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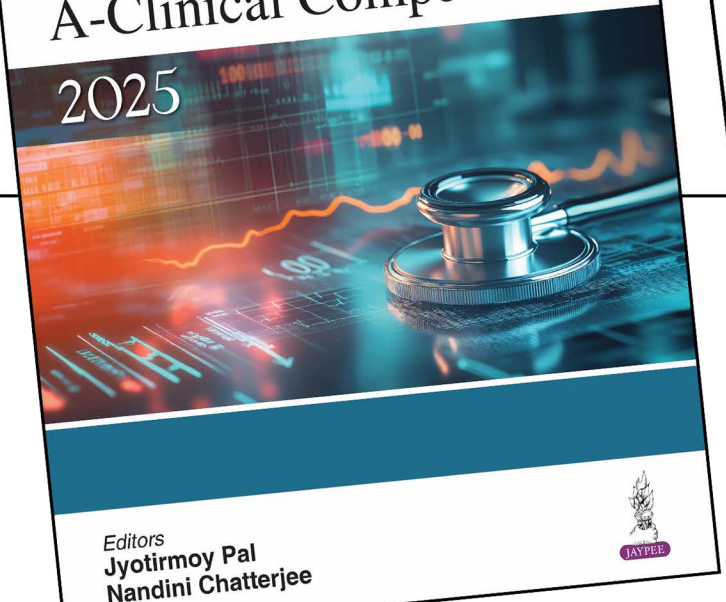

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Education, Ethics and Empathy

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Volume 35 2025

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CHAPTER
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Clinical Approach to Peripheral Neuropathy

Amit Aggarwal, MPS Chawla

ABSTRACT

Peripheral neuropathy is one of the most commonly encountered clinical entities in the routine neurological practice. It may affect the motor, sensory, or autonomic elements, either in isolation or in combination. The site of localization may be dorsal or ventral nerve roots (radiculopathy), nerve plexus (plexopathy), cranial nerves, or other sensory, motor, autonomic, and mixed nerves (mono or polyneuropathy). It may be axonal, demyelinating, or neuronopathy on the basis of underlying pathological processes. Based on the extent of involvement, the symptoms may vary from paresthesia or hyperalgesia to twitching, cramping, fatigue, weakness or wasting, gait imbalance, and dysautonomia. A stepwise clinical approach is necessary for accurate diagnosis and appropriate management.

INTRODUCTION

Peripheral nervous system (PNS) consists of the neural structures outside the pia mater. It consists of the anterior and posterior nerve roots, plexuses, spinal nerves, neuromuscular junction, motor end-plate, and sensory receptors, and cranial nerves excluding the first and second ones, after exiting the cranium, sub-serving sensory, motor, and/or autonomic functions. The concept of separate PNS is obviously an artificial one since the cell bodies of many PNS motor neurons lie within the central nervous system (CNS), and some peripheral sensory neurons have extensive central projections. The first distinction that should be made is whether there is involvement of one peripheral nerve, as in mononeuropathies, or multiple nerves, as in the case of multifocal neuropathies and polyneuropathies. These broad categories can be subdivided into smaller groups, making distinctions according to the underlying cause of the disease (compressive or noncompressive), the time course of progression (acute or chronic), or type of pathological injury (axonal or demyelinating). A brief discussion regarding the various terminologies involved, different clinical phenotypes, underlying causes and risk factors, and associated typical characteristics is undertaken in this chapter to define a valid clinical approach toward the diagnosis of peripheral neuropathies.

CLASSIFICATION OF PERIPHERAL NEUROPATHY

There are several patterns of involvement in various peripheral nerve diseases:

- *Radiculopathy*: Involvement of nerve root
- *Plexopathy*: Involvement of nerve plexus
- *Mononeuropathy*: Involvement of single peripheral or cranial nerve
- *Mononeuritis multiplex (multiple mononeuropathies)*: Simultaneous or sequential involvement of multiple noncontiguous spinal nerves.
- *Polyneuropathy*: Usually symmetrical involvement of multiple nerves at the same time, which is length dependent in glove and stocking type of distribution. The involvement is diffuse, distal, and commencing peripherally.

The clinical classification of peripheral neuropathy is briefed in **Box 1**.

BOX 1: Clinical classification of peripheral neuropathy.

- Mononeuropathy
- *Plexopathy*:
  - Brachial plexopathy
  - Lumbar plexopathy
  - Sacral plexopathy
- *Radiculopathy*:
  - Cervical radiculopathy
  - Thoracic radiculopathy
  - Lumbosacral radiculopathy
- Multiple mononeuropathy (mononeuropathy multiplex)
- *Polyneuropathy*:
  - Symmetrical polyneuropathy
  - Asymmetrical polyneuropathy
- Polyradiculoneuropathy

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NERVE PATHOLOGIES

Despite varied etiological causes for neuropathy, the pathological reactions of peripheral nerves to different insults remain limited. These pathological processes are:

- *Demyelination*: There is disruption of myelin sheath with conduction block, as in Guillain–Barré syndrome and chronic inflammatory demyelinating neuropathy. Recovery occurs in weeks to months.
- *Axonopathy*: There is disruption of axis cylinder. Recovery occurs in months to years.
- *Wallerian degeneration*: There is disruption of axon, myelin, and surrounding connective tissues. Recovery is incomplete or never.
- *Compression*: The compression of nerve leading to focal demyelination
- *Infarction*: Interrupted blood supply to vasa nervorum leading to neural infarction
- *Infiltration*: Infiltration of nerves due to infection, malignant, autoimmune or protein deposition

Some of the clinical features that help distinguish these pathological processes in neuropathies are presented in **Table 1**.

EXTENT OF NERVE INJURIES

Based on the extent of involvement of neural structures, nerve injuries are classified as *(Seddon and Sunderland's classification)*:

- *Neurapraxia (Grade 1)*: No major structural damage occurs. There is involvement of myelin sheath only, resulting in conduction blocks. Recovery usually occurs in days to weeks.
- *Axonotmesis (Grade 2)*: Disruption of axon cylinder occurs with intact endoneurium. Recovery occurs in months to years.
- *Neurotmesis (Grade 3–5)*: Complete nerve disruption occurs. Subdivided further into different grades based on endoneurium, perineurium, and epineurium preservation. Recovery is often incomplete.

