Pattern-Recognition Approach to Neuropathy and Neuronopathy

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KEYWORDS

• Neuropathy • Neuronopathy • Myelinopathy • Axonopathy • Plexopathy
• Radiculopathy • Mononeuritis multiplex

KEY POINTS

- The initial key to the diagnosis of neuropathy and neuronopathy is recognition of a clinical pattern.
- There are 6 key questions the clinician should consider in arriving at the pattern that fits the patient best.
- Most neuropathy and neuronopathy patients can be placed into one of 10 patterns.
- After arriving at the pattern that fits best, then the clinician can determine the most appropriate diagnostic tests and management.

INTRODUCTION

A discussion of neuropathic disorders encompasses those diseases that affect the neuron's cell body, or neuronopathies, and those affecting the peripheral process, or peripheral neuropathies (**Box 1**).[1,2] Neuronopathies can be further subdivided into those that affect only the anterior horn cells, or motor neuron disease, and those involving only the sensory neurons, also called sensory neuronopathies or ganglionopathies. Peripheral neuropathies can be broadly subdivided into those that primarily affect myelin, or myelinopathies, and those that affect the axon, or axonopathies.

Each of these pathologic categories has distinct clinical and electrophysiologic features that allow the clinician to place a patient's disease into 1 of these groups. Therefore, the first 2 goals in the approach to a neuropathic disorder are to determine: (1) where the lesion is located; and (2) the cause of the lesion (**Box 2**).

Disclosures/Conflicts of Interest: Dr Barohn: Speaker's bureau for Genzyme and Grifols; Advisory Board for MedImmune and Novartis. Dr Amato: Medical advisory board/consultant for Amgen, Baxter, Biogen, MedImmune, Questor.

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Neurol Clin 31 (2013) 343–361
http://dx.doi.org/10.1016/j.ncl.2013.02.001 **neurologic.theclinics.com**
0733-8619/13/$ – see front matter

Box 1
Pathologic classification of neuropathic disorders

- Neuronopathies (pure sensory or pure motor or autonomic):
  - Sensory neuronopathies (ganglionopathies)
  - Motor neuronopathies (motor neuron disease)
  - Autonomic neuropathies
- Peripheral neuropathies (usually sensorimotor):
  - Myelinopathies
  - Axonopathies
    - Large- and small-fiber
    - Small-fiber

For example, is the disorder hereditary or acquired? If it is acquired, is the neuropathic disorder due to a systemic dysmetabolic state? Is it drug induced or toxin induced? Is it mediated by an immune or infectious process? Or, is the cause unknown? The third goal in approaching the patient with a neuropathic disorder is to determine whether therapy is possible, and if so, what the course of therapy should be. Even if a specific therapy is not available, a management plan should be developed. These final 2 steps are often frustrating, as it is not always possible to determine the cause or alter the natural history of neuropathic disorders.

What is the chance of correctly determining the pathologic type and etiology of a neuropathic disorder? If one considers only peripheral neuropathies, some information is available. Of 205 patients referred to the Mayo Clinic with an undiagnosed peripheral neuropathy, a diagnosis was made in 76%.[3] A hereditary neuropathy was found in 42%, an inflammatory demyelinating disorder (chronic inflammatory demyelinating polyneuropathy [CIDP]) was diagnosed in 21%, and 13% were diagnosed as having a peripheral neuropathy associated with other diseases (diabetes and other metabolic disorders, nutritional deficiency, toxins, and cancer). The authors' experience of 402 consecutive patients referred to the University of Texas neuromuscular outpatient clinics in Dallas and San Antonio through 1997 for a peripheral neuropathy[4] is shown in **Table 1**. The authors recently performed a similar analysis on cohorts of neuropathy between North American (Kansas City and Dallas) and South American (Rio de Janeiro, Brazil) (NA-SA) cities.[5,6]

This NA-SA analysis underscored that a hereditary neuropathy is common, accounting for 27% in NA and 10% in SA. Acquired demyelinating polyneuropathies in tertiary care neuropathy clinics accounted for 20% in NA and 18% in SA. Diabetic neuropathies, while common (13% in NA and 23% in SA), may have been underreported in these tertiary care neuropathy center populations. (See the articles by Pasnoor and colleagues elsewhere in this issue for further exploration of this topic.) Approximately one-quarter of the patients are ultimately found to have a predominantly sensory polyneuropathy with no identifiable cause (28% in NA and 23% in SA), that is, cryptogenic sensory polyneuropathy (CSPN).[7–9] (See the article by Pasnoor and colleagues elsewhere in this issue for further exploration of this topic.) Overall, SA tertiary care centers were more likely to see patients with infections (Chagas, human T-lymphotropic virus 1, leprosy), and diabetic and hereditary disorders such as familial

