies that show only conduction slowing or block at common entrapment sites (such as median neuropathy at the wrist or peroneal neuropathy across the fibular head) should lead the clinician to consider other etiologies that increase the likelihood for compression neuropathies, such as some forms of diabetic neuropathies (carpal tunnel syndrome and ulnar neuropathy at the elbow), non-vasculitic rheumatoid arthritis or hereditary neuropathy with liability to pressure palsies (HNPP).

Laboratory evaluation of suspected cases of vasculitic neuropathy should almost always include a complete blood count (CBC); metabolic panel (electrolytes, blood urea nitrogen, creatinine, and glucose); erythrocyte sedimentation rate (ESR); c-reactive protein (c-RP); antinuclear antibody (ANA); rheumatoid factor (RF); anti-neutrophil cytoplasmic antibody, with cytoplasmic immunofluorescence pattern, directed against the neutrophil serine protease proteinase 3 (PR3/c-ANCA) and anti-neutrophil cytoplasmic antibody, with perinuclear immunofluorescence pattern, directed against myeloperoxidase (MPO/p-ANCA); hepatitis B and C panel; and cryoglobulins.41,5 Serum complement determinations are appropriate in suspected mixed cryoglobulinemia or systemic lupus syndromes. It is also appropriate to check extractable nuclear antigen, serum angiotensin converting enzyme level, serum protein electrophoresis, and HIV in many instances. Cerebrospinal fluid analysis is usually not helpful, unless you are also investigating mimickers, including infectious (e.g., Lyme) or...
Table 1 A partial list of clinical characteristics and treatments for six common forms of systemic vasculitis affecting small and/or medium-sized vessels of nerve

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Wegener granulomatosis</th>
<th>Churg-Strauss syndrome</th>
<th>Polyarteritis nodosa</th>
<th>Microscopic polyangiitis</th>
<th>Rheumatoid vasculitis</th>
<th>Mixed cryoglobulinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral nerve disease</td>
<td>40-50%</td>
<td>65-80%</td>
<td>35-75%</td>
<td>60-70%</td>
<td>50% (of cases of rheumatoid vasculitis—a secondary vasculitis that occurs in 5-15% of cases of rheumatoid arthritis)</td>
<td>20-90%</td>
</tr>
<tr>
<td>Upper airway disease</td>
<td>95%</td>
<td>50-60%</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pulmonary disease, radiographic nodule/ infiltrates</td>
<td>70-85%</td>
<td>40-70%</td>
<td>No</td>
<td>15-70%</td>
<td>5-30%</td>
<td>No</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>70-80%</td>
<td>10-40%</td>
<td>No</td>
<td>75-90%</td>
<td>10-25%</td>
<td>33-55%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>&lt; 5%</td>
<td>30-50%</td>
<td>15-55%</td>
<td>30%</td>
<td>10-30%</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Arthralgia/arthritis</td>
<td>60-70%</td>
<td>40-50%</td>
<td>50-75%</td>
<td>40-60%</td>
<td>90-100%</td>
<td>20-90%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>10-25%</td>
<td>10-40%</td>
<td>5-30%</td>
<td>10-15%</td>
<td>10-30%</td>
<td>No</td>
</tr>
<tr>
<td>Skin</td>
<td>40-50%</td>
<td>50-55%</td>
<td>25-60%</td>
<td>50-65%</td>
<td>5-15%</td>
<td>60-100% (e.g., palpable purpura)</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>5-10%</td>
<td>5-30%</td>
<td>3-30%</td>
<td>10-15%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>c-ANCA (PR3)</td>
<td>75-90%</td>
<td>3-35%</td>
<td>Rare</td>
<td>10-50%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>p-ANCA (MPO)</td>
<td>5-20%</td>
<td>2-50%</td>
<td>Rare</td>
<td>50-80%</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Vessel size involved</td>
<td>Small to medium vessels (e.g., capillaries, venules, arterioles, arteries)</td>
<td>Small to medium vessels</td>
<td>Medium to small arteries (not arterioles, capillaries or venules)</td>
<td>Small vessels (e.g., capillaries, arterioles, venules)</td>
<td>Medium to small arteries (histologically indistinguishable from polyarteritis nodosa)</td>
<td>Small (e.g., capillaries, arterioles, venules)</td>
</tr>
<tr>
<td>Other features</td>
<td>Asthma, fever, hyper eosinophilia</td>
<td>Fever, hypertension</td>
<td>Fever</td>
<td>Elevated serum rheumatoid factor (RF) and ESR, extraarticular disease (e.g., nodules) fever, weight loss, scleritis</td>
<td>Hepatitis C infection, mixed cryoglobulins, fatigue, Raynaud’s phenomenon, leg ulcers, Sicca syndrome</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Glucocorticoid plus cytotoxic agent</td>
<td>Glucocorticoid; add cyclophosphamide if life-threatening disease</td>
<td>Glucocorticoid; add cyclophosphamide if life-threatening disease</td>
<td>Glucocorticoid plus cytotoxic agent such as cyclophosphamide</td>
<td>Glucocorticoid; add cyclophosphamide if life-threatening vasculitis if not responsive to steroids alone</td>
<td>Pegylated interferon alpha ± Ribavirin; plasma exchange in fulminant cases; monitor for interferon α-associated exacerbation of vasculitis</td>
</tr>
<tr>
<td>Viral association?</td>
<td>Sometimes associated with hepatitis B, hepatitis C, or HIV; if so, antiviral agent and/or plasmapheresis should be considered</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hepatitis C &gt; 80%</td>
</tr>
</tbody>
</table>

c-ANCA = anti-neutrophil cytoplasmic antibody, with cytoplasmic immunofluorescence pattern, directed against the neutrophil serine protease proteinase 3 (PR3); ESR = erythrocyte sedimentation rate; HIV = human immunodeficiency virus; p-ANCA = anti-neutrophil cytoplasmic antibody, with perinuclear immunofluorescence pattern, directed against myeloperoxidase (MPO)
other inflammatory etiologies (e.g., carcinomatous root involvement). In SVN, serologic testing is abnormal and helps further define the etiology or syndrome (see Table 1). In NSVN, the ESR or c-RP may be slightly elevated, but other markers of inflammation or systemic disease are usually normal.

