Peripheral Neuropathy Due to Vitamin Deficiency, Toxins, and Medications

Nathan P. Staff, MD, PhD; Anthony J. Windebank, MD, FAAN

ABSTRACT

Purpose of Review: Peripheral neuropathies secondary to vitamin deficiencies, medications, or toxins are frequently considered but can be difficult to definitively diagnose. Accurate diagnosis is important since these conditions are often treatable and preventable. This article reviews the key features of different types of neuropathies caused by these etiologies and provides a comprehensive list of specific agents that must be kept in mind.

Recent Findings: While most agents that cause peripheral neuropathy have been known for years, newly developed medications that cause peripheral neuropathy are discussed.

Summary: Peripheral nerves are susceptible to damage by a wide array of toxins, medications, and vitamin deficiencies. It is important to consider these etiologies when approaching patients with a variety of neuropathic presentations; additionally, etiologic clues may be provided by other systemic symptoms. While length-dependent sensorimotor axonal peripheral neuropathy is the most common presentation, several examples present in a subacute severe fashion, mimicking Guillain-Barré syndrome.

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Address correspondence to Dr Nathan P. Staff, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, *staff.nathan@mayo.edu*.

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INTRODUCTION

Toxins, medication side effects, and vitamin deficiencies frequently damage the peripheral nervous system. This susceptibility is likely a result of the metabolic demands of a neuron whose cell body and distal axon can be several feet apart. While the peripheral nervous system may be the primary organ system affected in these conditions, peripheral neuropathy often occurs within a multisystem constellation of dysfunction (**Table 7-1**). Knowledge of the syndromic presentations can facilitate prompt, accurate diagnosis and subsequent treatments.

As with most types of peripheral neuropathies, acquiring a detailed history is crucial to the diagnosis of neuropathies caused by toxic agents and vitamin deficiencies. Careful attention must be paid to occupational and home exposures. In particular, asking about recent changes in exposures may provide useful information, as many of the toxic exposures result from new day-to-day habits. While most forms of malnutrition no longer plague developed societies, a history of gastric surgery, chronic malabsorption, or alcoholism may predict the presence of vitamin deficiencies. It is important to take a complete review of systems to determine whether a multisystem syndrome is present as this may lead to a correct diagnosis.

It is also important to recognize that other causes of neuropathy may

KEY POINTS

- Acquiring a detailed history is crucial to diagnosis of neuropathies caused by toxic agents and vitamin deficiencies.
- In a neuropathy with significant asymmetry, polyradicular, or mononeuritis multiplex presentation, other etiologies should be explored further, even in the setting of documented toxicity or vitamin deficiency.

TABLE 7-1 Other Systems Involvement That May Provide Clues to Etiology of a Peripheral Neuropathy Due to Toxicity or Vitamin Deficiency

System Involvement	Toxicity or Deficiency
Central nervous system	
Cognitive	Vitamin B_{12} deficiency, niacin deficiency (pellagra), thiamine (vitamin B_1) deficiency (Wernicke-Korsakoff syndrome), lead toxicity, arsenic toxicity, mercury toxicity, disulfiram toxicity
Cerebellum	Vitamin E deficiency, mercury toxicity
Corticospinal	Vitamin B_{12} deficiency, copper deficiency
Posterior column	Vitamin B_{12} deficiency, copper deficiency
Integument	
Skin	Thiamine deficiency (beriberi), lead toxicity, arsenic toxicity (alopecia), thallium toxicity (alopecia)
Nails	Arsenic toxicity (Mees lines), thallium toxicity (Mees lines)
Musculoskeletal	
Muscle	Vitamin E deficiency (myopathy)
Gastrointestinal	
Intestinal	Vitamin E deficiency, lead toxicity, arsenic toxicity, thallium toxicity
Liver	Vitamin E deficiency, arsenic toxicity
Cardiovascular	
Cardiac	Thiamine deficiency (wet beriberi)
Renal	
Kidneys	Mercury toxicity
Hematologic	
Anemia	Vitamin B_{12} deficiency, copper deficiency, lead toxicity
Pancytopenia	Arsenic toxicity

mimic what is suspected to arise from a toxic source or a vitamin deficiency. For example, a patient with more sensory loss on examination than expected from considering his or her history, combined with high arches and hammertoes, may reflect a long-standing hereditary neuropathy that has finally become symptomatic (especially in the setting of a positive family history of neuropathy). Most toxic and vitamin deficiency–related neuropathies present in a length-dependent fashion with axonal pathology (apart from some notable exceptions detailed below). Therefore, in a neuropathy with significant asymmetry, polyradicular, or mononeuritis multiplex presentation, other etiologies should be explored further, even in the setting of documented toxicity or vitamin deficiency.

