Overview of polyneuropathy

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Literature review current through: May 2014. | **This topic last updated:** May 12, 2014.

INTRODUCTION AND TERMINOLOGY — The terms "polyneuropathy," "peripheral neuropathy," and "neuropathy" are frequently used interchangeably, but are distinct. Polyneuropathy is a specific term that refers to a generalized, relatively homogeneous process affecting many peripheral nerves, with the distal nerves usually affected most prominently. Peripheral neuropathy is a less precise term that is frequently used synonymously with polyneuropathy, but can also refer to any disorder of the peripheral nervous system including radiculopathies and mononeuropathies. Neuropathy, which again is frequently used synonymously with peripheral neuropathy and/or polyneuropathy, can refer even more generally to disorders of the central and peripheral nervous system.

The polyneuropathies must be distinguished from other diseases of the peripheral nervous system, including the mononeuropathies and mononeuropathy multiplex (multifocal neuropathy), and from some disorders of the central nervous system.

- Mononeuropathy refers to focal involvement of a single nerve, usually due to a local cause such as trauma, compression, or entrapment. Carpal tunnel syndrome is a common example of a mononeuropathy.
- Mononeuropathy multiplex refers to simultaneous or sequential involvement of noncontiguous nerve trunks. Used loosely, this term can refer to multiple compressive mononeuropathies. However, in its more specific meaning, it identifies multiple nerve infarcts due to a systemic vasculitic process that affects the vasa nervorum. (See "Clinical manifestations of vasculitic neuropathy".)
- Diseases of the central nervous system such as a brain tumor, stroke, or spinal cord lesion occasionally present with symptoms that are difficult to distinguish from polyneuropathy. (See "Differential diagnosis of peripheral nerve and muscle disease".)

This topic will review a general approach to polyneuropathy. Specific polyneuropathies are discussed in more detail separately.

EPIDEMIOLOGY — The epidemiologic data on polyneuropathy are relatively limited, in part because the disease is remarkably variable in its severity, etiology, and even pathology within a population. Defining a group with polyneuropathy requires multiple assumptions and restrictive definitions.

In one study, 4191 subjects ages 55 and older from two regions of Italy were screened by their general practitioner for symptoms of possible polyneuropathy [1]. Suggestive symptoms were present in 734, each of whom was subsequently examined by a neurologist for the presence of symptoms associated with bilateral impairment of at least two of the following: strength; sensation; or deep tendon reflexes. Possible (one abnormality) and probable (two abnormalities) polyneuropathy were diagnosed in 307 (7 percent) and 151 (4 percent) patients, respectively. The prevalence of polyneuropathy among patients with no recognized exposure to diseases or neurotoxic agents was 2 percent; among patients with one or two risk factors the prevalence was 12 and 17 percent, respectively. Diabetes mellitus was the most common risk factor, present in 44 percent of the patients with polyneuropathy. The next most common risk factors were alcoholism, non-alcoholic liver disease, and malignancy.

In a population-based study from India, 2 percent of patients interviewed met the criteria for peripheral neuropathy,

but this included patients with polyneuropathy, entrapment neuropathies, and peripheral nerve disorders [2]. A third study from Sicily found that 7 percent of the population responded positively to screening questions for polyneuropathy; diabetic neuropathy was diagnosed in 0.3 percent of the population [3].

More comprehensive data are available regarding the frequency of specific types of polyneuropathy or those with specific causes, such as diabetic polyneuropathy or inflammatory demyelinating polyneuropathy.

- A natural history study following patients with type 2 diabetes mellitus noted a baseline prevalence of polyneuropathy of 8 percent compared with a control population in whom 2 percent of patients were affected [4]. After 10 years, the number of patients who had nerve conduction abnormalities consistent with polyneuropathy reached 42 percent in the diabetic population versus 6 percent in controls. (See "Epidemiology and classification of diabetic neuropathy".)
- In a study of patients with clinical AIDS, 12 percent had evidence of a polyneuropathy, the majority of who were affected with a distal symmetric axonal neuropathy [5]. Inflammatory polyneuropathies, including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and mononeuritis multiplex have also been described, often in patients with more recent onset of HIV infection.
- The prevalence of the Charcot-Marie-Tooth diseases, a group of hereditary polyneuropathies characterized by some common clinical features, varies significantly in different countries, from a low of 8 per 100,000 population in Libya to a high of 41 per 100,000 in Norway [6]. (See "Hereditary primary motor sensory neuropathies, including Charcot-Marie-Tooth disease".)
- Amyloid polyneuropathy, another common inherited polyneuropathy that presents in later life with progressive pain and sensory loss, also has a variable frequency [7,8]. It is especially common in Sweden where the gene prevalence is 1500 per 100,000, although the frequency of the disorder is only 31 per 100,000 [9].
- The prevalence of Guillain-Barré syndrome in most studies ranges from 0.4 to 1.7 per 100,000 population with a relatively even distribution throughout the world [10]. Guillain-Barré syndrome has been linked in some cases to preceding Campylobacter jejuni infection; the incidence may be much higher in areas of the world such as northern China where this is a common pathogen. (See "Pathogenesis of Guillain-Barré syndrome in adults".)
- The prevalence of CIDP, like most axonal polyneuropathies, is not well studied, but is estimated to be 0.8 to 3.6 per 100,000. (See "Chronic inflammatory demyelinating polyneuropathy: Etiology, clinical features, and diagnosis", section on 'Epidemiology'.)

ETIOLOGY AND PATHOGENESIS — Polyneuropathy has a wide variety of causes, ranging from the common, such as diabetes mellitus, alcohol abuse, and HIV infection [11], to the rare, such as some unusual forms of Charcot-Marie-Tooth (CMT) disease. It often occurs as a side effect of medication or as a manifestation of systemic disease. The rate of progression of the polyneuropathy in conjunction with its character (axonal or demyelinating) can help identify its etiology (table 1A-C).

The peripheral nerves are susceptible to a variety of toxic, inflammatory, hereditary, infectious, and parainfectious factors that can impair their health and function, leading to the clinical disorder of polyneuropathy. Unfortunately, there are no simple rules to apply that can reliably distinguish the type of polyneuropathy (eg, demyelinating versus axonal, chronic versus acute, sensory versus motor) produced by these disease categories.

Diabetic — Diabetic polyneuropathy is generally considered predominantly axonal; however, variable degrees of demyelination are often present, at least electrophysiologically. The mechanism underlying the development of diabetic neuropathy is extremely complex and likely relates to inflammatory, metabolic, and ischemic effects. (See "Pathogenesis and prevention of diabetic polyneuropathy".)

Other systemic — Other systemic diseases generally cause predominantly axonal polyneuropathies. Examples of these include the polyneuropathies associated with the following conditions:

- Longstanding human immunodeficiency virus (HIV) infection (see "Epidemiology, clinical manifestations, diagnosis, and treatment of HIV-associated peripheral neuropathy")
- Critical illness (see "Neuromuscular weakness related to critical illness", section on 'Critical illness polyneuropathy')
- Amyloidosis (see "An overview of amyloidosis", section on 'Neurologic abnormalities')
- Hypothyroidism (see "Clinical manifestations of hypothyroidism", section on 'Neurological dysfunction')
- Vitamin deficiencies (see "Overview of water-soluble vitamins" and "Etiology and clinical manifestations of vitamin B12 and folate deficiency", section on 'Neurologic changes')
- Lyme disease (see "Nervous system Lyme disease", section on 'Peripheral nervous system')

However, some important exceptions exist. As an example, polyneuropathy associated with monoclonal gammopathies is often demyelinating.

