General Approach to Peripheral Nerve Disorders

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ABSTRACT

Purpose of Review: This article provides a conceptual framework for the evaluation of patients with suspected polyneuropathy to enhance the clinician's ability to localize and confirm peripheral nervous system pathology and, when possible, identify an etiologic diagnosis through use of rational clinical and judicious testing strategies.

Recent Findings: Although these strategies are largely time-honored, recent insights pertaining to the pathophysiology of certain immune-mediated neuropathies and to evolving genetic testing strategies may modify the way that select causes of neuropathy are conceptualized, evaluated, and managed.

Summary: The strategies suggested in this article are intended to facilitate accurate bedside diagnosis in patients with suspected polyneuropathy and allow efficient and judicious use of supplementary testing and application of rational treatment when indicated.

INTRODUCTION

Peripheral neuropathy is a very common problem in neurology practice. Estimates of its incidence and prevalence are variable, undoubtedly based on the population studied, the definition of neuropathy used, and the intensity of the evaluation employed.1–6 In the Netherlands, neuropathy incidence in an adult population approximates 77 per 100,000 person-years.1 Also in the Netherlands, the prevalence of definite neuropathy is estimated at 5.5%, and the prevalence of probable and definite neuropathy combined is estimated at 13.1%, but these are likely underestimated.3 Sensory loss in the feet often goes unrecognized, particularly in those with diabetes mellitus or who are elderly; only 10% to 15% of patients with diabetes mellitus reported to be aware of their neuropathy.1,7 The incidence and prevalence of neuropathy in general, and chronic idiopathic axonal neuropathy in particular, increase with age.1,3 The prevalence of probable or definite polyneuropathy in those who are older than 80 years of age was estimated to exceed 30% in one large population study.3

Lack of consensus in diagnostic criteria and variable terminology add to uncertainty regarding the epidemiology of peripheral neuropathy,8 and variable opinions exist regarding the role of electrodiagnosis in neuropathy determination.6,9 However, it is generally accepted that the minimal standards for diagnosing neuropathy include at least two of the following features: distal symmetric sensory symptoms, distal symmetric sensory loss, and diminished or absent ankle reflexes.6 The commonly used
designations of distal symmetric polyneuropathy, chronic axonal polyneuropathy, or chronic idiopathic axonal polyneuropathy, which have subtle conceptual differences, are generally used synonymously.

The etiologies of peripheral neuropathy are legion, exceeding 200 depending on the classification system used. Identification and assignment of an etiology are influenced by variables that include the population studied, the nature and intensity of the evaluation, and the willingness to assign causation to a laboratory abnormality that may be coincidental. One study reporting a 58% prevalence of test abnormalities in patients with peripheral neuropathy considered only 9% of these abnormalities to be diagnostically significant. To be confident of a causal relationship between a test abnormality and peripheral neuropathy, the clinician should consider the neuropathy pattern and the contextual features in each case, allowing generation of a relevant differential diagnosis aligned with these features. Judicious testing in the proper clinical context reduces the risk of false-positive testing.

As with any diagnostic assessment, the patient should be advised of the risks and benefits involved in the diagnostic workup. Ideally, a treatable disorder is identified; however, diagnosis may be elusive. Following evaluation, 20% to 50% of patients are designated as chronic idiopathic axonal polyneuropathy or chronic axonal polyneuropathy. Although a 2016 study reported that a diagnosis could be achieved in two-thirds of 284 patients with chronic idiopathic axonal neuropathy when reevaluated, over half of these individuals were assigned a diagnosis that should have been apparent on initial evaluation (eg, diabetic neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy [CIDP], the neuropathy of monoclonal gammopathy of undetermined significance).

Patients should be informed that good treatment options do not necessarily follow from a diagnosis, such as hereditary neuropathy, estimated to include as many as one-third of cases. However, informed diagnostic pursuit provides the opportunity for diagnostic closure, education regarding the disorder’s natural history, and counseling germane to the prevention and management of potential future morbidity. In the case of distal sensory polyneuropathy, the patient can be reassured that progression to nonambulation or amputation is uncommon.

ANATOMIC, PHYSIOLOGIC, AND PATHOPHYSIOLOGIC CONSIDERATIONS IN PERIPHERAL NEUROPATHY

Understanding peripheral nerve anatomy and physiology is required for adequate clinical assessment and electrodiagnostic study design. Understanding the pathophysiology of the disorder allows for rational therapeutic strategy and prognostication. In view of their unique anatomic and physiologic properties, peripheral nerves are vulnerable to multiple potential insults.

Axonal Polyneuropathies

The viability of peripheral nerves depends on the metabolic capabilities of anterior horn cells and dorsal root ganglia and effective axon transport. The latter is bidirectional and essential for axonal nutrition and support for the normal turnover of organelles (particularly mitochondria) and proteins (such as microtubules and neurofilaments). Anterograde transport from cell body to neuromuscular...
Disordered axonal transport is thought to be the mechanism underlying the pathophysiology of most toxic and metabolic neuropathies and some hereditary neuropathies.