NUTRITIONAL DEFICIENCIES

Vitamin B_{12}

Causes of vitamin B_{12} deficiency can be organized by where the absorption defect occurs. A diet containing

minimal animal products provides sufficient vitamin B_{12}, so severe deficiency due to poor intake occurs only in the case of strict veganism. Within the stomach there are several etiologies that degrade the ability of vitamin B_{12} to bind with intrinsic factor, including pernicious anemia, atrophic gastritis, prolonged antacid use (proton-pump inhibitor or H2-antagonists),[1] and gastric bypass. The final absorption of vitamin B_{12} in the terminal ileum may be interrupted by Crohn disease or surgical resection.[2] The main pathology of vitamin B_{12} deficiency is subacute combined degeneration within the spinal cord with loss of both corticospinal tracts and posterior columns with a concomitant axonal sensorimotor peripheral neuropathy. It is important to note that because of the involvement of the cervical spinal cord early in disease, sensory symptoms in both hands and feet may present simultaneously and provide a clue to etiology.[3]

On examination, the patient will exhibit signs of both upper and lower motor neuron dysfunction (sometimes appearing as decreased reflexes with a Babinski sign). Vitamin B_{12} deficiency is also associated with cognitive dysfunction. Megaloblastic anemia may be present as well, owing to the importance of vitamin B_{12} in DNA synthesis.

Testing to confirm vitamin B_{12} deficiency should include both serum vitamin B_{12} and methylmalonic acid, which is a more accurate marker of cellular vitamin B_{12} levels and may be abnormal in the setting of low-normal vitamin B_{12} levels. Elevated levels of gastrin and intrinsic factor antibodies can also establish the diagnosis of pernicious anemia. Supplementation for vitamin B_{12} deficiency should be provided parenterally since poor oral absorption is usually the cause of the disease. Supplementation with vitamin B_{12} typically halts progression of the disease, but does not reverse it since much of the disability is secondary to the spinal cord pathology. Supplementation recommendations for vitamin B_{12} and other vitamin deficiencies are outlined in **Table 7-2**.

Copper

Acquired copper deficiency may look very clinically similar to vitamin B_{12} deficiency and should be investigated in parallel with patients presenting with a myeloneuropathy.[4] Copper is absorbed in the stomach and small bowel, and gastric surgery has been associated with copper deficiency. Additionally, copper absorption is competitive with zinc absorption and reports have shown an association between use of zinc supplementation and presence of copper deficiency (**Case 7-1**). Therefore, it is useful to test both copper and zinc when this condition is suspected. Anemia is also a common complication of copper deficiency.

The treatment strategy for copper deficiency is to combine copper supplementation with identifying and removing excess zinc intake.[5] The goal is to halt progression of the myeloneuropathy as reversibility may be limited.

Vitamin E

While the primary neurologic deficit in vitamin E deficiency is a spinocerebellar syndrome, there is often a concomitant large fiber sensory-predominant axonal peripheral neuropathy. Vitamin E deficiency occurs in the setting of severe fat malabsorption (eg, biliary dysfunction, cystic fibrosis) or genetic disorders (eg, ataxia with vitamin E deficiency or abetalipoproteinemia). Strategies to treat vitamin E deficiency include improving fat absorption and oral vitamin E supplementation.

Vitamin B_6

Vitamin B_6 is unusual in that it is associated with peripheral neuropathy

KEY POINTS

- Causes for vitamin B_{12} deficiency include pernicious anemia, strict veganism, gastric bypass, prolonged antacid use, atrophic gastritis, or diseases of the terminal ileum (eg, resection, Crohn disease).
- Copper deficiency may look very clinically similar to vitamin B_{12} deficiency and should be investigated in parallel in patients with a myeloneuropathy presentation.