Box 2
Etiology of neuropathic disorders

I. Acquired

Dysmetabolic states
- Diabetes mellitus
- Neuropathy related to renal disease
- Vitamin deficiency states (eg, vitamin B_{12} deficiency)

Immune mediated
- Guillain-Barré syndrome (GBS)
- Chronic inflammatory demyelinating polyneuropathy and variants
- Multifocal motor neuropathy
- Anti–myelin-associated glycoprotein distal acquired demyelinating symmetric neuropathy
- Radiculoplexus neuropathy: cervical, thoracic, and lumbosacral
- Vasculitis
- Sarcoidosis

Infectious
- Herpes zoster
- Leprosy, Lyme, human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr related

Cancer-related and lymphoproliferative disorders
- Lymphoma, myeloma, carcinoma related
- Paraneoplastic subacute sensory neuronopathy
- Primary amyloidosis

Drugs or toxins
- Chemotherapy induced
- Other drugs
- Heavy metals and industrial toxins

Mechanical/compressive
- Radiculopathy
- Mononeuropathy

Unknown etiology
- Cryptogenic sensory and sensorimotor neuropathy
- Amyotrophic lateral sclerosis

II. Hereditary

Charcot-Marie-Tooth disease and related disorders

Hereditary sensory and autonomic neuropathy

Familial brachial plexopathy

Familial amyloidosis

Porphyria

Other rare peripheral neuropathies (Fabry disease, metachromatic leukodystrophy, adrenoleukodystrophy, Refsum disease, and so forth)

Motor neuron disease
- Spinal muscular atrophy
- Familial amyotrophic lateral sclerosis
- X-linked bulbospinal muscular atrophy
- Hereditary motor neuropathy
- Hereditary spastic paraplegia

amyloid neuropathies.[5,6] NA tertiary centers were more likely to see Charcot-Marie-Tooth (CMT) neuropathy. Immune and cryptogenic neuropathies were seen equally in NA and SA.

To accomplish the goal of determining the site and cause of the lesion, and, if possible, a therapy, the clinician gathers information from the history, the neurologic examination, and various laboratory studies. While gathering this information, 6 key questions are asked. From the answer to these 6 questions, the patient is placed into 9 different phenotypic patterns. Therefore, the authors call this the 3-6-10–step clinical approach to neuropathy: 3 goals, 6 key questions, 10 phenotypic patterns.

IMPORTANT INFORMATION FROM THE HISTORY AND PHYSICAL: 6 KEY QUESTIONS

The first step in this approach is to ask 6 key questions based on the patient's symptoms and signs (**Box 3**):

What Systems are Involved?

It is important to determine if the patient's symptoms and signs are pure motor, pure sensory, autonomic, or some combination of these. If the patient has only weakness without any evidence of sensory loss, a motor neuronopathy or motor neuron disease is the most likely diagnosis. The majority of patients with adult-onset motor neuron

Table 1
Breakdown by diagnosis of 402 consecutive polyneuropathy patients referred to the University of Texas at Dallas/San Antonio neuromuscular clinics

Diagnosis	No. of Patients	%
Hereditary	120	29.8
Cryptogenic sensory polyneuropathy	93	23.1
Diabetes mellitus	62	15.4
Inflammatory demyelinating polyneuropathy	53	13.1
Multifocal motor neuropathy	21	5.2
Vitamin B_{12} deficiency	9	2.2
Cryptogenic sensorimotor polyneuropathy with severe distal weakness	7	1.7
Drug-induced	6	1.5
Sensory neuronopathy (3 idiopathic, 1 anti-Hu)	4	1.0
Other[a]	27	6.7

[a] Includes: motor neuron disease plus sensorimotor polyneuropathy (SMPN) (4), SMPN associated with a solid tumor (4), mononeuritis multiplex (4), post polio with SMPN (3), vasculitis (3), infectious (3), axonal motor neuropathy (2), SMPN associated with collagen vascular disease (1), thyrotoxicosis (1), SMPN associated with leukemia (1), toxin-induced (1).

Data from Barohn RJ. Approach to peripheral neuropathy and neuronopathy. Sem Neurol 1998;18:7–18.

