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Electrodiagnostic approach to the patient with suspected peripheral polyneuropathy

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The true prevalence of peripheral neuropathy remains unknown; however some have speculated, based on limited epidemiological studies, that the prevalence might be as high as 8% [1,2]. Peripheral neuropathy is a common manifestation of many systemic diseases, with diabetes and alcohol abuse (plus its associated nutritional factors) being the most common etiologies in the developed world, and leprosy being the primary cause of treatable neuropathy in the world [3]. The myriad of etiologies of peripheral neuropathy seems to pose a daunting task for the clinician. Despite the increasing number of diagnostic tests (namely antibody panels and genetic testing), up to 22% of neuropathies will be of an idiopathic etiology, although approximately 42% of undiagnosed neuropathies may be attributed to a familial neuropathy if a meticulous family history is taken and relatives are carefully examined [4,5].

To many clinicians, the evaluation of peripheral neuropathy invokes much pessimism and skepticism at the likelihood of discovering a cause or a treatment for the underlying neuropathy. Investigating peripheral neuropathy may be costly, because physicians frequently use a "shotgun" approach by ordering a standard battery of tests, including serology evaluations [6,7]. This approach is common and frequently results in an incorrect diagnosis secondary to incidental abnormalities found on serology testing, such as an insignificantly elevated antibody titer or an incomplete history (medical, family, social, or occupational). Recently Dyck et al. described a methodology they identified as the "Gestalt" approach [6]. This methodol-

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ogy is used by many clinicians and is based on recognition of the clinical pattern of neuropathy to help guide investigations. It is based on a standard series of questions that can help hone in on the cause of the neuropathy by limiting the number of disorders included in the differential diagnosis [8]. By focusing on symptoms, signs, and electrodiagnostic (EDX) features, the most likely causes of the neuropathy are identified. These features include inquiry about the presence or absence of weakness, sensory complaints including pain, autonomic dysfunction, plus clinical examination to identify the magnitude and distribution of neurologic impairments. When combined with the characteristics of the EDX testing, this information allows the clinician to identify the cause of the neuropathy in a cost-effective way by using a systematic rational approach that tailors laboratory investigations based on the more limited differential diagnosis [9]. This approach is limited, at least in part, by the experience of the clinician and the ability to recognize patterns of abnormality.

Several individuals have suggested the use of a series of algorithms to establish the etiology of a neuropathy. Dyck et al described the ''10 P's for characterizing peripheral neuropathy'' (Box 1) [6]. These are a series of 10 questions designed to lead the clinician in a logical and sequential manner to help establish a correct diagnosis. Questions asked range from inquiry about the distribution of symptoms and signs to the results of serologic testing. Barohn (Box 2) proposed a slightly different set of questions that are used to identify the evolution of symptoms and to establish the presence or absence of symmetry, sensory or motor involvement, pain, autonomic dysfunction, a positive family history, and the opportunity for neurotoxic exposure, to mention a few [10]. Others have developed diagrammatic algorithms to guide the clinician through the differential diagnosis of peripheral neuropathies [11,12].

Box 1
The 10 P's for characterizing peripheral neuropathy [6]

1 Pattern: anatomic and temporal
2 Population of neurons
3 Part of neuron assumed to be the primary site of pathologic abnormality
4 Physiology
5 Pathology
6 Prickling
7 Phenomena: toxic exposures, diseases, or signs
8 Pedigree
9 Plasma: laboratory abnormalities
10 Pharmacology: response to therapies

Box 2
Peripheral neuropathy patterns [10]

1. Symmetric sensory loss without motor involvement
   - Cryptogenic
   - Metabolic
   - Toxic
2. Symmetric distal motor with sensory loss
   - Metabolic
   - Hereditary
   - Toxic
3. Symmetric distal and proximal motor with sensory loss
   - AIDP
   - CIDP
4. Asymmetric distal motor with sensory loss
   - HNPP
   - Infectious
   - Vasculitis
5. Asymmetric distal motor without sensory loss
   - Motor neuron disease
   - Multifocal motor neuropathy with conduction block
6. Asymmetric proximal and distal motor with sensory loss
   - Plexopathy
   - Radiculopathy/polyradiculopathy
7. Asymmetric sensory loss without motor involvement
   - Sensory neuropathy (neuronopathy)
8. Autonomic

Abbreviations: AIDP = acute inflammatory demyelinating polyneuropathy; CIDP = chronic inflammatory demyelinating polyneuropathy; HNPP = hereditary neuropathy with liability to pressure palsy.

The following approach is a combination of the above algorithms that should provide clinicians with an efficient and logical approach to the evaluation of peripheral neuropathy. Although there are few cardinal or diagnostic features that are specific for any particular form of neuropathy, there are features useful in limiting the number of diagnostic considerations. In the material that follows, individual characteristics of the patient's neuropathy are used to identify disorders that share those characteristics. For example, features related to symptom localization, the presence of pain, temporal progression, EDX evidence of demyelination, exclusive or predominant motor or sensory involvement, and the presence of asymmetry all suggest a limited number of known possible causes for the neuropathy. Those causes are identified in the tables and briefly discussed. For neuropathies that are

characterized by several uncommon features, a small number of explanations may be common to the lists of possible cause for each feature. At the very least, by identifying the most likely explanations, the need for additional diagnostic testing is greatly reduced.

Localization, anatomic, and pathology considerations

Patients may present with several sensory or motor complaints, not all of which are necessarily caused by peripheral nerve disease, and accurate localization within the nervous system is critical in establishing a correct diagnosis. Sensory symptoms and signs should either follow a dermatomal distribution, a stocking-and-glove distribution, or a distribution of complaints that make anatomic sense. These findings should be associated with hyporeflexia. The patient's presenting clinical syndrome may include symptoms and signs of autonomic dysfunction. In addition, the clinical features of the neuropathy should follow one of the eight patterns of peripheral neuropathy (Box 2). Individuals not fulfilling any of these descriptions should be evaluated for a possible central nervous system or somatic etiology to their disorder. Subjects with corresponding cervical or lumbosacral pain should be evaluated for a potential radiculopathy. Polyneuropathies are generally symmetric in distribution and nerves are affected in a length-dependent manner, whereas polyradiculopathies or polyradiculoneuropathies typically involve proximal and distal nerves.

