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Pattern Recognition Approach to Neuropathy and Neuronopathy

Richard J Barohn, M.D.[a] and **Anthony A. Amato, M.D.**[b]

[a]Chairman, Department of Neurology, and Gertrude and Dewey Ziegler Professor of Neurology, University of Kansas Medical Center, Kansas City, Kansas

[b]Vice-chairman, Department of Neurology, Brigham and Women's Hospital, Professor of Neurology, Harvard Medical School, Boston, MA

Synopsis

Neuropathic disorders encompass those that affect the neuron's cell body or neuronopathies, those affecting the peripheral process, or peripheral neuropathies. The peripheral neuropathies can be broadly subdivided into the myelinopathies and axonopathies. These conditions can be hereditary or acquired. Each of these disorders has distinct clinical features that enable neurologists to recognize the various patterns of presentation. Once a particular pattern is established, further laboratory studies can be performed to confirm the clinical impression.

Keywords

neuropathy; neuronopathy; myelinopathy; axonopathy; plexopathy; radiculopathy; mononeuritis; multiplex; entrapment neuropathy; hereditary neuropathy; autonomic neuropathy

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 (Table 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 which allow the clinician to place a patient's disease into one of these groups. Therefore, the

Corresponding Author: [a]Richard J. Barohn, M.D., Department of Neurology, University of Kansas Medical Center, 3901 Rainbow Blvd., Mail Stop 2012, Kansas City, KS 66160, Phone: 913.588.6094, Fax: 913.588.6948, rbarohn@kumc.edu.

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first two goals in the approach to a neuropathic disorder are to determine: (1) Where the lesion is; and (2) What the cause of the lesion is (Table 2).

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 or toxin induced? Is it mediated by an immune or infectious process? Or, is the cause unknown? The final goal in approaching the patient with a neuropathic disorder is to determine whether or not 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 two 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 or 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). Our 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 3. We recently did a similar analysis on cohorts of neuropathy between North American (Kansas City and Dallas) and South America (Rio de Janeiro, Brazil)[5, 6]

Our NA-SA analysis underscored that a hereditary neuropathy is common, accounting for 27% in NA and 10% in SA. Acquired demyelinating polyneuropathies accounted for 20% in NA and 18% in SA tertiary care neuropathy clinics. Diabetic neuropathies, while common (13% in NA and 23% in SA), may have been under-reported in these tertiary care neuropathy center populations.[7, 8] Approximately a quarter of the patients are ultimately found to have a predominantly sensory polyneuropathy with no identifiable cause (28% in NA and 23% in SA), i.e., cryptogenic sensory polyneuropathy (CSPN).[9-12] Overall, SA tertiary care centers were more likely to see patients with infections (Chagas, HTLV-1, leprosy), diabetic and hereditary disorders such as familial amyloid neuropathies.[5, 6] NA tertiary centers were more likely to see Charcot-Marie-Tooth neuropathy. Immune and cryptogenic neuropathies were seen equally in NA and SA).

In order 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, six key questions are asked. From the answer to these six key questions, the patient is placed into nine different phenotype patterns. Therefore, we 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 - Six Key Questions

The first step in our approach is to ask six key questions based on the patients symptoms and signs (Table 4):

1. What systems are involved?

It is important to determine if the patients symptoms and signs are pure motor, pure sensory, autonomic, or some combination of the above. 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 disease have evidence of

both upper and lower motor neuron dysfunction on examination, i.e., amyotrophic lateral sclerosis (ALS), which is the primary diagnostic hallmark of this disorder.[13, 14] On the other hand, nearly one-third of adult patients with acquired motor neuron disease may present initially without definite upper motor neuron findings,[15] and these patients are often referred to as 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)[16] and the version restricted to the legs has been termed leg amyotrophic diplegia (LAD).[17, 18] Spinal muscular atrophy (SMA) is the autosomal recessive motor neuronopathy of childhood.[19] Patients with pure motor distal weakness with a clinical phenotype of Charcot-Marie-Tooth (CMT) neuropathy but with no sensory involvement are now classified as hereditary motor neuropathy (HMN).[20-22] However, with advances in genetics we 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 or HSP).