Autoimmune — Most acute autoimmune neuropathies, namely Guillain-Barré syndrome, are predominantly demyelinating, and a variety of clinical and experimental data have implicated both humoral factors and cell-mediated immune phenomena, which damage myelin and/or the myelin-producing Schwann cells. (See "Pathogenesis of Guillain-Barré syndrome in adults".)

However, axonal forms of this disease also exist. For example, one unusual but well-described variant of Guillain-Barré syndrome is that of acute motor axonal polyneuropathy (AMAN). In this disorder, primary invasion of axons by inflammatory cells has been described [12]. (See "Clinical features and diagnosis of Guillain-Barré syndrome in adults" and "Overview of Guillain-Barré syndrome in children".)

Toxic — Many toxic neuropathies, such as those due to alcohol, chemotherapy exposure, or most heavy metals, produce a predominantly axonal disorder that can be acute, subacute, or chronic, depending on the level and severity of the exposure. Nonetheless, it is incorrect to simply classify all toxic neuropathies as axonal, since many exceptions exist [13]. As an example, n-hexane exposure leads to neuropathy that has a substantial demyelinating component [14].

Hereditary — The most common forms of hereditary neuropathy, namely Charcot-Marie-Tooth types 1A, 1B, and X-linked, are all predominantly demyelinating in nature, although substantial coexistent axonal loss is usually also identified. (See "Hereditary primary motor sensory neuropathies, including Charcot-Marie-Tooth disease".)

Other rare hereditary diseases that cause predominantly demyelinating polyneuropathies include those secondary to metabolic diseases of childhood, such as Krabbe disease, metachromatic leukodystrophy, and adrenoleukodystrophy.

Peripheral neuropathies associated with mitochondrial disorders most often exhibit an axonal pattern, as occurs with Charcot-Marie-Tooth type 2A and the syndrome of neuropathy, ataxia, and retinitis pigmentosa (NARP) [15]. Other mitochondrial disorders are associated with a demyelinating neuropathy, as occurs with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).

Porphyric neuropathy is primarily an axonal motor neuropathy that usually presents in the context of acute neurovisceral attacks, with variable manifestations of neuropathy, abdominal pain, confusion, and other neurologic and systemic symptoms. The acute hepatic porphyrias are inherited disorders caused by partial enzyme deficiencies affecting heme biosynthesis. Neurovisceral attacks are manifestations of four types of hepatic porphyria. The most common of these is acute intermittent porphyria; the others are hereditary coproporphyria, variegate porphyria, and delta-aminolevulinic acid dehydratase porphyria. (See "Clinical manifestations and diagnosis of acute intermittent porphyria" and "Hereditary coproporphyria" and "Variegate porphyria" and "ALA dehydratase porphyria".)

Environmental — Environmental factors can also impact nerve health in substantial ways. Neuropathies

associated with vibration-induced nerve damage, prolonged cold exposure, or hypoxemia [16] have been well described. These disorders are mainly axonal in nature.

Idiopathic — Although population-based data are lacking, no specific cause is identified in up to one-quarter of patients with polyneuropathy at referral centers despite extensive investigations [17-19]. A variety of terms have been employed to describe this disorder, including chronic idiopathic axonal polyneuropathy (CIAP), chronic sensory polyneuropathy, chronic polyneuropathy of undetermined cause, unclassified peripheral neuropathy, and idiopathic neuropathy. Most such cases present in those ≥50 years old and progress slowly over months to years. The symptoms are typically sensory, involving paresthesia, numbness or pain. Electrodiagnostic studies show a primarily axonal polyneuropathy. Proposed but unproven causes include impaired glucose tolerance, hypertension, dyslipidemia, and increased oxidative stress [19].

CLINICAL PRESENTATION — Polyneuropathy is typically characterized by symmetric distal sensory loss, burning, or weakness. Patients with very mild or asymptomatic polyneuropathy occasionally are identified on detailed sensory examination of the lower extremities. Alternatively, a patient may undergo electrodiagnostic testing for an unrelated problem, such as carpal tunnel syndrome, and mild abnormalities suggestive of polyneuropathy are identified. More advanced cases, however, typically present with symptoms suggestive of peripheral nerve disease, which may or may not be supported by findings on physical examination (table 2A-C).

History — The presentation of patients with polyneuropathy varies significantly depending upon the underlying pathophysiology.

- Chronic axonal polyneuropathies (eg, due to diabetes mellitus or uremia) are by far the most common of the polyneuropathies. Injury tends to be related to axon length; thus, longer axons are affected first, resulting in symptoms that begin in the lower extremities. Sensory symptoms usually precede motor symptoms. Patients typically present with slowly progressive sensory loss and dysesthesias such as numbness, a burning sensation and pain in the feet, and mild gait abnormalities. As the syndrome progresses, mild weakness of the lower legs and hand symptoms may begin, resulting in the classic "stocking and glove" distribution of sensory loss. The numbness may continue to extend proximally in severe cases, affecting the intercostal nerves (the next longest nerve fibers after the arms), and causing sensory loss over the sternum. The top of the head may be affected with further progression.

- In acute axonal polyneuropathies, such as that produced by toxic exposures or porphyria, patients may present with similar but much more fulminant symptoms. Pain is often a predominant component, although it can be distinctly absent. The polyneuropathy tends to worsen over two to three weeks, plateau, and then recover over months.

- In patients with acute demyelinating polyneuropathies, primarily Guillain-Barré syndrome (GBS), the presentation is often quite distinct from that of most axonal polyneuropathies. GBS tends to affect predominantly motor nerve fibers; thus, weakness rather than sensory loss typically is one of the earliest signs of the disease. Eventually, however, most patients will complain of some dysesthesias distally in the legs or arms. Gait difficulties or hand clumsiness secondary to reduced proprioception are also common complaints.

- Weakness and generalized sensory loss are often present simultaneously in patients with chronic inflammatory demyelinating polyneuropathy. (See "Chronic inflammatory demyelinating polyneuropathy: Etiology, clinical features, and diagnosis".)

- Patients with hereditary polyneuropathies generally do not complain of positive symptoms such as paresthesias or pain. Often neither patients nor their families appreciate marked neurologic deficits or atrophy since the progression of the disease is slow and insidious [20].

The history is important for distinguishing between polyneuropathy and mononeuropathy multiplex. Occasionally patients with the former will have symptoms that begin in one foot shortly before the other or are more pronounced

in one foot. Mononeuropathy multiplex, in its acute form, usually presents with multiple mononeuropathies with involvement of entirely unrelated nerves, such as the median nerve in the arm and the sciatic nerve in the leg. However, patients may occasionally present with more symmetric sensory and motor symptoms affecting both legs that can be difficult to differentiate on clinical grounds from a severe subacute polyneuropathy. On detailed examination, relative preservation of one nerve (eg, posterior tibial) compared with another (eg, peroneal) may be identified.