Confirmation of a peripheral nerve disorder may be achieved by way of EDX testing. The results of electromyography (EMG) (ie, nerve conduction studies and the needle EMG examination) may yield vital information regarding nerve pathology. These results can be used to characterize the disorder as either axonal or demyelinating (hereditary or acquired), or a mixture of axonal degeneration and demyelination (Box 3a & Box 3b). Axonal neuropathies generally display a distal-to-proximal gradient as longer nerves tend to be affected first. Primary demyelinating neuropathies affect the nerve at multiple segments and thus produce distal and proximal symptoms and signs [13].

Clinical history

Pain

Frequently patients present for evaluation of allodynia (pain following nonpainful stimulation), dysesthesias (unpleasant sensation following a nonpainful stimulus), hyperalgesia (increased pain sensation, greater than normal), or paresthesias (irritating spontaneous sensations). The presence of a painful neuropathy raises the possibility of several etiologies (Tables 1a, 1b, and Box 4). Most neuropathies are not particularly painful, however,

Box 3a
Electrodiagnostic criteria for demyelinating polyneuropathy [30]

1. Nerve conduction studies must have three of the following four criteria:
   - A. Decreased conduction velocity (CV) in 2 or more motor nerves
     - i. <80% lower limit of normal (LLN) if CMAP amplitude >80% LLN
     - ii. <70% LLN if CMAP amplitude <80% LLN
   - B. Partial conduction block or abnormal temporal dispersion in at least one motor nerve
   - C. Prolonged distal latencies in greater than two nerves
     - i. >125% of upper limit of normal (ULN) if amplitude >80% LLN
     - ii. >150% of ULN if amplitude <80% LLN
   - D. Absent F waves or prolonged minimum F-wave latencies in two or more nerves
     - i. >120% of ULN if amplitude >80% of LLN
     - ii. >150% of ULN if amplitude <80% of LLN
2. Additional supportive findings:
   - A. Sensory conduction velocity <80% LLN
   - B. Absent H reflex

and the presence of severe pain is an important feature. In Table 1, distinction is made between those neuropathies in which pain is a predominant feature (Table 1a), and those neuropathies that may be associated with pain, although typically not as a characteristic feature (Table 1b). The association of severe pain and dysautonomia raises the possibility of amyloidosis,

Box 3b
Dutch Guillain-Barre Study Group criteria for acute inflammatory demyelinating polyneuropathy [31]

1. Distal motor latency of >150% upper limit normal (ULN)
2. F-wave latency >150% ULN
3. Conduction velocities <70% lower limit normal
4. Abnormal proximal-to-distal CMAP drop
5. Distal CMAP duration >300% ULN
6. Temporal dispersion >150% ULN

although other disorders, including diabetes mellitus, produce similar problems. Physical examination may demonstrate angiokeratomas suggestive of Fabry disease in a patient with painful neuropathy. A neuropathy with episodes of lancinating pain associated with enlarged, yellow/orange tonsils and hypocholesterolemia suggests a diagnosis of Tangier disease. This genetic disease is characterized by a deficiency in high density lipoproteins, which leads to abnormal fatty deposits in the tonsils giving them their classic appearance. This disorder is distinct from most of the other forms of small fiber neuropathy as there are additional findings on neurological examination. Some of these patients develop a progressive, symmetric polyneuropathy with dissociative loss of pain and temperature in the upper trunk and extremities, with combined faciobrachial muscle wasting in a pattern similar to that associated with syringomyelia. Painful HIV neuropathy generally presents in the late stages of the disease, making the diagnosis apparent because the systemic diagnosis is typically established by the time neuropathy develops [14]. A list of painful mononeuropathies is found in Box 4.

Altered sensation to pain and temperature sensation associated with painful dysesthesias and on occasion autonomic dysfunction is characteristic of *small fiber neuropathies*, most of which are characterized by pain. Small fiber neuropathies have few objective signs on neurological examination. Deep tendon reflexes are usually preserved, as is the balance and the motor examination, compared with the large fiber neuropathies in which they are typically abnormal. Nerve conduction studies that evaluate large nerve fibers are often normal, although there may be some minor abnormalities because most small fiber-predominant neuropathies also have some compo-

Table 1a
Primary painful polyneuropathies [32,33]

	Diagnosis
Idiopathic	
Idiopathic distal small fiber neuropathy[a]	
Inflammatory	
Vasculitic neuropathy	Vasculitic workup/biopsy
Perineuritis	Biopsy
Hereditary	
Fabry[a] disease	Alpha-galactosidase A
HSAN type V	
Tangier disease[a]	Hypocholesterolemia, low serum alpha-lipoprotein
Metabolic	
Amyloidosis[a]	Biopsy/genetic testing
Diabetes[a]	AM glucose/2 hour GTT
Painful symmetrical polyneuropathy	
Asymmetric polyradiculoneuropathy	
Truncal mononeuropathy	

[a] Denotes small fiber neuropathy.

Table 1b
Polyneuropathies associated with pain [30,31]

	Diagnosis
Idiopathic	
Cryptogenic sensory neuropathy	Skin biopsy PGP 9.5 stain
Infectious	
HIV	HIV serology
Inflammatory	
AIDP	EMG/lumbar puncture
Malignancies	
Paraneoplastic	
Small cell carcinoma	CT chest
Lymphoma	Bone marrow
Other carcinomas	Malignancy workup
Paraproteinemia	Protein electrophoresis
Multiple myeloma	Bence-Jones proteins
Waldenstrom	Bone marrow
Metabolic	
Hypothyroidism	TSH
Uremia	BUN, creatinine
Nutritional	
Alcohol	History
B12/thiamine deficiency	B12/folate
Toxic	
Arsenic/thallium	Mees lines
Dideoxyinosine	EMG/history
Dideoxycytosine	EMG/history
Isoniazid/pyridoxine deficiency	EMG/history
Nitrofurantoin	EMG/history
n-Hexane	EMG/history/biopsy
Vincristine	EMG/history

nent of large fiber involvement. Abnormalities may be found on sympathetic skin response testing. Quantitative thermal sensory threshold testing and qualitative and quantitative evaluation of skin sweating (distribution and amount) are sometimes helpful adjunctive tests to evaluate small nerve fiber function. The short list of potential etiologies is found in Table 1a.

