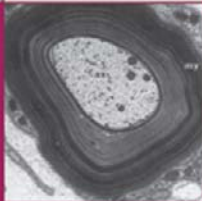


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PERIPHERAL NEUROPATHIES IN CLINICAL PRACTICE



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Preface

In the almost two decades since the last edition of this text, *Disorders of Peripheral Nerves* (2nd ed.), there have been enormous advances in elucidation of the biologic, genetic, and clinical bases of the peripheral nerve disorders. Our goal in this fully updated edition of the book remains to *inform but not overwhelm*. The name change, to *Peripheral Neuropathies in Clinical Practice*, reflects the clinical emphasis of the book. Except for the first two chapters on fundamental concepts and anatomic classification of peripheral nerve disorders, most of the rest of the book has been substantially revamped to reflect new information and improve clarity. Peripheral nerve diseases remain a difficult area for most practitioners. We have sought to combine a thorough review of the neurologic literature with our clinical experience in presenting a comprehensive, concise, and readable approach to the understanding, evaluation, and management of these disorders.

We are pleased to acknowledge the following individuals who assisted us in this project: Drs. Phyllis Bieri, Ann Hanley, Howard Geyer, Mark Milstein, Fabreena Napier and Beth Stein; Craig Panner and David D'Addona at Oxford University Press; and our understanding families.

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**PERIPHERAL NEUROPATHIES IN
CLINICAL PRACTICE**

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Basic Concepts and Glossary of Common Clinical Terms

DEFINITION OF THE PERIPHERAL NERVOUS SYSTEM (PNS) RELATIONSHIPS FUNDAMENTAL TO AN UNDERSTANDING OF DISEASE OF PERIPHERAL NERVE FIBERS

Neuron Cell Body and Axon
Axon, Schwann Cell, and Myelin

Axon and End Organ
Wallerian Degeneration and Axon Regeneration
GLOSSARY OF COMMON CLINICAL TERMS

DEFINITION OF THE PERIPHERAL NERVOUS SYSTEM (PNS)

The PNS may be defined as those portions of motor neurons, autonomic neurons, and primary sensory neurons that extend outside the central nervous system (CNS) and are associated with Schwann cells or ganglionic satellite cells. The concept of a separate PNS is obviously artificial, since the cell bodies of many PNS motor neurons lie within the CNS and some peripheral sensory neurons have extensive central projections. The justification for this concept stems from several notions, two of which are especially relevant to this book: one is the predilection for many diseases to affect primarily the PNS, and the other is its ability, in contrast to the CNS, to regenerate.

The PNS, so defined, usually includes the dorsal and ventral spinal roots, spinal and cranial nerves (with the exception of the first and second cranial nerves), dorsal root and other sensory ganglia, sensory and motor terminals, and the bulk of the autonomic nervous system. The connective tissue and vasculature of

peripheral nerves have several unique features, including the perineurial and blood-nerve barriers, and play a major role in PNS disorders. Lymphatic vessels are present in the epineurium but not within the fascicles. Salient components of a peripheral nerve are diagrammed in Figures 1–1 to 1–3.

RELATIONSHIPS FUNDAMENTAL TO AN UNDERSTANDING OF DISEASE OF PERIPHERAL NERVE FIBERS

Neuron Cell Body and Axon

The axons of peripheral nerves, despite their occasional great length, are simply cytoplasmic extensions of the nerve cell bodies. The volume of cytoplasm in a long myelinated axon is actually far greater (about 1000:1) than that of the neuron cell body region (perikaryon). The PNS axons derive most of the proteins essential for maintenance and function from ribosomes in the nerve cell body.

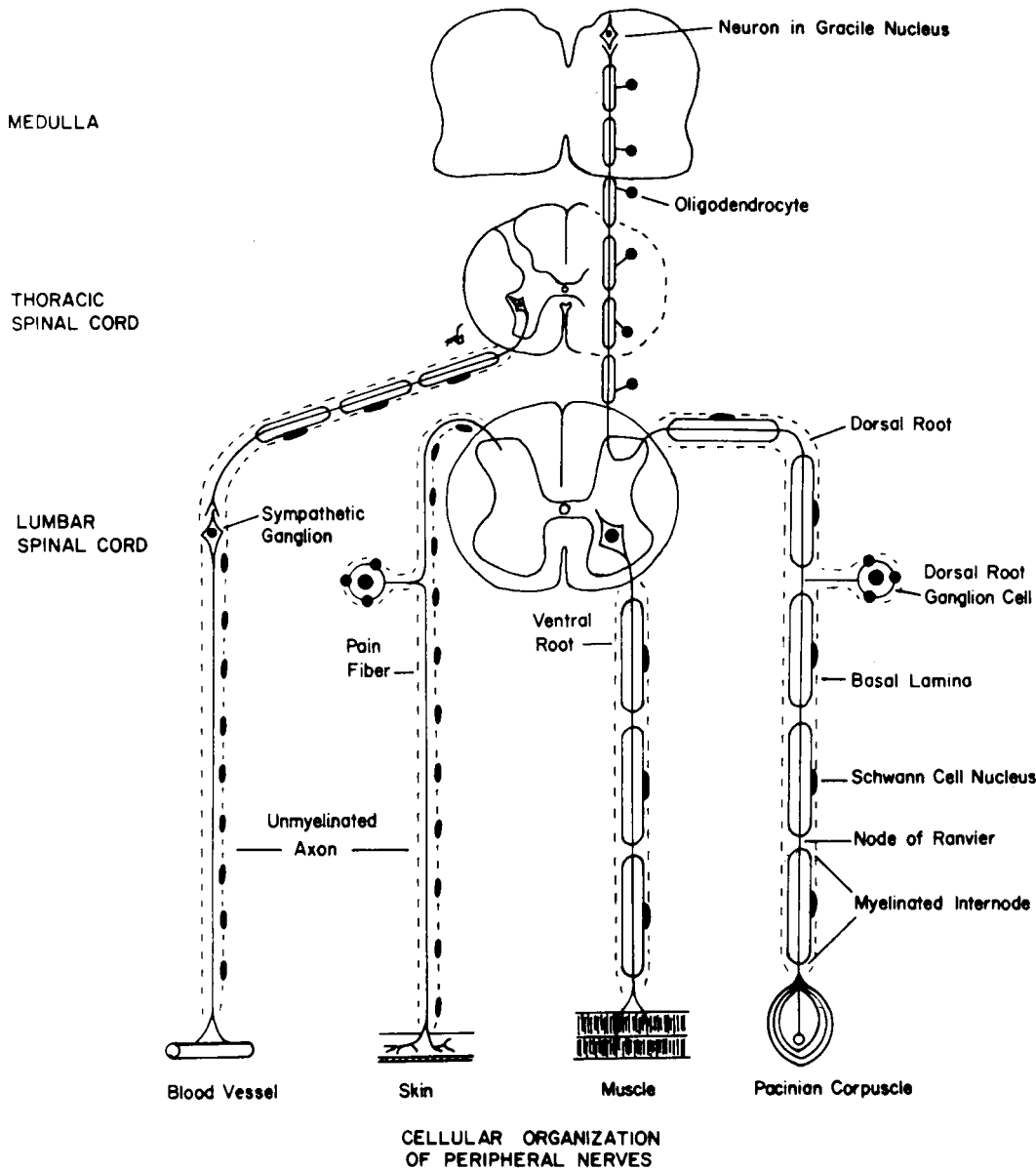


Figure 1-1. The principal components of the PNS.

Figure 1-3 illustrates prominent cytoskeletal-structural elements (neurotubules and intermediate neurofilaments), which are synthesized by free polyribosomes, aligned, slowly transported down the axon at a rate of 0.2–3 mm per day, and disassembled at the terminal. Slow transport is mostly anterograde; there is some retrograde transport of neurofilament protein. Intermediate neurofilaments convey structural

conformity to the axon: they occupy and appear to organize considerable axonal space. Changes in the number of neurofilaments directly influence axonal caliber and local accumulations cause axonal swelling (e.g., hexane and carbon disulfide neuropathies), while depletion results in atrophy (e.g., Charcot-Marie-Tooth and uremic neuropathies). Neurotubules, although themselves slowly transported, are directly responsible

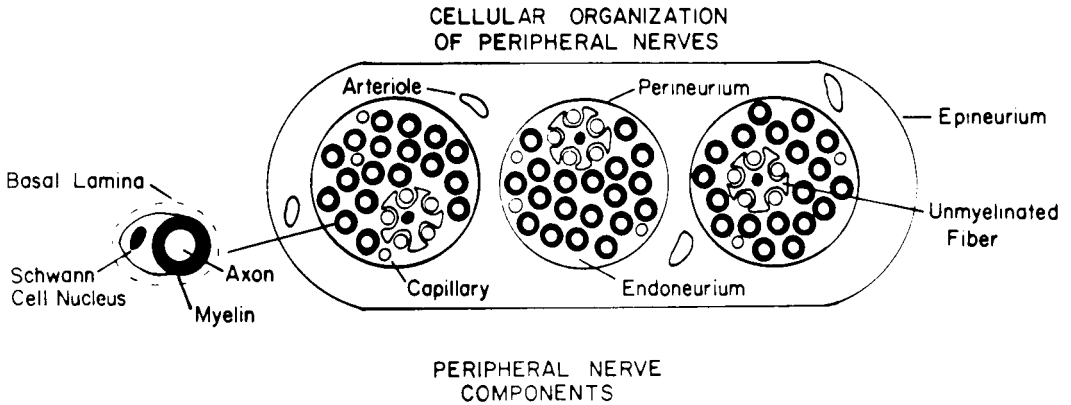


Figure 1-2. Diagram of a peripheral nerve in cross section. The nerve contains three fascicles. The figure on the left represents a high magnification of a myelinated axon in cross section.

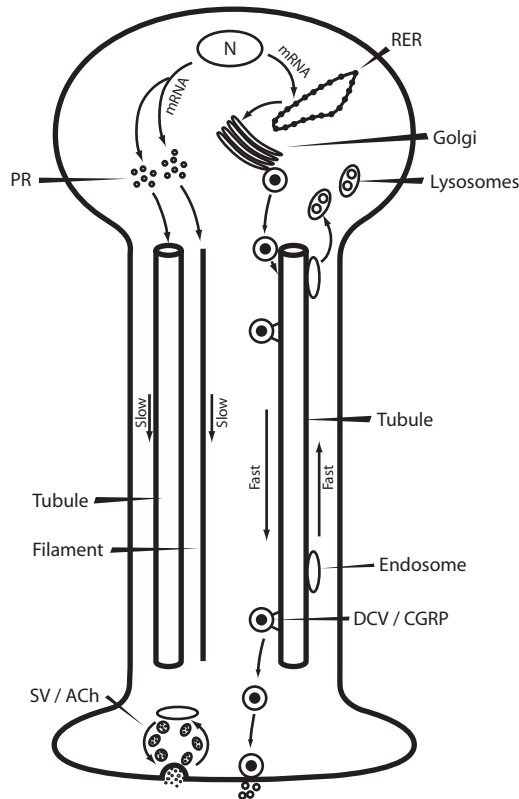


Figure 1-3. Schematic diagram of the anterior horn cell and axon illustrating salient features of the functional anatomy. Structures depicted on the left, neurofilaments and neurotubules, are assembled by free polyribosomes (PR) and slowly transported and disassembled at the axon terminal. Structures on the right are assembled by the rough endoplasmic reticulum (RER) and the Golgi apparatus, then rapidly transported to the terminal for use, recycling, and subsequent retrograde transport. ACh: acetylcholine; CGRP: calcitonin gene related peptide; DCV: dense core vesicles; mRNA: messenger ribonucleic acid; SV: synaptic vesicle.

for maintenance of bidirectional *fast* transport (Fig. 1–3). Alterations in neurotubules by agents that depolymerize tubulin (vinca alkaloids) or increase assembly (taxanes) disrupt rapid transport.

Small vesicles and particulate organelles, containing proteins essential for membrane maintenance and transmitter function, are synthesized by ribosomes of the rough endoplasmic reticulum and glycosylated by the Golgi apparatus (Fig. 1–3). They are packaged into vesicles and transported anterogradely rapidly along neurotubules at a rate of 400 mm per day. The propulsive protein, kinesin, depicted in Figure 1–3 as small feet on vesicles, mediates anterograde vesicular transport. There is also retrograde rapid transport along neurotubules, at a rate of about 200 mm per day, of lysosomes and multivesicular bodies. Retrograde transport returns, for lysosome processing, much of the recycled membrane previously delivered in an anterograde fashion, and conveys nonneural material (e.g., nerve growth factor, herpes simplex virus, tetanus toxin) from the periphery to the cell body. Some of the toxins described in Chapters 16 and 17 cause distal axonopathy by affecting bidirectional rapid transport.

In general, injury to the distal portion of the axon does not result in permanent damage to the nerve cell body; the latter undergoes transient swelling and breakdown of endoplasmic reticulum (chromatolysis), but usually survives and supports regeneration of the damaged axon (Fig. 2–1, Chapter 2). The converse is not true; severe damage to the nerve cell body (Fig. 2–6, Chapter 2) or disruption of proximal axonal integrity results in rapid degeneration of the entire distal portion (see later discussion of Wallerian degeneration).

Axon, Schwann Cell, and Myelin

Schwann cells envelop axons to form unmyelinated and myelinated fibers surrounded by a basal lamina. The PNS myelin is derived from the Schwann cell and is dependent both on the Schwann cell itself and on the axon for its continued integrity. A single Schwann cell occupies each myelinated internode and almost never associates itself with more than one axon. Death of the axon results in the prompt breakdown of myelin but not of the Schwann cell (Fig. 2–1, Chapter 2). The opposite is not true; acute

loss of myelin does not usually result in disruption of the axon. This principle is of fundamental importance to an understanding of PNS disorders. An axon denuded of several segments of myelin simply awaits Schwann cell division and remyelination before resuming normal impulse conduction (Fig. 2–3, Chapter 2). In contrast, long-standing or recurrent demyelination may, through faulty Schwann cell–axon interactions, cause axonal atrophy, impair axonal transport, or eventuate in axonal loss.

Axon and End Organ

The effect of axonal transection on muscle is dramatic. Within weeks or months, the muscle undergoes progressive denervation atrophy and will not recover unless reinnervated. The loss of the normal *trophic* effect of nerve on muscle is widely accepted.

Less certain are the other alleged trophic functions of nerve for skin, blood vessels, and subcutaneous tissue. Prolonged denervation results in changes in these tissues (red skin, ulcers) sometimes attributed to loss of maintenance function provided by the nerve fiber. Such changes may also represent the effects of trauma and autonomic dysfunction on these tissues.

Wallerian Degeneration and Axon Regeneration

The morphologic events following a focal crush injury to peripheral nerve are depicted in Figure 2–10 in Chapter 2. Transection of a nerve fiber results in total degeneration of the axon(s) and myelin distal to the site of injury (Wallerian degeneration). Within 4 days, the entire distal axon and myelin become fragmented; electrical conduction declines rapidly after day 3 and ceases by day 9 to 11. The nerve cell body undergoes a chromatolytic reaction; subsequently, regenerating axonal sprouts emerge from the injured axons at the site of injury. After 1 week, the distal Schwann cells have divided and are arranged in columns inside their tubes of basal lamina. If regenerating axons reach one of these Schwann cell columns, they can regenerate steadily toward the terminal and be myelinated by the waiting Schwann cells. Injuries that do not disrupt

connective tissue continuity of a nerve (closed injuries) often have a good prognosis, since regenerating axons usually arrive at their former peripheral terminations, guided by the preexisting Schwann cell columns. Injuries that transect fascicles or the entire nerve are frequently associated with ineffective or aberrant regeneration. Many sprouting axons may never reach the distal stump, but grow in an aberrant fashion (Fig. 2–11, Chapter 2) or a random tangled fashion (traumatic neuroma).

GLOSSARY OF COMMON CLINICAL TERMS

Axonal neuropathy (axonopathy): Any PNS condition characterized by the initial appearance of histopathologic changes in the axon, followed by myelin degeneration and muscle denervation. Commonly, this process begins at the ends of long, large-diameter fibers (distal axonopathy).

Channelopathies: A group of disorders involving dysfunctional axonal membrane ion channels resulting in hypofunction or hyperexcitability.

Demyelinating neuropathy (myelinopathy): Any PNS condition characterized by the initial appearance of histopathologic changes in myelin or the Schwann cell followed by demyelination of several or multiple internodal segments and slowed (or blocked) nerve conduction.

Electrodiagnostic studies (EDS): Include electromyography (EMG) and nerve conduction studies (NCS).

Entrapment neuropathy: A compression neuropathy at anatomic entrapment sites (e.g., carpal tunnel syndrome).

Focal and multifocal neuropathy: Indicates involvement of one or more individual peripheral nerves. It is equivalent to the more cumbersome terms *mononeuropathy* and *multiple mononeuropathies* (*mononeuropathy multiplex*).

Large-fiber neuropathy: Peripheral nervous system disorders characterized by loss of position, vibration, and touch-pressure sensitivity, tendon areflexia, and lower motor neuron involvement. Sensory ataxia and pseudoathetosis may be prominent if muscle power is preserved.

Negative symptoms: Complaints of loss of function or sensibility (e.g., weakness and numbness).

Neuronopathy (ganglionopathy): Any PNS condition in which the initial histopathologic changes are manifest in the cell body region (perikaryon, cyton). Neuropathologies may be either sensory (e.g., herpes zoster), in which case they are called a *ganglionopathy*, or motor (e.g., poliomyelitis).

Neuropathic pain: Pain stemming from intrinsic disease or injury to the nervous system (e.g., diabetic neuropathy).

Neuropathy (peripheral neuropathy): A nerve disorder. A broad term including any disorder—infective, toxic, metabolic, and so on—affecting peripheral nerves. It replaces the older term *peripheral neuritis*.

Nociceptive pain: Pain stemming from stimulation of peripheral nociceptive transducers (e.g., laceration or burn).

Plexopathy (plexitis): A term designating disease confined to either the lumbar or brachial plexus.

Polyneuropathy: A generalized process producing widespread and bilaterally symmetrical effects on the PNS. It may be motor, sensory, sensorimotor, or autonomic in its effects.

Positive symptoms: Complaints of abnormal spontaneous sensations or movement (e.g., tingling or fasciculations).

Quantitative sensory testing (QST): The use of biomedical devices that accurately measure thermal or vibratory-touch senses in the distal limbs.

Radiculopathy: Disease confined to one (mono) or more (poly) spinal roots.

Sensory phenomena:

Allodynia – pain to a nonnoxious stimulus

Analgesia – absence of pain to a painful stimulus

Anesthesia – absence of all sensory modalities

Dysesthesia – unpleasant or unusual sensation, either spontaneous or evoked

Hypalgesia – diminished sensitivity to a painful stimulus

Hyperalgesia – increased response to a painful stimulus

Hyperesthesia – increased sensitivity to stimulation

Hyperpathia – exaggerated response to a painful stimulus, especially a repetitive stimulus

Hypesthesia (hypoesthesia) – diminished sensitivity to a nonnoxious stimulus (numbness)

Neuralgia – pain in the distribution of a nerve or nerves

Paresthesia – abnormal sensation (e.g., tingling, buzzing), spontaneous or evoked, not as unpleasant as in dysesthesia

Small-fiber neuropathies: Conditions in which there is prominent disturbance of small myelinated and unmyelinated fibers characterized

by diminished pain and temperature sensation, often with spontaneous pain and autonomic involvement. There is relative preservation of strength, tendon reflexes, and sensory modalities subserved by the larger myelinated fibers (touch-pressure, vibration, joint position). The results of conventional nerve conduction studies may be normal if dysfunction is limited to small fibers.

Anatomic Classification of Peripheral Nervous System Disorders

SYMMETRIC GENERALIZED NEUROPATHIES (POLYNEUROPATHIES)

Distal Axonal Degeneration
Segmental (Nonuniform) Myelinopathy
Diffuse (Uniform) Myelinopathy
Neuronopathy (Ganglionopathy)

FOCAL (MONONEUROPATHY) AND MULTIFOCAL (MULTIPLE MONONEUROPATHY) NEUROPATHIES

Ischemia
Infiltration
Physical Injuries

The authors endorse an anatomic classification of disorders of the peripheral nervous system (PNS) based on whether the condition is characterized by generalized symmetrical or focal/multifocal involvement. This simple classification stresses the site of apparent primary pathologic change and does not suggest the pathophysiologic mechanism. For example, although demyelination is a feature of uremic neuropathy, it is clearly secondary to changes in the axon, and uremic neuropathy is considered an axonopathy. This classification generally lends itself to clinical-pathologic and electrodiagnostic correlation; it is especially useful when initially evaluating a patient with a peripheral nerve disorder. Exceptions occur: vasculitic and demyelinating neuropathies may eventuate in distal symmetric patterns of dysfunction, and toxic axonopathies and neuronopathies may vary in pattern and tempo, depending on the dose of medication and the rate of administration.^{1,2}

SYMMETRIC GENERALIZED NEUROPATHIES (POLYNEUROPATHIES)

Distal Axonal Degeneration

This is the most common morphologic reaction of the PNS and central nervous system (CNS) to exogenous toxins; it probably also underlies many metabolic and hereditary neuropathies. The biochemical mechanisms and pathophysiology of most axonopathies are poorly understood. Most human axonopathies are distal, but proximal axonopathies may be encountered, for example, in porphyric neuropathy.

HYPOTHETICAL MECHANISMS

In distal axonopathy, a metabolic abnormality initially occurs in the cell body and/or throughout the axon. The traditional view of distal axonal degeneration was that failure of metabolic support from the targeted cell body

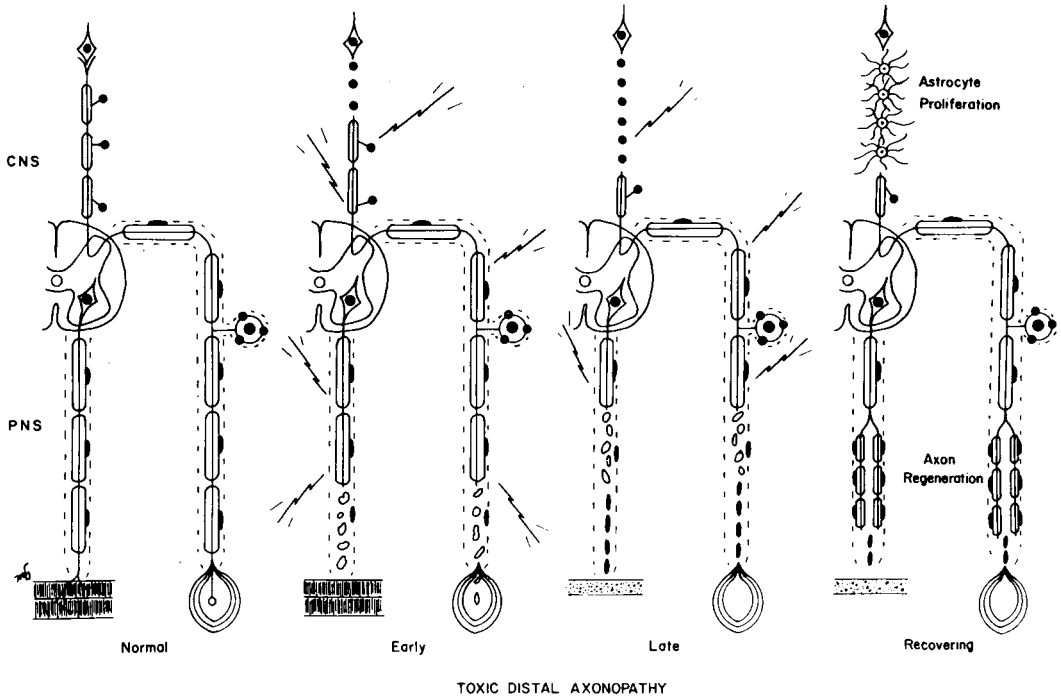


Figure 2-1. Diagram of the cardinal pathologic features of a toxic distal axonopathy. The jagged lines (lightning bolts) indicate that the toxin is acting at multiple sites along motor and sensory axons in the PNS and CNS. Axon degeneration has moved proximally (dying-back) by the late stage. Recovery in the CNS is impeded by astroglial proliferation.

caused a failure of nutritional support of the ribosome-poor axon; degeneration began at the ends of the axon in a manner analogous to that of a far-parched meadow that is no longer supplied with water by a failing pump.³ Recent studies suggest that the opposite is true; the axon, much larger in cytoplasmic volume than the cell body, is the aim. Specifically, the target is the retrograde transport of growth factors from the periphery essential for the survival of the neuron cell body and its ability to maintain anterograde transport.^{4,5} Eventual failure of axon transport results in degeneration of vulnerable distal regions of axons. Long and large-diameter fibers are usually first affected, although the reason is unclear. Degeneration appears to advance proximally toward the nerve cell body (dying-back) as long as the metabolic abnormality persists; its reversal allows the axon to regenerate along the distal Schwann cell tube to the appropriate terminal. An identical sequence usually occurs simultaneously in the distal ends of long CNS axons (e.g., dorsal columns, corticospinal and optic

tracts), although regeneration is less effective. Two important determinants are distance from the cell body and fiber diameter.

CARDINAL PATHOLOGIC FEATURES (FIG. 2-1)

1. Initial distal axonal changes may be generalized or multifocal; the nature of the change may be characteristic of the disorder. Atrophy (dwindling) and focal swelling are especially common.
2. Eventual axonal disintegration resembles Wallerian degeneration; the myelin sheath breaks down concomitantly with the axon. Secondary demyelination and remyelination may occur where the axon is still intact. This frequently accompanies axonal atrophy.
3. Distal muscles undergo denervation atrophy.
4. Nerve cell chromatolysis may occur in severe cases.

5. Schwann cell basal lamina tubes remain in distal nerves and facilitate appropriate peripheral regeneration.
6. Astroglial proliferation triggered by distal axonal degeneration may impede regeneration in the CNS.

CLINICOPATHOLOGIC CORRELATIONS

1. Gradual, insidious onset: chronic metabolic disease or prolonged, low-level intoxication usually produce prolonged subclinical disease, with signs and symptoms gradually appearing later. Biochemical and physiologic axonal abnormalities precede fiber degeneration in some subclinical cases and likely account for their rapid recovery. High-level intoxications are associated with subacute onset, and agents (e.g., Vacor) that disrupt fast axoplasmic transport are associated with acute onset.
2. Initial findings frequently in the lower extremities: large and long axons are usually affected early; thus, the fibers of sciatic nerve branches are especially vulnerable.
3. Stocking-glove sensory and motor loss: axonal degeneration commences distally and proceeds slowly toward the neuron cell body, resulting in symmetric, distal clinical signs in the legs and arms. The earliest symptoms are usually sensory; toe-tip sensations of tingling or numbness are common initial complaints. The pattern of sensory loss is depicted in Figure 2-2.
4. Early and symmetric loss of ankle jerks: the axons supplying the calf muscles are of extremely large diameter and are among the first affected in experimental acrylamide and hexacarbon neuropathies.
5. Normal to mildly slowed motor nerve conduction: in contrast to the demyelinating neuropathies, where the motor nerves or roots are diffusely affected. Since some motor fibers remain intact in the axonal neuropathies, motor nerve conduction velocity may remain normal or only slightly slowed despite clinical signs of neuropathy. Sensory amplitudes are frequently diminished with only mild slowing. Exception: severe impulse slowing may accompany distal

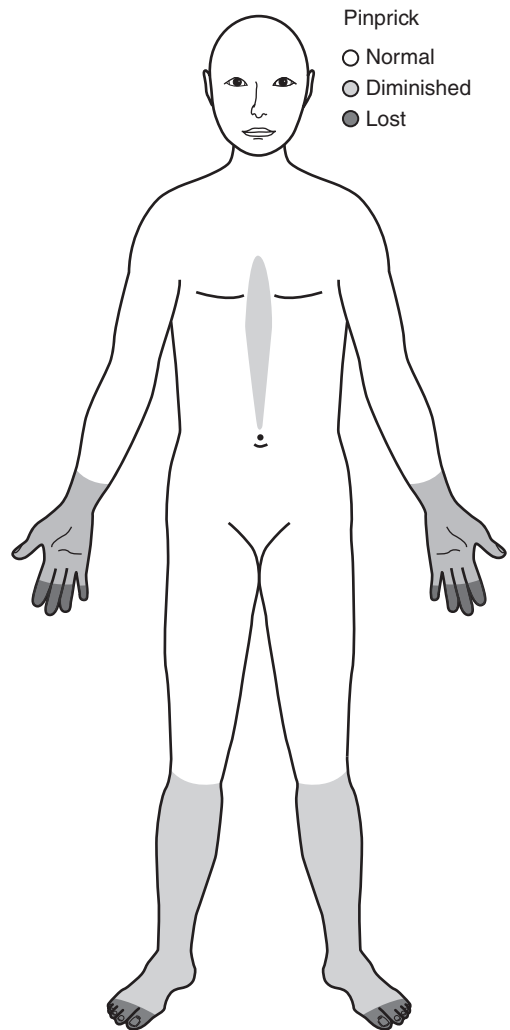


Figure 2-2. Stocking-glove pattern of sensory loss in an advanced stage of distal axonopathy. The area of diminished sensation over the midthorax (*cuirass distribution*) reflects involvement of distal ends of intercostal nerves.

axonopathies in which the axon swells and demyelinate focally.

6. Normal cerebrospinal fluid (CSF) protein level: since the pathologic changes are usually distal and the nerve roots are spared, most patients with axonal neuropathies have a normal or only slightly elevated CSF protein value.
7. Slow recovery: since axonal regeneration (in contrast to remyelination) is a very slow process, proceeding at a rate of 1 to

5 mm/day, recovery may take many months or several years or may never completely occur. Function is restored in reverse order to the sequence of loss.

8. Coasting: following withdrawal from toxic exposure, symptoms and signs may intensify for weeks before recovery commences. This does not imply a persistent body burden of toxin but likely reflects continued axonal degeneration and reconstitution.
9. Signs of CNS disease: these have been encountered in individuals recovering from certain toxic neuropathies. Most toxic central-peripheral distal axonopathies are characterized by tract degeneration of the distal extremities of long, large-diameter fibers in the CNS *pari passu* with changes in the PNS. Thus, the clinical signs of degeneration in the corticospinal and spinocerebellar pathways are usually not prominent features early in the illness. However, on recovery from neuropathy, the patient may manifest hyperreflexia, extensor plantar responses, and a stiff-legged, ataxic gait.

Segmental (Nonuniform) Myelinopathy

The term *segmental myelinopathy*, when applied to the PNS, refers to conditions in which the lesion primarily affects internodal segments of myelin or the myelinating (Schwann) cell. Thus, the moderate segmental demyelination that accompanies some axonal disorders is not evidence of a primary myelinopathy. Stated another way, demyelination is not always synonymous with primary myelinopathy. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP), an immune-mediated disorder, is the only frequently encountered disease that primarily affects PNS myelin (see Chapter 6) in a segmental manner.