Physical examination — Abnormalities on physical examination are similarly dependent upon the type of polyneuropathy (axonal versus demyelinating) and which classes of nerve fibers are most involved (motor versus sensory). Causes of painful sensory polyneuropathy are shown in the table (table 3). In patients with an axonal polyneuropathy, motor examination may disclose wasting of the intrinsic muscles of the feet or lower leg; similar findings are evident in the hands in more severe cases. Distal loss of sensation to pin prick, light touch, vibration, cold, and proprioception may also occur. Reflexes become hypoactive or absent distally, usually at the ankles initially.

In contrast, generalized weakness is the rule in patients with symptoms of a more fulminant polyneuropathy secondary to demyelination. Distal muscles are predominantly affected, although weakness may affect proximal muscles to a greater extent in some individuals. Sensation is also reduced; large myelinated fibers are most damaged, resulting in abnormalities of vibratory testing and proprioception that are often out of proportion to loss of pin prick or temperature sensation. Reflexes are reduced diffusely and are often absent.

Clinical course — Patients with chronic axonal polyneuropathies generally experience a slow progression of disease over a period of years. As examples, in patients with diabetic polyneuropathy or elderly individuals with an idiopathic axonal polyneuropathy, sensory loss will slowly ascend and increase in severity in the legs before the hands become affected. (See "Clinical manifestations and diagnosis of diabetic polyneuropathy".) In patients with axonal polyneuropathy secondary to toxins, such as alcoholic polyneuropathy, exacerbations will follow increasing exposure to the pathogen. When a one-time event has occurred, such as axonal polyneuropathy secondary to critical illness, gradual but incomplete recovery in distal sensation and strength is the rule, often over a period of many months or years.

The course of inflammatory demyelinating polyneuropathy is extremely variable. In patients with Guillain-Barré syndrome, a two- to six-week period of decline is followed by stabilization and eventual improvement over several months; recovery generally depends upon the initial illness severity. (See "Treatment and prognosis of Guillain-Barré syndrome in adults" and "Overview of Guillain-Barré syndrome in children".)

In patients with chronic inflammatory demyelinating polyneuropathy, exacerbations may be followed by periods of stability in some, while in others there is a steady prolonged decline. (See "Chronic inflammatory demyelinating polyneuropathy: Etiology, clinical features, and diagnosis" and "Chronic inflammatory demyelinating polyneuropathy: Treatment and prognosis".)

Patients with congenital demyelinating polyneuropathy, such as Charcot-Marie-Tooth disease, also have a variable course, even between family members with the disease. Some patients may first present in childhood, while others not until they are well into the seventh or eighth decade of life. After presentation, however, a very slow but inevitable progression of symptoms will occur. (See "Hereditary primary motor sensory neuropathies, including Charcot-Marie-Tooth disease".)

DIFFERENTIAL DIAGNOSIS — As previously mentioned, diseases of the central nervous system can be difficult to distinguish from polyneuropathy. As an example, progressive numbness and weakness in the lower extremities may be due to a spinal cord process or polyneuropathy. Furthermore, acute myopathy, neuromuscular junction disease, or a central process may mimic Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy. (See "Differential diagnosis of peripheral nerve and muscle disease".)

DIAGNOSTIC EVALUATION — There are a number of issues to consider when evaluating patients who present with symptoms consistent with polyneuropathy [11,20,21]. Extensive diagnostic testing is probably not necessary

in a patient with mild symptoms who has a known underlying reason (eg, diabetes mellitus or alcohol abuse). On the other hand, a diagnostic evaluation is warranted in patients with no clear etiology or in whom symptoms are severe or rapidly progressive. In addition to the history of the neuropathy itself, the patient should be asked about recent viral illnesses, other systemic symptoms, new medications, exposures to solvents, heavy metals, or other potential toxins, alcohol use, and a family history of neurologic disease.

Diagnostic criteria — A case definition of distal symmetric polyneuropathy has been developed by an expert panel with representatives from the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPM&R) [22]. While the definition was developed primarily for research purposes, it may aid clinicians by providing diagnostic criteria with a relatively high sensitivity and specificity.

The expert panel assessed the diagnostic accuracy of neuropathic symptoms, neurologic signs (decreased or absent ankle reflexes, decreased distal sensation, distal muscle weakness or atrophy), and nerve conduction study (NCS) findings based on evidence from 12 high-quality studies. Diabetic peripheral neuropathy was the focus of most of these studies. The following observations were noted [22]:

- Symptoms alone have a relatively poor diagnostic accuracy. Multiple neuropathic symptoms are more accurate than single symptoms.
- Signs are better predictors of polyneuropathy than symptoms and should be weighted more heavily. A single abnormality on examination is less sensitive than multiple abnormalities. Therefore, an examination for polyneuropathy should look for a combination of signs.
- Abnormal electrodiagnostic studies provide a higher level of specificity to the case definition, but they should not be used alone to make the diagnosis. Abnormal NCS are the most informative part of the electrodiagnostic evaluation.

A set of case definitions was rank ordered by estimated likelihood of distal symmetric polyneuropathy (table 4) [22]. The highest likelihood of polyneuropathy occurred when a combination of multiple symptoms and signs were accompanied by abnormal electrodiagnostic studies. A modest likelihood of polyneuropathy occurred when a combination of multiple symptoms and signs were present but electrodiagnostic studies were not available. A lower likelihood of polyneuropathy occurred when electrodiagnostic studies and signs were discordant.

The expert panel found insufficient evidence to provide an adequate definition for isolated or pure small-fiber polyneuropathy.

Electrodiagnostic testing — We suggest electrodiagnostic testing with electromyography and/or nerve conduction studies (EMG/NCS) as the initial diagnostic procedure for patients with suspected polyneuropathy when there is no clear etiology or when symptoms are severe or rapidly progressive (algorithm 1). (See "Overview of electromyography".)

Electrodiagnostic studies can determine if the disorder is due to a primary nerve (neuropathy) or muscle disorder (myopathy). These tests also can identify whether the patient's symptoms are secondary to a polyneuropathy or another peripheral nerve disorder (eg, polyradiculopathy from lumbar stenosis); if it is a polyneuropathy, EMG/NCS will reveal whether it is axonal or demyelinating in character. The clinical examination alone generally cannot make the latter distinction.

Electrodiagnostic features of demyelinating disorders include:

- Slow nerve conduction velocity
- Dispersion of evoked compound action potentials
- Conduction block (decreased amplitude of muscle compound action potentials on proximal compared with distal nerve stimulation)
- Marked prolongation of distal latencies

In contrast, axonal neuropathies are characterized by a reduced amplitude of evoked compound action potentials with relative preservation of the nerve conduction velocity.

Laboratory tests — We recommend selective use of laboratory tests in patients with polyneuropathy, based upon the history and the results of electrodiagnostic tests (table 5). In practice, this means that most blood tests should be deferred until the results of electromyography and nerve conduction studies testing are known.

One clear distinction that can be made by clinical neurophysiology is whether a neuropathy is due to axon loss or demyelination. As an example, thyroid function studies are unlikely to be useful if the neuropathy has prominent demyelinating features. Thus, instead of obtaining a laboratory "screen" for neuropathy, specific tests should be ordered based upon the pathophysiology of the underlying process (table 5). This approach is more cost-effective and less confusing than ordering multiple unneeded diagnostic tests.

