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another chronic inflammatory disorder such as vasculitis, sarcoidosis, or lymphoma. Many cases previously thought to represent ADEM are now recognized as MOGAD. The hallmark of ADEM is the presence of widely scattered foci of perivenular inflammation and demyelin ation that can involve both white matter and gray matter structures, in contrast to larger confluent white matter lesions typical of MS. In the most explosive form of ADEM, acute hemorrhagic leukoencephalitis, the lesions are vasculitic and hemorrhagic, and the clinical course is devastating.

Postinfectious encephalomyelitis is most frequently associated with the viral exanthems of childhood. Infection with measles virus is the most common antecedent (1 in 1000 cases). Worldwide, measles encephalomyelitis is still common, although use of the live measles vaccine has dramatically reduced its incidence. In developed countries, ADEM is now most frequently associated with varicella (chickenpox) infections (1 in 4000–10,000 cases). It may also follow infection with rubella, mumps, influenza, parainfluenza, Epstein-Barr virus, human herpesvirus-6, HIV, dengue, Zika, other viruses, and Mycoplasma pneumoniae. Cases have also been described in association with SARSCoV-2 infection. Some patients may have a nonspecific upper respira tory infection or no known antecedent illness. Modern vaccines appear to pose no meaningful risk for ADEM; one large study (Vaccine Safety Datalink) of 24 different vaccines in >9 million individuals (64 million doses in total) revealed no excess risk for ADEM, with the possible exception of Tdap (tetanus, diphtheria, acellular pertussis) vaccine estimated at less than one case per million doses. PART 13 Neurologic Disorders All forms of ADEM presumably result from a cross-reactive immune response to the infectious agent that then triggers an inflam matory demyelinating response. Autoantibodies to MBP and other myelin antigens have been detected in the CSF from some patients with ADEM, and as noted above, ADEM cases with serum or CSF antibod ies against MOG are now considered to be MOGAD. ■ ■CLINICAL MANIFESTATIONS In severe cases, onset is abrupt and progression rapid (hours to days). In postinfectious ADEM, the neurologic syndrome generally begins late in the course of the viral illness as the exanthem is fading. Fever reappears, and headache, meningismus, and lethargy progressing to coma may develop. Seizures are common. Signs of disseminated neu rologic disease are consistently present (e.g., hemiparesis or quadripa resis, extensor plantar responses, lost or hyperactive tendon reflexes, sensory loss, and brainstem involvement). In ADEM due to chicken pox, cerebellar involvement is often conspicuous. CSF protein is mod estly elevated (0.5–1.5 g/L [50–150 mg/dL]). Lymphocytic pleocytosis, generally ≥200 cells/μL, occurs in 80% of patients. Occasional patients have higher counts or a mixed polymorphonuclear-lymphocytic pat tern during the initial days of the illness. Transient CSF

oligoclonal banding was reported in a minority of cases. MRI usually reveals extensive changes in the brain and spinal cord, consisting of white matter hyperintensities on T2 and fluid-attenuated inversion recovery (FLAIR) sequences with gadolinium enhancement on T1-weighted sequences. ■ ■DIAGNOSIS The diagnosis is most reliably established when there is a history of a recent infectious illness. In severe cases with predominantly cerebral involvement, acute encephalitis due to infection with herpes simplex or other viruses including HIV may be difficult to exclude; other consid erations include hypercoagulable states including the antiphospholipid antibody syndrome, autoimmune (paraneoplastic) limbic encephalitis, vasculitis, sarcoidosis, primary CNS lymphoma, or metastatic cancer. An explosive presentation of MS can mimic ADEM, and especially in adults, it may not be possible to distinguish these conditions acutely. The simultaneous onset of disseminated symptoms and signs is com mon in ADEM and rare in MS. Similarly, meningismus, encephalopa thy (drowsiness, stupor or coma), and seizures suggest ADEM rather than MS. Unlike MS, in ADEM, optic nerve involvement is generally bilateral and transverse myelopathy complete. MRI findings that favor ADEM include extensive and relatively symmetric white matter

abnormalities, basal ganglia or cortical gray matter lesions, and gado linium enhancement of all abnormal areas. In contrast, OCBs in the CSF are more common in MS. In one study of adult patients initially thought to have ADEM, 30% experienced additional relapses over a follow-up period of 3 years, and they were reclassified as having MS. Other patients initially classified as ADEM are subsequently found to have NMO, MOGAD, or GFAP autoimmunity. Occasional patients with “recurrent ADEM” have also been reported, especially children; however, it is not possible to distinguish this entity from atypical MS. Because of the clinical overlap at presentation between ADEM and MS, it is important that routine surveillance imaging be performed follow ing recovery from ADEM so that subclinical disease activity due to MS can be recognized and treatment for MS initiated. ■ ■TREATMENT Initial therapy is with high-dose glucocorticoids; depending on the response, treatment may need to be continued for 8 weeks. Patients who fail to respond within a few days may benefit from a course of plasma exchange or IV immunoglobulin. The prognosis reflects the severity of the underlying acute illness. In modern case series of pre sumptive ADEM in adults, mortality rates of 5–20% are reported, and many survivors have permanent neurologic sequelae. ■ ■FURTHER READING Banwell B et al: Diagnosis of myelin oligodendrocyte glycoprotein antibody-associated disease: International MOGAD Panel proposed criteria. Lancet Neurol 22:268, 2023. Baxter R et al: Acute demyelinating events following vaccines: A casecentered analysis. Clin Infect Dis 63:1456, 2016. Cacciaguerra L et al: Updates in NMOSD and MOGAD diagnosis and treatment: A tale of two central nervous system autoimmune inflammatory disorders. Neurol Clin 42:77, 2024. Cree BAC et al: Inebilizumab for the treatment of neuromyelitis optica spectrum disorder (N-MOmentum): A double-blind, randomised placebo-controlled phase 2/3 trial. Lancet 394:1352, 2019. Hagbohm C et al: Clinical and neuroimaging phenotypes of autoim mune glial fibrillary acidic protein astrocytopathy: A systematic review and meta-analysis. Eur J Neurol 20:e16284, 2024. Pittock SJ et al: Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N Engl J Med 381:614, 2019. Qin C et al: Single-cell analysis of anti-BCMA CAR T cell therapy in patients with central nervous system autoimmunity. Sci Immunol 9:eadj9730, 2024. Traboulsee A, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: A randomised, doubleblind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol 19:402, 2020. Wingerchuk DM et al: International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85:177, 2015. Section 3 Nerve and Muscle Disorders Anthony A. Amato, Richard J. Barohn

Peripheral Neuropathy Peripheral nerves are composed of sensory, motor, and autonomic elements. Diseases can affect the cell body of a neuron or its periph eral processes, namely the axons or the encasing myelin sheaths. Most peripheral nerves are mixed and contain sensory and motor as well as autonomic fibers. Nerves can be subdivided into three major

classes: large myelinated, small myelinated, and small unmyelin ated. Motor axons are usually large myelinated fibers that conduct rapidly (~50 m/s). Sensory fibers may be any of the three types. Large-diameter sensory fibers conduct proprioception and vibra tory sensation to the brain, while the smaller-diameter myelinated and unmyelinated fibers transmit pain and temperature sensation. Autonomic nerves are also small in diameter. Thus, peripheral neu ropathies can impair sensory, motor, or autonomic function, either singly or in combination. Peripheral neuropathies are further classi fied into those that primarily affect the cell body (e.g., neuronopathy or ganglionopathy), myelin (myelinopathy), and the axon (axonopa thy). These different classes of peripheral neuropathies have distinct clinical and electrophysiologic features. This chapter discusses the clinical approach to a patient suspected of having a peripheral neuropathy, as well as specific neuropathies, including hereditary and acquired neuropathies. The inflammatory neuropathies are discussed in Chap. 458. GENERAL APPROACH In approaching a patient with a neuropathy, the clinician has three main goals: (1) identify where the lesion is, (2) identify the cause, and (3) determine the proper treatment. The first goal is accomplished by obtaining a thorough history, neurologic examination, and electrodiag nostic and other laboratory studies (Fig. 457-1). While gathering this information, seven key questions are asked (Table 457-1), the answers to which help identify the pattern of involvement and the cause of the neuropathy (Table 457-2). Despite an extensive evaluation, in approximately half of patients, no etiology is ever found; these patients typically have a predominately sensory polyneuropathy and have been labeled as having idiopathic or cryptogenic sensory and sensorimotor polyneuropathy (CSPN). History and examination compatible with neuropathy? No Yes Mononeuropathy Mononeuropathy multiplex Polyneuropathy Evaluation of other disorder or reassurance and follow-up EDx EDx Axonal Demyelinating with focal conduction block Is the lesion axonal or demyelinating? Is entrapment or compression present? Is a contributing systemic disorder present? Consider vasculitis or other multifocal process Consider multifocal form of CIDP Decision on need for surgery (nerve repair, transposition, or release procedure) Possible nerve biopsy Test for paraprotein, HIV, Lyme disease Treatment appropriate for specific diagnosis If tests are negative, consider treatment for CIDP Treatment appropriate for specific diagnosis FIGURE 457-1 Approach to the evaluation of peripheral neuropathies. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EDx, electrodiagnostic; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin.

■ ■INFORMATION FROM THE HISTORY AND PHYSICAL EXAMINATION: SEVEN KEY

QUESTIONS (TABLE 457-1)

1. What Systems Are Involved? It is important to determine if the patient’s symptoms and signs are motor, sensory, autonomic, or a combination of these. If the patient has only weakness without any evidence of sensory or autonomic dysfunction, a motor neuropathy, neuromuscular junction abnormality, or myopathy should be con sidered. Some peripheral neuropathies are associated with significant autonomic nervous system dysfunction. Symptoms of autonomic involvement include fainting spells or orthostatic

lightheadedness; heat intolerance; or any bowel, bladder, or sexual dysfunction (Chap. 451). There will typically be an orthostatic fall in blood pressure without an appropriate increase in heart rate. Autonomic dysfunction in the absence of diabetes should alert the clinician to the possibility of amy loid polyneuropathy. Rarely, a pandysautonomic syndrome can be the only manifestation of a peripheral neuropathy without other motor or sensory findings. The majority of neuropathies are predominantly sensory in nature. CHAPTER 457

2. What Is the Distribution of Weakness? Delineating the pattern of weakness, if present, is essential for diagnosis, and in this regard, two additional questions should be answered: (1) Does the weakness only involve the distal extremity, or is it both proximal and distal? and (2) Is the weakness focal and asymmetric, or is it sym metric? Symmetric proximal and distal weakness is the hallmark of acquired immune demyelinating polyneuropathies, both the acute form (Guillain-Barré syndrome [GBS]) and the chronic form (chronic inflammatory demyelinating polyneuropathy [CIDP]) (Chap. 458). The importance of finding symmetric proximal and distal weakness in a patient who presents with both motor and sensory symptoms cannot Peripheral Neuropathy Patient Complaint: ? Neuropathy EDx Axonal Demyelinating Chronic course (years) Uniform slowing, chronic Nonuniform slowing, conduction block Subacute course (months) Review history for toxins; test for associated systemic disease or intoxication Test for paraprotein, if negative If chronic or subacute: CIDP If acute: GBS IVIg or plasmapheresis; supportive care including respiratory assistance Review family history; examine family members; genetic testing Treatment for CIDP; see Ch. 458 Genetic counseling if appropriate

TABLE 457-1 Approach to Neuropathic Disorders: Seven

Key Questions

1. What systems are involved? • Motor, sensory, autonomic, or combinations
2. What is the distribution of weakness? • Only distal versus proximal and distal • Focal/asymmetric versus symmetric
3. What is the nature of the sensory involvement? • 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? PART 13 Neurologic Disorders • 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 be overemphasized because this identifies the important subset of patients who may have a treatable acquired demyelinating neuropathic disorder (i.e., GBS or CIDP). Findings of an asymmetric or multifocal pattern of weakness narrow the differential diagnosis. Some neuropathic disorders may present with unilateral extremity weakness. In the absence of sensory symp toms and signs, such weakness

evolving over weeks or months would be worrisome for motor neuron disease (e.g., amyotrophic lateral scle rosis [ALS]), but it would be important to exclude multifocal motor neuropathy that may be treatable (Chap. 458). In a patient presenting with asymmetric subacute or acute sensory and motor symptoms and signs, radiculopathies, plexopathies, compressive mononeuropathies, or multiple mononeuropathies (e.g., mononeuropathy multiplex) must be considered. ALS (Chap. 448) can produce prominent neck extensor weakness (head drop), tongue and pharyngeal weakness (dysarthria and dyspha gia), or shortness of breath. These focal symmetric weakness patterns can also be seen in neuromuscular junction disorders (myasthenia gravis, Lambert-Eaton myasthenic syndrome [LEMS] [Chap. 459]) and some myopathies, particularly isolated neck extensor myopathy (Chap. 460).

8. What Is the Nature of the Sensory Involvement? The patient may have loss of sensation (numbness), altered sensation to touch (hyperpathia or allodynia), or uncomfortable spontaneous sen sations (tingling, burning, or aching) (Chap. 27). Neuropathic pain can be burning, dull, and poorly localized (protopathic pain), presumably transmitted by polymodal C nociceptor fibers, or sharp and lancinating (epicritic pain), relayed by A-delta fibers. If pain and temperature per ception are lost, while vibratory and position sense are preserved along with muscle strength, deep tendon reflexes, and normal nerve conduc tion studies (NCS), a small-fiber neuropathy is likely. The most likely causes of small-fiber neuropathies, when one is identified, are diabetes mellitus (DM) or glucose intolerance. Amyloid neuropathy should be considered as well in such cases, but most of these small-fiber neuropa thies remain idiopathic despite extensive evaluation. Severe proprioceptive loss also narrows the differential diagnosis. Affected patients will note imbalance, especially in the

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 B12, vitamin E, and copper deficiency with combined system 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 B6 toxicity 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 Abbreviations: ALS, amyotrophic lateral sclerosis; CIDP, chronic inflammatory demyelinating polyneuropathy; CANVAS, cerebellar ataxia, neuropathy, and vestibular areflexia syndrome; CMT, Charcot-Marie-Tooth disease; CMV, cytomegalovirus; GBS, Guillain-Barré syndrome; HIV, human immunodeficiency virus; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; HSP-plus, hereditary spastic paraplegia plus neuropathy; PLS, primary lateral sclerosis; SMA, spinal muscular atrophy; SOB, shortness of breath; SORD, sorbitol dehydrogenase deficiency.

dark. A neurologic examination revealing a dramatic loss of pro prioception with vibration loss and normal strength should alert the clinician to consider a sensory neuronopathy/ganglionopathy (Pattern 9, Table 457-2). In particular, if this loss is asymmetric or affects the arms more than the legs, this pattern suggests a non-length-dependent process as seen in sensory neuronopathies. 4. Is There Evidence of Upper Motor Neuron Involvement? If the patient presents with symmetric distal sensory symptoms and signs suggestive of a distal sensory neuropathy, but there is additional evidence of symmetric upper motor neuron involvement (Chap. 26), the physician should consider a combined system degeneration with neuropathy. The most common cause for this pattern is vitamin B12 deficiency, but other etiologies should also be considered (e.g., copper deficiency, human immunodeficiency virus [HIV] infection, severe hepatic disease, adrenomyeloneuropathy [AMN]), and hereditary spastic paraplegia plus a neuropathy. 5. What Is the Temporal Evolution? It is important to deter mine the onset, duration, and evolution of symptoms and signs. Does the disease have an acute (days to 4 weeks), subacute (4–8 weeks), or chronic (>8 weeks) course? Is the course monophasic, progressive, or relapsing? Most neuropathies are insidious and slowly progressive in nature. Neuropathies with acute and subacute presentations include GBS, vasculitis, and radiculopathies related to diabetes or Lyme dis ease. A relapsing course can be present in CIDP and porphyria. 6. Is There Evidence for a Hereditary Neuropathy? In patients with slowly progressive distal weakness over many years with few sensory symptoms yet significant sensory deficits on clinical exam ination, the clinician should consider a hereditary neuropathy (e.g., Charcot-Marie-Tooth disease [CMT]). On examination, the feet may show high or flat arches or hammer toes, and scoliosis may be present. In suspected cases, it may be necessary to perform neurologic and elec trophysiologic studies on family members in addition to the patient. 7. Does the Patient Have Any Other Medical Conditions? It is important to inquire about associated medical conditions (e.g., DM, systemic lupus erythematosus [SLE]); preceding or concurrent infec tions (e.g. diarrheal illness preceding GBS); surgeries (e.g., gastric bypass and nutritional neuropathies); medications (toxic neuropathy), including over-the-counter vitamin preparations (B6); alcohol; dietary habits; and use of dentures (e.g., fixatives contain zinc that can lead to copper deficiency). ■ ■PATTERN RECOGNITION APPROACH TO NEUROPATHIC DISORDERS