History is of crucial importance as it helps eliminate or identify potential nutritional disorders, toxic exposures, or hereditary disorders. For example, a history of substantial weight loss or anemia and fatigue may suggest an underlying malignancy. A history of possible toxic exposure does not indicate that the exposure produced the neuropathy, but the opportunity for exposure is one of several important aspects of establishing causation. Conversely, a careful history may eliminate the many potential etiologies, and investigations may focus on appropriate laboratory investigations that may include evaluation of fasting blood sugar, thyroid and renal function studies (TSH, BUN, creatinine) and serum protein electrophoresis (SPEP) to help establish a diagnosis in a cost-effective manner.

Box 4
Painful mononeuropathies [30,31]

Idiopathic
  Trigeminal neuralgia
Infectious
  Post herpetic neuralgia
Metabolic
  Median mononeuropathy
    Amyloidosis
    Diabetes
    Hereditary liability to pressure palsies
    Hypothyroidism
    Pregnancy

Time course of symptoms

The history also helps establish the tempo of the neuropathy (i.e., whether it is subacute or chronic). Subacute neuropathies tend to progress over days to several weeks, whereas chronic neuropathies progress over many months to years, usually with insidious onset. Insidious onset of a chronic neuropathy should raise a red flag, as this type of presentation is frequently associated with the hereditary neuropathies.

A history of subacute onset is suggestive of acute inflammatory demyelinating polyneuropathy (AIDP) and a limited number of disorders that mimic AIDP, including porphyric neuropathy, Tick paralysis, and acute arsenic intoxication. The list of neuropathies with a subacute onset is short (Table 2).

Table 2
Acute/subacute neuropathies

	Diagnosis
Axonal	
Porphyria	EMG, urine porphyrin excretion, enzyme levels
Tick paralysis	
Toxins (arsenic)	(See Table 1)
Demyelinating	
Arsenic (acute exposure)	EMG/urine and hair analyses
AIDP	EMG/lumbar puncture
Diphtheria	URI/culture
Other	
Mononeuritis multiplex	EMG/vasculitic workup
Parneoplastic sensory neuronopathy	ANNA-1 (anti-Hu) antibody
Parsonnage-Turner (Idiopathic brachial plexopathy)	EMG
Proximal diabetic neuropathy	EMG/GTT

Nerve conduction studies and history help further tailor the diagnosis by establishing whether the neuropathy is axonal or demyelinating or if a plexopathy or polyradiculopathy is involved. An AIDP-like presentation picture may be seen with diphtheria where there is associated ophthalmoparesis. Among patients with diphtheria, examination of the oropharynx may reveal a green exudate or history may reveal a concurrent upper respiratory infection, a non-specific association in isolation. Demyelinating features are seen on the EMG, and like AIDP, albumino-cytologic dissociation may be seen in the spinal fluid. The presence of associated abdominal pain, nausea, vomiting, dysautonomia, and neuropathy is characteristic of acute porphyric neuropathy. Tick paralysis should be suspected in individuals with recent travel to endemic areas. The development of acute arm pain in a radicular or polyradicular pattern may suggest an idiopathic brachial plexopathy (Parsonnage-Turner syndrome), whereas the acute onset of a painful lower extremity in association with diabetes mellitus suggests diabetic amyotrophy. Finally, mononeuritis multiplex should always be considered in an individual who experiences an acute or subacute onset of an asymmetric and progressive neuropathy. Physical examination and investigations should always focus on ruling out an underlying systemic vasculitic disorder. Chronic neuropathies should be assessed by symptoms, history, and physical examination in conjunction with the pattern of distribution.

Chronic demyelinating polyneuropathies have a restrictive differential diagnosis in which nerve conduction studies can help group these disorders in two categories based on uniform versus nonuniform slowing (Table 3). Nonuniform slowing is seen in acquired demyelinating polyneuropathies such as chronic inflammatory demyelination polyneuropathy (CIDP),

Table 3
Chronic demyelinating polyneuropathies

	Diagnosis
Uniform slowing	
Cerebrotendinous xanthomatosis	Cholestanol
Congenital hypomyelinating neuropathy	Nerve biopsy, PO point mutation
	EGR2 point mutation
HMSN I,III	PMP-22 Dupl/Del
Leukodystrophies	
Adrenomyeloneuropathy	VLCFA
Metochromatic	Arylsulfatase A
Krabbes	Galactosylceramidase
Cockaynes	Sudanophilic material
Refsum disease	Phytanic acid
Tangier disease	Orange tonsils, HDL and total cholesterol level
Nonuniform slowing	
CIDP	See Box 3a, Box 3b
Dysproteinemias	SPEP, immunoglobulins, bone marrow
Osteosclerotic myeloma	Skeletal survey, SPEP

including those forms of CIDP associated with paraproteinemias and osteosclerotic myeloma. Lumbar puncture, quantitative immunoglobulins, and a skeletal survey may distinguish these disorders. Uniform conduction slowing is seen in hereditary demyelinating neuropathies such as hereditary motor sensory neuropathy (HMSN) type I or III. The presence of central nervous system findings on clinical examination should raise the possibility of an inherited white matter disease as described in Table 3.

Prominent motor symptoms

The number of neuropathies that present with pure motor symptoms or primarily motor symptoms is limited, and analysis of the pattern of weakness may help establish the diagnosis (Table 4). Hereditary motor and sensory neuropathy (HMSN) presents as a distal motor greater than sensory neuropathy generally associated with pes cavus deformities. Examination of family members or a history of relatives with similar problems may support the diagnosis. Nerve conduction studies further classify these disorders as either demyelinating or axonal. Genetic testing is currently available for HMSN I (PMP-22 duplication/deletion, PO and EGR2 point mutations), HMSN II (Myelin Protein Zero, Neurofilament Light). An acquired demyelinating neuropathy with symmetric distal weakness identified in association with a monoclonal gammopathy may suggest the need for additional evaluation. This evaluation should begin with a skeletal survey, looking for the presence of an underlying lymphoproliferative disorder such as osteosclerotic myeloma.