In patients with distal symmetric polyneuropathy who are not initially evaluated with nerve conduction studies, the laboratory tests with the highest yield for detecting abnormalities are blood glucose, serum B12 level with methylmalonic acid (with or without homocysteine), and serum protein electrophoresis (table 5) [23]. This observation does not imply, however, that this screening approach is superior to choosing appropriate blood tests after clinical neurophysiologic evaluation has been performed.

Additional testing for select patients may include lumbar puncture, genetic testing, and muscle or nerve biopsy. As an example, a lumbar puncture is helpful in identifying patients with inflammatory demyelinating polyneuropathies, as most of these disorders have a radicular component which produces a marked increase in spinal fluid protein with minimal elevation in cerebrospinal fluid white cells (albuminocytologic dissociation).

Nerve biopsy — Nerve biopsy is occasionally useful for diagnosing the underlying etiology of polyneuropathy. Nerve biopsy generally is reserved for patients in whom it is difficult to define whether the process is predominantly axonal or demyelinating. Identifying demyelination with associated inflammation in these individuals may help guide treatment (see 'Management' below).

Pathologic study of nerve is sometimes helpful for picking up infiltrative diseases such as amyloid neuropathy [7], infectious diseases such as leprosy, and inflammatory neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP), mononeuropathy multiplex due to vasculitis, and sarcoidosis [24]. Clinically, all of these entities are characterized by some degree of asymmetry or focality. Nerve biopsy is also useful in patients with symptoms that suggest involvement primarily of small fibers (eg, painful polyneuropathies affecting pin and temperature sensation with relatively normal electrophysiology). As previously mentioned, EMG/NCS cannot effectively evaluate these neurons.

Nerve biopsy is of low yield and should generally be avoided in patients with subacute or chronic distal symmetric polyneuropathies. The literature pertaining to this issue is sparse. A systematic review from the AAN, the AANEM, and the AAPM&R found no evidence to support or refute the role of nerve biopsy in the evaluation of distal symmetric polyneuropathy [25].

The sural nerve at the ankle is the preferred site for cutaneous nerve biopsy. Rarely, other nerves including the superficial radial, saphenous, or intermediate cutaneous nerve of the thigh can be biopsied.

Skin biopsy — Epidermal skin biopsy is an especially useful test in the diagnosis of polyneuropathy that predominantly affects small, unmyelinated nerve fibers [26-28]. Typical symptoms of small fiber neuropathy are distal burning, pain, numbness, and paresthesias.

In disorders affecting mainly small, unmyelinated nerve fibers, standard electrophysiologic testing is often normal, and sural nerve biopsy may be normal or only minimally abnormal.

The test is performed by removing a very small piece of skin just proximal to the ankle; the wound is allowed to heal by secondary intention. Special stains are then applied to the skin tissue and the number and morphology of axons within the epidermis evaluated, either by qualitative assessment, or by careful counting to determine intraepidermal

nerve fiber density [29]. These values are compared with age-dependent normal values [30].

A systematic review and practice parameter published in 2009 by the AAN, the AANEM, and the AAPM&R concluded that intraepidermal nerve fiber density determination, using anti-protein gene product 9.5 immunohistochemistry, is a validated and reproducible marker of small fiber sensory neuropathy [25].

Given the relative simplicity of the technique and its ability to provide quantitative data, the test is also likely to be useful in following disease progression or response to treatment.

Autonomic testing — Autonomic testing can be useful for evaluating patients with small fiber sensory neuropathy [25]. The composite autonomic scoring scale (CASS), which includes measurements of orthostatic blood pressure, the quantitative sudomotor axon reflex test, heart rate response to tilt, heart rate variability with deep breathing, and changes in blood pressure with the Valsalva maneuver, appears to provide a useful measure of autonomic function and can help support a diagnosis of small fiber sensory neuropathy [25]. The evaluation of intraepidermal sweat glands is a viable technique to evaluate sudomotor function [31].

Quantitative sensory testing — Quantitative sensory testing measures the degree of sensory loss to various modalities, including temperature and vibration. It is helpful in some patients to identify subtle abnormalities and demonstrate the progression or stability of disease.

MANAGEMENT — There are two separate aspects to the treatment of polyneuropathy: treatment of the underlying disease; and alleviation of symptoms related to the illness.

Treatment of the underlying process — Disease-specific treatment of polyneuropathy obviously depends upon the underlying process. Nevertheless, some generalizations can be made for treating the axonal and demyelinating polyneuropathies.

Axonal polyneuropathies — Reducing exposure to endogenous or exogenous toxins that may be causing the polyneuropathy is the single most important step in treating and preventing the progression of axonal polyneuropathies. As an example, in patients with axonal polyneuropathy secondary to alcohol or drugs, avoidance of the offending agent is extremely important.

In patients with diabetes mellitus, tight control of blood glucose may help maintain nerve function. (See "Treatment of diabetic neuropathy", section on 'Glycemic control for established neuropathy'.)

Similarly, in patients with a polyneuropathy secondary to one of the rheumatic diseases, treatment of the underlying illness is important to at least halt the progression, if not to reverse symptoms. Thyroid replacement typically ameliorates the symptoms of hypothyroid polyneuropathy. (See "Neurologic manifestations of hypothyroidism", section on 'Peripheral neuropathy'.)

Demyelinating polyneuropathies — Unlike axonal polyneuropathy, many treatment options are available for most acquired demyelinating polyneuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP) or Guillain-Barré syndrome (GBS). (See "Chronic inflammatory demyelinating polyneuropathy: Treatment and prognosis" and "Treatment and prognosis of Guillain-Barré syndrome in adults".)

Treatment of the underlying disease is most important in patients with CIDP secondary to a lymphoproliferative disorder such as multiple myeloma or Waldenström's macroglobulinemia. The mainstays of treatment for CIDP are intravenous immune globulin, glucocorticoids, and plasma exchange. These treatments appear to be equally effective. (See "Chronic inflammatory demyelinating polyneuropathy: Treatment and prognosis".)

Some disorders respond better than others; patients with IgG and IgA monoclonal gammopathies of undetermined significance tend to respond better than patients with IgM [32].

Treatment of symptoms and prevention of complications — Gabapentin substantially reduces pain associated with polyneuropathy and is generally well tolerated [33]. Tricyclic antidepressants have been utilized for many years for this condition and are generally considered effective.

Many other medications have also been tried in the treatment of painful polyneuropathy with varying success, including carbamazepine, phenytoin, topiramate, baclofen, mexiletine, and dextromethorphan. Unfortunately, there are no well-executed studies comparing the effectiveness of these drugs for this condition, thereby limiting the ability of practitioners to make evidence- based decisions.

For the treatment of painful diabetic polyneuropathy, measures include glycemic control, antidepressant drugs (eg, amitriptyline, other tricyclics, duloxetine), anticonvulsants (eg, gabapentin, pregabalin), and alpha-lipoic acid. These are discussed in detail separately. (See "Treatment of diabetic neuropathy", section on 'Pain control'.)