Because of the need for long-term treatment with potentially toxic medications, the diagnosis of vasculitis—especially SVN—usually warrants histologic confirmation. One exception might be polyarteritis nodosa (PAN), which, because it affects larger vessels, can sometimes be diagnosed with the aid of angiography. In general, the sensitivity of a nerve or nerve and muscle biopsy is believed to be about 60% for vasculitis if inflammation and vessel wall destruction are mandatory criteria. Sensitivity of nerve biopsy increases but specificity decreases if other features, such as ischemic injury (multifocal nerve fiber loss) with inflammation and vessel wall destruction, are considered sufficient for diagnosis. Some investigators recommend biopsy of both nerve and muscle, for example the superficial peroneal nerve and ipsilateral peroneus brevis muscle. The sensitivity of a nerve biopsy depends on several factors, including patient selection, which nerve is biopsied, timing in relation to symptoms, and the histologic criteria required for diagnosis.

In large arteriole SVN, pathologic changes are typically found in epineural and perineural vessels 75-200 μm in diameter. The vessels involved in microvasculitis are usually smaller arterioles without an internal elastic lamina (i.e., < 40 μm), microvessels, and venules. Whereas in nerve large arteriole vasculitis, fibrinoid necrosis of the tunica media is often prominent and characteristic, obvious fibrinoid necrosis is usually not found in nerve microvasculitis. In microvasculitis, there is inflammation of the vessel wall with separation, fragmentation, and necrosis of the thin tunica media. In both groups of necrotizing vasculitis, evidence of ischemic injury or repair (multifocal fiber loss, injury neuroma, neovascularization, and perineurial thickening) is often found. Inflammatory cells separate muscle layers. With increased severity there is separation of the muscle leaflets, which become fragmented and separated from the microvessel. Obvious occlusion of vessels is usually not encountered but recent or previous bleeding (hemosiderin in macrophages) is typical. Hemosiderin is typically found adjacent to affected microvessels. Fibrinoid degeneration of the media (seen to advantage in Trichrome stain in paraffin sections in nerve large arteriole vasculitis) is almost never observed in microvasculitis but is commonly seen in large arteriole SVN. Typical of vessel inflammation is angioneogenesis—closely spaced thin walled microvessels in regions of previously ischemic areas. Associated with microvasculitis all stages of perineurial injury have been found, from acute fibrinoid degeneration to thickening and scarring and regrowth of microfasciculi through the perineurium into the epineurium (injury neuroma). Although segmental demyelination may be found in acute ischemic injury, it is usually at borders of ischemic injury and may relate to axonal atrophy (distal to sites of axonal stasis) or to sites of axonal enlargement. Immune complex deposition in vessel walls is commonly seen in both SVN and NSVN.

**CLINICAL FEATURES OF LUMBROSACRAL AND CERVICAL RADICULOPLEXUS NEUROPATHY**

Both diabetic and nondiabetic LRPN are unique forms of vasculitic neuropathy because of the stereotypic presentation, relatively confined distribution of nerve injury, frequent weight loss, and monophasic course. Both forms (diabetic and nondiabetic) of LRPN present with acute or subacute pain followed by weakness in the lower extremities (both proximal and distal segments), typically beginning unilaterally but often spreading to the other lower extremity. Pain is usually severe. A concomitant thoracic radiculopathy is common which presents with a band and pain in the abdomen or chest and weakness of abdominal wall musculature. A cervicobrachial plexus neuropathy (a BPN) may accompany LRPN in up to 15% of cases, although upper extremity manifestations are very much overshadowed by the lower extremity neuropathic symptoms, impairments, and disability. The LRPNs are monophasic illnesses—in contrast to most other cases of NSVN—with progression lasting weeks, months and rarely years and with slow but incomplete recovery of motor function. Although it appears that this disorder is more prevalent in diabetes mellitus, glycemic exposure does not appear to be the direct metabolic cause. The frequently associated weight loss may perhaps provide an indication of systemic involvement.

In contrast, the pathologic basis of both noninherited and inherited immune BPN (a cervical radiculoplexus neuropathy) has not been as extensively studied, but inflammation and nerve microvasculitis has been demonstrated in some cases. Some cases of hereditary BPN (also called hereditary neuralgic amyotrophy) are caused by a mutation in the SEPT9 gene. Biopsy of a superficial radial nerve during an attack has shown changes suggestive of microvasculitis.

**GENERAL COMMENTS ABOUT TREATMENT OF VASCULITIC NEUROPATHIES**

An important role of the EDX physician in vasculitic neuropathy management is the assessment of clinical response, especially in terms of neuropathic impairment. Reliable endpoints include routine examination of muscle power, deep-tendon reflexes, and sensory thresholds, functional rating scores, and EDX testing, while worsening pain appears to be a less reliable endpoint. If, in the course of treatment, new neurological deficits develop, more aggressive therapy is indicated. Treatment decisions should be made in consultation with a rheumatologist or internist, and are based in part on the form of systemic vasculitis, extent and degree of organ involvement, prior responsiveness to any treatments, and presence or absence of viral infection. For example, chronic immunosuppressive agents, which may be first-line therapy for nonviral vasculitis, are often relatively contraindicated in viral-associated SVN.
COMMENTS ABOUT THE TREATMENT OF SYSTEMIC VASCULITIC NEUROPATHIES

Vasculitic Neuropathy Not Associated with Virus

For nonviral SVN, corticosteroids are usually the initial therapy. Treatment strategies have been developed to rapidly stop inflammatory damage (induction) followed by safer long-term suppression (maintenance). Corticosteroids plus an additional immunosuppressant, such as cyclophosphamide, are usually required to treat microscopic polyangiitis or Wegener’s granulomatosis.\(^{23,41}\) In PAN and Churg-Strauss syndrome, cyclophosphamide should be added in life-threatening cases, such as those with cardiac, gastrointestinal, or central nervous system (CNS) involvement. Some Wegener’s granulomatosis or microscopic polyangiitis patients will require long-term immunosuppression due to relapsing disease.\(^{39,41,52}\)

Corticosteroids for Vasculitic Neuropathies

In general, corticosteroids remain first-line therapy for systemic vasculitis (Table 2), either alone or combined with other immunosuppressants. Dosage titration should be based on the patient’s disease severity and response to treatment. In severe cases, intravenous (IV) methylprednisolone may be appropriate for initial therapy (e.g., 1000 mg IV daily for 3-5 days followed by daily oral prednisone). Daily oral steroids should be continued until the patient has shown a clear response. During the subacute phase of treatment, usually after 6-8 weeks, the patient may be transitioned to alternate-day dosing, either at the same or at a lower averaged daily dose. At this time or after another 1-2 months of observation, the physician should begin tapering the steroid dose, for example by 5 to 10 mg/day/month, perhaps with lesser decrements occurring near the end of the taper. Table 2 lists the potential adverse effects of steroid therapy.