Based on the answers to the seven key questions, neuropathic disor ders can be classified into several patterns based on the distribution or pattern of sensory, motor, and autonomic involvement (Table 457-2). Each pattern has a limited differential diagnosis, and information from laboratory studies usually permits a final diagnosis to be established. ■ ■ELECTRODIAGNOSTIC STUDIES The electrodiagnostic (EDx) evaluation of patients with a suspected peripheral neuropathy consists of NCS and needle electromyography (EMG). In addition, studies of autonomic function can be valuable. The electrophysiologic data can confirm whether the neuropathic disorder is a mononeuropathy, multiple mononeuropathy (mononeu ropathy multiplex), radiculopathy, plexopathy, or generalized poly neuropathy. Similarly, EDx evaluation can ascertain whether the process involves only sensory fibers, motor fibers, autonomic fibers, or a combination of these. Finally, the electrophysiologic data can help distinguish axonopathies from myelinopathies as well as axonal degeneration secondary to ganglionopathies from the more common length-dependent axonopathies. NCS are most helpful in classifying a neuropathy as due to axonal degeneration or segmental demyelination (Table 457-3). In general, low-amplitude potentials with relatively preserved distal latencies, conduction velocities, and late potentials, along with fibrillations on needle EMG, suggest an axonal neuropathy. On the other hand, slow

TABLE 457-3 Electrophysiologic Features: Axonal Degeneration versus Segmental Demyelination SEGMENTAL DEMYELINATION AXONAL DEGENERATION Motor Nerve Conduction Studies CMAP amplitude Decreased Normal (except with CB or distal dispersion) Distal latency Normal Prolonged Conduction velocity Normal Slow 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 CHAPTER 457 SNAP amplitude Decreased Normal or decreased Distal latency Normal Prolonged Conduction velocity Normal Slow Needle EMG Spontaneous activity Peripheral Neuropathy Fibrillations Present Absent Fasciculations Present Absent Motor unit potentials Recruitment Decreased Decreased Morphology Long duration, large amplitude, polyphasic

(if there is reinnervation) Normal Abbreviations: CB, conduction block; CMAP, compound motor action potential; EMG, electromyography; SNAP, sensory nerve action potential. conduction velocities, prolonged distal latencies and late potentials, relatively preserved amplitudes, and the absence of fibrillations on needle EMG imply a primary demyelinating neuropathy. The presence of nonuniform slowing of conduction velocity, conduction block, or temporal dispersion further suggests an acquired demyelinating neu ropathy (e.g., GBS or CIDP) as opposed to a hereditary demyelinating neuropathy (e.g., CMT type 1). Autonomic studies are used to assess small myelinated (A-delta) or unmyelinated (C) nerve fiber involvement. Such testing includes heart rate response to deep breathing, heart rate and blood pressure response to both the Valsalva maneuver and tilt-table testing, and quantitative sudomotor axon reflex testing (Chap. 451). These studies are par ticularly useful in patients who have pure small-fiber neuropathy or autonomic neuropathy in which routine NCS are normal. ■ ■OTHER IMPORTANT LABORATORY INFORMATION In patients with generalized symmetric peripheral neuropathy, a stan dard laboratory evaluation should include a complete blood count, basic chemistries including serum electrolytes and tests of renal and hepatic function, fasting blood glucose (FBS), hemoglobin (Hb) A1c, thyroid function tests, B12, folate, erythrocyte sedimentation rate (ESR), rheumatoid factor, antinuclear antibodies (ANA), serum protein electrophoresis (SPEP) and immunoelectrophoresis or immunofixa tion, and free light chains in serum and urine. Quantification of the concentration of serum-free light chains and the

kappa/lambda ratio is more sensitive than SPEP, immunoelectrophoresis, or immunofixation to detect a monoclonal gammopathy and therefore should be done if amyloidosis is suspected. A skeletal survey should be performed in patients with acquired demyelinating neuropathies and M-spikes to look for osteosclerotic or lytic lesions. Patients with monoclonal gam mopathy should also be referred to a hematologist for consideration of a bone marrow biopsy. An oral glucose tolerance test is indicated in patients with painful sensory neuropathies even if FBS and HbA1c are normal, as the test is abnormal in about one-third of such patients. In addition to the above tests, patients with a mononeuropathy multiplex

pattern of involvement should have a vasculitis workup, including antineutrophil cytoplasmic antibodies (ANCAs), cryoglobulins, hepa titis serology, Western blot for Lyme disease, HIV, and occasionally a cytomegalovirus (CMV) titer.

There are many autoantibody panels (various antiganglioside anti bodies) marketed for screening routine neuropathy patients for a treat able condition. These autoantibodies have no proven clinical utility or added benefit beyond the information obtained from a complete clinical examination and detailed EDx. A heavy metal screen is also not necessary as a screening procedure, unless there is a history of possible exposure or suggestive features on examination (e.g., severe painful sensorimotor and autonomic neuropathy and alopecia— thallium; severe painful sensorimotor neuropathy with or without gastrointestinal [GI] disturbance and Mee's lines—arsenic; wrist or finger extensor weakness and anemia with basophilic stippling of red blood cells—lead). In patients with suspected GBS or CIDP, a lumbar puncture is indicated to look for an elevated cerebrospinal fluid (CSF) protein. In idiopathic cases of GBS and CIDP, CSF pleocytosis is usually absent. If cells are present, one should consider HIV infection, Lyme disease, sarcoidosis, or lymphomatous or leukemic infiltration of nerve roots. Recently, serum IgG4 antibodies to neurofascin and contactin-2 have been discovered in CIDP with severe sensory ataxia, tremor, and distal weakness (Chap. 458). These cases are difficult to treat with standard immunotherapies but may respond to rituximab. Some patients with GBS and CIDP have abnormal liver function tests. In these cases, it is important to also check for hepatitis B and C, HIV, CMV, and EpsteinBarr virus (EBV) infection. In patients with an axonal GBS (by EMG/ NCS) or those with a suspicious coinciding history (e.g., unexplained abdominal pain, psychiatric illness, significant autonomic dysfunc tion), it is reasonable to screen for porphyria. PART 13 Neurologic Disorders In patients with a severe sensory ataxia, a sensory ganglionopathy or neuronopathy should be considered. The most common causes of sensory ganglionopathies are Sjögren's syndrome (Chap. 373) and a paraneoplastic neuropathy (Chap. 99). Neuropathy can be the initial manifestation of Sjögren's syndrome. Thus, one should always inquire about dry eyes and mouth in patients with sensory signs and symptoms. Further, some patients can manifest sicca complex without other manifestations of Sjögren's syndrome. Thus, patients with sen sory ataxia should be tested for antibodies to SS-A/Ro and SS-B/La, in addition to the routine ANA. To evaluate a possible paraneoplastic sensory ganglionopathy, antineuronal nuclear antibodies (e.g., anti-Hu antibodies) should be obtained. These antibodies are most commonly seen in patients with small-cell carcinoma of the lung but are also present with breast, ovarian, lymphoma, and other cancers. Impor tantly, the paraneoplastic neuropathy can precede the detection of the cancer, and detection of these autoantibodies should lead to a search for malignancy. ■ ■NERVE BIOPSIES Nerve biopsies are now rarely performed in the evaluation of neuropa thies. The primary indication for nerve biopsy is suspicion for amyloid neuropathy or vasculitis. In most instances, the abnormalities present on biopsies do not help distinguish one

form of peripheral neuropathy from another (beyond what is already apparent by clinical examination and the NCS). Nerve biopsies should only be performed when the NCS are abnormal. The sural nerve is most commonly biopsied because it is a pure sensory nerve and biopsy will not result in loss of motor func tion. In suspected vasculitis, a combination biopsy of a superficial pero neal nerve (pure sensory) and the underlying peroneus brevis muscle obtained from a single small incision increases the diagnostic yield. Tissue can be analyzed to assess for evidence of inflammation, vasculi tis, or amyloid deposition. Semithin plastic sections, teased fiber prepa rations, and electron microscopy are used to assess the morphology of the nerve fibers and to distinguish axonopathies from myelinopathies. ■ ■SKIN BIOPSIES Skin biopsies are sometimes used to diagnose a small-fiber neuropathy. Following a punch biopsy of the skin in the distal lower extremity,

immunologic staining can be used to measure the density of small unmyelinated fibers. The density of these nerve fibers is reduced in patients with small-fiber neuropathies in whom NCS and routine nerve biopsies are often normal. This technique may allow for an objective measurement in patients with mainly subjective symptoms. However, it often adds little to what one already knows from the clinical examina tion and EDx. SPECIFIC DISORDERS ■ ■HEREDITARY NEUROPATHIES CMT disease is the most common type of hereditary neuropathy (Pattern 2, Table 457-2). Rather than one disease, CMT is a syndrome of many genetically distinct disorders (Table 457-4). The various sub types of CMT are classified according to the nerve conduction veloci ties (NCVs) and predominant pathology (e.g., demyelination or axonal degeneration), inheritance pattern (autosomal dominant, autosomal recessive, or X-linked), and the specific mutated genes. Type 1 CMT (or CMT1) refers to inherited demyelinating sensorimotor neuropa thies, whereas the axonal sensory neuropathies are classified as CMT2. By definition, motor conduction velocities in the arms are slowed to <38 m/s in CMT1 and are >38 m/s in CMT2. However, most cases of CMT1 actually have motor NCVs between 20 and 25 m/s. CMT1 and CMT2 usually begin in childhood or early adult life; however, onset later in life can occur, particularly in CMT2. Both are inherited in an autosomal dominant fashion, with a few exceptions. There are no medical therapies for any of the CMTs, but physical and occupational therapy can be beneficial, as can bracing (e.g., ankle-foot orthotics for foot drop) and other orthotic devices. ■ ■CMT1 CMT1 is the most common form of hereditary neuropathy. Affected individuals usually present in the first to third decade of life with distal leg weakness (e.g., foot drop), although patients may remain asymp tomatic even late in life. People with CMT generally do not complain of numbness or tingling, which can be helpful in distinguishing CMT from acquired forms of neuropathy in which sensory symptoms usu ally predominate. Although usually asymptomatic, reduced sensation to all modalities is apparent on examination. Muscle stretch reflexes are unobtainable or reduced throughout. There is often atrophy of the muscles below the knee (particularly the anterior compartment), lead ing to so-called inverted champagne bottle legs. Motor NCVs are generally in the 20–25 m/s range. Nerve biopsies usually are not performed on patients suspected of having CMT1, because the diagnosis usually can be made by less invasive testing (e.g., NCS and genetic studies). However, when done, the biopsies reveal reduced numbers of myelinated nerve fibers with a predilection for loss of large-diameter fibers and Schwann cell proliferation around thinly or demyelinated fibers, forming so-called onion bulbs. CMT1A is the most common subtype of CMT1, representing 70% of cases, and is caused by a 1.5-megabase (Mb) duplication within chromo some 17p11.2-12 encoding the gene for peripheral myelin protein-22 (PMP-22). This results in patients having three copies of the PMP-22 gene rather than two. This protein accounts for 2–5% of myelin protein and is expressed in compact regions of

the peripheral myelin sheath. Approximately 20% of patients with CMT1 have CMT1B, caused by mutations in the myelin protein zero (MPZ). CMT1B is for the most part clinically, electrophysiologically, and histologically indistinguish able from CMT1A. MPZ is an integral myelin protein and accounts for more than half of the myelin protein in peripheral nerves. Other forms of CMT1 are much less common and also indistinguishable from one another clinically and electrophysiologically (Table 457-4). ■ ■CMT2 CMT2 occurs approximately half as frequently as CMT1, and CMT2 tends to present later in life. Affected individuals usually become symp tomatic in the second decade; some cases present earlier in childhood, whereas others remain asymptomatic into late adult life. Clinically, CMT2 is for the most part indistinguishable from CMT1. NCS are helpful in this regard; in contrast to CMT1, the velocities are normal or

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 CMT1G AD 8q21 PMP22 HNPP AD 17p11.2 PMP22 (deletion of gene) 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 CMT recessive-intermediate (CMT-RI) CMT-RIA CMT-RIB CMT-RIC CMT-RI D AR AR AR AR 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 CMT2E (allelic to CMT1F) CMT2EE AD AD 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 AD 12q24 HSPB8 type 2) 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 CMT2RCMT2S CMT2T CMT2U CMT2V CMT2W CMT2X CMT2Y CMT2Z AD AD AD ADAD AD AD AD AD AD

1q21-23 MPZ CHAPTER 457 1q22 14q32.33 3q26 8p31 MPZ IFN-2 GNB4 NEFL Peripheral Neuropathy 8q21.1 6q23 1p36 12q24 GDAP1 KARS5 PLEKHG5 COX6A1 7p14 1p13 GARS1 ATP1A1 8p21 2p23 NEFL MPV17 10p14 4q 11q13.3 3q25.2 12q13 17q11 5q31 15q21.1 9p13 22q12 DHTKD1 TRIM2 IGHMBP2 MME MARS1 NAGLU HARS1 SPB11 VCP MORC2 (Continued)

TABLE 457-4 Classification of Charcot-Marie-Tooth Disease and Related Neuropathies NAME INHERITANCE GENE LOCATION GENE CMT3 AD 17p11.2 PMP22 (Dejerine-Sottas disease, congenital hypomyelinating AD 1q21-23 MPZ neuropathy) AR 10q21.1-22.1 ERG2 AR 19q13 PRX CMT4 CMT4A AR 8q13-21.1 GDAP1 CMT4B1 AR 11q23 MTMR2 CMT4B2 CMT4B3 AR AR CMT4C AR 5q23-33 SH3TC2 CMT4D (HMSN-Lom) AR 8q24 NDRG1 CMT4E (congenital hypomyelinating neuropathy) AR 10q21.3 ERG2 PART 13 Neurologic Disorders CMT4F AR 19q13.1-13.3 PRX CMT4G AR 10q23.2 HK1 CMT4H AR 12p11.21 FGD4 CMT4J CMT4K AR AR CMTX (X-linked) CMTX1 CMTX4 CMTX5 CMTX6 X-linked dominant X-linked recessive X-linked recessive X-linked dominant HSAN1A AD 9q22 SPTLC1 HSAN1C AD 14q24.3 SPTLC2 HSAN1D AD 14q21.3 ATL1 HSAN1E AD 19p13.2 DNMT1 HSAN1F AD 11q13.1 ATL3 HSAN2A AR 12p13.33 WNK1 HSAN2B AR 5p15.1 RETREG1 (FAM134B) HSAN2C AR 12q13.13 KIF1A HSAN2D AR 2q24.3 SCN9A HSAN3A (Riley-Day syndrome; hereditary dysautonomia) AR 9q21 ELP1 (IKBKAP) HSAN4 AR 3q NTRK1 HSAN5 AR 1p13.2 NGF HSAN6 AR

6p12.1 DST HSAN7 HSAN8 HSAN9 AD AR AR Others HNA SORD neuropathy (allelic to distal HMN8) Hereditary neuropathy with neuromyotonia CANVAS AD AR AR AR Abbreviations: AARS, alanyl-tRNA synthetase; AD, autosomal dominant; AR, autosomal recessive; ATL, atlastin; CANVAS, cerebellar ataxia, neuropathy, and vestibular areflexia syndrome; CMT, Charcot-Marie-Tooth; DNMT1, DNA methyltransferase 1; DYS, dystonin; DYNC1HI, cytoplasmic dynein 1 heavy chain 1; ELP1, elongator complex protein 1; ERG2, early growth response-2 protein; FAM134B, family with sequence similarity 134, member B; FIG4, FDG1-related F actin-binding protein; GDAP1, gangliosideinduced differentiation-associated protein-1; HK1, hexokinase 1; HMSN-P, hereditary motor and sensory neuropathy proximal; HNA, hereditary neuralgic amyotrophy; HNPP, hereditary neuropathy with liability to pressure palsies; HSAN, hereditary sensory and autonomic neuropathy; IFN2, inverted formin-2; IKBKAP, kB kinase complexassociated protein; LGMD, limb girdle muscular dystrophy; LITAF, lipopolysaccharide-induced tumor necrosis factor α factor; LRSAM1, E3 ubiquitin-protein ligase; MED25, mediator 25; MFN2, mitochondrial fusion protein mitofusin 2 gene; MPZ, myelin protein zero protein; MTMR2, myotubularin-related protein-2; NDRG1, N-myc downstream regulated 1; NGF, Beta-nerve growth factor; NTRK, 1trkA/NGF receptor; PMP-22, peripheral myelin protein-22; PRKWNK1, protein kinase, lysine deficient 1; PRPS1, phosphoribosylpyrophosphate synthetase 1; RAB7, Ras-related protein 7; RFC1, replication factor C subunit 1; SEPT9, septin 9; SH3TC2, SH3 domain and tetratricopeptide repeats 2; SMA, spinal muscular atrophy; SORD, sorbitol dehydrogenase; SPTLC, serine palmitoyltransferase long-chain base; TFG, TRK-fused gene; TrkA/NGF, tyrosine kinase A/nerve growth factor; tRNA, transfer ribonucleic acid; TRPV4, transient receptor potential cation channel, subfamily V, member 4; WNK1, WNK lysine deficient; YARS, tyrosyl-tRNA synthetase. Source: Modified from AA Amato, J Russell: Neuromuscular Disorders, 2nd ed. New York, McGraw-Hill, 2016, Table 11-1, pp. 265–266.

