Peripheral Neuropathy

Chapter 457 | Part 13: Neurologic Disorders

KEY CLINICAL POINTS

1. Approximately 50% of patients with generalized symmetric peripheral neuropathy have no identifiable etiology (idiopathic or cryptogenic).
2. Symmetric proximal and distal weakness with sensory loss is the hallmark of inflammatory demyelinating polyneuropathy (GBS and CIDP).
3. CMT1 is the most common hereditary neuropathy, characterized by motor conduction velocities <38 m/s and onion bulb formation on biopsy.
4. Small-fiber neuropathy: suspected if pain/temperature are lost while vibratory/position sense and muscle strength are preserved with normal NCS.
5. Vitamin B12 deficiency is a primary cause of combined system degeneration (CNS involvement + neuropathy).
6. Nerve biopsy is rarely performed; primarily indicated for suspected amyloid neuropathy or vasculitis.
7. Skin biopsy can diagnose small-fiber neuropathy by measuring the density of small unmyelinated fibers.
8. Autonomic dysfunction without diabetes should trigger suspicion for amyloid polyneuropathy.
9. CSF pleocytosis in GBS/CIDP suggests non-inflammatory causes like HIV, Lyme, sarcoidosis, or lymphomatous infiltration.
10. Distinction between axonopathy and myelinopathy is critical: Axonopathy shows low-amplitude potentials; Myelinopathy shows slow conduction velocities and prolonged latencies.

DEFINITION & CLASSIFICATION

- **Nerve Composition:** Mixed fibers including sensory, motor, and autonomic.
- **Fiber Classifications:**
  - Large myelinated: Motor axons (typically ~50 m/s) and large-diameter sensory fibers (proprioception, vibration).
  - Small myelinated & unmyelinated: Sensory fibers (pain, temperature) and autonomic nerves.
- **Pathology Classification:**
  - Neuronopathy/Ganglionopathy: Affecting the cell body.
  - Myelinopathy: Affecting the myelin sheath.
  - Axonopathy: Affecting the axon.

General Approach

- **Primary Goals:** (1) Identify lesion location, (2) identify cause, (3) determine treatment.
  - **Clinical Evaluation:** Includes history, physical exam, and electrodiagnostic (EDx) studies.
  - **Idiopathic/Cryptogenic:** ~50% of cases have no identifiable etiology; typically predominantly sensory polyneuropathy.

EPIDEMIOLOGY

- **Idiopathic Cases:** Approximately 50% of generalized symmetric peripheral neuropathies.
- **Hereditary:** CMT is the most common form of hereditary neuropathy.
- **Acquired:** Diabetes mellitus is a common cause of acquired neuropathy.
- **Sensory Predominance:** The majority of neuropathies are predominantly sensory.

ETIOLOGY & PATHOPHYSIOLOGY

- **General Causes:** Hereditary factors, metabolic disorders, drugs, toxins, infections, autoimmune diseases, and paraneoplastic syndromes.
- **Axonopathy Characteristics:**
  - Low-amplitude potentials.
  - Relatively preserved distal latencies, conduction velocities, and late potentials.
  - Fibrillations on needle EMG.
- **Segmental Demyelination Characteristics:**
  - Slow conduction velocities.
  - Prolonged distal latencies and late potentials.
  - Relatively preserved amplitudes.
  - Absence of fibrillations on needle EMG.
  - Indicators of acquired demyelinating neuropathy: Nonuniform slowing, conduction block, or temporal dispersion.

Hereditary Neuropathies

- **Charcot-Marie-Tooth (CMT):** A syndrome of genetically distinct disorders.
  - **CMT1:** Inherited demyelinating sensorimotor neuropathies.

→ Most cases have motor NCVs between 20 and 25 m/s.

  - **CMT2:** Axonal sensory neuropathies.

→ Defined by motor conduction velocities in the arms slowed to 38 m/s.