One approach for patients who have pain associated with polyneuropathy is to start treatment with gabapentin at a dose of 100 to 300 mg three times a day, and then gradually increase up to a total daily dose of 4000 mg or more as needed, as long as side effects (eg drowsiness, peripheral edema) are not evident. Tricyclic antidepressants (eg, desipramine 10 to 50 mg at night) may also be useful, but are often not as well tolerated as gabapentin.

Treatment with carbamazepine or other anticonvulsants may be helpful if gabapentin and tricyclics are ineffective or poorly tolerated. The use of pregabalin and duloxetine is also a reasonable consideration at this point, regardless of the etiology of the polyneuropathy. Duloxetine has the potential advantage of having antidepressant effects, and thus may be useful in patients with pain and depression.

Topiramate may be especially useful for patients who are obese, since it has the often-beneficial side effects of reduced appetite and weight loss. However, this drug has the prominent untoward effect of drowsiness and cannot be tolerated by many patients.

Simultaneous treatment with drugs such as tramadol, NSAIDs, or low-dose narcotics may be necessary in some patients for occasional "breakthrough pain."

Physical therapy evaluation is important in patients with significant weakness. Appropriate use of ankle-foot orthoses, splints, and walking assistance devices can significantly improve lifestyle in the face of significant disability.

Patients with distal polyneuropathy are at increased risk for developing foot ulcers; proper foot and nail care is especially important in this population. Regular visits to a podiatrist can also help prevent problems. (See "Evaluation of the diabetic foot".)

SUMMARY AND RECOMMENDATIONS

- Polyneuropathy is a specific term that refers to a generalized, relatively homogeneous process affecting many peripheral nerves, with the distal nerves usually affected most prominently. (See 'Introduction and terminology' above.)
- Polyneuropathy has a wide variety of causes, ranging from the common, such as diabetes mellitus, alcohol abuse, and HIV infection, to the rare. It often occurs as a side effect of medication or as a manifestation of systemic disease, but many cases are idiopathic. The rate of progression of the polyneuropathy in conjunction with its character (axonal or demyelinating) can help identify its etiology (table 1A-C).The peripheral nerves are susceptible to a variety of toxic, inflammatory, hereditary, infectious, and parainfectious factors that can impair their health and function, leading to the clinical disorder of polyneuropathy. (See 'Etiology and pathogenesis' above.)
- Polyneuropathy is typically characterized by symmetric distal sensory loss, burning, or weakness. The presentation of patients with polyneuropathy varies significantly depending upon the underlying pathophysiology. Abnormalities on physical examination are similarly dependent upon the type of polyneuropathy (axonal versus demyelinating) and which classes of nerve fibers are most involved (motor versus sensory). (See 'Clinical presentation' above.)
- Electromyography/nerve conduction studies (EMG/NCS) should be the initial diagnostic study in all patients with symptoms and signs of polyneuropathy (algorithm 1). We recommend selective use of laboratory tests in

patients with polyneuropathy, based upon the history and the results of electrodiagnostic tests (table 5). (See 'Diagnostic evaluation' above.)

- There are two separate aspects to the treatment of polyneuropathy: treatment of the underlying disease; and alleviation of symptoms related to the illness. (See 'Management' above.)

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Topic 5284 Version 13.0

GRAPHICS

Polyneuropathy associated with systemic diseases

Systemic disease	Axonal			Demyelinating			Sensory versus motor	Autonomic
	A	SA	C	A	SA	C		
Common								
Diabetes mellitus	-	±	+	-	±	+	S, SM, rarely M	± to +
Critical illness (sepsis)	-	+	±	-	-	-	M > S	-
Carcinoma (late)	-	+	+	-	-	-	S > M	±
Less common								
Uremia	±	+	+	-	-	-	SM	±
Vitamin deficiency (excluding B12)	-	+	+	-	-	-	SM	±
Vitamin B12 deficiency	-	±	+	-	-	-	S	-
Chronic liver disease	-	-	-	-	-	+	S or SM	-
Malabsorption (sprue, celiac disease)	-	±	±	-	-	-	S or SM	±
Carcinoma (sensorimotor)	-	+	+	-	-	-	SM	±
Carcinoma (demyelinating)	-	-	_	+	+	±	SM	-
HIV infection	-	±	+	-	-	-	S >> M	-
Lyme disease	-	±	+	-	-	-	S > M	-
Lymphoma, including Hodgkin's	-	±	+	+	+	±	See above	±
Multiple myeloma, osteosclerotic or solitary plasmacytoma type*	-	-	±	-	±	+	SM	-
Benign monoclonal gammopathy								
IgA	-	±	+	-	-	-	SM	-
IgG	-	±	+	-	-	-	SM	-
IgM	-	-	-	-	±	+	SM or S	-
Rare								
Porphyria (four types)	+	±	-	-	-	-	M or SM	± to +
Hypoglycemia	±	+	±	-	-	-	M	-
Primary biliary cirrhosis	-	±	+	-	-	-	S	-
Primary systemic amyloidosis	-	±	+	-	-	-	SM	+
Hypothyroidism	-	±	+	-	-	-	S	-

Chronic obstructive lung disease	-	±	+	-	-	-	S or SM	-
Acromegaly	-	-	+	-	-	-	S	-
Carcinoma (sensory)	-	+	+	-	-	-	Pure S	-
Polycythemia vera	-	±	+	-	-	-	S	-
Cryoglobulinemia	-	±	+	-	-	-	SM	-

+: usually; ±: sometimes; -: rare if ever; A: acute; SA: subacute; C: chronic; S: sensory; M: motor; SM: sensorimotor.
* Some cases associated with POEMS syndrome.

Modified with data from: Fauci AS, Braunwald E, Isselbacher KJ, et al (Eds). Harrison's Principles of Internal Medicine, 14th ed, McGraw-Hill Company, Inc., New York 1998. p.2460.

Graphic 54853 Version 4.0

Polyneuropathy associated with drugs and environmental toxins

Systemic disease	Axonal			Demyelinating			Sensory versus motor	Autonomic	CNS
	A	SA	C	A	SA	C			
Drugs									
Amiodarone	-	-	+	-	-	+	SM	-	-
Aurothioglucose	±	±	-	+	+	-	SM	-	-
Cisplatin	-	+	+	-	-	-	S	-	-
Dapsone	-	±	+	-	-	-	M	-	-
Disulfiram	±	+	+	-	-	-	SM	-	±
Hydralazine	-	±	+	-	-	-	S > M	-	-
Isoniazid	-	±	+	-	-	-	SM	±	-
Leflunomide	±	±	+	-	-	-	S, or SM	?	?
Linezolid	-	±	+	-	-	-	SM	?	?
Metronidazole	-	-	±	-	-	-	S or SM	-	+
Misonidazole	-	±	+	-	-	-	S or SM	-	+
Nitrofurantoin	-	±	+	-	-	-	SM	-	-
Nucleoside analogues (ddC, ddI, d4T)	±	+	+	-	-	-	S >> M	-	?
Oxaliplatin	+	-	+	-	-	-	S	-	-
Phenytoin	-	-	+	-	-	-	S > M	-	-
Pyridoxine	-	±	+	-	-	-	S	-	-
Suramin	+	+	-	+	+	-	M > S	-	-
Taxol	±	+	±	±	+	±	S > M	-	-
Vincristine	-	+	+	-	-	-	S > M	-	-
Toxins*									
Acrylamide	-	±	+	-	-	-	S > M	±	+
Arsenic	±	+	+	-	-	-	SM	±	±
Diphtheria toxin	-	-	-	+	+	-	SM	-	-
Gamma-Diketone hexacarbons	-	±	+	-	-	+	SM	±	+
Inorganic lead	-	-	+	-	-	-	M > S, or M	-	±
Organophosphates	-	±	+	-	-	-	SM	-	+
Thallium	-	+	+	-	-	-	SM	-	+

+: usually; ±: sometimes; -: rare if ever; A: Acute; SA: Subacute; C: Chronic; S: sensory; M: Motor;

SM: Sensorimotor; CNS: Central nervous system.