Asymmetry associated with pure motor symptoms is a worrisome sign for possible motor neuron disease (MND), but such asymmetry is also frequently seen in multifocal motor neuropathy with conduction block. Clinically, MND usually has preserved (early in the disorder) or increased

Table 4
Etiologies of exclusively motor/predominantly motor neuropathies

	Diagnosis
Predominantly Distal	
HMSN	EMG/genetic testing
Lead	EMG/lead level/skeletal x-ray
Monoclonal gammopathy with demyelinating neuropathy	EMG
	Immunoglobulins
Motor neuron disease	EMG
Multifocal motor neuropathy with conduction block	EMG/anti GM1
Proximal and Distal	
AIDP/CIDP	See Box 3a, Box 3b, EMG/CSF
Lymphoma motor neuronopathy	Bone marrow
Plexopathy	EMG
Porphyria	EMG, urine porphyrin excretion, enzyme levels

reflexes associated with fasciculations and atrophy. Multifocal motor neuropathy generally causes asymmetric weakness in the upper extremities without significant atrophy but with associated hyporeflexia or areflexia. EDX studies demonstrate a motor neuropathy associated with conduction block, helping differentiate multifocal motor neuropathy with conduction block from MND. The presence of anti-ganglioside M-1(GM1) antibodies supports the diagnosis of multifocal motor neuropathy with conduction block but are found in only 20–80% of patients [15,16].

Predominant or exclusive proximal weakness or proximal and distal weakness of comparable magnitude generally are associated with either a plexopathy or radiculopathy. Either AIDP (predominantly the axonal form) or CIDP have also been associated with proximal weakness. Other rare disorders presenting with this pattern of weakness are porphyria and a motor neuronopathy secondary to lymphoma.

Prominent sensory symptoms

Pure sensory neuropathies/neuronopathies are uncommon and, like pure motor neuropathies, carry a limited differential diagnosis (Box 5) [17]. The

Box 5
Sensory neuropathies (neuronopathies)

Symmetric Distal
- Amyloidosis
- Hereditary
- Friedrich ataxia
- HSAN
- HIV
- Toxic
- Cisplatin
- Ethyl alcohol
- Metronidazole
- Pyridoxine
- Styrene
- Thalidomide
- Thallium

Vitamin E deficiency

Asymmetric
- Idiopathic sensory ganglionitis
- Fisher variant of GBS
- Leprosy
- Praneoplastic (ANNA-1/anti-Hu syndrome)
- Sjogren syndrome

presence of keratoconjuctivitis sicca and xerostomia associated with a predominantly sensory neuropathy with or without multifocal features or cranial neuropathies are considered classical findings of Sjogren syndrome. The most common neuropathy in the third world is leprosy, which may present as an asymmetric predominantly sensory neuropathy. The Fisher variant of AIDP may be distinguished from AIDP based on its acute onset, prominent or exclusive sensory involvement with sensory ataxia, and ophthalmoparesis. Most challenging is the anti-Hu/ANNA-1 paraneoplastic syndrome generally associated with small cell lung cancer. Individuals with risk factors for carcinoma of the lung and a sensory neuronopathy should be screened routinely, as the antibody and the sensory neuropathy frequently are detected before the diagnosis of the cancer.

Symmetric, distal, pure sensory neuropathies may be seen with amyloidosis. Amyloid neuropathy is generally painful and associated with prominent autonomic dysfunction. Hereditary sensory autonomic neuropathy (HSAN) types I–V present at either birth or up to the second decade with concomitant mutilation and autonomic dysfunction. History may also be helpful in identifying HSAN I, because this is the only autosomal dominant HSAN. A careful history of potential exposures, including use of vitamins or other substances not considered neurotoxic, may identify a possible cause for a sensory neuropathy. A list of potential offending agents that cause a sensory neuropathy are found in Box 5. Of note, pyridoxine intoxication and cisplatin toxicity, when severe, may have proximal (in addition to distal) involvement, as opposed to the distal-predominant sensory loss characteristic of most sensory neuropathies.

Proximal and distal sensorimotor neuropathies

Identification of proximal involvement in any sensorimotor neuropathy should herald an additional element of anticipation from the clinician, as frequently these neuropathies are treatable. Again, history and physical examination in conjunction with EDX studies narrows the differential diagnosis. Proximal and distal sensorimotor neuropathies may be further subcategorized as symmetric or asymmetric. AIDP and CIDP generally present symmetrically. The duration of symptoms, the temporal profile, and the EDX findings (Box 3a and Box 3b) differentiate these two entities. Both disorders are responsive to plasmapheresis or intravenous immunoglobulin.

Etiologies of proximal and distal sensorimotor neuropathies:
Asymmetric
Diabetic amyotrophy
Infiltrative of inflammatory plexopathies
Infectious or infiltrative polyradiculopathies
Vasculitis
Symmetric
AIDP
CIDP

Asymmetry in a neuropathy should always raise the possibility of an underlying vasculitis. A careful history may suggest the presence of an initial mononeuropathy, possible with proximal symptoms, with subsequent progression to a confluent mononeuritis multiplex that may appear as a symmetric, distal predominant sensorimotor neuropathy by the time the patient presents for evaluation. Infiltration of nerve roots or of the plexus by a carcinomatous process may also present with proximal sensorimotor symptoms and signs. The presence of pain, supraclavicular masses, a Horner syndrome, or even chronic headache may suggest the possibility of carcinomatous meningitis. Hereditary neuropathy with liability to pressure palsies (HNPP) may occasionally cause a proximal neuropathy. One of the more common proximal asymmetric neuropathies (or more specifically polyradiculoneuropathy) is diabetic amyotrophy. Fairly abrupt in onset, it most commonly involves predominantly the L2 to L4 nerve roots (iliopsoas, quadriceps femoris, and hip adductors) associated with mild sensory loss over the anterior thigh [18]. With time, symptoms spread from proximal to distal. Finally, idiopathic brachial plexitis is a diagnosis by exclusion.