PRINCIPLES OF CLINICAL EVALUATION AND ALGORITHMIC APPROACH

The evaluation of a possible neuropathy begins with the recognition that dysfunction at central or separate peripheral loci may mimic a neuropathy clinically. Such a situation is termed "pseudoneuropathy" or "neuropathy mimic", and does not imply a psychogenic mechanism. Pseudoneuropathies mimicking the pattern of a polyneuropathy are most often myelopathies, which may produce distal sensory or sometimes, motor dysfunction in a stocking pattern, without typical features of a sensory level, long-tract weakness, sphincter disturbance, or hyperreflexia, as seen in cervical spondylotic myelopathy and spinal multiple sclerosis. Intramedullary spinal lesions (e.g., multiple sclerosis plaques at dorsal root entry or a syrinx) can mimic a structural radiculopathy or even mononeuropathy such as carpal tunnel syndrome or ulnar neuropathy. Based on history and physical examination, one must establish the cardinal features of neuropathy along with symptoms onset, duration, temporal evolution, prior episodes, subtle early features, and functional difficulties.

One should look for *6 D's*:

1. *D*istribution of deficits
2. *D*uration
3. *D*eficits (fibers involved)
4. *D*isease pathology (axonal, demyelinating, or mixed)
5. *D*evelopmental or inherited
6. *D*rug or toxin exposure

Motor Symptoms

- *Negative*: Weakness (distal, proximal, multifocal, and diffuse) and fatigability
- *Positive*: Twitching and cramps
- *Signs*:
  - *Negative*: Weakness, hypotonia, hyporeflexia, atrophy (weakness without atrophy suggests demyelination), and skeletal deformities
  - *Positive*: Neuropathic tremor, fasciculations, myokymia, neuromyotonia, hemifacial spasm, restless legs, or tightness

Sensory Symptoms

- *Negative*: Numbness
- *Positive*: Hyperalgesia, paresthesia, dysesthesia, and allodynia
- *Signs*:
  - *Small fiber*: Loss of pain and temperature sensations
  - *Large fiber*: Loss of vibration, joint position, and touch-pressure; pseudoathetosis; sensory ataxia; hyporeflexia; hypotonia; and Rombergism

TABLE 1: Clinical clues to the underlying pathophysiology in polyneuropathies.

	Axonopathy	Myelinopathy	Sensory neuronopathy
Pattern	Distal and symmetric	Distal, proximal, diffuse symmetric, or multifocal	Diffuse, patchy, or rarely unilateral
Tempo	Acute, subacute, or mostly chronic	Acute, subacute, or chronic	Acute, subacute, or chronic
Sensory and motor involvement	Usually sensory >motor, "stocking-glove"	Often motor > sensory; weakness without atrophy (conduction block)	Distal sensory loss or non length-dependent diffuse/patchy pattern, including the face and torso; pseudoathetosis
Reflexes	Distal-to-proximal loss	Early, diffuse areflexia	Areflexia
Gait	Variable	Sensory ataxia	Severe sensory ataxia
Cerebrospinal fluid	–	Albuminocytologic dissociation	–
Recovery	Slow regeneration	Rapid remyelination	Limited loss of cell body

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Autonomic Symptoms/Signs

- *Loss of functions (negative symptoms)*: Constipation, hypohidrosis, impotence, urinary incontinence, skin color changes, orthostasis or hypotension, and bradycardia
- *Disordered functions (positive symptoms)*: Diarrhea, hyperhidrosis, hypertension, and arrhythmias
- *Gait imbalance and falls*: Tandem, toe/heel walk, hop, and squat
- *Deep tendon reflexes*: Length-dependent loss with ankles first (in most neuropathies); early, diffuse involvement (in demyelination or neuronopathy)
- *Skeletal deformities*: Pes cavus, pes planus, hammer toes, kyphoscoliosis (Charcot–Marie–Tooth); claw hand (ulnar) and foot drop
- *Nerve enlargement*: Infection (leprosy), demyelination/remyelination (onion bulb formation; Charcot–Marie–Tooth), and neoplasia (neurofibromatosis)
- *Skin lesions*: Vasculitis (purpura/livedo reticularis), hypopigmentation (leprosy), angiokeratomas (Fabry disease), neurofibromas/café-au-lait spots (neurofibromatosis), ichthyosis (Refsum disease), hyperpigmentation (POEMS syndrome), foot ulcers (hereditary sensory and autonomic neuropathy and diabetes mellitus), trophic changes (dysautonomia), and lipomas (mitochondrial disease)
- *Gum lesions*: Lead lines
- *Nail lesions*: Mees' lines (arsenic and thallium exposure).
- *Hair lesions*: Alopecia (thallium toxicity and connective tissue disease) and curly (giant axonal neuropathy)

Approach to Clinical Assessment

- Systems involved?
  - Motor, sensory, autonomic, or mixed
- Distribution of deficit?
  - Only distal versus proximal and distal
  - Focal/asymmetric versus symmetric
- Nature of sensory involvement?
  - Loss of temperature; burning or stabbing pain (small fiber)
  - Loss of vibration or proprioception (large fiber)
- Evidence of upper motor neuron involvement?
  - Without sensory loss
  - With sensory loss
- Temporal evolution?
  - Acute (days to 4 weeks)
  - Subacute (4–8 weeks)
  - Chronic (>8 weeks)
- Evidence of hereditary neuropathy?
  - Family history of neuropathy
  - Lack of sensory symptoms despite sensory signs
- Any other associated medical comorbidity?
  - Cancer, diabetes mellitus, connective tissue disorder, autoimmune disease, infection (HIV, Lyme's disease, and leprosy)
  - Medications causing toxic neuropathy
  - Preceding events, drugs, or toxin exposure

The accurate diagnosis of peripheral neuropathies is dependent on neuroanatomical localization and the distributive pattern of the involvement, which can only be ascertained on the basis of a detailed clinical history. The common types of anatomic patterns in peripheral neuropathies based on etiologies and clinical localization have been described in **Box 2**, whereas the less common patterns have been elucidated in **Box 3**. Recognition of a specific pattern narrows down the differential diagnosis and focuses on the diagnostic evaluation. Any pattern other than typical neuropathy, or the presence of any atypical "red flag" should prompt additional diagnostic evaluation.