**Demyelinating Polyneuropathies**

Optimal peripheral nerve function is also dependent on the integrity of the myelin sheath. Peripheral nerve myelin of Schwann cell origin is compacted along the internode, noncompacted at the paranode (allowing for increased surface area of potential pathogenic significance), and absent at the nodes of Ranvier (where ion channels are concentrated). Predominantly demyelinating peripheral neuropathies affecting myelin or Schwann cells may be either acquired or heritable (Table 1-1).19,22,23 Demyelinating neuropathies impair nerve conduction by allowing current leakage through exposed axons where a paucity of ion channels exists, thus impeding action potential propagation.24

Acquired demyelinating neuropathies are thought to be immune mediated through either cellular or humoral mechanisms. Antigenic targets are located in the paranodal or

**TABLE 1-1 Predominantly Demyelinating Polyneuropathies/ Polyradiculoneuropathies**

- Charcot-Marie-Tooth disease type 1
- Charcot-Marie-Tooth disease type 3
- Charcot-Marie-Tooth disease type 4
- Hereditary neuropathy with liability to pressure palsies (HNPP)
- Krabbe disease
- Metachromatic leukodystrophy
- Refsum disease
- Cockayne syndrome
- Acute inflammatory demyelinating polyradiculoneuropathy (AIDP)
- Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
- Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome
- Multifocal motor neuropathy (MMN)
- Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
- Distal acquired demyelinating symmetric neuropathy (DADS)
- Toxins (diphtheria, buckthorn, amiodarone, n-hexane, arsenic)
juxtaparanodal regions of the internode (Figure 1-1). Identifiable autoantibodies in some of these disorders have diagnostic or, in some cases, probable pathogenic relevance. Their presence serves to justify immunomodulating treatment in certain syndromes. Some peripheral nerve antigens associated with well-defined peripheral nerve syndromes are found exclusively in peripheral nerves (e.g., sulfoglucuronyl glycosphingolipid and the distal acquired demyelinating symmetric [DADS] neuropathy associated with IgM monoclonal proteins). Other autoantibodies demonstrate strong correlations between the predominant location of their target antigens and the clinical neuropathy pattern they are associated with. For example, the ceramide content of gangliosides differs between motor and sensory nerves. Autoantibodies directed against GM1, GD1a, and GT1b gangliosides preferentially affect motor nerves and are most commonly found in high titer in motor-predominant neuropathies. Conversely, GD1b autoantibodies preferentially target sensory nerves and are most commonly associated with ataxic neuropathy syndromes. GQ1b autoantibodies, found in the vast majority of patients with Miller Fisher syndrome, are concentrated in the paranodal regions of cranial nerves III, IV, and VI. They have been demonstrated to block nerve conduction and represent the most convincing example of peripheral nerve disease linking an autoantibody with a specific neuropathy syndrome.

The concept that autoantibodies might cause neuropathy is also reinforced by the observation that the blood-nerve barrier is less well established at the nerve roots, dorsal root ganglia, and terminal nerve twigs. This correlates with the pathologic observation that these regions are often preferentially involved in the inflammatoryimmune polyradiculoneuropathies. Additional support for immune-mediated nerve injury comes from the observation that the sera of patients with certain immune-mediated neuropathies (e.g., multifocal motor neuropathy) is disruptive to the blood-nerve barrier. Little or no overlap appears to exist in the molecular targets of autoimmune and hereditary neuropathy. In general, hereditary neuropathies are associated with genes coding for structural myelin

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**KEY POINT**

In some cases, good correlation appears to exist between the anatomic location of peripheral nerve antigenic targets, autoantibodies against these targets, and specific peripheral neuropathy syndromes.

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**FIGURE 1-1** Diagram of a myelinated axon, showing subdivision into sections with different diameters.

proteins, whereas the autoantibodies associated with acquired immune-mediated neuropathies, with the exception of myelin-associated glycoprotein (MAG), typically target gangliosides.19,33

**Nodopathies**

The anatomic classification of neuropathies has been historically divided into disorders of axons or myelin. Now it is recognized that some toxic, immune-mediated, and hereditary disorders target proteins and ion channels in the nodal region.19,36 These disorders have been referred to as nodopathies or channelopathies.26,30,36 The best example is the acute motor axonal neuropathy (AMAN) variant of the Guillain-Barré syndrome. This disorder is characterized by rapid decline of compound muscle action potential (CMAP) amplitudes, suggesting motor axon loss. The rapid resolution of clinical and nerve conduction study changes, however, is not compatible with expected recovery from that mechanism of injury. Conduction block produced by impaired ion channel function unassociated with anatomic myelin or axonal injury provides a more likely explanation for the rapidly reversible conduction failure seen in this disorder. This hypothesis is also consistent with the recognition that AMAN is frequently associated with autoantibodies directed against GM1 and GD1a gangliosides, localized on the nodal axolemma, particularly in the terminal nerve twigs where the blood-nerve barrier is less well established.24,26–36

Like demyelination, nodopathies are not necessarily limited to disrupted conduction and may be associated with subsequent axon loss. Impairment of sodium-calcium pump function is hypothesized to lead to intracellular calcium accumulation contributing to eventual axonal degeneration.24–36 Other neuropathies in which nodal dysfunction is hypothesized to play a role in disease pathogenesis are listed in Table 1-2.36

**CLASSIFICATION AND CAUSES OF POLYNEUROPATHIES**

Classification of peripheral neuropathies is commonly based on the initial location of pathology derived from phenotypic and electrodiagnostic pattern recognition.2,57 Figure 1-2 shows

<table>
<thead>
<tr>
<th>TABLE 1-2 Nodopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>▶ Acute motor axonal variant of Guillain-Barré syndrome</td>
</tr>
<tr>
<td>▶ Guillain-Barré syndrome with autoantibodies associated with nodal antigens</td>
</tr>
<tr>
<td>▶ Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) associated with autoantibodies to nodal antigens</td>
</tr>
<tr>
<td>▶ Miller Fisher syndrome</td>
</tr>
<tr>
<td>▶ Multifocal motor neuropathy (MMN)</td>
</tr>
<tr>
<td>▶ Marine toxins (saxitoxin, ciguatoxin, tetrodotoxin)</td>
</tr>
<tr>
<td>▶ Drugs with ion channel blocking properties (phenytoin) (more electrophysiologic than clinical)</td>
</tr>
<tr>
<td>▶ Possibly critical illness polyneuropathy</td>
</tr>
<tr>
<td>▶ Possibly ischemic monomelic neuropathy</td>
</tr>
<tr>
<td>▶ Possibly thiamine deficiency</td>
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</tbody>
</table>
the prevalence of common categories of neuropathy. Neuropathies that appear to originate in motor or sensory cell bodies are referred to as neuronopathies. These disorders have clinical and electrodiagnostic features that suggest axonal degeneration. Sensory neuronopathies are presumed to result from selective damage to dorsal root ganglia. A significant percentage are considered idiopathic. Recognized etiologies include paraneoplastic, immune-mediated, infectious, toxic, and hereditary causes (Table 1-3).