HYPOTHETICAL MECHANISMS

It is generally held that the segmental demyelination of spinal roots and nerves in AIDP results from an immune-mediated attack on PNS myelin.⁶ The precipitating event or

antigen is not known for all cases, but about 70% are preceded by an infectious illness.⁷ The reported segmental demyelination of diphtheritic neuropathy results from toxic inhibition of Schwann cell synthesis of myelin constituents.⁸ By contrast, AIDP appears to be a primary attack on the Schwann cell surface membrane and myelin.⁶

CARDINAL PATHOLOGIC FEATURES (FIG. 2–3)

1. Primary destruction of the myelin sheath occurs, usually leaving the axon intact.
2. The initial attack on myelin is mediated by inflammatory cells.
3. Destruction often begins at the nodes of Ranvier.
4. Spinal roots are usually heavily involved, but destruction also affects multiple sites in the nerve.
5. The Schwann cell divides and remyelinate the axon to form short internodes of thin myelin.
6. Muscle often does not undergo denervation change, but it may undergo disuse atrophy if paralysis is prolonged. Axonal loss may occur in chronic primary demyelinating disorders and is occasionally profound. The explanation for this is unclear. It may reflect effects of the nearby inflammatory cells and mediators or impaired critical Schwann cell–axon interactions.

CLINICOPATHOLOGIC CORRELATIONS

1. Onset: in toxic and inflammatory myelinopathies, the process of segmental demyelination occurs over a period of hours, days, or weeks.
2. Initial changes may occur in the lower extremities, but not always distally. The diffuse process may occasionally become manifest in the short cranial nerves, but more commonly, the nerves to the lower extremities are initially involved. Presumably this occurs because the myelinated axons of the sciatic nerve are longest, contain the most myelin, and are statistically most likely to be involved in a random demyelinating process.

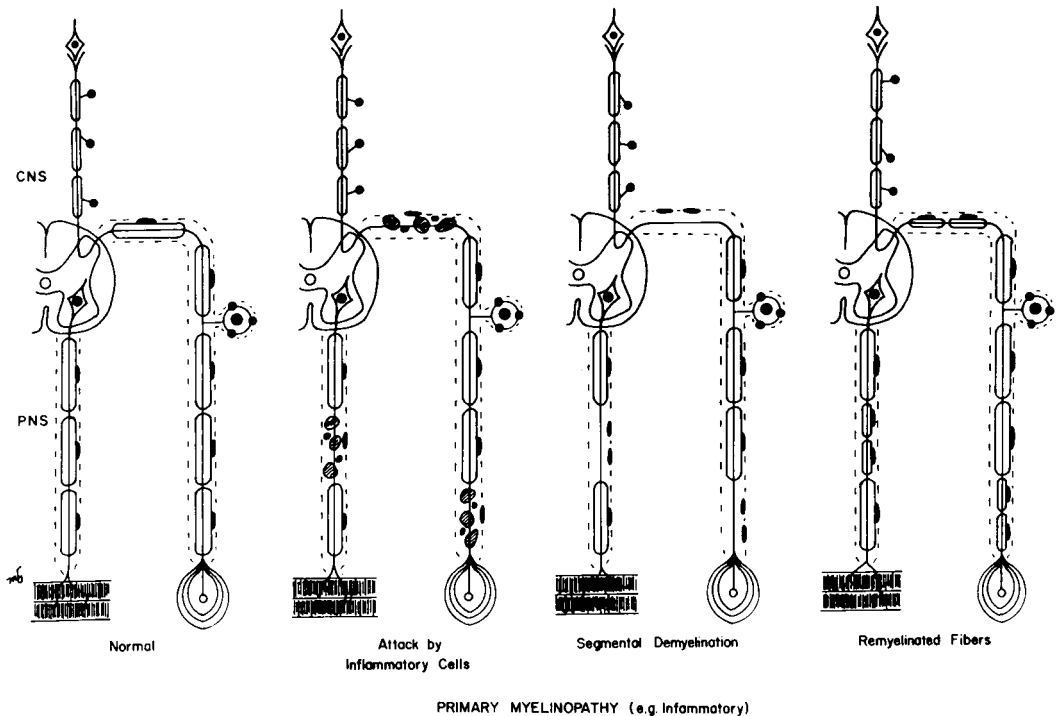


Figure 2-3. Diagram of the cardinal pathologic features of an inflammatory segmental (nonuniform) PNS myelinopathy. Axons are depicted as spared (although they are often involved to varying degrees); CNS myelin is not affected. Following the attack, the remaining Schwann cells divide. The denuded segments of axons are remyelinated, leaving them with shortened internodes.

3. Generalized weakness with mild sensory loss: the large-diameter, heavily myelinated motor axons and ventral roots are involved, resulting in diffuse symmetric weakness or paralysis of the extremities and bulbar muscles. Relative sensory sparing may reflect in part the continued function of small-diameter myelinated and unmyelinated fibers. Sensory ataxia may occur from involvement of proprioceptive afferent fibers. The patterns of sensory and motor loss are illustrated in Figure 2-4.
4. Absent tendon reflexes in all extremities: both the afferent and efferent limbs of the monosynaptic stretch reflex are mediated by large-diameter myelinated fibers, which are especially vulnerable in the toxic and inflammatory myelinopathies. Generalized areflexia is a characteristic of these conditions.
5. Marked slowing of nerve conduction: the widespread demyelination prolongs conduction and may also give rise to conduction block. Conduction velocity in remyelinated fibers with thin myelin sheaths is reduced.
6. Elevated CSF protein: inflammatory and toxic demyelination heavily involves the spinal roots, with leakage of protein into the surrounding subarachnoid space.
7. Rapid recovery: recovery is dependent on remyelination to restore impulse conduction. Effective remyelination of an internode may take only a few weeks, and clinical recovery may be dramatic. Especially rapid recovery from weakness may reflect reversal of the conduction block that stemmed from sodium channel dysfunction.
8. No signs of CNS disease: most toxic and inflammatory PNS myelinopathies spare the CNS for various reasons. One is that many myelinotoxic agents are unable to cross the blood-brain barrier; another is that many inflammatory conditions are immune-mediated, and the response is directed at antigens present in peripheral myelin.

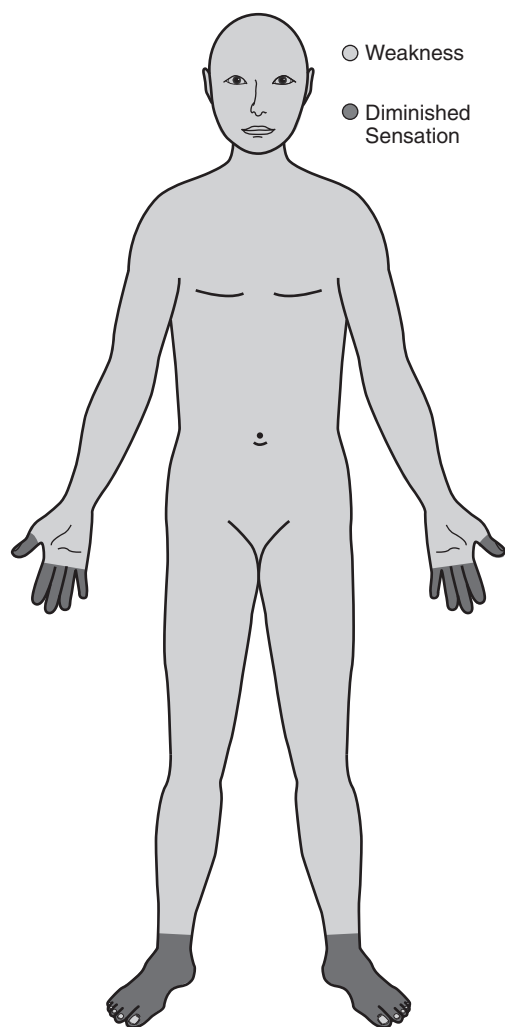


Figure 2-4. Pattern of motor and sensory loss in a severe case of acute inflammatory demyelinating polyneuropathy. There is diffuse weakness of limb, intercostal, and facial muscles. Sensory impairment is usually mild and involves only the distal portions of the limbs.

Diffuse (Uniform) Myelinopathy

The term *diffuse myelinopathy*, when applied to the PNS, refers to conditions in which all Schwann cells display a metabolic dysfunction. The metabolic disorder occurs uniformly throughout the PNS, in sharp contrast to the scattered demyelination of the dysimmune segmental myelinopathies. Among the hereditary motor and sensory neuropathies, some of the Charcot-Marie-Tooth (CMT) family of

disorders (CMT1, CMTX), are the only frequently encountered conditions characterized by diffuse myelin dysfunction.⁹ Some of the rare hereditary disorders of lipid metabolism (e.g., leukodystrophies) are also classified as diffuse myelinopathies.

HYPOTHETICAL MECHANISMS

It is now believed that the diffuse PNS demyelination in the CMT1 subgroup stems from a hereditary, insidiously progressive degeneration of the myelin sheath (the cytoplasm of Schwann cells). The linkage between the metabolic instability of the Schwann cell and the pathophysiologic events of demyelination is unclear. A paradox in these disorders of myelin is the eventually disabling, age-related, progressive distal axonal degeneration. The chronic, profound demyelination of the type found in CMT1 alters the phenotype of the underlying axon, with reduction in diameter and alteration of transport.¹⁰ Another factor in axonal degeneration may be loss of myelin-associated glycoprotein (MAG).¹¹

CARDINAL PATHOLOGIC FEATURES

The sequence of morphologic change in CMT1 myelinated nerve fibers is unknown. It presumably commences with reasonably structurally intact sheaths and axons and eventuates in fiber loss, onion bulbs, and profound distal axonal atrophy and distal axonal degeneration. Animal models of CMT1 are in development. There are no human postmortem studies of the entire PNS that have utilized contemporary histopathologic techniques. Figure 2-5 is a hypothetical depiction of a cascade of myelin degeneration, attempted remyelination, axonal atrophy, and eventual fiber loss.

1. A normal-appearing myelinated axon gradually loses its sheath as myelin degenerates and debris accumulates in the Schwann cell cytoplasm (1, 2).
2. The original Schwann cells divide and are moved aside as their daughter cells encase the atrophying axon; the processes of the original cell wrap around the remyelinated axon (3).
3. Another cycle of myelin sheath loss gradually occurs (4). Eventually, another cycle of Schwann cell division results in

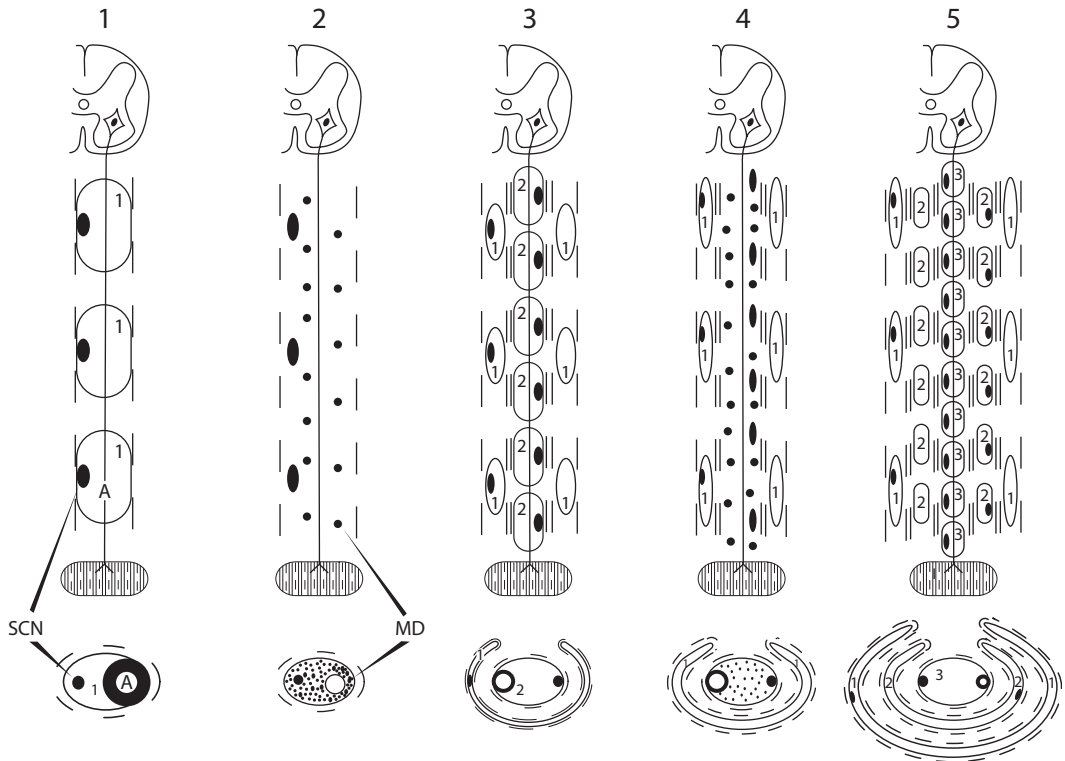


Figure 2-5. Diagram of the cardinal features of a diffuse, CMT-type myelinopathy. The top figures show a longitudinal view of a myelinated axon, the bottom figures a cross section. In (1), there is a normal-appearing myelinated axon (A) with Schwann cell nuclei (SCN). In (2), the axon loses its myelin sheath and myelin debris (MD) accumulates in the Schwann cell cytoplasm. In (3), the processes of the daughter cells wrap around the atrophying axon. In (4) and (5), there are more cycles of myelin degeneration; the multiple layers of Schwann cell processes result in an onion bulb (cross section) formation, and axonal atrophy increases.

a second layer of processes encircling the remyelinated, atrophied axon (5).

4. At distal sites, in time, more cycles of myelin degeneration are accompanied by axonal loss and muscle atrophy. The many layers of Schwann cell processes that have accumulated by this late stage constitute the onion bulb formations characteristic of CMT1. Endoneurial fibrosis may be profound at this stage.
5. It is held that some Schwann cells undergo apoptotic death and that some remyelinated axons represent an attempt at axonal regeneration by a dysfunctional neuron.
6. While myelin degeneration and onion bulb formation appear to occur at proximal as well as distal levels of the PNS, the degree of proximal axonal loss is unclear. The selective atrophy of

distal muscles suggests proximal sparing of axons.

CLINICOPATHOLOGIC CORRELATIONS

1. Onset: in CMT1, the onset is gradual and the process steadily evolves over many years; recovery or improvement does not occur.
2. Initial changes are motor and commence in the distal lower limbs; weakness and atrophy of foot muscles may cause local deformities (pes cavus). Weakness is held to reflect primarily fiber loss.
3. Weakness usually remains distal in the upper and lower limbs; even after several years, atrophy and severe weakness are largely confined to foot, calf, and hand

muscles. Sensory symptoms are modest; numbness is common; positive symptoms (paresthesias, pain, ataxia) are less common.

4. Marked uniform slowing of nerve conduction and widespread loss of deep tendon reflexes reflect the widespread myelin degenerative changes and ineffectual remyelination in CMT1.
5. Evidence of asymptomatic nerve disease in vulnerable relatives is common (high arches, slowed motor conduction); this reflects variable expressivities that may cause phenotypes with mild disease.
6. Palpable peripheral nerves stem from enlargement due to extensive endoneurial fibrosis and, possibly, onion bulb formation.
7. Usually there are no signs of CNS disease. CMT1 is a disorder of Schwann cells with secondary dysfunction of peripheral axons; some of the hereditary neuropathies do have associated CNS features (e.g., CMTX).

Neuronopathy (Ganglionopathy)

The term *neuronopathy* describes conditions in which the initial morphologic changes likely occur in the neuron cell body. Clinical manifestations of PNS neuronopathies are restricted to the segments innervated by the affected cell bodies. They may be focal, involving one segment (e.g., herpes zoster); multifocal, involving multiple motor segments (e.g., poliomyelitis); or diffuse sensory (e.g., from massive doses of intravenous pyridoxine or cisplatin in humans and doxorubicin and methyl mercury in experimental animals).¹² The neuronopathies are a heterogeneous, poorly understood group of conditions and, in the broadest sense, include many disorders of motor, sensory, and autonomic neurons. They may commence prenatally or in infancy, adolescence, or adult life. Infectious neuronopathies include familial conditions such as poliomyelitis and herpes zoster ganglionitis. An idiopathic type of diffuse sensory neuronopathy may follow nonspecific infections. Some connective tissue diseases (e.g., Sjögren syndrome) are associated with a multifocal sensory neuronopathy syndrome. Motor and sensory neuronopathy syndromes occur as remote complications of carcinoma.

HYPOTHETICAL MECHANISMS

No single mechanism explains the pathophysiology of these heterogeneous conditions. Indeed, even when the pathologic changes are obvious, as in some of the infectious conditions, there is as yet no rationale for these events. Experimental studies of diffuse sensory neuronopathy involving megadoses of pyridoxine indicate that the pathogenesis and evolution of the changes are best understood as initial disruption of metabolism of sensory nerve cells followed rapidly by degeneration throughout the length of their processes.¹³ Cisplatin experimental neuronopathy likely reflects apoptotic degeneration of ganglion cells.¹⁴ The dorsal root and gasserian ganglion neurons are believed to be particularly vulnerable to some circulating toxins because of the special permeability of their blood vessels.

CARDINAL PATHOLOGIC FEATURES (EXPERIMENTAL PYRIDOXINE DIFFUSE SENSORY NEURONOPATHY) (FIG. 2–6)

1. Circulating pyridoxine leaks through the normally fenestrated blood vessels in dorsal root sensory and autonomic ganglia.
2. Pathologic changes appear in the neuronal perikaryon, soon followed by degeneration throughout the length of the axon.
3. Motor cells are not affected, and muscle undergoes no change.
4. Regeneration cannot occur, and sensory loss is therefore permanent.

CLINICOPATHOLOGIC CORRELATIONS (ACUTE MEGADOSE PYRIDOXINE-INDUCED SYNDROME)

1. Rapid or subacute onset follows massive intravenous administration.
2. Initial sensory loss may occur anywhere: characteristic of this disorder is the early appearance of numbness of the face coincident with diffuse sensory loss in the limbs. Presumably this occurs because gasserian ganglion neurons are affected simultaneously with dorsal root ganglion neurons.
3. Diffuse sensory loss and ataxia with preservation of strength: the loss of

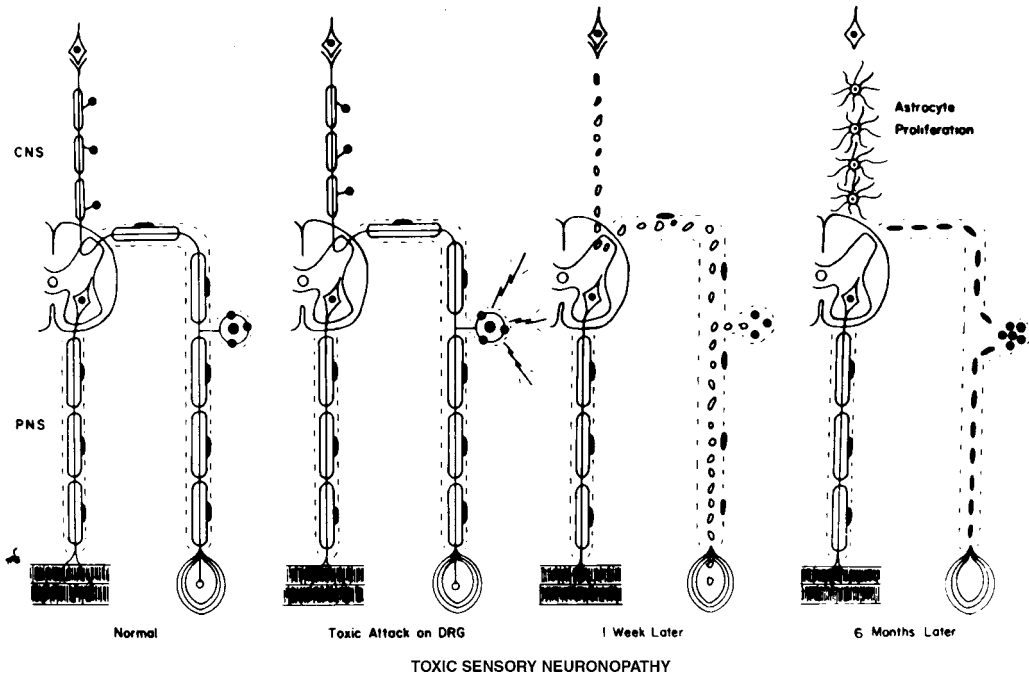


Figure 2-6. Diagram of the cardinal features of a rapidly evolving toxic sensory neuropathy. The jagged lines (lightning bolts) indicate that the toxin is directed at neurons in the dorsal root ganglion (DRG). Degeneration of these cells is accompanied by fragmentation and phagocytosis of their peripheral-central processes. The Schwann cells remain; there is no axonal regeneration.

sensation, sensory ataxia, and dysesthesia reflect the disappearance of sensory neurons. In most subacute sensory neuropathies, large-fiber modalities are heavily affected, so that the proprioceptive deficit is greater than pain or thermal sense loss. Sparing of anterior horn cells accounts for preservation of strength. The pattern of sensory loss is depicted in Figure 2-7.

4. Absent tendon reflexes: one of the characteristics of this condition that reflects the large-fiber sensory loss.
5. Normal motor nerve conduction, abnormal or absent sensory conduction: this mirrors the pattern of selective nerve cell loss.
6. Variable recovery: this reflects the death of the nerve cell body and consequent permanent loss of axons. Some cells may be only slightly impaired and transiently function poorly but are able to reconstitute themselves without losing their axons. The phenomenon of collateral sprouting from surviving axons may account for the variable recovery that occurs.

7. No signs of CNS disease: the pure PNS sensory neuropathy syndrome is not accompanied by CNS degeneration aside from fiber loss in the central projections of the sensory neurons (dorsal columns). However, some sensory neuropathy syndromes (e.g., carcinomatous sensory neuropathy, human immunodeficiency virus) accompany pathologic processes that involve the CNS as well.

FOCAL (MONONEUROPATHY) AND MULTIFOCAL (MULTIPLE MONONEUROPATHY) NEUROPATHIES

Ischemia

The PNS, unlike the CNS, is uncommonly affected by large-vessel disorders. The principle reason for this resistance is the richly collateralized blood supply of peripheral nerve. In general, ischemia of peripheral

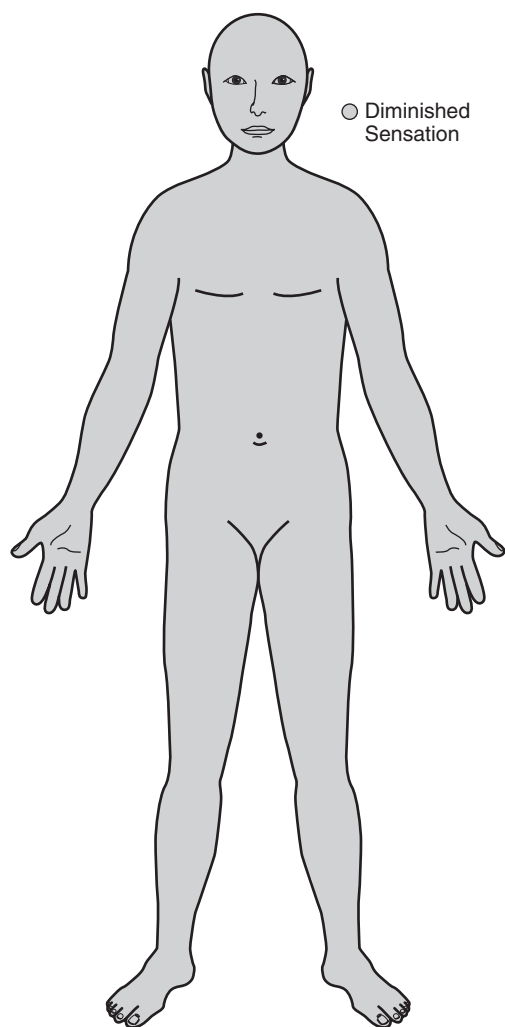


Figure 2-7. Pattern of sensory loss in an advanced stage of the diffuse sensory neuropathy syndrome. Sensation, particularly large-fiber function, is diminished, often markedly, throughout. This distribution reflects widespread destruction of sensory ganglion neurons.

nerve is synonymous with widespread small and medium-sized arteries or arteriolar disease and is most frequently associated with the necrotizing, immune-mediated vasculitides and diabetes mellitus.¹⁵

PATHOGENETIC HYPOTHESIS

There is considerable controversy surrounding the nature and mechanism of vascular injury to peripheral nerve. It is generally held that in the immune-mediated vasculitides, the nerve fiber damage results from a focal attack on some

component of the wall of the blood vessel, with resultant ischemia.¹⁶

CARDINAL PATHOLOGIC FEATURES

1. Compromise of several small arteries at one level in a nerve produces ischemia to an entire segment of nerve (mononeuropathy). Occasionally, multiple levels of several nerves may be simultaneously affected, resulting in diffuse, patchy neuropathy (multiple mononeuropathy). The lesions may summate to produce bilaterally distal symmetric involvement mimicking a distal axonopathy.
2. Axonal degeneration occurs in many fibers, and Wallerian-like degeneration appears below the level of ischemia. Central fascicular degeneration is often pronounced.
3. Infarct necrosis is rare, and connective tissue elements usually are little disrupted.
4. Muscles undergo denervation atrophy.
5. Collateral circulation begins.
6. Regenerative potential is usually good (especially in diabetic mononeuropathies) because of intact connective tissue. The vasculitides may have a poor prognosis because of continuing arteriolar necrosis and involvement of other organs.

CLINICOPATHOLOGIC CORRELATIONS (POLYARTERITIS NODOSA)

1. Rapid onset is characteristic but not invariable, possibly reflecting occlusion of vessels. Pain frequently accompanies this neuropathy, often local and probably related to ischemia of the nervorum.
2. Initial findings are in the distribution of the ischemic nerves. The distribution of sensory loss in a typical case of multiple mononeuropathy is depicted in Figure 2-8.
3. Weakness is more striking than sensory loss: this may reflect the relative resistance of small myelinated and unmyelinated sensory axons to ischemia. Pain may persist for several weeks.
4. Reflex loss is in the distribution of affected nerves: this probably reflects

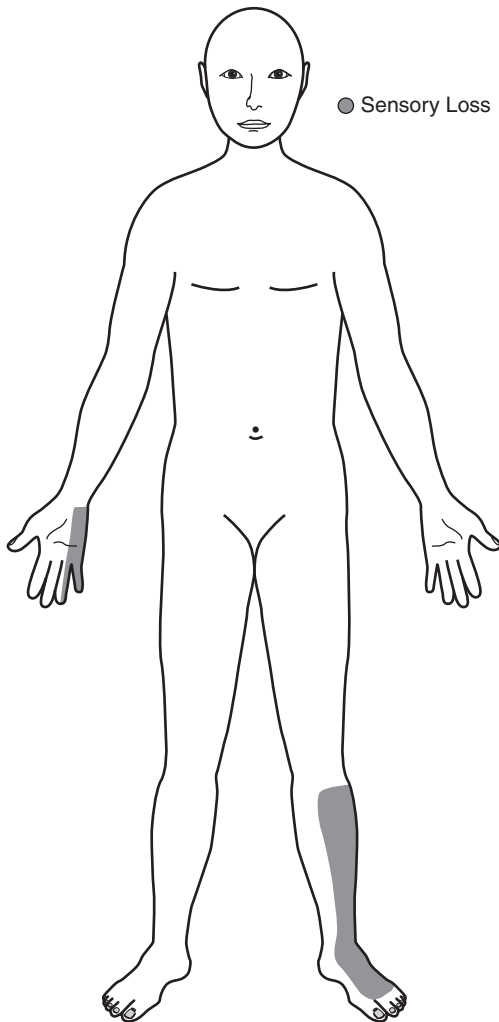


Figure 2-8. Illustration of the scattered distribution of sensory loss in ischemic multiple mononeuropathy, with involvement of contralateral ulnar and peroneal nerves.

the vulnerability of large-diameter myelinated fibers to ischemia.

5. Motor and sensory nerve potential amplitudes are diminished or abolished. Spontaneous activity, reflecting muscle denervation, may be prominent.
6. Cerebrospinal fluid protein is usually normal or mildly elevated; it is often elevated in diabetic patients and those with paraneoplastic neuropathy.
7. Gradual recovery: this reflects the slow rate of axonal regeneration and will vary inversely with the locus of the ischemia; that is, a more distal lesion will recover sooner.

Infiltration

This heterogeneous group of neuropathies includes conditions that disrupt the continuity of nerve fibers and connective tissue; eventually, they may totally destroy the internal architecture of a nerve. Leprosy, amyloidosis, sarcoidosis, leukemic and lymphomatous infiltrates, perineural xanthoma, and schwannoma are examples.

MECHANISM

Each condition produces secondary effects on nerve fibers. Most are subacute conditions and randomly destroy fibers. Some, especially the granulomas, give rise to an inflammatory response that, in concert with fibroblast proliferation, may totally disrupt axons and Schwann cell basal lamina tubes.¹⁷ Eventually, segments of nerve fascicles are converted into bundles of scar tissue through which regenerating fibers cannot pass.

CARDINAL PATHOLOGIC FEATURES (TUBERCULOID LEPROSY)

1. Granulomas form in distal branches of vulnerable cutaneous nerves.
2. Axons are disrupted and Schwann cell tubes are disorganized at the level of the granuloma; the segments of the affected nerves become hypertrophied. Schwann cells harbor *Mycobacterium leprae*.¹⁷
3. Wallerian degeneration occurs distal to the level of the granuloma, resulting in anesthetic skin.
4. Reactive connective tissue proliferation prevents axonal regeneration.

CLINICOPATHOLOGIC CORRELATIONS (TUBERCULOID LEPROSY)

1. Early onset of nerve dysfunction: this reflects the intense inflammatory response to the bacilli. It may simulate a focal mononeuropathy in the early stages.
2. There is predominant involvement of superficial cooler region cutaneous nerves, as *M. leprae* bacilli proliferate more rapidly at lower temperatures. The

manifestations are therefore predominantly sensory.

- 3. Permanent anesthesia: the granulomatous lesion often totally destroys the architecture of the nerve.
- 4. Nerve entrapment may occur because of the granulomatous enlargement of nerve trunks.
- 5. The CSF protein is normal: the spinal roots are not involved.