Immunosuppressant Adjuvant Therapies for Vasculitic Neuropathies

The decision as to whether or not to add a cytotoxic or corticosteroid-sparing agent, such as cyclophosphamide, methotrexate, azathioprine, or mycophenolate mofetil, is an important one preferably made by a rheumatologist or internist with more experience caring for patients with SVN. In general, most experts recommend starting a cytotoxic agent such as cyclophosphamide in cases of Wegener’s granulomatosis or microscopic polyangiitis.\(^{39,41,53}\) Cytotoxic agents are also indicated in patients with other forms of systemic vasculitis who progress despite corticosteroid therapy or who have severe multiorgan involvement, such as pulmonary-renal syndrome, rapidly progressive necrotizing glomerulonephritis, CNS involvement, or other life-threatening organ involvement. The physician must keep in mind that adjuvant therapies have a delayed onset of action, often weeks to months. Table 2 lists some of these agents, typical doses, and a partial list of side effects.

Regardless of the treatment, it is important that the physician monitor for and promptly identify any life-threatening organ involvement by vasculitis, including of the gastrointestinal tract, heart, or CNS.\(^{52,53}\) The involvement of these systems should prompt the physician to add an adjuvant therapy, if not yet done, or to escalate the doses of existing therapy. Worsening subjective constitutional symptoms may not reliably signify relapse, however, therefore clinical and laboratory parameters must be followed closely. This includes a thorough general and neurologic examination, and surveillance CBC, chemistries, ESR, and urinalysis at least every 3 months and chest radiograph at least annually.\(^{52}\)

Cyclophosphamide is an effective drug for induction and prolonging survival in the nonviral systemic vasculitides. Patients usually require between 3 and 12 months of cyclophosphamide induction therapy before they can be switched to a maintenance immunosuppressant.\(^{1,23,41,53}\) Oral cyclophosphamide is typically dosed at 2 mg/kg/day. Current available data does suggest that pulse-dosing cyclophosphamide results in fewer adverse effects but might be associated with an increased risk for relapses compared to oral cyclophosphamide.\(^{13}\)

Methotrexate has been used most commonly for remission maintenance after cyclophosphamide induction.\(^{41}\) A common approach is to use cyclophosphamide as the adjuvant agent until remission, then to switch to methotrexate or azathioprine for maintenance.\(^{31}\) Once the vasculitis is in remission, it is reasonable to continue maintenance therapy for at least a year before attempting to taper the methotrexate or azathioprine. Methotrexate dosing in the range of 15-25 mg once weekly is used for systemic vasculitis.\(^{23,53}\)

Azathioprine may be considered for patients unable to tolerate cyclophosphamide therapy.\(^{36,39,41,53}\) Azathioprine may be as effective as cyclophosphamide in maintaining remission in Wegener’s granulomatosis or microscopic polyangiitis.\(^{36}\) Azathioprine is initially dosed at 50 to 100 mg or 1 mg/kg p.o., usually divided twice daily. The dose is then increased by 50 mg/day every 4 weeks to a goal dose of 2 to 2.5 mg/kg/day divided twice daily.

Mycophenolate mofetil and leflunomide have been reported in pilot studies to be potentially useful for maintaining remission after cyclophosphamide induction in Wegener’s granulomatosis.\(^{41,54,58}\)

IV immunoglobulin (IVIg) has been used in nonvasculitic immune-mediated neuropathies and generally has a benign safety profile, making it an attractive consideration a adjuvant therapy. Small, open-label trials of IVIg in SVN have suggested clinical benefit.\(^{37,56}\)