It has been speculated that the fenestrated nature of dorsal root ganglia capillaries diminishes the blood-nerve barrier, rendering these cells more susceptible to immune-mediated causes. Motor neuronopathies (motor neuron diseases) preferentially target anterior horn cells as a result of a select group of infectious, hereditary, and degenerative conditions (Table 1-4).

Neuropathies, more so than neuronopathies, lend themselves to subclassification. Classification can be based on the primary anatomic target (axon or myelin), neuropathy pattern (length dependent or non-length dependent), or size of peripheral nerve fibers preferentially affected (ie, small or large). These subclassifications are not mutually exclusive. It is common, for example, to describe a neuropathy as a small fiber length-dependent axonopathy. The purpose of subclassification is to limit the differential diagnostic considerations.

The majority of neuropathies have predominantly axonal, symmetric, and length-dependent patterns. Length-dependent peripheral neuropathy is attributed to disordered axonal transport leading to dying back, or centripetal degeneration of the longest axons. The apparent sensory predominance of most length-dependent peripheral neuropathies has led to their designation as distal sensory polyneuropathy. In fact, distal motor involvement of intrinsic foot muscles is often present but difficult to clinically detect.

Small fiber neuropathies are typically considered a subcategory of
painful length-dependent neuropathies, but one-fourth to a one-third may be non-length dependent based upon distribution of symptoms and intraepidermal nerve fiber density assessment.\(^{40-42}\) Despite their characteristic length-dependent clinical pattern, it has been postulated that small fiber neuropathies may represent dorsal root ganglionopathies.\(^{40}\)

Length-dependent presentations may also occur with demyelinating neuropathies, both acquired and inherited.\(^{24,29}\) A notable example of an acquired demyelinating length-dependent neuropathy is the ataxic sensory neuropathy associated with IgM monoclonal proteins related, in many cases, with MAG autoantibodies.\(^{24,29}\) Hereditary length-dependent neuropathies include Charcot-Marie-Tooth disease (CMT) and the hereditary motor neuropathies (also referred to as distal forms of spinal muscular atrophy).\(^{2,19,22,23}\)

Non-length-dependent polyneuropathies include neuronopathies, multifocal neuropathies, polyradiculopathies, and polyradiculoneuropathies.\(^{2,45}\) Multifocal neuropathies commonly result from disorders that

### TABLE 1-3 Sensory Neuronopathies\(^{a}\)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Notable Examples</th>
<th>% of Sensory Neuropathy Patients</th>
<th>% of Patients With the Disease Who Have Sensory Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic</td>
<td>NA</td>
<td>50</td>
<td>NA</td>
</tr>
<tr>
<td>Inflammatory/immune mediated</td>
<td>Sjögren syndrome</td>
<td>5</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic sensory neuronopathy (anti-Hu positive)</td>
<td>Unknown</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Autoimmune hepatitis</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Toxic</td>
<td>Pyridoxine toxicity</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Platin chemotherapy</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Infectious</td>
<td>Herpes zoster</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Epstein-Barr virus</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Human T-cell lymphotrophic virus type 1 (HTLV-1)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Human immunodeficiency virus (HIV)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hereditary/degenerative</td>
<td>Mitochondrial: polymerase (\gamma) (POLG), sensory ataxic neuropathy, dysarthria, and ophthalmoplegia (SANDO)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Cerebellar ataxia, neuronopathy, vestibular ataxia syndrome (CANVAS)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Spinocerebellar degeneration</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Facial-onset sensory and motor neuropathy (FOSMN)</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

\(\text{NA} = \text{not applicable.}\)

\(^{a}\) Data from Gwathney KG, Muscle Nerve.\(^{38}\)
Infarct, inflame, or infiltrate nerves or render them more susceptible to compression (Table 1-5). Diabetes mellitus and vasculitides are common causes.45,46 Most are associated with axon loss and have both motor and sensory characteristics, dependent, in part, on the fiber types within the affected nerve(s). Those with demyelinating characteristics include multifocal motor neuropathy (MMN), multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), hereditary neuropathy with liability to pressure palsies (HNPP), and CMT type X in some cases.2,23,45

Polyradiculopathies are disorders that affect multiple nerve roots. Lumbar spinal stenosis is the most common cause, resulting in mechanical compression of lumbar nerve roots within an anatomically compromised spinal canal. Polyradiculopathies may also result from disorders that inflame or infiltrate meninges and the nerve roots and cranial nerves that traverse them (Table 1-6).

Polyradiculoneuropathies are typically acquired and axonal or demyelinating. Guillain-Barré syndrome (or acute inflammatory demyelinating polyradiculoneuropathy [AIDP]) and CIDP are the most common forms of this neuropathy syndrome (Table 1-7).