Box 3
Approach to neuropathic disorders: 6 key questions

1. What systems are involved?
   a. Motor, sensory, autonomic, or combinations
2. What is the distribution of weakness?
   a. Only distal versus proximal and distal
   b. Focal/asymmetric versus symmetric
3. What is the nature of the sensory involvement?
   a. Severe pain/burning or stabbing
   b. Severe proprioceptive loss
4. Is there evidence of upper motor neuron involvement?
   a. Without sensory loss
   b. With sensory loss
5. What is the temporal evolution?
   a. Acute (days to 4 weeks)
   b. Subacute (4–8 weeks)
   c. Chronic (>8 weeks)
   d. Preceding events, drugs, toxins
6. Is there evidence for a hereditary neuropathy?
   a. Family history of neuropathy
   b. Skeletal deformities
   c. Lack of sensory symptoms despite sensory signs

disease have evidence of both upper and lower motor neuron dysfunction on examination, that is, amyotrophic lateral sclerosis (ALS), which is the primary diagnostic hallmark of this disorder.[10] On the other hand, nearly one-third of adult patients with acquired motor neuron disease may present initially without definite upper motor neuron findings,[11,12] and these patients are often referred to as having progressive muscular atrophy (PMA). A slow pure lower motor neuron variant restricted to the arms for many years has been termed brachial amyotrophic diplegia (BAD),[13] and the version restricted to the legs has been termed leg amyotrophic diplegia (LAD).[14,15] Spinal muscular atrophy (SMA) is the autosomal recessive motor neuronopathy of childhood.[16] Patients with pure motor distal weakness with a clinical phenotype of CMT neuropathy but with no sensory involvement are now classified as hereditary motor neuropathy (HMN).[17,18] However, with advances in genetics the authors have found variable presentations, such that mutations in the same gene may cause motor and sensory CMT or a pure motor HMN; some may also be associated with upper motor neuron findings (hereditary spastic paraplegia [HSP]).

The neuropathic disorders that may present with pure motor symptoms are listed in **Box 4**. Although some peripheral neuropathies may present with only motor symptoms, the clinician can usually find evidence of sensory involvement on neurologic examination. An exception to this rule is a patient with multifocal motor neuropathy who generally has a normal sensory examination.[19] (See the article by Saporta and colleagues elsewhere in this issue for further exploration of this topic.)

Box 4
Neuropathic disorders that may have only motor symptoms at presentation

Motor neuron disease

Multifocal motor neuropathy

GBS[a]

CIDP[a]

Lead intoxication[a]

Acute porphyria[a]

Hereditary motor sensory neuropathy[a] (CMT disease)

Hereditary motor neuropathy

[a] Usually has sensory signs on examination.

Some peripheral neuropathies are associated with significant autonomic nervous system dysfunction (**Box 5**).

Inquire if the patient has had fainting spells or orthostatic lightheadedness, heat intolerance, or any bowel, bladder, or sexual dysfunction. If these symptoms are present, check for an orthostatic decrease in blood pressure without an appropriate increase in heart rate. Autonomic dysfunction in the absence of diabetes should alert the clinician to the possibility of amyloid polyneuropathy, an autoimmune small-fiber ganglionopathy, or (in a young child) hereditary sensory and autonomic neuropathy (HSAN). Rarely, idiopathic pandysautonomic syndrome can be the only manifestation of a peripheral neuropathy without other motor or sensory findings.[20,21] (see the article by Dimachkie and colleagues elsewhere in this issue for further exploration of this topic.)

What is the Distribution of Weakness?

The distribution of the patient's weakness is crucial for an accurate diagnosis, and in this regard 2 questions should be asked: (1) does the weakness only involve the distal extremity or is it both proximal and distal? and (2) is the weakness focal and asymmetric or is it symmetric? The finding of weakness in both proximal and distal muscle groups in a symmetric fashion is the hallmark for acquired immune demyelinating polyneuropathies, both the acute form (GBS) and the chronic form (CIDP).[22–25] (See the

Box 5
Peripheral neuropathies with autonomic nervous system involvement

Hereditary sensory autonomic neuropathy

Diabetes mellitus

Amyloidosis (familial and acquired)

GBS

Vincristine induced

Porphyria

HIV-related autonomic neuropathy

Idiopathic pandysautonomia

articles by Dimachkie and colleagues and Gorson and colleagues elsewhere in this issue for further exploration of this topic.) Patients with proximal muscle weakness will complain of difficulty raising their arms to brush their teeth or comb their hair, as well as problems climbing stairs or rising from a chair. On the neurologic examination, the clinician needs to pay particular attention for the presence of facial, neck, shoulder, and hip weakness in addition to the more distal muscle groups in the hands and feet.