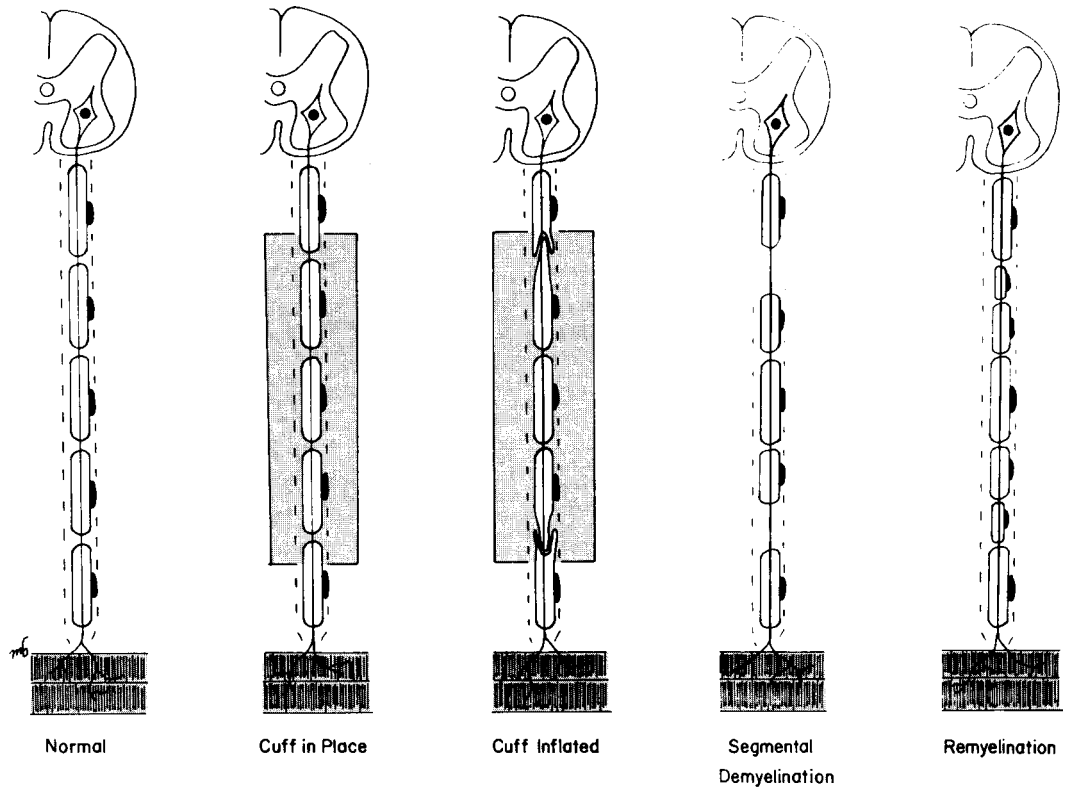
traumatic agent, with the additional factors of traction and friction exaggerating the degree of injury. There is widespread agreement about the basic three-stage classification of nerve injury, although the pathogenesis of these lesions, especially the mild lesions, remains controversial. This section outlines and illustrates the salient stages of nerve response to injury. The features of acute and chronic nerve trauma are discussed in Chapter 18.

Physical Injuries

Nerves are susceptible to the effects of externally applied pressures. In general, damage to a nerve fiber appears to increase in proportion to the velocity, force, and duration of the

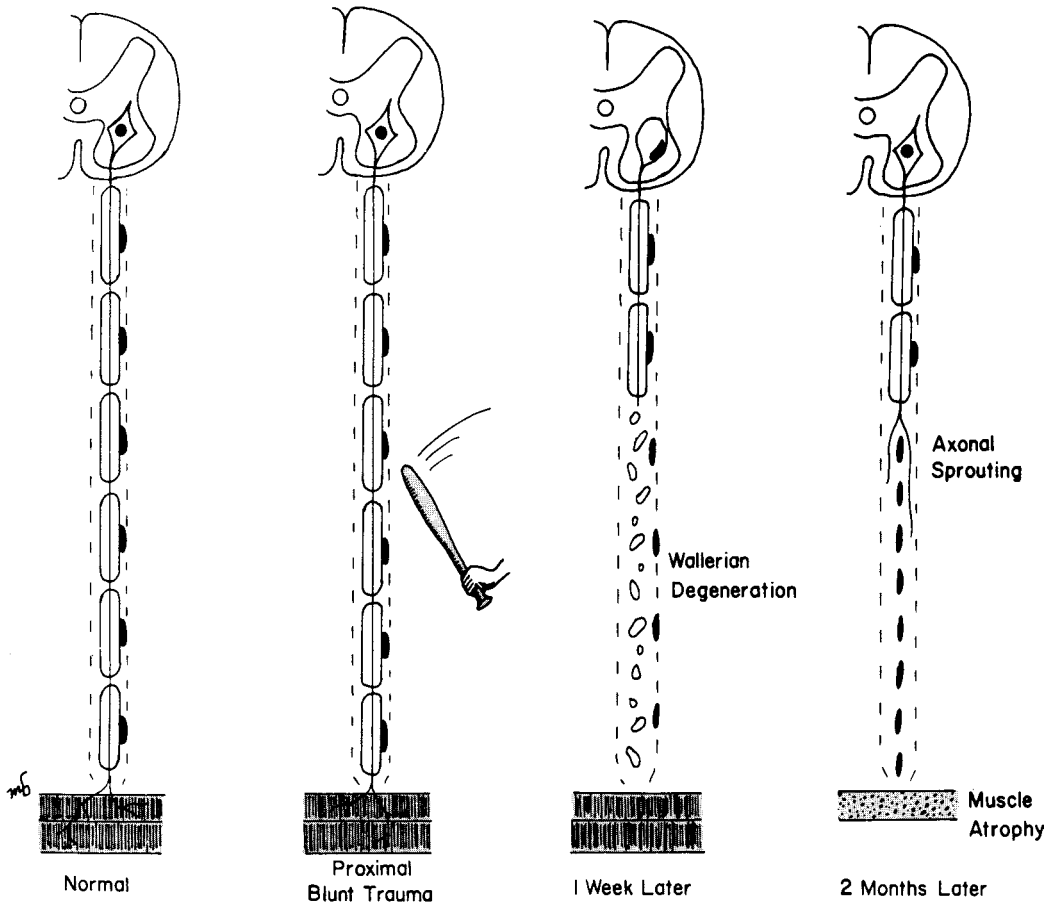
CLASSIFICATION

This classification is based on three stages (Classes [or Types, or Degrees] 1, 2, and 3) of seriate vulnerability of components of peripheral nerve to injury; thus, slight injury affects myelin, more severe injury affects the axon,



CLASS I — ACUTE NERVE INJURY
(e.g. Compression)

Figure 2-9. Neurapraxia (Class/Type 1 nerve injury) associated with compression by a cuff. Axon displacement at both edges of the cuff causes intussusception of the attached myelin across the nodes of Ranvier into the adjacent paranode. Affected paranodes demyelinate. Remyelination begins following cuff removal, and conduction eventually resumes. Conduction is normal in the nerve above and below the cuff since the axon has not been damaged.



CLASS 2 NERVE INJURY

Figure 2-10. Axonotmesis (Class/Type 2 nerve injury) from a crush injury to a limb. Axonal disruption occurs at the site of injury. Wallerian degeneration takes place throughout the axon distal to the injury with loss of axon, myelin, and nerve conduction. Preservation of Schwann cell tubes and other endoneurial connective tissue ensures that regenerating axons have the opportunity to reach their previous terminals and perhaps reestablish functional connections.

and the most severe injury disrupts connective tissue. The subject is authoritatively reviewed by Birch and colleagues.¹⁸

Class/Type 1 (Neurapraxia)

Conduction block is the hallmark of Class 1 compression injury and may be due to either transient ischemia or paranodal demyelination. Ischemia results in a rapidly reversible loss of function associated with transient nerve impulse blockade. Paranodal demyelination occurs with more severe compression and is a mild structural nerve injury. Dysfunction persists in the distribution of the affected nerve

until paranodal remyelination occurs, usually after a few weeks (Fig. 2-9).¹⁹

Class/Type 2 (Axonotmesis)

A crush lesion interrupts axons, but the Schwann cell basal lamina and endoneurial tissue remain largely intact. Wallerian degeneration occurs below the site of injury. Axonal regeneration commences promptly after injury, and the growing axons reach proximal targets before distal sites of innervation (Fig. 2-10). If the lesion is at a proximal site in a long nerve (e.g., the sciatic nerve), the distal Schwann cell tubes may begin to

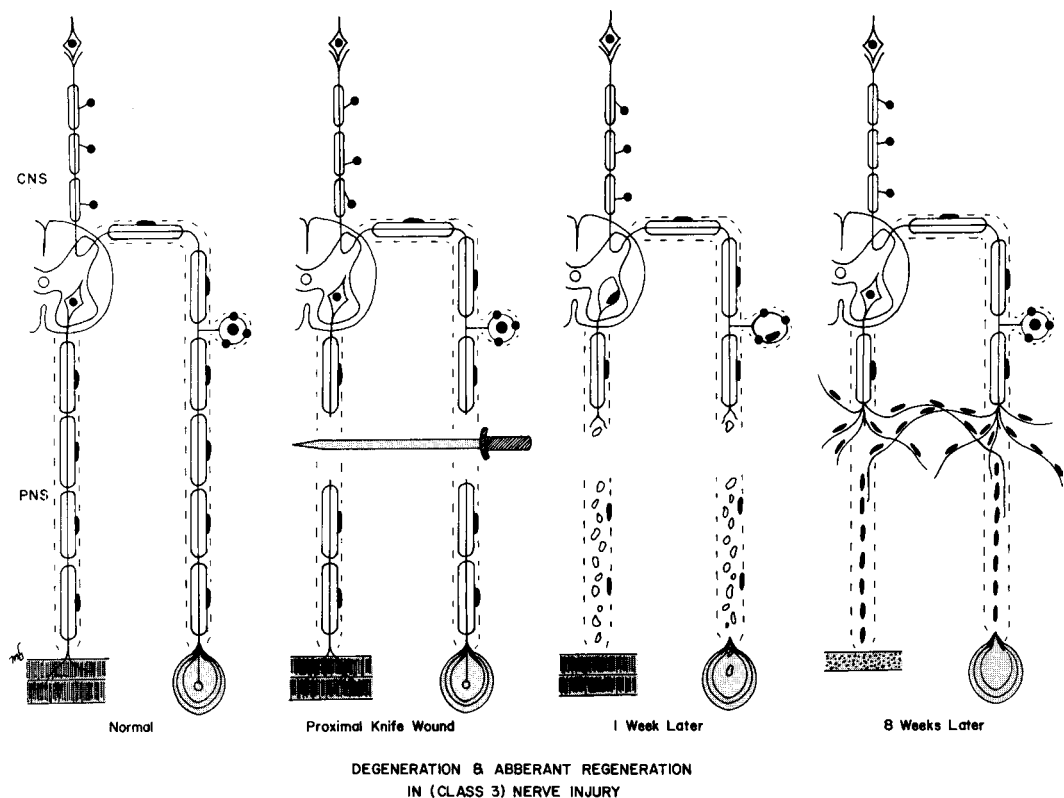


Figure 2-11. Neurotmesis (Class/Type 3 nerve injury) with severance of all neural and connective tissue elements. There is little hope of functional recovery without skilled surgery. Regenerating axons are entering inappropriate Schwann cell tubes (aberrant regeneration).

disappear after a year; this can limit recovery at distant sites.

Class/Type 3 (Neurotmesis)

The axon is severed and the connective tissue disrupted, ranging from endoneurial and Schwann cell tube transection to total nerve severance. Wallerian degeneration is inevitable, and axon regeneration is severely limited by distorted connective tissue. Neuroma formation and aberrant regeneration are common (Fig. 2-11).

**CLINICOPATHOLOGIC
CORRELATION OF NERVE INJURIES**

Class/Type 1 (Neurapraxia)

This lesion is commonly associated with moderate focal compression of nerve (e.g., Saturday night palsy). The motor deficit usually exceeds the sympathetic and sensory loss. This

reflects the low vulnerability of unmyelinated sympathetic and small myelinated sensory fibers and the dependence of motor function on larger myelinated axons, which undergo focal demyelination. Nerve conduction remains preserved in the intact, still-myelinated axons below the injury. The good prognosis and rapid recovery (usually weeks) from Class 1 lesions reflect both the preservation of axonal continuity and the ability of Schwann cells to remyelinate the demyelinated segments rapidly and effectively. Unlike recovery from axonal lesions, recovery occurs simultaneously throughout the distribution of the affected nerve.

Class/Type 2 (Axonotmesis)

This lesion is commonly associated with severe closed-crush injuries to an extremity. Complete loss of sensory, sympathetic, and motor function may occur from interruption of unmyelinated

and myelinated axons; Schwann cell basal lamina tubes are largely intact. Nerve conduction fails below the lesion as the axons degenerate; muscle atrophy ensues. The prognosis is good (especially after distal lesions), since the axons can regenerate within their original Schwann cell tubes and the pattern of motor and sensory restoration will be appropriate. The course of recovery is slow (usually months) and proximal to distal, reflecting the rate and course of axonal regeneration.

Class/Type 3 (Neurotmesis)

These lesions are usually associated with severe traction injuries or open wounds. They have a poor prognosis because connective tissue disruption and scarring interfere with axonal regeneration. Surgical repair with or without autografts is often required.

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Evaluation and Management of the Patient with Peripheral Neuropathy

GENERAL PRINCIPLES AND THE ALGORITHMIC APPROACH CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY (CIAP)/SMALL-FIBER NEUROPATHY (SFN)

GENERAL PRINCIPLES AND THE ALGORITHMIC APPROACH

The evaluation of a possible neuropathy begins with the recognition that dysfunction at other central and peripheral loci may mimic a neuropathy clinically. We use the term *pseudoneuropathy* to refer to this situation and do not imply a psychogenic mechanism by its use;¹ other authors prefer the term *neuropathy mimics*. Pseudoneuropathies mimicking the pattern of a polyneuropathy (*pseudopolyneuropathies*) are most often myelopathies, which can produce distal sensory and sometimes motor dysfunction in a stocking pattern, without telltale features of a sensory level, long tract weakness, sphincter disturbance, or hyperreflexia. Cervical spondylotic myelopathy and spinal multiple sclerosis are two of the more common conditions we encounter. Bilateral L5/S1 radiculopathies can also occasionally mimic distal polyneuropathies. Intramedullary spinal lesions (e.g., a multiple sclerosis plaque at the dorsal root entry zone, or syrinx) can mimic a structural radiculopathy (*pseudoradiculopathy*) or even mononeuropathy such as

TREATMENT OF NEUROPATHIC PAIN DIFFERENTIAL DIAGNOSES AND WORK-UPS FOR THE VARIED NEUROPATHY PHENOTYPES

carpal tunnel syndrome or ulnar neuropathy (pseudomononeuropathy).²⁻⁴ Cerebral lesions must also be considered; small cerebral infarcts have rarely simulated ulnar neuropathies,⁵ and in the evaluation of bilateral distal leg weakness, parasagittal lesions, as well as distal myopathies, are possibilities.

Some of the pitfalls we have observed in the recognition of pseudopolyneuropathy include not appreciating the significance of: early (non-length-dependent) hand involvement, preserved or brisk reflexes in the setting of significant vibration/position sense loss (suggesting posterior column dysfunction), asymmetric features, the clinical complaint of leg stiffness/heaviness (suggesting pyramidal dysfunction), or very proximal sensory involvement (e.g., up to the groin) without the hands. It should also be borne in mind that patients with myelopathy or lumbosacral radiculopathy do not always have neck, back, or radicular pain. The evaluation of neuropathy is so critically dependent on electrodiagnostic testing that this is all too frequently a source of misleading, incidental, or frankly erroneous results when not performed by properly trained, thoughtful

practitioners. Selected neuroimaging studies and occasionally somatosensory evoked potentials are helpful in defining pseudoneuropathies.

The historical and physical examination features that should be explored, and that suggest neuropathy and guide analysis, are outlined in Table 3–1. A systematic algorithmic approach tends to be helpful in sorting through the myriad presentations and possible etiologies (Fig. 3–1). Neuropathies of widely varying etiologies can be indistinguishable clinically and electrophysiologically. After establishing that a neuropathy and not a pseudoneuropathy is present, the next step is an anatomic subclassification based on clinical and electrodiagnostic features.

Is the pattern that of a focal neuropathy involving a single nerve (mononeuropathy), segmental (radiculopathy), monomelic/regional/multisegmental (polyradiculopathy, plexopathy, or radiculoplexopathy), multiple individual nerves (mononeuropathy multiplex or multifocal neuropathy), or diffuse, symmetric (polyneuropathy)? The term *polyradiculoneuropathy* is occasionally applied to processes affecting both roots and more distal nerve segments (e.g., Guillain-Barré syndrome [GBS], chronic inflammatory demyelinating polyradiculoneuropathy [CIDP], Lyme disease, sarcoidosis). Clinical and electrodiagnostic criteria are then applied to establish the pathophysiology as predominant axonopathy,

Table 3–1 History and Physical Examination of the Neuropathy Patient

History	Physical Examination
Cardinal features: onset, duration, tempo, prior episodes, subtle early features, functional difficulties Motor symptoms: Negative: weakness (distal, proximal, multifocal, diffuse), fatigability Positive: twitching, cramps Sensory symptoms: Negative: numbness, sensory ataxia Positive: pain, paresthesias, dysesthesias Autonomic symptoms: constipation, orthostasis, anhidrosis, impotence, hyperhidrosis, urinary incontinence, diarrhea Gait imbalance, falls Family history: detailed, including exam of family members Social history: ethnic background, occupation, toxic exposure, coworker illness, alcohol, illicit drug use, dietary habits, sexual history Neurotoxic medications: prescribed and over-the-counter ROS/associated features: history of rash (e.g., erythema migrans), restless legs syndrome, heat-provoked attacks of painful erythematous feet (erythromelalgia), constitutional symptoms (systemic disorders, malignancy)	Motor signs: Negative: weakness, atrophy; weakness without atrophy suggests demyelination Positive: neuropathic tremor, peripheral nerve hyperexcitability (fasciculations, myokymia, neuromyotonia, hemifacial spasm, cramps) Sensory signs: Small fiber: pain and temperature loss Large fiber: vibration, joint position and touch-pressure loss; pseudoathetosis; sensory ataxia; Rombergism Autonomic signs: orthostasis, tachycardia Deep tendon reflexes: length-dependent loss with ankles first (most neuropathies); early, diffuse (demyelinating or neuronopathy) Gait: tandem, toe/heel walk, hop, squat Skeletal deformities: pes cavus, pes planus, hammer toes, kyphoscoliosis (CMT); claw hand (ulnar) Nerve enlargement: infection (leprosy), demyelination/remyelination (onion bulb formation; CMT), neoplasia (neurofibromatosis) Skin lesions: vasculitic (purpura, livedo reticularis), hypopigmentation (leprosy), angiokeratomas (Fabry disease), neurofibromas/café-au-lait spots (neurofibromatosis), ichthyosis (Refsum disease), hyperpigmentation (POEMS syndrome), foot ulcers (HSAN, diabetes), trophic changes (dysautonomia), lipomas (mitochondrial disease) Gum lesions: lead lines Nail lesions: Mees lines (arsenic, thallium) Hair lesions: alopecia (thallium, connective tissue disease), curly (giant axonal neuropathy)

CMT: Charcot-Marie-Tooth; HSAN: hereditary sensory and autonomic neuropathy; POEMS: polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes; ROS: review of systems.

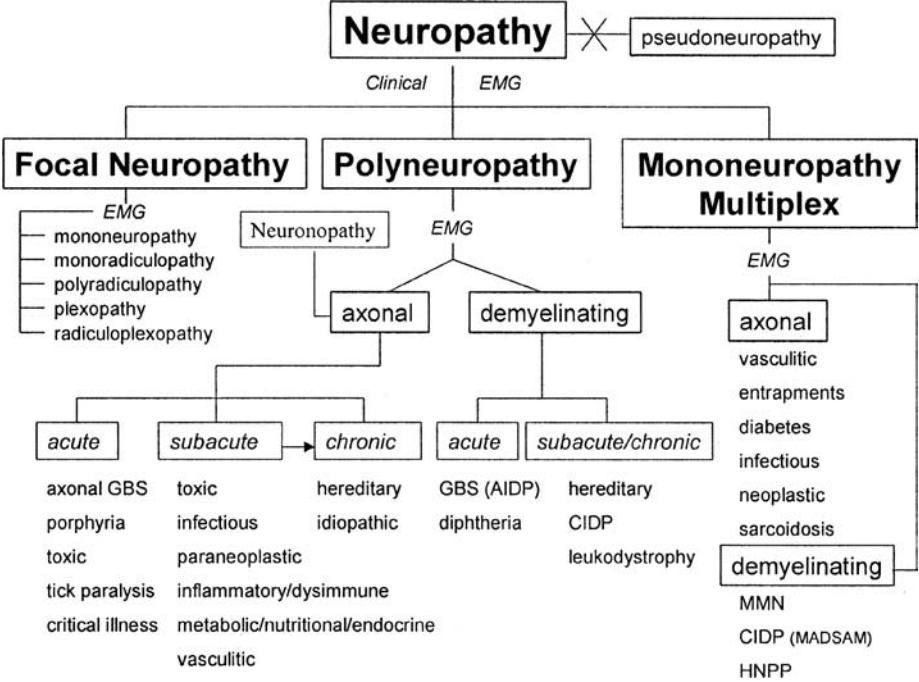


Figure 3–1. Algorithm for the classification and differential diagnosis of neuropathy. AIDP: acute inflammatory demyelinating polyradiculoneuropathy; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; EMG: electromyography; GBS: Guillain-Barré syndrome; HNPP: hereditary neuropathy with liability to pressure palsies; MADSAM: multifocal acquired demyelinating sensory and motor neuropathy; MMN: multifocal motor neuropathy.

myelinopathy (demyelinating), mixed axonal-demyelinating, or neuronopathy (ganglionopathy). Some of the clinical features that help distinguish these patterns are presented in

Table 3–2. In most cases, electrophysiologic studies readily distinguish axonopathy from myelinopathy, but in most respects axonopathy and neuronopathy are indistinguishable in that the

Table 3–2 Clinical Clues to the Underlying Pathophysiology in Polyneuropathies

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

end result in both cases is axon loss (although a generalized amplitude reduction favors a diagnosis of neuronopathy, particularly in motor neuron diseases). Further helpful characterization can be based on the fiber types involved (sensory—small or large fiber, motor, autonomic, sensory and autonomic, sensorimotor), distribution (proximal, distal, generalized; limb predominance; symmetry or asymmetry), temporal profile (acute, subacute, chronic, monophasic, episodic, relapsing-remitting), age of onset, ethnic origin, geography, and associated features (central, systemic). The temporal profile, sensory symptoms, age of onset, symmetry, and associated skeletal abnormalities suggest whether a neuropathy is likely to be acquired or hereditary; with some exceptions, a hereditary neuropathy is more likely to have insidious progression, lack of positive sensory symptoms, early onset, and symmetric distal weakness, and may have bony abnormalities such as pes cavus or kyphoscoliosis.

Clinical and electrodiagnostic (electromyography/nerve conduction study [EMG/NCS], quantitative sensory testing [QST], autonomic studies) assessments are almost invariably adequate for establishing the presence of a neuropathy and characterizing its nature. Small fiber neuropathy is an exception wherein a skin biopsy for epidermal nerve fiber density may be the only means of confirming the disorder. Nerve biopsy is almost never necessary to establish the presence of a neuropathy, but it is helpful in limited and selected cases to define the pathology and etiology; the yield is best in acute or subacute, asymmetric and severe, progressive neuropathies and when vasculitic, inflammatory, infectious, granulomatous, infiltrative, or storage disorders are suspected (vasculitis, leprosy, amyloidosis, sarcoidosis, tumor, adult polyglucosan body disease). Analysis of CSF demonstrating elevated protein can help support the diagnosis of an immune demyelinating neuropathy when electrodiagnostic studies are inconclusive; pleocytosis may suggest disorders such as human immunodeficiency virus (HIV), cytomegalovirus (CMV), Lyme disease, West Nile virus, or neoplasia. Magnetic resonance imaging (MRI) in selected cases can demonstrate inflammatory, hypertrophic, or neoplastic nerve enlargement or enhancement. Batteries of autonomic studies, where available, may suggest the need for a tissue biopsy to establish the diagnosis of amyloidosis and may be abnormal without overt autonomic symptoms; a

useful scale of autonomic function is the composite autonomic scoring scale (CASS), which includes the quantitative sudomotor axon reflex test (QSART), orthostatic blood pressure, heart rate response to tilt and deep breathing, the Valsalva ratio, and beat-to-beat blood pressure measurements during Phases II and IV of the Valsalva maneuver, tilt, and deep breathing.^{6,7}

The differential diagnoses of the varied neuropathy phenotypes, established by clinical and electrodiagnostic features, are presented at the end of the chapter in table form (Table 3–5 to 3–19). Suggested workups to consider are based on the disorders listed. We do not imply that every one of these tests should be employed in every case. Testing should be guided by clinical judgment, evidence-based where available (admittedly limited), and performed in a rational order to minimize expense and iatrogenic harm. Neuropathy in patients with established diabetes should not invariably be attributed to diabetes alone; a substantial number of diabetic patients may have an alternative potential cause of neuropathy.⁸ Atypical features (prominent weakness, asymmetries, severe demyelination on NCS) may be clues.

CHRONIC IDIOPATHIC AXONAL POLYNEUROPATHY (CIAP)/ SMALL-FIBER NEUROPATHY (SFN)

Careful, intensive evaluation of undiagnosed neuropathies will uncover an etiology in many cases, particularly inherited and inflammatory-demyelinating disorders.^{9,10} Despite extensive evaluations, a substantial number of polyneuropathies, perhaps one third to one half, will remain idiopathic or cryptogenic.^{11–14} These are almost exclusively axonal, either sensory or sensorimotor, or small-fiber types. The patients tend to be older adults presenting with acral numbness, paresthesias, or pain (often burning or sharp, lancinating) beginning in the feet. Symptom progression is slow. Most patients do not develop significant motor impairment and related disability, but quality-of-life measurements are significantly affected.¹⁵ Progression of sensory loss often plateaus after several months or years. Patients with small-fiber neuropathy by definition have no motor involvement, a normal NCS,

and mostly intact large-fiber sensory function, although mild distal vibratory loss and reduced ankle reflexes are present in some individuals who otherwise fit this phenotype. Allodynia/hyperalgesia is seen. Occasionally, a more generalized, non-length-dependent pattern is present, suggestive of a small-fiber neuropathy.^{16,17} Skin biopsy for intraepidermal nerve fiber (IENF) density is the most sensitive test to establish small-fiber involvement, more so than QST, autonomic testing (QSART), or sural nerve biopsy.¹⁸ Isolated small-fiber neuropathy may evolve to include large fibers, and one is more likely to uncover an etiology in this pattern. The presence of overt autonomic dysfunction with SFN increases the likelihood of diabetes or amyloidosis as the etiology. Some cases have an acute or subacute rather than chronic presentation, and these are more likely to improve. A pattern of chronic involvement restricted to small fibers is more likely to remain idiopathic. Mimickers of SFN may include other neuropathic (tarsal tunnel syndrome, erythromelalgia, Morton neuroma, bilateral L5/S1 radiculopathy) and non-neuropathic (plantar fasciitis, tendonitis, arthritis, bursitis), painful disorders of the foot. Complex regional pain syndrome may reflect local/regional small-fiber neuropathic dysfunction.

Routine nerve biopsy cannot be recommended for CIAP or SFN since in general it shows only nerve fiber loss, without specific abnormalities that may establish an etiology. This statement is tempered by occasional case reports that purport, for example, to uncover vasculitis presenting as SFN,¹⁹ or sensory CIDP masquerading as CIAP, responding to intravenous immunoglobulin (IVIg).²⁰ Clinical and electrodiagnostic clues should be sought to justify a nerve biopsy (multifocal/asymmetric features, rapid or considerable clinical or electrophysiologic progression, systemic disorders presenting a risk for vasculitis or infiltrative disease, occasionally subtle, inconclusive demyelinating features). Reexamination of patients over time may establish a diagnosis,¹⁴ although other studies suggest that in no instance do repeated extensive laboratory and neurophysiologic studies shed any new light on this slowly progressive disorder.²¹

Recommended work-ups for chronic axonal sensory or sensorimotor polyneuropathies and small-fiber-predominant neuropathies are outlined in the tables that follow. An evidence-based review and recommendations for

distal symmetric polyneuropathy were provided in an American Academy of Neurology/American Association of Neuromuscular and Electrodiagnostic Medicine/American Academy of Physical Medicine and Rehabilitation Practice Parameter in 2009.²² Studies with the 2-hour 75 g oral glucose tolerance test (OGTT) have suggested a high prevalence (25%–36%) of impaired glucose tolerance (>140 and <200 mg/dL) or overt diabetes (>200 mg/dL; or fasting blood sugar [FBS] >125 mg/dL) in this setting,^{12,23,24} but this has not been invariably observed.^{25,26} The OGTT is more sensitive than fasting blood glucose (impaired fasting glucose: 100–125 mg/dL; diabetes: >125 mg/dL) or hemoglobin A1c (HbA1c; abnormal >6%) in establishing an abnormality of glucose metabolism. The yield is higher in persons with a painful neuropathy. Testing for vitamin B₁₂ is fruitful, and if it is in the low normal range (200–500 pg/dL), methylmalonic acid with or without homocysteine levels should be measured; methylmalonic acid is more specific, and the two metabolites have similar very high sensitivity.¹² Homocysteine may be elevated in folate deficiency, pyridoxine deficiency, and heterozygous homocystinemia; both metabolites may be elevated in renal insufficiency, hypothyroidism, and hypovolemia. Vitamin B₁₂ deficiency may be associated with the use of metformin in diabetics. Screening for a monoclonal protein with serum protein immunofixation electrophoresis (IFE), which is more sensitive than serum protein electrophoresis (SPEP), is probably reasonable; however, monoclonal gammopathy of undetermined significance (MGUS) is common as an incidental finding in older persons without neuropathy, so its significance may be uncertain. All patients should have a comprehensive metabolic panel (CMP), a complete blood count (CBC), and probably an erythrocyte sedimentation rate (ESR). Anemia, elevated ESR, and renal disease suggests multiple myeloma or another hematologic malignancy. There is little data to support the utility of other screening tests, and choices should be based on clinical judgment.

Anti-nerve antibody studies tend to be unrevealing in this population and are generally not recommended, particularly in *panel* form.^{12,13,18} Their use should be mostly restricted to particular neuropathy phenotypes

(Table 3–3). A strong correlation and particular utility have been shown for antibodies to GM1 in multifocal motor neuropathy, particularly when NCSs are not diagnostic, GQ1b in Fisher syndrome and related disorders, Hu in paraneoplastic sensory neuronopathy/limbic encephalitis, voltage-gated potassium channels (VGKCs) in neuromyotonia, and myelin-associated glycoprotein (MAG) in a distal chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) phenotype associated with IgM-MGUS and very prolonged distal

latencies (although the utility is arguable since the presence or absence of MAG does not seem to affect the natural history, risk of Waldenström macroglobulinemia, or response to immunosuppression). Routine screening for heavy metals is not advised without a relevant exposure history. There are no studies regarding the yield of genetic testing in cryptogenic polyneuropathies without a classical hereditary neuropathy phenotype; guidelines for testing for hereditary neuropathies are discussed in Chapter 14.

