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CLINICAL MEDICINE UPDATE

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Contents

SECTION 1: NEUROLOGY

1. **Antiseizure Medications: Therapy in Epilepsy** 1
   Manjari Tripathi

2. **Clinical Approach to Peripheral Neuropathy** 9
   MPS Chawla, Amit Aggarwal

3. **Stroke in the Young: An Approach** 27
   Naval K Vikram, Hari Narayan A

4. **Drug-induced Movement Disorders** 34
   Ram Babu, Raghavi Abhilesh Bembey

5. **An Approach to a Patient Presenting with Acute Flaccid Paralysis** 51
   Praveen Kumar Yadav

6. **Ophthalmoplegia and Ptosis: An Overview** 58
   TP Singh, Sahil Vij, Zeeshan Akhtar, Milind

7. **Management of Acute Ischemic Stroke in the First 24 Hours** 65
   Abhishek Anand, Rohit Bhatia

SECTION 2: CARDIOVASCULAR MEDICINE

8. **Coronary Artery Disease in Females: How is it Different?** 83
   G Thiyagarajan

9. **Heart Failure with Preserved Ejection Fraction: Diagnostic Pitfalls and Management** 89
   Subhash Chandra, SN Yadav

10. **Nocturnal Hypertension and its Clinical Implications** 103
    Girish Verma, Shubhankar, Tanushree Verma

11. **Orthostatic Hypotension: Evaluation and Management** 110
    Ankan Pathak

12. Advances in the Management of Resistant Hypertension **114**
KK Pareek, Girish Mathur, GD Ramchandani

13. Ten Years of Novel Oral Anticoagulants: What have We Learnt? **125**
Gurinder Mohan, Chandan Goyal, Karandeep Malhi

14. Masked Hypertension: Current Concepts **133**
Debaprasad Chakrabarti, Anirban Saha

15. The Changing Panorama of Heart Failure **138**
HS Pathak, Ankan Pathak

SECTION 3: PULMONARY MEDICINE

16. Indian Guidelines for Spirometry **143**
Prashant Prakash, Abhishek Raj, Shubham Jain

17. Healthcare-associated Pneumonia **157**
Atul Bhasin, RK Singal

18. Allergic Bronchopulmonary Aspergillosis: Update 2024 **161**
DP Singh, Ashok Kumar, Shyam Narayan

19. Challenges and Pitfalls in the Diagnosis and Management of Bronchial Asthma **168**
DG Jain, VD Jain

20. Role of Biologics in Management of Bronchial Asthma **183**
Prashant Prakash, Raj Kumar Verma, Raj Kumar Gupta

21. Nonresolving Pneumonia **193**
Desh Deepak, Prateek Gupta

22. Obstructive Sleep Apnea **209**
Puneet Rijhwani, Mahima Aneja, Deepak Gupta, Pardeep Agarwal, RamKishan Jat

SECTION 4: CRITICAL CARE MEDICINE

23. Advanced Hemodynamic Monitoring in the Intensive Care Units **221**
Ajay Chhabra

24. Sepsis Mimics **228**
Saikat Datta

25. An Approach to a Patient with Undifferentiated Shock **232**
Prabhat Agrawal, Sandipta Kumar Panda, Nikhil Pursnani, Ashish Gautam

26. Recent Advances in Acute Respiratory Distress Syndrome Management 238
Ganesh Narwade, Rajnish Kaushik

27. Toxicology: Changing Paradigms 249
Mohan Kumar H, Ashish Bhalla

28. Fluid Therapy in Emergencies: Which, When, and Why? 253
Ashima Arora, Vikas Loomba

SECTION 5: ENDOCRINOLOGY

29. Thyroid Disorders in Pregnancy 263
Raminder Pal Singh Sibia

30. Thyroid and Drugs 271
Sunil Bansal, AK Gupta, Mohamad Husain, Piyush Tageja

31. Recurrent Hypoglycemia in a Patient without Diabetes 277
Vijay Kumar

32. Diabetic Bone Disease: Overlooked But Ominous 294
Ajoy Tewari

33. Diagnostic Approach to Hypercalcemia 300
Tarun Satija

SECTION 6: NEPHROLOGY

34. Acute Kidney Injury: Present Perspective 305
HK Aggarwal, Deepak Jain, Diksha Nayak, Aviral Dua

35. Recent Advances in the Management of Diabetic Kidney Disease 313
Pulin Kumar Gupta, Kaushik Mandal, Brahaspati Hansda