Rituximab, a chimeric anti-CD20 antibody, has shown promise in the treatment of cryoglobulinemic vasculitis and rheumatoid arthritis.\(^{40,50}\)
### Table 2: Treatment options, potential side effects, and suggested measures to monitor for and manage side effects for nonviral systemic vasculitic neuropathy (Schaublin 2005)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Partial list of potential side effects</th>
<th>Management of potential side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Acute: Increased susceptibility to infections, hyperglycemia, increased appetite and weight gain, anxiety, confusion, insomnia, impaired wound healing, electrolyte disturbances. Chronic: Avascular necrosis of the femoral heads, hyperlipoproteinemia, accelerated atherosclerosis, osteoporosis, myopathy, alteration in fat deposition, peptic ulcer disease, cataracts.</td>
<td>Patients should start or continue an exercise program, monitoring their diet and weight. Blood glucose monitoring periodically during treatment. Bone mineral density testing baseline and annually. Consider bisphosphonates for prophylaxis of steroid-induced osteoporosis (avoid during pregnancy).</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Hemorrhagic cystitis, transitional cell carcinoma of the bladder, oncogenicity, bone marrow suppression, gonadal toxicity, teratogenicity. About one-half of patients will develop hematuria, usually due to cystitis. Dose-related bone marrow suppression is common, with an increased risk of infection associated with leucopenia. Nausea and vomiting. Increased risk of Pneumocystis carinii pneumonia (PCP), especially with combined steroids and cytotoxic therapy. Potential increased risk of other malignancies, including myelo- and lymphoproliferative disorders, years after its discontinuation. Permanent infertility may also occur due to its ability to interfere with spermatogenesis and oogenesis, which is related to its cumulative dose. Teratogenicity may occur.</td>
<td>Hematuria is a sensitive marker for cyclophosphamide-induced bladder injury. Injury is due to acrolein, a toxic metabolite which is excreted into the urine. Shortening the duration of acrolein exposure to the bladder epithelium may minimize the risk of toxicity. Hence, oral administration should be q.d., usually in the morning, followed by a large amount of fluids. TCCA, when it develops, almost always does so after episodes of hematuria. Urinalyses every 3-6 months, even after discontinuation, as TCCA may develop decades after cyclophosphamide is stopped. In cases of hematuria, discontinuation and referral to a urologist is necessary. CBC with platelets weekly the first month, then every month while on treatment. Total leukocyte counts below 3500/mL or absolute neutrophil counts below 1500/mL mandate titration or suspension of the drug. Lower neutrophil counts may warrant admission to the hospital and perhaps treatment with broad-spectrum antibiotics. A precipitous drop in cell counts also warrants more aggressive intervention, including cessation of cyclophosphamide. Taking oral cyclophosphamide with or after a meal lessens the likelihood of nausea and vomiting. Consider antiinflammatory medications. IV monthly cyclophosphamide also shortens the time patients experience nausea. Patients not allergic to sulfa who are on combination therapy may be treated with “low-dose” oral trimethoprim (160 mg) and sulfamethoxazole (800 mg) t.i.w. Counseling and birth-control measures.</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Bone marrow toxicity. Hepatic fibrosis and cirrhosis; elevated LFTs. Nephrotoxicity. Increased risk for opportunistic infections. Stevens-Johnson syndrome, erythema multiforme, and toxic epidermal necrolysis. Pulmonary fibrosis (rare). Lowers seizure threshold.</td>
<td>Baseline CBC with platelets should be obtained prior to initiation (usually performed as part of VN evaluation) and every 3 months thereafter. Repeat testing with fever, rash, or mouth ulcers. Baseline LFTs should be obtained prior to initiation of therapy and at least every 3 months. Repeat testing with fever, rash, or jaundice, especially within the first 3 months of treatment. Consider other adjuvant therapy in patients with hepatitis or frequent alcohol consumption. Relatively uncommon, but extra caution should be used in patients with baseline renal impairment. A baseline BUN and creatinine is probably sufficient, provided the vasculitis itself does not involve the kidneys. Prophylactic trimethoprim/ sulfamethoxazole (160 mg/800 mg) t.i.w. is recommended. Discontinue the drug in suspected rash secondary to methotrexate. Baseline PFTs in those with rheumatoid vasculopathy may be helpful for comparison if symptoms develop; PFTs not helpful for subclinical detection. Discontinue drug in cases of new or worsening pulmonary function. Consider other adjuvant therapies in patients with seizures.</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>May be used for maintenance, once SVN is in remission.</td>
<td></td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen, CBC = complete blood count, IV = intravenous, LFT = liver function test, PFT = pulmonary function test, SVN = systemic vasculitic neuropathy, TCCA = trichloroisocyanuric acid, VN = vasculitic neuropathy.
Vasculitic Neuropathy Associated with Hepatitis B or Hepatitis C

It is necessary to determine whether or not the vasculitic neuropathy is associated with a virus, such as hepatitis B or C or HIV. A detailed discussion of treatment of viral-associated vasculitis is beyond the scope of this review. A physician experienced in treating viral hepatitis, for example a hepatologist, should make the treatment decisions and manage such patients. In general, chronic immunosuppression is relatively contraindicated in viral-associated vasculitides because such treatment may increase viremia. Shorter courses of immunosuppression, however, are still sometimes employed for polyarteritis nodosa associated with hepatitis B. Corticosteroids are typically followed by a longer course of an antiviral agent (either interferon (INF)-α2a or the nucleoside analogue lamivudine) often with concomitant plasma exchange. Treatment of hepatitis C typically involves pegylated interferon-α2a or 2b, often with ribavirin. INF-α treatment has been associated with clinical improvement in patients with hepatitis C-cryoglobulinemic vasculitic neuropathy. The clinician must be aware, however, that exacerbation of vasculitic neuropathy subsequent to initiation of pegIFN-α is an infrequent but well-reported complication of treatment. In such cases, drug discontinuation may lead to improvement and should be considered. Rituximab may hold promise for treatment of patients with hepatitis C-cryoglobulinemic vasculitic neuropathy. Plasma exchange should be considered in fulminant cases.

Comments about the Treatment of Nonsystemic Vasculitic Neuropathy, Lumbosacral Radiculoplexus Neuropathy, and Other Radiculoplexus Neuropathies

There are a number of things to keep in mind about NSVN and RP when considering treatment options. First, NSVN and RP are almost always not fatal and thus differ from that of untreated SVN. DLRPN and LRPN are usually monophasic whereas other forms of NSVN are often chronic. Also, the neurological deficits seen with NSVN are different. In patients with NSVN, severe neurologic symptoms may remit for years or even decades before relapsing. Immunosuppressive treatment may not be indicated for NSVN patients with either mild or improving neuropathy. On the other hand, for more fulminant disease, treatment is indicated. Patients with active and severe DLRPN or LRPN are often treated with either intravenous immunoglobulin or intravenous methylprednisolone.

Immunosuppressive Treatment of Nonsystemic Vasculitic Neuropathy

Corticosteroids for Nonsystemic Vasculitic Neuropathy

For cases of NSVN warranting treatment, oral prednisone therapy is the usual first-line agent. Most experts recommend either 40 to 60 mg/day or 1 mg/kg/day for 2-3 months followed by steroid taper and transition to alternate-day dosing if the patient has clinically responded, although others think that smaller doses will suffice.

Adjuvant Therapies for Nonsystemic Vasculitic Neuropathy

A relatively recent retrospective study for NSVN (not DLRPN or LRPN) argue for both corticosteroids and cytotoxic adjuvant therapy, based on statistically significant better response rates and disability scores. However, patients exposed to immunosuppressant therapy also experienced significantly more episodes of pneumonia, Varicella zoster, and sepsis in this study. A prospective, randomized trial would be ideal but seems impractical given the infrequency of NSVN.