TABLE 7-2 Vitamin Supplementation Recommendations in Symptomatic Vitamin Deficiencies

Vitamin	Testing (Confirmatory Testing)	Dosage/Route	Length of Treatment	Comments
Vitamin B_{12}	Serum vitamin B_{12} (methylmalonic acid, [marker of cellular B_{12} deficiency] gastrin, and intrinsic factor antibodies [markers of pernicious anemia])	1 mg Intramuscular/ subcutaneously weekly for 1 month; then monthly	Lifelong unless a reversible cause is identified	Investigate for concomitant folate deficiency
Copper	Serum copper (ceruloplasmin, urine copper)	Elemental copper: 8 mg/d orally for 1 week; 6 mg/d orally for 1 week; 4 mg/d orally for 1 week; 2 mg/d orally thereafter	Lifelong unless a reversible cause is identified	Investigate for zinc excess
Vitamin E	Serum vitamin E	50–200 IU orally daily depending on severity and serum concentration guidance	Lifelong unless a reversible cause is identified	
Vitamin B_6	Vitamin B_6	50 mg/d orally	Only necessary in setting of isoniazid or prolonged hydralazine treatment	High-dose vitamin B_6 supplementation can cause sensory neuropathy or neuronopathy

Case 7-1

A 65-year-old man with no significant past medical history developed progressive gait ataxia over a 3-month period. He had multiple falls without significant injuries. He progressed to requiring a walker for gait stability at the time of his examination. He denied any frank weakness, bowel/bladder difficulties, erectile dysfunction, orthostatism, dry eyes/dry mouth, or cognitive changes. There was no family history of neuromuscular diseases.

On neurologic examination, the patient had normal mentation and cranial nerves. He exhibited mild weakness in toe extensors, but strength was otherwise intact. Tone was normal and no tremor was present. He had decreased sensory perception to light touch, vibration, and joint position sense up to the ankles, and heat-pain sensation was normal. Reflexes were brisk at the knees and reduced at the ankles, and Babinski sign was present bilaterally. There were no abnormalities on finger-to-nose or heel-to-shin testing when allowing visual cues. He exhibited a wide-based gait, but was able to rise on his toes and heels. He was unable to tandem walk and had a positive Romberg sign.

MRI of the cervical spine demonstrated nonenhancing, mild T2 hyperintensity of the dorsal columns from C3 to C6 without any spinal canal stenosis. Nerve conduction study showed reduced amplitudes of lower extremity compound muscle action potentials and absent sural

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sensory nerve action potentials. Conduction velocities, distal latencies, and F waves were normal. On EMG, long-duration motor unit potentials were observed in distal musculature. The study was interpreted as consistent with an axonal sensorimotor peripheral neuropathy.

Laboratory studies were notable for a microcytic anemia, reduced serum copper level, and increased serum zinc level.

On further review of systems, the patient endorsed taking megadoses of zinc supplementation, and was treated with oral supplementation of 2 mg elemental copper daily. His symptoms stabilized, and he noted some functional improvement after intensive physical therapy.

Comment. This case illustrates a copper deficiency myeloneuropathy, which presents in a similar fashion to subacute combined degeneration and may be associated with excessive exogenous zinc supplementation (either through supplements or zinc-containing dental cream). Copper supplementation stabilizes neurologic deficits, but reversibility is minimal.

KEY POINTS

- Vitamin B_6 is unusual in that it is associated with peripheral neuropathy either when deficient or in excess.
- Neuropathy due to thiamine deficiency has many presentations, including length-dependent sensorimotor, cranial nerve, and motor-predominant polyneuropathy, all of which may precede cognitive and systemic symptoms.

either when deficient or in excess. Vitamin B_6 deficiency-related peripheral neuropathy primary occurs in the setting of isoniazid treatment for tuberculosis, which can be prevented with concurrent supplementation with vitamin B_6. Excess of vitamin B_6 can lead to a sensory neuropathy or neuronopathy, which most obviously occurs with megadoses of vitamin B_6 (greater than 2 g/d), but has also been reported in patients taking lower doses (50 mg/d) over long periods.[6] Since many patients with neuropathy take B-vitamin supplementation, it is worthwhile to ensure they are not taking high doses of vitamin B_6 and worsening their disease.