  - **Inheritance:** Mostly autosomal dominant (AD).
  - **Management:** No medical therapies; physical/occupational therapy and bracing (e.g., AFOs) are used.
  - **Key Genetic Variants (Table 4):**
  - CMT1A: AD, 17p11.2, PMP22 (usually duplication).
  - CMT1B: AD, 1q21-23, MPZ.
  - CMT2B: AD, 3q13-q22, RAB7.
  - CMT2P: AD and AR, 9q31.3-34.2, LRSAM1.
  - Other variants include mutations in NEFL, MFN2, LMNA, etc.

Acquired Neuropathies

- **Metabolic/Systemic:** Diabetes mellitus (common), Amyloidosis (consider in small-fiber cases).
  - **Inflammatory/Autoimmune:** Vasculitis, Sjögren's syndrome, SLE.
  - **Infectious:** HIV, Lyme disease, leprosy, hepatitis B, C, or E.

- **Toxic:** Medications (vincristine, cisplatin), alcohol, heavy metals (arsenic, lead, thallium).
- **Paraneoplastic:** Various syndromes associated with malignancy.

CLINICAL FEATURES

- **Symptoms:** Numbness, altered sensation to touch (hyperpathia or allodynia), spontaneous sensations (tingling, burning, aching).
  - **Pain Types:**

→ Protopathic: Burning, dull, poorly localized (polymodal C nociceptor fibers).

→ Epicritic: Sharp and lancinating (A-delta fibers).

- **Small-Fiber Neuropathy Indicators:**

→ Loss of pain/temperature perception.

→ Preservation of vibratory/position sense, muscle strength, and deep tendon reflexes.

→ Normal Nerve Conduction Studies (NCS).

→ Common causes: Diabetes mellitus or glucose intolerance.

- **Sensory Neuronopathy/Ganglionopathy Indicators:**

→ Severe proprioceptive loss + vibration loss + normal strength.

→ Asymmetric or affects arms more than legs (non-length-dependent).

- **Laboratory Evaluation for Generalized Symmetric Polyneuropathy:**
  - CBC, basic chemistries (electrolytes, renal/hepatic function).
  - Fasting blood glucose (FBS), HbA1c, thyroid function.
  - B12, folate, ESR, RF, ANA.
  - SPEP, immunoelectrophoresis/immunofixation, and free light chains (serum/urine) for amyloid suspicion.
  - Skeletal survey if M-spikes are present.
  - Oral glucose tolerance test (even if FBS/HbA1c normal) for painful sensory neuropathies.

History & Physical Examination

- **Seven Key Questions (Table 1):**

1. **Systems involved:** Motor, sensory, autonomic, or combinations.
2. **Distribution of weakness:** Only distal vs. proximal and distal; Focal/asymmetric vs. symmetric.
3. **Nature of sensory involvement:** Temperature loss/burning/stabbing (small fiber) vs. Vibratory/proprioceptive loss (large fiber).
4. **Upper motor neuron (UMN) involvement:** With or without sensory loss.
5. **Temporal evolution:** Acute (days to 4 weeks), Subacute (4–8 weeks), Chronic (>8 weeks); Monophasic, progressive, or relapsing-remitting.
6. **Hereditary evidence:** Family history; Lack of sensory symptoms despite sensory signs.
7. **Associated conditions:** Cancer, DM, autoimmune disease, infection, medications, preceding events/toxins.

DIFFERENTIAL DIAGNOSIS

- **Pattern 1:** Inflammatory demyelinating polyneuropathy (GBS and CIDP).
- **Pattern 2:** CSPN, DM, metabolic disorders, drugs, toxins, familial (HSAN), CMT, amyloidosis, CANVAS, SORD.
- **Pattern 3:** Multifocal CIDP, vasculitis, cryoglobulinemia, amyloidosis, sarcoid, infectious (leprosy, Lyme, Hep B/C/E, HIV, CMV), HNPP, tumor infiltration; or mononeuropathy/plexopathy/radiculopathy.
- **Pattern 4:** Polyradiculopathy or plexopathy due to DM, meningeal carcinomatosis/lymphomatosis, sarcoid, amyloid, hereditary plexopathy (HNPP, HNA), idiopathic.
- **Pattern 5:** Motor neuron disease (with UMN) or progressive muscular atrophy, juvenile monomelic amyotrophy, multifocal motor neuropathy, multifocal acquired motor axonopathy (without UMN).
- **Pattern 6:** Vitamin B12, E, and copper deficiency; chronic liver disease; hereditary leukodystrophies; HSP-plus.
- **Pattern 7:** SMA (proximal/distal) or hereditary motor neuropathy (distal SMA) or atypical CMT.
- **Pattern 8:** ALS (neck extensor), ALS/PLS, isolated bulbar ALS, Kennedy's syndrome, bulbar presentation GBS.
- **Pattern 9:** Sensory neuronopathy (ganglionopathy): Cancer, CANVAS, Sjögren's, Idiopathic, Cisplatin, Vitamin B6 toxicity, HIV-related.
- **Pattern 10:** Hereditary sensory and autonomic neuropathy, Amyloidosis, DM, GBS, Idiopathic pandysautonomia, Porphyria, HIV-related, Vincristine/chemotherapy.