Treatment of Diabetic Lumbosacral Radiculoplexus Neuropathy and Lumbosacral Radiculoplexus Neuropathy

There is no proven course-altering therapy for DLRPN or LRPN and only one randomized, controlled trial has been performed. However, based on anecdotal case reports, patients with DLRPN or LRPN are often treated with IV corticosteroids or IVIg. One noncontrolled study of a series of LRPN patients treated with IV corticosteroids showed that they all improved, many to a marked degree, but the authors warned that the results should be viewed with caution since the monophasic disease improves spontaneously. Treatment should be considered for patients in the acute phase or for those in the subacute phase who do not appear to be improving. We tend to treat with IV methylprednisolone because steroids have been first-line therapy for other forms of microvasculitis. Patients treated with steroids (e.g., DLRPN patients) must be closely monitored for hyperglycemia. A randomized, controlled trial comparing IV methylprednisolone versus IV placebo in DLRPN is completed but all of the data has not yet been completed analyzed.

Connective Tissue Disorders and Neuropathy

This section will review neuropathies associated with Sjögren’s syndrome and systemic lupus erythematosus. Neuropathy associated with rheumatoid arthritis was briefly discussed in the vasculitic neuropathy section. The neuropathies associated with these disorders commonly presents with a sensory or sensorimo-
tor polyneuropathy, although mononeuritis multiplex caused by vasculitis can be the presentation in a sizeable minority of cases.

**Sjögren’s Syndrome and Neuropathy**

Primary Sjögren’s syndrome is a chronic autoimmune disease that most commonly affects women (90% of cases). The principal histological finding is infiltration of the lacrimal and salivary glands by mononuclear cells, causing dry eyes (xerophthalmia) and dry mouth (xerostomia). Approximately one-half of patients develop extraglandular manifestations, including arthralgias, rash, and myalgias. The most common forms of neuropathy associated with Sjögren’s syndrome are sensorimotor polyneuropathies and pure sensory neuropathy/neuronopathy. For example, in one study out of Japan, out of 93 patients with primary Sjögren’s syndrome and neuropathy, 36 patients were categorized as having the sensory ataxic neuropathy form (often with autonomic features such as abnormal pupils) and 18 patients as having painful neuropathy without sensory ataxia (also often associated with autonomic features). In this series, 11 patients presented with multiple mononeuropathies and 15 patients with trigeminal neuropathy. Other less common forms were multiple cranial neuropathies, radiculoneuropathy, and autonomic neuropathy. In this series, corticosteroids or IVIg were the most commonly prescribed therapies. Multiple mononeuropathy and multiple cranial neuropathy forms showed the most favorable response to immunotherapy, whereas the sensory ataxic neuropathy responded favorably less than half of the time. In another case series of 33 patients seen at Mayo Clinic, 23 had a distal sensorimotor polyneuropathy and 10 had a sensory polyneuropathy. In this cohort, “asleep” or “prickling numbness” was the initial manifestation in most patients. The following laboratory studies were abnormal in approximately half these patients: ESR, RF, ANA, anti-SSA antibodies. In this series, anti-SSB antibodies and anti-ribonucleoprotein (anti-RNP) antibodies were less frequently abnormal. Salivary gland biopsies were abnormal in all patients for which the study was performed (n=14). Adie’s pupil (6) and trigeminal neuropathy (5) were infrequent accompaniments. In another case series from Mayo Clinic (54 patients with neuropathy and sicca complex), cases of pure sensory neuropathies outnumbered cases of sensorimotor polyneuropathy. The pure sensory neuropathies were distal polyneuropathies in two-thirds and polyganglionopathy (i.e., ataxic sensory ganglionopathy or sensory neuronopathy) in one-third of the sensory neuropathy presentations. Three-quarters of patients demonstrated abnormal minor salivary gland biopsy. Serum antibodies to extractable nuclear antigens (e.g., SSA, SSB) were only found in 10% of cases. Vasculitis or perivascular inflammation is commonly observed on nerve biopsy (e.g., sural nerve or dorsal root ganglion) in many of these patients.

The classification of primary Sjögren’s syndrome has varied over the years and the different case series of Sjögren’s syndrome and neuropathy have all used different criteria. Consensus classification criteria for primary Sjögren’s syndrome basically recommend that symptoms of sicca complex be corroborated by confirmatory histopathology and/or antibodies in serum to SSA (i.e., Ro) and/or SSB (La). It is important to note that most patients with neuropathy and Sjögren’s syndrome are only diagnosed with Sjögren’s syndrome after the onset of neuropathy. For example, in one Japanese series of 93 patients, 86 were diagnosed with having Sjögren’s syndrome after neurological symptoms developed. Regarding symptoms, patients should be asked if they have experienced “daily, persistent, dry eyes,” “recurrent sensation of sand or gravel in the eyes,” “a daily feeling of dry mouth,” “recurrently or persistently swollen salivary glands,” and the need to “frequently drink liquids to aid in swallowing dry food.” Secondary causes warranting exclusion include hepatitis C, HIV, and sarcoidosis, among others.

**Systemic Lupus Erythematosus and Neuropathy**

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disorder that most frequently affects women (90% of cases). The most common initial organs of involvement are joints and skin, followed by kidneys, blood, lung (e.g., pleuritis), CNS, and heart (e.g., pericarditis). A positive ANA is detected in over 95% of patients. More specific but less sensitive antibodies for SLE are antibodies to double-stranded deoxyribonucleic acid (DNA) and smith antigen.

Polyneuropathy occurs in 10-25% of SLE patients, most commonly as a sensorimotor polyneuropathy. Up to one-third of these patients have overlapping mononeuropathies, which in some instances is on the basis of small-to-medium vessel vasculitis.

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INTRODUCTION

The neuropathies of medical diseases, other than those associated with diabetes mellitus, are often underappreciated. As new or more effective treatments for these chronic disorders have emerged some of these neuropathies, such as those associated with chronic hepatic disease or bariatric surgery, are seen more often. Some diseases are now less common because of more effective treatment, such as uremic polyneuropathy. Although patients may be asymptomatic, neurologic examination and electrophysiologic studies may reveal neuropathy in a fair number of patients with these disorders. The relationship of some of these disorders with neuropathy, such as with celiac disease, remains controversial.