Vitamin B_1 (Thiamine)

A progressive axonal sensorimotor peripheral neuropathy due to vitamin B_1 (thiamine) deficiency is a part of beriberi syndrome. Atrophic skin changes are also commonly present. The neuropathic presentation of thiamine deficiency is quite varied and may precede the systemic and cognitive symptoms. When thiamine deficiency occurs due to strict malnutrition, there is often involvement of cranial nerves (tongue, facial, and laryngeal weakness), but progressive motor-predominant neuropathy mimicking Guillain-Barré syndrome has also been reported.[7] Classic beriberi is very rare in developed countries, where it is often precipitated by gastrectomy; however, neuropathy occurring in severe alcoholics often shares qualities with beriberi (see discussion below). Finally, Wernicke-Korsakoff syndrome in alcoholics is due to thiamine deficiency, and administration of parenteral thiamine supplementation prior to glucose-containing IV solutions can help prevent onset of this condition.

TOXIC NEUROPATHIES

Alcohol

Alcoholism is one of the most common associations with the development of a progressive axonal sensorimotor peripheral neuropathy. In 2012, 6.5% of Americans age 12 or older self-reported to having five or more drinks on each of 5 or more days in the past 30 days.[8] Therefore, it is very important to take a careful history of alcohol use in all patients presenting with neuropathy. Underreporting of alcohol consumption is very common, and approaching this questioning in a nonjudgmental fashion is key. If alcoholism is suspected, it is helpful to have early involvement of trained chemical dependency personnel.

KEY POINTS

- It has been difficult to determine whether alcohol directly causes neuropathy or if its association with neuropathy is due more to chronic malnutrition and vitamin deficiencies in alcoholics.
- Intoxication from arsenic or thallium is preceded by severe gastrointestinal illness, and the neuropathy may mimic Guillain-Barré syndrome.

Because alcoholism is common and often has associated malnutrition, it has been difficult to epidemiologically determine whether this association is a direct toxic effect of alcohol,[9] a secondary effect of chronic malnutrition and multiple vitamin deficiencies,[10] or both. Treatment of alcoholism-associated peripheral neuropathy requires abstinence and a return to a well-balanced diet, which thus treats both possible etiologies. Furthermore, given that alcohol is a known neurotoxin in laboratory studies,[11] it is appropriate to counsel any patient with an established peripheral neuropathy, regardless of etiology, on the moderation of alcohol intake. For further information on the neuromuscular complications of alcohol, refer to the article "Neurologic Complications of Alcoholism" by James M. Noble, MD, and Louis H. Weimer, MD, FAAN, in the June 2014 issue of CONTINUUM.

Renal Failure

Chronic renal failure has long been associated with a length-dependent axonal sensorimotor peripheral neuropathy. Referred to as uremic neuropathy, this condition occurs irrespective of the cause of renal failure (eg, diabetes mellitus, glomerulonephritis), and increasing evidence suggests that chronic hyperkalemia may play a role in the development of this neuropathy.[12] The pathologic features of uremic neuropathy on nerve biopsy are distinctive, and the characteristic axonal atrophy and secondary segmental demyelination are not associated with underlying conditions that cause renal failure.[13] Fortunately, the more severe forms of this condition are rare today, presumably due to early and aggressive dialysis and kidney transplantation. Because of the current rarity of this condition, it is important that other causes of neuropathy be explored in the setting of a patient with neuropathy on chronic dialysis.

Heavy Metals

Exposure to several metals has been shown to cause peripheral neuropathy and may be discovered on laboratory testing of a 24-hour urine sample.[14] Lead neurotoxicity may present as a combination of motor-predominant peripheral neuropathy (classically described as wrist-drop) and encephalopathy. There is often concomitant systemic disease, including constipation (likely secondary to autonomic nerve involvement) and microcytic anemia. Fortunately, the incidence of overt lead toxicity with peripheral neuropathy has substantially declined with changes in lead mining practices and decreased human exposure to the major sources in the environment, such as lead-based paint and lead supplements in gasoline. In cases of lead-induced peripheral neuropathy, chelation therapy should be used.[15]

Inorganic arsenic neurotoxicity may occur from well water contamination, accidental exposure to industrial or agricultural agents, or in the setting of homicidal/suicidal intent. This is to be distinguished from the non-neurotoxic organic arsenic found in some fish and crustaceans, which is often found on urine heavy metal screening. Arsenic neurotoxicity from acute poisoning often occurs 1 to 2 weeks after a severe acute systemic syndrome characterized by nausea, vomiting, and diarrhea. The neuropathy often starts as a length-dependent sensory-predominant painful neuropathy, but in severe forms it may progress to a diffuse sensorimotor polyradiculoneuropathy mimicking Guillain-Barré syndrome (**Case 7-2**).[16] Chronic arsenic exposure can cause an indolent sensory-predominant peripheral neuropathy. Nerve conduction studies in both settings are characterized by slowed conduction velocities. While 24-hour urine sampling will reveal chronic arsenic poisoning, it