(Continued) 11p15 22q13.33 SBF2 SBF1 6q21 9q34 FIG4 SURF1 Xq13 Xq26.1 Xq22.3 Xp22.11 GJB1 AIFM1 PRPS1 PDK3 3p22.2 9q34.12 14q32.31 SCN11A PRDM12 TECPR2 17q24 15q21.1 5q23.3 4p14 SEPT9 SORD HINT1 RFC1

only slightly slowed. The most common cause of CMT2 is a mutation in the gene for mitofusin 2 (MFN2), which accounts for ~20–30% of CMT2 cases overall. MFN2 localizes to the outer mitochondrial mem brane, where it regulates the mitochondrial network architecture by participating in mitochondrial fusion. The other genes associated with CMT2 are much less common (Table 457-4). ■ ■CMT DOMINANT AND RECESSIVE INTERMEDIATE In CMT dominant-intermediate (CMT-DI) and CMT recessiveintermediate (CMT-RI), the NCVs are faster than usually seen in CMT1 (e.g., >38 m/s) but slower than in CMT2 (Table 457-4). ■ ■CMT3 CMT3 was originally described by Dejerine and Sottas as a hereditary demyelinating sensorimotor polyneuropathy presenting in infancy or early childhood. Affected children are severely weak. Motor NCVs are markedly slowed, typically ≤5–10 m/s. Most cases of CMT3 are caused by point mutations in the genes for PMP-22, MPZ, or ERG-2, which are also the genes responsible for CMT1. The term CMT3 is no longer recommended, but rather, the neuropathy is classified as CMT1 if autosomal dominant or as CMT4 in cases of autosomal recessive inheritance. ■ ■CMT4 CMT4 is extremely rare and is characterized by a severe, childhoodonset sensorimotor polyneuropathy that is usually inherited in an autosomal recessive fashion. Electrophysiologic and histologic evalua tions can show demyelinating or axonal features. CMT4 is genetically heterogeneous (Table 457-4). ■ ■CMTX There are several forms of X-linked CMT, the most common type is CMTX1 (Table 457-4). This shares clinical features similar to CMT1 and CMT2, except that the neuropathy is much more severe in males than in females. CMT1X

accounts for ~10–15% of CMT overall. Males usually present in the first two decades of life with atrophy and weak ness of the distal arms and legs, areflexia, pes cavus, and hammer toes. Obligate female carriers are frequently asymptomatic but can develop signs and symptoms of CMT. Onset in females is usually after the sec ond decade of life, and the neuropathy is milder in severity. NCS reveal features of both demyelination and axonal degeneration. In males, motor NCVs in the arms and legs are moderately slowed (in the low to mid 30-m/s range). About 50% of males with CMTX1 have motor NCVs between 15 and 35 m/s with ~80% of these falling between 25 and 35 m/s (intermediate slowing). In contrast, ~80% of females with CMTX1 have NCVs in the normal range and 20% have NCVs in the intermediate range. CMT1X is caused by mutations in GJB1, which encodes for gap junction protein-beta or connexin-32. Connexins are gap junction structural proteins that are important in cell-to-cell communication. Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) HNPP is an autosomal dominant disorder related to CMT1A. While CMT1A is usually associated with a 1.5-Mb duplica tion in chromosome 17p11.2 that results in an extra copy of the PMP22 gene, HNPP is caused by inheritance of the chromosome with the corresponding 1.5-Mb deletion of this segment, and thus, affected individuals have only one copy of the PMP-22 gene. Patients usually manifest in the second or third decade of life with painless numbness and weakness in the distribution of single peripheral nerves, although multiple mononeuropathies can occur (Pattern 3, Table 457-2). Symp tomatic mononeuropathy or multiple mononeuropathies are often precipitated by trivial compression of nerve(s) as can occur with wear ing a backpack, leaning on the elbows, or crossing one’s legs for even a short period of time. These pressure-related mononeuropathies may take weeks or months to resolve. In addition, some affected individuals manifest with a progressive or relapsing, generalized and symmetric, sensorimotor peripheral neuropathy that resembles CMT.

Hereditary Neuralgic Amyotrophy (HNA) HNA is an auto somal dominant disorder characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus often beginning in childhood (Pattern 4, Table 457-2). These attacks are similar to those seen with idiopathic brachial plexitis (see below). Attacks may occur in the postpartum period, following surgery, or at other times of stress. Most patients recover over several weeks or months. Slightly dysmorphic features, including hypotelorism, epican thal folds, cleft palate, syndactyly, micrognathia, and facial asymmetry, are evident in some individuals. EDx demonstrate an axonal process. HNA is genetically heterogeneous but can be caused by mutations in septin 9 (SEPT9). Septins may be important in formation of the neu ronal cytoskeleton and have a role in cell division, but it is not known how mutations in SEPT9 lead to HNA.

Hereditary Sensory and Autonomic Neuropathy (HSAN) The HSANs are a very rare group of hereditary neu ropathies in which sensory and autonomic dysfunction predominates over muscle weakness, unlike CMT, in which motor findings are most prominent (Pattern 2, Table 457-2; Table 457-4). Nevertheless, affected individuals can develop motor weakness, and there can be overlap with CMT. There are no medical therapies available to treat these neuropathies, other than prevention and treatment of mutilating skin and bone lesions. CHAPTER 457 Peripheral Neuropathy Of the HSANs, only HSAN1 typically presents in adults. HSAN1 is the most common of the HSANs and is inherited in an autosomal dominant fashion. Affected individuals usually manifest in the second through fourth decades of life. HSAN1 is associated with the degen eration of small myelinated and unmyelinated nerve fibers leading to severe loss of pain and temperature sensation, deep dermal ulcerations, recurrent osteomyelitis, Charcot joints, bone loss, gross foot

and hand deformities, and amputated digits. Although most people with HSAN1 do not complain of numbness, they often describe burning, aching, or lancinating pains. Autonomic neuropathy is not a prominent feature, but bladder dysfunction and reduced sweating in the feet may occur. HSAN1A, which is most common, is caused by mutations in the serine palmitoyltransferase long-chain base 1 (SPTLC1) gene. OTHER HEREDITARY NEUROPATHIES (TABLE 457-5) ■ ■SORBITAL DEHYDROGENASE DEFICIENCY WITH PERIPHERAL NEUROPATHY Sorbitol dehydrogenase deficiency with peripheral neuropathy (SORD) is a newly reported entity that is very important as it appears to be the most common autosomal recessive inherited form of neuropathy. It presents as a slowly progressive, length-dependent, axonal motor greater than sensory polyneuropathy or pure motor neuropathy. Age of onset is usually in the late teens. It is caused by pathogenic mutations in the SORD gene. SORD is the second enzyme of the two-step polyol pathway whereby glucose is metabolized into sorbitol, and then SORD oxidizes sorbitol into fructose. Sorbitol is a relatively nonmetabolizable sugar, and levels are markedly increased. ■ ■FABRY'S DISEASE Fabry's disease (angiokeratoma corporis diffusum) is an X-linked dominant disorder. Although men are more commonly and severely affected, women can also manifest symptoms and signs of the disease. Angiokeratomas are reddish-purple maculopapular lesions that are usually found around the umbilicus, scrotum, inguinal region, and perineum. Burning or lancinating pain in the hands and feet often develops in males in late childhood or early adult life (Pattern 2, Table 457-2). However, the neuropathy is usually overshadowed by com plications arising from an associated premature atherosclerosis (e.g., hypertension, renal failure, cardiac disease, and stroke) that often lead to death by the fifth decade of life. Some patients also manifest primar ily with a dilated cardiomyopathy. Fabry's disease is caused by mutations in the α-galactosidase gene that lead to the accumulation of ceramide trihexoside in nerves and

TABLE 457-5 Rare Hereditary Neuropathies 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) PART 13 Neurologic Disorders 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 Source: Modified from AA Amato, J Russell: Neuromuscular Disorders, 2nd ed. New York, McGraw-Hill, 2016, Table 12-1, p. 299. blood vessels. A decrease in α-galactosidase activity is evident in leukocytes and cultured fibroblasts. Glycolipid granules may be appre ciated in ganglion cells of the peripheral and sympathetic nervous sys tems and in perineurial cells. Enzyme replacement therapy (ERT) may improve the neuropathy if patients are treated early, before irreversible nerve fiber loss develops. Current U.S. Food and Drug Administra tion (FDA)-approved recombinant ERTs are agalsidase-α (Replagal; 0.2 mg/kg body weight) and agalsidase-β (Fabrazyme; 1 mg/kg body weight) and pegunigalsidase (Elfabrio), which are each given intrave nously every 2 weeks. In addition, migalastat is an oral pharmacologic chaperone that increases the enzyme activity of "amenable" mutations (defined as those mutations in the catalytic domain of the enzyme that lead to misfolding of the enzyme but otherwise would not signifi cantly impair its function). Such mutations occur in ~50% of patients. Migalastat had been shown to reduce left ventricular mass and stabi lize kidney function, but

studies have not assessed if the neuropathy improves or stabilizes. ■ ■ADRENOLEUKODYSTROPHY/ ADRENOMYELONEUROPATHY Adrenoleukodystrophy (ALD) and AMN are allelic X-linked dominant disorders caused by mutations in the peroxisomal transmembrane ade nosine triphosphate-binding cassette (ABC) transporter gene. Patients with ALD manifest with central nervous system (CNS) abnormalities. However, ~30% of patients with mutations in this gene present with the AMN phenotype that typically manifests in the third to fifth decade of life as mild to moderate peripheral neuropathy combined with pro gressive spastic paraplegia (Pattern 6, Table 457-2) (Chap. 453). Rare patients present with an adult-onset spinocerebellar ataxia or only with adrenal insufficiency. EDx is suggestive of a primary axonopathy with secondary demy elination. Nerve biopsies demonstrate a loss of myelinated and

unmyelinated nerve fibers with lamellar inclusions in the cytoplasm of Schwann cells. Very-long-chain fatty acid (VLCFA) levels (C24, C25, and C26) are increased in the urine. Laboratory evidence of adrenal insufficiency is evident in approximately two-thirds of patients. The diagnosis can be confirmed by genetic testing. Adrenal insufficiency is managed by replacement therapy; however, there is no proven effective therapy for the neurologic manifestations of ALD/AMN. Diets low in VLCFAs and supplemented with Lorenzo's oil (erucic and oleic acids) reduce the levels of VLCFAs and increase the levels of C22 in serum, fibroblasts, and liver; however, several large, open-label trials of Lorenzo's oil failed to demonstrate efficacy. Although allogeneic bone marrow transplantation and gene therapy have been successful in slowing progression of cognitive decline in some patients with ALD treated early in their disease, these approaches are ineffective for the myelopathy or neuropathy. ■ ■REFSUM'S DISEASE Refsum's disease can manifest in infancy to early adulthood with the classic tetrad of (1) peripheral neuropathy, (2) retinitis pigmentosa, (3) cerebellar ataxia, and (4) elevated CSF protein concentration. Most affected individuals develop progressive distal sensory loss and weak ness in the legs leading to foot drop by their twenties (Pattern 2, Table 457-2). Subsequently, the proximal leg and arm muscles may become weak. Patients may also develop sensorineural hearing loss, cardiac conduction abnormalities, ichthyosis, and anosmia. Serum phytanic acid levels are elevated. Sensory and motor NCS reveal reduced amplitudes, prolonged latencies, and slowed conduc tion velocities. Nerve biopsy demonstrates a loss of myelinated nerve fibers, with remaining axons often thinly myelinated and associated with onion bulb formation. Refsum's disease is genetically heterogeneous but autosomal reces sive in nature. Classical Refsum's disease with childhood or early adult onset is caused by mutations in the gene that encodes for phytanoylCoA α-hydroxylase (PAHX). Less commonly, mutations in the gene encoding peroxin 7 receptor protein (PRX7) are responsible. These mutations lead to the accumulation of phytanic acid in the central and peripheral nervous systems. Treatment is removal of phytanic precur sors (phytols: fish oils, dairy products, and ruminant fats) from the diet. ■ ■TANGIER DISEASE Tangier disease is a rare autosomal recessive disorder that can present as (1) asymmetric multiple mononeuropathies, (2) a slowly progres sive symmetric polyneuropathy predominantly in the legs, or (3) a pseudo-syringomyelia pattern with dissociated sensory loss (i.e., abnormal pain/temperature perception but preserved position/vibra tion in the arms [Chap. 453]). The tonsils may appear swollen and yellowish-orange in color, and there may also be splenomegaly and lymphadenopathy. Tangier disease is caused by mutations in the ATP-binding cassette transporter 1 (ABC1) gene, which leads to markedly reduced levels of high-density lipoprotein (HDL) cholesterol levels, whereas triacylg lycerol levels are increased. Nerve biopsies reveal axonal degeneration with demyelination and remyelination. Electron microscopy demon strates abnormal accumulation of lipid in Schwann cells, particularly those encompassing unmyelinated and small

myelinated nerves. There is no specific treatment. ■ ■PORPHYRIA Porphyria is a group of inherited disorders caused by defects in heme biosynthesis (Chap. 428). Three forms of porphyria are associated with peripheral neuropathy: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP). The acute neurologic manifestations are similar in each, with the exception that a photosensitive rash is seen with HCP and VP but not in AIP. Attacks of porphyria can be precipitated by certain drugs (usually those metabolized by the P450 system), hormonal changes (e.g., pregnancy, menstrual cycle), and dietary restrictions. An acute attack of porphyria may begin with sharp abdominal pain. Subsequently, patients may develop agitation, hallucinations, or

seizures. Several days later, back and extremity pain followed by weak ness ensues, mimicking GBS (Pattern 1, Table 457-2). Weakness can involve the arms or the legs and can be asymmetric, proximal, or distal in distribution, as well as affecting the face and bulbar musculature. Dysautonomia and signs of sympathetic overactivity are common (e.g., pupillary dilation, tachycardia, and hypertension). Constipation, urinary retention, and incontinence can also be seen. The CSF protein is typically normal or mildly elevated. Liver function tests and hematologic parameters are usually normal. Some patients are hyponatremic due to inappropriate secretion of antidi uretic hormone (Chap. 390). The urine may appear brownish in color secondary to the high concentration of porphyrin metabolites. Accu mulation of intermediary precursors of heme (i.e., d-aminolevulinic acid, porphobilinogen, uroporphobilinogen, coproporphyrinogen, and protoporphyrinogen) is found in urine. Specific enzyme activities can also be measured in erythrocytes and leukocytes. The primary abnor malities on EDx are marked reductions in compound motor action potential (CMAP) amplitudes and signs of active axonal degeneration on needle EMG. The porphyrias are inherited in an autosomal dominant fashion. AIP is associated with porphobilinogen deaminase deficiency, HCP is caused by defects in coproporphyrin oxidase, and VP is associated with protoporphyrinogen oxidase deficiency. The pathogenesis of the neuropathy is not completely understood. Treatment with glucose and hematin may reduce the accumulation of heme precursors. Intrave nous glucose is started at a rate of 10–20 g/h. If there is no improve ment within 24 h, intravenous hematin 2–5 mg/kg per day for 3–14 days should be administered. Givosiran is a small interfering RNA (siRNA) that neutralizes excess aminolevulinic acid (ALA) mRNA in hepatocytes for patients with recurrent attacks of acute intermittent porphyria. In clinical trials, givosiran 2.5 mg/kg subcutaneously per month led to reduced attack frequency, better daily pain scores for pain, improved quality of life, lower levels of urinary ALA and porpho bilinogen, and fewer days of hematin compared with placebo. ■ ■CEREBELLAR ATAXIA, NEUROPATHY, AND VESTIBULAR AREFLEXIA SYNDROME (CANVAS) Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) appears to be the most common cause of autosomal reces sive ataxia. It usually manifests in middle adult life with a sensory neuropathy/neuronopathy that progresses over the course of 10–15 years to cerebellar and vestibular dysfunction, as well as a dry cough. Examination reveals loss of large-fiber sensory modalities with a sen sory ataxia as well as cerebellar ataxia. The clinical spectrum is quite broad, however, and some patients manifest with upper and low motor neuron involvement (spasticity, brisk reflexes, muscle atrophy, and fas ciculations) similar to amyotrophic lateral sclerosis. CANVAS can also present with dysautonomia and features of parkinsonism. NCS reveal low-amplitude or absent sensory responses that are in a non-lengthdependent pattern, and EMG can show signs of active denervation and chronic reinnervation. Brain magnetic resonance imaging (MRI) scans can reveal cerebellar atrophy. Sural nerve biopsies have shown loss of large myelinated axons, and autopsy studies demonstrate

degenera tion of the dorsal root ganglia and posterior columns. In most cases, CANVAS is associated with biallelic (AAGGG)n repeat expansions in the second intron of the replication factor complex subunit 1 (RFC1). The is a DNA polymerase accessory protein required for the coordi nated synthesis of both DNA strands during replication and after DNA damage. ■ ■FAMILIAL AMYLOID POLYNEUROPATHY Familial amyloid polyneuropathy (FAP) is phenotypically and geneti cally heterogeneous and is caused by mutations in the genes for transthyretin (TTR), apolipoprotein A1, or gelsolin (Chap. 117). The majority of patients with FAP have mutations in the TTR gene. Amy loid deposition may be evident in abdominal fat pad, rectal, or nerve biopsies. The clinical features, histopathology, and EDx reveal abnor malities consistent with a generalized or multifocal, predominantly axonal but occasionally demyelinating, polyneuropathy.