SECTION 7: RHEUMATOLOGY

36. Pregnancy and Autoimmune Disorders: The Intricate Interplay 319
Rashmi Mishra, Sumeet Singla

37. Connective Tissue Diseases–Associated Emergencies 328
Harpreet Singh, Ekal Arora, Jaideep Phougat

38. Sjögren Syndrome: A Grossly Missed Diagnosis 334
Ved Chaturvedi

39. Infection-associated Arthritis **338**
Narendra Bagri, Uma Kumar

40. Approach to Lupus Nephritis **344**
Renu Saigal, Amit Kansal

41. Diabetes and Arthritis: Rheumatologists' and Diabetologists' Interface **353**
Udas Chandra Ghosh

SECTION 8: GASTROENTEROLOGY AND HEPATOLOGY

42. Tools for Primary Care Management of Inflammatory Bowel Disease: Treat to Target **361**
Bharath HR, Sunil K Dadhich, Naveen Mehla

43. Alcoholic Hepatitis: What's New? **369**
Parimita Barua

44. Acute-on-Chronic Liver Failure: State of Art **379**
Jayati Samanta, Saptarshi Bishnu

45. Approach to Chronic Diarrhea **388**
SS Dariya, Aniket V Inamdar

46. Clinical Evaluation of Irritable Bowel Syndrome **396**
Anil Samaria, Meenakshi Samaria, Pranav Sharma, Anurag Tiwari, Pearl Samaria

47. Approach to a Patient with Drug-induced Hepatitis **405**
Kirandeep Kaur

48. Metabolic Dysfunction–associated Steatotic Liver Disease: An Approach **409**
Manish Sharma, Abhishek Dahiya, Reshma Prakash, Nitin Sinha

SECTION 9: HEMATOLOGY

49. Perioperative Management of Hematological Disorders **417**
Sunita Aggarwal, Mansi Hans, Soumia M

50. An Approach to Hemolytic Anemias **426**
Dibyendu De, Neelesh Jain

51. Approach to Thrombocytopenia **434**
BL Bhardwaj, Kanchan Bhardwaj, Harnoor Singh

52. Hypercoagulable States: Clinical Clues and Diagnostic Approach **446**
Yadati Sathyanarayana Raju

53. Hemophagocytic Lymphohistiocytosis: What a Physician Needs to Know? **455**
Chakrapani Mahabala

SECTION 10: ONCOLOGY

54. Hepatocellular Carcinoma: Clinical Practice Essentials **465**
Madhuchanda Kar

55. Immunotherapy in Cancer: Getting Down to Brass Tacks **470**
Vineet Talwar, Arpit Jain

56. Tumor Markers in Internal Medicine Practice in India and Globally **479**
Gursaran Kaur Sidhu, Satinder Singh, Rajeshwar Singh Sidhu

SECTION 11: INFECTIOUS DISEASES AND TROPICAL MEDICINE

57. Malaria **487**
Sarit Chatterjee, Geeta Kampani

58. Fever in Immunocompromised Patients **498**
Rajesh Kumar, Lokesh Verma

59. Atypical Mycobacterial Infections **510**
Debasis Chakrabarti

60. Management of Latent Tuberculosis: Recent Updates **519**
S Anuradha

61. Antiretroviral Therapy: Current Strategy and Future Perspectives **528**
Bharat Bhushan Rewari, Vijay Arora

62. Fever with Jaundice **536**
Pradip Bhaumik

63. Antibiotic Myths for the Infectious Disease Physician **544**
Amit Aggarwal

64. Use of Anti-tuberculosis Treatment in Special Situations **549**
Kamal Chopra, Kranti Garg

65. Long COVID: Aftermath of Coronavirus Disease 2019 **554**
Dhruva Chaudhary, Vineela Surapaneni

66. Neglected Tropical Diseases **565**
Dipanjan Bandyopadhyay, A Shafeek Ahamed, Dipayan Saha

SECTION 12: CLINICAL SKILLS

67. Dynamic Auscultation of Heart Sounds **579**
Vijay Garg, Chandrakant Salve, Masum Talesara, Yash Deshmukh

68. Jugular Venous Pulse: Interpretation **587**
Archith Boloor, Vidarshan Mathavan

69. You must See a Patient Eye to Eye **594**
Sandipan Banik, Smarajit Banik

70. Relevance of Clinical Examination in the Era of Artificial Intelligence **608**
Alladi Mohan, Nagachandra Kiran Dharamvaram Harirao, Saumya Ahluwallia, Srishti Ahluwalia