The neuropathic disorders that may present with pure motor symptoms are listed in Table 5. While 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.[23, 24]

Some peripheral neuropathies are associated with significant autonomic nervous system dysfunction (Table 6). 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 fall 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.[25, 26]

2. What is the distribution of weakness?

The distribution of the patient's weakness is crucial for an accurate diagnosis and in this regard two 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 (Guillain-Barré Syndrome - GBS) and the chronic form (CIDP).[27-32] 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 (Table 7). Amyotrophic lateral sclerosis 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 symmetrical weakness patterns can also be seen in neuromuscular junction disorders (MG, LEMS) and some myopathies, particularly isolated neck extensor myopathy (INEM).[33] Therefore, these patterns are considered an overlap with myopathic disorder.

Other overlap patterns with muscle disease is seen with pure motor symmetric proximal > distal limb weakness. When this occurs due to a neuropathic basis, the primary consideration is spinal muscular atrophy. But of course, this is also the 'limb-girdle' pattern seen in many myopathies. Pure motor distal symmetrical weakness is the presentation for hereditary motor neuropathy, as noted above, but this pattern can also be seen in distal myopathies and rarely myasthenia gravis.[34, 35]

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 which can present with focal, asymmetric leg or arm weakness.[36] 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.[37] Unilateral combined motor and sensory presentations in a single extremity are usually due to a simple entrapment or compressive neuropathy or radiculopathy.[38]

The importance of finding symmetric proximal and distal weakness in a patient who presents with both motor and sensory symptoms cannot be over emphasized because this identifies the important subset of patients who may have a treatable acquired demyelinating neuropathic disorder, i.e. acute or chronic inflammatory demyelinating polyneuropathy. 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 unresponsive to 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.[23, 24, 29, 39, 40] In addition, the acquired demyelinating neuropathies associated with IgM kappa monoclonal antibodies, which are typically targeted to(and usually myelin associated glycoprotein have the curious pattern of predominantly distal symmetric sensory loss and weakness, with little or no proximal weakness. These patients, which we now call DADS neuropathy -M (Distal Acquired Demyelinating Symmetric with Monoclonal gammopathy).[29, 31,]

Another important exception to the rule that distal, symmetric sensory and motor sensory and motor loss is unresponsive to immunosuppressive therapy are the occasional patients with vasculitis of the peripheral nervous system. Approximately 20-30% of patients with vasculitis of the peripheral nervous may present with a distal, symmetric motor and sensory dysfunction[41, 42] 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 which help make the distinction from metabolic, toxic, or hereditary disorders.

3. What is the nature of the sensory involvement?

When taking the history from a patient with a peripheral neuropathy, it is important to determine if 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 two 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 (Table 8).

The cryptogenic sensory polyneuropathy (CSPN) and neuropathy due to diabetes mellitus are the most common neuropathies that are associated with severe pain.[10, 11, 12] In addition, painful peripheral neuropathies due to peripheral nerve vasculitis or Guillain-Barré Syndrome (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 is symmetric and usually worse in the feet. Another painful form of diabetic neuropathy is lumbosacral radiculoplexopathy (also known as diabetic amyotrophy), in which patients may present with the abrupt onset of back, hip or thigh pain that may precede weakness by days or weeks.[8, 43]

The other important sensory abnormality that significantly narrows the differential diagnosis is severe proprioceptive loss. This 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. While the symptoms of gait unsteadiness is 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 (i.e., ganglionopathy). In addition to the severe proprioceptive and vibration deficits, sensory neuronopathies usually have a pan-modality sensory loss in the affected extremities. Light touch and pain sensation are also affected due to injury of all sensory cell bodies. The various causes of sensory neuronopathy are listed in Table 9.

A variant of CIDP termed chronic immune sensory polyradiculopathy (CISP) manifests as a sensory ataxia and clinically resembles a sensory neuronopathy/ganglionopathy.[44] Normal sensory nerve action potentials (because the lesion is proximal to the ganglion cells) differentiates this disorder from sensory neuronopathy. We probably have seen these patients in the past, and were perplexed by the preserved sensory nerve action potentials.[45, 46] 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 may be more proximal potentials on somatosensory evoked potentials due to proximal demyelination of the sensory roots. CSF protein may be elevated. In addition, enlarged and enhancing nerve roots may be appreciated on magnetic resonance imaging. Rroot biopsies have demonstrated demyelination and inflammation. Most of these patients respond to immunomodulating therapy similar to CIDP. Therefore, CISP should be in the differential of severe ataxia, and 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, posterior column myelopathy is generally symmetric, in general is less profound than most of the patients with true dorsal root ganglion loss and is often associated with evidence of upper motor neuron pathology (see below). One notable exception is Vitamin E deficiency which can affect both sensory nerves and posterior columns and produce a profound symmetric proprioceptive deficit.[47]