Autonomic nervous system dysfunction

Autonomic nervous system dysfunction may be manifest by labile blood pressure, orthostatic intolerance, erectile dysfunction, syncope, postprandial fatigue, gastroparesis, bladder dysfunction, and absent sweating. Neuropathies associated with autonomic system involvement may be divided into acute or chronic neuropathies (Box 6). Vacor or vincristine exposure may cause acute autonomic dysfunction, with vincristine also causing an associated motor greater than sensory or sensorimotor polyneuropathy without

Box 6
Neuropathies associated with autonomic nervous system dysfunction

Acute
- Idiopathic pandysautonomic neuropathy
- Guillain-Barre syndrome
- Toxic
  - Vincristine
  - Vacor

Chronic
- Amyloid
- Diabetes mellitus
- HIV
- HSAN
- Paraneoplastic sensory neuropathy

substantial conduction slowing. The presence of acute areflexia associated with EDX evidence of a demyelinating polyradiculoneuropathy, albuminocytologic dissociation, and autonomic dysfunction frequently occurs in AIDP. A rapid onset pandysautonomia is sometimes associated with this syndrome, and patients may develop severe orthostatic hypotension, anhidrosis, dry mouth and eyes, a fixed heart rate and fixed pupils with bowel and bladder dysfunction before onset of areflexia.

Chronic autonomic dysfunction is most commonly seen with diabetes mellitus and may involve the sympathetic, parasympathetic, or both autonomic nervous systems. The presence of pain associated with chronic autonomic dysfunction is frequently seen in amyloidosis and in HIV neuropathy (which presents late in the course of the illness). A paraneoplastic sensory neuronopathy associated with autonomic dysfunction presents with an accompanied sensory ataxia, global areflexia, and evidence of sensory neuronopathy on EDX testing. HSAN is generally found at infancy or in the early second decade and frequently it is associated with mutilation or a history of multiple painless fractures. Diabetes mellitus, however, is the most likely culprit of autonomic dysfunction in the western world.

Facial nerve involvement

Bell palsy is a benign condition, however on rare occasion, facial neuropathy may be found in conjunction with either an acute or chronic polyneuropathy.

Neuropathies associated with facial nerve involvement:
AIDP
Amyloid (Gelsolin familial)
CIDP
Lyme disease
Sarcoid
Tangier disease

In the acute setting of AIDP, bifacial weakness is present in up to 50% of patients. Less frequently, facial weakness occurs in association with CIDP [17]. Tangier disease (see small fiber neuropathies) may present with faciobrachial weakness. There is usually, however, an associated small fiber neuropathy and the presence of orange tonsils helps clarify the diagnosis. Lyme disease should be considered in patients with recurrent facial palsy or bilateral facial mononeuropathy, particularly if they are from endemic areas. Early in the course of the illness, there may be an accompanying painful (poly)radiculopathy. In the later stages of Lyme disease, a reversible polyradiculoneuropathy may be present. Sarcoidosis may be distinguished from other forms of neuropathy by its association with several atypical features: multiple cranial neuropathies, multiple mononeuropathies, truncal sensory neuropathy, a cauda equina syndrome, and a chronic symmetric sensorimotor

neuropathy accompanied by wrist extensor and foot dorsiflexion weakness. The diagnosis of sarcoidosis may be made by nerve, muscle, or lymph node biopsy and supported by abnormal angiotensin converting enzyme (ACE) levels or systemic evidence of sarcoidosis.

Neurocutaneous manifestations

In addition to the neurological evaluation, the general physical examination may provide clues helpful in identifying the cause of the underlying peripheral neuropathy (Table 5). The presence of alopecia is suggestive of thallium poisoning, whereas evidence of Mees lines in the fingernails suggests an acute intoxication such as that from arsenic or thallium. Skin hypopigmentation is seen in leprosy and the POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome, a lymphoproliferative disorder associated with an acquired demyelinating neuropathy. Raised skin lesions suggestive of angiokeratomas are found in Fabry disease. The presence of purpura and neuropathy should suggest the possibility of cryoglobulinemia, whereas purpura associated with livido reticularis is frequently seen in individuals with an underlying vasculitis. In Tangier disease, orange tonsils may be seen in association with a small fiber neuropathy, with sensory and motor symptoms similar to those associated with syringomyelia. The presence of unhealed foot ulcers in conjunction with neuropathic symptoms should alert the physician to possible undiagnosed diabetes mellitus.

Family history

Increasingly, hereditary neuropathies are being implicated in and are believed to make up a large percentage of those patients diagnosed with "idiopathic" chronic neuropathy [18]. A detailed family history can be rewarding for the physician, particularly when faced with a patient referred

Table 5
Neuropathies with neurocutaneous manifestations

Diagnosis	Neurocutaneous findings
Arsenic intoxication	Mees lines
Cryoglobulinemia	Purpura
Fabry disease	Angiokeratomas
Giant axonal neuropathy	Curly hair
Leprosy	Hypopigmented skin
POEMS	Hypopigmented skin
Tangier	Orange tonsils
Thallium poisoning	Mees lines, alopecia
Variegate porphyria	Bullous lesions
Vasculitis	Livedo reticularis, purpura

for an idiopathic neuropathy for which no cause is apparent. Detailed questioning regarding other family members who may have a history of poor athletic performance, difficulty running, gait difficulties requiring orthotics or braces, inability to walk on the heels or toes, difficulty getting up from a seated position, high arched feet, hammer toes or claw hands, frequent foot ulcers, or atrophic hand or foot muscles. The answers to these questions may help elucidate a history of a familial neuropathy. It is frequently helpful to have the patient contact other family members to inquire about the presence of the above symptoms. It is reported that only 20% of individuals with hereditary neuropathy seek medical attention. Thus, obtaining a thorough family history may limit an otherwise potentially expensive investigation [19].