Case 7-2

A 47-year-old woman was transferred to a tertiary medical center for progressive weakness and sensory loss. She was initially hospitalized with severe nausea, vomiting, and dehydration requiring intensive care unit–level treatment. During her recovery from gastrointestinal illness, she began to develop ascending sensory loss and weakness. She was diagnosed with Guillain-Barré syndrome and given a 5-day course of IV immunoglobulin. Unfortunately, she continued to progress and was transferred for further workup and treatment. She had a history of irritable bowel syndrome and reported some baseline numbness in her toes, but otherwise had been healthy. There was no family history of neuromuscular diseases.

Examination was notable for moderate-to-severe length-dependent weakness, multimodal sensory loss, and areflexia. Extensive blood work and CSF analysis was normal (at 3 weeks out from her original illness). Nerve conduction studies and EMG showed a severe length-dependent axonal peripheral neuropathy. Twenty-four-hour urine heavy metals showed detectable levels of arsenic, but were within normal limits. Due to clinical suspicion, hair samples were sent for testing for inorganic arsenic levels, which were found to be very elevated.

Comment. Arsenic neurotoxicity may mimic Guillain-Barré syndrome and is usually associated with severe gastrointestinal symptoms. Urine levels may be normal if tested weeks after acute poisoning, therefore, hair or nail samples may be required for diagnosis when there is clinical suspicion. While cases of arsenic neurotoxicity secondary to groundwater occur, intentional poisoning should be considered when making a diagnosis.

may not disclose late effects of single or repeated exposures, in which case, it is important to sample hair and nails for arsenic levels.

Thallium was previously used in pesticides and rodenticides, but this has been removed in most Western countries, which, fortunately, has dramatically decreased the frequency of poisoning. Thallium poisoning begins with a severe gastrointestinal illness. In surviving patients, a painful sensory followed by motor neuropathy mimicking Guillain-Barré syndrome occurs within 1 to 2 days, similar to that seen in arsenic poisoning.[17] Of note, alopecia, which is a hallmark of thallium intoxication, usually does not occur until 2 to 3 weeks after intoxication. Prussian blue is approved as an oral agent to prevent absorption of thallium.[15]

The main sources of mercury poisoning come from contaminated fish (organic mercury), industrial mercury salts (inorganic mercury), and vaporized metallic mercury. Organic mercury affects the dorsal root and trigeminal ganglia, causing paresthesia, often before causing widespread CNS dysfunction. Inorganic mercury poisoning primarily causes renal disease, but psychiatric manifestations also commonly occur (eg, *Alice in Wonderland*'s Mad Hatter was exposed to inorganic mercury in the production of felt hats). Chelation therapy with British anti-Lewisite (BAL) or penicillamine should be tried in patients with nervous system involvement.[15]

Industrial Agents

Peripheral neuropathy arising from exposure to industrial agents is uncommon in developed worlds,[18] primarily due to the restricted (or banned) use of these agents once clear neurotoxicity is

KEY POINT

- Toxic exposure from industrial agents may be more likely to occur in people using these agents for personal use or in small businesses.

established. Where these agents are still used in industrial processes, strict exposure precautions have also reduced the incidence of neurotoxicity. A careful history is warranted as exposure to organic solvents (eg, diketone degreasing agents used in engine shops) is now more commonly encountered in the setting of either personal use or within small businesses that are less carefully regulated than larger industries. **Table 7-3** delineates the neuropathies secondary to industrial agents.