The modalities of light touch, pain sensation (with an unused safety pin), vibration and proprioception should be assessed in all four limbs in a patient with a peripheral neuropathy. We have found the use of nylon monofilaments of different tensile strengths very useful in assessing and grading the loss of touch sensation.[37, 49] Another useful quantitative bedside test that is easy to perform is maximal timed vibratory testing with a 128 Hz tuning fork. Our 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, we allow 1 second of vibration perception loss per decade (authors' unpublished observations). 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 re-checked at each follow-up visit to monitor the course.

On the other hand, we believe that it is extremely difficult to determine with any degree of certainty if temperature sensation deficits are present with bedside testing and therefore we do not routinely check this modality. We suspect that temperature sensation can only be assessed reliably with computerized quantitative sensory testing (QST). QST has now become commercially available through a number of manufacturers.[50] However, our experience in measuring QST for temperature and vibration thresholds in over 800 neuropathy patients, was disappointing in ultimately assisting us in diagnosis and management.[51] At this time, we do not believe that QST is useful in routine clinical practice.

In general, we have found the concept trying to place patients into categories of "large" 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 (e.g., CSPN and diabetes) will clinically have diminished light touch, pin, and vibration sensation, with proprioception affected in more severe cases.[10-12, 52] In addition, quantitative sensory testing for vibration and temperature thresholds in these common disorders usually shows abnormalities in both modalities. Truly, selective involvement of small sensory fibers for pain and temperature sensation is uncommon and seen in rare disorders such as hereditary sensory neuropathy, Fabry's 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 confirming the clinical suspicion obtained from the history and clinical exam.[52-53] The value of skin biopsies lie more in their potential as an objective marker for research studies.[54]

4. Is there evidence of upper motor neuron involvement?

In patients with symptoms of signs suggestive of lower motor neuron pathology without sensory loss, the presence of concomitant upper motor neuron signs is the hallmark of amyotrophic lateral sclerosis.[13, 14] As noted above, 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),[55, 56] as well as hereditary spastic paraparesis.

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 B12 deficiency, but other causes of combined system degeneration with neuropathy should be considered (e.g., copper deficiency, HIV infection, severe hepatic disease, adrenomyeloneuropathy).[57-60] In our 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 B12 deficiency (i.e., assessing for elevated serum methymalonic acid and homocysteine levels), if the B12 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, what we have called the “numb hand syndrome”.[58-60, 61-62]

A similar myeloneuropathy or myelopathy may occur secondary to copper deficiency.[63-66] 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), 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 can be due to prior gastric surgery. The use of denture adhesives contain zinc has also been associated with copper deficiency.[67] In such cases, zinc levels are elevated and the metal may compete with copper leading to the syndrome.[67] Treatment with either daily oral copper supplements, or in severe cases, intravenous copper therapy.

5. 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 to 8 weeks), or chronic (greater than 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 (B6), alcohol, and dietary habits.

6. Is there evidence for a hereditary neuropathy?

Finally, a hereditary cause for a peripheral neuropathy should not be overlooked.[22, 68, 69] 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.[3-6] While 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, have no sensory symptoms, but have 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.

10 Phenotype Patterns of Neuropathic Disorders

After answering the six key questions obtained from the history and neurologic examination outlined above, one can classify neuropathic disorders into several patterns based on sensory and motor involvement and distribution of signs (Table 10, Table 11). Each syndrome has a limited differential diagnosis. A final diagnosis is arrived at by utilizing other clues such as the temporal course, presence of other disease states, and family history and information from laboratory studies. We use this pattern recognition approach to neuropathic disorders routinely in our patients, and we suspect many clinicians use a similar approach without being aware of it. While this may seem like an over-simplification, the recognition of these patterns will usually get the clinician very close to the final diagnosis. After placing a patient in one of the 10 phenotype patterns, then one can more appropriately begin the laboratory evaluation and potential treatments.[70, 71]

References:

1. Pasnoor M, Dimachkie MM, Kluding P, Barohn RJ. Diabetic Neuropathy Part 1: Overview and Symmetric Phenotypes. Neurology Clinics. this issue.
2. Amato, AA.; Russell, J. Neuromuscular Disease. McGraw-Hill; New York: 2008. p. 3-69.
3. Amato, AA.; Barohn, RJ. Peripheral Neuropathy. In: Longo, DL.; Fauci, AS.; Kasper, DL.; Hauser, SL.; Jameson, JL.; Loscalzo, J., editors. Harrison's Principles of Internal Medicine. 18th Edition. p. 3448-3472.
4. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. Ann Neurol. 1981; 10:222–226. [PubMed: 7294727]
5. Barohn RJ. Approach to peripheral neuropathy and neuronopathy. Sem Neurol. 1998; 18:7–18.
6. Khan S, Pasnoor M, Mummaneni RB, McVey A, Herbelin L, Saperstein D, Gronseth G, Barohn RJ, Wolfe GI, Nations SP, Trivedi JR, Vernino S, Nascimento OJM, de Freitas MRG, Quintanilha G. North America and South America (NA-SA) Neuropathy Project. J Child Neurol. 2006; 21(3)
7. Pasnoor M, Nascimento O, Trivedi J, Wolfe G, Nations S, Herbelin L, Freitus M, Quintanilha G, Khan S, Dimachkie M, Barohn RJ. North America and South America (NA-SA) Neuropathy Project. nt J Neurosci. in press.
8. Pasnoor M, Dimachkie MM, Kluding P, Barohn RJ. Diabetic Neuropathy Part 1: Overview and Symmetric Phenotypes. Neurology Clinics. this issue.
9. Pasnoor M, Dimachkie MM, Barohn RJ. Diabetic Neuropathy Part 2: Proximal and Assymetric Phenotypes. Neurology Clinics. this issue.
10. Grahmann F, Winterholler M, Neundorfer B. Cryptogenetic polyneuropathies: an out-patient follow-up study. Acta Neurol Scand. 1991; 84:221–225. [PubMed: 1659105]
11. Wolfe GI, Barohn RJ. Cryptogenic sensory and sensorimotor polyneuropathies. Sem Neurol. 1998; 18:105–112.
12. Pasnoor M, Dimachkie MM, Barohn RJ. Cryptogenic Sensory Polyneuropathy. Neurology Clinics. this issue.
13. Wolfe GI, Baker NS, Amato AA, Jackson CE, Nations SP, Saperstein DS, Bryan WW, Barohn RJ. Chronic cryptogenic sensory polyneuropathies: clinical and laboratory characteristics. Arch Neurol. 1999; 56:540–547. [PubMed: 10328248]
14. Jackson CE, Bryan WW. Amyotrophic lateral sclerosis. Sem Neurol. 1998; 18:27–40.
15. Barohn, RJ. CONTINUUM: *Lifelong Learning in Neurology*. Lippincott Williams & Wilkins; 2009. Clinical spectrum of motor neuron disorders; p. 111-131.
16. Tan E, Lynn DJ, Amato AA, Kissel JT, Rammohan KW, Sahenk Z, Warmolts JR, Jackson CE, Barohn RJ, Mendell JR. Immunosuppressive treatment of motor neuron syndromes: attempts to distinguish a treatable disorder. Arch Neurol. 1994; 51:194–200. [PubMed: 8304845]