BOX 2: Common anatomic patterns in peripheral neuropathies based on etiologies and clinical localization.

Focal:

- Acromegaly
- Amyloidosis
- Direct trauma to nerves, such as repeated minor trauma, traction, injection, cold exposure, burns, and radiation
- Entrapment/compressive neuropathies
- Ischemic lesions
- Leprosy
- Myxedema
- Neoplastic infiltration
- Rheumatoid arthritis
- Sarcoidosis

Symptoms:

- Sensory and motor symptoms
- Predominantly sensory symptoms, including pain and paresthesia
- In severe or chronic cases, motor symptoms may include weakness and atrophy

Multifocal:

- Connective tissue diseases
- Diabetes mellitus
- Hereditary predisposition to pressure palsies
- Infections (HIV/AIDS)
- Leprosy
- Vasculitis

Symptoms:

- Sensory and motor symptoms are asymmetrical and affect multiple areas of the body
- Sensory symptoms include pain, paresthesia, vibration, and proprioception
- Motor symptoms may include weakness and atrophy
- Autonomic symptoms may be present

Symmetrical distal sensorimotor:

- Acromegaly
- Alcohol use
- Amyloidosis
- Celiac disease
- Chronic kidney disease
- Connective tissue diseases
- Cryoglobulinemia
- Diabetes
- Gouty neuropathy
- Hypothyroidism/hyperthyroidism

Continued

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Continued

- Infections (HIV/AIDS, Lyme disease)
- Inherited diseases (Charcot–Marie– Tooth disease and familial amyloidosis)
- Liver disease
- Malignancy
- Medication-induced **(Table 4)**
- Nutritional deficiencies (vitamins B6, B12, and E; thiamine; folate, copper, and phosphate)
- Postgastrectomy syndrome
- Toxin exposure (heavy metals, carbon monoxide, acrylamide, hexacarbons, ethylene oxide, and glue)
- Vasculitis
- Whipple disease

Symptoms:

- Distal sensory and motor symptoms involve both sides symmetrically
- Sensory symptoms include pain, paresthesias, vibration, and proprioception
- Motor symptoms may include weakness and atrophy
- Autonomic symptoms may be present

Symmetrical proximal motor:

- Acute arsenic poisoning
- Chronic inflammatory demyelinating
- Polyradiculoneuropathy
- Diabetes
- Guillain–Barré syndrome
- Hypothyroidism
- Infections (HIV/AIDS, Lyme disease, and diphtheria)
- Malignancies
- Porphyria
- Vincristine exposure

Symptoms: Motor symptoms include weakness and atrophy of proximal muscles in a symmetrical anatomic distribution

BOX 3: Less common anatomic patterns in peripheral neuropathies based on etiologies and clinical localization.

Neuropathies with cranial nerve involvement:

- Diabetes
- Guillain–Barré syndrome
- Infections (HIV/AIDS, Lyme disease, and diphtheria)
- Neoplastic invasion of the skull base or meninges
- Sarcoidosis

Symptoms: Sensory and motor symptoms involve the cranial nerves, such as problems with speech, swallowing, taste, and sensory or autonomic functions; coughing; head, pharyngeal, or neck pain; and weakness of the trapezius, sternocleidomastoid, or tongue muscles

Neuropathies predominant in upper extremities:

- Diabetes
- Guillain–Barré syndrome
- Hereditary amyloid neuropathy type II

Continued

Continued

- Hereditary motor sensory neuropathy
- Lead toxicity
- Porphyria
- Vitamin B12 deficiency

Symptoms: Sensory and motor symptoms predominantly involve the upper limb sensory symptoms including pain, paresthesias, vibration, and proprioception. Motor symptoms may include weakness and atrophy.

Neuropathies with autonomic involvement:

- Amyloidosis
- Diabetes
- Lymphoma
- Paraneoplastic neuropathy
- Porphyria
- Thallium, arsenic, or mercury toxicity

Symptoms: Autonomic symptoms may include orthostatic intolerance, gastroparesis, bowel and bladder changes, erectile dysfunction, and blurry vision

An algorithm for the classification and differential diagnosis of neuropathy based on clinical features is given in **Flowchart 1**. This systematic algorithmic approach tends to be helpful in sorting through the myriad presentations and possible etiologies.

In mononeuropathy, the neurological deficit follows the distribution of a single nerve and implies a local process. Direct trauma, compression, entrapment, vascular lesions, and neoplastic compression or infiltration are the most common causes. Electrophysiological studies provide a more precise localization, distinguishing axonal loss from focal segmental demyelination, and sometimes, revealing a more widespread pathological process indicating a generalized underlying polyneuropathy that has made the nerve more susceptible to entrapment, such as in diabetes mellitus, hypothyroidism, acromegaly, alcoholism, and hereditary amyloidosis. In multiple mononeuropathies, the neurological findings point to simultaneous or sequential damage to two or more noncontiguous peripheral nerves. Confluent multiple mononeuropathies may manifest with sensory loss that can simulate a length-dependent peripheral neuropathy. Some of the common causes of mononeuropathy multiplex are shown in **Box 4**. Almost two-thirds of patients with multiple mononeuropathies display a pattern of axonal damage.

Polyneuropathy is most commonly characterized by symmetrical distal motor and/or sensory deficits that typically have a graded increase in severity distally with distal attenuation of reflexes. The sensory and motor deficits generally follow a length-dependent stocking–glove pattern. Most neuropathies are fairly symmetrical, but some are asymmetrical, and sometimes the result of a confluent mononeuropathy multiplex. A small number of polyneuropathies (e.g., that associated with acute intermittent porphyria) may be predominantly proximal. Motor deficits tend to dominate the clinical picture in acute and chronic inflammatory demyelinating polyneuropathies, hereditary motor and sensory neuropathies (Charcot–Marie–Tooth disease), and in neuropathies associated with porphyria, lead intoxication, organophosphate toxicity, and osteosclerotic myeloma. Various