Asymmetry or focality of the weakness is also a feature that can narrow the diagnostic possibilities (**Box 6**).

ALS can present with either prominent neck extensor weakness (head drop) or prominent tongue and pharyngeal weakness (dysarthria and dysphagia). The latter is the so-called bulbar presentation. These focal symmetric weakness patterns can also be seen in neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton myasthenic syndrome) and some myopathies, particularly isolated neck extensor myopathy.[26] Therefore, these patterns are considered an overlap with myopathic disorder.

Other overlap patterns with muscle disease are seen with pure motor symmetric proximal to distal limb weakness. When this occurs on a neuropathic basis, the primary consideration is SMA. But of course, this is also the limb-girdle pattern seen in many myopathies. Pure motor distal symmetric weakness is the presentation for hereditary motor neuropathy, as already noted, but this pattern can also be seen in distal myopathies and, rarely, myasthenia gravis.[27,28]

Some neuropathic disorders may present with unilateral leg weakness. If sensory symptoms and signs are absent, and an elderly patient presents with painless foot drop evolving over weeks or months, motor neuron disease is the leading and most worrisome diagnostic possibility. On the other hand, if a patient presents with subacute or acute sensory and motor symptoms of one leg, lumbosacral radiculopathies, plexopathies, vasculitis, and compressive mononeuropathy need to be considered. Similarly, if the clinical manifestations are pure motor weakness in one arm or hand, motor neuron disease is probably the leading consideration. If sensory symptoms are also present, cervical radiculopathy, brachial plexopathy, or a mononeuropathy are likely possibilities. Hereditary neuropathy with predisposition to pressure palsies (HNPP) or familial brachial plexus neuropathies are also conditions that can present with focal, asymmetric leg or arm weakness.[29] Leprosy often presents with asymmetric sensory or sensorimotor features, and one needs to have a high index of suspicion for this disorder, particularly in immigrant populations from developing countries.[30] Unilateral combined motor and sensory presentations in a single extremity are usually due to a simple entrapment or compressive neuropathy or radiculopathy (See the article by Arnold and colleagues in this issue for further exploration of this topic).

The importance of finding symmetric proximal and distal weakness in a patient who presents with both motor and sensory symptoms cannot be overemphasized, because this identifies the important subset of patients who may have a treatable acquired demyelinating neuropathic disorder, that is, acute or CIDP. On the other hand, if a patient with both symmetric sensory and motor findings has weakness involving only the distal lower and upper extremities, the disorder generally reflects a primarily axonal peripheral neuropathy and is much less likely to represent a treatable entity.

Exceptions

There are important exceptions to this generalization that symmetric distal sensory and motor weakness reflects an axonal process that is likely to be unresponsive to

Box 6
Neuropathic disorders that produce asymmetric/focal weakness

- Motor neuron disease
  - ALS
- Radiculopathy: cervical or lumbosacral
  - Root compression from osteoarthritis
  - Root compression from herniated disc
  - Herpes zoster focal paresis (with rash)
  - Meningeal carcinomatosis and lymphomatosis
  - Sarcoid
  - Amyloid
  - Chronic immune sensory polyradiculopathy
- Plexopathy: cervical, thoracic, or lumbosacral
  - Immune-mediated/Idiopathic
  - Neoplastic infiltration
  - Diabetic radiculoplexopathy (primarily lumbosacral)
  - Familial brachial plexopathy
  - Hereditary neuropathy with liability to pressure palsy
- Mononeuropathy multiplex due to:
  - Vasculitis
  - Multifocal motor neuropathy
  - Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
  - Multifocal acquired motor axonopathy (MAMA)
  - Lyme disease
  - Sarcoid
  - Leprosy
  - HIV infection
  - Hepatitis B and C
  - Cryoglobulinemia
  - Amyloidosis
  - Hereditary neuropathy with liability to pressure palsy
- Compressive/entrapment mononeuropathies
  - Median neuropathy
  - Ulnar neuropathy
  - Peroneal neuropathy

therapy, and that acquired demyelinating neuropathies present with proximal and distal symmetric weakness. Patients with multifocal motor neuropathy and multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy have distal, asymmetric extremity involvement, but these disorders respond to immunosuppressive therapy.[19,24,31] (See the articles by Saporta and colleagues and Arnold and colleagues

elsewhere in this issue for further exploration of this topic.) In addition, the acquired demyelinating neuropathies associated with immunoglobulin M–κ monoclonal antibodies, which are typically targeted to myelin-associated glycoprotein, have the curious pattern of predominantly distal symmetric sensory loss and weakness, with little or no proximal weakness. This condition is now known as DADS-M (distal acquired demyelinating symmetric with monoclonal gammopathy) neuropathy.[24,32]