Medications

Many drugs within a variety of medication classes are associated with peripheral neuropathy. It is important to note that before discontinuing a medication thought to be causing a neuropathy, the patient should discuss the need for the medication and reasonable alternatives with the prescriber. Often, the need for the medication may outweigh the desire to stop it (especially if the association with the neuropathy is in doubt). A list of medications most

TABLE 7-3 Occupational Exposures of Specific Toxins

Toxin	Common Exposure	Neuropathy Phenotype	Prognosis
Acrylamide (monomer, not polymerized form)	Industrial (skin)	Length-dependent sensorimotor peripheral neuropathy (PN), acral hyperhidrosis, dermatitis, ataxia, axonal PN	Removal of exposure results in near-complete reversibility of neurotoxicity
Allyl chloride	Industrial (inhalation)	Length-dependent sensorimotor PN, axonal PN	Removal of exposure results in near-complete reversibility of neurotoxicity
Carbon disulfide	Industrial (inhalation)	Length-dependent sensorimotor PN, axonal PN, encephalopathy (high doses)	Poor recovery
Dimethylaminopropionitrile (DMAPN)	Industrial (inhalation)	Urogenital dysfunction (and sacral sensory loss), length-dependent sensorimotor PN, axonal PN	Good recovery
Ethylene oxide	Industrial (inhalation)	Length-dependent sensorimotor PN, axonal PN, encephalopathy	Good recovery
Hexacarbons (eg. *n*-hexane and methyl *n*-butyl ketone)	Industrial, inhalant abuse	Length-dependent sensorimotor PN, occasionally severe (especially in inhalant abusers), coasting occurs, mixed axonal/demyelinating PN	Good recovery in mild cases and modest recovery in more severe cases
Organophosphates	Industrial, insecticides (eg, skin, inhalation, gastrointestinal)	Occurs 1 to 3 weeks after exposure (after cholinergic syndrome), motor greater than sensory PN, corticospinal tract signs	Good recovery only in very mild cases Poor recovery if myelopathy present

TABLE 7-4 Medications Associated With the Development of Peripheral Neuropathy

Class and Drug	Neuropathy Phenotype	Comments
Anesthetic		
Nitrous oxide	Myeloneuropathy	Causes myeloneuropathy syndrome (including subacute combined degeneration), seen in vitamin B_{12} deficiency, by irreversibly oxidizing cobalamin
Antialcoholism		
Disulfiram	Sensorimotor axonal	
Antiarrhythmic		
Amiodarone	Sensorimotor axonal/ demyelinating	
Procainamide	Sensorimotor demyelinating	Can mimic chronic inflammatory demyelinating polyradiculopathy (CIDP)
Antigout		
Colchicine	Mild sensory-predominant axonal	Myopathy usually more prominent; disrupts microtubules; risk is high in patients with renal disease
Antihypertensive		
Hydralazine	Sensory-predominant axonal	Rare except with prolonged high doses; prevented with pyridoxine treatment
Antimicrobial		
Chloramphenicol	Mild, painful sensory-predominant axonal	
Dapsone	Motor-predominant axonal	May mimic mononeuritis multiplex
Ethambutol	Sensory-predominant axonal	May also cause retrobulbar optic neuropathy
Fluoroquinolones	Sensorimotor axonal	Still controversial as to whether it causes peripheral neuropathy
Metronidazole	Sensory-predominant axonal	May also cause encephalopathy
Nitrofurantoin	Sensorimotor axonal	Can be severe, mimicking Guillain-Barré syndrome; usually occurs in patients with renal impairment

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TABLE 7-4 Medications Associated With the Development of Peripheral Neuropathy *(Continued)*

Class and Drug	Neuropathy Phenotype	Comments
Antineoplastic		
Ado-trastuzumab emtansine	Sensorimotor	Antibody-drug conjugate
Brentuximab vedotin	Sensorimotor	
Epothelones (eg, ixabepilone)	Sensorimotor axonal	
Eribulin mesylate	Sensorimotor axonal	
Etoposide and teniposide	Sensorimotor axonal	
Platinum-based chemotherapy (eg, cisplatin, oxaliplatin, carboplatin)	Sensory axonal/neuronopathy	Cold-induced dysesthesia with oxaliplatin
Proteasome inhibitors (eg, bortezomib, carfilzomib)	Sensory-predominant axonal	Carfilzomib less commonly causes peripheral neuropathy; occasionally mimics mononeuritis multiplex
Suramin	Sensorimotor axonal/ demyelinating	
Taxanes (eg, paclitaxel, docetaxel)	Sensorimotor axonal	
Thalidomide, lenalidomide	Sensory axonal	
Vinca alkaloids (eg, vincristine, vinblastine)	Sensorimotor axonal	
Antiseizure		
Phenytoin	Mild sensorimotor axonal	
Antituberculosis		
Isoniazid	Sensory-predominant axonal	Prevented with pyridoxine treatment
Immunosuppressant		
Chloroquine	Sensorimotor axonal/ demyelinating	Myopathy usually more prominent
Gold salts	Sensorimotor axonal/ demyelinating	
Leflunomide	Painful sensory-predominant axonal neuropathy	
Nucleoside analogue reverse transcriptase inhibitor		
Zalcitabine (ddC), Didanosine (ddI), Stavudine (d4T)	Painful sensory axonal	May have coasting; associated with elevated lactate