CHRONIC RENAL FAILURE

Polyneuropathy in chronic renal failure (uremia), or endstage renal disease (ESRD), is common, but is seen primarily in those patients with longstanding, advanced disease. It tends to plateau with chronic dialysis and may improve after successful renal transplantation. The development of neuropathy as a manifestation of chronic renal failure is complicated by the frequent coexistence of diabetes. Diabetes generally is the cause of nephropathy, as well as the neuropathy. This section will focus on the polyneuropathy that occurs in those without diabetes. Mononeuropathies may also occur independently of polyneuropathy. These include carpal tunnel syndrome (CTS) and ischemic monomelic neuropathy, a complication that may occur acutely distal to an arterial–venous (A–V) shunt placed in the forearm for dialysis access.

Polyneuropathy

Neuropathy as a result of chronic renal failure is a function of the duration and severity of the renal failure, as well as the effects of the various forms of treatment. The neuropathy is absent, subclinical, or mild early in the disease. By the time ESRD is present, polyneuropathy is present in over 50% of patients, although only a relatively small percentage have severe neuropathy.\textsuperscript{2,16} However, given the incidence of ESRD, there are many patients who ultimately develop significant polyneuropathy.

As with most metabolic or toxic polyneuropathies, the deficits develop in a length-dependent pattern. Tingling parasthesias in the feet are a common early symptom. On occasion, weakness or gait imbalance may be the first clinical manifestation. The signs that are generally noted first are loss of vibration sensation in the toes and reduced or absent ankle jerk reflexes. As the neuropathy progresses, distal toe extensor and ankle dorsiflexor weakness develop. Severe cases producing quadriparasis rarely are seen given the early introduction of dialysis in the modern era. A neuropathy of this severity in patient on dialysis should arouse suspicion of an alternative diagnosis, such as vasculitis or chronic inflammatory demyelinating polyneuropathy.

Some symptoms appear to be more common in this form of polyneuropathy. Restless legs syndrome is present in 51% and muscle cramps in 65%.\textsuperscript{3} On the other hand, unlike the case with diabetic polyneuropathy, overt clinical features of autonomic neuropathy are uncommon. Orthostatic hypotension and erectile dysfunction may occur in patients with ESRD, but not more so than in patients without polyneuropathy.\textsuperscript{20}
The electrophysiologic features of this polyneuropathy are primarily those of a length-related, axonal sensory–motor neuropathy. Sensory nerve amplitude potential (SNAP) and compound motor action potential (CMAP) response amplitudes fall as the neuropathy progresses and is most evident in the lower extremity studies. The degree of slowing may be more than expected for the degree of axonal loss present, as has been demonstrated in diabetic polyneuropathy. However, the degree of conduction velocity slowing, also reflected in distal motor and F wave latencies, does not generally fall in the range of primary demyelinating neuropathies. Conduction block is not seen. Needle electromyography (EMG) abnormalities reflect a chronic denervating disorder with distal muscles most affected.

The etiology of this polyneuropathy is uncertain. There is no evidence that it is due to deficiencies of B vitamins, accumulation of any specific toxins, or ischemia. The polyneuropathy has been associated with the impaired clearance of “middle molecules” in the 0.5 to 500 kDA range that accumulate and may be toxic to axons. However, the data supporting the neurotoxic effects of these middle molecules has been mixed.

When polyneuropathy has developed in a patient with ESRD, the introduction of hemodialysis or peritoneal dialysis generally halts the progression of the neuropathy and the clinical deficits. Early introduction of dialysis in this population of patients developing neuropathy is particularly important. Renal transplantation is the best treatment for the neuropathy of chronic renal failure. Patients with early mild neuropathy may completely recover with normalization of the nerve conduction abnormalities. The improvement of the neuropathy after transplantation is more protracted in those with significant axonal loss and, in those patients, residual symptoms and signs persist to a variable degree.

Mononeuropathies

CTS may occur more commonly in those patients with dialysis-dependent chronic renal failure, even in the absence of diabetes. The clinical and electrophysiologic manifestations of CTS are the same in patients on dialysis as in other patient populations with CTS. The early and most disabling symptoms are sensory symptoms, numbness and paraesthesias, as well as pain. Progression of CTS in dialysis patients has been associated with the deposition of beta2-microglobulin-associated amyloid that accumulates in the flexor retinaculum that roofs the carpal tunnel. Although this beta2-microglobulin deposition is more common with some dialysis membranes, it can occur with any membranes as well as in those undergoing chronic peritoneal dialysis. The approach to the surgical treatment of CTS in this setting is the same as with those patients with CTS and diabetic polyneuropathy. Surgical decompression may relieve much of the pain and bothersome paraesthesias, particularly the nocturnal symptoms.

An acute, painful neuropathy may develop in the limb distal to the placement of an upper limb A–V fistula for dialysis access. This has been termed ischemic monomelic neuropathy (IMN). The clinical presentation follows soon after the placement of the shunt between the radial or brachial artery to the cephalic vein. Typically there is severe, burning pain in the hand distal to the fistula, associated with a varying degree of numbness and weakness. On examination, there is sensory loss and weakness in the distal distribution of the radial, median, and ulnar nerves. Electrodiagnostic (EDX) studies demonstrate reduced amplitudes in the sensory and motor territories of these nerves consistent with acute axonal loss. This is especially evident with comparison to these values in the unaffected limb. A feature that is characteristic of the clinical and electrophysiologic abnormalities is that they are most severe in the distal part of the affected limb and are shaded in a less severe pattern up the forearm, in a marked length-related pattern. At the same level in the limb the different nerves are affected equally.

IMN occurs presumably as a result of too much shunting of arterial blood, leading to ischemic neuropathy. Surgical reversal of the fistula in patients significantly affected results in restored distal perfusion and often rapid improvement of pain. The distal numbness and weakness and the electrophysiologic correlates improve but to a varying degree that depends on the severity of axonal loss.

GASTROINTESTINAL DISEASE

Chronic Hepatic Diseases

Polyneuropathy commonly is present in patients with chronic hepatic disease, ranging in incidence from 15% to 90%. The true incidence that can be attributable to hepatic disease alone can be difficult to determine, in that many medical disorders may produce both neuropathy and hepatic injury. The neuropathy may be secondary to that medical disease rather than the hepatic disease per se. These medical disorders include alcoholism, amyloidosis, porphyria, systemic vasculitis, and hepatitis C infection as well as some therapeutic agents.