DIAGNOSTIC APPROACH

1. **Electrodiagnostic (EDx) Study:**
   - Consists of Nerve Conduction Studies (NCS) and needle electromyography (EMG).
   - Purpose: Confirm mononeuropathy, multiple mononeuropathy, radiculopathy, plexopathy, or polyneuropathy.
   - Differentiation: Distinguish sensory vs. motor/autonomic involvement; axonopathy vs. myelinopathy.
   - Axonopathy Indicators: Low-amplitude potentials, preserved distal latencies/conduction velocities, fibrillations on needle EMG.
   - Myelinopathy Indicators: Slow conduction velocities, prolonged distal latencies/late potentials, presence of conduction block or temporal dispersion.
2. **Autonomic Studies:**
   - Used for small myelinated (A-delta) or unmyelinated (C) fiber involvement.
   - Tests: Heart rate response to deep breathing; heart rate and blood pressure response to Valsalva maneuver and tilt-table testing; quantitative sudomotor axon reflex testing.
   - Indicated when: Patient has pure small-fiber neuropathy or autonomic neuropathy where routine NCS are normal.
3. **Laboratory Screening:**
   - Standard panel: CBC, chemistry, glucose (FBS/HbA1c), thyroid, B12, folate, ESR, RF, ANA, SPEP/immunofixation, free light chains.
   - Specific tests: Oral glucose tolerance test for painful sensory neuropathies; heavy metal screen only if exposure suspected or specific features present (e.g., thallium).
4. **Biopsy:**

- Nerve biopsy: Rarely performed; primary indications are suspicion of amyloid neuropathy or vasculitis.
- Skin biopsy: Used to diagnose small-fiber neuropathy by measuring density of small unmyelinated fibers.

Flowchart: Approach to Evaluation

1. **Initial Screening:** History and examination compatible with neuropathy?

→ No → Evaluate other disorder or reassurance.

→ Yes → Proceed to EDx.

2. **Mononeuropathy Path:**

→ If Axonal → Determine if systemic disorder present → Treatment for specific diagnosis.

→ If Demyelinating with focal conduction block → Consider multifocal CIDP → If tests negative, consider treatment for CIDP.

3. **Polyneuropathy Path:**

→ If Axonopathy → Determine if Subacute (months) or Chronic (years).

→ Subacute/Chronic: Review history for systemic disease/infection; treat specific diagnosis.

→ If Demyelinating → Assess conduction velocity characteristics.

→ Uniform slowing, chronic → Test for paraneoplastic; if negative, review family history/genetics → Treatment for CIDP.

→ Nonuniform slowing, conduction block → If acute: GBS → IVIg or plasmapheresis + supportive care (respiratory).

4. **Mononeuropathy Multiplex:**

→ If Axonal → Consider vasculitis/multifocal process → Possible nerve biopsy.

→ If Demyelinating with focal conduction block → Consider multifocal CIDP.