17. Katz JS, Wolfe GI, Anderson PB, Saperstein DS, Elliott J, Nations SP, Byran WW, Barohn RJ. Brachial amyotrophic diplegia: a slowly progressive motor neuron disorder. Neuorlogy. 1999; 53:1071–1076.
18. Rosenfeld J, Chang SW, Jackson CE, Elchami Z, Barohn RJ. Lower extremity amyotrophic diplegia (LAD): A new clinical entity in the spectrum of motor neuron disease. Neurology. 2002; 58:A411–A412.
19. Muzyka IM, Dimachkie MM, Barohn RJ, Katz JS, Jackson C, Wang Y, McVey A, Dick A, Pasnoor M, Mozaffar T, Rosenfeld J. Lower extremity amyotrophic diplegia (LAD): prevalance and pattern of weakness. J Clin Neuromusc Dis. 2010; 11(3):14–15.
20. Iannaccone ST. Spinal Muscular Atrophy. Sem Neurol. 1998; 18:19–26.
21. Workshop report, 2nd Workshop of the European CMT Consortium. 53rd ENMC International Workshop on Classification and Diagnostic Guidelines for Charcot-Marie-Tooth Type 2 (CMT2-HMSN II) and Distal Hereditary Motor Neuropathy (Distal HMN-Spina CMT) 26-28, September 1997, Naarden, The Netherlands. Neuromuscular Disorders. 1998; 8:426–431. [PubMed: 9713862]
22. Nanjiani Z, Nations SP, Elliott JL, Wolfe GI, Bryan WW, Barohn RJ. Distal hereditary motor neuropathy: A distinct form of Charcot-Marie-Tooth disease. J Child Neurol. 2000; 15:200–2001. abstract.
23. Saporta MA, Shy ME. Inherited Peripheral Neuropathies. Neurology Clinics. this issue.
24. Katz JS, Wolfe GI, Bryan WW, Jackson CE, Amato AA, Barohn RJ. Electrophysiologic findings in multifocal motor neuropathy. Neurology. 1997; 48:700–707. [PubMed: 9065551]
25. Dimachkie MM, Barohn RJ, Katz J. Multifocal Motor Neuropathy, Multifocal Acquired Demyelinating Sensory and Motor Neuropathy and Other Chronic Acquired Demyelinating Polyneuropathy Variants. Neurology Clinics. this issue.
26. Hart RG, Kanter MC. Acute autonomic neuropathy: two cases and a clinical review. Arch Intern Med. 1990; 150:2373–2376. [PubMed: 2241448]
27. Suarez GA, Fealey RD, Camilleri M, Low PA. Idiopathic autonomic neuropathy: clinical, neurophysiologic, and follow-up studies on 27 patients. Neurology. 1994; 44:1675–1682. [PubMed: 7936295]
28. Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyneuropathy. Clinical characteristics, course, and recommendations for diagnostic criteria. Arch Neurol. 1989; 46:878–884. [PubMed: 2757528]
29. Barohn RJ, Saperstein DS. Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy. Sem Neurol. 1998; 18:49–62.
30. Saperstein DS, Katz JS, Amato AA, Barohn RJ. Clinical spectrum of chronic acquired demyelinating polyneuropathies. Muscle Nerve. 2001; 24(3):311–324. [PubMed: 11353415]
31. Dimachkie MM, Barohn RJ. Guillain-Barre Syndrome and Variants. Neurology Clinics. this issue.
32. Gorson KC, Katz J. Chronic Inflammatory Demyelinating Polyneuropathy. Neurology Clinics. this issue.
33. Dimachkie, MM.; Barohn, RJ.; Tawil; Venance. Neurology in Practice: Neuromuscular Diosrders. 2011. Acute inflammatory demyelinating neuropathies and variants; p. 183-189.
34. Katz JS, Wolfe GI, Burns DK, Bryan WW, Fleckenstein JL, Barohn RJ. Isolated neck extensor myopathy: a common cause of dropped head syndrome. Neurology. 1996; 46:917–921. [PubMed: 8780064]
35. Saperstein DS, Amato A, Barohn RJ. Clinical and genetics aspects of the distal myopathies. Muscle Nerve. 2001; 24:1440–1450. [PubMed: 11745945]
36. Nations SP, Wolfe GI, Amato AA, Jackson CE, Bryan WW, Barohn RJ. Distal myasthenia gravis. Neurology. 1999; 52:632–634. [PubMed: 10025802]
37. Amato AA, Gronseth GS, Callerame KJ, Kagan-Hallet KS, Bryan WW, Barohn RJ. Tomaculous neuropathy: a clinical and electrophysiological study in patients with and without 1.5-Mb deletions in chromosome 17p11.2. Muscle Nerve. 1996; 19:16–22. [PubMed: 8538664]
38. Nations SP, Katz JS, Lyde CB, Barohn RJ. Leprous neuropathy: an American perspective. Sem Neurol. 1998; 18:113–124.