* The following drugs and environmental toxins are also neurotoxic, mainly affecting the peripheral nervous system: Drugs - Amitriptyline, chloramphenicol, colchicine, ethambutol, nitrous oxide, perhexiline maleate, sodium cyanate, thalidomide, L-tryptophan. Environmental toxins - Allyl chloride; buckthorn berry, carbon disulfide, dimethylaminopropionitrile (DMAPN), ethylene oxide, metallic mercury, methyl bromide, polychlorinated biphenyls, styrene, trichloroethylene, vacor.

Modified with data from: Asbury, A. Approach to the patient with peripheral neuropathy. In: Harrison's Principles of Internal Medicine, 15th ed, Braunwald, E, Fauci, AS, Isselbacher, KJ, et al (Eds), McGraw-Hill Company, Inc., New York 2001.

Graphic 69751 Version 1.0

Genetically determined neuropathies

Genetic disorder	Basic process	Other features	Other systems involved
CMT type 1	Demyelinating	Hypertrophic change with onion bulbs; severe slowing of conduction velocity in both the motor and sensory nerves	--
CMT type 2	Axonal	Normal or mildly reduced nerve conduction velocity with decreased amplitude	--
Hereditary amyloid polyneuropathies	Axonal	Small-fiber involvement; endoneurial amyloid deposition	In some families: cornea, kidneys, heart
Hereditary sensory neuropathy type I	Neuronopathic	Dorsal root ganglia neurons selectively involved	Sensorineural deafness (some families)
Porphyric neuropathy	Axonal	Neuropathy part of attacks; may be recurrent	Widespread cellular abnormality
Hereditary liability to pressure palsy	Demyelinating	Tomaculous changes in myelin	--
Fabry disease	Neuronopathic	Sensory neuropathy, small dorsal root ganglia neurons	Kidney, skin, lung
CMT 1, X-linked	Demyelinating	Heterozygote females have symptoms	--
Adrenomyeloneuropathy	?Axonal	Mild neuropathy, spastic paraparesis, baldness, hypogonadism	Adrenal cortex, cerebral white matter, spinal cord
Hereditary sensory neuropathy type II	Neuronopathic	Dorsal root ganglia neurons selectively involved	--
Déjérine-Sottas syndrome	Demyelinating	Hypertrophic change with onion bulb formation	May be mentally retarded

CMT type 4A	Demyelinating	Hypomyelination	--
Refsum disease	Demyelinating	Hypertrophic change with onion bulb formation	Retinitis pigmentosa, ichthyosis, sensorineural deafness
Ataxia-telangiectasia	Axonal	Neuropathy moderate	Cell nuclear aneuploidy, skin and scleral telangiectasia, cerebellar atrophy, immunopathy
Abetalipoproteinemia	Neuronopathic	Large dorsal root ganglia neurons	Retinitis pigmentosa, acanthocytosis of red blood cells
Giant axonal neuropathy	Axonal	Massive segmented accumulation of neurofilaments in axons	Slowly progressive encephalopathy with Rosenthal fibers
Metachromatic leukodystrophy	Demyelinating	Schwannopathy with cerebroside accumulation	Cerebral white matter disease predominates
Friedrich ataxia	Axonal	Spinocerebellar and corticospinal tracts involved; also primary sensory neurons	Cardiomyopathy (usual cause of death)

CMT: Charcot-Marie-Tooth disease

Modified with data from: Fauci AS, Braunwald E, Isselbacher KJ, et al (Eds). Harrison's Principles of Internal Medicine, 14th ed, McGraw-Hill Company, Inc., New York, 1998, p.2460.

Graphic 58391 Version 4.0

Function and peripheral and segmental innervation of muscles: part A

Function	Muscle	Nerve
Plexus cervicalis: C1-C4		
		Cervical nerves
Flexion, extension, rotation and lateral bending of the back	Colli profundi (+ sternocleidomastoideus + trapezius)	C1-C4
Lifting of upper thorax; inspiration	Scaleni	C3-C5
		Phrenic nerve
Inspiration	Diaphragm	C3-C5
Plexus brachialis: C5-T1		
		Anterior thoracic nerve
Adduction and internal rotation of arm and dorsoventral lowering of shoulder	Pectoralis major and minor	C5-T1
		Long thoracic nerve
Fixation of scapula during lifting of arm (anterior movement of shoulder)	Serratus anterior	C5-C7
		Dorsal scapular nerve
Elevation and adduction of scapula toward spinal column	Levator scapulae Rhomboidei	C4-C5
		Suprascapular nerve
Lifting and outward rotation of arm	Supraspinatus	C4-C6
Outward rotation of arm in shoulder joint	Infraspinatus	C4-C6
		Dorsal thoracic nerve
Inward rotation of shoulder joint; adduction from ventral to dorsal; lowering of elevated arm	Latissimus dorsi Teres major Subscapularis	C5-C8 (from dorsal portion of plexus)
		Axillary nerve
Lateral lifting (abduction) of arm up to the horizontal line	Deltoideus	C5-C6

Outward rotation of arm	Teres minor	C4-C5
		Musculocutaneous nerve
Flexion of upper and lower arm and supination of lower arm	Biceps brachii	C5-C6
Elevation and adduction of arm	Coracobrachialis	C5-C7
Flexion of lower arm	Brachialis	C5-C6
		Median nerve
Flexion and radial deviation of hand	Flexor carpi radialis	C6-C7
Pronation of lower arm	Pronator teres	C6-C7
Flexion of hand	Palmaris longus	C7-T1
Flexion of fingers II-V in middle phalanges	Flexor digitorum superficialis	C7-T1
Flexion of end phalanx of the thumb	Flexor pollicis longus	C6-C8
Flexion of end phalanges of index and middle finger	Flexor digitorum profundus (radial portion)	C7-T1

Data from Duus, P. Topical Diagnosis in Neurology, 2nd ed. Thieme Medical Publishers, New York, 1989.