Patients with TTR-related FAP usually develop insidious onset of numbness and painful paresthesias in the distal lower limbs in the third to fourth decade of life, although some patients develop the disorder later in life (Pattern 2, Table 457-2). Carpal tunnel syndrome (CTS) is common. Autonomic involvement can be severe, leading to postural hypotension, constipation or persistent diarrhea, erectile dysfunction, and impaired sweating (Pattern 10, Table 457-2). Amyloid deposition also occurs in the heart, kidneys, liver, and corneas. Patients usually die 10–15 years after the onset of symptoms from cardiac failure or complications from malnutrition. Because the liver produces much of the body’s TTR, liver transplantation has been used to treat FAP related to TTR mutations. Serum TTR levels decrease after transplantation, and improvement in clinical and EDx features has been reported. Both tafamidis meglumine (20 mg daily) and diflunisal (250 mg twice daily), which prevent misfolding and deposition of mutated TTR, appear to slow the rate of deterioration in patients with TTR-related FAP. Several forms of gene therapy are also now available. Random ized, placebo-controlled trials of antisense oligonucleotides, patisiran 0.3 mg/kg intravenous every 3 weeks, vutrisiran 25 mg subcutaneous every 3 months, and eplontersen 45 mg subcutaneous every 4 weeks, as well as the siRNA inotersen 300 mg subcutaneous weekly, have been shown to be effective in FAP related to TTR mutations. These drugs block expression of both mutant and wild-type TTR, reducing amyloid precursor protein synthesis.

CHAPTER 457 Peripheral Neuropathy Patients with apolipoprotein A1–related FAP (Van Allen type) usu ally present in the fourth decade with numbness and painful dyses thesias in the distal limbs. Gradually, the symptoms progress, leading to proximal and distal weakness and atrophy. Although autonomic neuropathy is not severe, some patients develop diarrhea, constipa tion, or gastroparesis. Most patients die from systemic complications of amyloidosis (e.g., renal failure) 12–15 years after the onset of the neuropathy. Gelsolin-related amyloidosis (Finnish type) is characterized by the combination of lattice corneal dystrophy and multiple cranial neu ropathies that usually begin in the third decade of life. Over time, a mild generalized sensorimotor polyneuropathy develops. Autonomic dysfunction does not occur. ACQUIRED NEUROPATHIES ■ ■PRIMARY OR AL AMYLOIDOSIS (SEE CHAP. 117) Besides FAP, amyloidosis can also be acquired. In primary or AL amyloidosis, the abnormal protein deposition is composed of immuno globulin light chains. AL amyloidosis occurs in the setting of multiple myeloma (MM), Waldenström’s macroglobulinemia, lymphoma, other plasmacytomas, or lymphoproliferative disorders, or without any other identifiable disease. Approximately 30% of patients with AL primary amyloidosis pres ent with a polyneuropathy, most typically painful dysesthesias and burning sensations in the feet (Pattern 2, Table 457-2). However, the trunk can be involved, and some patients manifest with a mononeu ropathy multiplex pattern. CTS occurs in 25% of patients and may be the initial

manifestation. The neuropathy is slowly progressive, and eventually, weakness develops along with large-fiber sensory loss. Most patients develop autonomic involvement with postural hypertension, syncope, bowel and bladder incontinence, constipation, impotence, and impaired sweating (Pattern 10, Table 457-2). Patients generally die from their systemic illness (renal failure, cardiac disease). The monoclonal protein may be composed of IgG, IgA, IgM, or only free light chain. Lambda (λ) is more common than κ light chain (>2:1) in AL amyloidosis. The CSF protein is often increased (with normal cell count), and thus, the neuropathy may be mistaken for CIDP (Chap. 458). Nerve biopsies reveal axonal degeneration and amyloid deposition in either a globular or diffuse pattern infiltrating the perineurial, epineurial, and endoneurial connected tissue and in blood vessel walls. The median survival of patients with primary amyloidosis is <2 years, with death usually from progressive congestive heart failure or renal failure. Chemotherapy with melphalan, prednisone, and colchicine, to

reduce the concentration of monoclonal proteins, and autologous stem cell transplantation may prolong survival, but whether the neuropathy improves is controversial.

■ ■DIABETIC NEUROPATHY DM is the most common cause of peripheral neuropathy in developed countries. DM is associated with several types of polyneuropathy: distal symmetric sensory or sensorimotor polyneuropathy, autonomic neuropathy, diabetic neuropathic cachexia, polyradiculoneuropathies, cranial neuropathies, and other mononeuropathies. Risk factors for the development of neuropathy include long-standing, poorly controlled DM and the presence of retinopathy and nephropathy. Diabetic Distal Symmetric Sensory and Sensorimotor Polyneuropathy (DSPN) DSPN is the most common form of diabetic neuropathy and manifests as sensory loss beginning in the toes that gradually progresses over time up the legs and into the fingers and arms (Pattern 2, Table 457-2). When severe, a patient may develop sensory loss in the trunk (chest and abdomen), initially in the midline anteriorly and later extending laterally. Tingling, burning, deep aching pains may also be apparent. NCS usually show reduced amplitudes and mild to moderate slowing of conduction velocities. Nerve biopsy reveals axonal degeneration, endothelial hyperplasia, and, occasionally, perivascular inflammation. Tight control of glucose may reduce the risk of developing neuropathy or improve the underlying neuropathy. A variety of medications have been used with variable success to treat painful symptoms associated with DSPN, including anticonvulsants, antidepressants, sodium channel blockers, and other analgesics (Table 457-6). PART 13 Neurologic Disorders Diabetic Autonomic Neuropathy Autonomic neuropathy is typically seen in combination with DSPN. The autonomic neuropathy can manifest as abnormal sweating, dysfunctional thermoregulation, dry eyes and mouth, pupillary abnormalities, cardiac arrhythmias, postural hypotension, GI abnormalities (e.g., gastroparesis, postpran dial bloating, chronic diarrhea, or constipation), and genitourinary dysfunction (e.g., impotence, retrograde ejaculation, incontinence) (Pattern 10, Table 457-2). Tests of autonomic function are generally abnormal, including sympathetic skin responses and quantitative sudomotor axon reflex testing. Sensory and motor NCS generally dem onstrate features described above with DSPN. TABLE 457-6 Treatment of Painful Sensory Neuropathies 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 Carbamazepine PO 200–400 mg q 6–8 h Cognitive changes, dizziness, leukopenia, liver dysfunction Phenytoin PO 200–400 mg qhs Cognitive changes, dizziness, liver dysfunction Venlafaxine PO 37.5–150 mg/d Asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence Tramadol PO 50 mg qid Cognitive changes, gastrointestinal upset Third-Line Mexiletine PO 200–300 mg tid Arrhythmias Other Agents EMLA cream Apply cutaneously qid Local erythema 2.5% lidocaine 2.5% prilocaine Capsaicin 0.025–0.075% cream Apply cutaneously qid Painful burning skin Source: Modified from AA Amato, J Russell: Neuromuscular Disorders, 2nd ed. New York, McGraw-Hill, 2016, Table 22-3, p. 485.

Diabetic Radiculoplexus Neuropathy (Diabetic Amyotrophy or Bruns-Garland Syndrome) Diabetic radiculoplexus neuropa thy is the presenting manifestation of DM in approximately one-third of patients. Typically, patients present with severe pain in the low back, hip, and thigh in one leg. Rarely, the diabetic polyradiculoneuropathy begins in both legs at the same time (Pattern 4, Table 457-2). Atrophy and weakness of proximal and distal muscles in the affected leg become apparent within a few days or weeks. The neuropathy is often accom panied or heralded by severe weight loss. Weakness usually progresses over several weeks or months but can continue to progress for 18 months or more. Subsequently, there is slow recovery, but many are left with residual weakness, sensory loss, and pain. In contrast to the more typical lumbosacral radiculoplexus neuropathy, some patients develop thoracic radiculopathy or, even less commonly, a cervical polyradicu loneuropathy. CSF protein is usually elevated, while the cell count is normal. ESR is often increased. EDx reveals evidence of active denerva tion in affected proximal and distal muscles in the limbs and in para spinal muscles. Nerve biopsies may demonstrate axonal degeneration along with perivascular inflammation. Patients with severe pain are sometimes treated in the acute period with glucocorticoids, although a randomized controlled trial has yet to be performed, and the natural history of this neuropathy is gradual improvement. Diabetic Mononeuropathies or Multiple Mononeuropa thies The most common mononeuropathies are median neuropathy at the wrist and ulnar neuropathy at the elbow, but peroneal neuropa thy at the fibular head and sciatic, lateral femoral, cutaneous, or cranial neuropathies also occur (Pattern 3, Table 457-2). In regard to cranial mononeuropathies, seventh nerve palsies are relatively common but may have other, nondiabetic etiologies. In diabetics, a third nerve palsy is most common, followed by sixth nerve and, less frequently, fourth nerve palsies. Diabetic third nerve palsies are characteristically pupilsparing (Chap. 34). ■ ■HYPOTHYROIDISM Hypothyroidism is more commonly associated with a proximal myopa thy, but some patients develop a neuropathy, most typically CTS. Rarely, a generalized sensory polyneuropathy characterized by painful paresthesias and numbness in both the legs and hands can occur. Treat ment is correction of the hypothyroidism.

■ ■SJÖGREN’S SYNDROME Sjögren’s syndrome, characterized by the sicca complex of xerophthal mia, xerostomia, and dryness of other mucous membranes, can be complicated by neuropathy (Chap. 373). Most common is a lengthdependent axonal sensorimotor neuropathy characterized mainly by sensory loss in the distal extremities (Pattern 2, Table 457-2). A pure small-fiber neuropathy or a cranial neuropathy, particularly involv ing the trigeminal nerve, can also be seen. Sjögren’s syndrome is also associated with sensory neuronopathy/ganglionopathy. Patients with sensory ganglionopathies develop progressive numbness and tingling of the limbs, trunk, and face in a non-length-dependent manner such that symptoms can involve the face or arms more than the

legs. The onset can be acute or insidious. Sensory examination demonstrates severe vibratory and proprioceptive loss leading to sensory ataxia. Patients with neuropathy due to Sjögren's syndrome may have ANAs, SS-A/Ro, and SS-B/La antibodies in the serum, but most do not. NCS demonstrate reduced amplitudes of sensory studies in the affected limbs. Nerve biopsy demonstrates axonal degeneration. Nonspecific perivascular inflammation may be present, but only rarely is there necrotizing vasculitis. There is no specific treatment for neuropathies related to Sjögren's syndrome. When vasculitis is suspected, immu nosuppressive agents may be beneficial. Occasionally, the sensory neuronopathy/ganglionopathy stabilizes or improves with immuno therapy, such as intravenous immunoglobulin. ■ ■RHEUMATOID ARTHRITIS Peripheral neuropathy occurs in at least 50% of patients with rheu matoid arthritis (RA) and may be vasculitic in nature (Chap. 370). Vasculitic neuropathy can present with a mononeuropathy multiplex (Pattern 3, Table 457-2), a generalized symmetric pattern of involve ment (Pattern 2, Table 457-2), or a combination of these patterns (Chap. 375). Neuropathies may also result from drugs used to treat RA (e.g., tumor necrosis blockers, leflunomide). Nerve biopsy often reveals thickening of the epineurial and endoneurial blood vessels as well as perivascular inflammation or vasculitis, with transmural inflammatory cell infiltration and fibrinoid necrosis of vessel walls. The neuropathy is usually responsive to immunomodulating therapies. ■ ■SYSTEMIC LUPUS ERYTHEMATOSUS Between 2 and 27% of individuals with SLE develop a peripheral neu ropathy (Chap. 368). Affected patients typically present with a slowly progressive sensory loss beginning in the feet. Some patients develop burning pain and paresthesias with normal reflexes, and NCS suggest a pure small-fiber neuropathy (Pattern 2, Table 457-2). Less common are multiple mononeuropathies presumably secondary to necrotizing vasculitis (Pattern 3, Table 457-2). Rarely, a generalized sensorimotor polyneuropathy meeting clinical, laboratory, electrophysiologic, and histologic criteria for either GBS or CIDP may occur. Immunosuppres sive therapy may be beneficial in SLE patients with neuropathy due to vasculitis. Immunosuppressive agents are less likely to be effective in patients with a generalized sensory or sensorimotor polyneuropathy without evidence of vasculitis. Patients with a GBS or CIDP-like neu ropathy should be treated accordingly (Chap. 458). ■ ■SYSTEMIC SCLEROSIS (SCLERODERMA) A distal symmetric, mainly sensory polyneuropathy complicates 5–67% of scleroderma cases (Pattern 2, Table 457-2) (Chap. 372). Cranial mononeuropathies can also develop, most commonly of the trigeminal nerve, producing numbness and dysesthesias in the face. Multiple mononeuropathies also occur (Pattern 3, Table 457-2). The EDx and histologic features of nerve biopsy are those of an axonal sensory greater than motor polyneuropathy. ■ ■MIXED CONNECTIVE TISSUE DISEASE A mild distal axonal sensorimotor polyneuropathy occurs in ~10% of patients with mixed connective tissue disease. ■ ■SARCOIDOSIS The peripheral nervous system or CNS is involved in ~5% of patients with sarcoidosis (Chap. 379). The most common cranial nerve

involved is the seventh nerve, which can be affected bilaterally. Some patients develop radiculopathy or polyradiculopathy (Pattern 4, Table 457-2). With a generalized root involvement, the clinical presenta tion can mimic GBS or CIDP. Patients can also present with multiple mononeuropathies (Pattern 3, Table 457-2) or a generalized, slowly progressive, sensory greater than motor polyneuropathy (Pattern 2, Table 457-2). Some have features of a pure small-fiber neuropathy. EDx reveals an axonal neuropathy. Nerve biopsy can reveal noncaseating granulomas infiltrating the endoneurium, perineurium, or epineurium along with lymphocytic necrotizing angiitis. Neurosarcoidosis may respond to treatment with glucocorticoids or other immunosuppres sive agents.

■ ■HYPEREOSINOPHILIC SYNDROME Hypereosinophilic syndrome is characterized by eosinophilia associ ated with various skin, cardiac, hematologic, and neurologic abnor malities. A generalized peripheral neuropathy or a mononeuropathy multiplex occurs in 6–14% of patients (Pattern 2, Table 457-2). CHAPTER 457 ■ ■CELIAC DISEASE (GLUTEN-INDUCED ENTEROPATHY OR NONTROPICAL SPRUE) Neurologic complications, particularly ataxia and peripheral neu ropathy, are estimated to occur in 10% of patients with celiac dis ease (Chap. 336). A generalized sensorimotor polyneuropathy, pure motor neuropathy, multiple mononeuropathies, autonomic neuropa thy, small-fiber neuropathy, and neuromyotonia have all been reported in association with celiac disease or antigliadin/antiendomysial anti bodies (Patterns 2, 3, and 9; Table 457-2). Nerve biopsy may reveal a loss of large myelinated fibers. The neuropathy may be secondary to malabsorption of vitamins B12 and E. However, some patients have no appreciable vitamin deficiencies. The pathogenic basis for the neuropa thy in these patients is unclear but may be autoimmune in etiology. The neuropathy does not appear to respond to a gluten-free diet. In patients with vitamin B12 or vitamin E deficiency, replacement therapy may improve or stabilize the neuropathy. Peripheral Neuropathy ■ ■INFLAMMATORY BOWEL DISEASE Ulcerative colitis and Crohn’s disease may be complicated by GBS, CIDP, generalized axonal sensory or sensorimotor polyneuropathy, small-fiber neuropathy, or mononeuropathy (Patterns 2 and 3, Table 457-2) (Chap. 337). These neuropathies may be autoimmune, nutri tional (e.g., vitamin B12 deficiency), treatment related (e.g., metronida zole), or idiopathic in nature. An acute neuropathy with demyelination resembling GBS, CIDP, or multifocal motor neuropathy may occur in patients treated with tumor necrosis factor α blockers. ■ ■UREMIC NEUROPATHY Approximately 60% of patients with renal failure develop a poly neuropathy characterized by length-dependent numbness, tingling, allodynia, and mild distal weakness (Pattern 2, Table 457-2). Rarely, a rapidly progressive weakness and sensory loss very similar to GBS can occur that improves with an increase in the intensity of renal dialysis or with transplantation (Pattern 1, Table 457-2). Mononeuropathies can also occur, the most common of which is CTS. Ischemic monomelic neuropathy (see below) can complicate arteriovenous shunts created in the arm for dialysis (Pattern 3, Table 457-2). EDx in uremic patients reveals features of a length-dependent, primarily axonal, sensorimotor polyneuropathy. Sural nerve biopsies demonstrate a loss of nerve fibers (particularly large myelinated nerve fibers), active axonal degenera tion, and segmental and paranodal demyelination. The sensorimotor polyneuropathy can be stabilized by hemodialysis and improved with successful renal transplantation. ■ ■CHRONIC LIVER DISEASE A generalized sensorimotor neuropathy characterized by numbness, tingling, and minor weakness in the distal aspects of primarily the lower limbs commonly occurs in patients with chronic liver failure. EDx studies are consistent with a sensory greater than motor axonopa thy. Occasionally patients with severe liver disease develop a combined neuropathy and myopathy. Sural nerve biopsy reveals both segmental

demyelination and axonal loss. It is not known if hepatic failure in iso lation can cause peripheral neuropathy, as the majority of patients have liver disease secondary to other disorders, such as alcoholism or viral hepatitis, which can also cause neuropathy.