39. Arnold WD, Elsheikh B. Entrapment Neuropathies. Neurology Clinics. this issue.
40. Saperstein DS, Amato A, Wolfe GI, et al. Multifocal acquired demyelinating sensory and motor neuropathy: the Lewis-Sumner syndrome. Muscle Nerve. 1999; 22:560–566. [PubMed: 10331353]
41. Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ. Distal acquired demyelinating symmetric (DADS) neuropathy. Neurology. 2000; 54:615–620. [PubMed: 10680792]
42. Kissel JT, Slivka AP, Warmolts JR, Mendell JR. The clinical spectrum of necrotizing angiopathy of the peripheral nervous system. Ann Neurol. 1985; 18:251–257. [PubMed: 4037764]
43. Collins MP, Arnold WD, Kissel JT. The neuropathies of vasculitis. Neurology Clinics. this issue.
44. Barohn RJ, Zahenk Z, Warmolts JR, Mendell JR. The Bruns-Garland syndrome (diabetic amyotrophy): revisited 100 years later. Arch Neurol. 1991; 48:1130–1135. [PubMed: 1953396]
45. Sinnreich M, Klein CJ, Daube JR, Engelstad J, Spinner RJ, Dyck P. Chronic immune sensory polyradiculopathy: A possibly treatable sensory ataxia. Neurology. 2004; 63:1662–1669. [PubMed: 15534252]
46. Greenfield F, Bryan WW, Katz JS, Barohn RJ. Chronic sensory ataxia: an usual case. J Child Neurol. 1995; 10:161. abstract.
47. Manek S, Nations SP, Wolfe GI, Bryan WW, Burns DK, Barohn RJ. Idiopathic chronic sensory ataxia: where is the lesion? J Child Neurol. 2000; 15:193. abstract.
48. Jackson CE, Amato AA, Barohn RJ. Case of the month: Isolated vitamin E deficiency. Muscle Nerve. 1996; 19:1161–1165. [PubMed: 8761274]
49. Caputo GM, Cavanaugh PR, Ulbrecht JS, Gibbons GW, Karchmer AW. Assessment and management of foot disease in patients with diabetes. N Engl J Med. 1994; 331:854–860. [PubMed: 7848417]
50. Yarnitsky D. Quantitative sensory testing. Muscle Nerve. 1997; 20:198–204. [PubMed: 9040659]
51. Saperstein DS, Wolfe GI, Longeria O, Herbelin LL, Nations SP, Jackson CE, Bryan WW, Barohn RJ. Quantitative sensory testing in a large cohort of neuropathy patients. Muscle Nerve. 2001; 24:1417–1418. abstract.
52. Barohn RJ. Intra-epidermal nerve fiber assessment: a new window on peripheral neuropathy. Arch Neurol. 1998; 88:1505–1520. [PubMed: 9865792]
53. England JD, Gronseth GS, Franklin G, et al. Practice parameter: the evaluation of distal symmetric polyneuropathy: the role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. Muscle Nerve. 2009; 39:106–115. [PubMed: 19086069]
54. England JD, Gronseth GS, Franklin G, et al. Evaluation of distal symmetric polyneuropathy: The role of laboratory and genetic testing (an evidence-based review). Muscle Nerve. 2009; 39:116–25. [PubMed: 19086068]
55. Kluding PM, Pasnoor M, Singh R, Jernigan S, Farmer K, Rucker J, Sharma NK, Wright DE. The effect of exercise on neuropathic symptoms, nerve function, and cutaneous innervation in people with diabetic peripheral neuropathy. JNNP. 2012; 26:424–429.
56. Singer MA, Kojan S, Barohn RJ, Herbelin L, Nations SP, Trivedi JR, Jackson CE, Burns DK, Boyer PJ, Wolfe GI. Primary lateral sclerosis: clinical and laboratory findings in 25 patients. J Clin Neuromusc Dis. 2005; 7:1–9.
57. Singer MA, Statland JM, Wolfe GI, Barohn RJ. Primary lateral sclerosis. Muscle Nerve. 2007; 35(3):291–302. [PubMed: 17212349]
58. Saperstein, DS.; Barohn, RJ. Polyneuropathy due to nutritional and vitamin deficiency. In: Dyck, PJ.; Thomas, PK., editors. Peripheral Neuropathy. Elsevier Saunders; Philadelphia: 2005. p. 2051-2062.
59. Saperstein DS, Barohn RJ. Peripheral neuropathy due to cobalamin deficiency. Current Treatment Options in Neurology. 2002; 4:197–201. [PubMed: 11931726]
60. Saperstein DS, Wolfe GI, Gronseth GS, Nations SP, Herbelin LL, Barohn RJ. Challenges in the identification of cobalamin deficiency polyneuropathy. Arch Neurol. 2003; 60:1296–1301. [PubMed: 12975298]

61. Kojan S, Cheema Z, Nations SP, Wolfe GI, Bryan WW, Barohn RJ. Neurophysiologic abnormalities in adrenymyeloneuropathy: selective central and peripheral nervous system involvement. J Child Neurol. 2000; 15:197.