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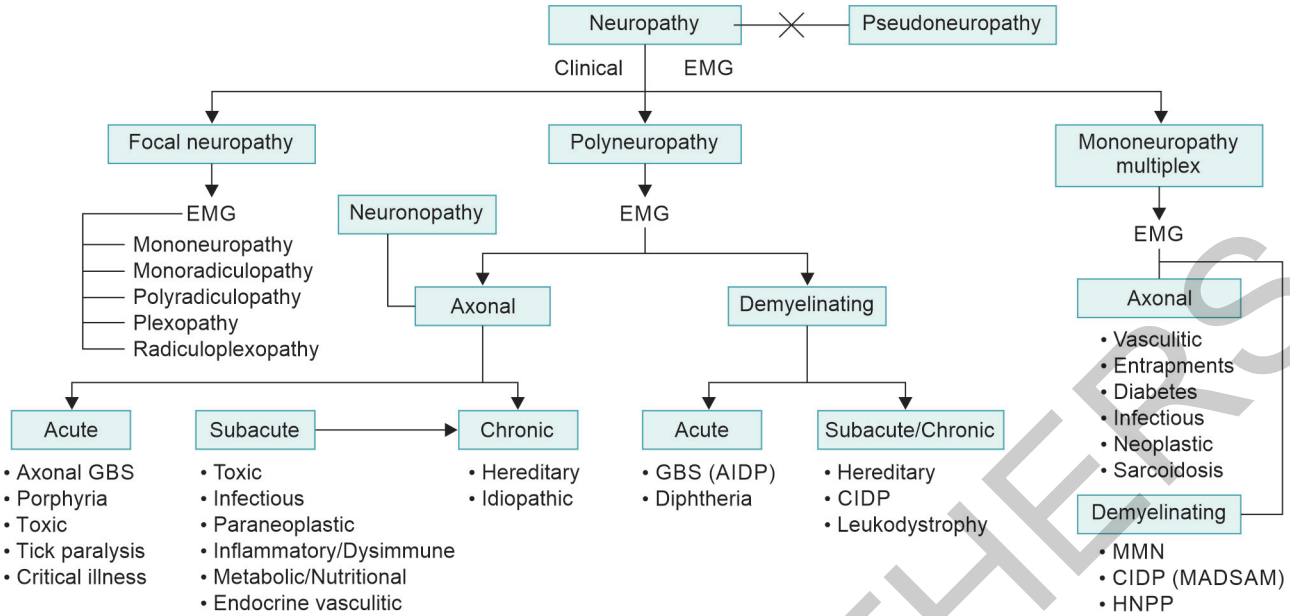

FLOWCHART 1: An algorithm for the classification and differential diagnosis of neuropathy.

(AIDP: acute inflammatory demyelinating polyneuropathy; CIDP: chronic inflammatory demyelinating polyneuropathy; EMG: electromyography; GBS: Guillain–Barré syndrome; HNPP: hereditary neuropathy with pressure palsies; MMN: multifocal motor neuropathy; MADSAM: multifocal acquired demyelinating sensory and motor neuropathy)

BOX 4: Causes of mononeuropathy multiplex.

- *Axonal mononeuropathy multiplex*:
  - Vasculitis (systemic and nonsystemic)
  - Diabetes mellitus
  - Sarcoidosis
  - Leprosy (Hansen disease)
  - Human immunodeficiency virus 1 infection
- *Demyelinating mononeuropathy multiplex*:
  - Multifocal motor neuropathy
  - Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM and Lewis–Sumner syndrome)
  - Multiple compressive neuropathies (hypothyroidism and diabetes)
  - Hereditary neuropathy with liability to pressure palsies (HNPPs)

BOX 5: Neuropathies with predominantly motor manifestations.

- Guillain–Barré syndrome
- Acute motor axonal neuropathy*
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy*
- Neuropathy with osteosclerotic myeloma
- Diabetic lumbar radiculoplexopathy
- Charcot–Marie–Tooth disease (hereditary motor sensory neuropathies)
- Lead intoxication

*Pure motor syndromes with normal sensory nerve action potentials.

neuropathies with predominantly motor involvement are mentioned in **Box 5**.

The distribution of weakness provides important clinical clues toward the possible etiology. Asymmetrical weakness without sensory loss suggests a motor neuronopathy such as motor neuron disease (MND) or multifocal motor neuropathy (MMN). Cranial nerves may also get affected in several peripheral nerve disorders as enlisted in **Table 2**.

In most polyneuropathies, the legs are more severely affected than the arms, with several notable exceptions as depicted in **Box 6**.

Autonomic dysfunction of clinical significance is seen in association with specific acute (e.g., Guillain–Barré syndrome) or chronic (e.g., amyloidosis and diabetes mellitus) sensorimotor polyneuropathies, as shown in **Box 7**. Rarely, an autonomic neuropathy may be the exclusive manifestation of a peripheral nerve disorder, without somatic nerve involvement.

TABLE 2: Neuropathies with cranial nerve involvement.

Neuropathy	Most commonly involved cranial nerves	Less commonly involved cranial nerves
Diphtheria	IX	II, III
Sarcoid	VII	I, III, IV, VI
Diabetes	III*	IV, VI, VII
Guillain–Barré syndrome (GBS)	VI, VII	
Miller–Fisher variant of GBS	III, IV	
Sjögren's syndrome	V	
Celiac disease		V
Polyarteritis nodosa	III, VII, VIII	
Wegener's granulomatosis	VIII	

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Neuropathy	Most commonly involved cranial nerves	Less commonly involved cranial nerves
Lyme disease	VII, V	All but I
Porphyria	VII, X	III, IV, V, XI, XII
Refsum disease	I, VIII	
Primary amyloidosis	III, V, VII	VI, XII
Syphilis	III	IV, V, VII, VIII
Arsenic	V	

*Pupil is usually spared.

BOX 6: Polyneuropathies with predominantly upper-limb motor involvement.

- Multifocal motor neuropathy
- Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) and Lewis–Sumner syndrome
- Lead neuropathy*
- Porphyria
- Tangier disease
- Familial amyloid neuropathy type 2
- Hereditary motor neuropathy (uncommon forms)

*Frequently presents with wrist drop.

BOX 7: Neuropathies with autonomic nervous system involvement.

- *Acute*:
  - Acute pandysautonomic neuropathy (autoimmune and paraneoplastic)
  - Guillain–Barré syndrome
  - Porphyria
  - Toxic: Vincristine and Vacor (rodenticide)
- *Chronic*:
  - Diabetes mellitus
  - Amyloid neuropathy (familial and primary)
  - Paraneoplastic sensory neuronopathy (malignant inflammatory sensory polyganglionopathy)
  - Human immunodeficiency virus-related autonomic neuropathy
  - Hereditary sensory and autonomic neuropathy

BOX 8: Small-fiber neuropathies.