Electrodiagnostic studies

EDX testing is an essential tool in the diagnostic approach to peripheral nerve disease and can be thought of as a direct extension of the neurological examination. In the EMG laboratory, one can identify the predominant pathophysiology: axonal loss, uniform or segmental demyelination or conduction block. Occasionally, history may be inadequate and EDX studies may add further information regarding the duration of the symptoms (acute, chronic, and actively ongoing). Individuals with a primarily motor neuropathy may be unaware of concomitant involvement of peripheral sensory nerves or vice versa. Demonstration of unanticipated involvement therefore completely alters the differential diagnosis. In addition, EDX results not only quantify the severity of the disorder but also allow the clinician to confirm which aspects of the peripheral nervous system are involved and confirm the distribution of involvement. Individuals with an underlying neuropathy may be predisposed (secondary to pre-existing nerve injury) to developing a superimposed mononeuropathy. All individuals with a mononeuropathy should be screened for an underlying polyneuropathy. More importantly, it is essential that in the evaluation of a peripheral neuropathy several nerves be compared bilaterally to establish if there is substantial asymmetry. Some investigators have even proposed classifying neuropathies by their EDX studies [8]. The value of this approach is seen in the evaluation of toxic neuropathies (Table 6). Frequently, one is left with a history of a possible toxic exposure, and the EDX profile not only confirms the presence of a polyneuropathy but also identifies a particular pattern of the neuropathy on nerve conduction studies (motor or motor > sensory with conduction slowing, motor or motor > sensory without conduction slowing, pure sensory, sensorimotor without conduction slowing). Recognition of these patterns helps develop a rational approach to find the cause of the neuropathy.

Axonal and demyelinating neuropathies have distinct electrophysiologic pictures. Axonal neuropathies are characterized by decreased distal amplitudes with relative preservation of conduction velocities, whereas demyeli-

Table 6
Toxic agents associated with neuropathy [29]

Motor or motor>sensory neuropathies with conduction slowing	
Arsenic	Amiodarone
Cytosine arabinoside (ara-C)	Methyl n-butyl ketone
n-Hexane	Saxitoxin
Suramin	Swine flu vaccine
Motor or motor>sensory involvement, without conduction slowing	
Cimetidine	Dapsone
Disulfiram	Doxorubicin
Hyperinsulin/hypoglycemia	Nitrofurantoin
Organophosphate esters	Vincristine
Sensorimotor involvement without conduction slowing	
Acrylamide	Amitriptyline
Arsenic	Carbon monoxide
Colchicine	Ethambutol
Ethyl alcohol	Ethylene oxide
Elemental mercury	Gold
Hydralazine	Isoniazid
Lithium	Metronidazole
Nitrofurantoin	Nitric oxide
Paclitaxil	Perhexiline
Phenytoin	Thallium
Vincristine	

nating neuropathies result in significant slowing of conduction velocities with preservation of distal amplitudes. In *axonal neuropathies*, the loss of axons leads to atrophy of the target muscle and results in a decreased compound muscle action potential (CMAP) or sensory nerve action potential (SNAP) (Fig. 1A). The loss of amplitude reflects the degree of axonal loss (Fig. 1B). In severe axonal neuropathies, more large, fast conducting fibers may be affected. In addition to a severely decreased CMAP or SNAP amplitude, there is also some resultant slowing of conduction velocity. The degree of slowing reflects the conduction velocity of the remaining nerve fibers. In general, conduction velocities are normal or mildly slowed in axonal neuropathies, which also results in normal or prolonged distal latencies; the degree of prolongation is proportionate to conduction velocity slowing. Most axonal neuropathies are length-dependent (dying back neuropathies), and the most distal nerve terminals are affected first.

EDX information derived from the results of nerve transection is helpful in understanding the abnormalities associated with axonal neuropathy. Following complete nerve transection, evoked responses disappear in 3 to 7 days, and increased insertional activity on needle examination may be noted as early as 7 to 10 days or as late as 3 weeks, depending on the distance of the target muscle or sensory fiber from the site of transection. With partial motor axon loss, a decreased recruitment pattern is seen on needle EMG. At onset, Motor Unit Action Potentials (MUAPs) are of normal amplitude and duration. Within 10 to 14 days, however, polyphasic MUAPs are seen

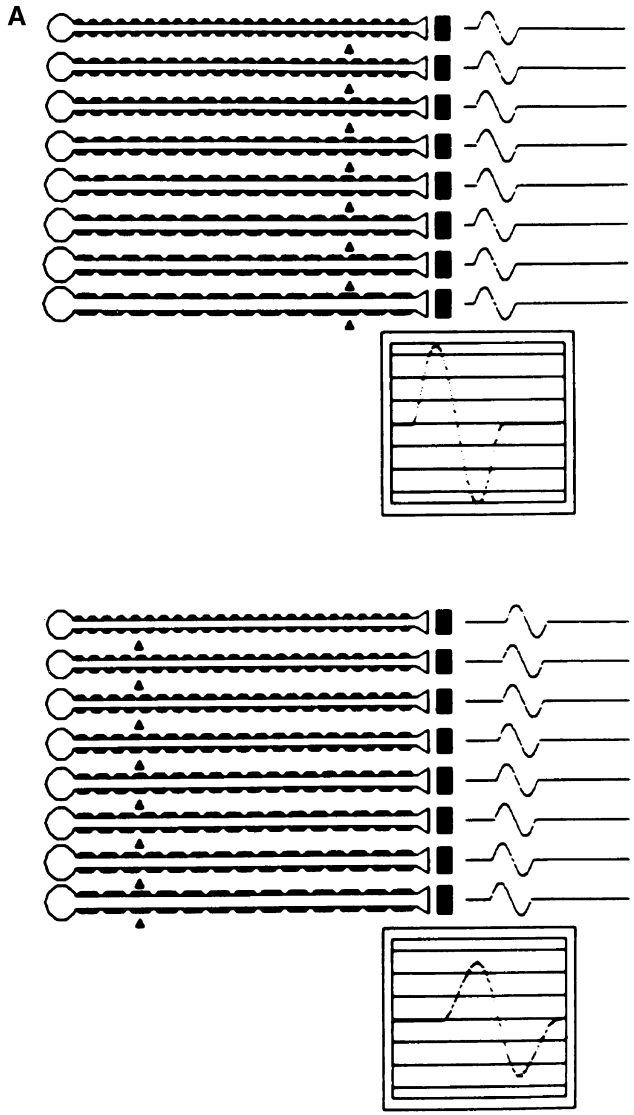

Fig. 1. Computerized model of peripheral motor nerve. Muscle fibers are denoted by solid bars to the right of each axon. The arrows represent the stimulation sites. The compound muscle action potentials (CMAP) are shown below each nerve in the schematic screen. Upper trace recording: resultant CMAP following distal nerve stimulation. Lower recording: resultant CMAP following proximal nerve stimulation. (A) Normal nerve demonstrating summation of eight individual muscle fiber action potentials to produce the CMAP. Individual axons are of slightly different sizes and, therefore, conduct at different rates.