Table 3–3 Autoantibodies and Neuropathy

Autoantibody	Disorder
Gangliosides	
GM1	Multifocal motor neuropathy (~50%; high titers are highly specific); GBS (~20%–30%), esp. AMAN (acute motor axonal neuropathy) s/p <i>Campylobacter jejuni</i> (GM1 and GD1a)
GQ1b	Fisher syndrome (up to 95%) > Bickerstaff brainstem encephalitis, GBS with ophthalmoplegia, ataxic GBS, pharyngeal-cervical-brachial variant, acute ophthalmoplegia without ataxia
GT1a	Pharyngeal-cervical-brachial variant of GBS
GD1b	CANOMAD (chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and anti-GD1b disialosyl antibodies)
Glycoproteins/ Glycolipids	
MAG	DADS-M (distal acquired demyelinating symmetric neuropathy variant of CIDP with monoclonal M-protein); prolonged distal latencies, prominent slowing, little or no conduction block
Sulfatide	Sensory-predominant neuropathy, axonal or demyelinating; no well-defined clinical syndrome
Paraneoplastic Conditions	
Hu	Sensory neuronopathy (>90%); limbic/brainstem encephalitis, cerebellar degeneration, intestinal pseudo-obstruction
CV2	Mixed axonal demyelinating sensorimotor neuropathy; cerebellar degeneration, limbic encephalitis, uveitis, optic neuritis, intestinal pseudo-obstruction
VGKC	Acquired neuromyotonia, Morvan syndrome
Vasculitis	
c-ANCA	Wegener granulomatosis > microscopic polyangiitis, Churg-Strauss syndrome
p-ANCA	Microscopic polyangiitis > Wegener granulomatosis, Churg-Strauss syndrome
RNP: Ro (SS-A), La (SS-B)	Sjögren syndrome
ANA, dsDNA, SM	Systemic lupus erythematosus
Scl-70	Scleroderma
Centromere	CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia)
U1-RNP	Mixed connective tissue disease
RF, CCP	Rheumatoid arthritis > other connective tissue disorders

ANA: antinuclear antibody; ANCA: anti-neutrophil cytoplasmic antibody; CCP: cyclic citrullinated peptides; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; CV2: Crossveinless-2; dsDNA: double-stranded DNA; GBS: Guillain-Barré syndrome; MAG: myelin-associated glycoprotein; RF: rheumatoid factor; RNP: ribonucleoprotein; SM: Smith; VGKC: voltage-gated potassium channel.

TREATMENT OF NEUROPATHIC PAIN

No controlled clinical treatment trials have been described in CIAP.²⁷ CIAP/SFN and other painful neuropathies are managed symptomatically with neuropathic pain control. Some of the more effective treatment options are outlined in Table 3–4.^{28,29,30,31,32,33,34} Because of their excellent side effect profiles and established efficacy in clinical trials, we

recommend starting with gabapentin, pregabalin, duloxetine, one of the less sedating tricyclics, tramadol, or topical lidocaine, and then, if necessary, consider combination therapy or proceed systematically through the rest of the list. Lifestyle interventions in prediabetes/impaired glucose tolerance appear to have a salutary effect on skin biopsies and pain.³⁵ One report describes four patients with an acute small-fiber sensory neuropathy that responded to corticosteroids.³⁶

Table 3–4 Treatment of Neuropathic Pain

Drug	Dosage Range	Comments/Adverse Effects
First Line		
Gabapentin	300–1200 mg po TID	No major drug interactions; edema, drowsiness, dizziness, fatigue; adjust for renal dysfunction; titrate slowly
Pregabalin	150–600 mg daily (BID or TID regimen)	Similar to gabapentin; may be titrated more rapidly
Tricyclic antidepressants Nortriptyline Desipramine Amitriptyline	75–150 mg daily (start with 10–25 mg HS)	Cardiotoxicity, anticholinergic effects (drowsiness, confusion, xerostomia, constipation, sexual dysfunction, urinary retention), weight gain, orthostasis, glaucoma; nortriptyline and desipramine better tolerated; special care or avoid in treating elderly patients
SSNRIs Duloxetine	30–60 mg po BID (60 mg/day efficacy equal to that of 120 mg/day regimen)	Nausea, anorexia, headache, insomnia, dizziness, fatigue, xerostomia, constipation
Venlafaxine	75–150 mg po BID	Hypertension, nausea, dizziness, irritability, xerostomia, sexual dysfunction
5% Lidocaine patch	1–3 patches/12 h daily	Skin reaction
Second Line		
Tramadol	50–100 mg po QID	Drowsiness, constipation, dizziness, nausea, seizures, dependency; may be considered a first-line drug in some circumstances (e.g., acute pain, episodic exacerbations, during titration of a first-line drug); advantage: daily use optional
Opioids	Varied	Constipation, sedation, nausea; risk of substance abuse; first-line drug in selected clinical circumstances
Weak Efficacy, Discrepant Study Results, or Safety Concerns		
Capsaicin, carbamazepine,* oxcarbazepine,* topiramate, lamotrigine, valproate, mexiletine, SSRIs, NMDA antagonists		

*First-line drug for trigeminal neuralgia.
NMDA: N-methyl-d-aspartate; SSNRIs: selective serotonin-norepinephrine reuptake inhibitors; SSRIs: selective serotonin reuptake inhibitors.

DIFFERENTIAL DIAGNOSES AND WORK-UPS FOR THE VARIED NEUROPATHY PHENOTYPES

Table 3–5 Sensorimotor Polyneuropathies: Axonal*

Acute/Subacute	
GBS—AMSAN variant*	
Porphyria*	
Critical illness polyneuropathy*	
Tick paralysis* (nerve or NMJ channelopathy)	
Toxic, pharmaceutical:* amiodarone, gold salts, nitrofurantoin, vincristine	
Toxic, heavy metals: arsenic, mercury, thallium	
Graft-versus-host disease	
Subacute/Chronic	
Metabolic/endocrine	Diabetes, uremia, hypothyroidism, acromegaly, hepatic failure, hypoglycemia/hyperinsulinemia
Nutritional deficiency	Vitamin B ₁₂ , folate, thiamine, vitamin E, copper, bariatric surgery (multifactorial), Cuban epidemic optic and peripheral neuropathy (multifactorial)
Vascular	Vasculitis: systemic (primary or secondary) and nonsystemic, pulmonary failure (chronic hypoxia), polycythemia, large-vessel atherosclerotic vascular disease
Neoplastic (infiltrative)	Leukemia, lymphoma, lymphomatoid granulomatosis, multiple myeloma, neurofibromatosis 1 and 2
Paraneoplastic	Various tumors
Infectious/granulomatous	Lyme disease, HIV, HTLV-1, HCV, sarcoidosis, Whipple disease
Toxic	Most peripheral neurotoxic drugs and industrial agents, alcohol, nitrous oxide–associated vitamin B ₁₂ deficiency
Inflammatory/immune-mediated/connective tissue disorders	Sjögren syndrome, SLE, RA, scleroderma, mixed connective tissue disease, primary biliary cirrhosis, celiac disease, graft-versus-host disease, hypereosinophilic syndrome
Paraproteinemias	MGUS (IgG/IgA), amyloidosis (acquired or familial), Waldenström macroglobulinemia, cryoglobulinemia
Hereditary	CMT2,* abetalipoproteinemia, cerebrotendinous xanthomatosis, chorea-acanthocytosis and McLeod neuroacanthocytosis syndromes, adult polyglucosan body disease, adult-onset Tay-Sachs disease

Considered Work-up
Acute/subacute: CSF analysis, porphyrins, examine for tick, toxic exposure history, heavy metal screen
Subacute/chronic: vast differential demands particular attention to clinical clues from the history and exam; if there are none, perform screening work-up to uncover disorders that occur with reasonable frequency and that may be treatable:
Tier 1: in all cases: CBC, CMP, FBS/HgbA1c/OGTT, vitamin B₁₂ (methylmalonic acid/homocysteine), ESR, serum protein immunofixation electrophoresis (IFE), toxic exposure history; **consider also:** CXR, urinalysis, TFTs, lipid profile, ANA, RF, anti-Ro/La, Lyme ELISA/WB, HCV titer, ACE
Tier 2: additional vitamin/mineral studies in those with risk factors for deficiency or excess: copper/zinc, vitamin E, vitamins B₁ and B₆, folate; celiac panel (anti-gliadin and tissue transglutaminase antibodies), HIV/HTLV-1, UPEP/immunofixation, cryoglobulins, ANCA, CK
Tier 3: CMT 2 genetic testing, minor salivary gland biopsy, abdominal fat pad biopsy, malignancy work-up, chest CT/gallium scan, occasionally nerve/muscle biopsy, anti-neural antibodies (gangliosides, Hu, CV2) have a very low yield in this situation, as does CSF analysis

* Most are sensory predominant; those that can be motor predominant are labeled with an asterisk.
ACE: angiotensin converting enzyme; AMSAN: acute motor sensory axonal neuropathy;
CBC: complete blood count; CK: creatine kinase; CMP: comprehensive metabolic panel; CMT: Charcot-Marie-Tooth disease;
CT: computed tomography; CXR: chest x-ray; ESR: erythrocyte sedimentation rate; FBS: fasting blood sugar; HCV: hepatitis C virus;
HgbA1c: hemoglobin A1c; HTLV: human T-cell lymphotropic virus; Lyme ELISA/WB: Lyme enzyme-linked immunosorbent assay/
Western blot; MGUS: monoclonal gammopathy of undetermined significance; NMJ: neuromuscular junction; OGTT: oral glucose tolerance
test; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; TFTs: thyroid function tests; UPEP: urine protein electrophoresis.

Table 3–6 **Sensorimotor Polyneuropathies: Demyelinating or Mixed**

Acute/Subacute	
GBS (AIDP)	
Diphtheria	
Hypophosphatemia	
Toxic, pharmaceutical: amiodarone, suramin, perhexilene, tacrolimus, L-tryptophan, cytosine arabinoside, bortezomib, tumor necrosis factor- α blockers	
Graft-versus-host disease	
Arsenic, acute phase	
n-Hexane (glue sniffer's neuropathy)*	
Subacute/Chronic	
Inflammatory/dysimmune	Idiopathic CIDP CIDP associated with systemic lupus erythematosus, inflammatory bowel disease, diabetes, HIV, HCV, HBV, graft-versus-host disease tumor necrosis factor- α antagonists
Dysproteinemias/hematologic disorders/malignancies	MGUS – IgM/anti-MAG, IgG, IgA; osteosclerotic myeloma/POEMS syndrome, Castleman disease, Waldenström macroglobulinemia, cryoglobulinemia, melanoma, lymphoma
Hereditary/genetic	CMT1, CMT4, DSD/CHN, CMTX, DI-CMT, lysosomal leukodystrophies (metachromatic leukodystrophy, Krabbe disease), peroxisomal disorders (Refsum disease, adrenomyeloneuropathy), lipoprotein disorders (Tangier disease), transthyretin familial amyloid polyneuropathy, cerebrotendinous xanthomatosis, Cockayne syndrome, xeroderma pigmentosum, mitochondrial disorders (Leigh disease, MNGIE, occasionally MELAS or MERRF), occasionally neurofibromatosis 1 or 2

Considered Work-up

Acquired demyelinating, acute: CSF analysis, toxic exposure history, arsenic, serum phosphate

Acquired demyelinating, subacute/chronic: CBC, CMP, CSF analysis, ESR, ANA, diabetes usually well established, HIV, hepatitis panel, cryoglobulins, serum and urine IFE, skeletal survey, endocrine evaluation, malignancy work-up as indicated, toxic exposure history, rarely nerve biopsy

Hereditary demyelinating: specific genetic testing or biochemical assays and neuroimaging based on clinical and electrodiagnostic clues, rarely nerve biopsy

*Demyelinating electrophysiologic features are related to primary axonal pathology, with paranodal myelin changes caused by axonal swellings.

AIDP: acute inflammatory demyelinating polyneuropathy; CIDP: chronic inflammatory demyelinating polyneuropathy; DI-CMT: dominant intermediate CMT; DSD/CHN: Dejerine-Sottas disease/congenital hypomyelinating neuropathy; HBV: hepatitis B virus; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF: myoclonus epilepsy with ragged red fibers; MNGIE: mitochondrial neurogastrointestinal encephalomyopathy; POEMS: polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes.

Table 3–7 **Sensory, Small-Fiber, Painful Polyneuropathies: Isolated, Predominant, or Associated**

Idiopathic
Diabetes and impaired glucose tolerance
Amyloidosis—familial, acquired
Alcoholic
HIV
Connective tissue disorders (Sjögren syndrome, SLE)

(continued)

Table 3–7 (continued)

Less Common Diseases or Uncommonly Reported Phenotypes	
Leprosy	
Vitamin B ₁₂ deficiency	
Hypothyroidism	
Paraneoplastic	
Celiac disease	
Hepatitis C	
Hypertriglyceridemia	
Toxic: arsenic, thallium, nucleoside analogues, chemotherapeutic agents, others	
Gammopathies: multiple myeloma, cryoglobulinemia	
Hereditary sensory and autonomic neuropathies	
Channelopathy-associated insensitivity to pain	
Erythromelalgia	
Fabry disease	
Tangier disease	
Vasculitis	
Sarcoidosis	
Considered Work-up	
CBC, CMP, ESR, ANA, RF, anti-Ro/La, IFE, FBS/HgbA1c/OGTT, TTR, HIV, lipid profile, celiac panel, TFTs, vitamin B ₁₂ , ACE, anti-Hu, HCV titer, cryoglobulins, α -galactosidase (Fabry disease); skin biopsy; fat pad, rectal or minor salivary gland biopsy	

Table 3–8 **Sensory, Large-Fiber, Ataxic Neuropathies: Isolated or Predominant**

Sensory neuropathy (ganglionopathy)	Sjögren syndrome	
	Paraneoplastic	
	Idiopathic	
	Toxic: pyridoxine hypervitaminosis, cisplatin, thalidomide, linezolid, metronidazole, podophyllotoxin, taxanes	
	HIV (rare)	
Demyelinating or mixed	Epstein-Barr virus	
	Acute:	Chronic:
	Ataxic GBS	Sensory CIDP
	Fisher syndrome	Anti-MAG/IgM MGUS
	Diphtheritic neuropathy	CANOMAD* CISP†
Miscellaneous	Tabes dorsalis (dorsal root/posterior columns)	
	Anti-sulfatide antibodies (axonal or demyelinating)	
	Celiac disease	
	HTLV-1 or -2 (tropical ataxic neuropathy)	
	Vitamin deficiencies: B ₁₂ , B ₁ , E	

(continued)

Table 3–8 (Continued)

ConsideredWork-up	
Sensory neuropathy: CBC, CMP, ESR, RF, ANA, anti-Ro/La, minor salivary gland biopsy, anti-Hu, malignancy work-up, careful toxic history, HIV, EBV	
Demyelinating or mixed electrophysiology: IFE, UPEP/immunofixation, anti-MAG, anti-GQ1b, anti-GD1b, lumbar puncture	
Miscellaneous: RPR, anti-sulfatide, celiac panel, HTLV-1; vitamins B ₁₂ , B ₁ , E	
* CANOMAD—chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and anti-GD1b disialosyl antibodies.	
† CISP—chronic immune sensory polyradiculopathy (dorsal root, demyelinating variant of CIPD; nerve conduction studies, other than H-reflex, are normal).	
EBV, Epstein-Barr virus.	

Table 3–9 Motor Neuropathies: Isolated* or Predominant

Axonal	Demyelinating
Distal hereditary motor neuropathies*	Multifocal motor neuropathy*
GBS—AMAN*	GBS—AIDP
CMT2	CIDP
Porphyric neuropathy	CMT1 and CMT4
Toxic: lead, dapson, amiodarone, vincristine	Toxic: amiodarone
ConsideredWork-up	
Axonal, acute/subacute: CSF analysis, <i>Campylobacter jejuni</i> antibody, porphyrins, toxic exposure history	
Axonal, chronic: careful family history, CMT II genetic testing, toxic exposure history	
Demyelinating, acute: CSF analysis, toxic exposure history	
Demyelinating, chronic: anti-GM1 antibody, CSF analysis, toxic exposure history, CMT1/CMT4 genetic testing, rarely nerve biopsy	
* Isolated motor involvement.	
AMAN: acute motor axonal neuropathy.	

Table 3–10 Autonomic Neuropathies: Isolated, Predominant, or Associated

Diabetes

Amyloidosis—primary (AL) and familial

Hereditary disorders: HSANs, porphyria, Fabry disease

Infectious diseases: HIV, leprosy, diphtheria, Chagas disease

Acute/subacute autonomic neuropathies:

- Guillain-Barré syndrome
- Paraneoplastic
- Autoimmune autonomic ganglionopathy (ganglionic AChR antibodies)
- Connective tissue diseases (SS, RA, SLE, MCTD)
- Viral/postviral: HSV, EBV, Coxackie B, rubella, mumps

Toxins—Vacor, vincristine, heavy metals, marine toxins, alcohol

Considered Work-up

FBS/HgbA1c/OGTT, IFE, porphyrins, HIV, ESR, ANA, RF, anti Ro/La, CSF analysis, toxic exposure history, heavy metals, anti-Hu, ganglionic AchR antibodies, transthyretin, α -galactosidase, fat pad/rectal/minor salivary gland/nerve biopsy

HSAN: hereditary sensory autonomic neuropathy; HSV: herpes simplex virus; MCTD: mixed connective tissue disease
SS: Sjögren syndrome.

Table 3–11 **Mononeuropathy Multiplex**

Sensory and Motor, Axonal
Vasculitis • Primary systemic: classic PAN, MPA, WG, CSS, GCA • Secondary systemic: CTDs, Behçet disease, MC, infections, drugs, paraneoplastic • Nonsystemic vasculitic neuropathy (NSVN) Multiple entrapments Sarcoidosis Infections: HIV, CMV, HCV, HBV, leprosy, Lyme disease Neoplastic: neurofibromatosis, neurolymphomatosis, neuroleukemiosis, multiple myeloma Celiac disease Cholesterol emboli neuropathy Diabetes (uncommon) Regional, multifocal radiculoplexus distribution: - Immune brachial plexus neuropathy (neuralgic amyotrophy) - Lumbosacral radiculoplexus neuropathy - Herpes zoster - Ischemic monomelic neuropathy (IMN) Considered Work-up CBC including eosinophil count, CMP for glucose, renal and liver function tests, ESR, CRP, RF, ANA, complement, ENA (Ro, La, Sm, RNP, Scl-70), c-ANCA and p-ANCA, IFE, hepatitis panel, celiac panel, cryoglobulins, HIV, ACE, Lyme ELISA/WB, Urinalysis and CXR. Angiography or MRA (cPAN, IMN), minor salivary gland biopsy (Sjögren syndrome), chest CT or MRI (sarcoidosis, neoplasm), paraneoplastic antibodies (anti-Hu, anti-CV2), nerve/muscle biopsy
Sensory and Motor, Demyelinating
HNPP CIDP (MADSAM variant) GBS/AIDP (rarely) Tangier disease (rare) Considered Work-up PMP-22 deletion; CSF analysis; lipid profile
Motor, Demyelinating
Multifocal motor neuropathy Considered Work-up Anti-GM1 antibody
Motor, Axonal
Multifocal acquired motor axonopathy (MAMA) Considered Work-up Anti-GM1 antibody, CSF analysis
Sensory, Axonal
Wartenberg migrant sensory neuropathy Sensory perineuritis Considered Work-up Screen for systemic associations (diabetes, connective tissue disorders, inflammatory bowel disease, vasculitis, malignancies) before concluding idiopathic conditions; sensory nerve biopsy
CMV: cytomegalovirus; CRP: C-reactive protein; CSS: Churg-Strauss syndrome; CTDs: connective tissue diseases; ENA: extractable nuclear antigens; GCA: giant cell arteritis; HNPP: hereditary neuropathy with liability to pressure palsies; MADSAM: multifocal acquired demyelinating sensory and motor neuropathy; MC: mixed cryoglobulinemia; MPA: microscopic polyangiitis; PAN: polyarteritis nodosa; WG: Wegener granulomatosis.

Table 3–12 **Myeloneuropathies (Combined Myelopathy and Polyneuropathy)**

Vitamin/mineral deficiencies	Vitamin B ₁₂ , copper, vitamin E, folate, Cuban epidemic (multiple vitamin deficiency)
Toxic	Nitrous oxide (<i>anesthesia parasthetica</i>), cassava (cyanide), organophosphate insecticides
Inflammatory	Connective tissue diseases, sarcoidosis
Infectious	HTLV1, HIV, Lyme disease
Hereditary	Adrenomyeloneuropathy, “complicated” hereditary spastic paraplegia subtypes, hereditary neuropathies: CMT2A/HMSN-V, CMT2H, CMT2D/dHMN-V, SCA subtypes
Considered Work-up	
Vitamin B ₁₂ , methylmalonic acid/homocysteine, copper/zinc, HIV, HTLV1, Lyme ELISA/WB, ACE/CXR/chest CT/gallium scan, connective tissue disease serologies, very long chain fatty acids, genetic testing, toxic exposure history	

dHMN-V: distal hereditary motor neuropathy, type V; HMSN-V: hereditary motor sensory neuropathy, type V; SCA: spinocerebellar ataxias.

Table 3–13 **Neuromyopathies (Combined Myopathy and Polyneuropathy)**

Uremia
Sarcoidosis
Amyloidosis
Paraneoplastic
Connective tissue disorders
Acromegaly
HIV
HTLV1
Lyme disease
Critical illness polyneuropathy and myopathy
Mitochondrial disorders
Inclusion body myopathy
Adult polyglucosan body disease
Toxic: colchicine, chloroquine, hydroxychloroquine, amiodarone, ethanol, L-tryptophan, vincristine
Considered Work-up
Renal function tests, ACE/CXR/chest CT/gallium scan, IFE, malignancy work-up/paraneoplastic antibodies, connective tissue disease serologies, growth hormone, HIV, HTLV1, Lyme ELISA/WB, lactate/pyruvate, toxic exposure history, fat pad/rectal/nerve/muscle biopsy

Table 3–14 **Polyneuropathy and Optic Neuropathy**

Vitamin B ₁₂ deficiency
Copper deficiency
Thiamine deficiency
Tobacco-alcohol amblyopia
Cuban epidemic (nutritional multiple vitamin deficiencies)
Cassava toxicity (cyanide)
Hereditary: CMT2A/HMSN-VI, Leber hereditary optic neuropathy
Toxic: amiodarone, chloramphenicol, chloroquine, disulfiram, ethambutol, isoniazid, linezolid, penicillamine, vincristine
Considered Work-up
Vitamin B ₁₂ , methylmalonic acid/homocysteine, copper/zinc, thiamine, genetic testing, toxic exposure history

Table 3–15 **Polyradiculopathies**

Inflammatory/Infectious	Structural/Ischemic/Neoplastic
Lyme disease	Spinal stenosis
Herpes zoster radiculitis	Large herniated disc
Epstein-Barr virus	Arachnoiditis
HIV-related polyradiculitis: cytomegalovirus,	Epidural lipomatosis
syphilis, tuberculosis, lymphoma, herpes simplex,	Radiation
cryptococcus	Dural arteriovenous malformations
Sarcoidosis	Meningeal carcinomatosis or lymphomatosis
Diabetic L/S and cervical radiculoplexus neuropathy	Primary and metastatic vertebral neoplasms
Diabetic thoraco-abdominal neuropathy	Neurofibromatosis
Chronic immune sensory polyradiculopathy (CISP)	
Connective tissue diseases	
Considered Work-up	
Spinal MRI (+gadolinium), CSF analysis, Lyme ELISA/WB, HIV, EBV, ACE, CXR/chest CT/gallium scan, malignancy work-up, FBS/HgbA1c/OGTT, connective tissue disease work-up, somatosensory evoked potentials (CISP)	

Table 3–16 **Plexopathies/Radiculoplexopathies**

Brachial	Lumbosacral
Immune brachial plexus neuropathy (neuralgic amyotrophy, Parsonage-Turner syndrome)	Diabetic L/S radiculoplexus neuropathy
Hereditary brachial plexus neuropathy (hereditary neuralgic amyotrophy [HNA])	Nondiabetic L/S radiculoplexus neuropathy
HNPP	Retroperitoneal hematoma
Thoracic outlet syndrome	Psoas abscess
Diabetic cervical radiculoplexus neuropathy	Perioperative: obstetric, hip surgery
Trauma: postmedian sternotomy, obstetric paralysis, stingers/burners, rucksack paralysis	
	Violent closed trauma
	Neoplasm
	Radiation
	Inflammatory/infectious (Lyme disease, sarcoidosis, herpes zoster, ehrlichiosis, CTDs)
	Ischemic monomelic neuropathy
	Vasculitis
	Toxic (heroin)
	Amyloidosis
Considered Work-up	
Plexus MRI (+ gadolinium), spinal MRI, ESR, ANA, RF, Lyme ELISA/WB, Human Granulocytic Ehrlichiosis, FBS/HgbA1c/OGTT, ACE, vascular studies, genetic testing for HNA (research) or HNPP, toxic exposure history	

Table 3–17 **Facial Neuropathy**

Unilateral (acute)	Bell's palsy Lyme disease Herpes zoster cephalicus (Ramsay-Hunt syndrome) HIV Trauma Tumors: cerebellopontine angle, VIIth nerve, parotid, carcinomatous meningitis
Unilateral (slow)	Tumor
Recurrent (unilateral)	Bell's palsy Tumor
Recurrent (alternating)	Bell's palsy Melkersson-Rosenthal syndrome
Bilateral (acute, simultaneous, or sequential)	Lyme disease Guillain-Barré syndrome Sarcoidosis Vasculitis Basilar meningitis
Bilateral (chronic)	Gelsolin familial amyloid polyneuropathy Tangier disease Leprosy Möbius syndrome
Partial (branch)	FOSMN (facial-onset sensory and motor neuropathy) Marginal mandibular branch trauma Asymmetric crying facies

Considered Work-up
Lyme ELISA/WB, CSF analysis, HIV, ACE/CXR/chest CT/gallium scan, ESR, ANA, RF, other vasculitic serologies, brain MRI (+ gadolinium), skin biopsy, blink reflex study

Table 3–18 **Trigeminal Sensory Neuropathy**

Connective tissue disorders: Sjögren syndrome, mixed CTD, undifferentiated CTD, scleroderma
Leprosy
Sarcoidosis
Tumor
Lyme disease
Toxic: trichloroethylene/dichloroacetylene
Idiopathic (central: multiple sclerosis)

Considered Work-up
CTD serologies (ESR, ANA, RF, anti-Ro/La, anti-RNP, anti-Scl 70), ACE/CXR/chest CT/gallium scan, brain MRI + gadolinium, Lyme ELISA/WB, toxic exposure history

Table 3–19 **Unusual Neuropathy Patterns**

Tangier disease: syringomyelia-like presentation
FOSMN (facial-onset sensory and motor neuropathy)
Porphyric neuropathy: proximal weakness
Non-length-dependent small-fiber ganglionopathy
Leprosy: patchy sensory loss
Mental nerve neuropathy (numb chin syndrome): carcinoma, lymphoma, dental procedure

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Electrodiagnostic, Imaging, Nerve, and Skin Biopsy Investigations in Peripheral Nerve Disease

ELECTROMYOGRAPHY AND NERVE CONDUCTION STUDIES

Sensory Nerve Conduction Studies

Motor Nerve Conduction Studies

Late Responses

Blink Reflex Studies

Needle Electromyography

STUDIES OF AUTONOMIC FUNCTION

Quantitative Sudomotor Axon Reflex Test (QSART)

Thermoregulatory Sweat Test (TST)

Sympathetic Skin Response (SSR)

Heart Rate Response to Deep Breathing

Valsalva Maneuver

QUANTITATIVE SENSORY TESTING (QST)

DEVELOPING ELECTROPHYSIOLOGIC AND IMAGING TECHNIQUES

Motor Unit Number Estimation (MUNE)

Electrical Impedance Myography (EIM)

High-Resolution Sonography of Peripheral Nerve

Magnetic Resonance (MR) Neurography

Muscle MRI

Positron Emission Tomography (PET)

NERVE BIOPSY

Indications

Technical Considerations

SKIN BIOPSY

ELECTROMYOGRAPHY AND NERVE CONDUCTION STUDIES

Electromyography (EMG) and nerve conduction studies (NCS), sometimes referred to collectively as *electrodiagnostic studies*, are an essential part of assessing nerve and muscle function in neuromuscular diseases. The term *electromyography* is sometimes used to refer to both EMG and NCS, but more properly it refers to needle examination of muscle electrical activity (needle EMG). EMG/NCS quantitatively assess nerve and muscle function in terms of localization, type (axonal versus demyelinating neuropathy), extent (focal versus generalized), and severity. EMG/NCS

are tailored to the clinical question at hand. This is why it is essential to evaluate every patient clinically to assist in planning and interpreting the study. EMG/NCS are usually used to help confirm a clinical diagnosis or differentiate clinical possibilities. However, they also have utility in monitoring disease progression objectively over time. Electrodiagnostic studies should be planned, performed (or directly supervised), and interpreted only by physicians with extensive neuromuscular and electrophysiologic training to avoid pitfalls. In the authors' experience, improperly performed or interpreted EMG/NCS are common in clinical practice, leading to misdiagnosis and erroneous therapies with associated morbidity.

EMG/NCS cause discomfort, but the risk of morbidity is minimal with needle EMG. There is a very small risk of hematoma formation (accentuated by the use of antiplatelet drugs or anticoagulants)¹ or minor burns from heating pads and an even smaller risk of infection (the authors have never seen a resulting cellulitis in practice); very rarely, misplaced needle insertion has resulted in pneumothorax.

Nerve conduction studies involve electrical stimulation with a square wave pulse and recording over a nerve or muscle, usually using surface electrodes. The amplitude of the resultant waveform (potential height) reflects the number of functioning nerve fibers, and the conduction velocity and distal latency (distal conduction time) reflect myelinated, large-fiber function.

Needle EMG assesses the electrical activity of voluntary muscles at rest and with contraction by inserting a needle electrode in muscles at varying depths and trajectories. Abnormal spontaneous activity at rest (i.e., fibrillation potentials) suggests axonal or muscle fiber degeneration, and increased motor unit

potential size (duration and amplitude) suggests reinnervation. Reduced recruitment of motor unit potentials and increased firing frequency with increasing voluntary contraction suggests a neurogenic lesion.