Patients with cryptogenic hepatic disease may also develop neuropathy. This likely reflects the metabolic impact of the hepatic disease, in that the severity of the neuropathy correlates with the severity of the hepatic dysfunction. This neuropathy, like most metabolic neuropathies, is that of a length-related, distally-predominant sensory–motor disorder. The degree of sensory and motor deficits varies but is most often mild. Electrophysiologic studies identify a subclinical neuropathy in up to 40% of patients.

Early pathologic and electrophysiologic reports suggested that the neuropathy of chronic hepatic disease was a demyelinating one. However, careful electrophysiologic studies show that this neuropathy is an axonal neuropathy manifested primarily by distally-predominant loss of sensory (SNAP) and motor (CMAP) responses amplitudes. The conduction velocities are rarely in the demyelinating range and the slowing of conduction velocity can be accounted by the loss of axons alone.

Patients with chronic hepatic disease due to primary biliary cirrhosis (PBC) make up a distinctive group. PBC is an autoimmune inflammatory disorder of the hepatic biliary system. These patients develop a purely sensory neuropathy with or without xanthomatous infiltration of nerve. The symptoms are those of distal numbness,
burning pain, paresthesias, and imbalance. The examination reveals purely sensory manifestations with distal sensory loss and hyporeflexia, but no weakness. Electrophysiologic abnormalities are limited to low amplitude or absent sensory responses. Motor responses and the needle electromyography (EMG) examination are normal. Some, but not all, of these patients with PBC and sensory neuropathy have distinctive nerve pathology. Sural nerve biopsy may reveal lipid-laden xanthomas within and distorting the nerve fascicles.  

Celiac Disease

Celiac disease (CD) is a T-cell mediated autoimmune disorder that primarily affects the gastrointestinal tract. The ingestion of dietary gluten protein results in the production of antibodies against tissue transglutaminase (tTG) and other intestinal antigens. This produces an inflammatory response and injury to the mucosa in the small bowel. This produces gastrointestinal symptoms, diarrhea, or malabsorption, and often extraintestinal manifestations, such as dermatitis herpetiformis. These clinical manifestations respond to a gluten-free diet. There have been numerous case reports of neurologic complications of this disorder including neuropathy, but the literature is controversial. There is disagreement as to whether the association with neuropathy is causal or coincidental.

The diagnosis of CD is established by serologic studies and small bowel biopsy. The best screening serologies are those that are the most sensitive and specific; these include the immunoglobulin A (IgA) tissue transglutaminase (tTG) antibody (sensitivity 90-96% and specificity > 90%) and IgA endomysial (EMA) antibody (sensitivity 90% and specificity 99.6%). Antigliadin antibodies are much less helpful due to their low specificity. Patients who have positive tTG or EMA antibodies should undergo small bowel biopsy while on a gluten-rich diet.

In the group of patients with classic CD confirmed by specific antibodies (tTG and EMA) and positive duodenal biopsy, sensory neuropathy is seen in a small percentage of patients. Chin and colleagues reported the incidence of neuropathy and CD of about 2.5% in all neuropathy patients seen at their tertiary care center. Most of these were mild, axonal sensory neuropathies and only 10% had weakness. Whether this represents a casual relationship between the autoimmune disease, malabsorption, or reflects coincidental occurrence of cryptogenic neuropathy has not been firmly established.

A diagnostic approach to celiac disease has been suggested in recent reviews (see Table 1).

### Table 1 Diagnostic approach to celiac disease

<table>
<thead>
<tr>
<th>Probability of disease &gt; 5% (e.g., family history of celiac disease, unexplained steatorrhea or iron deficiency anemia, characteristic rash)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IgA tissue transglutaminase (tTG) and IgA endomysial (EMA) serology, AND</td>
</tr>
<tr>
<td>2. Small bowel biopsy</td>
</tr>
<tr>
<td>If both are positive, the diagnosis is confirmed.</td>
</tr>
<tr>
<td>If either is negative, repeat on normal diet (not gluten-free).</td>
</tr>
<tr>
<td>Probability &lt; 5%</td>
</tr>
<tr>
<td>1. IgA tissue transglutaminase (tTG) and IgA endomysial (EMA) serology</td>
</tr>
<tr>
<td>2. Perform on normal diet (not gluten-free)</td>
</tr>
<tr>
<td>If positive, perform small bowel biopsy.</td>
</tr>
<tr>
<td>If negative, the diagnosis is adequately excluded.</td>
</tr>
</tbody>
</table>

The treatment of classic, biopsy-proven CD is the dietary restriction of gluten. This is effective in ameliorating the gastrointestinal symptoms of CD, but there have been no convincing reports of response to gluten-free diet in patients with CD and neuropathy. In that light, there is little likelihood of a patient responding to dietary restriction of gluten who has neuropathy without gastrointestinal symptoms, positive antigliadin antibodies, but normal tTG and EMA antibodies.

**NUTRITIONAL DEFICIENCIES**

With the exception of vitamin B12 deficiency, neuropathies due to vitamin deficiency are uncommon in the developed world. They are, however, an important cause of neuropathy in that they can be easily treated or prevented. With the exception of chronic alcoholics, for patients who practice certain strict forms of diet, and patients after bariatric surgery, chronic malnutrition rarely is a cause of the vitamin deficiency. Some, such as vitamin B12 deficiency, are due to a medical disease (pernicious anemia) that prevents absorption of that vitamin. Others deficiencies may be due to the secondary effects of certain medications, as with vitamin B6 deficiency with isoniazid use.

**Vitamin B12 Deficiency**

Vitamin B12 (cobalamin) deficiency is most often due to pernicious anemia. Other causes also are important to consider and include gastrectomy or bariatric surgery (see below), strict vegetarian or vegan dietary practice, and chronic nitrous oxide abuse. In large series of patients with polyneuropathy, vitamin B12 deficiency may be identified in up to 8% of patients screened for causes of neuropathy in referral centers.