- Diabetes mellitus and impaired glucose tolerance
- Sjögren (sicca) syndrome
- Celiac disease
- Amyloid neuropathy (early familial and primary)
- Human immunodeficiency virus-associated sensory neuropathy
- Hereditary sensory and autonomic neuropathies
- Fabry disease
- Tangier disease
- Cryptogenic small-fiber neuropathy

BOX 9: Sensory ataxic neuropathies.

- *Sensory neuronopathies (polyganglionopathies)*:
  - Paraneoplastic sensory neuronopathy (malignant inflammatory sensory polyganglionopathy)
  - Sjögren syndrome
  - Idiopathic
  - Toxic (cisplatin and analogs, vitamin B6 excess)
- Chronic immune sensory polyradiculopathy
- *Demyelinating polyradiculoneuropathies*:
  - Guillain–Barré syndrome (Miller–Fisher variant)
  - Immunoglobulin M monoclonal gammopathy MAG** antibody
- *CANOMAD**
  - Tabes dorsalis

*Chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and anti-GD1b disialosyl antibodies.

**Myelin-associated glycoprotein.

Predominant sensory involvement may be a feature of polyneuropathies caused by diabetes mellitus, malignancy, Sjögren's syndrome, paraproteinemia, acquired immunodeficiency syndrome (AIDS), vitamin B12 deficiency, celiac disease, inherited and idiopathic sensory neuropathies, and toxicity associated with cisplatin, thalidomide, or pyridoxine. Loss of sensation in peripheral neuropathies often involves all sensory modalities. However, the impairment may be restricted to selective sensory modalities in many clinical situations, which makes it possible to correlate the type of sensory loss with the diameter size of affected afferent fibers. Pain and temperature sensations are mediated by unmyelinated and small myelinated A-delta fibers, whereas vibratory sense, proprioception, and the afferent limb of the tendon reflex arc are subserved by large myelinated A-alpha and A-beta fibers. Light touch is mediated by both large and small myelinated fibers. In polyneuropathies preferentially affecting small fibers, diminished pain and temperature sensation predominate, along with spontaneous burning pain, painful dysesthesia, and autonomic dysfunction. There is preservation of tendon reflexes, balance, and motor strength, and hence few abnormal objective neurological signs are observed on clinical examination. A pattern of sensory loss that is very characteristic is distal loss of pinprick sensation, above which is a band of hyperalgesia, with normal sensation above this level. Relatively few disorders cause selective small-fiber neuropathies as shown in **Box 8**. Selective large-fiber sensory loss is characterized by areflexia, sensory ataxia, and loss of joint position and vibration sense. Loss of joint position may also manifest as pseudoathetosis and/or Romberg sign. Striking sensory ataxia, together with pseudoathetosis or asymmetrical truncal or facial sensory loss, directs attention to a primary disorder of sensory neurons or polyganglionopathies. The differential diagnosis of sensory ataxic neuropathies is limited and enumerated in **Box 9**.

Palpation of peripheral nerves is an important though unreliable part of the clinical examination. Hypertrophy of a single nerve trunk is suggestive of either a neoplastic process (e.g., neurofibroma, schwannoma, and malignant nerve sheath

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tumor) or a localized perineurial hypertrophic neuropathy. Generalized or multifocal nerve hypertrophy is found in a limited number of peripheral nerve disorders, including leprosy, neurofibromatosis, Charcot–Marie–Tooth disease types 1 and 3, acromegaly, Refsum disease, and rarely CIDP. Certain cutaneous markers may also guide toward a specific etiology as described in **Table 3**.

Neuropathic pain can be a prominent presenting symptom in a large number of peripheral neuropathies. Pain is characteristic of neuropathies with predominant small-fiber involvement, but even in large-fiber neuropathies, a sufficient number of small fiber may be afflicted causing pain. Some of the causes of peripheral neuropathies associated with pain are mentioned in **Box 10**.

TABLE 3: Neuropathies with skin, nail, or hair manifestations.

Disease	Skin, nail, or hair manifestations
Vasculitis	Purpura and livedo reticularis
Cryoglobulinemia	Purpura
Fabry disease	Angiokeratomas
Leprosy	Skin hypopigmentation
Osteosclerotic myeloma (POEMS syndrome)	Skin hyperpigmentation
Variegate porphyria	Bullous lesions
Refsum disease	Ichthyosis
Arsenic or thallium intoxication	Mees lines
Thallium poisoning	Alopecia
Giant axonal neuropathy	Curled hair

(POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes)

BOX 10: Peripheral neuropathies frequently associated with pain.

- *Diabetic neuropathies*:
  - Painful symmetrical polyneuropathy
  - Asymmetrical polyradiculoplexopathy
  - Truncal mononeuropathy
- Brachial and lumbosacral plexopathy
- Vasculitic neuropathy
- *Toxic neuropathies*:
  - Arsenic and thallium
  - Alcohol
  - Vincristine and cisplatin
  - Dideoxynucleosides
- *Amyloid neuropathies*: Primary and familial
- Paraneoplastic sensory neuropathy
- Neuropathy associated with Sjögren syndrome
- Human immunodeficiency virus-related distal symmetrical polyneuropathy
- Uremic polyneuropathy
- Neuropathy associated with Fabry disease
- Hereditary sensory autonomic neuropathy
- Cryptogenic small-fiber neuropathy

Neuropathic pain is mainly of two types: Dysesthetic pain and nerve trunk pain. "Dysesthetic pain" usually affects distal skin and subcutaneous structures, may be constant or intermittent, often has a temporal pattern of worsening at periods of rest or bedtime, and is described as searing, burning, or icy-cold. Sensory examination should use techniques to elicit abnormal positive sensory phenomena. Allodynia can be provoked by light touch or nonpainful cold stimuli. When testing for hyperpathia, single and repeated pin-pricks are used. Patients with hyperpathia may often complain of "summation" (pain perception increasing with repeated stimulation) and "after-sensations" (pain continuing after ceasing stimulation). "Nerve trunk pain" is a deep-seated, sharp, knifelike proximal pain along nerve roots or trunks that improves with rest or optimal position, but is aggravated by movement. It seems to be mediated by spontaneous impulses arising from nervi nervorum innervating the nerve sheaths of affected nerve roots or trunks. Muscle pain and tenderness may develop with acutely evolving denervation of muscle, as occurs in Guillain–Barré syndrome (GBS) or acute poliomyelitis.