Sensory Nerve Conduction Studies

Conduction velocity and amplitude measurements of sensory and mixed (motor and sensory) nerve action potentials assess sensory and sensorimotor nerve function and integrity (Fig. 4-1). Recordings may be either orthodromic (in the direction of sensory impulses), with distal stimulation and proximal recordings, or antidromic (in the opposite direction), with proximal stimulation and distal recordings. Normative values should be established by the performing laboratory. Antidromic recordings are of larger amplitude than orthodromic ones because the nerve is closer to the recording electrode, but antidromic responses are more likely to be contaminated by motor artifacts. A supramaximal stimulus (one that is

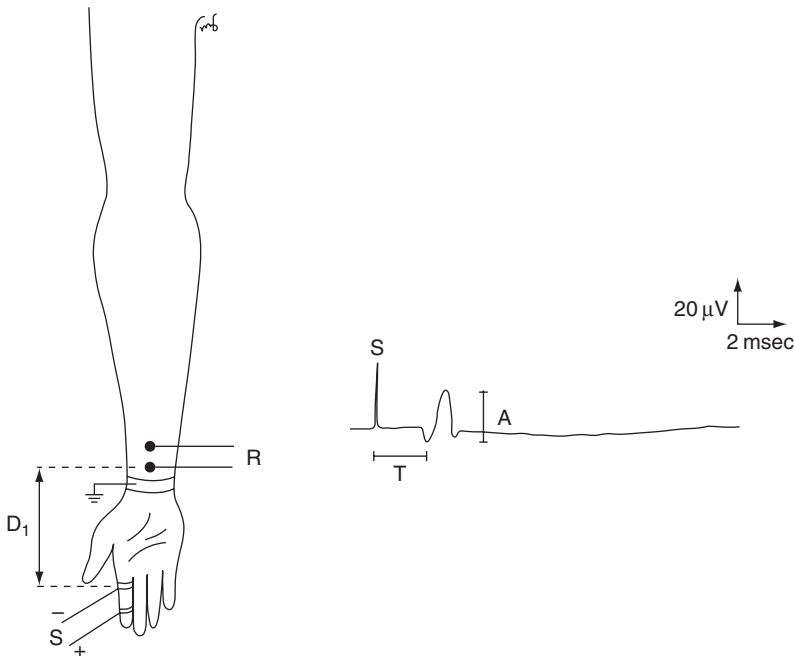


Figure 4-1. Sensory nerve conduction study. The technique illustrated is an orthodromic study of the median nerve, stimulating (S) the digital nerves with the cathode at the proximal interphalangeal joint and recording (R) at the wrist. Latency (T) to the onset of the waveform and distance (D) are measured, with conduction velocity calculated as D/T in meters per second. The amplitude (A) is measured from initial peak to peak.

incrementally increased until the response amplitude is maximal) is used to ensure activation of all sensory nerve fibers. This allows for reproducibility of the data and measurement of the largest-diameter, fast-conducting fibers. Limb temperature is generally maintained above 32°C. Proper positioning of recording and stimulating electrodes is critical.

Sensory responses are of relatively low amplitude and even smaller in certain nerves (antebrachial cutaneous, plantar), elderly patients, and diseased nerves. As such, they often require computer averaging to increase the signal-to-noise ratio. Sensory and mixed (motor and sensory) nerve action potentials are affected early in the course of most polyneuropathies. This reflects early pathologic involvement of large-diameter sensory fibers in many polyneuropathies. In length-dependent axonal polyneuropathies, there is a reduction in sensory nerve action potential (SNAP) amplitudes beginning in longer nerves (i.e., sural or peroneal sensory) because of large-fiber loss (Wallerian degeneration). Distal latencies and conduction velocities are relatively

preserved, since a proportion of large-diameter, fast-conducting fibers often remain intact. In demyelinating polyneuropathies, conduction velocities may be slowed or distal latencies prolonged, although amplitude reduction may also occur prior to axonal loss from temporal dispersion with resulting phase cancellation (action potentials arriving at different times). In entrapment neuropathies (particularly median nerve entrapment at the wrist), focal slowing of sensory or mixed nerve conduction occurs early across entrapment sites due to focal demyelination. Lesions proximal to the dorsal root ganglion do not affect the sensory potential, which is recorded in the distal limb (Fig. 4-2). As such, sensory response abnormalities place the lesion distal to the dorsal roots (a helpful localizing feature) (Table 4-1).

Motor Nerve Conduction Studies

Motor conduction studies involve the supramaximal stimulation of mixed or motor nerves and recording over a muscle in the

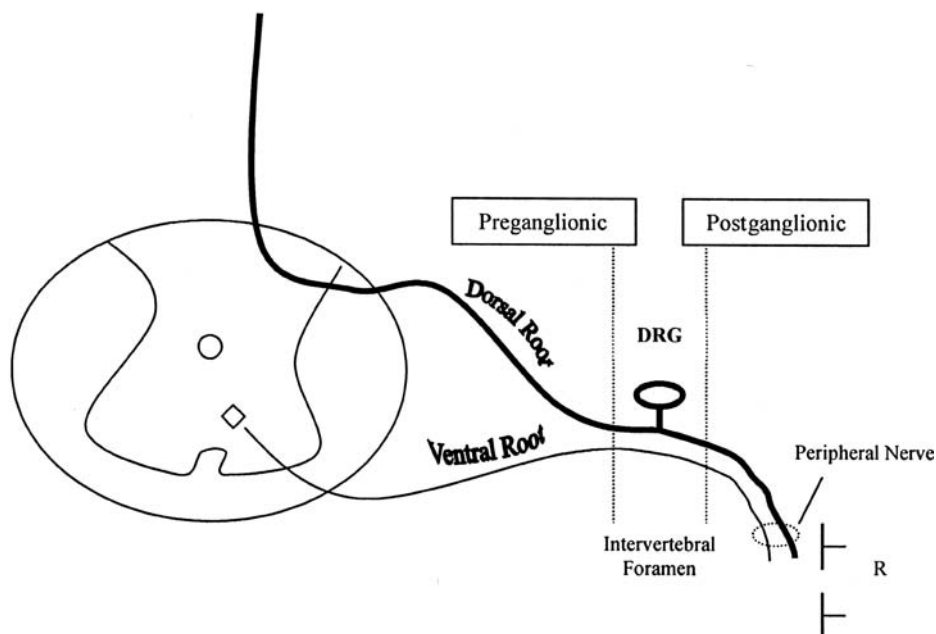


Figure 4-2. Diagram illustrating the dorsal root ganglion cell (DRG) inhabiting the intervertebral foramen as a bipolar cell with pre- and postganglionic processes. Preganglionic lesions (most structural root lesions; cerebrospinal fluid [CSF] processes; intramedullary lesions) will spare the SNAP, which is recorded (R) from the peripheral process. Lesions involving the DRG (neuronopathies/ganglionopathies) or the postganglionic nerve (plexopathies, mononeuropathies, polyneuropathies) will affect the SNAP.

Table 4–1 Possible Localizations for a Sensory Disturbance with a Normal or Low-Amplitude SNAP

Low-amplitude or absent SNAP
Polyneuropathy
Mononeuropathy
Plexopathy
Neuronopathy
Age-related / technical difficulty
Normal SNAP
Radiculopathy
Intramedullary spinal cord or cerebral lesion
Small-fiber neuropathy

endplate region (usually a midpoint where innervation predominates). The resulting response is a compound muscle action potential (CMAP), which reflects the summation of multiple muscle action potentials and the number of excitable motor nerve fibers. The size and shape of the CMAP

(amplitude, duration, area, and phases) also reflect varying conduction times of individual motor axons. Unlike sensory nerve recordings, two points of stimulation (a proximal and a distal site) are necessary, so velocity recordings reflect solely conduction along the nerve, eliminating neuromuscular transmission time (Fig. 4–3). To calculate a motor conduction velocity, the distance between the two stimulation sites is divided by the latency difference between the sites. In addition to conduction velocity, distal latency, amplitude, and duration are measured. Compound muscle action potentials are usually much larger than sensory potentials, making averaging unnecessary. As with sensory conduction, distal latencies and conduction velocities measure the function of the largest-diameter, fast-conducting fibers.

Compound muscle action potential amplitudes may be reduced from nerve fiber loss caused by dysfunction of the motor neurons, ventral roots, plexus, motor nerve, neuromuscular junction, or muscle (Table 4–2). Varying conduction

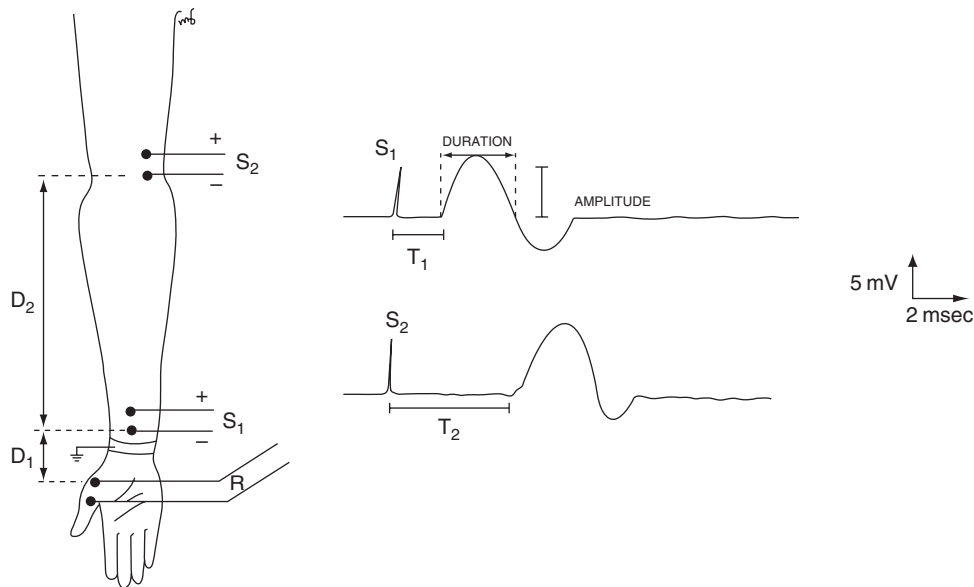


Figure 4–3. Motor nerve conduction study. The technique illustrated is a median nerve study recording (R) from the abductor pollicis brevis muscle, stimulating supramaximally at two sites (S₁ and S₂). Latencies (T₁ and T₂) are recorded to the resultant CMAP. Conduction velocity between the stimulation sites is calculated as D₂/T₂–T₁ in meters per second. The amplitude is measured from baseline to negative peak. The duration is measured as shown.

Table 4–2 **Possible Localizations for Weakness with a Normal or Low-Amplitude CMAP**

Low-amplitude CMAP	
Neuropathic	
Axonal	
Anterior horn cell	
Ventral root	
Plexus	
Nerve	
Demyelinating	
Distal conduction block	
Inexcitable nerve	
Myopathic	
Neuromuscular junction (presynaptic)	
Normal CMAP	
Proximal conduction block	
Central or functional process	
Neuromuscular junction (postsynaptic)	

times between motor nerve fibers, such as seen in demyelinating neuropathies, may also result in amplitude reduction through phase cancellation (when the negative/upward deflection of one muscle action potential

arrives at the same time as the positive/downward deflection of another). In axonal neuropathies, motor conduction velocities are usually unchanged until there is considerable loss of large, fast-conducting fibers. In radiculopathies, motor conduction slowing is typically absent. Demyelinating polyneuropathies are characterized by prolonged distal motor latencies, slow motor conduction velocities, conduction block, and temporal dispersion (including prolonged distal CMAP durations). Conduction block occurs when the proximal CMAP amplitude is reduced compared to the more distal response amplitude without a significant increase in duration (Fig. 4–4). Temporal dispersion is similar to conduction block but *with* prolongation of the response duration and often with a more complex morphology (Fig. 4–5). Distal CMAPs may also show temporal dispersion (increased response durations). Low-amplitude CMAPs with normal sensory potential amplitudes, in disorders with sensory involvement, suggest a localization at or proximal to the root. Focal slowing of motor conduction or conduction block across an entrapment site suggests nerve compression or entrapment.

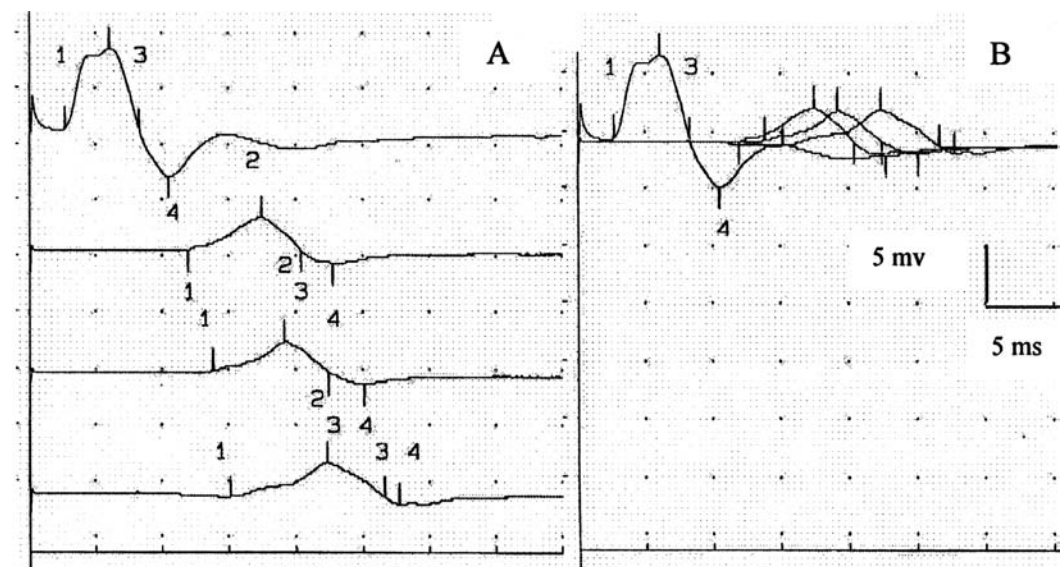


Figure 4–4 (A, B). Partial conduction block/temporal dispersion between the wrist (1) and below-elbow (2) stimulation sites of the ulnar nerve, also demonstrable upon stimulation at the above-elbow (3) and axilla (4) sites, in a patient with multifocal motor neuropathy with conduction block. Waveforms are rastered in (A) and superimposed in (B).

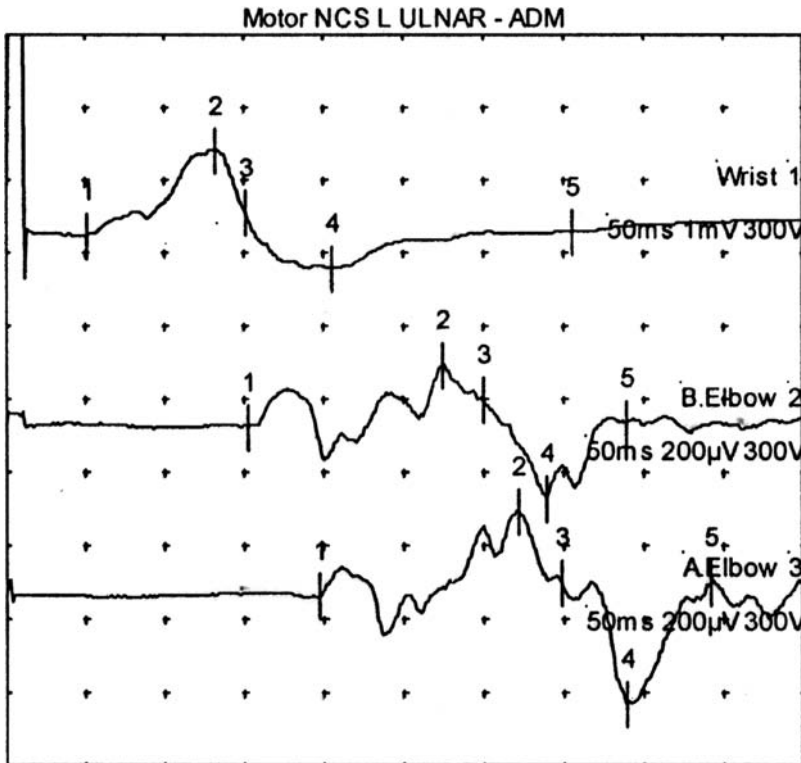


Figure 4-5. Marked temporal dispersion of the CMAP waveform between the wrist and below-elbow stimulation sites in an ulnar motor conduction study of a patient with chronic inflammatory demyelinating polyneuropathy.

Late Responses

F waves are obtained by distal supramaximal stimulation of motor nerves, reversing the polarity of the stimulator (cathode proximal), and recording with a surface electrode over a distal muscle in the same manner as with distal motor conduction (Fig. 4-6). The nerve depolarization under the cathode elicits a nerve action potential that travels both proximally toward the anterior horn cells and distally to the muscle. The distal recording is the CMAP (or M wave). The proximal volley depolarizes a fraction of the anterior horn cells (about 5%), particularly the larger motor neurons, and a recurrent action potential discharge then travels toward the distal muscle. The F wave is recorded with a broader time base and higher sensitivity than the distal CMAP recording. The principal F wave parameter measured is the minimal latency, which is the shortest latency of

10–20 responses, representing the fastest, largest motor fibers. Impersistence (a reduced number of responses) and the degree of chronodispersion (the difference between the maximal and minimal latency) are also recorded in some laboratories.

F waves are sensitive indicators of motor nerve function, since they reflect conduction along the entire course of the nerve. However, they are not very sensitive in detecting proximal root dysfunction, probably because root conduction makes up a small proportion of the total conduction time and muscles are characteristically innervated by more than one root. F waves have greatest utility in differentiating a demyelinating from an axonal polyneuropathy and in detecting early or mild polyneuropathy. In demyelinating polyneuropathies, F wave latencies are markedly increased or F waves may be impersistent or absent (due to conduction block or inexcitability). Since the degree of demyelination often differs between fibers,

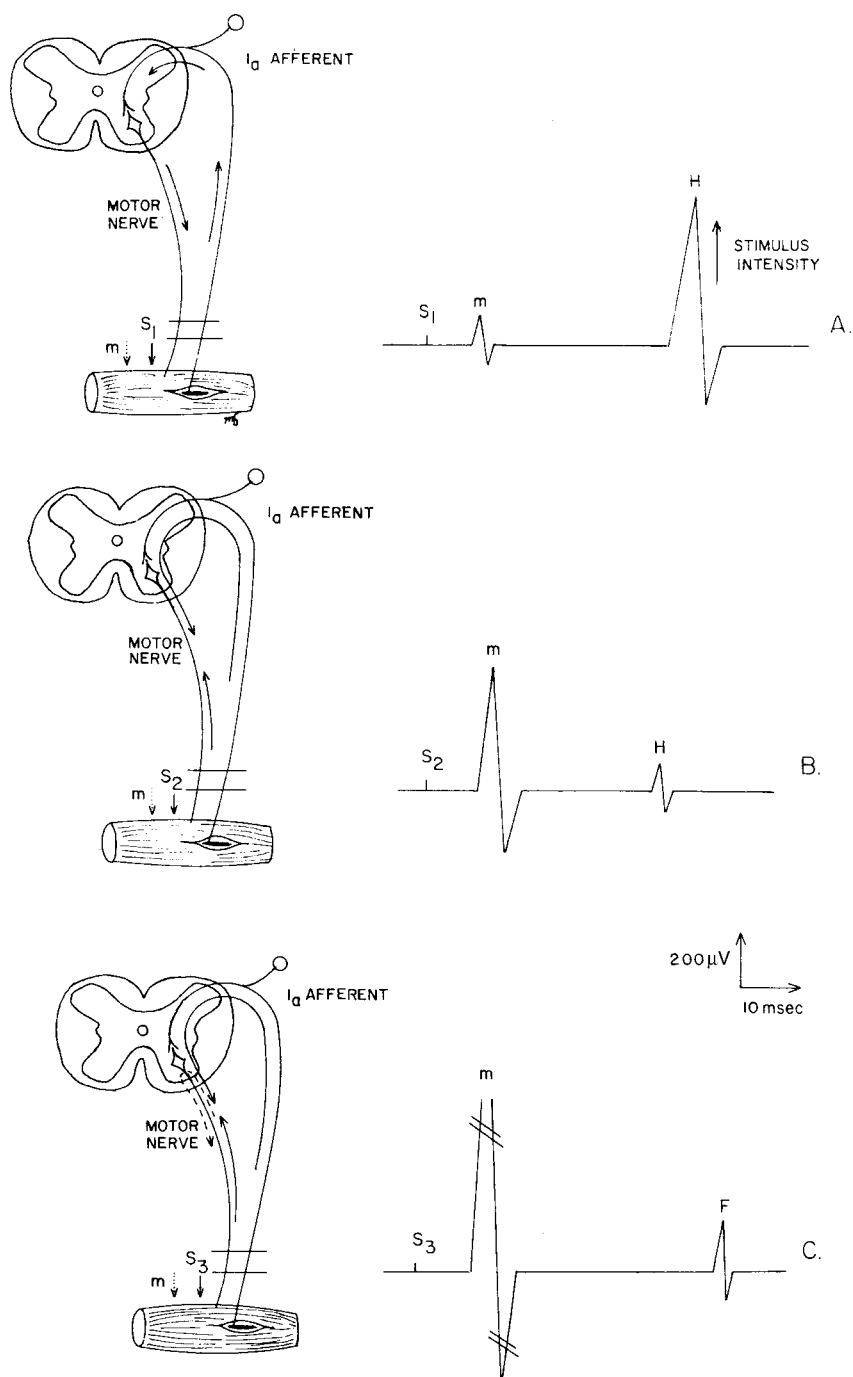


Figure 4-6. (A) The technique for recording late responses is illustrated. A submaximal stimulus with a long pulse duration is applied to a mixed nerve, causing excitation of the low-threshold Ia fibers with minimal stimulation of motor fibers. A long-latency potential (H reflex) is indirectly evoked following motor neuron synaptic stimulation by Ia afferents at a time when the short-latency, directly evoked CMAP (M response) is of minimal amplitude. (B) With larger stimulus intensity, more motor axons are excited: the larger antidromic potential collides with and reduces the reflexly generated H response, while the orthodromically induced M response is larger. (C) With supramaximal stimulation of the motor nerve, the H reflex is completely blocked, while the M response is maximal. The antidromic volley in the motor axons leads to retrograde firing of a small population of anterior horn cells, which generates descending impulses that give rise to low-amplitude, long-latency muscle action potential (F waves). S: stimulus shock artifact.

F wave latencies often have increased chronodispersion, although normative values are less well established. F waves have some diagnostic utility in radiculopathies (C8/T1, L5/S1) and in median nerve entrapment at the wrist (median exceeding ulnar minimal latency by >1 ms).²

An H reflex recorded from the soleus muscle is the electrophysiologic equivalent of the Achilles reflex. A submaximal stimulus with a long pulse duration (1 ms) is applied to the tibial nerve at the popliteal fossa with the cathode placed proximally; a surface electrode is placed over the soleus muscle at the distal aspect in the midline, and the latency is recorded (Fig. 4–6). As the stimulus is gradually increased, an H reflex occurs with a longer latency than the preceding distal CMAP (M wave). The stimulus is optimized to maximize the H reflex amplitude; the distal M wave should be smaller. This method selectively activates large-diameter IA afferent (sensory) fibers that form a monosynaptic reflex arc with anterior horn cells in the spinal cord. H reflex abnormalities occur in polyneuropathies, S1 radiculopathies, and sciatic neuropathies. Unlike F waves, H reflexes reflect both sensory and motor conduction and only assess the S1 root level. Like F waves, the H reflex assesses conduction along the course of the nerve, along proximal nerve segments, and is an early abnormality in both demyelinating and axonal polyneuropathies (though nonspecific). In the setting of corticospinal tract dysfunction, a tibial H reflex may be elicited in a tibial innervated foot muscle (analogous to a Babinski response).

Blink Reflex Studies

Blink reflex studies are performed by supra-maximal stimulation of the supraorbital nerve and recording over the orbicularis oculi muscle with surface electrodes. The blink reflex is the electrical equivalent of the corneal reflex and measures conduction in the trigeminal and facial nerves. It is composed of an oligosynaptic pontine reflex (R1 potential) and a polysynaptic pathway through the pons and lateral medulla (R2 or late component). The R2 corresponds to the actual blink (orbicularis oculi contraction). Latencies are recorded. Different patterns of blink reflex abnormalities are associated with dysfunction at selective sites along the reflex pathway. Blink reflex studies are

often performed with facial motor recordings, stimulating the facial nerve at the stylomastoid foramen and recording over a muscle of facial expression. Demyelinating polyneuropathies, especially those with facial involvement, may show prolonged blink or distal facial motor latencies. Polyradiculopathies may demonstrate low facial motor response amplitudes and absent blink responses. In Bell's palsy, the facial CMAP amplitude is the best electrophysiologic prognostic indicator.

Needle Electromyography

Needle EMG testing involves inserting a needle electrode in various limb and axial muscles at rest and contracting the muscles to varying degrees. Potential differences are recorded between a central core and the surrounding hub of the needle (concentric needle) or a single shaft of a needle (monopolar) with a surface reference electrode. In a normal muscle, needle electrode insertion shows no spontaneous electrical activity at rest, only brief insertional discharges with needle movement. The presence of spontaneous activity such as fibrillations (triphasic waves) or positive waves (biphasic waves) suggests motor axon degeneration (occurring at least 7–14 days earlier) or muscle fiber degeneration. Fibrillations represent spontaneous depolarizations of individual muscle fibers. A fasciculation potential, which in isolation is not pathologic, represents the spontaneous depolarization of a single motor neuron or axon. These potentials are most frequent in motor neuron diseases but also occur in other neurogenic disorders.

During a muscle contraction, needle EMG measures individual motor unit potential morphology (duration, amplitude, and the degree of polyphasia) and the pattern of recruitment with a more forceful contraction. As chronic reinnervation occurs in a recovering neurogenic lesion, motor unit potential size increases with increased duration (width), amplitude (height), and polyphasia (number of baseline crossings plus one). In reinnervation, each axon innervates a greater number of muscle fibers, hence the larger motor unit potential size. Polyphasic potentials also make up a minority of motor unit potentials in normal muscle. Motor unit potential duration and amplitude

are reduced in myopathies (fewer muscle fibers per axon).

Motor unit potential recruitment patterns with a more forceful contraction also differ between neurogenic disorders and myopathic disorders. In neurogenic disorders, voluntary recruitment is decreased with increased firing frequencies, since there are fewer axons to contribute to the muscle contraction. In myopathic disorders, the motor unit recruitment pattern is normal or increased. The degree and extent (proximal versus distal, unilateral versus bilateral) of active denervation changes aid in determining whether a polyneuropathy is distal and symmetric or multifocal and if there is associated radicular involvement. The presence of fibrillations in paraspinal muscles places a neurogenic lesion at or proximal to the spinal nerves, usually implicating ventral roots or anterior horn cells.

STUDIES OF AUTONOMIC FUNCTION

Autonomic dysfunction is associated with several disorders causing polyneuropathy including diabetes, amyloidosis, acute inflammatory demyelinating polyneuropathy (AIDP), and porphyria, as well as primary dysautonomias. Although a few simple tests can be performed by most electrophysiology laboratories (sympathetic skin response and R-R interval variation), such tests generally have low sensitivity and specificity and, as such, low clinical utility. More quantitative tests of sympathetic and parasympathetic function, for example the quantitative sudomotor axon reflex test and the Valsalva maneuver, are performed in specialized autonomic laboratories. Distal extremity loss of autonomic function may imply the presence of a distal small-fiber polyneuropathy. The presence of a small-fiber polyneuropathy may also be suggested pathologically by obtaining an epidermal nerve fiber density by skin biopsy.

Quantitative Sudomotor Axon Reflex Test (QSART)

The QSART is a routine, noninvasive, quantitative test of sudomotor, adrenergic, and cardiovascular functions. The test evaluates an axon reflex produced by postganglionic sympathetic

sudomotor axons. The terminal axon is stimulated by iontophoresis (transdermal delivery using a low electrical current) of acetylcholine using a multicompartmental sweat cell, typically over distal and proximal limb sites. A separate compartment quantifies the sweat response. The QSART is the most sensitive physiologic autonomic test in distal small-fiber polyneuropathies, with a sensitivity of 74%–80%, with 80% showing a length-dependent pattern of hypo-/anhydrosis.^{3,4}

Thermoregulatory Sweat Test (TST)

The TST involves administering a controlled heat stimulus in a moderately humid environment to produce a generalized sweat response and observing the sweat pattern using an indicator powder such as alizarin red, cornstarch, and sodium carbonate, iodinated cornstarch, or starch and iodine in solution.^{5,6} The target temperature is 38°C oral.⁶ The test assesses the function of both central and peripheral efferent sympathetic sudomotor fibers. Areas of reduced or absent sweating are computed as a percentage of the total anterior body surface.^{5,7} Patients with polyneuropathy characteristically show a distal pattern of hypo-/anhydrosis.³ The test evaluates sudomotor sympathetic dysfunction in primary autonomic failure and central or peripheral secondary autonomic dysfunctions such as neuropathies, myelopathy, sympathectomy, and skin or sweat gland disorders.⁸

Sympathetic Skin Response (SSR)

The SSR measures sympathetic sudomotor nerve fibers and change in skin resistance. Because of low sensitivity in detecting autonomic dysfunction in small-fiber polyneuropathies (5% in Fabry disease), poor reproducibility, and habituation, the response has low clinical utility, but the test can be easily done on most EMG machines.⁹ Recording electrodes are placed on the dorsal and ventral surfaces of the hand or foot and an electrical stimulus is usually applied in the distal limb to elicit a startle response. The sensitivity of SSR is also low in complex regional pain syndrome (27%), but it may be more useful in confirming the disease in chronic cases (>6 months), where sensitivity may approach 80%

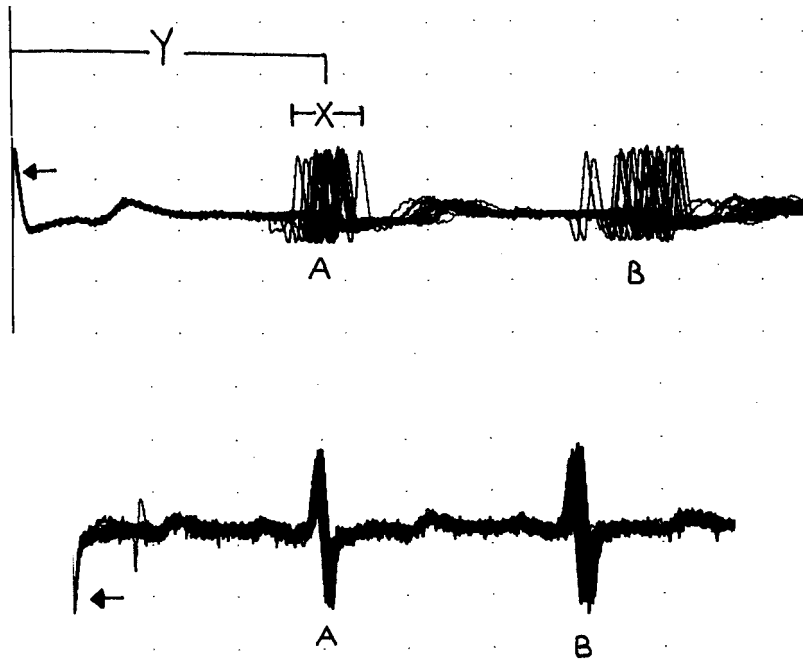


Figure 4-7. R-R interval variation testing during normal breathing in a normal subject showing substantial variation (top tracing), and in a patient with chronic dysautonomia (bottom tracing), demonstrating almost no variation between the superimposed triggered potential (arrow) and the subsequent untriggered QRS complexes (A and B). Percent R-R interval variation is calculated by mean R-R variation (X ms) divided by the R-R interval measured from the midpoints of the triggered and untriggered potential complexes (Y ms) multiplied by 100.