Another important exception to the rule that distal, symmetric sensory and motor sensory and motor loss is unresponsive to immunosuppressive therapy is the occasional patients with vasculitis of the peripheral nervous system. Approximately 20% to 30% of patients with vasculitis of the peripheral nervous system may present with a distal, symmetric motor, and sensory dysfunction[33] rather than with asymmetric, multiple mononeuropathies. The clue to diagnosing these patients is the subacute evolution over weeks with severe pain and prominent motor involvement, features that help to make the distinction from metabolic, toxic, or hereditary disorders (See the article by Collins and colleagues in this issue for further exploration of this topic).

What is the Nature of the Sensory Involvement?

When taking the history from a patient with a peripheral neuropathy, it is important to determine whether the patient has loss of sensation (numbness), altered sensation (tingling), or pain. Sometimes patients may find it difficult to distinguish between uncomfortable tingling sensations (dysesthesias) and pain. Neuropathic pain can be burning, dull, and poorly localized (protopathic pain), presumably transmitted by polymodal C nociceptor fibers, or sharp and lancinating (epicritic pain), relayed by Aδ fibers.

Complaints of numbness or tingling, and the type of neuropathic pain while implicating sensory involvement, are in general not very helpful in suggesting a specific diagnosis, as these symptoms can accompany many peripheral neuropathies. However, 2 sensory features may be helpful to the clinician in arriving at a diagnosis. If severe pain is one of the patient's symptoms, certain peripheral neuropathies should be considered (**Box 7**).

The CSPN and neuropathy due to diabetes mellitus are the most common neuropathies associated with severe pain.[7–9] In addition, painful peripheral neuropathies attributable to peripheral nerve vasculitis or GBS are important to recognize because these disorders are treatable. The pain in vasculitic neuropathy is generally distal and asymmetric in the most severely involved extremity. Some patients with GBS have severe back pain associated with symmetric numbness and paresthesias in the extremities. The pain associated with CSPN and diabetic distal sensory neuropathy

Box 7
Peripheral neuropathies often associated with pain

- Cryptogenic sensory or sensorimotor neuropathy
- Diabetes mellitus
- Vasculitis
- GBS
- Amyloidosis
- Toxic (arsenic, thallium)
- HIV-related distal symmetric polyneuropathy
- Fabry disease

is symmetric and is usually worse in the feet. Another painful form of diabetic neuropathy is lumbosacral radiculoplexopathy (also known as diabetic amyotrophy), whereby patients may present with the abrupt onset of back, hip, or thigh pain that may precede weakness by days or weeks.[34] (See the article by Pasnoor and colleagues elsewhere in this issue for further exploration of this topic.)

The other important sensory abnormality that significantly narrows the differential diagnosis is severe proprioceptive loss. This disorder is sometimes difficult to discern from the history, but complaints of loss of balance (especially in the dark), incoordination of the limbs, or symptoms suggesting disequilibrium may be helpful. Although the symptoms of gait unsteadiness are common to many neuropathies with sensory involvement, if the neurologic examination reveals a dramatic asymmetric loss of proprioception with significant vibration loss and normal strength, the clinician should immediately consider a sensory neuronopathy (ie, ganglionopathy). In addition to the severe proprioceptive and vibration deficits, sensory neuronopathies usually have a panmodality sensory loss in the affected extremities. Light touch and pain sensation are also affected, owing to injury of all sensory cell bodies. The various causes of sensory neuronopathy are listed in **Box 8**.

A variant of CIDP termed chronic immune sensory polyradiculopathy (CISP) manifests as a sensory ataxia and clinically resembles a sensory neuronopathy/ganglionopathy.[35] Normal sensory nerve action potentials (because the lesion is proximal to the ganglion cells) differentiate this disorder from sensory neuronopathy. Clinicians probably have encountered such patients in the past, being perplexed by the preserved sensory nerve action potentials (SNAPs).[36,37] The discordance between the sensory ataxia and loss of reflexes but normal SNAPs should make one consider CISP. Although the SNAPs may be normal, often the H-reflexes are prolonged or absent, as perhaps are more proximal potentials on somatosensory evoked potentials, owing to proximal demyelination of the sensory roots. Cerebrospinal fluid protein may be elevated. In addition, enlarged and enhancing nerve roots may be appreciated on magnetic resonance imaging. Root biopsies have demonstrated demyelination and inflammation. Most of these patients respond to immunomodulating therapy, similar to CIDP patients. Therefore, CISP should be in the differential of severe ataxia, proprioceptive loss, and areflexia.