MANAGEMENT & TREATMENT

1. **Pain Management (Table 6):**
   - First-Line:
     - Lidoderm 5% patch: Apply to painful area; up to 3 patches qd.
     - Tricyclic antidepressants (amitriptyline, nortriptyline): PO; 10–100 mg qhs.
     - Gabapentin: PO; 300–1200 mg tid.
     - Pregabalin: PO; 50–100 mg tid.
     - Duloxetine: PO; 30–60 mg qd.
   - Second-Line:
     - Carbamazepine: PO; 200–400 mg q 6–8 h.
     - Phenytoin: PO; 200–400 mg qhs.
     - Venlafaxine: PO; 37.5–150 mg/d.
   - Third-Line:
     - Mexiletine: PO; 200–300 mg tid.
2. **Acute Demyelinating (GBS):**

→ IVIg or plasmapheresis → Supportive care including respiratory assistance.

Toxic Neuropathies (Table 7 & 8)

- **Vinca alkaloids:** Axonal degeneration; symmetric S-M, large/small fiber PN; autonomic symptoms common.
- **Cisplatin:** Predominant large-fiber sensory neuronopathy; sensory ataxia.
- **Taxanes:** Symmetric, predominantly sensory PN; large-fiber modalities affected more than small-fiber.
- **Cytarabine:** GBS-like syndrome; pure sensory neuropathy; brachial plexopathy.
- **Bortezomib:** Length-dependent, sensory, predominantly small-fiber PN.
- **Misonidazole:** Painful paresthesias and loss of large/small-fiber sensory modalities.
- **Chloroquine/Hydroxychloroquine:** Loss of large/small-fiber; may have superimposed myopathy.
- **Colchicine:** Numbness, paresthesias, loss of large-fiber; potential for myopathy.
- **Thalidomide:** Axonal degeneration of dorsal root ganglia.
- **Dapsone:** Distal weakness (may progress to proximal) or paresthesias/numbness.
- **Nitrofurantoin:** Numbness, painful paresthesias, severe weakness (GBS-like).
- **Isoniazid:** Dysesthesias and sensory ataxia; impaired large-fiber modalities.
- **Antinucleosides:** Dysesthesia and sensory ataxia.
- **Lithium:** Numbness with loss of large-fiber modalities.

COMPLICATIONS & PROGNOSIS

- **GBS/CIDP:** Acute GBS requires monitoring for respiratory failure; CIDP is a chronic condition requiring long-term management.
- **Toxicity:** Certain drugs (e.g., Vincristine, Cisplatin) cause significant axonal degeneration and may require discontinuation or dose adjustment.

SPECIAL POPULATIONS

- **Pediatric/Genetic:** CMT patients require early identification for physical therapy and orthotics.
- **Cancer Patients:** Paraneoplastic syndromes and chemotherapy-induced toxic neuropathies (e.g., Vincristine, Cisplatin) must be differentiated from primary neurological disorders.

KEY PEARLS & HIGH-YIELD POINTS

- **Rule of Thumb:** If it's symmetric and demyelinating → GBS/CIDP. If it's asymmetric or involves specific nerve roots → Radiculopathy/Plexopathy.
- **Small Fiber Alert:** Pain/temp loss + normal NCS = Small-fiber neuropathy (think DM, Amyloid).
- **Autonomic Clue:** Autonomic dysfunction without DM → suspect Amyloid.
- **EDx Distinction:** Axonopathy (Low amplitude) vs. Myelinopathy (Slow conduction/Block).

REFERENCE TABLES

TABLE 457-1

Approach to Neuropathic Disorders: Seven Key Questions 1. What systems are involved? 2. What is the distribution of…

• 1. What systems are involved? • Motor, sensory, autonomic, or combinations 2. What is the distribution of weakness? • Only distal versus proximal and distal • Focal/asymmetric versus symmetric 3. What is the nature of the sensory involvement? • Temperature loss or burning or stabbing pain (e.g., small fiber) • Vibratory or proprioceptive loss (e.g., large fiber) 4. Is there evidence of upper motor neuron involvement? • Without sensory loss • With sensory loss 5. What is the temporal evolution? • Acute (days to 4 weeks) • Subacute (4–8 weeks) • Chronic (>8 weeks) • Monophasic, progressive, or relapsing-remitting 6. Is there evidence for a hereditary neuropathy? • Family history of neuropathy • Lack of sensory symptoms despite sensory signs 7. Are there any associated medical conditions? • Cancer, diabetes mellitus, connective tissue disease or other autoimmune diseases, infection (e.g., HIV, Lyme disease, leprosy) • Medications including over-the-counter drugs that may cause a toxic neuropathy • Preceding events, drugs, toxins