A careful history including over-the-counter nutritional and vitamin preparations should be obtained for every patient with polyneuropathy. Some of the drugs reported to cause peripheral neuropathy are listed in **Table 4**.

TABLE 4: Pharmaceutical drugs causing neuropathies.

Drugs	Clinical and pathological features	Comments
Antineoplastic		
Cisplatin	S, DA, N	Binds to DNA; disrupts axonal transport?
Suramin	SM, DA, SD	DA—inhibits binding of growth factors; SD—immunomodulating effects?
Taxanes (paclitaxel and docetaxel)	S, DA	Promote microtubule assembly; disrupt axonal transport
Vincristine	S > M, M, DA	Interferes with microtubule assembly; disrupts axonal transport
Antimicrobial		
Chloroquine	SM, DA	Myopathy
Dapsone	M, DA	Optic atrophy
Isoniazid	SM, DA	Pyridoxine antagonist
Metronidazole	S, DA	
Nitrofurantoin	SM, DA	
Antiviral (NRTIS)		
Didanosine (ddI)	SM, DA	Reversible neuropathy
Fialuridine (FIAU)	S, DA	Irreversible neuropathy; also myopathy
Lamivudine (3TC)	S, DA	Least common NRTI neuropathy
Stavudine (d4T)	SM, DA	More associated with lipodystrophy syndrome
Zalcitabine (ddC)	SM, DA	Single most neurotoxic NRTI
Zidovudine (AZT)	–	Myopathy only

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Drugs	Clinical and Pathological Features	Comments
Cardiovascular		
Amiodarone	SM, SD	Lysosomal lamellar inclusions; myopathy
Hydralazine	SM, DA	Pyridoxine antagonist
Perhexiline	SM, SD	Lipid inclusions
Other		
Colchicine	SM, DA	Neuromyopathy and raised creatine kinase levels
Disulfiram	SM, DA	
Gold	SM, DA	Myokymia
Lipid-lowering agents (statins)	SM, DA	May also cause rhabdomyolysis
Nitrous oxide	S, DA	Inhibits vitamin B12-dependent methionine synthase and myelopathy
Phenytoin	SM, DA	Asymptomatic in most
Pyridoxine	S, N, DA	Doses > 250 mg/day
Thalidomide	S, N	
L-tryptophan (tainted)	SM, DA	Eosinophilia–myalgia syndrome

(DA: distal axonopathy; M: motor; N: neuronopathy; NRTI: nucleoside analog reverse transcriptase inhibitor; S: sensory; SD: segmental demyelination; SM: sensorimotor neuropathy)

ELECTRODIAGNOSTIC STUDIES

It is of utmost importance to follow a decision-making pathway based initially on the overall pattern of distribution of deficits, followed by the electrophysiological findings, and finally, the clinical course, as described in **Flowchart 2**. Electrodiagnostic studies play a key role in the evaluation by confirming the presence of neuropathy, precisely locating the focal nerve lesions, and ascertaining the nature of underlying nerve pathology. In nerve conduction studies, axonal polyneuropathies reduce the action potential amplitudes of sensory nerves, and also the muscle action potential amplitudes, if there is motor axonal involvement. However, the conduction velocities and latencies remain normal. Demyelinating neuropathies slow conduction velocities and prolong distal latencies. Hereditary demyelinating polyneuropathies cause uniform conduction slowing, but acquired demyelinating neuropathies cause nonuniform slowing.

On electromyography, abnormal insertional and spontaneous activities such as fibrillations or positive sharp waves, suggest acute or active axonal injury. The presence of large, polyphasic motor units suggests partial reinnervation of muscle by regenerating axons (i.e., a chronic process). Recruitment of motor units (firing too few motor units at a higher than normal frequency) is reduced in patients with demyelinating and axonal neuropathies.

Imaging

High-resolution neuromuscular ultrasound is an extremely useful tool in the diagnosis of mononeuropathies, including entrapment neuropathies and traumatic nerve injuries. Focal nerve enlargement, measured as cross-sectional area, is the most common indicator of nerve entrapment, including carpal tunnel syndrome and ulnar neuropathy at the elbow. It is also helpful in visualizing fasciculations in limb muscles and tongue, more readily than needle EMG. Muscle ultrasound is also useful in inflammatory myopathies and muscular dystrophies by showing increased echogenicity of muscles, thus aiding in selection of muscle biopsy sites.

Skin Biopsy

Skin punch or blister biopsies may demonstrate the loss of intraepidermal nerve fibers, documenting small-fiber neuropathy, as in diabetic and HIV-associated sensory or sensorimotor polyneuropathies. It is more useful in patients with suspected small-fiber neuropathy when nerve conduction studies are normal. The diagnosis of small-fiber neuropathy is best accomplished when at least two abnormal results are met, including positive clinical findings—quantitative sensory testing, QSART, and skin biopsy.

Nerve Biopsy

The most common indications for biopsy of a distal nerve, usually the sural or superficial peroneal nerve, are peripheral nerve vasculitis and suspected light chain amyloidosis. A simultaneous muscle biopsy increases the diagnostic yield to almost 70%. The usual indications for nerve biopsy in cases of peripheral neuropathy have been listed in **Box 11**.

Laboratory Investigations

The usual laboratory investigations in peripheral neuropathy include complete blood counts, kidney and liver functions, glycosylated hemoglobin, and thyroid profile. Some of the laboratory parameters targeting specific underlying etiologies have been mentioned in **Table 5**.

A basic approach to laboratory testing in peripheral neuropathy has been described in **Flowchart 3**.

TREATMENT

Treatment of peripheral neuropathy has two key tenets—to control the underlying disease process and treat the troublesome symptoms. The first one is usually done by eliminating the offending agents, such as pharmaceutical agents or toxins; correcting the nutritional deficiency; or treating the underlying disease (e.g., steroids for immune-mediated neuropathy). These measures may help to improve the symptoms by halting the progression of the pathological process causing neuropathy.