Graphic 73819 Version 1.0

Function and peripheral and segmental innervation of muscles: part B

Function	Muscle	Nerve
Plexus brachialis: C5-T1 (cont'd)		
Abduction of metacarpal I	Abductor pollicis brevis	C7-T1
Flexion of proximal phalanx of thumb	Flexor pollicis brevis	C7-T1
Opposition of metacarpal I	Opponens pollicis brevis	C6-C7
		Median nerve
Flexion of proximal phalanges and extension of other joints	Lumbricales: Index and middle fingers	C8-T1
		Ulnar nerve
Flexion of proximal phalanges and extension of other joints	Lumbricales: Fourth and little fingers	C8-T1
		Ulnar nerve
Flexion and ulnar bending of hand	Flexor carpi ulnaris	C7-T1
Flexion of proximal phalanges of fourth and little fingers	Flexor digitorum profundus (ulnar portion)	C7-T1
Adduction of metacarpal I	Adductor pollicis	C8-T1
Abduction of middle finger	Abductor digiti V	C8-T1
Opposition of little finger	Opponens digiti V	C7-T1
		Ulnar nerve
Flexion of little finger in metacarpo- phalangeal joint	Flexor digiti brevis V	C7-T1
Bending of proximal phalanges; stretching of fingers III, IV, and V in middle and distal joints as well as spreading and closing of these fingers	Interossei palmares and dorsales Lumbricales 3 and 4	C8-T1

		Radial nerve
Extension of elbow	Triceps brachii and M. anconeus	C6-C8
Flexion of elbow	Brachioradialis	C5-C6
Extension and radial abduction of hand	Extensor carpi radialis	C6-C8
Extension of proximal phalanges II-V Extension and dorsoflexion of hand; stretching and spreading of fingers	Extensor digitorum	C6-C8
Extension of proximal phalanx of little finger	Extensor digiti V	C6-C8
Extension and ulnar deviation of hand	Extensor carpi ulnaris	C6-C8
Supination of forearm	Supinator	C5-C7
Abduction of metacarpal I; radial extension of hand	Abductor pollicis longus	C6-C7
Extension of thumb in proximal phalanx	Extensor pollicis brevis	C7-C8
Extension of distal phalanges of thumb	Extensor pollicis longus	C7-C8
Extension of proximal phalanx of index finger	Extensor indicis proprius	C6-C8
		Thoracic nerves
Elevation of ribs; expiration; abdominal compression; anteroflexion and lateroflexion of trunk	Thoracis and abdominalis	T1-L1

Data from Duus, P. Topical Diagnosis in Neurology, 2nd ed. Thieme Medical Publishers, New York, 1989.

Graphic 50878 Version 1.0

Function and peripheral and segmental innervation of muscles: part C

Function	Muscle	Nerve
Plexus lumbalis: T12-L4		
		Femoral nerve
Flexion and outward rotation of hip	Iliopsoas	L1-L3
Flexion and inward rotation of lower leg	Sartorius	L2-L3
Extension of lower leg in knee joint	Quadriceps femoris	L2-L4
		Obturator nerve
Adduction of thigh	Pectineus	L2-L3
	Adductor longus	L2-L3
	Adductor brevis	L2-L4
	Adductor magnus	L3-L4
	Gracilis	L2-L4
Adduction and outward rotation of thigh	Obturatorius externus	L3-L4
Plexus sacralis: L5-S1		
		Superior gluteal nerve
Abduction and inward rotation of thigh	Gluteus medius and minimus	L4-S1
		L4-L5
Flexion of upper leg in hip; abduction and inward rotation	Tensor fasciae latae	L5-S1
Outward rotation of thigh and abduction	Piriformis	
		Inferior gluteal nerve
Extension of thigh in hip	Gluteus maximus	L4-S2
Outward rotation of thigh	Obturatorius internus	L5-S1
	Gemelli	L4-S1
	Quadratus	L4-S1
		Sciatic nerve
Flexion of lower leg	Biceps femoris	L4-S2
	Semitendinosus	L4-S2
	Semimembranosus	L4-S1
		Deep peroneal nerve
Dorsiflexion and supination of foot	Tibialis anterior	L4-L5

Extension of toes and foot	Extensor digitorum longus	L4-S1
Extension of toes II-V	Extensor digitorum brevis	L4-S1
Extension of large toe	Extensor hallucis longus	L4-S1
Extension of large toe	Extensor hallucis brevis	L4-S1
		Superficial peronealnerve
Lifting and pronation of outer portion of foot	Peronei	L5-S1
		Tibial nerve
Plantar flexion of foot in supination	Gastrocnemius Triceps surae Soleus	L5-S2
Supination and plantar flexion of foot	Tibialis posterior	L4-L5
Flexion of distal phalanges of toes II-V (plantar flexion of foot in supination)	Flexor digitorum longus	L5-S2
Flexion of distal phalanx of big toe	Flexor hallucis longus	L5-S2
Flexion of middle phalanges of toes II-V	Flexor digitorum brevis	S1-S3
Spreading, closing, and flexing of proximal phalanges of toes	Plantaris pedis	S1-S3
		Pudendal nerve
Closing of sphincters of bladder and rectum	Perineal and sphincter musculature	S2-S4

Data from Duus, P. Topical Diagnosis in Neurology, 2nd ed. Thieme Medical Publishers, New York, 1989.

Graphic 62629 Version 1.0

Primary types of painful sensory neuropathy

Type	Usual clinical setting
Idiopathic small fiber neuropathy	Prevalence increases with age Normal strength and deep tendon reflexes Normal position and vibration sensation Diminished pin sensation in lower extremities Normal electrodiagnostic testing Diminished sudomotor function Abnormal skin biopsy
Diabetic peripheral neuropathy	History or family history of diabetes Obesity, hypertension Diminished deep tendon reflexes Diminished distal sensation Usually abnormal electrodiagnostic testing Impaired glucose tolerance, impaired fasting glucose, elevated hemoglobin A1C
Hereditary neuropathies	Family history Pes cavus or hammer toe Usually diminished deep tendon reflexes Diminished distal sensation Abnormal electrodiagnostic testing
Neuropathy related to connective tissue disease	History of rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, Sjögren syndrome Diminished deep tendon reflexes Diminished distal sensation Abnormal electrodiagnostic testing Positive for autoimmune antibodies
Vasculitic neuropathy	Known systemic vasculitis (but vasculitic neuropathy may occur in isolation) Multifocal examination findings

	Abnormal electrodiagnostic testing Positive for autoimmune antibodies, hepatitis B or C, cryoglobulins Abnormal nerve biopsy
Neuropathy associated with monoclonal gammopathy	Prevalence increases with age Variable examination findings depending upon mode of presentation (mononeuritis multiplex, distal polyneuropathy, radiculopathy, or plexopathy) Abnormal electrodiagnostic testing Monoclonal gammopathy (often IgM)
Paraneoplastic sensory neuropathy	Tobacco smoking, family history, asbestos exposure Solid tumor cancer (mainly lung) Diminished deep tendon reflexes Diminished distal sensation Abnormal electrodiagnostic testing Anti-Hu antibodies
Familial or acquired amyloid polyneuropathy	Family history or known plasma cell dyscrasia (acquired form) Diminished deep tendon reflexes Sensory loss Autonomic dysfunction (eg, postural hypotension, impotence, bladder dysfunction) Compressive mononeuropathy (mainly carpal tunnel syndrome) Abnormal electrodiagnostic testing Monoclonal gammopathy (acquired form)

NCS: nerve conduction study.

Data from: Mendell JR, Sahenk Z. Clinical practice. Painful sensory neuropathy. N Engl J Med 2003; 348:1243.