TABLE 457-2

Patterns of Neuropathic Disorders

• Pattern 1: Symmetric proximal and distal weakness with sensory loss

• Consider: inflammatory demyelinating polyneuropathy (GBS and CIDP)

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

• Consider: cryptogenic or idiopathic sensory polyneuropathy (CSPN), diabetes mellitus and other metabolic disorders, drugs, toxins, familial (HSAN), CMT, amyloidosis, CANVAS, SORD neuropathy, and others

• Pattern 3: Asymmetric distal weakness with sensory loss

• With involvement of multiple nerves

• Consider: multifocal CIDP, vasculitis, cryoglobulinemia, amyloidosis, sarcoid, infectious (leprosy, Lyme, hepatitis B, C, or E, HIV, CMV), HNPP, tumor infiltration

• With involvement of single nerves/regions

• Consider: may be any of the above but also could be compressive mononeuropathy, plexopathy, or radiculopathy

• Pattern 4: Asymmetric proximal and distal weakness with sensory loss

• Consider: polyradiculopathy or plexopathy due to diabetes mellitus, meningeal carcinomatosis or lymphomatosis, sarcoid, amyloid, hereditary plexopathy (HNPP, HNA), idiopathic

• Pattern 5: Asymmetric distal weakness without sensory loss

• With upper motor neuron findings

• Consider: motor neuron disease

• Without upper motor neuron findings

• Consider: progressive muscular atrophy, juvenile monomelic amyotrophy (Hirayama's disease), multifocal motor neuropathy, multifocal acquired motor axonopathy

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

• Consider: vitamin B , vitamin E, and copper deficiency with combined system 12 degeneration with peripheral neuropathy, chronic liver disease, hereditary leukodystrophies (e.g., adrenomyeloneuropathy), HSP-plus

• Pattern 7: Symmetric weakness without sensory loss

- With proximal and distal weakness
- Consider: SMA
- With distal weakness
- Consider: hereditary motor neuropathy (“distal” SMA) or atypical CMT
- Pattern 8: Focal midline proximal symmetric weakness
- Neck extensor weakness
- Consider: ALS
- Bulbar weakness
- Consider: ALS/PLS, isolated bulbar ALS (IBALS), Kennedy’s syndrome (X-linked, bulbospinal SMA), bulbar presentation GBS
- Diaphragm weakness (SOB)
- Consider: ALS
- Pattern 9: Asymmetric proprioceptive sensory loss without weakness
- Consider causes of a sensory neuronopathy (ganglionopathy):
- Cancer (paraneoplastic) CANVAS
- Sjögren’s syndrome
- Idiopathic sensory neuronopathy (possible GBS variant)
- Cisplatin and other chemotherapeutic agents
- Vitamin B toxicity
- 6 HIV-related sensory neuronopathy
- Pattern 10: Autonomic symptoms and signs
- Consider neuropathies associated with prominent autonomic dysfunction:
- Hereditary sensory and autonomic neuropathy
- Amyloidosis (familial and acquired)
- Diabetes mellitus
- GBS
- Idiopathic pandysautonomia (may be a variant of GBS)
- Porphyria
- HIV-related autonomic neuropathy
- Vincristine and other chemotherapeutic agents

TABLE 457-3

Electrophysiologic Features: Axonal Degeneration versus Segmental Demyelination

	AXONAL DEGENERATION	SEGMENTAL DEMYELINATION
Motor Nerve Conduction Studies		
CMAP amplitude	Decreased	Normal (except with CB or distal dispersion)
Distal latency	Normal	Prolonged
Conduction velocity	Normal	Slow

	AXONAL DEGENERATION	SEGMENTAL DEMYELINATION
Conduction block	Absent	Present
Temporal dispersion	Absent	Present
F wave	Normal or absent	Prolonged or absent
H reflex	Normal or absent	Prolonged or absent
Sensory Nerve Conduction Studies		

TABLE 457-2

). In particular, if this loss is asymmetric or affects the arms more than the legs, this pattern suggests a...