62. Jackson CE, Barohn RJ. Lesion localization of the number hand syndrome in B12 deficiency. Muscle Nerve. 1993; 16:1111–1112. abstract.

63. Hammond N, Wang Y, Dimachkie M, Barohn R. Nutritional Neuropathies. Neurology Clinics. this issue.

64. Greenberg SA, Briemberg HR. A neurological and hematological syndrome associated with zinc excess and copper deficiency. J Neurol. 2004; 251:111–4. [PubMed: 14999501]

65. Hedera P, Fink JK, Bockenstedt PL, Brewer GJ. Myelopolyneuropathy and pancytopenia due to copper deficiency and high zinc levels of unknown origin: further support for existence of a new zinc overload syndrome. Arch Neurol. 2003; 60:1303–1306. [PubMed: 12975299]

66. Kumar N, Gross JB, Ahlskog JE. Copper deficiency myelopathy produces a clinical picture like acute combined degeneration. Neurology. 2004; 63:33–39. [PubMed: 15249607]

67. Kumar N. Copper deficiency myelopathy (human swayback). Mayo Clin Proc. 2006; 81(10):1371–1384. [PubMed: 17036563]

68. Nations SP, et al. Denture cream: an unusual source of excess zinc, leading to hypocupremia and neurologic disease. Neurology. 2008; 71(9):639–643. [PubMed: 18525032]

69. Mendell JR. Charcot-Marie-Tooth neuropathies and related disorders. Sem Neurol. 1998; 18:41–48.

70. Saporta AS, Sottile SL, Miller LJ, Feely SM, Siskind CE, Shy ME. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol. 2011; 69:22–33. [PubMed: 21280073]

71. Levine TD, Saperstein DS. Laboratory Evaluation of Peripheral Neuropathy. Neurology Clinics. this issue.

72. Trivedi JR, Silvestri NJ, Wolfe GI. Treatment of Painful Peripheral Neuropathy. Neurology Clinics. this issue.

Key Points

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

TABLE 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

TABLE 2

Etiology of Neuropathic Disorders

- **I.** ACQUIRED:
  - Dysmetabolic states
    - Diabetes mellitus
    - Neuropathy related to renal disease
    - Vitamin deficiency states (ex. vitamin B12 deficiency)
  - Immune-mediated
    - Guillain-Barre Syndrome
    - Chronic inflammatory demyelinating polyneuropathy (CIDP) and variants
    - Multifocal motor neuropathy
    - Anti-MAG associated DADS
    - Radiculoplexus neuropathy – cervical, thoracic, and lumbosacral
    - Vasculitis
    - Sarcoidosis
  - Infectious
    - Herpes zoster
    - Leprosy, Lyme, HIV, CMV, EBVrelated
  - 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 (HSAN)
  - Familial brachial plexopathy
  - Familial amyloidosis
  - Porphyria
  - Other rare peripheral neuropathies (Fabry’s, metachromatic leukodystrophy, adrenoleukodystrophy, Refsum’s disease, etc.)
  - Motor neuron disease
    - Spinal muscular atrophy
    - Familial amyotrophic lateral sclerosis
    - X-linked bulbospinal muscular atrophy

Hereditary motor neuropathy (HMN)

Hereditary Spastic paraplegia (HSP)

TABLE 3

Breakdown by Diagnosis of 402 Consecutive Polyneuropathy Patients Referred to the University of Texas at Dallas/San Antonio Neuromuscular Clinics[4]

Diagnosis	# 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 B12 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†	27	6.7

From Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. Ann Neurol 1981; 10:222-226; with permission.

†includes: motor neuron disease plus 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), collagen vascular disease associated SMPN (1), thyrotoxicosis (1), SMPN associated with leukemia (1), toxin-induced (1).