### CLINICAL APPROACH

Polyneuropathy is initially suspected based on characteristic symptoms occurring in characteristic patterns. The clinical strategy employed begins with identification of the pattern of involvement, with subsequent consideration of contextual features such as the time course and risk factors, including any indication of other end organ involvement. A differential diagnosis is then generated in consideration of these features and knowledge of the causes of neuropathy known to behave in this manner. Ancillary testing is then applied to confirm or refute these suspicions. The clinical approach to neuropathy should include an assessment of how the neuropathy impacts the patient’s lifestyle, considering both comfort and function. Appreciation of these factors allows rational testing and treatment determination.
Length-dependent Neuropathies

Patients with length-dependent neuropathy patterns with large fiber sensory involvement commonly describe numbness or loss of sensation and liken it to a sense of swelling or feeling as though their socks are balled up under their feet (Case 1-1). Table 1-8 lists common causes of length-dependent polyneuropathy. Mild loss of balance may be described. In very slowly progressive disorders such as hereditary neuropathies, the patient may not be aware of the sensory loss. The greatest proportion of patients with acquired length-dependent polyneuropathy will be characterized as having a distal symmetric polyneuropathy, a near-synonym for chronic idiopathic axonal polyneuropathy, as the former may have identifiable secondary as well as idiopathic etiologies. Approximately one-third of these patients are estimated to have neuropathic pain, suggesting that certain neuropathies have large and small fiber overlap.\(^5\) Motor involvement in length-dependent polyneuropathies may be implicated by intrinsic foot muscle atrophy as clinical detection of intrinsic foot muscle weakness is difficult. In the common axonal forms of length-dependent neuropathy, the ankle muscle stretch reflexes may be diminished or absent depending on severity, but other reflexes are typically initially preserved. A multifocal neuropathy may be mistaken for a length-dependent polyneuropathy if care is not taken to identify the initial focal nature of symptoms before their confluence.

Small Fiber Polyneuropathy

Patients with small fiber neuropathy commonly describe painful dysesthetic

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Electrophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary</td>
<td>Hereditary neuropathy with liability to pressure palsies (HNPP)</td>
<td>Demyelinating</td>
</tr>
<tr>
<td>Ischemic</td>
<td>Systemic vasculitic neuropathy</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>Nonsystemic vasculitic neuropathy</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>Ischemic monomelic neuropathy</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinemia</td>
<td>Axonal</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Multifocal motor neuropathy (MMN)</td>
<td>Demyelinating</td>
</tr>
<tr>
<td></td>
<td>Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)</td>
<td>Demyelinating</td>
</tr>
<tr>
<td></td>
<td>Acute brachial plexopathy (monomelic)</td>
<td>Axonal</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>sarcoidosis</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>amyloidosis</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>neurolymphomatosis</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>leprosy</td>
<td>Axonal</td>
</tr>
<tr>
<td></td>
<td>neurofibromatous</td>
<td>Axonal</td>
</tr>
</tbody>
</table>
sensations, such as burning or localized shooting pains, and may experience signs and symptoms referable to dysautonomia. Diagnostic criteria have been published for small fiber neuropathy, which may be conceptualized as a type of distal symmetric polyneuropathy.\textsuperscript{40,44} Possible small fiber neuropathy is defined by a length-dependent pattern of abnormal painful sensations that occur spontaneously or are provoked by tactile stimuli. Probable small fiber neuropathy requires two additional features: signs attributable to small fiber loss and a normal sural sensory nerve action potential (SNAP). Definite small fiber neuropathy requires either an abnormal intraepidermal nerve fiber density at the ankle or an abnormal thermal response to quantitative sensory testing at the foot.\textsuperscript{40} A pure small fiber neuropathy should have normal large fiber sensation, strength, and muscle stretch reflexes and normal routine nerve conduction studies. Operationally, patients diagnosed with small fiber neuropathy may have concomitant large fiber involvement; examples include diabetes mellitus and amyloidosis.

Not all patients with length-dependent neuropathy have chronic idiopathic axonal neuropathy or

**TABLE 1-6 Some Causes of Polyradiculopathy**

- Structural
  - Spondyloarthropathy
  - Spinal stenosis
- Radiation
- Neoplastic
  - Non-Hodgkin lymphoma
  - Acute leukemia
  - Melanoma
  - Carcinoma
- Infectious
  - Lyme disease
  - Cytomegalovirus
  - Human immunodeficiency virus (HIV)
  - Tuberculosis
  - Herpes zoster
  - Schistosomiasis
- Inflammatory
  - Sarcoïdosis

**TABLE 1-7 Causes of Polyradiculoneuropathy**

- Hereditary
  - Porphyria
- Inflammatory
  - Guillain-Barré syndrome
  - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
  - Polynévropathie, organomegalie, endocrinopathie, monoclonal plasma cell disorder, and skin changes (POEMS) syndrome
- Toxic
  - Arsenic
  - \textit{n}-Hexane
  - Amiodarone
  - Diphtheria
- Metabolic/Ischemic
  - Diabetic radiculoplexus neuropathy
- Idiopathic
  - Idiopathic radiculoplexus neuropathy
small fiber neuropathy. Patients with this pattern and prominent sensory ataxia may have DADS neuropathy or a sensory neuronopathy. Patients with DADS are likely to be globally areflexic, a characteristic of most acquired predominantly demyelinating neuropathies or polyradiculoneuropathies. In patients with a length-dependent pattern with motor predominance, CMT, hereditary motor neuropathies, and distal myopathies should be considered, particularly if symptoms are slowly progressive. Preservation of toe extension relative to foot dorsiflexion is one clue suggesting myopathy as a cause of symmetric footdrop.

**Non-length-dependent Neuropathies**

Non-length-dependent neuropathies (Case 1-2) may be subcategorized as neuronopathies, multifocal neuropathies, polyradiculopathies, and polyradiculoneuropathies.