Decreased		
Normal		
Normal		
Needle EMG		
Spontaneous activity		
Fibrillations	Present	Absent
Fasciculations	Present	Absent
Motor unit potentials		
Recruitment	Decreased	Decreased
Morphology	Long duration, large amplitude, polyphasic (if there is reinnervation)	Normal

TABLE 457-4

Classification of Charcot-Marie-Tooth Disease and Related Neuropathies

NAME	INHERITANCE	GENE LOCATION	GENE
CMT1			
CMT1A	AD	17p11.2	PMP22 (usually duplication of gene)
CMT1B	AD	1q21-23	MPZ
CMT1C	AD	16p13.1-p12.3	LITAF
CMT1D	AD	10q21.1-22.1	ERG2
CMT1E (with deafness)	AD	17p11.2	PMP22 gene (usually point mutations)
CMT1F	AD	8p13-21	NEFL

NAME	INHERITANCE	GENE LOCATION	GENE
CMT1G	AD	8q21	PMP22
	AD	17p11.2 1q21-23	
CMT dominant-intermediate (CMTDI)			
CMT-DIA	AD	10q24.1-25.1	?
CMT-DIB	AD	19.p12-13.2	DNM2
CMT-DIC	AD	1p35	YARS
CMT-DID **CMT-DIE** **CMT-DIF** **CMT-DIG**	AD AD AD AD	1q22 14q32.33 3q26 8p31	MPZ IFN-2 GNB4 NEFL
	AR AR AR AR	8q21.1 6q23 1p36 12q24	
CMT2			
CMT2A2 (allelic to HMSN VI with optic atrophy)	AD	1p36.2	MFN2
CMT2B	AD	3q13-q22	RAB7
CMT2B1 (allelic to LGMD 1B)	AR	1q21.2	LMNA
CMT2B2	AR	19q13	PNKP
CMT2C (allelic to scapuloperoneal neuropathy)	AD	12q23-24	TRPV4
CMT2D (allelic to distal SMA5) **CMT2DD**	AD AD	7p14 1p13	GARS1 ATP1A1
CMT2E (allelic to CMT1F) **CMT2EE**	AD AD	8p21 2p23	NEFL MPV17
CMT2F	AD	7q11-q21	HSPB1
CMT2G (allelic to CMT2P)	AD	9q31.3-34.2	LRSAM1
CMT2I (allelic to CMT1B)	AD	1q22	MPZ
CMT2J	AD	1q22	MPZ
CMT2H, CMT2K (allelic to CMT4A)	AD	8q13-q21	GDAP1
CMT2L (allelic to distal hereditary motor neuropathy type 2)	AD	12q24	HSPB8

NAME	INHERITANCE	GENE LOCATION	GENE
CMT2M	AD	16q22	DNM2
CMT2N	AD	16q22.1	AARS
CMT2O	AD	14q32.31	DYNC1H1
CMT2P	AD and AR	9q31.3-34.2	LRSAM1
CMT2P-Okinawa (allelic to HSMN2P)	AD	3q13-q14	TFG
CMT2Q	AD	10p14	DHTKD1
CMT2RCMT2S	AD	4q	TRIM2
CMT2T	AD	11q13.3	IGHMBP2
CMT2U	ADAD	3q25.2	MME
CMT2V	AD	12q13	MARS1
CMT2W	AD	17q11	NAGLU
CMT2X	AD	5q31	HARS1
CMT2Y	AD	15q21.1	SPB11
CMT2Z	AD	9p13	VCP
		22q12	MORC2

TABLE 457-5

Rare Hereditary Neuropathies Hereditary Disorders of Lipid Metabolism Metachromatic leukodystrophy Krabbe's disease...