Of course, profound proprioception and vibration loss can also be due to posterior column damage from disorders such as combined system degeneration. However, myelopathy of the posterior column is generally symmetric, in general is less profound than in most patients with true dorsal root ganglion loss, and is often associated with evidence of upper motor neuron abnormality (see later discussion). One notable exception is vitamin E deficiency, which can affect both sensory nerves and posterior columns and can produce a profound symmetric proprioceptive deficit.[38]

Box 8
Causes of sensory neuronopathy (ganglionopathy)

- Cancer (paraneoplastic)
- Sjögren syndrome
- Idiopathic sensory neuronopathy
- Cisplatinum and other analogues
- Vitamin B_6 toxicity
- HIV-related sensory neuronopathy

The modalities of light touch, pain sensation (with an unused safety pin), vibration, and proprioception should be assessed in all 4 limbs in a patient with a peripheral neuropathy. The authors have found the use of nylon monofilaments of different tensile strengths very useful in assessing and grading the loss of touch sensation.[30,39] Another useful quantitative bedside test that is easy to perform is maximal timed vibratory testing with a 128-Hz tuning fork. The examination technique consists of striking the tuning fork to obtain a maximal vibratory stimulus and immediately applying the top of the handle to the interphalangeal joint of the great toe. Using a clock, one determines how long the patient can perceive the vibratory stimulus. In children and young adults, this maximal vibratory stimulus is appreciated for at least 15 seconds over the great toe. As patients age, this time decreases even in the absence of overt peripheral neuropathy. As a basic rule of thumb, a 1-second loss of vibration perception per decade is allowed. Thus, it is not uncommon for a 70-year-old patient to have only 9 or 10 seconds of maximal vibration perception over the great toe. Both graded monofilament and timed vibration testing can be easily rechecked at each follow-up visit to monitor the course.

On the other hand, the authors believe that it is extremely difficult to determine with any degree of certainty whether temperature sensation deficits are present with bedside testing, and therefore do not routinely check this modality. It is suspected that temperature sensation can only be assessed reliably with computerized quantitative sensory testing (QST). QST has now become commercially available through several manufacturers.[40] However, the authors' experience in measuring QST for temperature and vibration thresholds in more than 800 neuropathy patients was disappointing in ultimately assisting in diagnosis and management.[41] At present, the authors do not believe that QST is useful in routine clinical practice.

In general, the authors have found the concept of trying to place patients into categories of "large-fiber" and "small-fiber" sensory involvement rarely to be clinically useful in establishing a diagnosis or in management. If a careful bedside examination is performed, most patients with sensory loss associated with the more common categories of peripheral neuropathy (eg, CSPN and diabetes) will clinically have diminished light touch, pin, and vibration sensation, with proprioception affected in more severe cases.[7–9] (See the article by Pasnoor and colleagues elsewhere in this issue for further exploration of this topic.) In addition, QST for vibration and temperature thresholds in these common disorders usually shows abnormalities in both modalities. In truth, selective involvement of small sensory fibers for pain and temperature sensation is uncommon and is seen in rare disorders such as hereditary sensory neuropathy, Fabry disease, and some cases of amyloidosis, but also is seen in some patients with CSPN who have normal nerve conduction studies, reflexes, and vibration. Epidermal nerve quantification by skin biopsy is used by some to confirm a small-fiber neuropathy, but often simply confirms the clinical suspicion obtained from the history and clinical examination.[42–44] The value of skin biopsies lies more in their potential as an objective marker for research studies.[42,45]

Is There Evidence of Upper Motor Neuron Involvement?

In patients with symptoms of signs suggestive of lower motor neuron abnormality without sensory loss, the presence of concomitant upper motor neuron signs is the hallmark of ALS.[10,11] As noted earlier, these patients typically present with asymmetric, distal weakness without sensory loss. Pure upper motor neuron involvement (limb or bulbar) is the presentation for primary lateral sclerosis (PLS),[46,47] as well as hereditary spastic paraparesis.