TABLE 4

Approach to Neuropathic Disorders: Six Key Questions

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

TABLE 5

Neuropathic Disorders That May Have Only Motor Symptoms At Presentation

Motor neuron disease
Multifocal motor neuropathy
Guillain-Barré Syndrome*
CIDP*
Lead intoxication*
Acute porphyria*
Hereditary motor sensory neuropathy*
(Charcot-Marie-Tooth disease)
Hereditary motor neuropathy

*usually has sensory signs on examination

TABLE 6

Peripheral Neuropathies With Autonomic Nervous System Involvement

Hereditary sensory autonomic neuropathy
Diabetes mellitus
Amyloidosis (familial and acquired)
Guillain-Barre syndrome
Vincristine induced
Porphyria
HIV-related autonomic neuropathy
Idiopathic pandysautonomia

TABLE 7

Neuropathic Disorders that Produce Asymmetric/Focal Weakness

Motor neuron disease
Amyotrophic lateral sclerosis
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

TABLE 8

Peripheral Neuropathies That Are Often Associated With Pain

Cryptogenic sensory or sensorimotor neuropathy
Diabetes mellitus
Vasculitis
Guillain-Barre syndrome
Amyloidosis
Toxic (arsenic, thallium)
HIV related distal symmetrical polyneuropathy
Fabry’s disease

TABLE 9

Causes of Sensory Neuronopathy (Ganglionopathy)

Cancer (Paraneoplastic)
Sjögren's syndrome
Idiopathic sensory neuronopathy
Cisplatinum and other analogues
Vitamin B6 toxicity
HIV-related sensory neuronopathy

TABLE 10

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 (Charcot-Marie-Tooth, amyloidosis and others)

Pattern 3: Asymmetric distal weakness with sensory loss

Multiple nerves, consider: vasculitis

hereditary neuropathy with liability to pressure palsies (HNPP)

multifocal acquired demyelinating sensory and motor (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: A. with upper motor neuron findings

1. motor neuron disease/ALS/PLS

B. without upper motor neuron findings

1. progressive muscular atrophy (PMA)
    a. brachial amyotrophic diplegia (BAD)
    b. leg amyotrophic diplegia (LAD)
2. multifocal motor neuropathy
3. multifocal acquired motor axonopathy (MAMA)
4. juvenile monomelic amyotrophy

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

Consider: B12 deficiency and other causes of combined system degeneration with peripheral neuropathy

Copper deficiency (including Zinc toxicity)

Inherited disorders (adrenomyeloneuropathy, MLD, Friedreich's)

Pattern 7: Symmetric weakness without sensory loss*

Consider: A. Proximal and distal weakness

1. Spinal muscular atrophy

B. Distal weakness

1. Hereditary motor neuropathy

Pattern 8: Focal midline proximal symmetric weakness*

Consider: Neck extensor weakness - ALS

Bulbar weakness - ALS, PLS

Pattern 9: Asymmetric proprioceptive sensory loss without weakness

Consider: sensory neuronopathy (ganglionopathy) (Table 10)

chronic immune sensory polyradiculopathy (CISP)

Pattern 10: Autonomic Symptoms and Signs

Consider: neuropathies associated with autonomic dysfunction (Table 7)

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* Overlaps with myopathies and NMJ disorders

Table 11

CLINICAL PATTERNS OF NEUROPATHIC DISORDERS

	Weakness								
	Prox	**Dis**	**Asymm**	**Symm**	**Sensory Symptoms**	**Severe Proprioceptive Loss**	**UMN Signs**	**Autonomic Symps/Signs**	**Diagnosis**
Pattern 1 - Symmetric prox & Distal weakness w/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 prox & distal weakness w/sensory loss	+	+	+		+				Polyradiculopathy, plexopathy
Pattern 5 - Asymmetric distal weakness w/out sensory loss		+	+				+/−		+ UMN – ALS Pure UMN - PLS - UMN – MMN, PMA, MAMA, BAD, LAD
Pattern 6 - Symmetric sensory loss & upper motor neuron signs		+		+	+	+	+		B12 defic; Copper deficiency, Friedreich's, adrenomyeloneuropathy
Pattern 7* Symmetric weakness without sensory loss	+/−	+		+					Prox & Distal SMA Distal Hereditary motor neuropathy
Pattern 8* Focal midline proximal symmetric weakness	+ Neck/extensor + Bulbar			+ +			+ +		ALS
Pattern 9 - Asymmetric proprioceptive loss w/out weakness			+		+	+			Sensory neuronopathy (ganglionopathy)
Pattern 10 - Autonomic dysfunction								+	HSAN, diabetes, GBS,

	Weakness								
	Prox	**Dis**	**Asymm**	**Symm**	**Sensory Symptoms**	**Severe Proprioceptive Loss**	**UMN Signs**	**Autonomic Symps/Signs**	**Diagnosis**
									amyloid, porphyria, Fabry's

Legend:

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

LMN lower motor neuron

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

* Overlap patterns with myopathy/NMJ disorders