prominently associated with the development of peripheral neuropathy is included in Table 7-4; for most of these agents, the incidence of peripheral neuropathy is rare.[19] Medications causing neuropathy that are no longer in general use have been omitted from this table. Because of the common occurrence of peripheral neuropathy as a dose-limiting side effect of certain chemotherapeutic agents, these are discussed in more detail next in this article.

Chemotherapy

Peripheral neuropathy secondary to chemotherapy treatments for cancers affect approximately 30% of patients

receiving one of the neurotoxic agents.[20] Peripheral neuropathy is one of the major dose-limiting toxicities and frequently decreases the amount of chemotherapy available to treat the underlying cancers. While much of the toxicity relates to dose (and is managed by oncologists), growing evidence also argues for contribution of the patient's genetics and type of cancer.[21–23] Therefore, in patients who develop severe neuropathies in the setting of chemotherapy (especially if not in a classic stocking-glove distribution), it is important to rule out other causes of neuropathy. For example, it has been reported that patients with underlying hereditary neuropathies likely develop more severe chemotherapy-induced peripheral neuropathy.[24] Also, there are many reports in the literature about immune-mediated neuropathies in the setting of chemotherapy, which may be a paraneoplastic process or triggered by chemotherapeutic agents.[25] Direct compression or invasion of nerve by the underlying malignancy should be considered as well.

Platinum-based compounds (cisplatin, carboplatin, and oxaliplatin) primarily produce a sensory neuropathy/neuronopathy (**Case 7-3**). Oxaliplatin also has a specific neuropathic syndrome in which patients develop a temporary, but very uncomfortable, cold-induced neuropathic pain

Case 7-3

A 39-year-old man with a history of testicular cancer presented with new-onset numbness and paresthesia in his hands and feet over the past 2 weeks. He denied any weakness or autonomic symptoms. He completed his final course of cisplatin-based chemotherapy 2 weeks prior to the onset of symptoms, but otherwise had been well.

Neurologic examination was notable for reduced perception of all sensory modalities in the hands and feet (up to the ankles) and areflexia.

His symptoms progressed over the next 2 weeks with sensory loss to the knees and forearms with some gait instability. Extensive blood work and CSF analysis was normal. Nerve conduction study was notable for absent sural sensory nerve action potentials and reduced amplitude median and ulnar sensory nerve action potentials with borderline slow conduction velocities.

A diagnosis of cisplatin-induced peripheral neuropathy was made. The patient had continued mild progression over the next month, which then stabilized. He reported modest improvement 1 year later, but was cured from his cancer.

Comment. Cisplatin-induced peripheral neuropathy usually develops within days of infusion, but may present up to 4 weeks after the last dose of cisplatin. Unlike most other types of chemotherapy-induced peripheral neuropathy, which tend to be length-dependent axonal sensorimotor neuropathies, platinum primarily causes a sensory neuronopathy. This likely contributes to the relative lack of reversibility of the neuropathy after cisplatin discontinuation. Additionally, platinum-based chemotherapy-induced peripheral neuropathies are known to develop the ''coasting phenomenon,'' wherein symptoms may progress for months after chemotherapy has stopped. Patients may also experience late progression of symptoms when positive, painful dysesthesia replace previous negative symptoms of loss of feeling. Typically, even though symptoms have worsened, the clinical examination and electrophysiologic changes are stable. These patients may need to be followed to establish that neuropathy due to a different underlying progressive problem is not present.

KEY POINTS

- Newer chemotherapy agents approved over the past several years continue to have frequent side effects of peripheral neuropathy.
- Ingestion of toxic seafood may be associated with peripheral nerve disorders, which often present as a syndrome of gastroenteritis and perioral paresthesia.

in the hands and face. These neuropathic symptoms from oxaliplatin arise from direct interaction with voltage-gated sodium channels leading to altered nerve excitability.[26–28] More generally, the platinum-based compounds are thought to cause neuropathy by binding to nuclear and mitochondrial DNA, leading to apoptosis. Neuropathies from platinum-based compounds are also notorious for progressing for several weeks following medication discontinuation, a phenomenon called coasting.