■ ■CRITICAL ILLNESS POLYNEUROPATHY The most common causes of acute generalized weakness leading to admission to a medical intensive care unit (ICU) are GBS and myas thenia gravis (Pattern 1, Table 457-2) (Chaps. 458 and 459). However, weakness developing in critically ill patients while in the ICU is usu ally caused by critical illness polyneuropathy (CIP) or critical illness myopathy (CIM) or, much less commonly, by prolonged neuromuscu lar blockade. From a clinical and EDx

standpoint, it can be quite diffi cult to distinguish these disorders. Most specialists believe that CIM is more common. Both CIM and CIP develop as a complication of sepsis and multiple organ failure. They usually present as an inability to wean a patient from a ventilator. A coexisting encephalopathy may limit the neurologic examination, in particular the sensory examination. Muscle stretch reflexes are absent or reduced. PART 13 Neurologic Disorders Serum creatine kinase (CK) is usually normal; an elevated serum CK would point to CIM as opposed to CIP. NCS reveal absent or markedly reduced amplitudes of motor and sensory studies in CIP, whereas sensory studies are relatively preserved in CIM. Needle EMG usually reveals profuse positive sharp waves and fibrillation potentials, and it is not unusual in patients with severe weakness to be unable to recruit motor unit action potentials. The pathogenic basis of CIP is not known. Perhaps circulating toxins and metabolic abnormalities associated with sepsis and multiorgan failure impair axonal transport or mitochondrial function, leading to axonal degeneration. ■ ■LEPROSY (HANSEN'S DISEASE) Leprosy, caused by the acid-fast bacteria Mycobacterium leprae, is the most common cause of peripheral neuropathy in Southeast Asia, Africa, and South America (Chap. 184). Clinical manifestations range from tuberculoid leprosy at one end of the spectrum to lepro matous leprosy at the other end, with borderline leprosy in between. Neuropathies are most common in patients with borderline leprosy. Superficial cutaneous nerves of the ears and distal limbs are com monly affected. Mononeuropathies, multiple mononeuropathies, or a slowly progressive symmetric sensorimotor polyneuropathy may develop (Patterns 2 and 3, Table 457-2). Sensory NCS are usually absent in the lower limb and are reduced in amplitude in the arms. Motor NCS may demonstrate reduced amplitudes in affected nerves but occasionally can reveal demyelinating features. Leprosy is usually diagnosed by skin lesion biopsy. Nerve biopsy can also be diagnostic, particularly when there are no apparent skin lesions. The tuberculoid form is characterized by granulomas, and bacilli are not seen. In con trast, with lepromatous leprosy, large numbers of infiltrating bacilli, TH2 lymphocytes, and organism-laden, foamy macrophages with minimal granulomatous infiltration are evident. The bacilli are best appreciated using the Fite stain, where they can be seen as red-staining rods often in clusters free in the endoneurium, within macrophages, or within Schwann cells. Patients are generally treated with multiple drugs: dapsone, rifampin, and clofazimine. Other medications that are used include thalidomide, pefloxacin, ofloxacin, sparfloxacin, minocycline, and clarithromycin. Patients are generally treated for 2 years. Treatment is sometimes complicated by the so-called reversal reaction, particularly in borderline leprosy. The reversal reaction can occur at any time dur ing treatment and develops because of a shift to the tuberculoid end of the spectrum, with an increase in cellular immunity during treatment. The cellular response is upregulated as evidenced by an increased release of tumor necrosis factor α, interferon γ, and interleukin 2, with new granuloma formation. This can result in an exacerbation of the rash and the neuropathy as well as in appearance of new lesions. High-dose glucocorticoids blunt this adverse reaction and may be used prophylactically at treatment onset in high-risk patients. Ery thema nodosum leprosum (ENL) is also treated with glucocorticoids or thalidomide.

■ ■LYME DISEASE Lyme disease is caused by infection with Borrelia burgdorferi, a spiro chete usually transmitted by the deer tick Ixodes dammini (Chap. 191). Neurologic complications may develop during the second and third stages of infection. Facial neuropathy is most common and is bilateral in about half of cases, which is rare for idiopathic Bell's palsy. Involve ment of nerves is frequently asymmetric. Some patients present with a polyradiculoneuropathy or multiple mononeuropathies (Pattern 3 or 4, Table 457-2). EDx is suggestive of a primary axonopathy. Nerve

biop sies can reveal axonal degeneration with perivascular inflammation. Treatment is with antibiotics. ■ ■DIPHTHERITIC NEUROPATHY Diphtheria is caused by the bacteria Corynebacterium diphtheriae (Chap. 155). Infected individuals present with flu-like symptoms of generalized myalgias, headache, fatigue, low-grade fever, and irritabil ity within a week to 10 days of the exposure. Between 20 and 70% of patients develop a peripheral neuropathy caused by a toxin released by the bacteria. Three to 4 weeks after infection, patients may note decreased sensation in their throat and begin to develop dysphagia, dysarthria, hoarseness, and blurred vision due to impaired accommo dation. A generalized polyneuropathy may manifest 2 or 3 months fol lowing the initial infection, characterized by numbness, paresthesias, and weakness of the arms and legs and occasionally ventilatory failure (Pattern 1, Table 457-2). CSF protein can be elevated with or without lymphocytic pleocytosis. EDx suggests a diffuse axonal sensorimotor polyneuropathy. Antitoxin and antibiotics should be given within 48 h of symptom onset. Although early treatment reduces the incidence and severity of some complications (i.e., cardiomyopathy), it does not appear to alter the natural history of the associated peripheral neuropa thy. The neuropathy usually resolves after several months. ■ ■COVID-19 GBS (Chap. 458) has been reported in the setting of acute COVID-19 infection though a causal relationship has not been clearly established. There does appear to be an increased risk of GBS with adenovirusvector vaccines but not the messenger RNA vaccines. ■ ■HUMAN IMMUNODEFICIENCY VIRUS HIV infection can result in a variety of neurologic complications, including peripheral neuropathies (Chap. 208). Approximately 20% of HIV-infected individuals develop a neuropathy as a direct result of the virus itself or as a result of other associated viral infections (e.g., CMV) or neurotoxicity secondary to antiviral medications (see below). The major presentations of peripheral neuropathy associated with HIV infection include (1) distal symmetric polyneuropathy (DSP), (2) inflammatory demyelinating polyneuropathy (including both GBS and CIDP), (3) multiple mononeuropathies (e.g., vasculitis, CMV-related), (4) polyradiculopathy (usually CMV-related), (5) autonomic neuropa thy, and (6) sensory ganglionitis. HIV-Related Distal Symmetric Polyneuropathy DSP is the most common form of peripheral neuropathy associated with HIV infection and usually is seen in patients with AIDS. It is characterized by numbness and painful paresthesias involving the distal extremities (Pattern 2, Table 457-2). The pathogenic basis for DSP is unknown but is not due to actual infection of the peripheral nerves. The neuropathy may be immune mediated, perhaps caused by the release of cytokines from surrounding inflammatory cells. Vitamin B12 deficiency may contribute in some instances but is not a major cause of most cases of DSP. Older antiretroviral agents (e.g., dideoxycytidine, dideoxyino sine, stavudine) are also neurotoxic and can cause a painful sensory neuropathy. HIV-Related Inflammatory Demyelinating Polyradiculoneu ropathy Both acute inflammatory demyelinating polyneuropathy (AIDP) and CIDP can occur as a complication of HIV infection (Pat tern 1, Table 457-2). AIDP usually develops at the time of seroconver sion, whereas CIDP can occur any time in the course of the infection. Clinical and EDx features are indistinguishable from idiopathic AIDP

or CIDP (Chap. 458). In addition to elevated protein levels, lympho cytic pleocytosis is evident in the CSF, a finding that helps distinguish this HIV-associated polyradiculoneuropathy from idiopathic AIDP/ CIDP. HIV-Related Progressive Polyradiculopathy An acute, pro gressive lumbosacral polyradiculoneuropathy usually secondary to CMV infection can develop in patients with AIDS (Pattern 4, Table 457-2). Patients present with severe radicular pain, numbness, and weakness in the legs, which is usually asymmetric. CSF is abnormal, demonstrating a high protein level, along with a reduced glucose con centration and notably a neutrophilic pleocytosis. EDx studies reveal

features of active axonal degeneration. The polyradiculoneuropathy may improve with antiviral therapy. HIV-Related Multiple Mononeuropathies Multiple mono neuropathies can also develop in patients with HIV infection, usually in the context of AIDS. Weakness, numbness, paresthesias, and pain occur in the distribution of affected nerves (Pattern 3, Table 457-2). Nerve biopsies can reveal axonal degeneration with necrotizing vasculitis or perivascular inflammation. Glucocorticoid treatment is indicated for vasculitis directly due to HIV infection. HIV-Related Sensory Neuronopathy/Ganglionopathy Dor sal root ganglionitis is a very rare complication of HIV infection, and neuronopathy can be the presenting manifestation. Patients develop sensory ataxia similar to idiopathic sensory neuronopathy/

ganglionopathy (Pattern 9, Table 457-2). NCS reveal reduced amplitudes or absence of sensory nerve action potentials (SNAPs). ■ ■HERPES VARICELLA-ZOSTER VIRUS Peripheral neuropathy from herpes varicella-zoster (HVZ) infection results from reactivation of latent virus or from a primary infection (Chap. 198). Two-thirds of infections in adults are characterized by dermal zoster in which severe pain and paresthesias develop in a der matomal region followed within a week or two by a vesicular rash in the same distribution (Pattern 3, Table 457-2). Weakness in muscles innervated by roots corresponding to the dermatomal distribution of skin lesions occurs in 5–30% of patients. Approximately 25% of affected patients have continued pain (postherpetic neuralgia [PHN]). A large clinical trial demonstrated that vaccination against zoster reduces the incidence of HVZ among vaccine recipients by 51% and reduces the incidence of PHN by 67%. Treatment of PHN is symptom atic (Table 457-6). ■ ■CYTOMEGALOVIRUS CMV can cause an acute lumbosacral polyradiculopathy and mul tiple mononeuropathies in patients with HIV infection and in other immune deficiency conditions (Pattern 4, Table 457-2) (Chap. 200). ■ ■EPSTEIN-BARR VIRUS EBV infection has been associated with GBS, cranial neuropathies, mononeuropathy multiplex, brachial plexopathy, lumbosacral radicu loplexopathy, and sensory neuronopathies (Patterns 1, 3, 4, and 9, Table 457-2) (Chap. 199). ■ ■HEPATITIS VIRUSES Hepatitis B and C can cause multiple mononeuropathies related to vasculitis, AIDP, or CIDP (Patterns 1 and 3, Table 457-2) (Chap. 352). NEUROPATHIES ASSOCIATED WITH MALIGNANCY Patients with malignancy can develop neuropathies due to (1) a direct effect of the cancer by invasion or compression of the nerves, (2) remote or paraneoplastic effect, (3) a toxic effect of treatment, or (4) as a consequence of immune compromise caused by immunosuppressive medications. The most common associated malignancy is lung cancer, but neuropathies also complicate carcinoma of the breast, ovaries, stomach, colon, rectum, and other organs, including the lymphopro liferative system.

■ ■PARANEOPLASTIC SENSORY NEURONOPATHY/ GANGLIONOPATHY Paraneoplastic encephalomyelitis/sensory neuronopathy (PEM/SN) usually complicates small-cell lung carcinoma (Chap. 99). Patients usually present with numbness and paresthesias in the distal extremi ties that are often asymmetric. The onset can be acute or insidiously progressive. Prominent loss of proprioception leads to sensory ataxia (Pattern 9; Table 457-2). Weakness can be present, usually secondary to an associated myelitis, motor neuronopathy, or concurrent LEMS. Many patients also develop confusion, memory loss, depression, hal lucinations or seizures, or cerebellar ataxia. Polyclonal antineuronal antibodies (IgG) directed against a 35- to 40-kDa protein or complex of proteins, the so-called Hu antigen, are found in the sera or CSF in the majority of patients with paraneoplastic PEM/SN. CSF may be normal or may demonstrate mild lymphocytic pleocytosis and elevated protein. PEM/SN is probably the result of antigenic similarity between proteins expressed in the tumor cells and neuronal cells, leading to an immune response directed against both cell

types. Treatment of the underlying cancer generally does not affect the course of PEM/SN. However, occasional patients may improve following treatment of the tumor. Unfortunately, plasmapheresis, intravenous immunoglobulin, and immunosuppressive agents have not shown benefit.

CHAPTER 457 Peripheral Neuropathy ■ ■NEUROPATHY SECONDARY TO

TUMOR INFILTRATION Malignant cells, in particular leukemia and lymphoma, can infiltrate cranial and peripheral nerves, leading to mononeuropathy, mononeu ropathy multiplex, polyradiculopathy, plexopathy, or even a generalized symmetric distal or proximal and distal polyneuropathy (Patterns 1, 2, 3, and 4; Table 457-2). Neuropathy related to tumor infiltration is often painful; it can be the presenting manifestation of the cancer or the heralding symptom of a relapse. The neuropathy may improve with treatment of the underlying leukemia or lymphoma or with glucocorticoids. ■ ■NEUROPATHY AS A COMPLICATION OF BONE MARROW TRANSPLANTATION Neuropathies may develop in patients who undergo bone marrow transplantation (BMT) because of the toxic effects of chemotherapy, radiation, infection, or an autoimmune response directed against the peripheral nerves. Peripheral neuropathy in BMT is often associated with graft-versus-host disease (GVHD). Chronic GVHD shares many features with a variety of autoimmune disorders, and it is possible that an immune-mediated response directed against peripheral nerves is responsible. Patients with chronic GVHD may develop cranial neurop athies, sensorimotor polyneuropathies, multiple mononeuropathies, and severe generalized peripheral neuropathies resembling AIDP or CIDP (Patterns 1, 2, and 3; Table 457-2). The neuropathy may improve by increasing the intensity of immunosuppressive or immunomodulat ing therapy and resolution of the GVHD. ■ ■LYMPHOMA Lymphomas may cause neuropathy by infiltration or direct compres sion of nerves or by a paraneoplastic process. The neuropathy can be purely sensory or motor but most commonly is sensorimotor. The pattern of involvement may be symmetric, asymmetric, or multifocal, and the course may be acute, gradually progressive, or relapsing and remitting (Patterns 1, 2, and 3; Table 457-2). EDx can be compatible with either an axonal or demyelinating process. CSF may reveal lym phocytic pleocytosis and an elevated protein. Nerve biopsy may dem onstrate endoneurial inflammatory cells in both the infiltrative and the paraneoplastic etiologies. A monoclonal population of cells favors lymphomatous invasion. The neuropathy may respond to treatment of the underlying lymphoma or immunomodulating therapies. ■ ■MULTIPLE MYELOMA MM usually presents in the fifth to seventh decade of life with fatigue, bone pain, anemia, and hypercalcemia (Chap. 116). Clinical and EDx features of neuropathy occur in as many as 40% of patients. The most common pattern is that of a distal, axonal, sensory, or sensorimotor

polyneuropathy (Pattern 2; Table 457-2). Less frequently, a chronic demyelinating polyradiculoneuropathy may develop (Pattern 1; Table 457-2) (see POEMS, Chap. 458). MM can be complicated by amyloid polyneuropathy and should be considered in patients with painful paresthesias, loss of pinprick and temperature discrimination, and autonomic dysfunction (suggestive of a small-fiber neuropathy) and CTS. Expanding plasmacytomas can compress cranial nerves and spinal roots as well. A monoclonal protein, usually composed of γ or μ heavy chains or κ light chains, may be identified in the serum or urine. EDx usually shows reduced amplitudes with normal or only mildly abnor mal distal latencies and conduction velocities. A superimposed median neuropathy at the wrist is common. Abdominal fat pad, rectal, or sural nerve biopsy can be performed to look for amyloid deposition. Unfor tunately, the treatment of the underlying MM does

not usually affect the course of the neuropathy.