Box 9
Ten patterns of neuropathic disorders

Pattern 1: Symmetric proximal and distal weakness with sensory loss

Consider:

Inflammatory demyelinating polyneuropathy (GBS and CIDP)

Pattern 2: Symmetric distal sensory loss with or without distal weakness

Consider:

Cryptogenic sensory polyneuropathy (CSPN)

Metabolic disorders

Drugs, toxins

Hereditary (CMT, amyloidosis, and others)

Pattern 3: Asymmetric distal weakness with sensory loss

Multiple nerves, consider:

Vasculitis

HNPP

MADSAM neuropathy

Infectious (leprosy, Lyme, sarcoid, HIV)

Single nerves/regions, consider:

Compressive mononeuropathy and radiculopathy

Pattern 4: Asymmetric proximal and distal weakness with sensory loss

Consider:

Polyradiculopathy or plexopathy due to diabetes mellitus, meningeal carcinomatosis or lymphomatosis, sarcoidosis, amyloidosis, Lyme, idiopathic, hereditary (HNPP, familial)

Pattern 5: Asymmetric distal weakness without sensory loss

Consider:

1. With upper motor neuron findings
   a. Motor neuron disease/ALS/PLS
2. Without upper motor neuron findings
   a. PMA
      i. BAD
      ii. LAD
   b. Multifocal motor neuropathy
   c. MAMA
   d. Juvenile monomelic amyotrophy

Pattern 6: Symmetric sensory loss and distal areflexia with upper motor neuron findings

Consider:

B_{12} deficiency and other causes of combined system degeneration with peripheral neuropathy

Copper deficiency (including zinc toxicity)

Inherited disorders (adrenomyeloneuropathy, metachromatic leukodystrophy, Friedreich ataxia)

Pattern 7: Symmetric weakness without sensory loss[a]

Consider:

1. Proximal and distal weakness
   a. SMA
2. Distal weakness
   a. Hereditary motor neuropathy

Pattern 8: Focal midline proximal symmetric weakness[a]

Consider:

Neck extensor weakness: ALS

Bulbar weakness: ALS, PLS

Pattern 9: Asymmetric proprioceptive sensory loss without weakness

Consider:

Sensory neuronopathy (ganglionopathy) (see **Box 9**)

CISP

Pattern 10: Autonomic symptoms and signs

Consider:

Neuropathies associated with autonomic dysfunction (see **Box 6**)

[a] Overlaps with myopathies and neuromuscular junction disorders.

On the other hand, if the patient presents with symmetric distal sensory symptoms and signs suggestive of a distal sensory neuropathy, but there is additional evidence of symmetric upper motor involvement, the physician should consider a disorder such as combined system degeneration with neuropathy. The most common cause for this pattern is vitamin B_{12} deficiency, but other causes of combined system degeneration with neuropathy should be considered (eg, copper deficiency, HIV infection, severe hepatic disease, or adrenomyeloneuropathy).[48–52] In the authors' experience, these patients may be distinguished from typical CSPN patients by the presence of crossed adductor reflexes or mild spread of reflexes in the arms, in the setting of absent ankle reflexes. This scenario in a patient who presents with distal sensory loss and unsteadiness should lead to an intensive search for vitamin B_{12} deficiency (ie, assessing for elevated serum methylmalonic acid and homocysteine levels), if the B_{12} level is in the lower limit of normal range. In addition, some of these patients develop sensory symptoms in the hands before they begin in the feet, otherwise known as the numb hand syndrome.[48–50,52]

A similar myeloneuropathy or myelopathy may occur secondary to copper deficiency.[53–56] (See the article by Hammond and colleagues elsewhere in this issue for further exploration of this topic.) Patients present with lower limb paresthesias, weakness, spasticity, and gait difficulties. Sensory loss is impaired distally, reflexes are brisk (but may be absent at the ankles), and plantar responses may be extensor. Electrophysiologic studies often show an axonal sensorimotor neuropathy. Patients may have neutropenia, microcytic anemia, and a pancytopenia. The copper deficiency may be due to prior gastric surgery. The use of denture adhesives containing zinc has also been associated with copper deficiency.[57] In such cases, zinc levels are elevated and the metal may compete with copper, leading to the syndrome. Treatment consists

Table 2
Clinical patterns of neuropathic disorders

	Weakness								
	Proximal	Distal	Asymmetric	Symmetric	Sensory Symptoms	Severe Proprioceptive Loss	UMN Signs	Autonomic Symptoms/ Signs	Diagnosis
Pattern 1: symmetric proximal and distal weakness with sensory loss	+	+		+	+				GBS/CIDP
Pattern 2: distal sensory loss with/ without weakness		+		+	+				CSPN, metabolic, drugs, hereditary
Pattern 3: distal weakness with sensory loss		+	+		+				Multiple: vasculitis, HNPP, MADSAM, infection Single: mononeuropathy, radiculopathy
Pattern 4: asymmetric proximal and distal weakness with sensory loss	+	+	+		+				Polyradiculopathy, plexopathy
Pattern 5: asymmetric distal weakness without sensory loss		+	+				±		LMN and UMN − ALS Pure UMN − PLS Pure LMN − MMN, PMA, BAD, LAD, MAMA