The microtubule toxins, taxanes and vinca alkaloids, produce a length-dependent sensorimotor peripheral neuropathy, likely by disruption of microtubule-dependent axonal transport. Taxanes (paclitaxel, docetaxel) cause stabilization of microtubules, whereas vinca alkaloids (vincristine, vinblastine) destabilize microtubules.

Newer chemotherapy agents approved by the US Food and Drug Administration over the past several years continue to have a frequent side effect of peripheral neuropathy. The proteasome inhibitor bortezomib, used primarily in multiple myeloma, causes a sensory-predominant axonal neuropathy that is frequently dose-limiting. Carfilzomib, a newer-generation proteasome inhibitor, is reported to produce less peripheral neuropathy than bortezomib.[29] Both brentuximab vedotin (for refractory large cell lymphoma) and ado-trastuzumab emtansine (for *HER2* positive breast cancer) are antibody-drug conjugations where the antibody is cancer specific (anti-CD20 and *HER2*, respectively), but also have a drug that targets microtubules (vedotin and mertansine), which likely cause the associated peripheral neuropathy.[30,31] Likewise, the breast cancer chemotherapeutics ixabepilone and eribulin mesylate, both of which act on microtubules, have been shown to cause a dose-limiting sensory-predominant peripheral neuropathy.[32]

Biological Toxins

There are several toxins produced by biological agents that affect the peripheral nervous system, some of which will be covered in the article ''Infectious Neuropathies'' by Eric L. Logigian, MD, FAAN, and Michael K. Hehir II, MD, in this issue of CONTINUUM.

Ingestion of toxic seafood may be associated with peripheral nerve disorders, often presenting as a syndrome of gastroenteritis and perioral paresthesia. In more severe cases, paresthesia is more widespread with concomitant weakness and occasional cardiovascular collapse. The mechanism of action for all of these toxins is binding of the voltage-gated sodium channel, and symptoms typically resolve within days to months. Ciguatera toxin is produced within dinoflagellate plankton, which then accumulates within fish that consume the plankton up the food chain, which leads to prominent perioral paresthesia, metallic taste, and temperature-related dysesthesia.[33] Saxitoxin and brevetoxin B are also produced by dinoflagellate plankton, which are associated with ''red tides,'' and tend to concentrate in bivalve mollusks and cause more paralysis than ciguatera toxicity.[34] Tetrodotoxin is produced within the puffer fish (fugu) ovaries. It is consumed in Japanese sushi, which must be carefully prepared to avoid the potentially fatal toxin.

In addition to neuropathies caused by Lyme disease (carried by *Ixodes* genus ticks), ticks can produce a ''tick paralysis'' syndrome that usually affects children under 6. The saliva of three female ticks (*Dermacentor andersoni, Dermacentor variabilis,* and *Ixodes holocyclus)* contains a neurotoxin that can lead to a rapidly progressive paralysis, which may include bulbar and respiratory muscles and associated dysautonomia, although sensory systems are spared. Treatment involves

supportive care and removal of the offending tick, which leads to rapid reversal of symptoms.

Ingestion of the fruit from the buckthorn plant (*Karwinskia humbodtiana*), which grows throughout the southwest United States and Mexico, produces a rapidly progressive sensorimotor demyelinating peripheral neuropathy that is very clinically similar to Guillain-Barré syndrome.[35] The neurologic symptoms develop 5 to 20 days after fruit ingestion, which may make diagnosis challenging, especially in small children, who are most commonly affected. Of note, the CSF should remain normal in buckthorn neuropathy, and treatment is supportive with slow recovery over many months.

CONCLUSION

The wide array of deficiencies and toxins that damage the peripheral nervous system highlight its vulnerability, and as illustrated with chemotherapy-induced peripheral neuropathies, even newer agents continue to frequently cause this unwanted problem. While many of these syndromes present as a length-dependent sensorimotor peripheral neuropathy, the more rare presentations with asymmetry and radicular localization require that these peripheral neuropathy causes should be considered in the differential diagnosis of most cases of neuropathy. Fortunately, a thorough history that includes a review of systemic illness, medication changes, and exposures will provide etiological clues in most cases of neuropathy due to vitamin deficiency, toxins, and medications.

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