71. What an Internist should do in Terminally-ill Patients? **612**
NK Soni

SECTION 13: MISCELLANEOUS

72. Nonsteroidal Anti-inflammatory Drugs: Painkillers or Killers? **615**
Amit Aggarwal, MPS Chawla

73. Management of Alcohol Use Disorders **627**
Gautam Bhandari, Shreyansh Singhvi, Naveen Mehla, Sunil K Dadhich, Bharath HR

74. Clinical Approach to Hiccups **636**
Aniket V Inamdar, Shriram V Kulkarni, Anushka Deogaonkar

75. Pregnancy as a Mirror to Systemic Diseases **644**
Manisha Bais Thakur, Rudra Sen

76. Heat Stroke **649**
Ajay Chauhan, Simranjit Kaur

Index ***659***

CHAPTER

2

Clinical Approach to Peripheral Neuropathy

MPS Chawla, Amit Aggarwal

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 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 process. Based on the extent of involvement, the symptoms may vary from paresthesiae or hyperalgesia to twitching, cramping, fatigue, weakness or wasting, gait imbalance, and dysautonomia. A stepwise clinical approach is needed for accurate diagnosis and appropriate management.

INTRODUCTION

Peripheral nervous system (PNS) consists of the neural structures outside the piamater. 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, subserving 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, like:

- *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**.

TYPES OF NERVE FIBERS

Nerve fibers are broadly classified into three subtypes—(1) group A, (2) group B, and (3) group C, in which groups A and B are myelinated and large fibers, whereas group C is unmyelinated and small fiber. These groups may carry both motor and sensory fibers. Group B fibers are less myelinated than group A fibers, but more myelinated than group C fibers.

The basic characteristics of the different nerve fibers and their functions are depicted in **Figure 1**.

NERVE PATHOLOGIES

Despite of 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 (GBS) 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**.

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

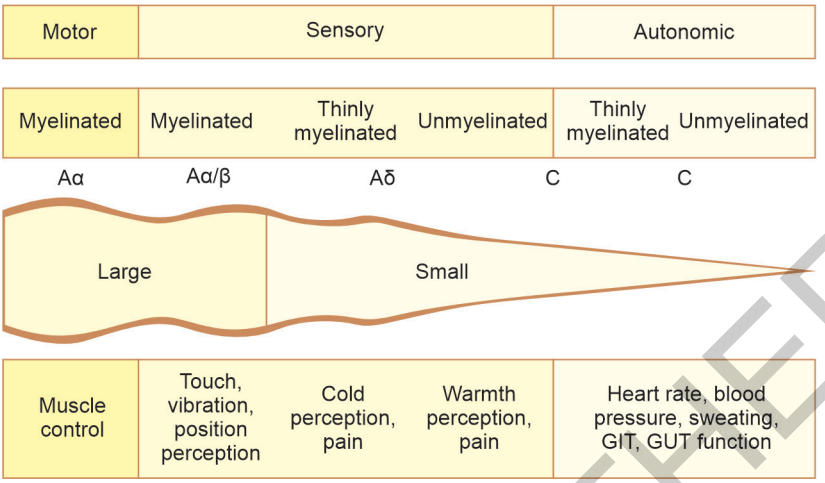


FIG. 1: Types of nerve fibers and functions.