The screening tests for vitamin B12 deficiency in a patient with polyneuropathy should include serum assays for vitamin B12 and select metabolites, such as methylmalonic acid with or without homocysteine. Although most patients with vitamin B12 deficiency will have B12 levels below 200 pg/dL, about 5-10% of those with low levels (200-300 pg/dL) will have cobalamin deficiency con-
firmed by elevated levels of methylmalonic acid and homocysteine. Both methylmalonic acid and homocysteine assays are sensitive for cobalamin deficiency, but methylmalonic acid has the advantage of greater specificity. In a large study of more than 400 patients with B$_{12}$ deficiency, the sensitivity of methylmalonic acid was 98.4%. Homocysteine was nearly as sensitive but also was elevated in isolated folate deficiency, renal insufficiency, and hypothyroidism as well as other disorders.

The neurologic manifestations of B$_{12}$ deficiency most often include features of both myelopathy and polyneuropathy. This combination should raise strong clinical suspicion of B$_{12}$ deficiency. However, in some patients the neuropathy may be the predominant or earliest manifestation of this disorder. The symptoms, distal numbness and paresthesias, and the signs, reduced distal sensation and absent ankle jerk reflexes, are not distinguishable from most cryptogenic neuropathies. Weakness, when it occurs, is mild. The EDX features of B$_{12}$ deficiency are those of an axonal polyneuropathy.

**Vitamin B$_{12}$ Deficiency**

Vitamin B$_{1}$ (thiamine) deficiency, or beriberi, is seen most commonly in the setting of chronic alcoholism and its associated malnutrition. It may also be seen on occasion in individuals receiving total parenteral nutrition, following bariatric surgery (see below), or in those individuals who follow a restricted diet devoid of thiamine. The greatest sources of thiamine are in unrefined cereal grains, yeast, pork, whole grain rice, and legumes. Severe thiamine deficiency can cause neuropathy (dry beriberi), cardiac failure (wet beriberi), and Wernicke's encephalopathy.

Peripheral neuropathy due to thiamine deficiency often presents with sensory symptoms, particularly burning feet, lancinating pain, and paresthesias. Sensory loss and weakness are distally predominant. Extraocular muscle weakness may also be seen secondary to coexistent Wernicke's disease. The progression may be acute in up to half of patients, subacute, or chronic. EDX studies are consistent with an axonal sensory-motor polyneuropathy that is distally predominant.

The evaluation for thiamine deficiency is best assessed with measurements of thiamine in whole blood or erythrocytes. Assays of serum thiamine have a low sensitivity, because only a small fraction of blood thiamine is found in serum. Measurement of thiamine diphosphonate in whole blood is the most sensitive and specific method for determining the status of thiamine in the body.

When there is a high likelihood of thiamine deficiency, supplemental thiamine is usually given intravenously at a dose of 100 mg/day before glucose for several days. This can be given intramuscularly for up to 2 weeks and then oral supplementation with 50 mg daily. Neurologic improvement is variable with regard to the neuropathy. If there is severe neuropathy before treatment is initiated, permanent distal deficits are likely.

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**Vitamin B$_6$ Excess or Deficiency**

Vitamin B$_6$ (pyridoxine)-related neuropathy is seen most often when this vitamin is taken in excess. The neuropathy that results from excessive dietary intake of pyridoxine produces a sensory neuropathy that evolves into an irreversible sensory neuropathy as the disease progresses. On occasion, pyridoxine deficiency can result in polyneuropathy as well.

Pyridoxine deficiency is seen most often in patients taking medications that produce this deficiency. This may be seen with use of the antituberculosis drug isoniazid or the antihypertensive hydralazine. B$_{6}$ deficiency may also be seen in the setting of chronic alcoholism and the resultant malnutrition. Vitamin B$_{6}$ is found in a wide variety of sources, including enriched grains, chicken, fruits, and vegetables.

The neuropathy, as with most nutritional deficiencies, is a sensory predominant, distal polyneuropathy. A diagnosis of vitamin B$_{6}$ deficiency can be made via an assay of vitamin B$_{6}$ in the blood. Supplemental vitamin B$_{6}$ at a dose of 50-100 mg/day is sufficient for those treated with isoniazid and hydralazine, as well as those with a dietary deficiency. Doses at or above 200 mg/day of vitamin B$_{6}$ should be avoided, since this can exert a direct neurotoxic effect itself.

**Postbariatric Surgery**

Polyneuropathy is a frequent complication of bariatric surgery for morbid obesity. Approximately 15% of patients undergoing bariatric surgery develop polyneuropathy. This usually occurs in the setting of rapid and substantial weight loss, usually in the 6 months following the procedure. Risk factors that increase the likelihood of developing neuropathy include the rate and absolute amount of weight loss, prolonged gastrointestinal symptoms (particularly protracted vomiting), not attending a nutritional clinic following surgery, and postoperative surgical complications requiring hospitalization (see Table 2).

<table>
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<th>Table 2 Risk factors for the development of neuropathy after bariatric surgery$^{21}$</th>
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<td>Rate and absolute amount of weight loss</td>
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<td>Prolonged gastrointestinal symptoms postoperatively, particularly prolonged vomiting</td>
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<tr>
<td>Not attending a nutritional clinic following surgery</td>
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<td>Postoperative surgical complications requiring hospitalization</td>
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The majority of patients develop a distal polyneuropathy with subacute sensory loss and weakness. Neuropathic pain may or may not be prominent. The severity varies from mild to severe with quadripariesis. An acute radiculoplexus neuropathy may occur in up to 5% of patients who develop neuropathy after bariatric surgery. This form is rapid in onset. The electrophysiologic features are that of a sensory–motor axonal neuropathy. Sural nerve biopsy shows prominent axonal degeneration.
CONCLUSION

The pathogenesis of these neuropathies is uncertain.\textsuperscript{18,21} In some patients, one or more vitamin deficiencies can be identified. Thiamine deficiency is not uniformly reported. In most cases, no specific deficiency can be identified. There is some data that this neuropathy may be prevented in part by nutritional counseling before bariatric surgery.\textsuperscript{22} Once the neuropathy has developed, management consists of parenteral nutrition and vitamin supplementation. Patients who have intractable vomiting after surgery should also receive parenteral nutrition and vitamin supplementation. Depending on the severity of neuropathy before treatment is initiated, permanent sensory and motor deficits may occur.

REFERENCES