■ ■NEUROPATHIES ASSOCIATED WITH MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE (SEE CHAP. 458) PART 13 Neurologic Disorders Toxic Neuropathies Secondary to Chemotherapy Many of the commonly used chemotherapy agents can cause a toxic neuropa thy (Table 457-7). The mechanisms by which these agents cause toxic neuropathies vary, as does the specific type of neuropathy produced. The risk of developing a toxic neuropathy or more severe neuropa thy appears to be greater in patients with a preexisting neuropathy (e.g., CMT disease, diabetic neuropathy) and those who also take other potentially neurotoxic drugs (e.g., nitrofurantoin, isoniazid, TABLE 457-7 Toxic Neuropathies Secondary to Chemotherapy MECHANISM OF NEUROTOXICITY CLINICAL FEATURES NERVE HISTOPATHOLOGY EMG/NCS DRUG Vinca alkaloids (vincristine, vinblastine, vindesine, vinorelbine) Interfere with axonal microtubule assembly; impairs axonal transport Symmetric, S-M, large-/smallfiber PN; autonomic symptoms common; infrequent cranial neuropathies Cisplatin 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 Taxanes (paclitaxel, docetaxel) Promotes axonal microtubule assembly; interferes with axonal transport Symmetric, predominantly sensory PN; large-fiber modalities affected more than small-fiber Suramin Axonal PN Unknown;? inhibition of neurotrophic growth factor binding;? neuronal lysosomal storage Symmetric, length-dependent, sensory-predominant PN Demyelinating PN Unknown;? immunomodulating effects Subacute, S-M PN with diffuse proximal and distal weakness; areflexia; increased CSF protein Cytarabine (ARA-C) Unknown;? selective Schwann cell toxicity;? immunomodulating effects GBS-like syndrome; pure sensory neuropathy; brachial plexopathy Etoposide (VP-16) Unknown;? selective dorsal root ganglia toxicity Length-dependent, sensorypredominant PN; autonomic neuropathy Bortezomib (Velcade) Unknown Length-dependent, sensory, predominantly small-fiber PN Abbreviations: CMAP, compound motor action potential; CSF, cerebrospinal fluid; CVs, conduction velocities; EMG, electromyography; GBS, Guillain-Barré syndrome; NCS, nerve conduction studies; PN, polyneuropathy; QST, quantitative sensory testing; S-M, sensorimotor; SNAP, sensory nerve action potential. Source: Reproduced with permission from AA Amato, J Russell: Neuromuscular Disorders, 2nd ed. New York: McGraw-Hill; 2016.

disulfiram, pyridoxine). Chemotherapeutic agents usually cause a sensory greater than motor length-dependent axonal neuropathy or neuronopathy/ganglionopathy (Patterns 2 and 9; Table 457-2). OTHER TOXIC NEUROPATHIES Neuropathies can develop as complications of toxic effects of various drugs and other environmental exposures (Table 457-8). The more common neuropathies associated with these agents are discussed here. ■ ■CHLOROQUINE AND HYDROXYCHLOROQUINE Chloroquine and hydroxychloroquine can cause a toxic myopathy characterized by slowly progressive, painless, proximal weakness and atrophy, which is worse in the legs than the arms. In addition, neuropathy can also develop with or without the myopathy leading to sensory loss and distal weakness. The “neuromyopathy” usually appears in patients taking 500 mg daily for a year or more but has been reported with doses as low as 200 mg/d. Serum CK levels are usually elevated due to the superimposed myopathy. NCS reveal mild slowing of motor and sensory NCVs with a mild to moderate reduc tion in the amplitudes, although NCS may be normal in patients with only the myopathy. EMG demonstrates myopathic muscle action potentials (MUAPs), increased insertional activity in the form of positive sharp waves, fibrillation potentials, and occasionally myo tonic potentials, particularly in the proximal muscles. Neurogenic MUAPs and reduced recruitment

are found in more distal muscles. Nerve biopsy demonstrates autophagic vacuoles within Schwann cells. Vacuoles may also be evident in muscle biopsies. The pathogenic basis Axonal degeneration of myelinated and unmyelinated fibers; regenerating clusters, minimal segmental demyelination Axonal sensorimotor PN; distal denervation on EMG; abnormal QST, particularly vibratory perception Loss of large > small myelinated and unmyelinated fibers; axonal degeneration with small clusters of regenerating fibers; secondary segmental demyelination Low-amplitude or unobtainable SNAPs with normal CMAPs and EMG; abnormal QST, particularly vibratory perception 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 None described Abnormalities consistent with an axonal S-M PN Loss of large and small myelinated fibers with primary demyelination and secondary axonal degeneration; occasional epi- and endoneurial inflammatory cell infiltrates Features suggestive of an acquired demyelinating sensorimotor PN (e.g., slow CVs, prolonged distal latencies and F-wave latencies, conduction block, temporal dispersion) Loss of myelinated nerve fibers; axonal degeneration; segmental demyelination; no inflammation Axonal, demyelinating, or mixed S-M PN; denervation on EMG None described Abnormalities consistent with an axonal S-M PN Not reported Abnormalities consistent with an axonal sensory neuropathy with early small-fiber involvement (abnormal autonomic studies)

TABLE 457-8 Toxic Neuropathies MECHANISM OF NEUROTOXICITY CLINICAL FEATURES NERVE HISTOPATHOLOGY EMG/NCS DRUG Misonidazole Unknown Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern Metronidazole Unknown Painful paresthesias and loss of large- and small-fiber sensory modalities and sometimes distal weakness in length-dependent pattern 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 Amiodarone 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 Colchicine Inhibits polymerization of tubulin in microtubules and impairs axoplasmic flow Numbness and paresthesias with loss of large-fiber modalities in a lengthdependent fashion; superimposed myopathy may lead to proximal in addition to distal weakness Podophyllin Binds to microtubules and impairs axoplasmic flow Sensory loss, tingling, muscle weakness, and diminished muscle stretch reflexes in length-dependent pattern; autonomic neuropathy Thalidomide Unknown Numbness, tingling, and burning pain and weakness in a length-dependent pattern Disulfiram Accumulation of neurofilaments and impaired axoplasmic flow Numbness, tingling, and burning pain in a length-dependent pattern Dapsone Unknown Distal weakness that may progress to proximal muscles; sensory loss Leflunomide Unknown Paresthesias and numbness in a length-dependent pattern Nitrofurantoin Unknown Numbness, painful paresthesias, and severe weakness that may resemble GBS Pyridoxine (vitamin B6) Unknown Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination Isoniazid Inhibits pyridoxal phosphokinase leading to pyridoxine deficiency Dysesthesias and sensory ataxia; impaired large-fiber sensory modalities on examination Ethambutol Unknown Numbness with loss of large-fiber modalities on examination Antinucleosides Unknown Dysesthesia and sensory ataxia; impaired large-fiber sensory modalities on examination Phenytoin Unknown Numbness with loss of

large-fiber modalities on examination Lithium Unknown Numbness with loss of large-fiber modalities on examination

Axonal degeneration of large, myelinated fibers; axonal swellings; segmental demyelination Low-amplitude or unobtainable SNAPs with normal or only slightly reduced CMAP amplitudes Axonal degeneration Low-amplitude or unobtainable SNAPs with normal CMAPs 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 CHAPTER 457 Axonal degeneration and segmental demyelination with myeloid inclusions in nerves and muscle fibers Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; can also have prominent slowing of CVs; distal denervation on EMG; irritability and myopathic-appearing MUAPs proximally in patients with superimposed toxic myopathy Peripheral Neuropathy 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 Axonal degeneration Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration; autopsy studies reveal degeneration of dorsal root ganglia Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration with accumulation of neurofilaments in the axons Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration and segmental demyelination Low-amplitude or unobtainable CMAPs with normal or reduced SNAP amplitudes Unknown Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes 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 Marked loss of sensory axons and cell bodies in dorsal root ganglia Reduced amplitudes or absent SNAPs 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 Axonal degeneration Reduced amplitudes or absent SNAPs Axonal degeneration Reduced amplitudes or absent SNAPs Axonal degeneration and segmental demyelination Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes (Continued)

(Continued) TABLE 457-8 Toxic Neuropathies MECHANISM OF NEUROTOXICITY CLINICAL FEATURES NERVE HISTOPATHOLOGY EMG/NCS DRUG Acrylamide Unknown; may be caused by impaired axonal transport Numbness with loss of large-fiber modalities on examination; sensory ataxia; mild distal weakness Carbon disulfide Unknown Length-dependent numbness and tingling with mild distal weakness Ethylene oxide Unknown; may act as alkylating agent and bind DNA Length-dependent numbness and tingling; may have mild distal weakness Organophosphates Bind and inhibit neuropathy target esterase Early features are those of neuromuscular blockade with generalized weakness; later axonal sensorimotor PN ensues PART 13 Neurologic Disorders Hexacarbons Unknown; may lead to covalent cross-linking between neurofilaments Acute, severe sensorimotor PN that may resemble GBS Lead Unknown; may interfere with mitochondria Encephalopathy; motor neuropathy (often resembles radial neuropathy with wrist and finger drop); autonomic neuropathy; bluish-black discoloration of gums Mercury Unknown; may combine with sulfhydryl groups Abdominal pain and nephrotic syndrome; encephalopathy; ataxia; paresthesias Thallium Unknown Encephalopathy; painful sensory symptoms; mild loss of vibration; distal or

generalized weakness may also develop; autonomic neuropathy; alopecia Arsenic Unknown; may combine with sulfhydryl groups Abdominal discomfort, burning pain, and paresthesias; generalized weakness; autonomic insufficiency; can resemble GBS Gold Unknown Distal paresthesias and reduction of all sensory modalities Abbreviations: CMAP, compound motor action potential; CVs, conduction velocities; EMG, electromyography; GBS, Guillain-Barré syndrome; MUAP, muscle action potential; NCS, nerve conduction studies; PN, polyneuropathy; S-M, sensorimotor; SNAP, sensory nerve action potential. Source: Reproduced with permission from AA Amato, J Russell: Neuromuscular Disorders, 2nd ed. New York: McGraw-Hill; 2016. of the neuropathy is not known but may be related to the amphiphilic properties of the drug. These agents contain both hydrophobic and hydrophilic regions that allow them to interact with the anionic phos pholipids of cell membranes and organelles. The drug-lipid complexes may be resistant to digestion by lysosomal enzymes, leading to the formation of autophagic vacuoles filled with myeloid debris that may in turn cause degeneration of nerves and muscle fibers. The signs and symptoms of the neuropathy and myopathy are usually reversible fol lowing discontinuation of medication. ■ ■AMIODARONE Amiodarone can cause a neuromyopathy similar to chloroquine and hydroxychloroquine. The neuromyopathy typically appears after patients have taken the medication for 2–3 years. Nerve biopsy dem onstrates a combination of segmental demyelination and axonal loss. Electron microscopy reveals lamellar or dense inclusions in Schwann cells, pericytes, and endothelial cells. The inclusions in muscle and nerve biopsies have persisted as long as 2 years following discontinua tion of the medication.

Degeneration of sensory axons in peripheral nerves and posterior columns, spinocerebellar tracts, mammillary bodies, optic tracts, and corticospinal tracts in

the CNS Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal swellings with accumulation of neurofilaments Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration along with degeneration of gracile fasciculus and corticospinal tracts Early: repetitive firing of CMAPs and decrement with repetitive nerve stimulation; late: axonal sensorimotor PN Axonal degeneration and giant axons swollen with neurofilaments Features of a mixed axonal and/ or demyelinating sensorimotor axonal PN—reduced amplitudes, prolonged distal latencies, conduction block, and slowing of CVs Axonal degeneration of motor axons Reduction of CMAP amplitudes with active denervation on EMG Axonal degeneration; degeneration of dorsal root ganglia, calcarine, and cerebellar cortex Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes Axonal degeneration Low-amplitude or unobtainable SNAPs with normal or reduced CMAP amplitudes; may have demyelinating features: prolonged distal latencies and slowing of CVs Axonal degeneration Low-amplitude or unobtainable SNAPs ■ ■COLCHICINE Colchicine can also cause a neuromyopathy. Patients usually pres ent with proximal weakness and numbness and tingling in the distal extremities. EDx reveals features of an axonal polyneuropathy. Muscle biopsy reveals a vacuolar myopathy, whereas sensory nerves demon strate axonal degeneration. Colchicine inhibits the polymerization of tubulin into microtubules. The disruption of the microtubules prob ably leads to defective intracellular movement of important proteins, nutrients, and waste products in muscle and nerves. ■ ■THALIDOMIDE Thalidomide is an immunomodulating agent used to treat MM, GVHD, leprosy, and other autoimmune disorders. Thalidomide is associated with severe teratogenic

effects as well as peripheral neu ropathy that can be dose-limiting. Patients develop numbness, painful tingling, and burning discomfort in the feet and hands and less com monly muscle weakness and atrophy. Even after stopping the drug for 4–6 years, as many as 50% patients continue to have significant symp toms. NCS demonstrate reduced amplitudes or complete absence of SNAPs, with preserved conduction velocities when obtainable. Motor

NCS are usually normal. Nerve biopsy reveals a loss of large-diameter myelinated fibers and axonal degeneration. Degeneration of dorsal root ganglion cells has been reported at autopsy. PYRIDOXINE (VITAMIN B6) TOXICITY Pyridoxine is an essential vitamin that serves as a coenzyme for trans amination and decarboxylation. However, at high doses (116 mg/d), patients can develop a severe sensory neuropathy with dysesthesias and sensory ataxia. NCS reveal absent or markedly reduced SNAP ampli tudes with relatively preserved CMAPs. Nerve biopsy reveals axonal loss of fiber at all diameters. Loss of dorsal root ganglion cells with subsequent degeneration of both the peripheral and central sensory tracts have been reported in animal models. ■ ■ISONIAZID One of the most common side effects of isoniazid (INH) is peripheral neuropathy. Standard doses of INH (3–5 mg/kg per day) are associated with a 2% incidence of neuropathy, whereas neuropathy develops in at least 17% of patients taking in excess of 6 mg/kg per d. The elderly, malnourished, and “slow acetylators” are at increased risk for develop ing the neuropathy. INH inhibits pyridoxal phosphokinase, resulting in pyridoxine deficiency and the neuropathy. Prophylactic administration of pyridoxine 100 mg/d can prevent the neuropathy from developing. ■ ■ANTIRETROVIRAL AGENTS The nucleoside analogues zalcitabine (dideoxycytidine or ddC), didano sine (dideoxyinosine or ddI), stavudine (d4T), lamivudine (3TC), and antiretroviral nucleoside reverse transcriptase inhibitor (NRTI) are used to treat HIV infection. One of the major dose-limiting side effects of these medications is a predominantly sensory, length-dependent, symmetrically painful neuropathy (Pattern 2; Table 457-2). Zalcitabine (ddC) is the most extensively studied of the nucleoside analogues, and at doses >0.18 mg/kg per d, it is associated with a subacute onset of severe burning and lancinating pains in the feet and hands. NCS reveal decreased amplitudes of the SNAPs with normal motor studies. The nucleoside analogues inhibit mitochondrial DNA polymerase, which is the suspected pathogenic basis for the neuropathy. Because of a “coasting effect,” patients can continue to worsen even 2–3 weeks after stopping the medication. Following dose reduction, improvement in the neuropa thy is seen in most patients after several months (mean time ~10 weeks). ■ ■HEXACARBONS (n-HEXANE, METHYL n-BUTYL KETONE)/GLUE SNIFFER’S NEUROPATHY n-Hexane and methyl n-butyl ketone are water-insoluble industrial organic solvents that are also present in some glues. Exposure through inhalation, accidentally or intentionally (glue sniffing), or through skin absorption can lead to a profound subacute sensory and motor polyneuropathy (Pattern 2; Table 457-2). NCS demonstrate decreased amplitudes of the SNAPs and CMAPs with slightly slow conduction velocities. Nerve biopsy reveals a loss of myelinated fibers and giant axons that are filled with 10-nm neurofilaments. Hexacarbon exposure leads to covalent cross-linking between axonal neurofilaments that results in their aggregation, impaired axonal transport, swelling of the axons, and eventual axonal degeneration. ■ ■LEAD Lead neuropathy is uncommon, but it can be seen in children who accidentally ingest lead-based paints in older buildings and in indus trial workers exposed to lead-containing products. The most common presentation of lead poisoning is an encephalopathy; however, symp toms and signs of a primarily motor neuropathy can also occur. The neuropathy is characterized by an insidious and progressive onset of weakness usually beginning in the arms, in particular involving the wrist and finger extensors, resembling a radial neuropathy. Sensation is generally preserved; however, the

autonomic nervous system can be affected (Patterns 2, 3, and 10; Table 457-2). Laboratory investigation can reveal a microcytic hypochromic anemia with basophilic stip pling of erythrocytes, an elevated serum lead level, and an elevated serum coproporphyrin level. A 24-h urine collection demonstrates elevated levels of lead excretion. The NCS may reveal reduced CMAP

amplitudes, while the SNAPs are typically normal. The pathogenic basis may be related to abnormal porphyrin metabolism. The most impor tant principle of management is to remove the source of the exposure. Chelation therapy with calcium disodium ethylene-diaminetetraacetic acid (EDTA), British anti-Lewisite (BAL), and penicillamine also dem onstrates variable efficacy.