(GIT: gastrointestinal tract)

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

	Axonopathy	Myelinopathy	Sensory neuronopathy
Pattern	Distal, 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 nonlength-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

EXTENT OF NERVE INJURIES

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

- *Neurapraxia (grade 1):* No major structural damage. 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 upon 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 a central or separate peripheral loci may mimic a neuropathy clinically. Such a situation is termed as "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 plaque 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 Ds*:
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, dysesthesias, 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

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, and 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:* Vasculitic (purpura/livedo reticularis), hypopigmentation (leprosy), angiokeratomas (Fabry's disease), neurofibromas/café-au-lait spots (neurofibromatosis), ichthyosis (Refsum disease), hyperpigmentation [polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome], foot ulcers (hereditary sensory and autonomic neuropathy, diabetes mellitus), trophic changes (dysautonomia), and lipomas (mitochondrial disease).
- *Gum lesions:* Lead lines
- *Nail lesions:* Mee's 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, and infection [human immunodeficiency virus (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 usual types of anatomic patterns in peripheral neuropathies based on clinical localization have been described in **Table 2**. 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.

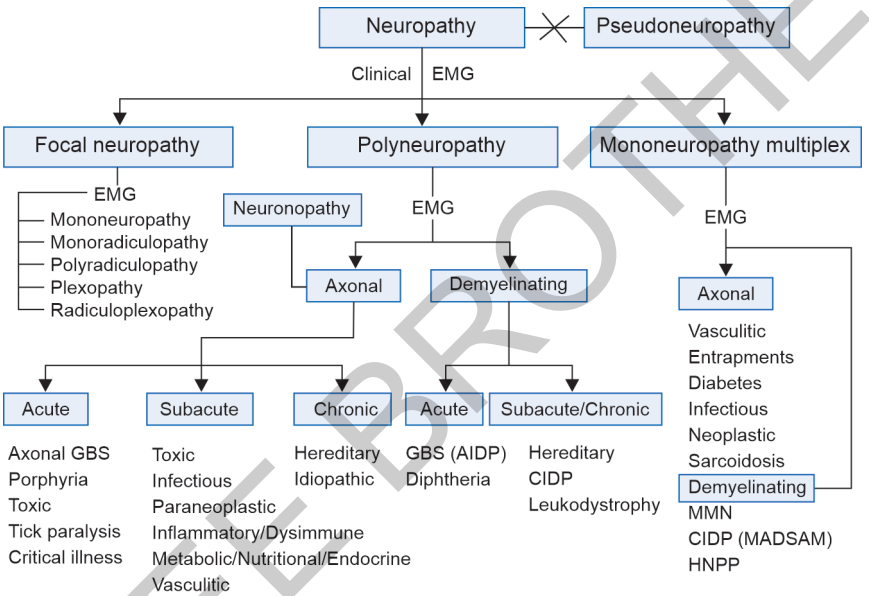
TABLE 2: Types of anatomic patterns based on clinical localization in peripheral neuropathies.

Anatomic pattern	Neuroanatomic localization	Differential diagnosis
Symmetrical proximal and distal weakness with sensory loss	Polyradiculoneuropathy	Acute inflammatory demyelinating polyradiculoneuropathy if acute and maximal involvement within the first 4 weeks, chronic inflammatory demyelinating polyneuropathy if progressive over >8 weeks
Symmetrical distal sensory loss with or without distal weakness	Peripheral polyneuropathy	Cryptogenic sensory peripheral neuropathy, diabetes or other metabolic disorders, toxic, and hereditary such as Charcot–Marie–Tooth
Asymmetrical distal weakness with sensory loss	Mononeuritis multiplex	Vasculitis, hereditary neuropathy with predisposition to pressure palsies, multifocal acquired demyelinating sensory and motor neuropathy, and infections (e.g., leprosy)
	Mononeuropathy or radiculopathy	Compression, trauma, or tumor
Asymmetrical proximal and distal weakness with sensory loss	Polyradiculopathy	Polyradiculopathy or plexopathy due to diabetes (diabetic lumbosacral radiculoplexus neuropathy) or a meningeal disorder (carcinoma, lymphoma, sarcoidosis, and chronic infection)
Asymmetrical distal weakness without sensory loss	• Motor neuronopathy with upper motor neuron signs (brisk reflexes, spasticity, and Babinski responses) • Motor neuronopathy (lower motor neurons) or motor neuropathy	• Amyotrophic lateral sclerosis • Progressive muscular atrophy, multifocal motor neuropathy, and monomelic amyotrophy (Hirayama disease)
Symmetrical sensory loss with distal areflexia with upper motor neuron findings	Mixed myelopathy and polyneuropathy	Severe combined degeneration due to vitamin B12 or copper deficiency or to inherited disorders (adrenomyeloneuropathy, metachromatic leukodystrophy, Friedreich ataxia)
Symmetrical weakness without sensory loss	• Motor neuronopathy • Motor neuropathy	• *Proximal and distal*: Spinal muscular atrophy or progressive muscular atrophy • *Distal predominant*: Hereditary motor neuropathy
Focal midline proximal weakness	Motor neuronopathy, neuromuscular junction disorder, and myopathy	• *Neck extensor weakness (head drop)*: Amyotrophic lateral sclerosis, myasthenia gravis, and myopathy • *Bulbar weakness*: Amyotrophic lateral sclerosis and myasthenia gravis