**Neuronopathies.** Motor neuronopathies typically present as painless progressive weakness and atrophy, often associated with muscle cramping and fasciculations. Both the pattern of weakness and chronologic course are dependent on cause. Hereditary causes commonly result in symmetric patterns of weakness that may be proximally predominant or generalized (as in the

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**Case 1-1**

A 72-year-old woman was evaluated for 2 years of foot numbness. She described this as a sensation of cotton stuffed between her toes that began insidiously and symmetrically with gradual ascent to midfoot level. She denied pain and disability. Her body mass index was 34, and she had mild hypertension, hypercholesterolemia, hypothyroidism, and a recently detected hemoglobin A1c of 5.9. Her medications included low doses of lisinopril, atorvastatin, and levothyroxine.

Examination showed normal strength, including toe flexion and extension. Ankle jerks were present but less active than the knee jerks. She had transient perception of vibration with a 128-Hz tuning fork applied to the great toes; ability to distinguish a pin from a monofilament was diminished distal to the ankles bilaterally. She could balance on one foot momentarily but could not sustain it for 5 seconds.

Her electrodiagnostic testing showed absent mixed plantar responses, reduced amplitudes of the sural and superficial fibular (peroneal) sensory nerve action potentials (SNAPs), and normal motor conduction studies. Needle examination showed fibrillation potentials only in intrinsic foot muscles.

**Comment.** This patient appears to have a length-dependent pattern consistent with chronic idiopathic axonal polyneuropathy. Even with more extensive evaluation, it is unlikely that a cause will be found. Her comorbidities are common and are of uncertain relevance. American Academy of Neurology guidelines suggest judicious testing, counseling the patient regarding the probable benign natural history of this disorder, and recommending strategies she can use to limit risk of future morbidity. These strategies include safety precautions to minimize risk of infection, such as daily inspection of the soles of the feet and avoidance of walking on bare feet to minimize risk of contact with foreign bodies. Night lights, durable medical equipment, and, in bathrooms, nonskid surfaces and grab bars can help to reduce the risk of falls.

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**KEY POINT**

- Newly acquired global areflexia in peripheral neuropathy is frequently associated with a predominantly demyelinating neuropathy.
spinal muscular atrophies) or distally predominant (as in the hereditary motor neuropathies). Infectious and degenerative motor neuronopathies begin focally in most cases. In the latter case, identifying concomitant upper motor neuron findings raises concern for the diagnosis of amyotrophic lateral sclerosis.

Sensory neuronopathies may manifest in a length-dependent pattern, but clues suggesting non-length-dependent features may be identified. Sensory ataxia is a common feature. Sensory symptoms in the hands developing before lower extremity sensory symptoms reach the knee would be atypical of a length-dependent axonal neuropathy and suggest a sensory neuronopathy, demyelinating neuropathy, or, in some cases, multifocal neuropathy. Patches of numbness on the arms, trunk, or scalp superimposed on an otherwise length-dependent pattern of sensory signs and symptoms should also suggest sensory neuronopathy.

In patients whose sensory symptoms begin in the hands, the differential diagnosis should include compressive cervical myelopathy, deficiency of vitamin B12 or copper, and carpal tunnel syndrome superimposed on polyneuropathy.

### TABLE 1-8 Common Causes of Length-dependent Polyneuropathy

<table>
<thead>
<tr>
<th>Category</th>
<th>Notable Examples</th>
<th>Estimated Prevalence of All Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Large fiber sensory predominant</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>Small fiber</td>
<td>10–25% of above</td>
</tr>
<tr>
<td></td>
<td>Impaired glucose tolerance</td>
<td>Unknown</td>
</tr>
<tr>
<td>Chronic idiopathic axonal polyneuropathy</td>
<td>Idiopathic</td>
<td>25–55%</td>
</tr>
<tr>
<td>Small fiber neuropathy</td>
<td>Idiopathic</td>
<td>2%</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Charcot-Marie-Tooth disease (hereditary motor sensory neuropathy), hereditary sensory and autonomic neuropathy, hereditary motor neuropathy</td>
<td>5–33%</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Vitamin B12/other nutritional deficiency, end organ failure/critical illness polyneuropathy</td>
<td>12%</td>
</tr>
<tr>
<td>Toxic</td>
<td>Chemotherapy, industrial/environmental toxins</td>
<td>14%</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Distal acquired demyelinating symmetric neuropathy associated with IgM monoclonal protein</td>
<td>9%</td>
</tr>
</tbody>
</table>

IgM = immunoglobulin M.
Multifocal neuropathies. The multifocal neuropathy pattern is characterized by the asymmetric, often stepwise, development of motor disturbances, sensory disturbances, or both. Multifocal neuropathies are often suspected by detailed history taking and may be more easily identified by EMG than by clinical examination. The differential diagnosis of multifocal neuropathy includes polyradiculopathy and asymmetric forms of polyradiculoneuropathy. Polyradiculopathy may be recognizable because of the segmental nerve pattern of deficits and the higher probability of cranial nerve involvement than in multifocal neuropathies. Polyradiculopathy resulting from lumbosacral spinal stenosis is typically associated with back and leg pain with neurogenic claudication, but a length-dependent pattern of motor and sensory findings evolving from initial asymmetry with limited discomfort may be occasionally seen. Although the majority of the inflammatory demyelinating polyradiculoneuropathies are characterized by symmetric patterns of greater motor deficits than sensory deficits, MADSAM is a notable exception.