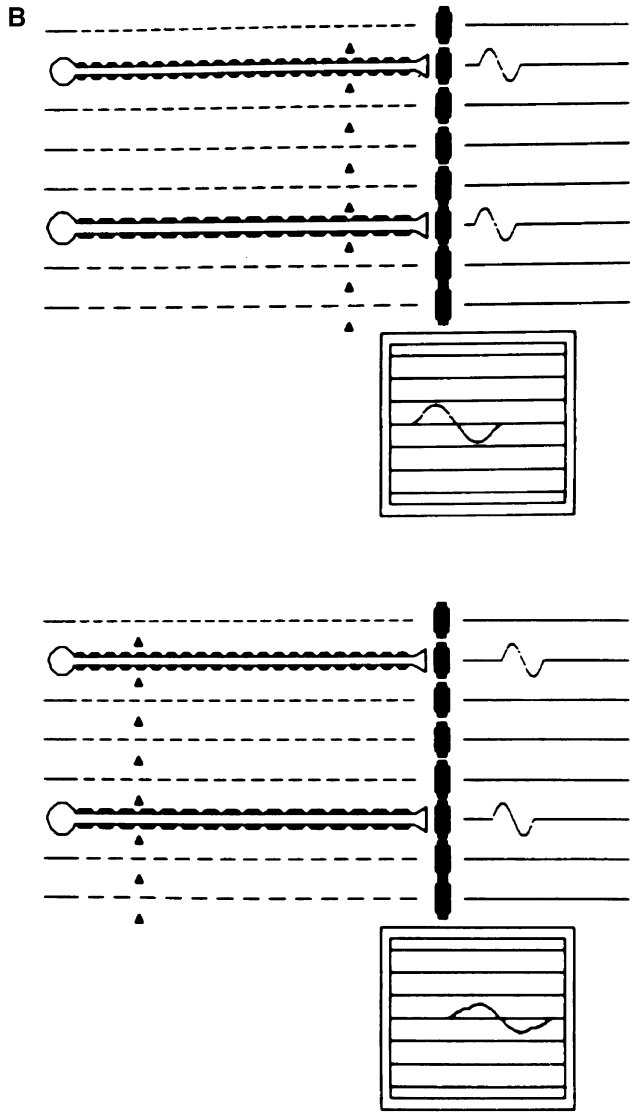

Fig. 1. (B) Nerve with axonal degeneration following random loss of 75% of axons.

because of axonal sprouting and reinnervation of some denervated muscle fibers. Within months of an acute lesion, large amplitude, long duration, polyphasic MUAPs develop [20,21]. Axonal neuropathies develop similar patterns of abnormality, depending in part on the duration and severity of axonal loss.

Demyelinating neuropathies are hallmarked by decreased conduction velocities secondary to impaired saltatory conduction. Criteria for demyelina-

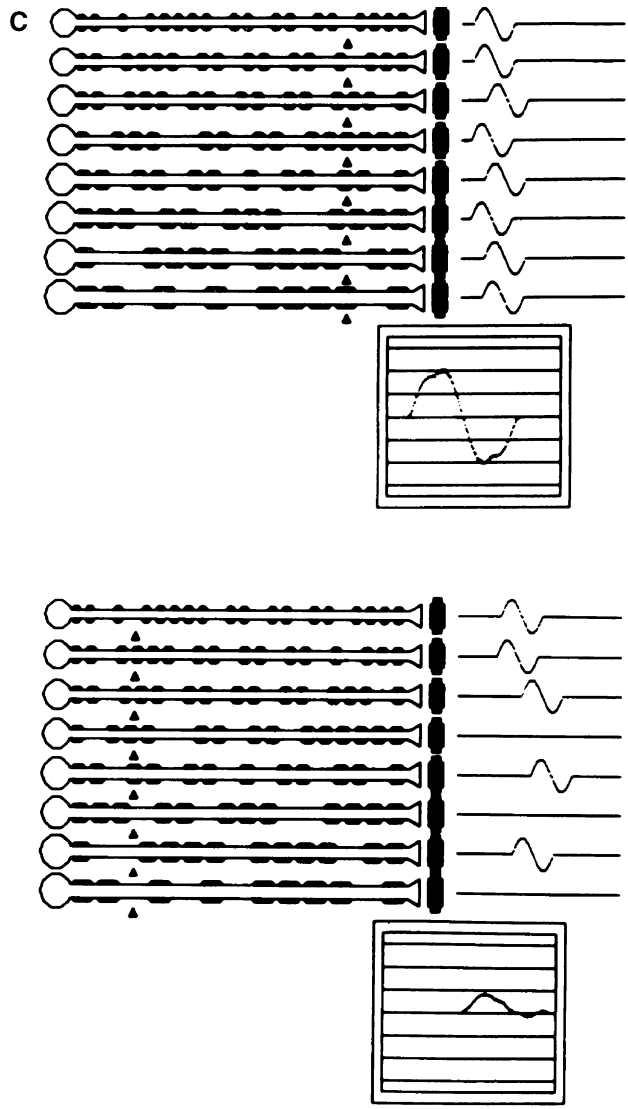

Fig. 1. (C) Nerve with multifocal segmental demyelination. The diminished CMAP amplitude with proximal stimulation results from temporal dispersion of individual muscle fiber action potentials and conduction block in some axons. (Adapted from Albers JW. Inflammatory demyelinating polyradiculoneuropathy. *From* Brown WF, Bolton CF, editors. Clinical electromyography. Boston: Butterworth-Heinemann; 1989; with permission.)