Graphic 74991 Version 7.0

Estimated likelihood of distal symmetric polyneuropathy

Neuropathic symptoms	Diminished or absent ankle reflexes*	Diminished distal sensation	Distal muscle weakness or atrophy	Nerve conduction studies	Ordinal likelihood
Yes	Yes	Yes	Yes	Abnormal	4
No	Yes	Yes	Yes	Abnormal	4
Yes	Yes	Yes	No	Abnormal	4
Yes	Yes	No	No	Abnormal	4
Yes	No	Yes	No	Abnormal	4
No	Yes	No	Yes	Abnormal	3
Yes	No	No	No	Abnormal	3
No	No	No	No	Abnormal	2
No	Yes	No	No	Abnormal	2
Yes	Yes	Yes	No	Normal	2
Yes•	No	Yes•	No	Normal•	1
YesΔ	YesΔ	YesΔ	YesΔ	NormalΔ	0

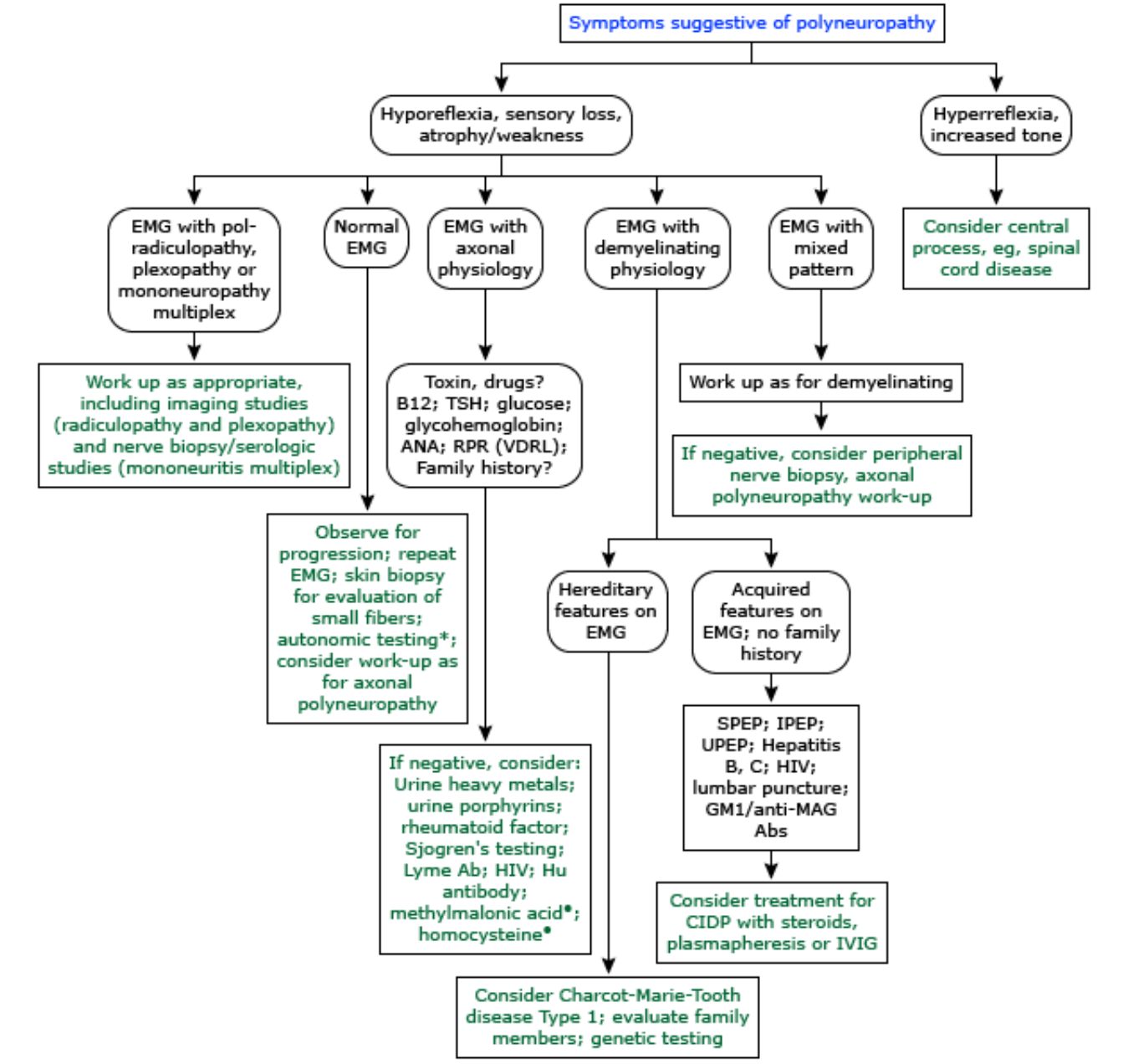
Neuropathic symptoms include numbness, altered sensation, or pain in the feet.

* Note that ankle reflexes may be diminished in normal people who are ≥65 years old.
• This phenotype is observed in small-fiber sensory polyneuropathy. Intraepithelial nerve fiber density determination by skin biopsy may be helpful to confirm the diagnosis.
Δ This phenotype is not a distal symmetric polyneuropathy when nerve conduction studies are normal.

Adapted with permission from: England JD, Gronseth GS, Franklin G, et al. Distal symmetric polyneuropathy: a definition for clinical research: report of the American Academy of Neurology, the American Association of Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2005; 64:199. Copyright © 2005 Lippincott Williams & Wilkins.

Graphic 53720 Version 10.0

Diagnostic approach to polyneuropathy



* Including sympathetic skin response, tilt table, R-R interval testing, valsalva maneuver.
• In patients with borderline normal serum B12.

Graphic 77479 Version 3.0

Diagnostic tests in polyneuropathy

Predominantly axonal pathophysiology
Initial tests:
Serum glucose
Serum protein electrophoresis
Vitamin B12 level
Anti-nuclear antibody
Erythrocyte sedimentation rate
Rapid plasma reagin (RPR)
Glycohemoglobin
Additional testing, if history suggestive:
HIV serology
Urine/blood for heavy metals
Urine/blood for porphyrins
Rheumatoid factor
Sjögren's syndrome testing (Anti-Ro, Anti-La Antibodies)
Lyme testing
Vitamin B1 (thiamine) erythrocyte transketolase activation assay or whole blood level
Methylmalonic acid and homocysteine levels (in patients with borderline low serum B12 levels)
Hepatitis screen (for types B and C)
Predominantly demyelinating pathophysiology
Initial tests:
Serum protein electrophoresis
Immunoelectrophoresis
Urine protein electrophoresis
Hepatitis screen (for types B and C)
Lumbar puncture
Additional testing, if history suggestive:
Antimyelin associated glycoprotein (MAG) testing (in patients with predominantly sensory symptoms)
Anti-GM1 test (in patients with predominantly motor symptoms)
HIV
Genetic testing for Charcot-Marie-Tooth Disease; generally, the electrophysiology is also suggestive of a hereditary condition

Graphic 64055 Version 6.0

Disclosures

Disclosures: **Seward B Rutkove, MD** Nothing to disclose. **Jeremy M Shefner, MD, PhD** Nothing to disclose. **John F Dashe, MD, PhD** Employee of UpToDate, Inc.

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