Pattern 6: symmetric sensory loss and upper motor neuron signs		+		+	+	+	+		B_{12} deficiency, copper deficiency, Friedreich ataxia, adrenomyeloneuropathy
Pattern 7[a]: symmetric weakness without sensory loss	±	+		+					Proximal and distal SMA Distal Hereditary motor neuropathy
Pattern 8[a]: focal midline proximal symmetric weakness	+ Neck/extensor + Bulbar			+ +			+ +		ALS
Pattern 9: asymmetric proprioceptive loss without weakness			+		+	+			Sensory neuronopathy (ganglionopathy)
Pattern 10: autonomic dysfunction								+	HSAN, diabetes, GBS, amyloid, porphyria, Fabry

Abbreviations: ALS, amyotrophic lateral sclerosis; BAD, brachial amyotrophic diplegia; CIDP, chronic inflammatory demyelinating polyneuropathy; CSPN, cryptogenic sensory polyneuropathy; GBS, Guillain-Barré syndrome; HNPP, hereditary neuropathy with liability to pressure palsy; HSAN, hereditary sensory and autonomic neuropathy; LAD, leg amyotrophic diplegia; MADSAM, multifocal acquired demyelinating sensory and motor; MAMA, multifocal acquired motor axonopathy; MMN, multifocal motor neuropathy; PMA, progressive muscular atrophy; SMA, spinal muscular atrophy; UMN, upper motor neuron.

[a] Overlap patterns with myopathy/neuromuscular junction disorders.

of either daily oral copper supplements or, in severe cases, intravenous copper therapy.

What is the Temporal Evolution?

Of obvious importance is the onset, duration, and evolution of symptoms and signs. Does the disease have an acute (days to 4 weeks), subacute (4–8 weeks), or chronic (>8 weeks) course? Is the course monophasic, progressive, or relapsing? Neuropathies with acute and subacute presentations include GBS, vasculitis, and diabetic lumbosacral radiculoplexopathy. A relapsing course can be present in CIDP and porphyria. It is also important to inquire about preceding or concurrent infections, associated medical conditions, drug use including over-the-counter vitamin preparations (B_6), alcohol, and dietary habits.

Is There Evidence for a Hereditary Neuropathy?

Finally, a hereditary cause for a peripheral neuropathy should not be overlooked.[18,58,59] In both the Mayo Clinic and University of Texas series, hereditary neuropathy accounted for the largest group of neuropathy patients referred to a tertiary referral center.[2–5] Although this may not be true in general neurology practice, it is still important for the clinician to look for the clues that suggest a hereditary neuropathy. In patients with a chronic, very slowly progressive distal weakness over many years, with very little in the way of sensory symptoms, the clinician should pay particular attention to the family history and inquire about foot deformities in immediate relatives. Patients with hereditary neuropathy often will present with significant foot drop, with no sensory symptoms, but significant vibration loss in the toes. In addition, episodes of recurrent compressive mononeuropathies may indicate an underlying hereditary predisposition to pressure palsies. On examining the patient, the clinician must look carefully at the feet for arch and toe abnormalities (high or flat arches, hammer toes), and look at the spine for scoliosis. In suspicious cases, it may be necessary to perform both neurologic and electrophysiologic studies on family members (See the article by Saporta and colleagues elsewhere in this issue for further discussion of this topic).

PHENOTYPE PATTERNS OF NEUROPATHIC DISORDERS

After answering the 6 key questions obtained from the history and neurologic examination outlined here, one can classify neuropathic disorders into several patterns based on sensory and motor involvement and the distribution of signs (**Box 9**, **Table 2**). Each syndrome has a limited differential diagnosis. A final diagnosis is arrived at by using other clues such as the temporal course, presence of other disease states, family history, and information from laboratory studies. The authors use this pattern-recognition approach to neuropathic disorders routinely in patients, and suspect that many clinicians use a similar approach without being aware of it. Although this may seem like an oversimplification, the recognition of these patterns will usually push the clinician very close to the final diagnosis. After placing a patient in 1 of the 10 phenotype patterns, one can more appropriately begin the laboratory evaluation and potential treatments.[59] (See the articles by Levine and colleagues and Trivedi and colleagues elsewhere in this issue for further exploration of this topic.)

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