■ ■MERCURY Mercury toxicity may occur as a result of exposure to either organic or inorganic mercurials. Mercury poisoning presents with paresthesias in hands and feet that progress proximally and may involve the face and tongue. Motor weakness can also develop. CNS symptoms often overshadow the neuropathy. EDx shows features of a primarily axonal sensorimotor polyneuropathy. The primary site of neuromuscular pathology appears to be the dorsal root ganglia. The mainstay of treat ment is removing the source of exposure. CHAPTER 457 ■ ■THALLIUM Thallium can exist in a monovalent or trivalent form and is primarily used as a rodenticide. The toxic neuropathy usually manifests as burn ing paresthesias of the feet, abdominal pain, and vomiting. Increased thirst, sleep disturbances, and psychotic behavior may be noted. Within the first week, patients develop pigmentation of the hair, an acne-like rash in the malar area of the face, and hyperreflexia. By the second and third weeks, autonomic instability with labile heart rate and blood pres sure may be seen. Hyporeflexia and alopecia also occur but may not be evident until the third or fourth week following exposure. With severe intoxication, proximal weakness and involvement of the cranial nerves can occur. Some patients require mechanical ventilation due to respira tory muscle involvement. The lethal dose of thallium is variable, ranging from 8 to 15 mg/kg body weight. Death can result in <48 h following a particularly large dose. NCS demonstrate features of a primarily axonal sensorimotor polyneuropathy. With acute intoxication, potassium fer ric ferrocyanide II may be effective in preventing absorption of thal lium from the gut. However, there may be no benefit once thallium has been absorbed. Unfortunately, chelating agents are not very efficacious. Adequate diuresis is essential to help eliminate thallium from the body without increasing tissue availability from the serum. Peripheral Neuropathy ■ ■ARSENIC Arsenic is another heavy metal that can cause a toxic sensorimotor polyneuropathy. The neuropathy manifests 5–10 days after ingestion of arsenic and progresses for several weeks, sometimes mimicking GBS. The presenting symptoms are typically an abrupt onset of abdominal discomfort, nausea, vomiting, pain, and diarrhea followed within sev eral days by burning pain in the feet and hands. Examination of the skin can be helpful in the diagnosis as the loss of the superficial epidermal layer results in patchy regions of increased or decreased pigmentation on the skin several weeks after an acute exposure or with chronic low levels of ingestion. Mee’s lines, which are transverse lines at the base of the fingernails and toenails, do not become evident until 1 or 2 months after the exposure. Multiple Mee’s lines may be seen in patients with long fingernails who have had chronic exposure to arsenic. Mee’s lines are not specific for arsenic toxicity as they can also be seen following thallium poisoning. Because arsenic is cleared from blood rapidly, the serum concentration of arsenic is not diagnostically helpful. However, arsenic levels are increased in the urine, hair, and fingernails of patients exposed to arsenic. Anemia with stippling of erythrocytes is com mon, and occasionally, pancytopenia and aplastic anemia can develop. Increased CSF protein levels without pleocytosis can be seen; this can lead to misdiagnosis as GBS.

NCS are usually suggestive of an axonal sensorimotor polyneuropathy; however, demyelinating features can be present. Chelation therapy with BAL has yielded inconsistent results; therefore, it is not generally recommended. NUTRITIONAL NEUROPATHIES ■ ■COBALAMIN (VITAMIN B12) Pernicious anemia is the most common cause of cobalamin defi ciency. Other causes include dietary avoidance (vegetarians), gastrec tomy, gastric bypass surgery, inflammatory bowel disease, pancreatic

insufficiency, bacterial overgrowth, and possibly histamine-2 blockers and proton pump inhibitors. An underappreciated cause of cobalamin deficiency is food-cobalamin malabsorption. This typically occurs in older individuals and results from an inability to adequately absorb cobalamin in food protein. No apparent cause of deficiency is identi fied in a significant number of patients with cobalamin deficiency. The use of nitrous oxide as an anesthetic agent or as a recreational drug can produce acute cobalamin deficiency neuropathy and subacute combined degeneration.

Complaints of numb hands typically appear before lower extremity paresthesias are noted. A preferential large-fiber sensory loss affecting proprioception and vibration with sparing of small-fiber modalities is present; an unsteady gait reflects sensory ataxia. These features, coupled with diffuse hyperreflexia and absent Achilles reflexes, should always focus attention on the possibility of cobalamin deficiency (Pat terns 2 and 6; Table 457-2). Optic atrophy and, in severe cases, behav ioral changes ranging from mild irritability and forgetfulness to severe dementia and frank psychosis may appear. The full clinical picture of subacute combined degeneration is uncommon. CNS manifestations, especially pyramidal tract signs, may be missing, and in fact, some patients may only exhibit symptoms of peripheral neuropathy. PART 13 Neurologic Disorders EDx shows an axonal sensorimotor neuropathy. CNS involvement produces abnormal somatosensory and visual evoked potential laten cies. The diagnosis is confirmed by finding reduced serum cobalamin levels. In up to 40% of patients, anemia and macrocytosis are lacking. Serum methylmalonic acid and homocysteine, the metabolites that accumulate when cobalamin-dependent reactions are blocked, are elevated. Antibodies to intrinsic factor are present in ~60% and anti parietal cell antibodies in ~90% of individuals with pernicious anemia. Cobalamin deficiency can be treated with various regimens of cobalamin. One typical regimen consists of 1000 µg cyanocobalamin IM weekly for 1 month and monthly thereafter. Patients with food cobalamin malabsorption can absorb free cobalamin and therefore can be treated with oral cobalamin supplementation. An oral cobalamin dose of 1000 µg/d should be sufficient. Treatment for cobalamin defi ciency usually does not completely reverse the clinical manifestations, and at least 50% of patients exhibit some permanent neurologic deficit. ■ ■THIAMINE DEFICIENCY Thiamine (vitamin B1) deficiency is an uncommon cause of peripheral neuropathy in developed countries. It is now most often seen as a con sequence of chronic alcohol abuse, recurrent vomiting, total parenteral nutrition, and bariatric surgery. Thiamine deficiency polyneuropathy can occur in normal, healthy young adults who do not abuse alcohol but who engage in inappropriately restrictive diets. Thiamine is watersoluble. It is present in most animal and plant tissues, but the greatest sources are unrefined cereal grains, wheat germ, yeast, soybean flour, and pork. Beriberi means “I can’t, I can’t” in Singhalese, the language of natives of what was once part of the Dutch East Indies (now Sri Lanka). Dry beriberi refers to neuropathic symptoms. The term wet beriberi is used when cardiac manifestations predominate (in reference to edema). Beriberi was relatively uncommon until the late 1800s when it became widespread among people for whom rice was a dietary main stay. This epidemic was due to a new technique of processing rice that removed the germ from the rice shaft, rendering the so-

called polished rice deficient in thiamine and other essential nutrients. Symptoms of neuropathy follow prolonged deficiency. These begin with mild sensory loss and/or burning dysesthesias in the toes and feet and aching and cramping in the lower legs. Pain may be the pre dominant symptom. With progression, patients develop features of a nonspecific generalized polyneuropathy, with distal sensory loss in the feet and hands. Blood and urine assays for thiamine are not reliable for diagnosis of deficiency. Erythrocyte transketolase activity and the percent age increase in activity (in vitro) following the addition of thiamine pyrophosphate (TPP) may be more accurate and reliable. EDx shows nonspecific findings of an axonal sensorimotor polyneuropathy. When a diagnosis of thiamine deficiency is made or suspected, thiamine replacement should be provided until proper nutrition is restored.

Thiamine is usually given intravenously or intramuscularly at a dose of 100 mg/d. Although cardiac manifestations show a striking response to thiamine replacement, neurologic improvement is usually more vari able and less dramatic. ■ ■VITAMIN E DEFICIENCY The term vitamin E is usually used for α-tocopherol, the most active of the four main types of vitamin E. Because vitamin E is present in animal fat, vegetable oils, and various grains, deficiency is usually due to factors other than insufficient intake. Vitamin E deficiency usually occurs secondary to lipid malabsorption or in uncommon disorders of vitamin E transport. One hereditary disorder is abetalipoproteinemia, a rare autosomal dominant disorder characterized by steatorrhea, pig mentary retinopathy, acanthocytosis, and progressive ataxia. Patients with cystic fibrosis may also have vitamin E deficiency secondary to steatorrhea. There are genetic forms of isolated vitamin E deficiency not associated with lipid malabsorption. Vitamin E deficiency may also occur as a consequence of various cholestatic and hepatobiliary disorders as well as short-bowel syndromes resulting from the surgical treatment of intestinal disorders. Clinical features may not appear until many years after the onset of deficiency. The onset of symptoms tends to be insidious, and progres sion is slow. The main clinical features are spinocerebellar ataxia and polyneuropathy, thus resembling Friedreich’s ataxia or other spinocer ebellar ataxias. Patients manifest progressive ataxia and signs of poste rior column dysfunction, such as impaired joint position and vibratory sensation. Because of the polyneuropathy, there is hyporeflexia, but plantar responses may be extensor as a result of the spinal cord involve ment (Patterns 2 and 6; Table 457-2). Other neurologic manifestations may include ophthalmoplegia, pigmented retinopathy, night blindness, dysarthria, pseudoathetosis, dystonia, and tremor. Vitamin E defi ciency may present as an isolated polyneuropathy, but this is very rare. The yield of checking serum vitamin E levels in patients with isolated polyneuropathy is extremely low, and this test should not be part of routine practice. Diagnosis is made by measuring α-tocopherol levels in the serum. EDx shows features of an axonal neuropathy. Treatment is replacement with oral vitamin E, but high doses are not needed. For patients with isolated vitamin E deficiency, treatment consists of 1500–6000 IU/d in divided doses. ■ ■VITAMIN B6 DEFICIENCY Vitamin B6, or pyridoxine, can produce neuropathic manifestations from both deficiency and toxicity. Vitamin B6 toxicity was discussed above. Vitamin B6 deficiency is most commonly seen in patients treated with isoniazid or hydralazine. The polyneuropathy of vitamin B6 is nonspe cific, manifesting as a generalized axonal sensorimotor polyneuropathy. Vitamin B6 deficiency can be detected by direct assay. Vitamin B6 supple mentation with 50–100 mg/d is suggested for patients being treated with isoniazid or hydralazine. This same dose is appropriate for replacement in cases of nutritional deficiency. ■ ■PELLAGRA (NIACIN DEFICIENCY) Pellagra is produced by deficiency of niacin. Although pellagra may be seen in alcoholics, this disorder has essentially been eradicated in most Western countries by means of enriching bread with niacin. Neverthe less, pellagra continues

to be a problem in a number of underdeveloped regions, particularly in Asia and Africa, where corn is the main source of carbohydrate. Neurologic manifestations are variable; abnormalities can develop in the brain and spinal cord as well as peripheral nerves. When peripheral nerves are involved, the neuropathy is usually mild and resembles beriberi. Treatment is with niacin 40–250 mg/d. ■ ■COPPER DEFICIENCY A syndrome that has only recently been described is myeloneuropathy secondary to copper deficiency (see also Chap. 453). Most patients present with lower limb paresthesias, weakness, spasticity, and gait difficulties (Pattern 6; Table 457-2). Large-fiber sensory function is impaired, reflexes are brisk, and plantar responses are extensor. In some

cases, light touch and pinprick sensation are affected, and NCS indicate sensorimotor axonal polyneuropathy in addition to myelopathy. Hematologic abnormalities are a known complication of copper deficiency; these can include microcytic anemia, neutropenia, and occasionally pancytopenia. Because copper is absorbed in the stomach and proximal jejunum, many cases of copper deficiency occur in the setting of prior gastric surgery. Excess zinc is an established cause of copper deficiency. Zinc upregulates enterocyte production of metallo thionine, which results in decreased absorption of copper. Excessive dietary zinc supplements or denture cream containing zinc can pro duce this clinical picture. Other potential causes of copper deficiency include malnutrition, prematurity, total parenteral nutrition, and ingestion of copper-chelating agents. Following oral or IV copper replacement, some patients show neu rologic improvement, but this may take many months or not occur at all. Replacement consists of oral copper sulfate or gluconate 2 mg one to three times a day. If oral copper replacement is not effective, elemen tal copper in the copper sulfate or copper chloride forms can be given as 2 mg IV daily for 3–5 days, then weekly for 1–2 months until copper levels normalize. Thereafter, oral daily copper therapy can be resumed. In contrast to the neurologic manifestations, most of the hematologic indices normalize in response to copper replacement therapy. ■ ■NEUROPATHY ASSOCIATED WITH

GASTRIC SURGERY Polyneuropathy may occur following gastric surgery for ulcer, cancer, or weight reduction. This usually occurs in the context of rapid, sig nificant weight loss and recurrent, protracted vomiting. The clinical picture is one of acute or subacute sensory loss and weakness. Neu ropathy following weight loss surgery usually occurs in the first several months after surgery. Weight reduction surgical procedures include gastrojejunostomy, gastric stapling, vertical banded gastroplasty, and gastrectomy with Roux-en-Y anastomosis. The initial manifestations are usually numbness and paresthesias in the feet (Pattern 2; Table 457-2). In many cases, no specific nutritional deficiency factor is identified. Management consists of parenteral vitamin supplementation, espe cially including thiamine. Improvement has been observed following supplementation, parenteral nutritional support, and reversal of the surgical bypass. The duration and severity of deficits before identifi cation and treatment of neuropathy are important predictors of final outcome. CRYPTOGENIC (IDIOPATHIC) SENSORY AND SENSORIMOTOR POLYNEUROPATHY Cryptogenic (idiopathic) sensory and sensorimotor polyneuropathy (CSPN) is a diagnosis of exclusion, established after a careful medical, family, and social history; neurologic examination; and directed labora tory testing. Despite extensive evaluation, the cause of polyneuropathy in as many as 50% of all patients is idiopathic. CSPN should be consid ered a distinct diagnostic subset of peripheral neuropathy. The onset of CSPN is predominantly in the sixth and seventh decades. Patients complain of distal numbness, tingling, and often burning pain that invariably begins in the feet and may eventually involve the fingers and hands (“burning feet syndrome”). Patients exhibit a distal sensory loss to pinprick, touch, and vibration in the toes and feet, and occasionally in the

fingers (Pattern 2; Table 457-2). It is uncommon to see signifi cant proprioception deficits, even though patients may complain of gait unsteadiness. However, tandem gait may be abnormal in a minority of cases. Neither subjective nor objective evidence of weakness is a promi nent feature. Most patients have evidence of both large- and smallfiber loss on neurologic examination and EDx. Approximately 10% of patients have only evidence of small-fiber involvement. The ankle muscle stretch reflex is frequently absent, but in cases with predomi nantly small-fiber loss, this may be preserved. The EDx findings range from isolated SNAP abnormalities (usually with loss of amplitude), to evidence for an axonal sensorimotor neuropathy, to a completely normal study (if primarily small fibers are involved). Therapy primar ily involves the control of neuropathic pain (Table 457-6) if present. A large comparative effectiveness study in CSPN showed that the drugs

nortriptyline and duloxetine outperformed pregabalin and mexiletine. These drugs should not be used if the patient has only numbness and tingling but no pain.

Although no treatment is available that can reverse an idiopathic distal peripheral neuropathy, the prognosis is good. Progression often does not occur or is minimal, with sensory symptoms and signs pro gressing proximally up to the knees and elbows. The disorder does not lead to significant motor disability over time. The relatively benign course of this disorder should be explained to patients. MONONEUROPATHIES/PLEXOPATHIES/ RADICULOPATHIES (PATTERN 3; TABLE 457-2) ■ ■MEDIAN NEUROPATHY CTS is a compression of the median nerve in the carpal tunnel at the wrist. The median nerve enters the hand through the carpal tunnel by coursing under the transverse carpal ligament. The symptoms of CTS consist of numbness and paresthesias variably in the thumb, index, middle, and half of the ring finger. At times, the paresthesias can include the entire hand and extend into the forearm or upper arm or can be isolated to one or two fingers. Pain is another common symp tom and can be located in the hand and forearm and, at times, in the proximal arm. CTS is common and often misdiagnosed as thoracic outlet syndrome. The signs of CTS are decreased sensation in the median nerve distribution; reproduction of the sensation of tingling when a percussion hammer is tapped over the wrist (Tinel sign) or the wrist is flexed for 30–60 s (Phalen sign); and weakness of thumb oppo sition and abduction. EDx is extremely sensitive and shows slowing of sensory and, to a lesser extent, motor median potentials across the wrist. Ultrasound can show focal swelling of the median nerve at the wrist. Treatment options consist of avoidance of precipitating activi ties; control of underlying systemic-associated conditions if present; nonsteroidal anti-inflammatory medications; neutral (volar) position wrist splints, especially for night use; glucocorticoid/anesthetic injec tion into the carpal tunnel; and surgical decompression by dividing the transverse carpal ligament. The surgical option should be considered if there is a poor response to nonsurgical treatments; if there is thenar muscle atrophy and/or weakness; and if there are significant denerva tion potentials on EMG. CHAPTER 457 Peripheral Neuropathy Other proximal median neuropathies are very uncommon and include the pronator teres syndrome and anterior interosseous neu ropathy. These often occur as a partial form of brachial plexitis. ■ ■ULNAR NEUROPATHY AT THE ELBOW—“CUBITAL TUNNEL SYNDROME” The ulnar nerve passes through the condylar groove between the medial epicondyle and the olecranon. Symptoms consist of paresthe sias, tingling, and numbness in the medial hand and half of the fourth and the entire fifth fingers, pain at the elbow or forearm, and weakness. Signs consist of decreased sensation in an ulnar distribution, Tinel’s sign at the elbow, and weakness and atrophy of ulnar-innervated hand muscles. The Froment sign indicates thumb adductor weakness and consists of flexion of the thumb at the interphalangeal joint when attempting to oppose the

thumb against the lateral border of the second digit. EDx may show slowing of ulnar motor NCV across the elbow with prolonged ulnar sensory latencies. Ultrasound can show swell ing of the ulnar nerve around the elbow as well. Treatment consists of avoiding aggravating factors, using elbow pads, and surgery to decom press the nerve in the cubital tunnel. Ulnar neuropathies can also rarely occur at the wrist in the ulnar (Guyon) canal or in the hand, usually after trauma. ■ ■RADIAL NEUROPATHY The radial nerve winds around the proximal humerus in the spiral groove and proceeds down the lateral arm and enters the forearm, dividing into the posterior interosseous nerve and superficial nerve. The symptoms and signs consist of wrist drop; finger extension weak ness; thumb abduction weakness; and sensory loss in the dorsal web between the thumb and index finger. Triceps and brachioradialis

strength is often normal, and triceps reflex is often intact. Most cases of radial neuropathy are transient compressive (neuropraxic) injuries that recover spontaneously in 6–8 weeks. If there has been prolonged compression and severe axonal damage, it may take several months to recover. Treatment consists of cock-up wrist and finger splints, avoiding further compression, and physical therapy to avoid flexion contracture. If there is no improvement in 2–3 weeks, an EDx study is recommended to confirm the clinical diagnosis and determine the degree of severity.