**DIAGNOSTIC TESTING STRATEGIES**

Testing practices in peripheral neuropathy vary considerably and are undoubtedly influenced by a number of factors. Electrodiagnostic testing; blood, genetic, and CSF analyses; imaging; and nerve biopsy should be used judiciously as targeted tools. In general, non–length-independent phenotypes, particularly those with the characteristics identified in Table 1-9,
warrant consideration of more extensive testing.\(^2,4,5,47\)

Electrodiagnostic Testing

An American Academy of Neurology (AAN) practice parameter endorses the use of electrodiagnostic testing in patients with suspected neuropathy.\(^8,11,46\) Patients with long-standing symptoms and minimal morbidity do not need electrodiagnostic testing unless results are likely to influence diagnosis and treatment. The routine use of electrodiagnostic testing in the evaluation of patients with suspected neuropathy has recently been both challenged and supported.\(^5,9\) For more information on electrodiagnostic testing, refer to the article “Neurophysiologic Studies in the Evaluation of Polyneuropathy” by John C. Kincaid, MD, FAAN,\(^51\) in this issue of *Continuum*.

The role of needle examination of intrinsic foot muscles in the evaluation of suspected peripheral neuropathy has been debated. Detractors point to discomfort and the possibility of finding denervation potentials in normal individuals. Proponents point out that denervation potentials in normal individuals are rare, foot muscles are the most likely place to find early abnormalities, denervation potentials indicate motor involvement, and examination of foot muscles facilitates definition of length dependency and symmetry.

**Blood and Cerebrospinal Fluid Testing**

AAN guidelines suggest that routine laboratory work include vitamin B\(_12\), methylmalonic acid, and glucose levels and serum protein immunofixation in patients with distal symmetric polyneuropathy patterns (Supplemental Digital Content 1–1; links.lww.com/CONT/A224).\(^11,46\) However, the guidelines also recognize the need for physician judgment in the evaluation of patients with neuropathy based upon the clinical situation, which may justify additional testing.\(^11\) Additional testing should be considered when a patient does not conform to a distal symmetric polyneuropathy or chronic idiopathic axonal polyneuropathy pattern and has clinical or electrodiagnostic features suggesting an alternative cause (Table 1-9). CSF analysis is not routinely recommended in the evaluation of distal symmetric polyneuropathy but should be considered with a polyradiculopathy or polyradiculoneuropathy pattern.\(^11\)

Diabetes mellitus is estimated to be the cause of neuropathy in one-third or more of cases in population-based studies and is widely recognized as the most common cause in developed countries.\(^1,3,5,6\) The prevalence of neuropathy is estimated at 8% at the time of diagnosis with diabetes mellitus, increasing with disease duration to eventually affect as many as two-thirds of individuals with long-standing disease.\(^5\) Of these, 10% to

### TABLE 1-9 Neuropathy Characteristics Suggesting the Need for a More Intensive Evaluation\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Neuropathy Characteristics Suggesting the Need for a More Intensive Evaluation(^a)</th>
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<tbody>
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<td></td>
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<tr>
<td></td>
<td>- Acute to subacute onset</td>
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<td></td>
<td>- Rapid progression</td>
</tr>
<tr>
<td></td>
<td>- Motor predominance</td>
</tr>
<tr>
<td></td>
<td>- Non-length dependence</td>
</tr>
<tr>
<td></td>
<td>- Associated dysautonomia</td>
</tr>
<tr>
<td></td>
<td>- Associated systemic disease</td>
</tr>
</tbody>
</table>

\(^a\) Modified with permission from Watson JC, Dyck PJB, Mayo Clin Proc.\(^7\) © 2015 Mayo Foundation for Medical Education and Research. mayoclinicproceedings.org/article/50025-6196(15)00378-Xipdf.
25% will have a painful variant. However, caution is required, as 10% of patients with diabetes mellitus are estimated to have an alternative or additional etiology for their neuropathy. Fasting blood sugar and hemoglobin A1c level are considered sufficient as screening tools. A 2-hour glucose tolerance test is considered a more sensitive means of detecting glucose intolerance at its earliest stage, potentially relevant in the evaluation of patients with small fiber neuropathy.

The relationship between the prediabetic state and neuropathy remains unsettled. Early in this century, a relationship between neuropathy and impaired glucose tolerance was promoted by multiple observations that the prevalence of neuropathy in individuals with impaired glucose tolerance was essentially double that of control populations, particularly in patients with a small fiber polyneuropathy pattern. More recently, these observations were refuted by a population study that failed to demonstrate an increased prevalence of neuropathy (painful or painless), as assessed by both clinical and electrodiagnostic means, in patients with abnormal glucose metabolism. Of note, determination of neuropathy in this study was based on electrodiagnostic and clinical assessment through the Neuropathy Impairment Score, which may lack sensitivity in the detection of small fiber neuropathy.

Investigations in patients with small fiber polyneuropathy are influenced by the recognition that diagnostic yield is lower than with the large fiber distal sensory polyneuropathy pattern. Up to 90% of small fiber polyneuropathy is considered idiopathic. The most common definable potential association with small fiber polyneuropathy is abnormal glucose metabolism, identified in approximately half of cases.

**Antibody Testing**

The role of autoantibody testing in the evaluation of a patient with peripheral neuropathy remains unclear. As incidental identification of autoantibodies in low titer is fairly common in clinical practice, the risk of false-positive results is significant. Therefore, it is generally recommended that the use of autoantibody panels be avoided, particularly those that test for disparate clinical patterns simultaneously. Autoantibody testing should target disorders based on relevant clinical patterns (Table 1-10).