- Hereditary Disorders of Lipid Metabolism
- Metachromatic leukodystrophy
- Krabbe's disease (globoid cell leukodystrophy)
- Fabry's disease
- Adrenoleukodystrophy/adrenomyeloneuropathy
- Refsum's disease
- Tangier disease
- Cerebrotendinous xanthomatosis
- Hereditary Ataxias with Neuropathy
- CANVAS (cerebellar ataxia, neuropathy, and vestibular areflexia syndrome) Friedreich's ataxia
- Vitamin E deficiency
- Spinocerebellar ataxia
- Abetalipoproteinemia (Bassen-Kornzweig disease)
- Disorders of Defective DNA Repair
- CANVAS Ataxia-telangiectasia
- Cockayne's syndrome
- Giant Axonal Neuropathy
- Porphyria
- Acute intermittent porphyria (AIP)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)

- Familial Amyloid Polyneuropathy (FAP)
- Transthyretin-related
- Gelsolin-related
- Apolipoprotein A1-related

TABLE 457-6

Treatment of Painful Sensory Neuropathies THERAPY First-Line Lidoderm 5% patch Tricyclic antidepressants (e.g., PO...

THERAPY	ROUTE	DOSE	SIDE EFFECTS
First-Line			
Lidoderm 5% patch	Apply to painful area	Up to 3 patches qd	Skin irritation
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)	PO	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation
Gabapentin	PO	300–1200 mg tid	Cognitive changes, sedation, peripheral edema
Pregabalin	PO	50–100 mg tid	Cognitive changes, sedation, peripheral edema
Duloxetine	PO	30–60 mg qd	Cognitive changes, sedation, dry eyes, diaphoresis, nausea, diarrhea, constipation
Second-Line			
PO	200–400 mg q 6–8 h		
PO	200–400 mg qhs		
PO	37.5–150 mg/d		
PO	50 mg qid		
Third-Line			
Mexiletine	PO	200–300 mg tid	Arrhythmias
Other Agents			
	Apply cutaneously	qid	
	Apply cutaneously	qid	

TABLE 457-7

Toxic Neuropathies Secondary to Chemotherapy DRUG Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine)...

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine)	Interfere with axonal microtubule assembly; impairs axonal transport	Symmetric, S-M, large-/small-fiber PN; autonomic symptoms common; infrequent cranial neuropathies	Axonal degeneration of myelinated and unmyelinated fibers; regenerating clusters, minimal segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
	Preferential damage to dorsal root ganglia: ? binds to and cross-links DNA ? inhibits protein synthesis ? impairs axonal transport	Predominant large-fiber sensory neuronopathy; sensory ataxia	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	
Taxanes (paclitaxel, docetaxel)	Promotes axonal microtubule assembly; interferes with axonal transport	Symmetric, predominantly sensory PN; large-fiber modalities affected more than small-fiber	Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination	Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception
	Unknown;? inhibition of neurotrophic growth factor binding;? neuronal lysosomal storage	Symmetric, length-dependent, sensory-predominant PN	None described	

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
	Unknown;? immunomodulating effects	Subacute, S-M PN with diffuse proximal and distal weakness; areflexia; increased CSF protein	Loss of large and small myelinated fibers with primary demyelination and secondary axonal degeneration; occasional epi- and endoneurial inflammatory cell infiltrates	
Cytarabine (ARA-C)	Unknown;? selective Schwann cell toxicity;? immunomodulating effects	GBS-like syndrome; pure sensory neuropathy; brachial plexopathy	Loss of myelinated nerve fibers; axonal degeneration; segmental demyelination; no inflammation	Axonal, demyelinating, or mixed S-M PN; denervation on EMG
	Unknown;? selective dorsal root ganglia toxicity	Length-dependent, sensory-predominant PN; autonomic neuropathy	None described	
Bortezomib (Velcade)	Unknown	Length-dependent, sensory, predominantly small-fiber PN	Not reported	Abnormalities consistent with an axonal sensory neuropathy with early small-fiber involvement (abnormal autonomic studies)

TABLE 457-8

Toxic Neuropathies DRUG Misonidazole

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Misonidazole	Unknown	Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration of large, myelinated fibers; axonal swellings; segmental demyelination	Low-amplitude or unobtainable SNAPs with normal or only slightly reduced CMAP amplitudes