tion are described in Box 3a and Box 3b. In pure demyelinating neuropathies, the axon is intact and there is no loss of contact with the motor or sensory target. As a result, there is no associated muscle atrophy, nor is there evidence of fibrillation potentials or positive sharp waves in affected muscles. When

present, these abnormalities are modest and commensurate with a mild degree of axonal loss. In focal demyelination with conduction block, motor and sensory responses cannot be obtained or are of low amplitudes when stimulating proximal to the lesion, but these responses are normal when the nerve is stimulated distal to the lesion (Fig. 1C). In focal demyelination without conduction block, EDX findings reveal a substantial reduction of conduction velocity across the lesion, findings also displayed with chronic nerve compression. In uniform demyelinating disorders (Table 3), there is homogenous involvement of all fibers and therefore a normal evoked response with distal and proximal stimulation, despite a markedly decreased conduction velocity. Multifocal demyelination will also show decreased conduction velocities with preserved evoked response amplitudes with distal stimulation. Proximal stimulation results in abnormal temporal dispersion of the CMAP, however, with the proximal response being of smaller amplitude and longer duration than the response obtained with distal stimulation. Distal demyelination may also produce prolonged distal latencies [8].

AIDP is a prototype of an acquired demyelinating neuropathy. In AIDP, EDX findings are variable depending on when they are performed relative to disease onset. Given the acute onset of this disorder, establishing a diagnosis entirely on EDX findings may be difficult. In the first 1 to 2 weeks of illness, when establishing a diagnosis is most important, the only finding may be absent or prolonged F wave latencies. Other abnormalities, such as reduced CMAP amplitudes, are more common than is conduction slowing [22]. Motor conduction abnormalities peak at about the third week. In AIDP, motor abnormalities are generally diffuse and homogenous when compared with the patchy nature of sensory nerve abnormalities. Another characteristic of AIDP seen in approximately 50% of patients in the first 4 weeks of illness is a pattern of a normal sural but an abnormal median sensory response, a finding unusual for most forms of polyneuropathy. On needle examination, abnormally increased insertional activity appears in distal and proximal muscles between weeks 2 and 4 of illness, whereas changes in MUAP morphology typically develop shortly thereafter (weeks 4 to 5). EDX findings in CIDP are similar to those seen in AIDP, differing primarily in association with the temporal profile of the illness.

Hereditary demyelinating neuropathies may also be identified on EDX studies by several pertinent features. HMSN I and III are characterized by conduction velocity slowing to less than 85% of the lower limit of normal. As this disorder is representative of uniform demyelination of all fibers, abnormal temporal dispersion is not usually present. Among HMSN type III patients with markedly reduced conduction velocity, the possibility of phase cancellation may lead to abnormal temporal dispersion and diagnostic confusion [23–25]. In general, however, the absence of abnormal temporal dispersion is helpful in distinguishing acquired from hereditary demyelinating neuropathies. In HMSN type I or III, F wave latencies, when obtainable, are prolonged, as are distal latencies, and SNAPs are generally

absent. There may be decrease in CMAP amplitudes, reflecting the degree of superimposed axonal degeneration. Needle examination reveals increased MUAP amplitude and duration with mild to moderate distal denervation proportionate to the amount of loss of axon.

HMSN II is an autosomal dominant sensorimotor polyneuropathy of the axonal type with an onset in the third to fifth decades. Nerve conduction studies are manifest by normal to decreased CMAP amplitudes and essentially normal conduction velocities. Approximately 50% of HMSN type II patients have absent SNAPs, and most of the remaining patients have abnormally low SNAP amplitudes. Needle EMG examination reveals chronic neurogenic changes that are most prominent distally. The magnitude of abnormal insertional activity in this disorder reflects the degree of partial denervation and the rate of progression.

Hereditary neuropathy with liability to pressure palsies (HNPP), also termed tomaculous neuropathy, is caused by a deletion of the PMP-22 gene on chromosome 17. HNPP most commonly affects the ulnar nerves at the elbow and the peroneal nerves at the fibular head. Other nerves commonly affected are those associated with localized focal compression, such as the radial nerve at the spiral groove of the humerus and the median nerve at the wrist. The mononeuropathies associated with HNPP are often precipitated by minor trauma and are usually painless. Complete recovery generally occurs in days to weeks [26–28]. The predominant abnormality on EDX testing is evidence of focal or multifocal demyelinating lesions at common pressure sites. Nerve conduction studies also may show prolonged distal latencies, often out of proportion to the mild slowing of conduction velocities, perhaps in association with a confluent mononeuropathy multiplex. Nerve conduction studies may demonstrate mild conduction slowing among asymptomatic but affected relatives. Thus, unexpected EDX findings of slowed conduction velocities or evidence of multifocal demyelination on evaluation of a patient with a ''routine entrapment'' neuropathy should raise a suspicion for HNPP.

Conclusion

There are a multitude of potential etiologies for peripheral neuropathy. For this and other reasons, the evaluation of patients with neuropathy may at times seem overwhelming and frustrating to the clinician. By combining information derived from a thorough history and clinical examination with the results of the EDX examination, however, it is possible to substantially reduce the number of disorders included in the differential diagnosis. Important features include information about the temporal course of symptoms, characterization of symptoms as predominantly sensory, motor, sensorimotor, or autonomic, and determining whether pain is a primary feature. The clinical examination is used to confirm the clinical impression based on the patient's symptoms, and also includes careful evaluation for autonomic

dysfunction, facial nerve involvement, and neurocutaneous manifestations. The EDX study results confirm the peripheral localization and characterize the neuropathy by the primary physiologic abnormality. This characterization includes documentation of the patterns and types of abnormality as symmetric or asymmetric, proximal or distal, and demyelinating or axonal. This process permits generation of a limited, more focused differential diagnosis that sometimes suggests the etiology or pathogenesis of the neuropathy. This process also results in an evaluation plan that is based on logical and cost-effective investigations that ultimately help to establish a final diagnosis.

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