Acute inflammatory polyneuropathies require aggressive management with intravenous immunoglobulins or plasmapheresis.

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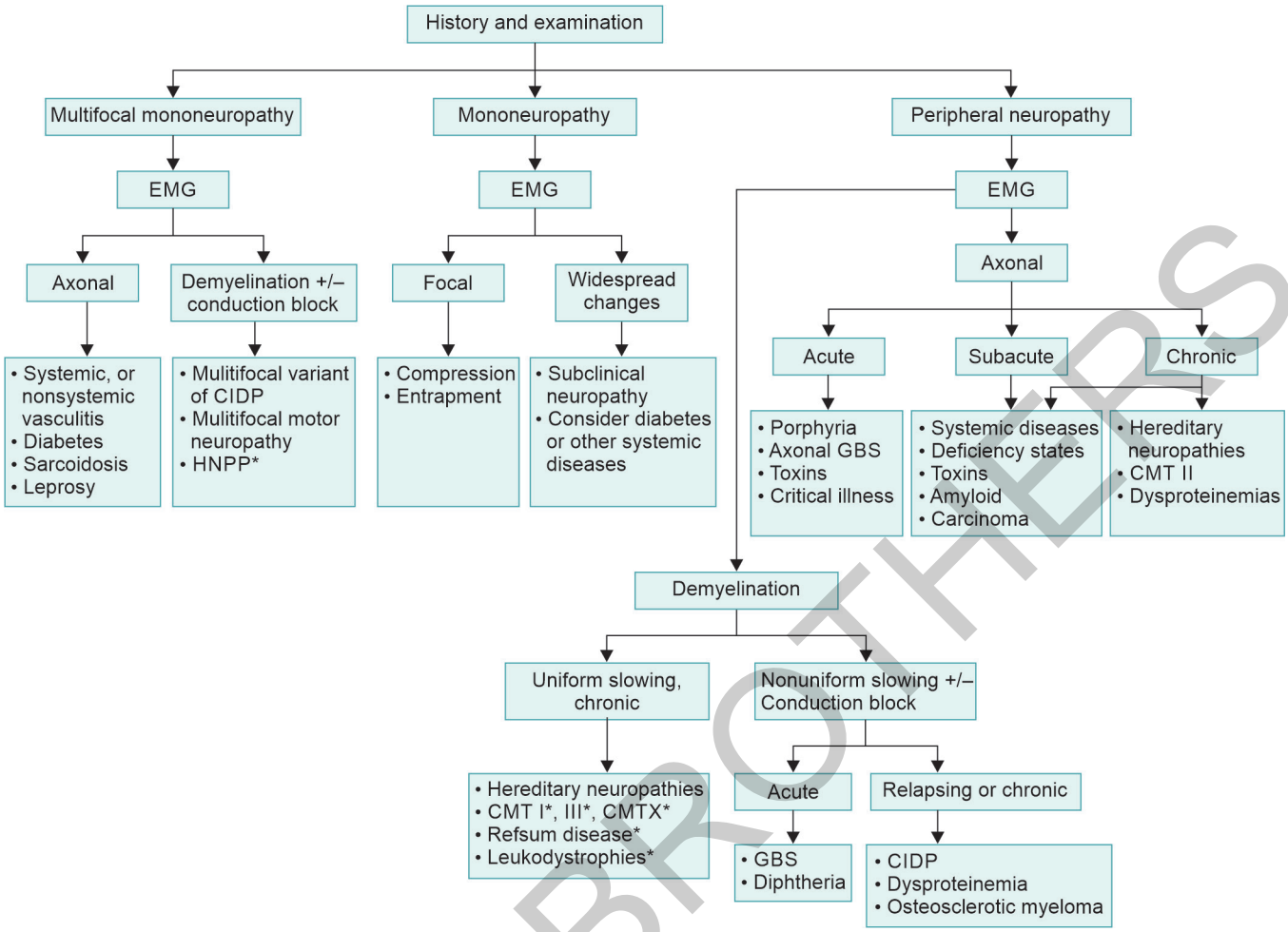

FLOWCHART 2: Diagnostic pathway for evaluation of a patient with peripheral neuropathy.

Note: Electromyography (EMG) denotes electrodiagnostic studies including nerve conduction studies and needle EMG. DNA diagnostic testing or specific biochemical tests are available for conditions marked with asterisks (*).

(CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; CMT: Charcot–Marie–Tooth disease; CMTX; Charcot–Marie–Tooth disease X-linked; GBS: Guillain–Barré syndrome; HNPP: hereditary liability to pressure palsies)

BOX 11: Indications for nerve biopsy.

- *Nerve biopsy is diagnostic and essential for diagnosis*:
  - Vasculitis*
  - Amyloidosis*
  - Sarcoidosis*
  - Hansen disease (leprosy)
  - Giant axonal neuropathy
  - Tumor infiltration
  - Polyglucosan body disease
- *Nerve biopsy is suggestive and only supportive of diagnosis*:
  - Charcot–Marie–Tooth disease types 1 and 3
  - Chronic inflammatory demyelinating polyradiculoneuropathy
  - Paraproteinemic neuropathy (immunoglobulin M monoclonal gammopathy with anti-myelin-associated glycoprotein antibody)

*Consider combined distal nerve and muscle biopsies.

TABLE 5: Testing indicated in patients with peripheral neuropathy.