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
	Unknown	Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern	Axonal degeneration	
Chloroquine and hydroxychloroquine	Amphiphilic properties may lead to drug-lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Loss of large- and small-fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration with autophagic vacuoles in nerves as well as muscle fibers	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; distal denervation on EMG; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy
	Amphiphilic properties may lead to drug-lipid complexes that are indigestible and result in accumulation of autophagic vacuoles	Paresthesias and pain with loss of large- and small-fiber sensory modalities and distal weakness in length-dependent pattern; superimposed myopathy may lead to proximal weakness	Axonal degeneration and segmental demyelination with myeloid inclusions in nerves and muscle fibers	

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Colchicine	Inhibits polymerization of tubulin in microtubules and impairs axoplasmic flow	Numbness and paresthesias with loss of large-fiber modalities in a length-dependent fashion; superimposed myopathy may lead to proximal in addition to distal weakness	Nerve biopsy demonstrates axonal degeneration; muscle biopsy reveals fibers with vacuoles	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy
	Binds to microtubules and impairs axoplasmic flow	Sensory loss, tingling, muscle weakness, and diminished muscle stretch reflexes in length-dependent pattern; autonomic neuropathy	Axonal degeneration	
Thalidomide	Unknown	Numbness, tingling, and burning pain and weakness in a length-dependent pattern	Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
	Accumulation of neurofilaments and impaired axoplasmic flow	Numbness, tingling, and burning pain in a length-dependent pattern	Axonal degeneration with accumulation of neurofilaments in the axons	
Dapsone	Unknown	Distal weakness that may progress to proximal muscles; sensory loss	Axonal degeneration and segmental demyelination	Low-amplitude or unobtainable CMAPs with normal or reduced SNAP amplitudes
	Unknown	Paresthesias and numbness in a length-dependent pattern	Unknown	

DRUG	MECHANISM OF NEUROTOXICITY	CLINICAL FEATURES	NERVE HISTOPATHOLOGY	EMG/NCS
Nitrofurantoin	Unknown	Numbness, painful paresthesias, and severe weakness that may resemble GBS	Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia and anterior horn cells	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes
	Unknown	Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia	
Isoniazid	Inhibits pyridoxal phosphokinase leading to pyridoxine deficiency	Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination	Marked loss of sensory axons and cell bodies in dorsal root ganglia and degeneration of the dorsal columns	Reduced amplitudes or absent SNAPs and, to a lesser extent, CMAPs
	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration	
Antinucleosides	Unknown	Dysesthesia and sensory ataxia; impaired large-fiber sensory modalities on examination	Axonal degeneration	Reduced amplitudes or absent SNAPs
	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration and segmental demyelination	
Lithium	Unknown	Numbness with loss of large-fiber modalities on examination	Axonal degeneration	Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes

TABLE 457-9

Causes of Radiculopathy • Herniated nucleus pulposus • Degenerative joint disease • Rheumatoid arthritis • Trauma •...

- • Herniated nucleus pulposus • Degenerative joint disease • Rheumatoid arthritis • Trauma • Vertebral body compression fracture • Pott's disease (tuberculosis) • Compression by extradural mass (e.g., meningioma, metastatic tumor, hematoma, abscess) • Primary nerve tumor (e.g., neurofibroma, schwannoma, neurinoma) • Carcinomatous meningitis • Perineurial spread of tumor (e.g., prostate cancer) • Acute inflammatory demyelinating polyradiculopathy • Chronic inflammatory demyelinating polyradiculopathy • Sarcoidosis • Amyloidoma • Diabetic radiculopathy • Infection (Lyme disease, herpes zoster, HIV, cytomegalovirus, syphilis, schistosomiasis, Strongyloides) • Arachnoiditis (e.g., postsurgical) • Radiation

TABLE 457-10

Lumbosacral Plexopathies: Etiologies • Retroperitoneal hematoma • Psoas abscess • Malignant neoplasm • Benign neoplasm...

- • Retroperitoneal hematoma • Psoas abscess • Malignant neoplasm • Benign neoplasm • Radiation • Amyloid • Diabetic radiculoplexus neuropathy • Idiopathic radiculoplexus neuropathy • Sarcoidosis • Aortic occlusion/surgery • Lithotomy positioning • Hip arthroplasty • Pelvic fracture • Obstetric injury