Continued

Continued

Anatomic pattern	Neuroanatomic localization	Differential diagnosis
Asymmetrical sensory loss with sensory ataxia without weakness	• Sensory neuronopathy/ganglionopathy • Sensory polyradiculoneuropathy	• Sjögren, paraneoplastic (anti-Hu antibody), idiopathic • Chronic immune sensory polyradiculoneuropathy
Autonomic symptoms and signs	Autonomic neuropathy	Diabetes, amyloid, and autoimmune autonomic neuropathies



FLOWCHART 1: The classification and differential diagnosis of neuropathy.

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

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 2**. 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 neuropathies with predominantly motor involvement are mentioned in **Box 3**.

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 3**.

In most polyneuropathies, the legs are more severely affected than the arms, with several notable exceptions as depicted in **Box 4**.

BOX 2 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, Lewis–Sumner syndrome)
  - Multiple compressive neuropathies (hypothyroidism, diabetes)
  - Hereditary neuropathy with liability to pressure palsies (HNPPs)

BOX 3 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.

TABLE 3: 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	VII, III, VIII	
Wegener's granulomatosis	VIII	
Lyme disease	VII, V	All but I
Porphyria	VII, X	III, IV, V, XI, XII
Refsum disease	I, VIII	
Primary amyloidosis	VII, V, III	VI, XII
Syphilis	III	IV, V, VII, VIII
Arsenic	V	

*Pupil is usually spared.

BOX 4 Polyneuropathies with predominantly upper limb motor involvement.

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

*Frequently presents with wrist drop.

Autonomic dysfunction of clinical significance is seen in association with specific acute (e.g., GBS) or chronic (e.g., amyloidosis and diabetes mellitus) sensorimotor polyneuropathies, as shown in **Box 5**. Rarely, an autonomic neuropathy may be the exclusive manifestation of a peripheral nerve disorder, without somatic nerve involvement.

Predominant sensory involvement may be a feature of polyneuropathies caused by diabetes mellitus, malignancy, Sjögren 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 make it possible to correlate the type of sensory loss with the diameter size of affected afferent fibers. Pain and temperature sensations are

BOX 5 Neuropathies with autonomic nervous system involvement.

- *Acute*:
  - Acute pandysautonomic neuropathy (autoimmune and paraneoplastic)
  - Guillain–Barré syndrome
  - Porphyria
  - Toxic: Vincristine, 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 6 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

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 dysesthesias, 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 6**.

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 7**.

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 tumor) or a localized perineurial hypertrophic neuropathy. Generalized or multifocal nerve hypertrophy is found in a limited number of peripheral nerve disorders, including leprosy,

BOX 7 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

(CANOMAD: chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and anti-GD1b disialosyl antibodies; MAG: Myelin-Associated Glycoprotein)

TABLE 4: Neuropathies with skin, nail or hair manifestations.

Disease	Skin, nail, or hair manifestations
Vasculitis	Purpura, 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)

neurofibromatosis, Charcot–Marie–Tooth disease types 1 and 3, acromegaly, Refsum disease, and rarely chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Certain cutaneous markers may also guide toward a specific etiology as described in **Table 4**.

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 fibers may be afflicted causing pain. Some of the causes of peripheral neuropathies associated with pain are mentioned in **Box 8**. Neuropathic pain is mainly of two types—(1) dysesthetic pain and (2) nerve trunk pain. "Dysesthetic pain" usually affects distal skin and subcutaneous structures, may be constant or intermittent, often have 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

BOX 8 Peripheral neuropathies frequently associated with pain.