Tests	Clinical disorders
Routine	
Complete blood count	–
Comprehensive metabolic panel	–
Erythrocyte sedimentation rate	–
Fasting blood glucose level	–
Thyroid-stimulating hormone level	–
Vitamin B12 level	–
If indicated by clinical suspicion	
Glucose tolerance test, A1c level	Diabetes mellitus
HIV antibodies	HIV
Hepatic panel	Liver disorders
Lyme antibodies	Lyme disease

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Tests	Clinical disorders
Rapid plasma reagin, VDRL	Syphilis
Urinalysis (including 24-hour urine collection)	Heavy metal toxicity, porphyrias, and multiple myeloma
Urine and serum protein electrophoresis with immunofixation	Demyelinating neuropathy
Angiotensin-converting enzyme levels	Sarcoidosis
Antinuclear antibodies, P-ANCA, and C-ANCA	Vasculitis
Tests for uncommon conditions	
Paraneoplastic panel	Underlying malignancy
Antimyelin-associated glycoprotein and antiganglioside antibodies	Sensorimotor neuropathy
Antisulfatide antibodies	Autoimmune polyneuropathy
Cryoglobulins	Cryoglobulinemia
Salivary flow rate, Schirmer test, Rose Bengal test, labial gland biopsy	Sjögren syndrome
Cerebrospinal fluid analysis	Acute or chronic inflammatory demyelinating neuropathy
Genetic testing	Hereditary neuropathy

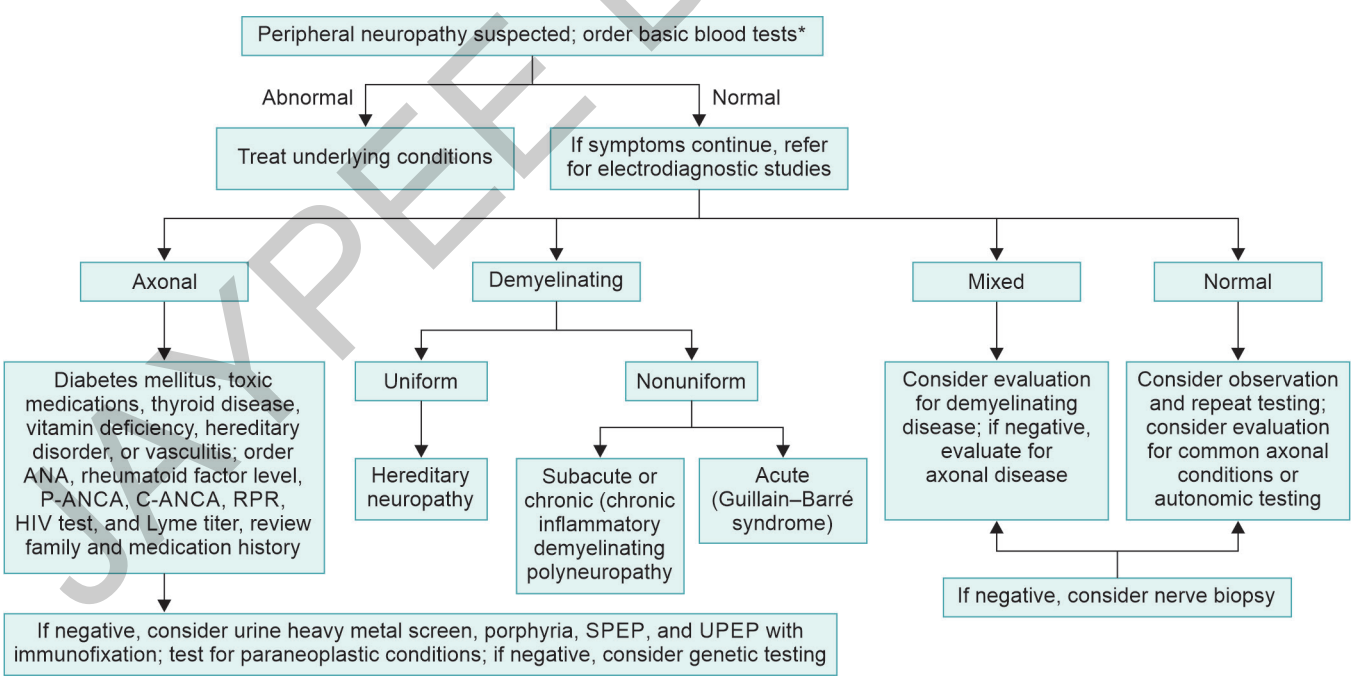
Note: Tests are listed in the approximate frequency of the potential underlying disorder.

(C-ANCA: cytoplasmic antineutrophil cytoplasmic antibodies; HIV: human immunodeficiency virus; P-ANCA: perinuclear antineutrophil cytoplasmic antibodies; VDRL: Venereal Disease Research Laboratory)

Neuropathic pain may be helped with certain antiepileptics (e.g., gabapentin, pregabalin, topiramate, and carbamazepine) and antidepressants (e.g., amitriptyline and duloxetine). Supportive treatment with proper foot care, weight reduction, and shoe selection may help some patients with chronic neuropathic pain. Opioids are the last resort in resistant cases.

CONCLUSION AND FUTURE RESEARCH

During the last two decades, significant research has been done to elucidate the pathophysiologic mechanisms of peripheral nerve disorders, which has led to considerably improved understanding of immune-mediated, hereditary, and diabetic neuropathies. Newer diagnostic modalities, like magnetic resonance neurography, have a supportive role in the workup of inflammatory neuropathies, can provide additional information in entrapment neuropathies, and have an emerging role in diffuse polyneuropathies. Diffusion tensor imaging is another magnetic resonance technique to investigate peripheral nerve diseases. This technique is sensitive to subtle changes in tissue microstructure and enables measurement of nerve integrity based on quantitative parameters such as fractional anisotropy, apparent diffusion coefficient, and mean, axial, and radial diffusivity. It has been used extensively in entrapment neuropathy and various plexopathies. Microneurography is a minimally invasive technique for the investigation of physiological properties and pathological changes in small-nerve fibers. Confocal corneal microscopy is a noninvasive modality for detecting small-fiber loss in neuropathies and initial findings correlate well with those of skin biopsy in small-fiber neuropathies. With advancements in investigative tools at the clinicians' disposal, newer pathological processes such as nodopathies and paranodopathies have recently



*Complete blood count, comprehensive metabolic panel, and measurement of erythrocyte sedimentation rate and fasting blood glucose, thyroid-stimulating hormone, and vitamin B, levels (possibly with methylmalonic acid and homocysteine levels.

FLOWCHART 3: Approach to laboratory diagnosis in peripheral neuropathy.

(ANA: antinuclear antibodies; C-ANCA: cytoplasmic anti- neutrophil cytoplasmic antibodies; HIV: human immunodeficiency virus; P-ANCA: perinuclear antineutrophil cytoplasmic antibodies; RPR: rapid plasma reagin; SPEP: serum protein electrophoresis; UPEP: urine protein electrophoresis)

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been studied. The microstructural changes restricted to the nodal/paranodal region may be the key to understanding the pathophysiology of antiganglioside antibody-mediated neuropathies.

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