(though the diagnosis is usually clinically obvious at this stage).¹⁰

Heart Rate Response to Deep Breathing

Normally, heart rate varies to a greater degree with deep breathing than at rest, and this measures efferent, and possibly afferent, pathways of the vagal nerve. Various methods have been employed including the R-R interval variation,¹¹ heart rate range, heart period range, or the E:I ratio (ratio of the longest R-R interval during expiration to the shortest R-R interval during inspiration).¹² The R-R interval can be measured on most EMG machines (Fig. 4-7).

Valsalva Maneuver

The Valsalva maneuver assesses both cardio-vagal and sympathetic vasomotor function and is usually performed in a specialized autonomic

laboratory. The maneuver involves blowing against airway resistance at a predetermined pressure, causing an abrupt elevation of intrathoracic and intra-abdominal pressures. The Valsalva ratio largely reflects parasympathetic function and is defined as the longest R-R interval (Phase IV) divided by the shortest R-R interval (Phase II). Changes in arterial pressure during Phase II (a decrease and partial recovery of arterial pressure and a continuous increase in heart rate) and Phase IV (overshoot of arterial pressure and bradycardia relative to the resting level) assess sympathetic vasomotor function.¹³ The Valsalva maneuver has high sensitivity in detecting autonomic dysfunction in patients with diabetic polyneuropathy and Guillain-Barré syndrome.^{14,15}

QUANTITATIVE SENSORY TESTING (QST)

Quantitative sensory testing involves administering a precisely measured and variable

stimulus (vibration, hot, or cold) to the ventral pad of the great toe or index finger to determine the absolute threshold of sensation to the various sensory modalities. Prior to the advent of epidermal nerve fiber density determinations, QST was a primary tool in identifying and quantifying the extent of small-fiber sensory dysfunction (heat and cold sensation), but it did not differentiate a peripheral from a central nervous system cause. Because of the noninvasive nature of the test, QST still has considerable utility in monitoring the clinical progression of neuropathy or the response to treatment. As such, it is an important outcome measure in clinical trials of polyneuropathy. Quantitative sensory testing is usually available only in specialized neuropathy or neuromuscular centers. The test is inexpensive, painless, and portable (for field studies).¹⁶ However, it is not precisely localizing and is dependent on the subjective response of the patient. Quantitative sensory testing cannot differentiate polyneuropathy from malingering.¹⁷ A recent consensus statement suggested that QST is probably or possibly useful in identifying small- or large-fiber sensory abnormalities in patients with diabetic polyneuropathy, small-fiber neuropathies, uremic neuropathy, and demyelinating neuropathy.¹⁸ The QSART test may have greater sensitivity (80%) than QST thermal thresholds (67%), but QST is a more direct measure of sensory function.⁴

DEVELOPING ELECTROPHYSIOLOGIC AND IMAGING TECHNIQUES

Motor Unit Number Estimation (MUNE)

Motor unit number estimation is an electrophysiologic technique that approximates the number of motor neurons or axons in a given nerve. Different techniques include incremental stimulation, multiple point stimulation, statistical, and spike-triggered averaging and decomposition methods. In all of them, the CMAP amplitude is divided by an estimate of the average surface motor unit action potential amplitude.^{19–21} It has been used as an experimental, objective outcome

variable in amyotrophic lateral sclerosis (ALS) clinical trials to monitor motor unit loss and has also been used to study the physiology and natural history of spinal muscular atrophy, Charcot-Marie-Tooth (CMT) disease, West Nile motor neuronopathy, and critical illness myopathy.^{21,22}

Electrical Impedance Myography (EIM)

Electrical impedance myography is an experimental electrophysiologic technique that measures reactance (accumulation of oscillating charges), resistance (opposition to current flow in tissue fluids), and anisotropy (greater current flow along muscle fibers than across them).²² It involves applying a variable, high-frequency, low-intensity, painless alternating current to a limb muscle using surface electrodes and recording voltage changes across an inner pair of surface electrodes. This method may lead to a noninvasive way to measure varying electrical properties of muscle in neuromuscular diseases. Data in a limited number of ALS patients differed significantly from control data.²³

High-Resolution Sonography of Peripheral Nerve

High-resolution sonography of peripheral nerves may aid in the diagnosis of entrapment mononeuropathies, particularly in mild cases where the electrophysiology study is equivocal.²⁴ The characteristic findings are focal nerve enlargement and loss of echogenicity just proximal to the entrapment site.^{24–26} Ultrasound may also reveal focal mass lesions such as cysts or neural tumors. The ratio of the area of the site of maximal enlargement to a normal adjacent segment may increase the yield in entrapment neuropathies.^{25,27} Ultrasound shows promise in identifying nerve enlargements in hereditary neuropathies, multifocal motor neuropathy, and possibly vasculitic polyneuropathy.^{28–30} A cadaver study shows high sensitivity and specificity of ultrasound in detecting nerve transection.³¹

Magnetic Resonance (MR) Neurography

Magnetic resonance imaging (MRI) of peripheral nerves, plexus, or nerve roots has known utility in identifying mass lesions (cysts or tumors) compressing or infiltrating peripheral nerves. Magnetic resonance neurography is a modification of traditional MRI using fat suppression, special contrast agents, and phased array coils.³² In carpal tunnel syndrome, MR neurography (inversion recovery with fat saturation) shows proximal nerve swelling, increased signal in the swollen segment, increased flattening ratios, and loss of signal in the distal carpal tunnel.³² Magnetization-prepared acquisition gradient echo (MPRAGE) shows promise in three-dimensional imaging of the sciatic nerve and brachial plexus.³³ Magnetic resonance neurography does not clearly differentiate various subtypes of CMT.³⁴ After crush injury in rats, the sciatic nerve shows increased T2 signal and contrast enhancement with a novel contrast agent, gadofluorine, within 48 hours throughout the nerve segment below the crush.³⁵ This may persist for months and diminishes in a proximal-to-distal gradient as reinnervation occurs.³⁶ Diffusion tensor imaging shows promise in demonstrating nerve transection and reinnervation after nerve repair.³⁷

Muscle MRI

Increased T2 signal and gadolinium enhancement occur in acutely denervated muscle in concert with the development of fibrillations on needle EMG; this may reflect capillary enlargement and increased muscular blood volume.³⁵ Chronically denervated, atrophic muscles with fatty replacement show decreased signal on T1-weighted images.

Positron Emission Tomography (PET)

Positron emission tomography may demonstrate increased fluorodeoxyglucose (FDG) uptake in segments of the neurovascular bundle suggesting leukemic infiltration of nerve.³⁸ However, the finding of increased FDG uptake has to be interpreted in the

clinical context because it is nonspecific and may be seen with inflammatory infiltrates. Resolution of increased FDG uptake in the common peroneal nerve following chemotherapy was reported in a patient with acute lymphoblastic leukemia and leukemic nerve infiltration; this correlated with clinical improvement.

NERVE BIOPSY

Indications

Nerve biopsy is a *diagnostic* test; it is of little help in early detection or in monitoring the progression of peripheral nervous system (PNS) disease and is useful in only a small number of patients with peripheral neuropathy. Nerve biopsy and tissue evaluation is expensive; it may occasionally involve considerable discomfort and may be overutilized as an early diagnostic procedure. It is performed best in centers with special expertise and facilities for full examination of the specimen.

Nerve biopsy is most helpful in identifying systemic illnesses that produce multiple mononeuropathy syndromes such as vasculitis, amyloidosis, sarcoidosis, and leprosy; simultaneous muscle biopsy may be informative in vasculitis, and sarcoidosis. The yield of nerve biopsy is best in acute or subacute, asymmetric and severe, progressive neuropathies. Inherited metabolic illnesses such as metachromatic leukodystrophy, Krabbe disease, adrenoleukodystrophy, and Fabry disease are associated with specific changes in peripheral nerve but are more readily identified by biochemical analysis of peripheral blood samples. Tumor nodules suggest an inherited tendency to pressure palsies but are not entirely specific. Demyelinating neuropathies may sometimes be identified on biopsy if the specimen is examined by epoxy resin and teased fiber techniques. Biopsy may occasionally be helpful in distinguishing acquired chronic inflammatory demyelinating polyneuropathy from inherited demyelinating polyneuropathies such as CMT1. Immunoglobulin deposition on myelin can be demonstrated immunohistochemically in many cases of demyelinating polyneuropathy associated with IgM paraproteinemia. Nerve biopsy can be helpful in the diagnosis of amyloidosis,

and immunohistochemical studies can differentiate between primary systemic (AL) amyloidosis and familial amyloid polyneuropathy; however, other, less invasive tissues are available for biopsy, and genetic testing is available for transthyretin mutations. Biopsy appears justified in cases of diffuse cryptogenic neuropathy whose investigation has failed to suggest an etiology. Conditions masquerading atypically as distal axonopathies (chronic inflammatory demyelinating neuropathy, vasculitis, and sarcoidosis) are occasionally revealed only at biopsy.

Individuals whose diagnosis is relatively secure on clinical grounds (diabetes, alcoholic malnutrition, porphyria, uremia, AIDP, and those metabolic-toxic disorders whose etiology is clearly established) do not require biopsy. Distal symmetric axonal neuropathies, of the type associated with most metabolic or toxic conditions, show similar nonspecific morphologic features, and biopsy is rarely as informative as meticulous medical evaluation.

Technical Considerations

SURGERY

The sural nerve above the ankle and the superficial peroneal nerve in the lateral calf are favored for nerve biopsy; the superficial radial nerve at the wrist is sometimes used. In persons suspected of having a granulomatous or vasculitic condition, more proximal leg sites are chosen in order to allow an additional biopsy from an adjacent muscle. All nerves used for biopsy are sensory nerves, and a suitable length may be excised under local anesthesia. Following biopsy at these sites, cutaneous sensory loss appears in the distribution of the nerve, and may be accompanied by dysesthesias for several weeks. Removal of the whole nerve is customary in many centers; it is indicated in cases in which vasculitis, amyloidosis, or granulomatous neuropathy is suspected, as the lesions may be scattered. It is helpful if a single individual in an institution becomes thoroughly familiar with the technique and performs all diagnostic biopsies. Although this seems to be a simple and trivial procedure, even an experienced surgeon can easily biopsy a vein or cause histologic artifacts by rough handling of a specimen of nerve.

HISTOLOGIC TECHNIQUES

Four preparations should be available for every nerve biopsy: conventional paraffin sections, teased fibers, frozen sections, and epoxy-embedded sections for light and electron microscopy. Each procedure has advantages, and each may be done on a separate section of the fixed tissue obtained at biopsy. A sample should also be taken and kept for frozen sections if required. If vasculitis is suspected, a quick answer can sometimes be obtained from frozen sections stained by hematoxylin and eosin.

Conventional Paraffin-Embedded Tissue

Paraffin sections, following routine staining, are useful for assessing cellular infiltrations, blood vessel changes, and granulomatous and neoplastic infiltrations. Special stains for amyloid and *Mycobacterium leprae* bacilli are sometimes indicated, although leprosy bacilli are more readily identified by electron microscopy. Subtle changes in axons, myelin, and Schwann cells are not well appreciated in conventional stained tissue. Immunolabeling for identification of lymphocyte subsets may be helpful in the evaluation of inflammatory infiltrates.

Single Teased Fibers

This technique readily allows the rapid identification of axonal degeneration and segmental demyelination in long lengths of nerve fibers. Quantitative studies of internodal length and diameter are easily performed but are laborious; the relationship between the length of internodes and the myelinated fiber diameter can be expressed graphically or statistically. Normally, there is little variation between internodal lengths in a single fiber. Teased-fiber studies are not required on every biopsy specimen but are helpful in confirming a demyelinating neuropathy and are mandatory if tomaculous neuropathy is suspected.

Frozen Section

This technique allows immune staining. Cell markers can differentiate different varieties of immunologically active cells (CD4, CD8). Other techniques can detect deposition of

immunoglobulins on nerve fibers (IgM anti-body to MAG) or in blood vessel walls.

Epoxy Resin–Embedded Tissue

Light microscopic examination of such sections is an especially useful technique for assessing changes in large numbers of axons, Schwann cells, and myelin since all are stained and well preserved by this technique. Both loss of myelinated fibers and the size of fiber affected can be appreciated by casual examination. The exact change in the population and caliber spectrum can be further determined, if necessary, by quantitative morphometric assessment of fiber numbers and diameters. Ultrathin sections may be cut from the same epoxy blocks and processed for electron microscopy. Electron microscopy is useful for determining ultrastructural features in axons, myelin, and Schwann cells and for identifying both subtle changes and specific pathologic features characteristic of some neuropathies, such as cellular inclusions in inherited storage disorders. As stated previously, it is an effective method for detecting leprosy bacilli.

SKIN BIOPSY

This simple, minimally invasive procedure provides a valuable anatomic measure of disorders of the preterminal and terminal ends of

unmyelinated axons in the epidermis and dermis.³⁹ These nerve fibers (C fibers) are involved in most neuropathies but are not assessed in conventional neurophysiologic studies. The technique is simple, but the analysis of biopsies is complex and is beyond the abilities of most medical centers. Specimen biopsy kits are available, and the fixed tissues may be sent to laboratories equipped to process and analyze the material. A 3-mm punch biopsy from hairy skin sites in either a distal or proximal limb is performed, the specimen is fixed in a paraformaldehyde mixture, frozen sections are taken, and immunohistochemical staining for several antigens may be done. The most common stain is for the highly immunoreactive PGP 9.5 (pan-axonal marker protein gene product 9.5). Unmyelinated axons in both dermis and epidermis can be counted and their morphology assessed (Fig. 4–8; see also Color Fig. 4–8). Normative data on intraepidermal nerve fiber (IENF) density for persons of all ages is available for the distal and proximal thigh, distal leg, trunk, forearm, and heel. A limitation of the technique is that smooth skin of the fingertips and toes is not biopsied, in most cases, and mechanoreceptor density in these sensitive areas is not determined. Most axonal neuropathies display focal swelling as a predictive indication of eventual degeneration and fiber loss.

Although most neuropathies will display loss of unmyelinated fibers with the skin biopsy

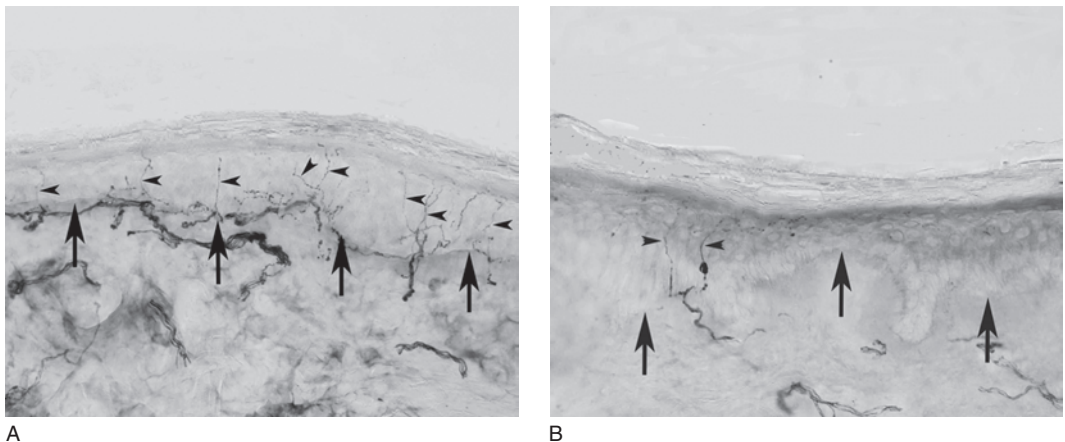


Figure 4–8 (A, B). (A) Skin biopsy demonstrating normal epidermal nerve fiber density (arrowheads); arrows indicate the basement membrane that separates the dermis from the epidermis. In (B) there is neuropathy with reduced epidermal nerve fiber density (arrowheads) and an axonal swelling. *Source:* Courtesy of Therapath. (See Color Plate 4–8, A–B.)

technique, those with prominent large-fiber components are usually most readily evaluated with conventional neurophysiology and clinical laboratory tests. Skin biopsies have proven most useful in longitudinal research studies assessing idiopathic small-fiber neuropathies, as these conditions are “invisible” to conventional clinical neurophysiology.³⁹ Since the biopsies can be repeated several times from both proximal and distal sites in the same patient, the technique has also been of value for measuring progress or improvement of axonal degeneration. Treatment protocols for neuropathies (diabetes, chemotherapy neuropathies, human immunodeficiency virus [HIV]) can utilize serial biopsies to assess efficacy. Intraepidermal nerve fiber density may be more sensitive than QSART, QST, or sural nerve biopsy in identifying small-fiber neuropathy.^{40,41}

There is a preliminary study that suggests that mechanoreceptor Meissner corpuscles, innervated by small myelinated axons, may be evaluated by in vivo examination with confocal microscopy. The usefulness and reliability of this procedure are unproven.⁴² A study of stimulated skin wrinkling in a glabrous hand (which results from vasoconstriction controlled by sympathetic fibers), using water and EMLA (eutectic mixture of local anesthetics), suggests that this technique is almost as sensitive as IENF density in detecting small-fiber neuropathy.⁴³

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Case Presentations Illustrating the Diagnostic Method

CASE 1: PAINFUL SMALL-FIBER NEUROPATHY AND DYSAUTONOMIA

CASE 2: INSIDIOUS ONSET OF DISTAL WEAKNESS IN AN ADULT WITH DEFORMED FEET

CASE 3: LOWER LIMB PARESTHESIAS IN A MIDDLE-AGED ADULT WITH DIABETES

CASE 4: A MIDDLE-AGED WOMAN WITH MUSCLE TWITCHING AND EPISODIC NUMBNESS

CASE 5: SIX DAYS OF CRANIAL NEUROPATHIES AND HYPOREFLEXIA

CASE 6: TWO-MONTH ONSET OF SENSORY NEUROPATHY IN A WOMAN WITH OVARIAN CARCINOMA

CASE 7: A 47-YEAR-OLD MAN WITH 10 YEARS OF PROGRESSIVE BILATERAL HAND WEAKNESS

CASE 8: CHRONIC SENSORY LOSS AND UNSTEADY GAIT IN A 59-YEAR-OLD WOMAN

CASE 9: AN ELDERLY MAN WITH ACRAL PARESTHESIAS AND GAIT UNSTEADINESS

CASE 10: FOOT DROP IN AN 81-YEAR-OLD WOMAN

CASE 11: A MIDDLE-AGED MAN WITH MULTIFOCAL PAIN, SENSORY LOSS, AND WEAKNESS

CASE 12: FIVE-DAY ONSET OF DIFFUSE WEAKNESS

The following cases, culled from the authors' clinical practice over several years, illustrate the diagnostic method used in the evaluation of peripheral neuropathy.

CASE 1: PAINFUL SMALL-FIBER NEUROPATHY AND DYSAUTONOMIA

History A 60-year-old man presented with 2 years of numbness, tingling, and burning discomfort in both feet up to the ankles. There was a longer history of similar symptoms in digits 1–4 of both hands; he underwent carpal tunnel decompression on the left hand 5 years

ago and on the right hand 2 years ago. He was unaware of any specific weakness or imbalance. He had to rise from bed or from a chair slowly to avoid getting lightheaded. He had been using Viagra for several years for erectile dysfunction. He drank two cocktails nightly, stopped smoking 20 years ago, was constitutionally well, and took no medication. There was no known family history of neurologic illness, but he was adopted.

Comment on History *The clinical symptoms suggest a chronic, painful sensory polyneuropathy, with autonomic dysfunction (orthostatic hypotension and erectile dysfunction) and a history of carpal tunnel syndrome. The pain*

and autonomic dysfunction, without gait ataxia, favor a predominantly small-fiber neuropathy. Diagnostic considerations for this type of painful small-fiber neuropathy include diabetes, uremia, alcohol abuse, nutritional deficiencies, human immunodeficiency virus (HIV), connective tissue disorders, and amyloidosis. At a younger age, one might also consider Fabry disease and hereditary sensory autonomic neuropathy (HSAN). The patient takes no drugs, is exposed to no toxins associated with painful neuropathy, and has no risk factors for HIV.

Physical Examination There were no skin, gum, tongue, nail, or fundoscopic lesions and no pes cavus, hammer toes, foot ulcers, or Charcot joints. There was a mild orthostatic drop in blood pressure. Mental status and cranial nerves were normal. There was mild atrophy of intrinsic hand and foot muscles, with mild weakness of toe extension and thumb abduction bilaterally. Deep tendon reflexes were normal in the arms and knees but were absent at the ankles. There was a stocking-glove loss of pain and temperature sensation up to the knees and elbows, only mildly diminished vibration, and normal position sense in the toes. The gait was normal; the Romberg test was negative. Tinel sign was positive at both wrists.

Comment on Physical Examination *The exam indicates a sensorimotor polyneuropathy, with small-fiber sensory and autonomic dysfunction predominating.*

Electrophysiologic Studies Nerve conduction studies demonstrated low-amplitude sural sensory and peroneal motor potentials with preserved velocities and moderately severe median nerve entrapments at both wrists. On needle electromyography (EMG), there was moderate active and chronic denervation in distal leg muscles and the abductor pollicis brevis muscles. These findings were consistent with an axonal sensorimotor polyneuropathy and bilateral median entrapment at the wrist. The R-R interval variation was reduced, indicating parasympathetic autonomic dysfunction.

Laboratory Studies Normal blood work included a complete blood count (CBC), comprehensive metabolic panel (CMP), glucose tolerance test (GTT), serum protein immunofixation electrophoresis (IFE), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF), vitamin B₁₂, and thyroid stimulating hormone (TSH). There was mild elevation of liver function tests. Cardiac work-up indicated a mild cardiomyopathy. A sural biopsy was performed on suspicion of amyloidosis, demonstrating diffuse amyloid deposits in endoneurial and epineurial connective tissue and blood vessels. Genetic testing confirmed a missense mutation of the transthyretin gene.

Comment on Case *Transthyretin amyloidosis is an autosomal dominant disorder and the most common of the familial amyloid polyneuropathies. It should be suspected in cases of predominant small-fiber neuropathy associated with dysautonomia; carpal tunnel syndrome and cardiac dysfunction are common accompaniments. Diagnosis can be achieved by demonstrating amyloid on tissue biopsy (abdominal fat, rectum, minor salivary gland, skin, sural nerve), with the protein component being established by immunohistochemistry. Molecular genetic testing for transthyretin mutations, however, is more sensitive, specific, and expeditious. Today, in a suspected case, we would perform genetic testing before subjecting a patient to a biopsy. Cardiomyopathy with congestive heart failure is the usual cause of death. The patient was treated symptomatically with neuropathic pain control and management of orthostatic hypotension. Liver transplantation is reported to improve or at least halt the progression of neurologic dysfunction, but cardiac disease progresses.*

CASE 2: INSIDIOUS ONSET OF DISTAL WEAKNESS IN AN ADULT WITH DEFORMED FEET

History A 42-year-old priest was referred for evaluation of unsteady gait and mild lower limb weakness for 2 years. The unsteadiness was most apparent while standing for prolonged periods in church; there were no falls, and he was able to climb stairs slowly without holding

a railing. Rapid walking was accompanied by a sense of unsteadiness, and he was no longer able to run. There were also occasional sensations of numbness in his toes but no tingling or burning. His upper limbs were asymptomatic, and there were no autonomic complaints. He had worn special shoes since childhood because of deformed feet and was never able to compete in field sports. His 52-year-old brother, who lived in another state, also had deformed feet but was asymptomatic. There was no other known neurological disease in the family, and he was in good health and took no medications.

Comment on History *The history of gradual onset of weakness, numbness without paresthesias, and childhood foot deformity in the patient and his brother indicate hereditary motor sensory neuropathy (Charcot-Marie-Tooth [CMT] disease).*

Physical Examination Positive physical findings in the upper limbs were mild (4+) weakness of the abductor pollicis brevis and interossei muscles and a mild, coarse tremor of the outstretched hands. In the lower limbs there were striking pes cavus deformities with hammer toes in concert with grade 4 strength of the extensor hallucis longus and anterior tibial muscles. Pin and vibration senses were mildly impaired over the distal feet. Position sense was normal in the toes, but there was a definite sway on the Romberg maneuver. Toe gait was normal; both heel and tandem gait were moderately impaired. Tendon reflexes were well preserved in the arms but only trace at the quadriceps and absent at the ankles.

Comment on Physical Examination *Symmetrical distal motor and sensory loss and preservation of tendon reflexes in the arms suggest a diffuse nonmultifocal process. This picture is compatible with either distal axonopathy or a diffuse, chronic demyelinating polyneuropathy of the hereditary type. The most striking physical finding, pes cavus with hammer toes, in concert with similar findings in the brother, is virtually diagnostic of a hereditary motor sensory polyneuropathy. Electrophysiologic studies should indicate if it is demyelinating or axonal.*

Electrophysiologic Studies Motor nerve conduction studies revealed uniform slowing without conduction block in all nerves examined. Velocities of 20–25 m/s were found in the peroneal, ulnar, and median nerves; sensory amplitude potentials were diminished but present. There was mild chronic denervation in the anterior compartment of the lower limb and intrinsic hand muscles.

Comment on Electrophysiologic Studies *Profound uniform slowing of conduction in this range without conduction block in concert with only mild denervation suggests a diffuse demyelinating neuropathy, characteristic of CMT1. Routine laboratory studies, to rule out the co-occurrence of a metabolic or immunologic condition, and special studies for genetic analysis are indicated.*

Laboratory Studies Negative tests included CBC, CMP, IFE, vitamin B₁₂, and ESR. A blood DNA test was positive for the CMT1A duplication in the PMP22 gene.

The patient's brother, who has children, received genetic counseling, and the patient was referred to a CMT support group.

Comment on Case *The presence of profound uniform slowing of motor conduction with relatively preserved strength is indicative of hereditary demyelinating neuropathy. If severe weakness appears in childhood, the condition is very disabling; however, adult onset of initial symptoms is frequently compatible with a relatively normal active life. Adult-onset hereditary neuropathies are frequently undiagnosed and are referred to neuromuscular specialists as "idiopathic neuropathies." The advent of commercially available genetic testing has been of considerable assistance in identifying these conditions.*

CASE 3: LOWER LIMB PARESTHESIAS IN A MIDDLE-AGED ADULT WITH DIABETES

History A 58-year-old housewife with diabetes, at a routine visit to her internist, complained of tingling and numbness in her feet for the past 9 months. She also noted a dull aching in her shins, as if the pain was coming

from her bones. This constellation of sensory complaints, initially mild and periodic, became constant and was a source of considerable nocturnal discomfort. She received a diagnosis of type 2 diabetes 8 years ago and was initially treated with diet modification and oral hypoglycemic agents. She did not adhere to the diet, and her blood glucose levels fluctuated widely; 4 years ago, after glycosuria became consistent, insulin therapy commenced. There was no weakness, sensory symptoms in the upper extremities, or autonomic complaints. She was mildly obese, in good health, ate a balanced diet, and took no other medications except for a diuretic for mild hypertension. There were no known neurologic diseases in the family; she had no exposure to environmental chemicals.

Comment on History *A history of progressive sensory complaints in the feet, which are now painful in this patient, suggests diabetic sensory polyneuropathy.*

Physical Examination Positive neurologic physical findings were restricted to the lower limbs. Strength was normal throughout. There was symmetric, profoundly diminished perception of thermal and pinprick sense over both feet; this gradually shaded to normal at the mid-shin level. Vibration sense was mildly impaired at the toes and normal at the ankles; position and touch sensation were spared. Tendon reflexes were 2+ in the upper limbs, 1+ at the patellae, and absent at the ankles. Stroking the soles caused an unpleasant sensation (allodynia).

Comment on Physical Examination *Symmetric impairment of pin and thermal senses with only a modestly diminished vibration sense and normal strength and proprioception indicates a mixed but small-fiber-predominant sensory neuropathy, one of the characteristic patterns of diabetic sensory polyneuropathy.*

Electrophysiologic Studies Motor and sensory nerve conduction velocities were normal; sural nerve amplitudes were present but markedly diminished. The R-R interval variation was reduced.

Comment on Electrophysiologic Studies *Involvement of the sural sensory potentials confirms that some large-fiber dysfunction is present in addition to the apparent clinical small-fiber dysfunction. Abnormal R-R interval variation indicates parasympathetic autonomic small-fiber dysfunction. Conventional electrophysiologic studies are unable to assess the integrity of unmyelinated fibers, which require autonomic, quantitative sensory (thermal) or skin biopsy studies.*

Laboratory Studies Normal laboratory tests included CBC, CMP (except for elevated glucose), IFE, ESR, thyroid function tests (TFTs), and vitamin B₁₂.

Comment on Case *The history and physical exam, taken in concert with the electrophysiologic findings, suggest that this is an instance of one of the common forms of diabetic sensory polyneuropathy. Autonomic abnormalities also reflect small unmyelinated fiber dysfunction and are especially strongly associated with this disorder. This overall pattern of disease is characteristic of diabetic neuropathy, although it should be borne in mind that diabetics may have alternative, concomitant etiologies for neuropathy; standard screening blood work is generally advisable. The patient was treated with weight loss, neuropathic pain medications, control of blood glucose levels, and foot care designed to prevent ulceration.*

CASE 4: A MIDDLE-AGED WOMAN WITH MUSCLE TWITCHING AND EPISODIC NUMBNESS

History A 45-year-old beautician was referred for evaluation of possible peripheral neuropathy. Although generally healthy, for the prior 7 weeks she had noted episodic arm and leg numbness and hand twitching. The sensory symptoms tended to be transient, in various distributions, and usually were precipitated by stretching or compressing various nerves. There was no constant acral sensory disturbance. Her hands constantly twitched and occasionally were stiff or cramped when writing or holding her automobile's steering

wheel. On one occasion, there was a 5-minute period when her whole body seemed to tremble and sweat, without loss of consciousness. There was no weakness, neck or back pain, bulbar symptoms, or sphincter dysfunction. There was no family history of neuromuscular disease. She took quinine for cramps.

Comment on History *The transient nature of the sensory phenomena suggests that this is not a typical polyneuropathy, as initially suspected. The muscle twitching suggests a disorder associated with peripheral nerve hyperexcitability. A myotonic disorder might be suspected to explain stiffness but would be inconsistent with associated sensory symptoms.*

Physical Examination Mental status and cranial nerves were normal. Muscle bulk, tone, and strength were normal throughout. There was no percussion myotonia, but slight delayed relaxation of grip was noted. There was marked undulating twitching of intrinsic hand muscles like a “bag of worms,” which occurred infrequently in other arm muscles. During the examination, she had an episode of painless increase in tone and dystonic-like posturing of the left hand that lasted for several seconds and resolved completely. Sensory testing, including touch, pinprick, vibration, and position sense, was normal. Deep tendon reflexes were all 1–2+ and plantar responses were flexor. Gait and coordination were normal. A Tinel sign was present over multiple nerves.

Comment on Physical Examination *The twitching in the hand muscles likely represents myokymia based on its clinical appearance, but it requires electrodiagnostic confirmation. There is no clinical suggestion of an underlying polyneuropathy.*

Electrophysiologic Studies Nerve conduction studies were normal, with no evidence of a polyneuropathy. The median and ulnar compound muscle action potentials demonstrated repetitive afterdischarges, indicating nerve hyperexcitability. Needle EMG of median and ulnar intrinsic hand muscles showed profuse myokymic discharges and occasional neuromyotonic discharges. There were no

fibrillations and no abnormalities of motor unit morphology or recruitment.