**Genetic Testing**

Hereditary neuropathies constitute a significant proportion of peripheral neuropathy, although prevalence estimates vary widely. In studies of middle-aged to elderly patients with neuropathy, hereditary causes have been estimated to represent as little as 0.3% to 3% of the neuropathy cohort. In other studies, the prevalence has been estimated to be as high as 30% to 42%. The majority of hereditary neuropathies fall into the CMT category. Currently, in excess of 80 recognized hereditary neuropathy genotypes are known, with dominant, recessive, and X-linked inheritance patterns (Table 1-11). Opinions differ regarding the role of genetic testing in the evaluation of patients, although judicious testing is endorsed by neurologic and neuromuscular professional organizations. Potential benefits include diagnostic closure, with both psychological and cost benefits, and optimal genetic counseling for family members. Genetic diagnosis can clarify prognosis and direct monitoring and treatment of end organ dysfunction.
involvement. This includes potential avoidance of neurotoxic drugs used for treatment of other disorders. In rare cases (eg, Fabry disease), genetic diagnosis can lead to disease-specific therapeutic intervention.

Sanger genotype sequencing provides single-gene mutational analysis, beneficial when a limited number of genes are known to produce a single phenotype. Hereditary neuralgic amyotrophy represents a disorder in which single-gene testing is optimally used. With single-gene testing, a positive result is likely to be a true positive.

With genetically heterogeneous disorders such as CMT, the diagnostic strategy is more complex. Commercially available panels of bundled single-gene tests are diagnostically tempting but, in many cases, cost-prohibitive. Expert opinion suggests that the majority of patients with a

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Autoantibodies</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>Acute motor axonal neuropathy (5-10% of Guillain-Barré syndrome cases)</td>
<td>GM1, GD1α, GD3</td>
<td>50%</td>
</tr>
<tr>
<td>Miller Fisher syndrome</td>
<td>GQ1α, GT1α</td>
<td>85%</td>
</tr>
<tr>
<td>Ataxic neuropathies (CANOMAD, acute sensory ataxic neuropathy)</td>
<td>GD1β</td>
<td>46%</td>
</tr>
<tr>
<td>Distal acquired demyelinating symmetric neuropathy (DADS)</td>
<td>IgM monoclonal protein</td>
<td>Approximately 100%</td>
</tr>
<tr>
<td></td>
<td>MAG</td>
<td>50%</td>
</tr>
<tr>
<td>POEMS syndrome</td>
<td>Lambda light chain</td>
<td>85%</td>
</tr>
<tr>
<td>Multifocal motor neuropathy (MMN)</td>
<td>IgM GM1</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td>IgM GM1:GalC</td>
<td>75%</td>
</tr>
<tr>
<td>Paraneoplastic sensory neuronopathy</td>
<td>ANNA-1 (Hu)</td>
<td>Approximately 60%</td>
</tr>
<tr>
<td></td>
<td>CRMP-5 (CV-2)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sensory neuronopathy associated with Sjögren syndrome</td>
<td>SSA (Ro), SSB (La)</td>
<td>Approximately 50%</td>
</tr>
</tbody>
</table>

ANCA = antineutrophil cytoplasmic antibody; ANNA-1 = antineuronal nuclear antibody type 1; CANOMAD = chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies; CRMP-5 = collapsin response mediator protein-5; IgM = immunoglobulin M; MAG = myelin-associated glycoprotein; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes; SSA = Sjögren syndrome A; SSB = Sjögren syndrome B.
CMT phenotype have one of four mutations.57 Accordingly, the strategy historically recommended by experts is a targeted strategy of discriminant single-gene testing limited to these four genes and refined by considerations of onset age and nerve conduction velocity.57

Next-generation sequencing provides both promise and challenges in genetic testing, particularly for genetically heterogeneous disorders such as CMT. It uses high-throughput technology to provide a far more cost-effective means of multigene testing by simultaneously assessing the whole exome or whole genome.56,58 Next-generation sequencing also provides the opportunity to identify new mutations previously unassociated with a patient’s phenotype.54,56,58–60 Limitations remain. Variants of unclear significance with initial next-generation sequencing techniques were both commonplace and confounding, and identification of unrelated pathologic mutations may pose ethical challenges. Whole-exome sequencing or whole-genome sequencing may also not be as comprehensive as their names imply.54 In one report, only one-third of kindreds previously undiagnosed by targeted-candidate gene testing were successfully genotyped.58 Even more recently, target-enrichment sequencing was used to supplement targeted whole-exome sequencing; when assessing 197 neuropathy-related genes in 93 genetically unresolved cases of chronic length-dependent neuropathy, 87 of which had a hereditary neuropathy phenotype, only 21% were successfully genotyped.59 Recognition of neuropathy before the age of 40 coupled with a positive family history increased the diagnostic yield to 33%, whereas later

<table>
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<th>TABLE 1-11 Hereditary Peripheral Neuropathies</th>
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CMT = Charcot-Marie-Tooth; MNGIE = mitochondrial neurogastrointestinal encephalomyopathy; NARP = neuropathy, ataxia, retinitis pigmentosa; SANDO = sensory ataxic neuropathy, dysarthria, and ophthalmoplegia.
Assessment of peripheral nerve biopsy

**KEY POINTS**

- Current recommendations for genetic evaluation of chronic neuropathies is to initially test for the PMP22 deletion/duplication in an individual with demyelinating conduction velocities. Targeted next-generation sequencing is recommended in those individuals with negative PMP22 analysis or in patients with chronic axonal neuropathies who are younger than 40 years of age, have a motor predominant pattern, or have other similarly affected family members.

- Peripheral nerve biopsy remains a valuable tool in a very select group of individuals whose pattern suggests a cause for which biopsy is likely to provide a diagnosis that cannot be confirmed with less invasive means.