■ ■LATERAL FEMORAL CUTANEOUS NEUROPATHY (MERALGIA PARESTHETICA) The lateral femoral cutaneous nerve arises from the upper lumbar plexus (spinal levels L2/3), crosses through the inguinal ligament near its attachment to the iliac bone, and supplies sensation to the anterior lateral thigh. The neuropathy affecting this nerve is also known as meralgia paresthetica. Symptoms and signs consist of paresthesias, numbness, and occasionally pain in the lateral thigh. Symptoms are increased by standing or walking and are relieved by sitting. There is normal strength, and knee reflexes are intact. The diagnosis is clinical, and further tests usually are not performed. EDx is only needed to rule out lumbar plexopathy, radiculopathy, or femoral neuropathy. If the symptoms and signs are classic, EMG is not necessary. Symptoms often resolve spontaneously over weeks or months, but the patient may be left with permanent numbness. Treatment consists of weight loss and avoiding tight belts. Analgesics in the form of a lidocaine patch, nonsteroidal agents, and occasionally medications for neuropathic pain can be used (Table 457-6). Rarely, locally injecting the nerve with an anesthetic can be tried. There is no role for surgery. PART 13 Neurologic Disorders ■ ■FEMORAL NEUROPATHY Femoral neuropathies can arise as complications of retroperitoneal hematoma, lithotomy positioning, hip arthroplasty or dislocation, iliac artery occlusion, femoral arterial procedures, infiltration by hematog enous malignancy, penetrating groin trauma, pelvic surgery including hysterectomy and renal transplantation, and diabetes (a partial form of lumbosacral diabetic plexopathy); some cases are idiopathic. Patients with femoral neuropathy have difficulty extending their knee and flexing the hip. Sensory symptoms occurring either on the anterior thigh and/or medial leg occur in only half of reported cases. A promi nent painful component is the exception rather than the rule, may be delayed, and is often self-limited in nature. The quadriceps (patellar) reflex is diminished. ■ ■SCIATIC NEUROPATHY Sciatic neuropathies commonly complicate hip arthroplasty, pelvic procedures in which patients are placed in a prolonged lithotomy posi tion, trauma, hematomas, tumor infiltration, and vasculitis. In addi tion, many sciatic neuropathies are idiopathic. Weakness may involve all motions of the ankles and toes as well as flexion of the leg at the knee; abduction and extension of the thigh at the hip are spared. Sen sory loss occurs in the entire foot and the distal lateral leg. The ankle jerk and, on occasion, the internal hamstring reflex are diminished or

more typically absent on the affected side. The peroneal subdivi sion of the sciatic nerve is typically involved disproportionately to the tibial counterpart. Thus, patients may have only ankle dorsiflexion and eversion weakness with sparing of knee flexion, ankle inversion, and plantar flexion; these features can lead to misdiagnosis of a common peroneal neuropathy. PERONEAL NEUROPATHY The sciatic nerve divides at the distal femur into the tibial and pero neal nerve. The common peroneal nerve passes posterior and laterally around the fibular head, under the fibular tunnel. It then divides into the superficial peroneal nerve, which supplies the ankle evertor mus cles and sensation over the anterolateral distal leg and dorsum of the foot, and the deep peroneal nerve, which supplies ankle dorsiflexors and toe extensor muscles and a small area of sensation dorsally in the area of the first and second toes.

Symptoms and signs consist of foot drop (ankle dorsiflexion, toe extension, and ankle eversion weakness) and variable sensory loss, which may involve the superficial and deep peroneal pattern. There is usually no pain. Onset may be on awakening in the morning. Peroneal neuropathy needs to be distinguished from L5 radiculopathy. In L5 radiculopathy, ankle invertors and evertors are weak and needle EMG reveals denervation. EDx can help localize the lesion. Peroneal motor conduction velocity shows slowing and amplitude drop across the fibular head. Management consists of rapid weight loss and avoiding leg crossing. Foot drop is treated with an ankle brace. A knee pad can be worn over the lateral knee to avoid further compression. Most cases spontaneously resolve over weeks or months. RADICULOPATHIES Radiculopathies are most often due to compression from degenerative joint disease and herniated disks, but there are a number of unusual etiologies (Table 457-9). Degenerative spine disease affects a num ber of different structures, which narrow the diameter of the neural foramen or canal of the spinal column and compromise nerve root integrity; these are discussed in detail in Chaps. 18 and 19. PLEXOPATHIES (PATTERN 4; TABLE 457-2) ■ ■BRACHIAL PLEXUS The brachial plexus is composed of three trunks (upper, middle, and lower), with two divisions (anterior and posterior) per trunk (Fig. 457-2). Subsequently, the trunks divide into three cords (medial, lateral, and posterior), and from these, arise the multiple terminal nerves innervating the arm. The anterior primary rami of C5 and C6 fuse to form the upper trunk; the anterior primary ramus of C7 continues as the middle trunk, while the anterior rami of C8 and T1 join to form the lower trunk. There are several disorders commonly associated with brachial plexopathy. Immune-Mediated Brachial Plexus Neuropathy Immunemediated brachial plexus neuropathy (IBPN) goes by various terms, including acute brachial plexitis, neuralgic amyotrophy, and ParsonageTurner syndrome. IBPN usually presents with an acute onset of severe pain in the shoulder region. The intense pain usually lasts several days to a few weeks, but a dull ache can persist. Individuals who are affected may not appreciate weakness of the arm early in the course because the pain limits movement. However, as the pain dissipates, weakness and often sensory loss are appreciated. Attacks can occasionally recur. Clinical findings are dependent on the distribution of involvement (e.g., specific trunk, divisions, cords, or terminal nerves). The most TABLE 457-9 Causes of Radiculopathy • 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

Upper subscapular L Axillary Musculocutaneous Radial P Median Ulnar Medial antibrachial cutaneous Thoracodorsal Lower subscapular Medial brachial cutaneous CORDS PERIPHERAL NERVES DIVISIONS TRUNKS ROOTS Anterior Posterior FIGURE 457-2 Brachial plexus anatomy. L, lateral; M, medial; P, posterior. (Reproduced with permission J Goodgold: Anatomical Correlates of Clinical Electromyography. Baltimore, Williams and Wilkins, 1974.) common pattern of IBPN involves the upper trunk or a single or multiple mononeuropathies primarily involving the suprascapular, long thoracic, or axillary nerves. Additionally, the phrenic and ante rior interosseous nerves may be concomitantly affected. Any of these nerves may also be affected in isolation. EDx is useful to confirm and localize the site(s) of involvement. Empirical treatment of severe pain with glucocorticoids is often used in the acute period. Brachial Plexopathies Associated with Neoplasms Neo plasms involving the brachial plexus may be primary nerve tumors, local cancers expanding into the plexus (e.g., Pancoast lung tumor or lymphoma), and metastatic tumors. Primary brachial plexus tumors are less common than the secondary tumors and include schwanno mas, neurinomas, and neurofibromas. Secondary tumors affecting the brachial plexus are more common and are always malignant. These may arise from local tumors, expanding into the plexus. For example, a Pancoast tumor of the upper lobe of the lung may invade or compress the lower trunk, whereas a primary lymphoma arising from the cervi cal or axillary lymph nodes may also infiltrate the plexus. Pancoast tumors typically present as an insidious onset of pain in the upper arm, sensory disturbance in the medial aspect of the forearm and hand, and weakness and atrophy of the intrinsic hand muscles along with an ipsilateral Horner’s syndrome. Chest computed tomography (CT) scans or MRI can demonstrate extension of the tumor into the plexus. Metastatic involvement of the brachial plexus may occur with spread of breast cancer into the axillary lymph nodes and local spread into the nearby nerves. Perioperative Plexopathies (Median Sternotomy) The most common surgical procedures associated with brachial plexopathy as a complication are those that involve median sternotomies (e.g., openheart surgeries and thoracotomies). Brachial plexopathies occur in as many as 5% of patients following a median sternotomy and typically affect the lower trunk. Thus, individuals manifest with sensory dis turbance affecting the medial aspect of forearm and hand along with weakness of the intrinsic hand muscles. The mechanism is related to the stretch of the lower trunk, so most individuals who are affected recover within a few months. Lumbosacral Plexus The lumbar plexus arises from the ventral primary rami of the first to the fourth lumbar spinal nerves (Fig. 457-3). These nerves pass downward and laterally from the vertebral column within the psoas major muscle. The femoral nerve derives from the dorsal branches of the second to the fourth lumbar ventral rami. The obturator nerve arises from the ventral branches of the same lumbar

Dorsal scapular Lateral anterior thoracic Suprascapular C5 C6 Subclavius C7 C8 M Medial anterior thoracic T1 Long thoracic CHAPTER 457 Peripheral Neuropathy rami. The lumbar plexus communicates with the sacral plexus by the lumbosacral trunk, which contains some fibers from the fourth and all of the fibers from the fifth lumbar ventral rami (Fig. 457-4). The sacral plexus is the part of the lumbosacral plexus that is formed by the union of the lumbosacral trunk with the ventral rami of the first to fourth sacral nerves. The plexus lies on the posterior and postero lateral wall of the pelvis with its components converging toward the sciatic notch. The lateral trunk of the sciatic nerve (which forms the common peroneal nerve) arises from the union of the dorsal branches of the lumbosacral trunk (L4, L5) and the dorsal branches of the S1 and S2 spinal nerve

ventral rami. The medial trunk of the sciatic nerve (which forms the tibial nerve) derives from the ventral branches of the same ventral rami (L4-S2). ■ ■LUMBOSACRAL PLEXOPATHIES Plexopathies are typically recognized when motor, sensory, and if applicable, reflex deficits occur in multiple nerve and segmental distributions confined to one extremity. If localization within the lumbosacral plexus can be accomplished, designation as a lumbar plexopathy, a sacral plexopathy, a lumbosacral trunk lesion, or a panplexopathy is the best localization that can be expected. Although lumbar plexopathies may be bilateral, usually occurring in a stepwise and chronologically dissociated manner, sacral plexopathies are more likely to behave in this manner due to their closer anatomic proxim ity. The differential diagnosis of plexopathy includes disorders of the conus medullaris and cauda equina (polyradiculopathy). If there is a paucity of pain and sensory involvement, motor neuron disease should be considered as well. The causes of lumbosacral plexopathies are listed in Table 457-10. Diabetic radiculopathy (discussed above) is a fairly common cause of painful leg weakness. Lumbosacral plexopathies are a well-recognized complication of retroperitoneal hemorrhage. Various primary and metastatic malignancies can affect the lumbosacral plexus as well; these include carcinoma of the cervix, endometrium, and ovary; osteosar coma; testicular cancer; MM; lymphoma; acute myelogenous leukemia; colon cancer; squamous cell carcinoma of the rectum; adenocarcinoma of unknown origin; and intraneural spread of prostate cancer. ■ ■RECURRENT NEOPLASTIC DISEASE OR RADIATION-INDUCED PLEXOPATHY The treatment for various malignancies is often radiation therapy, the field of which may include parts of the brachial plexus. It can be difficult in such situations to determine if a new brachial or lum bosacral plexopathy is related to tumor within the plexus or from

L1 L2 Genitofemoral nerve Iliohypogastric nerve L3 Ilioinguinal nerve Lateral cutaneous nerve of thigh To lliacus and psoas muscles L4 Obturator nerve L5 Femoral nerve Lumbo-sacral trunk S1 S2 S3 Gluteal nerves PART 13 Neurologic Disorders S4 Pudendal nerve Sciatic nerve Post. cutaneous nerve of thigh FIGURE 457-3 Lumbosacral plexus. (Reproduced with permission from AA Amato,

JA Russell (eds): Neuromuscular Disorders, 2nd ed. New York: McGraw-Hill Education; 2016.) PLEXUS ROOTS DIVISIONS (From anterior primary divisions) (Posterior [black] and anterior) TERMINAL AND COLLATERAL BRANCHES BRANCHES FROM POSTERIOR DIVISIONS (To lumbar plexus) (Lumbosacral trunk) Superior gluteal nerve (L4, 5, S1) Nerves to piriformis (S1, 2) Inferior gluteal nerve (L5, S1, 2) BRANCH FROM BOTH ANTERIOR AND POSTERIOR DIVISIONS Posterior femoral cutaneous nerve (S1, 2, 3) Sciatic nerve (To pudendal plexus) Inferior medial clunial nerve (S2, 3) Common peroneal nerve BRANCHES FROM ANTERIOR DIVISIONS Tibial nerve To quadratus femons and gemellus inferior muscles L4, 5, S1 (To hamstring muscles) L5, S1, 2 To obturator internus and gemellus superior muscles FIGURE 457-4 Lumbosacral trunk sacral plexus and sciatic nerve. (Reproduced with permission from AA Amato, JA Russell (eds): Neuromuscular Disorders, 2nd ed. New York: McGraw-Hill Education; 2016.)

TABLE 457-10 Lumbosacral Plexopathies: Etiologies • 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 radiation-induced nerve damage. Radiation can be associated with microvascular abnormalities and fibrosis of surrounding tissues, which can damage the axons and the Schwann cells. Radiation-induced plexopathy can develop months or years following therapy and is dose dependent. Tumor invasion is usually painful and more commonly affects the lower trunk, whereas radiation injury is often painless and

affects the upper trunk. Imaging studies such as MRI and CT scans are useful but can be misleading, especially when there is small microscopic inva sion of the plexus. EMG can be informative if myokymic discharges are appreciated, as this finding strongly suggests radiation-induced damage. ■ ■EVALUATION AND TREATMENT OF PLEXOPATHIES Most patients with plexopathies will undergo both imaging with MRI and EDx evaluations. Severe pain from acute idiopathic lumbosacral plexopathy may respond to a short course of glucocorticoids. ■ ■FURTHER READING Amato AA, Ropper AH: Sensory ganglionopathy. N Engl J Med L4 383:1657, 2020. Amato AA, Russell J: Neuromuscular Disorders, 2nd ed. New York, McGraw-Hill, 2016. Barohn RJ, Amato AA: Pattern-recognition approach to neuropathy L5 and neuronopathy. Neurol Clin 31:343, 2013. Barohn RJ et al: Patient Assisted Intervention for Neuropathy: Com S1 parison of Treatment in Real Life Situations (PAIN-CONTRoLS) Bayesian adaptive comparative effectiveness randomized trial. JAMA Neurol 78:68, 2021. Cortese A et al: Biallelic mutations in SORD cause a common and S2 potentially treatable hereditary neuropathy with implications for diabetes. Nat Genet 52:473, 2020. [Published correction appears in Nat Genet 52:640, 2020.] Cortese A et al: Cerebellar ataxia, neuropathy and vestibular areflexia S3 syndrome (CANVAS): Genetic and clinical aspects. Pract Neurol 22:14, 2022. Elafros MA et al: Towards prevention of diabetic peripheral neuropa thy: Clinical presentation, pathogenesis, and new treatments. Lancet Neurol 21:922, 2022. Hobson-Webb LD, Juel VC: Common entrapment neuropathies. Continuum (Minneap Minn) 23:487, 2017. Ioannou A et al: RNA Targeting and gene editing strategies for trans thyretin amyloidosis. BioDrugs 37:127, 2023. Jin PH, Shin SC: Neuropathy of connective tissue diseases and other systemic diseases. Semin Neurol 39:651, 2019. Klein CJ: Charcot-Marie-Tooth disease and other hereditary neuropa thies. Continuum (Minneap Minn) 26:1224, 2020.

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