Radiologic and Laboratory Studies Normal tests included CBC, CMP, ESR, ANA, RF, TFTs, Lyme enzyme-linked immunosorbent assay/Western blot (ELISA/WB), creatine kinase (CK), acetylcholine receptor antibody, and cerebrospinal fluid (CSF) analysis. A chest x-ray (CXR) and chest computed tomography (CT) scan were normal. Serum assay demonstrated antibodies to voltage-gated potassium channels.

Comment on Case *The patient has a disorder of peripheral nerve hyperexcitability characterized clinically by muscle twitching and stiffness and electrophysiologically by myokymic and neuromyotonic discharges. This is acquired neuromyotonia (Isaacs syndrome), an autoantibody-mediated potassium channelopathy resulting in generalized peripheral nerve hyperexcitability. Sensory axons may also be affected, resulting in transient sensory phenomena as described in this case. Muscle stiffness may mimic myotonia (pseudomyotonia). In severe cases there may be excessive sweating, perhaps related to muscle overactivity. An associated peripheral neuropathy is present in some cases. This syndrome may occur as an isolated autoimmune disorder, or may be paraneoplastic (usually chest tumors) or toxic (e.g., penicillamine, gold), and is occasionally familial or associated with other autoantibodies (e.g., acetylcholine receptor). Management in most cases is symptomatic, with cabamazepine or phenytoin, among other drugs, or in more problematic cases with immunosuppression. An associated neoplasm should be excluded and the patient followed over time. This patient responded symptomatically to gabapentin and has been clinically stable for over 10 years.*

CASE 5: SIX DAYS OF CRANIAL NEUROPATHIES AND HYPOREFLEXIA

History A 72-year-old man developed nausea and vomiting 2 weeks earlier after eating cooked mushrooms at a catering hall.

This lasted for 1 day, but 6 days later he awoke with nausea and vertigo. An internist found fluid in his ear and prescribed methylprednisolone and compazine. Four days prior to presentation, he developed progressive dysarthria, dysphagia to liquids and solids, and diplopia. Two days earlier, he noted mild dyspnea, particularly when eating. There was no ataxia, sensory complaints, weakness, or incontinence.

Comment on History *The symptoms of diplopia, dysarthria, and dysphagia suggest either a disorder of the neuromuscular junction (myasthenia gravis or botulism) or multiple cranial neuropathies. It was unclear whether the neurologic symptoms were preceded by a viral prodrome or food poisoning (bacterial infection). An acute brainstem disorder such as encephalitis or a stroke may be a consideration, but there was no altered consciousness or symptoms of long tract dysfunction.*

Physical Examination The patient was intubated for airway protection and due to concern that he could develop progressive respiratory muscle weakness. A forced vital capacity (FVC) test was unreliable prior to intubation because of severe bilateral facial weakness. He was alert and communicated effectively by hand gestures. He had complete bilateral ptosis and ophthalmoplegia. Pupils were 6 mm and minimally reactive to light. Touch and pin sensation in the face were normal. He had severe bifacial weakness, with only trace mouth movements. Neck flexion and bilateral deltoids were 4+/5, with otherwise normal strength. There was no limb dysmetria or truncal ataxia when sitting upright. Vibratory sense was moderately impaired at the fingertips and mildly impaired in the toes. Position, touch, and pin sensation were intact. Reflexes were 1+ except for brisk knee jerks with crossed adductors. Plantar responses were flexor.

Comment on Physical Examination *Dysfunction of extraocular muscles and pupils and severe bifacial weakness do not clearly differentiate multiple bilateral cranial neuropathies (in nerves III, IV, VI, and VII) from a neuromuscular junction disorder, although the severity of the bifacial weakness is atypical for myasthenia gravis. Preserved consciousness*

and the absence of long tract signs are evidence against a brainstem disorder. The vibratory loss is evidence against neuromuscular junction dysfunction.

Electrophysiologic Studies Ulnar and median sensory response amplitudes were reduced, with normal velocities and sural sensory conduction. Peroneal and facial motor response amplitudes were reduced; there was no immediate postexercise facilitation. Some F wave latencies had increased chronodispersion. Blink responses were absent. Repetitive stimulation of the facial nerve at 3 Hz showed no significant decremental response. Fibrillation potentials were present in the obicularis oris and tibialis anterior muscles (day 14).

Comment on Electrophysiologic Studies *The electrophysiology was most consistent with a multifocal, predominantly axonal sensorimotor polyneuropathy. However, since motor nerve involvement was relatively minor, demyelinating polyneuropathy cannot be entirely excluded. Demyelinating polyneuropathy is defined by motor conduction abnormalities. The findings in this case are typical of Fisher syndrome: sensory conduction abnormalities in the arm, sparing the sural sensory nerve action potential (SNAP), and modest F wave latency and motor nerve conduction abnormalities.*

Laboratory Studies A noncontrast CT scan of the brain was normal. Cerebrospinal fluid showed 5 white blood cells (polys), 155 red blood cells, protein level of 44 mg/dL, and glucose level of 91 mg/dL. The ANA test was positive at 1:320 in the serum, with a homogeneous pattern. The TSH level was normal. A GQ1B antibody titer was not commercially available.

Comment on Case *This patient had two of the three characteristic features of Fisher syndrome—ophthalmoparesis and hyporeflexia—but no clear ataxia. His symptom of vertigo, however, raised the possibility of unsteadiness, and it was difficult to assess truncal ataxia while he was on the ventilator. The cranial nerve dysfunction was relatively severe and included bilateral facial nerve dysfunction, which may occur in Fisher syndrome. Acral paresthesias may also occur.*

Respiratory compromise, suggesting phrenic nerve involvement, and dysphagia are unusual in Fisher syndrome. These additional symptoms raised the possibility of botulism. The electrophysiology clearly distinguished these two disorders. Fisher syndrome is considered a variant of Guillain-Barré syndrome, and patients presenting with the usual triad sometimes progress to develop generalized weakness. The GQ1b antibody is a sensitive marker for this disorder.

The electrophysiology has axonal features, but some researchers have argued that the typical rapid clinical and electrophysiologic recovery favors demyelinating polyneuropathy. Rare pathologic case reports favor demyelination.

CASE 6: TWO-MONTH ONSET OF SENSORY NEUROPATHY IN A WOMAN WITH OVARIAN CARCINOMA

History A 45-year-old woman was found to have ovarian carcinoma with widespread peritoneal metastases. She was treated with cisplatin and received a total dose of 400 mg/m² over a 4-month period. After 1 month of therapy, she noticed a suboccipital electric shock sensation that radiated down to her lumbar spine whenever she flexed her head; after 3 months, she experienced mild numbness in her toes, which soon also appeared in her fingertips. These symptoms were stable until 1 week following the last dose, when numbness and tingling spread up to her knees and wrists, accompanied by an unsteady gait and clumsy hands. Two weeks later her gait deteriorated, and she was unable to walk unaided without falling; her fingers moved involuntarily, and she was unable to button her clothing. She remained in this state, nearly totally disabled, for the past 2 months. She was well nourished and took no medications, and there was no family history of neurologic disease.

Comment on History *A history of rapidly evolving disabling sensory neuropathy in a cancer patient receiving cisplatin suggests either a toxic or paraneoplastic condition. Progression of symptoms for a period following*

withdrawal (“coasting”) is characteristic of some toxic neuropathies.

Physical Examination Abnormal neurologic findings were restricted to the sensory exam and reflex examinations. Strength was normal. Tendon reflexes were absent. Her fingers moved constantly in a writhing manner; she was able to suppress the movements voluntarily for only a few seconds. There was no perception of vibration or joint position senses at the toes, ankles, fingers, or wrists. These senses were moderately impaired at the knee and elbow and were normal at the iliac crest and acromion. Perception of pin and touch senses was slightly diminished at the fingertips and toe pads. She was unable to stand unaided with her eyes open and swayed markedly when her eyes were closed.

Comment on Physical Examination *Severe impairment of large-fiber sensory function causing pseudoathetotic finger movements and unstable stance and gait, with relative sparing of small fibers, suggests diffuse dysfunction of sensory ganglia. In this instance it could stem from the cisplatin or, less likely, reflect a paraneoplastic process.*

Electrophysiologic Studies Sensory nerve action potentials were absent throughout; motor potentials and velocities and needle EMG were normal.

Comment on Electrophysiologic Studies *These findings are consistent with either a severe large-fiber neuropathy or a ganglionopathy (sensory neuronopathy) and do not help to distinguish a toxic process from a paraneoplastic one.*

Laboratory Studies Routine laboratory tests, including vitamin B₁₂, were normal; immunologic evaluation revealed the presence of anti-Hu antibody. The C-spine MRI was normal.

Further History and Comment on Case *The patient was examined at 6-month intervals for 2 years following the initial evaluation. She gradually recovered near-normal use of her hands and was eventually able to walk unaided and*

return to work. Position and vibration perception remained moderately impaired at the fingers and toes. She died from metastatic disease 4 years later.

Recovery following drug withdrawal is the only certain diagnostic feature of a toxic neuropathy. Cisplatin neuropathy/neuronopathy may commence several months following cessation of therapy and can be difficult to distinguish from paraneoplastic neuropathy. Generally, the paraneoplastic cases have involvement of small-fiber modalities as well. The discovery of anti-Hu antibodies suggested a cancer-related process but proved to be misleading in this instance.

CASE 7: A 47-YEAR-OLD MAN WITH 10 YEARS OF PROGRESSIVE BILATERAL HAND WEAKNESS

History A 47-year-old man first noted “tremors” in his fingers at rest 20 years earlier. This was associated with twitching of intrinsic hand muscles. Approximately 15 years ago, when he played tennis more frequently, he began to notice less of a “snap” in his tennis serve. Ten years ago, he developed weakness in his dominant left hand greater than in his right hand. He had difficulty adjusting his collar while tying a tie and difficulty opening jars. He also noted an ache in the biceps muscles bilaterally when adjusting his collar.

About 5 years earlier, he began to run slightly more slowly and to jump less high while playing basketball. He had occasional muscle cramps involving his thighs and calves, but he continued to run. Four years ago, he stopped playing full-court basketball. There was no atrophy, numbness, paresthesia, neck pain, radicular pain, dysarthria, incontinence, or weight loss. He had a past history of Gilbert syndrome, which was asymptomatic, and mononucleosis at 18 years of age. His family history was essentially negative. His mother had questionable limb weakness, but EMG/nerve conduction studies (NCS) were normal.

Comment on History *The patient has slowly progressive, distal, asymmetric hand weakness with possible leg involvement, but no muscle wasting or sensory symptoms. A motor*

neuropathy, a slowly progressive motor neuron disease such as spinal muscular atrophy, or a distal myopathy are considerations. The lack of atrophy raises the possibility of upper motor neuron dysfunction or conduction block of motor nerves as a cause of weakness. Cervical spinal cord disease is a possibility, although a pure-motor, bibrachial presentation is unusual.

Physical Examination Higher cognitive functions and cranial nerves were intact. There was mild to moderate atrophy of the right flexor mass of the forearm and mild atrophy of the right distal quadriceps muscle. Fasciculations were present in bilateral first dorsal interossei, triceps, and gastrocnemius muscles. He had a minimal postural tremor bilaterally. Limb strength was graded as follows: bilateral flexor pollicis longus 4+, right flexor digitorum profundus (median) 4+, bilateral abductor pollicis brevis and interossei 4−, extensor digitorum 4+ left, 5− right, left extensor pollicis longus 4+, right iliopsoas 4+, quadriceps 5−, tibialis anterior 4 right, 5− left, bilateral evertors 5−, extensor hallucis longus 4−, and toe flexion 5−. He had difficulty walking on either heel. Toe walking was normal. Sensation to pin, touch, and vibration was intact. Tendon reflexes were 1+ in the right brachioradialis, biceps, and left triceps and were otherwise 2+ throughout. Plantar responses were flexor.

Comment on Physical Examination *There is multifocal weakness and hyporeflexia. Weakness is accentuated distally. It is unclear if the hand weakness resulted from involvement of multiple nerves or C8/T1 spinal segments. The paucity of atrophy is evidence against progressive spinal muscular atrophy. Weakness may relate to conduction block in the absence of upper motor neuron signs.*

Electrophysiologic Studies Bilateral median motor conduction studies showed marked partial conduction block, temporal dispersion, and mild conduction velocity slowing in the forearm segment. The distal latencies were normal. There was borderline motor conduction block of right ulnar motor conduction between the axilla and elbow and of right

peroneal motor conduction below the fibular head. The right peroneal motor response amplitude was reduced, with mild velocity slowing and distal latency prolongation. F waves were prolonged with increased chronodispersion. Sensory conduction studies were normal, including median sensory conduction across the site of median motor conduction block. Needle EMG showed multifocal fibrillations in the right first dorsal interosseous and iliopsoas muscles. Motor unit potential durations were increased, and voluntary recruitment was reduced in clinically weak muscles.

Comment on Electrophysiologic Studies *The electrophysiologic findings are characteristic of multifocal motor neuropathy with conduction block. There is partial conduction block of multiple motor nerves in the absence of sensory nerve conduction abnormalities. Other demyelinating features of motor nerve conduction, such as prolonged F waves and distal motor latencies, are negligible. Evidence of motor fiber loss (low compound muscle action potential amplitudes and fibrillation potentials) is patchy, often occurring in the distribution of the more affected nerves.*

Laboratory Studies The following blood tests were normal or negative: CMP, IFE, ESR, ANA, CK, GM1, asialo-GM1, GD1b, and MAG antibodies. Urine protein electrophoresis showed nonspecific proteinuria. The urine heavy metal screen was negative.

Comment on Case *This patient has a typical case of multifocal motor neuropathy with conduction block. Some patients present with a pattern of weakness that more clearly conforms to multiple nerve distributions. This patient was seen late in his course, with more advanced disease. As such, distal weakness was more confluent. While multifocal motor neuropathy may mimic motor neuron disease, upper motor neuron signs are characteristically absent. Upper extremity presentations are common. Patients often present with asymmetric distal weakness, although more proximal monoparesis, suggesting a brachial plexopathy, also occurs. A painless brachial plexus presentation has been described under various terms,*

including hypertrophic brachial plexus neuropathy and chronic relapsing brachial plexus neuropathy with persistent conduction block. In addition to multifocal, proximal motor conduction block, sensory nerve conduction abnormalities may be present in the brachial plexus variant. This more closely resembles MADSAM (multifocal acquired sensory and motor neuropathy, also called Lewis-Sumner syndrome). Hypertrophy of portions of the brachial plexus may present as a mass and reflects onion bulb formation pathologically.

All of these syndromes may be variants of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and frequently respond to intravenous immunoglobulin (IVIG). Cyclophosphamide may increase the interval between required IVIG infusions but is reserved for refractory patients because of adverse effects. Only patients with sensory nerve involvement tend to respond to prednisone. Axonal multifocal motor neuropathy without conduction block has also been described. Such patients generally respond less well to immune-modulating treatment.

This patient initially declined treatment. A few months later he received IVIG, 400 mg/kg daily for 5 days, with only modest improvement in hand strength. The patient declined further treatment and was lost to follow-up.

CASE 8: CHRONIC SENSORY LOSS AND UNSTEADY GAIT IN A 59-YEAR-OLD WOMAN

History A 59-year-old nurse's aid was referred for evaluation of 6 months' duration of hand and foot numbness along with gait imbalance. Symptoms began simultaneously and intermittently in both hands, involving all fingertips, and were initially ascribed to carpal tunnel syndrome. Three months later she developed numbness and paresthesias of her soles, which gradually spread to the calves; her feet felt as though they were "encased in ice." Her gait was very unsteady. She was afraid that she would drop items from her hands and had difficulty with buttoning. There was no focal weakness and no sphincter dysfunction. She was constitutionally well except for mild fatigue. She took medication for hypertension and glaucoma. She stopped smoking 11 years

ago and drank alcohol only occasionally. The family history was notable only for longevity.

Comment on History *The clinical syndrome appears to be chronic, diffuse, predominantly large-fiber sensory dysfunction. The onset of symptoms in the hands suggests that it is not a typical length-dependent neuropathic process. Considerations include a sensory neuronopathy, sensory CIDP, or posterior column myelopathic dysfunction.*

Physical Examination She appeared to be in good health. Mental status and cranial nerves were normal. There was no pain or limitation on neck movement. There was no pseudoathetosis. Tone, bulk, and strength were normal. There was a stocking pattern of hypoesthesia to light touch in the feet, which was milder in the hands. Pinprick sensation was unremarkable. Vibration was absent at the toes, severely affected at the ankles, and even diminished at the knees; it was mildly to moderately affected in the fingers. Position sense was moderately impaired in the toes. Reflexes were brisk at 2–3+, including knee jerks, and trace at the ankles. Plantar responses were flexor. The gait was mildly wide-based and ataxic; the Romberg sign was positive.

Comment on Physical Examination *The generally brisk reflexes make a sensory neuronopathy or demyelinating polyneuropathy unlikely. This degree of large-fiber sensory dysfunction with knee hyperreflexia favors posterior and lateral column dysfunction. The depressed ankle jerks, however, point to at least some degree of peripheral nerve dysfunction as well, so this may be a process affecting both central (myelopathic) and peripheral sensory pathways. This combination of findings is highly suggestive of vitamin B₁₂ deficiency.*

Electrodiagnostic Studies Sural sensory amplitudes were diminished, peroneal motor conduction were minimally slowed and late responses were slightly prolonged, findings consistent with a mild axonal sensorimotor polyneuropathy. There was no median nerve entrapment at the wrists. Needle EMG was normal.

Radiologic and Laboratory Studies Normal studies included CBC, CMP, ESR, TFTs, IFE, and copper/zinc levels. C-spine MRI revealed no cervical spondylotic myelopathy. The serum vitamin B₁₂ level was low normal at 210 pg/mL. Serum methylmalonic acid and homocysteine levels were highly elevated, confirming a cobalamin deficiency. A positive Schilling test and anti-intrinsic factor antibodies confirmed a diagnosis of pernicious anemia.

Comment on Case *Cobalamin deficiency is an important treatable condition in all patients presenting with a clinical picture of myelopathy, predominantly sensory polyneuropathy, cognitive dysfunction, or a combination of features. Sensory symptoms may begin in the hands or feet. As in this case, corticospinal tract dysfunction, megaloblastic anemia, or neuropsychiatric abnormalities may not be present. Methylmalonic acid/homocysteine are reliable markers for this disorder, and if their levels are normal, cobalamin deficiency is excluded; when clinical suspicion remains, they should be tested even when serum vitamin B₁₂ levels are low normal. Nitrous oxide anesthesia or abuse may unmask subclinical vitamin B₁₂ deficiency. Copper deficiency can present with a similar clinical picture. The patient showed symptomatic improvement after several months of intramuscular vitamin B₁₂ therapy.*

CASE 9: AN ELDERLY MAN WITH ACRAL PARESTHESIAS AND GAIT UNSTEADINESS

History A 65-year-old male subway conductor presented with at least 4 years of slowly progressive, symmetric acral sensory symptoms. Paresthesias and numbness began insidiously in the toes and were now found as high as the ankles. There was no burning pain. More recently, he developed mild gait unsteadiness and was vague regarding minor paresthesias in the fingers. He noted no specific weakness in climbing stairs, and there were no falls. There was no sphincter dysfunction or dysautonomia. He was constitutionally well; had no family history of neuropathy, abnormal feet, or diabetes; consumed alcohol in

moderation; took no medications; and had no occupational toxic exposure.

Comment on History *The clinical features are consistent with a chronic, distal, sensory-predominant polyneuropathy, most likely acquired. Most neuropathies with this type of presentation are axonal, although infrequently, demyelinating neuropathies are indistinguishable. There are no specific clues concerning the etiology.*

Physical Examination The general medical exam was normal. Cranial nerves, tone, and bulk were normal. There was mild weakness restricted to toe extension and flexion. Light touch and vibration sensation, more than pin and position, were moderately impaired in the feet. Deep tendon reflexes were diminished but present in the arms and absent in the legs. Plantar responses were flexor. A mild intention tremor was present on finger-to-nose testing. The gait was mildly to moderately ataxic.

Comment on Physical Examination *The exam indicates a distal sensorimotor polyneuropathy; the differential diagnosis includes a large number of axonal etiologies. The only clues that the electrophysiology may prove to have demyelinating features are the generally depressed reflexes, tremor, and ataxia.*

Laboratory and Electrodiagnostic Studies

Initial blood work disclosed normal CBC, CMP, vitamin B₁₂ level, GTT, ESR and thyroid functions. The IFE test demonstrated an IgM-kappa monoclonal protein.

Nerve conduction studies showed a mixed axonal and prominently demyelinating polyneuropathy with low-amplitude or absent sensory potentials, low-amplitude motor potentials with moderately slowed conduction velocities, and prolonged late responses in some nerves, with particular prolongation of distal motor latencies. There was active denervation in distal leg muscles on needle EMG.

Additional work-up that must, in most cases, follow identification of a monoclonal protein included a bone marrow aspirate/biopsy and a skeletal survey, which were normal. Anti-MAG (myelin-associated glycoprotein) antibodies were positive in high titer.

Comment on Case *This patient has an IgM-kappa-MGUS (monoclonal gammopathy of undetermined significance) with associated sensorimotor polyneuropathy. Since approximately one-third of identified monoclonal gammopathies are associated with an underlying disorder (multiple myeloma, amyloidosis, osteosclerotic myeloma, lymphoma, chronic lymphocytic leukemia, Waldenström macroglobulinemia), MGUS is applied only after completely excluding these disorders. Continued vigilance is required since a significant proportion of patients with MGUS will develop a hematologic malignancy on long-term follow-up. Excluding a monoclonal gammopathy by immunofixation is a critical part of the work-up for any unexplained neuropathy.*

The majority of patients with MGUS and neuropathy have IgM-kappa, the clinical picture being that of an older male with a slowly progressive, sensory-predominant, sensorimotor polyneuropathy. Tremor and ataxia may be notable features. The electrophysiology typically shows mixed axonal and demyelinating features. These cases have also been described under the umbrella of CIDP variants as DADS-M (distal acquired demyelinating symmetric neuropathy with M-protein). Like this patient, over half of IgM-MGUS patients show reactivity to MAG, characterized by particular involvement of distal nerve segments manifest by prolongation of distal motor latencies. The CSF protein level is often above 100 mg/dL without pleocytosis. Nerve biopsy, though generally unnecessary, typically shows widening of myelin lamellae and IgM deposition. Another subgroup of MGUS patients have the clinical picture of classic CIDP.

The optimal treatment of MGUS-related neuropathies remains unestablished, with less reliable responses to the usual immunosuppressive approaches. Symptomatic therapy may be appropriate for patients with indolent courses and mild impairment. This patient declined therapy.

CASE 10: FOOT DROP IN AN 81-YEAR-OLD WOMAN

History An 81-year-old diabetic, hypertensive woman was hospitalized with an acute left hemisensory deficit related to a right thalamic lacunar infarction. Two days later she

awoke with painless weakness of the right foot, with numbness over the dorsum, and was placed on anticoagulation. There was no back or radicular pain. For some time, she had had persistent numbness in the right hand involving digits 2–5 along with a sense of hand weakness. There were no symmetric acral sensory symptoms in the legs.

Five years earlier, she had presented with a painless left foot drop. Electrodiagnostic testing documented a peroneal neuropathy at the fibular head with marked conduction block. Mild nonspecific generalized nerve conduction abnormalities were noted. Significant recovery occurred over a few weeks. Mild diabetes was discovered at that time. She also recalled having had a foot drop about 32 years earlier that resolved completely over a few months.

The patient was constitutionally well. She took antihypertensives, and her diabetes was currently diet-controlled. One son reported having surgery for ulnar entrapment at the elbow on two occasions and for CTS once. Another son once had a foot drop.

Comment on History *Rather than another stroke, as initially suspected and prompting anticoagulation, a painless foot drop with dorsal foot numbness suggests a peroneal neuropathy; a less likely possibility is L5 radiculopathy. There are also more chronic symptoms in the right median and possibly ulnar nerve-distributions. The history also suggests prior mononeuropathies occurring over many years. This pattern of recurrent mononeuropathies, along with a family history suggestive of autosomal dominant inheritance, favors HNPP (hereditary neuropathy with liability to pressure palsies). The very long history, painless episodes, and absence of systemic features argue against a vasculitic mononeuropathy multiplex. Diabetic neuropathy with associated entrapments is a consideration.*

Physical Examination Mental status and cranial nerves were normal. In the right leg, there was weakness (4-/5) restricted to the tibialis anterior, extensor hallucis longus, and ankle evertors. Mild weakness (5-/5) was also present in the left tibialis anterior and right abductor pollicis brevis. Touch and pinprick sensation were diminished over the right dorsal foot

and lateral calf, and in all the digits of the right hand (along with a left hemisensory deficit). Vibration sense was impaired in both feet. Tendon reflexes were 2+ in the arms and absent at the knees and ankles. Plantar responses were flexor. She walked with a right foot drop, and heel walking was impaired bilaterally. There was no pes cavus. The straight leg raise test was negative.

Comment on Physical Examination *The deficits conform to an anatomic pattern of mononeuropathy multiplex, with bilateral common peroneal neuropathies, greater on the right than on the left, and right median and ulnar neuropathies. In addition, the absent lower extremity reflexes and vibratory loss point to a more generalized polyneuropathy.*

Electrodiagnostic and Laboratory Studies

Nerve conduction studies revealed severe bilateral common peroneal neuropathies, with marked slowing and partial conduction block across the fibular heads. This existed on the background of a generalized demyelinating sensorimotor polyneuropathy, with distally accentuated slowing of sensory and motor conduction, and particular slowing across both median and ulnar entrapment sites at the wrists and elbows. DNA testing revealed deletion of the PMP-22 gene on chromosome 17p11.2-12, establishing a diagnosis of HNPP.

Comment on Case *HNPP, initially called tomaculous neuropathy because of the sausage-shaped swellings composed of redundant loops of myelin on teased fiber studies, is an autosomal dominant hereditary neuropathy characterized by recurrent pressure palsies on the background of a generalized sensorimotor polyneuropathy with demyelinating features of varying severity. Rarely, it may manifest with a painless brachial plexus neuropathy. The genetic defect on chromosome 17p11.2-12 is at the same site as CMT1A, in this case usually a reciprocal deletion. Deficits related to pressure palsies typically improve. The differential diagnosis of mononeuropathy multiplex with demyelinating electrophysiology is limited and includes multifocal motor neuropathy (MMN; pure motor with conduction block), the multifocal variant of CIDP (MADSAM;*

sensory and motor, multifocal), and HNPP. This is an unusual pattern in diabetes except in rare cases of diabetes with superimposed CIDP.

CASE 11: A MIDDLE-AGED MAN WITH MULTIFOCAL PAIN, SENSORY LOSS, AND WEAKNESS

History A 40-year-old man was referred for another opinion regarding suspected polyneuropathy, with bilateral distal leg pain, numbness, and weakness over 4 months. Careful questioning revealed that symptoms began in the left leg with aching pain in the lateral calf, initially severe, now improved, and tripping over the left foot. Within a few weeks, both feet were entirely numb up to the ankles, and the patient noted dysesthetic pain over the right sole and lateral foot. There was no low back or radicular pain, sphincter dysfunction, or dysautonomia. A few days prior to this evaluation, he developed acute numbness and pain in digits 4 and 5 and in the medial aspect of the right hand, as well as weakness of hand grip, without neck pain. He felt fatigued and mildly dyspneic recently, but otherwise had no systemic constitutional symptoms, rashes, or arthralgias. The past medical, social, and family history was unremarkable. He took only analgesics.

Comment on History *The evolution of symptoms (pain, sensory loss, and weakness) in a stepwise, asymmetric, multifocal fashion identifies the anatomic pattern of peripheral nerve involvement as multiple mononeuropathies (mononeuropathy multiplex). A polyradicular process might also be considered. This is likely to be an axonal process, though occasionally demyelinating neuropathies will be multifocal (the MADSAM variant of CIDP). Involved nerves include particularly the left peroneal, right tibial and sural, and right ulnar. The dyspnea remains to be explained; if it does not reflect associated pulmonary disease, in this clinical setting one can consider a phrenic neuropathy as well. Diagnostic considerations would include first the various vasculitides and then a number of infectious, granulomatous, and neoplastic conditions. The pain would be most typical of acute nerve infarction.*

Physical Examination The patient was afebrile. There were decreased breath sounds in the right lung base, but his general medical exam was otherwise normal. Mental status and cranial nerves were normal. There was no focal atrophy. He had moderate weakness in the right ulnar intrinsic hand muscles, greater left than right foot dorsiflexion, and right toe flexion and foot inversion. There was a stocking pattern of sensory loss to pin and light touch up to the ankles, with areas of hyperesthesia or allodynia over the left lateral calf and right lateral foot. Vibration was mildly impaired in the feet; position sense was intact. In the right hand, sensory loss was found in D5 and medial D4. Deep tendon reflexes were intact except for absent ankle jerks; plantar responses were flexor. He walked with a left foot drop; heel walking was impaired bilaterally, and toe walking was poor on the right.

Comment on Physical Examination *The exam confirmed the asymmetric, multifocal nature of this sensorimotor neuropathy, with involvement of all the nerves suspected from the historical details. The extensive overlapping dysfunction of distal nerves in both feet might lead to the impression of a polyneuropathy, but the asymmetries should be apparent.*

Electrodiagnostic Studies Nerve conduction studies in the legs showed absent peroneal SNAPs, asymmetric sural SNAPs (absent on the right, low-amplitude on the left), low-amplitude but asymmetric peroneal and tibial compound muscle action potentials (CMAPs), absent tibial H-reflexes, and mildly prolonged late responses. In the arms, the right ulnar sensory potential was low-amplitude, while the left was normal. The ulnar CMAP was borderline low, but there was partial motor conduction block in the forearm segment and no focal slowing across the elbow or wrist. Phrenic nerve conduction studies showed a low-amplitude potential on the right. Needle EMG showed active denervation in distal and proximal leg muscles bilaterally.

A follow-up study 2 weeks later no longer demonstrated ulnar motor conduction block, only low-amplitude CMAPs at all sites of stimulation and active denervation in ulnar hand muscles.

Comment on Electrodiagnostic Studies *The involvement of sensory potentials excludes a preganglionic, polyradicular process, and the study confirms an axonal mononeuropathy multiplex, including phrenic nerve involvement. As demonstrated here with the ulnar nerve, conduction studies performed within only a few days of an acute axonal nerve lesion may show pseudoconduction block across the lesion site. That this was not focal demyelination became clear only after several more days elapsed, allowing Wallerian degeneration to proceed.*

Laboratory Studies Normal studies included CBC, CMP, and urinalysis. The ESR was 50. The CXR was clear but showed an elevated right hemidiaphragm. Additional tests were normal, including CK, ANA, RF, IFE, anti-neutrophil cytoplasmic antibody (ANCA), anti-Ro/anti-La, hepatitis panel, cryoglobulins, Lyme ELISA, ACE level, and HIV serology.