- Assessment of epidermal nerve fiber density through skin biopsy is useful in support of a diagnosis of small fiber neuropathy but rarely identifies the underlying cause.

onset and absence of family history reduced the yield to 5%.55

A proposed algorithm has been recently offered in consideration of these refined next-generation sequencing capabilities.55 This algorithm considers nerve conduction velocity, age at which the neuropathy is recognized, and family history to direct the genetic evaluation of a patient with a chronic length-dependent neuropathy pattern. In an individual with demyelinating conduction velocities, PMP22 deletion/duplication testing is recommended as the initial test performed following electrodiagnostic studies. Targeted next-generation sequencing with copy number evaluation (if possible) is recommended in patients with a negative PMP22 analysis with demyelinating conduction velocities or in patients with unexplained chronic neuropathy who are younger than 40 years of age, have a motor-predominant pattern, or have other family members with the same disorder.55

As with all algorithms, exceptions exist. Testing for an IgM monoclonal protein should be considered before genetic testing in an individual with a chronic demyelinating length-dependent neuropathy that is sensory predominant without other affected family members. Conversely, testing for hereditary neuropathy should be considered in older individuals without a family history or demyelinating electrophysiology if the phenotype is characteristic of a hereditary neuropathy. CMT type 1B is one genotype recognized to present at an older age without demyelinating electrophysiologic features.58

**Histologic Testing**

Peripheral nerve biopsy is a valuable tool for the evaluation of select patients with peripheral neuropathy.7,61,62 Table 1-12 lists the disorders for which biopsy can be useful as suggested by neuropathy pattern and clinical context. In consideration of invasiveness, cost, low yield, and sacrifice of sensory nerve fibers, nerve biopsy is considered a diagnostic procedure of last resort. It may be performed as a research tool on motor nerve branches but is almost always clinically performed on sensory nerves, such as the sural, superficial fibular (peroneal), or superficial radial.61,62 In general, nerve biopsies are always performed on nerves whose SNAP is reduced or absent. Nerve biopsy is rarely clinically used in patients with a distal sensory polyneuropathy, hereditary neuropathy, or inflammatory demyelinating polyradiculopathy pattern. Biopsy in patients with diabetes mellitus should be avoided unless a serious concern exists for a secondary (nondiabetic) cause because of its limited value and risk of poor wound healing.

Skin biopsy is primarily performed to assess the density of intraepidermal Aδ or C nerve fibers.44 The specimen can be obtained by different techniques and from different locations, but the standard is 10 cm proximal to the lateral malleolus. The biopsy is considered diagnostic of small fiber neuropathy if the intraepidermal nerve fiber density is less than 5% of age- and gender-matched controls. Other morphologic changes, such as axonal swelling, are considered less accurate. In general, skin biopsy is performed with the goal of identifying the existence, but not the cause, of small fiber neuropathy. Intraepidermal nerve fiber density has been reported to have a sensitivity of 90%, a specificity and positive predictive value of 95%, and a negative predictive value of 91% in the detection of small fiber neuropathy.44 As these numbers have been acquired in the absence of an ideal gold standard, their accuracy is not universally accepted.20,44 A normal study effectively
excludes small fiber neuropathy, but the specificity and ability to prove the existence of a small fiber neuropathy is less convincing.46

Muscle biopsy has a limited role in the diagnostic evaluation of patients with peripheral neuropathy. When performed, it is usually in conjunction with a nerve biopsy (eg, superficial fibular [peroneal] nerve/peroneus brevis muscle) to increase the diagnostic yield in disorders such as vasculitis or amyloidosis, in which the characteristic histologic findings may be identified in muscle as well as nerve. Biopsy of other tissues may be useful, such as minor salivary gland (lip) biopsy in suspected seronegative Sjögren syndrome, lymph node biopsy in suspected sarcoidosis, or small bowel biopsy in suspected celiac disease.

**CONCLUSION**

As with all neurologic problem-solving strategies, the approach to a patient with suspected peripheral neuropathy should be both individualized and rational, with the goal of identifying the underlying cause whenever possible. As always, a patient is best served when his or her physician applies both knowledge and judgment, allowing for diagnostic and therapeutic intervention when called for and providing education and

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**TABLE 1-12  Disorders for Which Nerve Biopsy Might Be Considered**

<table>
<thead>
<tr>
<th>Disorders for which nerve biopsy can be diagnostic where nerve biopsy is endorsed if not readily achieved by less invasive means</th>
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<tr>
<td>Vasculitic neuropathy (systemic or nonsystemic)</td>
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<tr>
<td>Amyloidosis (primary systemic)</td>
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<tr>
<td>Disorders for which nerve biopsy has characteristic or diagnostic features where diagnosis is preferably achieved by less invasive means</td>
</tr>
<tr>
<td>Amyloidosis (hereditary)</td>
</tr>
<tr>
<td>Leprosy</td>
</tr>
<tr>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Neurofibromatous neuropathy</td>
</tr>
<tr>
<td>Neurolymphomatosis</td>
</tr>
<tr>
<td>Hereditary metabolic/multisystem diseases</td>
</tr>
<tr>
<td>Fabry disease, metachromatic leukodystrophy, Krabbe disease, adrenomyeloneuropathy, polyglucosan body disease, giant axonal neuropathy, Tangier disease</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Distal acquired demyelinating symmetric (DADS) neuropathy</td>
</tr>
<tr>
<td>Hereditary neuropathy with liability to pressure palsies (HNPP)</td>
</tr>
<tr>
<td>Hexacarbon toxicity</td>
</tr>
<tr>
<td>Rare conditions for which nerve biopsy has been diagnostic in isolated reports</td>
</tr>
<tr>
<td>Silver toxicity</td>
</tr>
<tr>
<td>Hereditary disorders of uric acid metabolism</td>
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</tbody>
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reassurance without intervention when it is not. Despite advances in our understanding of these disorders, this process still begins at the bedside with a physician who is skilled in pattern recognition, knowledgeable about associated causes, and capable of evaluation and management.

REFERENCES