- *Diabetic neuropathies*:
  - Painful symmetrical polyneuropathy
  - Asymmetrical polyradiculoplexopathy
  - Truncal mononeuropathy
- Brachial and lumbosacral plexopathy
- Vasculitic neuropathy
- *Toxic neuropathies*:
  - Arsenic, thallium
  - Alcohol
  - Vincristine, 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

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 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 5**.

Electrodiagnostic Studies

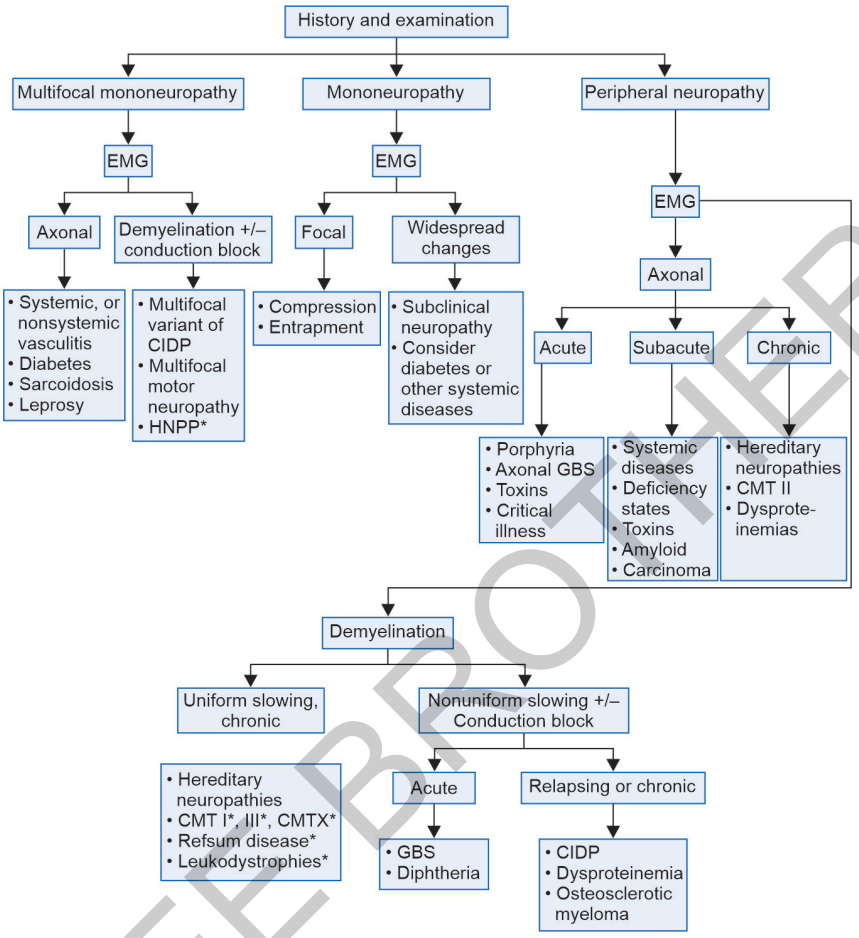
It is of utmost importance to follow a decision-making pathway based initially on the overall pattern of distribution of deficits, followed by the electrophysiological findings, and finally the clinical course, as described in **Flowchart 2**. Electrodiagnostic studies play a key role in the evaluation by confirming the presence of neuropathy, precisely locating the focal nerve lesions, and ascertaining the nature of underlying nerve pathology. On 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 (EMG), abnormal insertional and spontaneous activity, such as fibrillations or positive sharp waves, suggests acute or active axonal injury. The presence of large, polyphasic motor units suggest partial reinnervation of muscle by regenerating

TABLE 5: 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, 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
Cardiovascular		
Amiodarone	SM, SD	Lysosomal lamellar inclusions; myopathy
Hydralazine	SM, DA	Pyridoxine antagonist
Perhexiline	SM, SD	Lipid inclusions
Other		
Colchicine	SM, DA	Neuromyopathy, 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; 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)



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)

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, quantitative sudomotor axon reflex test (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 9**.

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 6**.

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

TREATMENT

Treatment of peripheral neuropathy has two key tenets—(1) to control the underlying disease process and (2) treating 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.

BOX 9 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.

CLINICAL MEDICINE UPDATE

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