Sural nerve biopsy confirmed necrotizing vasculitis of epineurial and perineurial vessels and asymmetric nerve fiber loss between and within nerve fascicles.

Comment on Case *In the absence of clinical or laboratory confirmation of any systemic organ involvement, this is a case of nonsystemic vasculitic neuropathy. Pain, sensory loss, and weakness may present in a classic stepwise mononeuropathy multiplex pattern. Alternatively, the deficits are often extensive and overlapping, but involvement of individual nerves can still be discerned. Most diagnostically challenging are the patients who present with a distal symmetric polyneuropathy pattern. Pain is very characteristic, though not invariable. Pathologic confirmation is mandatory. Due to the multifocal nature of the vasculitic lesions, nerve biopsy will occasionally be nondiagnostic. Muscle biopsy may show vasculitis even without a clinical or laboratory suggestion of muscle involvement. The prognosis in nonsystemic vasculitic neuropathy is generally more benign, with a more indolent course than in the systemic vasculitides. The patient was treated with prednisone and cyclophosphamide; improvement occurred after several months, and the cyclophosphamide was discontinued after 6 months.*

CASE 12: FIVE-DAY ONSET OF DIFFUSE WEAKNESS

History A 20-year-old man presented with 5 days of distal arm and leg weakness beginning a few days after a day of flu-like illness characterized by diarrhea, lightheadedness, myalgias, and rhinorrhea without fever. He first noted a pulsating pain in the left posterior thigh and calf and the following day developed left leg weakness. The next day the right leg became weak, with slapping of his foot and difficulty maneuvering steps. Subsequently, his hands became weak; opening jars was difficult. He had no numbness of his hands or feet, though pulsating pain in his calves continued, and his feet felt cold. There was no diplopia, dysarthria, ataxia, dyspnea, or bladder dysfunction. The patient had new onset of hypertension and tachycardia after admission to the hospital.

Comment on History *The patient developed quadriparesis over a period of days following a viral syndrome or a possible bacterial infection. Cranial nerve and sensory functions were spared. Possibilities are broad and include inflammatory polyradiculoneuropathies (Guillain-Barré syndrome, demyelinating or axonal), toxic polyneuropathies (arsenic poisoning), metabolic polyradiculoneuropathies (porphyria), an inflammatory polyradiculopathy (Lyme disease), an acute anterior horn cell disease (polio-like enterovirus, West Nile virus), tick paralysis, or polymyositis. The rapid progression and one-limb onset are evidence against polymyositis or other myopathies. Myelopathies are rarely pure motor. Myasthenia gravis typically involves ocular muscles and is less acute. The dysautonomia narrows the differential diagnosis to some degree.*

Physical Examination The patient was alert, with normal cognitive function. Extraocular movements were full. Pupils reacted normally to light and accommodation. Cranial nerves were otherwise intact. Strength was 4+/5 in the triceps and hip flexors and 3–4/5 in distal bilateral hand and leg muscles. His gait was wide-based and waddling, with slight bilateral

foot drop. Pin sensation was diminished in a glove distribution in the hands to the wrists. Light touch, vibration, and position sense were normal throughout the limbs. Deep tendon reflexes were trace in the right biceps and bilateral triceps and were otherwise absent. Plantar responses were silent.

Comment on Physical Examination *The exam confirms distally accentuated quadriparesis, hypo- or areflexia, and mild distal small-fiber dysfunction in the hands. This is consistent with one of the polyneuropathies listed above or a polyradiculopathy. The pattern is not that of the more common length-dependent, axonal, sensory-predominant polyneuropathies.*

Electrophysiologic Studies Routine motor conduction studies were normal except for mild reduction in ulnar CMAP amplitudes. F waves were absent, sparing the median nerve. A right tibial H reflex was absent. Sensory conductions were normal. Needle EMG showed reduced (neurogenic) recruitment but no fibrillation potentials.

Comment on Electrophysiologic Studies *The diffusely absent late responses, though nonspecific, are consistent with an acute demyelinating polyradiculoneuropathy (acute inflammatory demyelinating polyradiculoneuropathy-[AIDP]) in this clinical setting. The early timing of the study (day 5) may underestimate the nerve conduction abnormalities at the nadir of the disease. Repeat nerve conduction studies in 7–14 days may further support the diagnosis if doubt remains.*

Laboratory Studies Cerebrospinal fluid showed albuminocytologic dissociation with a mild protein elevation. A lumbar puncture is useful primarily to exclude a concurrent illness associated with an inflammatory CSF such as Lyme disease, HIV, or West Nile virus infection. In sera, GM1 IgG was markedly elevated. GM1 IgM, GD1b IgM, and asialo-GM1 IgM were negative. Acute and convalescent *Campylobacter jejuni* titers were positive.

Comment on Case *This patient had a typical case of the common form of Guillain-Barré syndrome, AIDP. The sole unusual feature was the absence of acral paresthesias at the onset, although this occurs in a minority of cases. Pain, in various forms, is common, as is dysautonomia. Following treatment with intravenous immunoglobulin, the patient had gradual improvement of muscle strength over several weeks.*

*Although the electrophysiology did not show definitive demyelinating changes, the albuminocytologic dissociation and rapid recovery favor an acute demyelinating polyradiculoneuropathy. The association with GM1 IgG and *Campylobacter jejuni* are also supportive. *Campylobacter jejuni* was a likely trigger of GBS in this patient. GM1 IgG titer elevations occur in a minority of patients with Guillain-Barré syndrome but are more frequent in patients with preceding *Campylobacter jejuni* infection. However, GM1 IgG titer elevations have both low sensitivity and low specificity in Guillain-Barré syndrome.*

Acute Immune-Mediated Neuropathies

DEMYELINATING IMMUNE-MEDIATED NEUROPATHIES

Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) and Fisher Syndrome (FS)

AXONAL IMMUNE-MEDIATED NEUROPATHIES

Acute Motor Axonal Neuropathy (AMAN) and Acute Motor and Sensory Axonal Neuropathy (AMSAN)

DEMYELINATING IMMUNE-MEDIATED NEUROPATHIES

Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP) and Fisher Syndrome (FS)

INTRODUCTION

The eponym *Guillain-Barré syndrome* (GBS) encompasses several clinical entities with the following common features: acute or subacute onset of motor or sensory (favoring motor) dysfunction, hyporeflexia, frequent antecedent triggers (usually infectious) with a probable immune-mediated mechanism, a monophasic course with a peak deficit at 2–4 weeks followed by improvement, and frequent cerebrospinal fluid (CSF) albuminocytologic dissociation. Several subtypes of GBS are defined by whether the pathology is predominantly demyelinating (AIDP) or axonal (AMAN or AMSAN), by whether mixed

NEURONOPATHIES

Sensory (Idiopathic, Sjogren Syndrome, Paraneoplastic) and Motor (Paraneoplastic) Neuronopathies and Autoimmune Autonomic Ganglionopathy (AAG)

motor and sensory (AIDP, AMSAN) or motor signs predominate (AMAN), and by unusual clinical presentations (FS, ataxic-sensory, pharyngeal-cervical-brachial variant; see Fig. 6–1). Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the common form of GBS in the United States and Europe.

CLINICAL FEATURES

Epidemiology

AIDP occurs worldwide and is the most common cause of acute generalized paralysis. The incidence in various regions is one to two cases per 100,000.^{1–5} There is a slight male predominance. The mean age at onset is about 45 years; the disease rarely occurs in young children. There is a trend toward a greater incidence in spring and winter months, likely reflecting antecedent infections, but cases occur throughout the year.

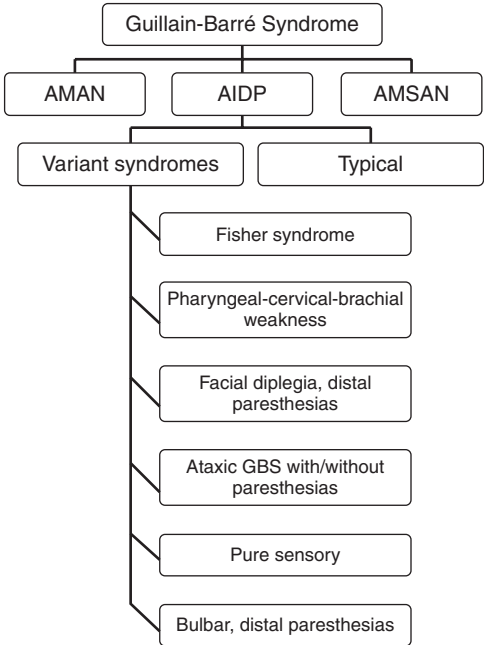


Figure 6–1. Guillain-Barré syndrome and its variants. AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensory axonal neuropathy; GBS: Guillain-Barré syndrome.

Antecedent Illnesses

Approximately two-thirds of patients with AIDP have a preceding viral-like prodrome within 1–4 weeks of the onset of neurologic symptoms.⁶ Preceding symptoms include fever (52%), cough (48%), sore throat (39%), rhinorrhea (30%), and diarrhea (27%).⁷ Various pathogens are associated with AIDP, and most are viral in North America and Europe (Table 6–1). Commonly associated viral infections include cytomegalovirus, Epstein-Barr virus, influenza A and B, and varicella-zoster virus. Most are not identified, and asymptomatic hepatitis, presumably viral, occasionally occurs. *Campylobacter jejuni* (Cj) is the most common preceding bacterial infection in GBS, occurring in 20%–36% of GBS patients.^{8–12} Infection with Cj is strongly associated with diarrhea and abdominal pain.⁷ In our series, surgery preceded GBS in 3 of 20 patients.¹³ Other, less commonly associated antecedent bacterial infections are listed in Table 6–1. In 1976, there was a sevenfold increase in swine flu vaccine-associated GBS limited to U.S. civilians.¹⁴ Guillain-Barré

syndrome following rabies vaccination is limited to a few case reports. An adjusted relative risk of 1.7 was shown for GBS following influenza vaccination between 1992 and 1994. This translated into slightly more than one extra case per million.¹⁵ Guillain-Barré syndrome may occur in pregnancy, typically late; there are no reports of fetal transmission, favoring a T-cell-mediated pathogenesis.⁶ Cancer (Hodgkin lymphoma) may also precede GBS.

Various antecedent infections are associated with different variants of GBS. With Cj infection, GBS is more commonly axonal, pure motor, with low CSF protein and elevated GM1 titers. Cytomegalovirus is associated with cranial neuropathies, severe sensorimotor polyneuropathy and GM2 antibodies.¹⁶

Symptoms and Signs

Patients typically present with subacute limb weakness over days following a flu-like syndrome or diarrhea. The infectious prodrome is usually in recovery by the time the neurologic symptoms commence. The disease

Table 6–1 Antecedent Events in GBS

Viral Infections	Vaccines
Cytomegalovirus	Swine flu
Epstein-Barr	Rabies
Varicella-zoster	Influenza
Influenza	Malignancy
Coxsackie	Hodgkin disease
Hepatitis A and C	Chronic lymphocytic leukemia
Herpes simplex	Lymphoma
Rubeola	Carcinoma
Rubella	Collagen vascular disease
Mumps	Systemic lupus erythematosus
Echo	Sarcoidosis
HIV	Parasitic
Vaccinia	Toxoplasmosis
Variola	Malaria
Bacterial Infections	Surgery
<i>Campylobacter jejuni</i>	Pregnancy
<i>Mycoplasma pneumoniae</i>	Wasp sting
<i>Escherichia coli</i>	Bone marrow transplantation
Salmonella	
Listeriosis	
Brucellosis	
Tularemia	
Ornithosis	
<i>Coxiella burnetii</i>	

typically progresses over 1–2 weeks, and most cases plateau by 4 weeks. Acral paresthesias typically accompany the limb weakness; facial or trunk paresthesias occur uncommonly. Both weakness and paresthesias begin largely symmetrically and spread over hours or days to previously unaffected regions. Onset of leg weakness is most common, though arms and legs are usually both affected at presentation.⁶ Limb weakness may be proximally or distally accentuated, but a proximal pattern was more common in our series overall. When weakness principally affects the arms, a distal pattern predominates. Ataxia may accompany weakness and may be the principal cause of gait dysfunction. When present, facial weakness is bilateral (it may be asymmetric, but it is not unilateral), accentuated periorally, and is more common than bulbar dysfunction or ophthalmoparesis. Bifacial weakness distinguishes AIDP from most polyneuropathies with the exception of sarcoidosis and Lyme disease. Ptosis is uncommon. Pain occurs in about 25% of patients at presentation and is typically characterized by aching of the lower back, flank, buttocks, and posterior thighs; less commonly, pain is characterized by L5/S1 radicular

symptoms or acral dysesthesias.⁶ More severe cases may affect the phrenic nerves, causing respiratory muscle weakness and failure. Neck flexion and deltoid weakness tend to parallel diaphragmatic weakness. Deep tendon reflexes are nearly always depressed or absent in AIDP, particularly in functionally weak muscles. Preservation of all tendon reflexes throughout the course of the disease is exceedingly uncommon, although it may occur in cranial nerve variants.

Autonomic dysfunction is usually subclinical except for a resting tachycardia in approximately 50% of patients. It likely reflects involvement of myelinated preganglionic fibers and the ganglia. In more severe cases, tachycardia and hypertension or bradycardia and hypotension may occur. Marked systolic blood pressure variations of >85 mmHg predict bradycardia.¹⁷ Bladder dysfunction is rare and should prompt a search for other causes. Other rare associated conditions include papilledema, myokymia (usually facial), ageusia, hypoacusis, and vocal cord paralysis.^{18–21}

In children, the aching lumbar and posterior thigh pain occurs more frequently, in up to

35%–80% of cases, and may be the predominant presenting complaint.²² Otherwise, children with AIDP present similarly to adults, except that paresthesias are reported less frequently, and incoordination more frequently, in children.²³

There are several recognized variants of GBS. The most common is **Fisher syndrome (FS)**, characterized by the triad of ophthalmoplegia, ataxia, and areflexia. Paralysis of extraocular muscles and areflexia are often partial. Early bilateral abducens paralysis often progresses to generalized ophthalmoparesis. Ptosis is common, and pupils are rarely involved. Weakness is minimal; occasional cases progress as classical GBS with quadriparesis and even respiratory failure. Distal paresthesias may occur.²⁴ This syndrome is associated with antibodies to GQ1B in about 85% of patients.²⁵ Rare patients have acute ophthalmoparesis without ataxia and variable reflex changes; laboratory features are consistent with FS.²⁶ Other relatively uncommon variants include pure motor (acute motor axonal neuropathy, AMAN), pharyngeal-cervical-brachial weakness, and facial diplegia with distal paresthesias.^{6,27} Rare variants presented as isolated case reports include paraparesis (or bilateral lumbar polyradiculopathy), ataxia with acral paresthesias, pure ataxia, abducens palsy with distal paresthesias, pure sensory, bulbar with distal paresthesias, and acute multiple cranial neuropathies (ophthalmoparesis, facial diparesis, and bulbar dysfunction).^{13,24,27–29} All variants are supported by hyporeflexia, albuminocytologic dissociation, and electrophysiologic evidence of polyneuropathy (usually demyelinating).

Differential Diagnosis

In a patient with progressive weakness over days with paresthesias and hyporeflexia consistent with GBS, a few disorders present a diagnostic challenge. Spinal cord compression or myelitis can mimic the illness. Reflexes may be depressed acutely, but sensory levels to pin and temperature and bladder symptoms suggest myelopathy. A polio-like illness mimics the time course of progressive weakness but weakness is usually asymmetric and may begin with fever, paresthesias and numbness are absent, and >50 cells are often present in the CSF;

serum and CSF titers for West Nile virus infection should be assessed in this clinical setting.

In patients with ocular or bulbar dysfunction, botulism is a consideration; however, sensory symptoms are absent, internal ophthalmoplegia occurs, constipation is common, and CSF is normal. Polyneuropathy in diphtheria may present with acute bulbar dysfunction that may be overlooked or with quadriparesis and distal sensory symptoms that develop several weeks later; the preceding severe throat infection, prominent bulbar symptoms, and biphasic course differentiate this condition from GBS.³⁰ Porphyric polyneuropathy may present with ascending paralysis or initial arm paralysis and cranial neuropathies in severe cases; it is differentiated from AIDP by associated abdominal pain, psychiatric manifestations, or seizures and axonal polyradicular dysfunction by electrophysiologic testing. Arsenic poisoning (usually secondary to a homicide or suicide attempt) and tick paralysis may mimic GBS both clinically and electrophysiologically. Arsenic poisoning is suspected by the presence of gastrointestinal symptoms, anemia/leukopenia, and subsequent skin rash and Mees lines. Tick paralysis is suggested by the presence of an engorged tick in the scalp. Tetrodotoxin poisoning from consumption of puffer fish can lead to a more explosive quadriparesis, paraparesis, perioral or acral paresthesia, and respiratory failure over hours. The proximal pattern of weakness and lack of sensory symptoms in polymyositis are usually distinctive. Impending basilar artery occlusion or brainstem encephalitis may mimic FS, though cognitive changes, preserved reflexes, and normal nerve conduction studies would favor a central cause.

Since it is rare for GBS patients to progress to quadriplegia over 24 hours, such hyperacute presentations over hours should raise the possibility of periodic paralysis, various intoxications, tick paralysis, and occasionally psychogenic weakness.

LABORATORY STUDIES

Blood Tests

White blood cell counts and transaminase levels are usually normal but may be elevated. Such elevations probably reflect an antecedent

viral infection. GM1 titers are positive in 9%–25% of patients with GBS overall.^{12,13,31,32} These are predominantly of the IgG class and may be associated with antibody activity to asialo-GM1 or GD1B.³² GM1 titers are more frequently present in the setting of antecedent *C. jejuni* infection, occurring in 50% of Cj-associated GBS. The presence of a positive GM1 titer does not clearly predict the prognosis or indicate whether the electrophysiology is axonal (AMAN or AMSAN) or demyelinating (AIDP). Axonal variants are more common in China and Japan than in the West. Cytomegalovirus (CMV) or Epstein-Barr antibody titers may be positive, particularly after an upper respiratory or flu-like prodromal illness. GQ1b antibodies are strongly associated with FS but may also be seen in Bickerstaff brainstem encephalitis, pharyngeal-cervical-brachial variant, GBS with ophthalmoplegia, and acute ophthalmoplegia without ataxia. The pharyngeal-cervical-brachial variant is most strongly associated with anti-GT1a IgG antibodies and frequent antecedent Cj infection.

Electrodiagnostic Studies

Nerve conduction studies are the most useful laboratory test to confirm the clinical diagnosis of GBS. In the United States and Europe, the electrophysiology is usually demyelinating without uniform conduction slowing, consistent with AIDP (Fig. 6–2). In China and Japan, the electrophysiology is more characteristically axonal and predominantly motor (AMAN). In early GBS, the most sensitive, but nonspecific, abnormality is absent H reflexes.³³ Within the first 4 days of onset of neurologic symptoms, electrophysiologic findings are frequently normal or nonspecific.³³ In AIDP, prolonged F-wave (late response) minimal latencies, an increased range of F-wave latencies, and impersistent or absent F waves are early findings, and marked prolongation (>120% of the upper limit of normal) suggests a demyelinating lesion (Table 6–2). Decreased motor unit recruitment on electromyography (EMG) is the earliest finding, but it is difficult to quantify. Prolonged distal motor latencies and temporally dispersed distal compound muscle action potentials (CMAPs) tend to develop prior to considerable (<70% of the lower limit of normal) conduction velocity

slowing. Motor conduction slowing, when present, is usually not uniform between nerves and may be associated with conduction block (>30%–50% drop in amplitude with proximal stimulation with <15% increase in duration) or temporal dispersion (>15% increase in duration). In children younger than 5 years old, severe generalized motor slowing may occur.³⁴ Sensory conduction may be normal or show amplitude reduction with mild or no slowing of velocity. Sensory responses in the arms, particularly in the median nerve, may have reduced amplitude with a relatively preserved sural response; this may relate to greater distal pathology. Both median and sural nerves may be affected in more advanced disease. Sensory response amplitudes are often spared in the first couple of weeks. A nadir is reached, on average, at 3 weeks for motor conduction and 4 weeks for sensory conduction.³⁵

In FS, there is a predilection for reduced sensory response amplitudes with or without mild prolongation in F-wave minimal latencies. Sensory responses may be more affected in the arm than in the leg. Although these findings appear to suggest axonal pathology, the predominant sensory nerve involvement limits differentiation from demyelinating neuropathy, since criteria for demyelinating polyneuropathy are based on motor conduction.^{24,36} Rapid clinical recovery may favor primary demyelination. However, low facial CMAP amplitudes with preserved distal latencies, minimal blink reflex prolongations (R1), and fibrillations in facial muscles suggest axonal disease affecting the facial nerves.^{24,36}

Cerebrospinal Fluid

The CSF protein level is often normal during the first week of the illness but is frequently elevated in the following several weeks, in 95% of patients in one series,³⁷ with few or no cells (albuminocytologic dissociation). Protein levels above 1 g/dL and more than 20 lymphocytes are unusual, and either finding should raise the possibility of another diagnosis. A pleocytosis may suggest West Nile virus or another polio-like illness (particularly if the patient is systemically ill at presentation), human immunodeficiency virus (HIV)

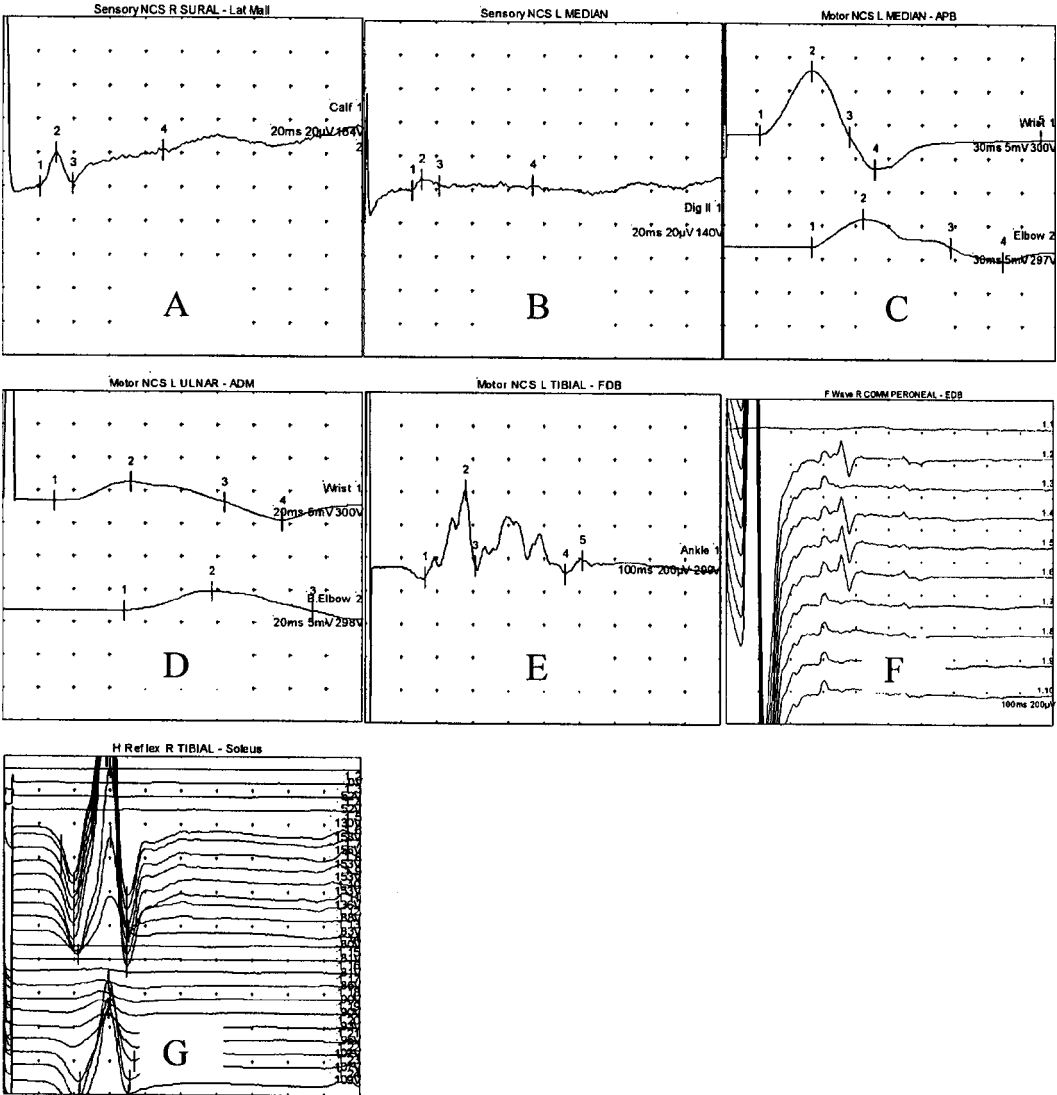


Figure 6-2. Electrodiagnostic studies in acute inflammatory demyelinating polyradiculoneuropathy illustrating the various multifocal, segmental demyelinating features that may be encountered: Sural-sparing pattern with a robust sural sensory nerve action potential (SNAP) (A) and low-amplitude median SNAP (B); partial conduction block/temporal dispersion of the median compound muscle action potential (CMAP) across the forearm (C); prolonged duration of the ulnar distal CMAP (D); marked temporal dispersion of the tibial CMAP (E); absent peroneal F wave but multiple A waves (axon reflexes) (F); absent tibial H reflex (G).

infection, Lyme disease, or myelitis. A marked CSF protein elevation may suggest spinal cord compression. Very rarely, CSF lymphocytic pleocytosis or polymorphonuclear granulocytes are present.³⁸ Oligoclonal bands or myelin basic protein may be seen in otherwise typical GBS and do not necessarily indicate central nervous system (CNS) disease.³⁹

Guillain-Barré syndrome in HIV infection tends to occur early in the course of HIV infection, before severe immunosuppression. When present, a mild pleocytosis (particularly with lymphadenopathy) suggests HIV infection, although this is often absent.^{40,41} Increased CSF protein is presumably related to breakdown of the blood-CSF barrier.

Table 6–2 **Electrophysiologic Features of GBS**

	AIDP	AMAN	AMSAN
Amplitude			
Motor	Normal or low	Low	Low
Sensory	Normal or low	Normal	Low
Conduction Velocity			
Motor	Slow or normal	Normal	Normal
Sensory	Slow or normal	Normal	Normal
Motor Distal	Prolonged	Normal	Normal
Latency			
Conduction Block	May be present	Absent	Absent
F-Wave Minimal	Prolonged	Variable	Variable
Latency			
Nerve Distribution	Diffuse > multifocal	Diffuse	Diffuse

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor and sensory axonal neuropathy.

Imaging

In a typical case of GBS, imaging adds little to the diagnostic work-up. However, magnetic resonance imaging (MRI) of the spine may be helpful to assess for spinal cord compression or myelitis in select cases, and may help confirm GBS in instances where the electrophysiologic findings are equivocal. Gadolinium enhancement of cauda equina nerve roots on T1-weighted MRI scans is common in GBS, occurring in 83%–95% of patients.^{42–44} Greater enhancement of ventral roots may occur. In one case of FS, a follow-up MRI scan of the spine showed increased T2 signal in the posterior column.⁴⁵

Genetics

The observation that many people have infection with Cj and other infectious triggers of GBS, but that only a small proportion of exposures lead to GBS, suggests that genetic factors play a role in the disease. The major histocompatibility complex (MHC) genotype considerably affects susceptibility and the disease course in experimental autoimmune neuritis induced with peripheral nerve myelin or a P2 peptide.⁴⁶ Non-MHC genes also contribute to disease susceptibility and resistance. Additionally, KM3 homozygotes are elevated in GBS patients compared to controls. KM genes are genetic markers of the constant region of kappa chains.⁴⁷

PATHOLOGY

Nerve biopsy is rarely indicated in AIDP unless there are unusual features. The commonly studied sural and superficial peroneal sensory nerves are frequently normal. Demyelinating changes and adjacent perivascular, endoneurial, inflammatory infiltrates, consisting of lymphocytes and macrophages, may be present.^{6,48} In severe cases, there may be reduced density of myelinated fibers and axonal degeneration with minimal inflammatory infiltrates.^{49,50}

In GBS, pathologic changes are often greatest in nerve roots but patchy involvement occurs in peripheral and cranial nerves. The pathologic hallmarks are demyelination and perivascular inflammatory infiltrates consisting of lymphocytes and macrophages with varying degrees of Wallerian degeneration. Vesicular changes of myelin are followed by macrophage process penetration of the basal lamina that strips off myelin lamellae. CD4+ and CD8+ T cells are also characteristically present.⁵¹

Immunohistochemistry may show complement deposition, which is thought to precede the myelin vesiculation.^{6,52} In some cases complement components C3d, C5b-9, and C9neo antigen are present on the outer surface of Schwann cells.⁵³

In FS, pathologic studies of peripheral nerve are lacking. However, sera from FS or GBS patients with ophthalmoplegia may show IgG

staining of the molecular layer of the cerebellum.⁵⁴

PATHOGENESIS

The animal model for AIDP is experimental autoimmune (or allergic) neuritis (EAN). Rats and rabbits injected with adjuvant and bovine peripheral nerve myelin (or specific myelin proteins such as MPZ, P2, and PMP-22) develop tail and limb paralysis; pathologic changes resemble those of AIDP, with T-cell and macrophage infiltrates, demyelination, and axonal degeneration.^{55,56} In Lewis rat EAN there is strong evidence that T-cell-mediated immunity results in inflammatory infiltrates and axonal degeneration. T-cell interleukin-2 (IL-2) receptor expression is increased.⁵² Passive transfer of MPZ and P2-specific T cells causes EAN in syngeneic animals, but B cells or immunoglobulin are necessary for demyelination. Both mechanisms may act synergistically, with autoreactive T cells compromising the blood-nerve barrier and providing access for anti-neural antibodies.

Despite the frequent presence of ganglioside antibodies of different specificities in GBS, gangliosides (GM1, GD1a, GD1b, and GT1b) are partially protective in experimental allergic neuritis.⁵⁷ GM1 IgG and IgM antibodies from patients with GBS have been shown to cause conduction block when injected into rat nerve by some researchers but not others.^{58,59} Murine monoclonal antibody to Cj and gangliosides also does not exacerbate disease in EAN. Complement activation may play a role in demyelination in both EAN and GBS.^{53,60,61} Macrophages may function as antigen presenters and inflammatory regulators through release of pro-inflammatory cytokines IL-1, IL-6, IL-12, and tumor necrosis factor (TNF)-alpha.⁶² They also cause damage by phagocytosis and release of oxygen radicals, arachadonic acid metabolites, and hydrolases.⁵² Late in the course of disease, macrophages may play a reparative role, with inhibition of T-cell apoptosis and secretion of the anti-inflammatory cytokines transforming growth factor (TGF)-beta1 and IL-10.⁶²

There is considerable evidence linking Cj infection, a common cause of bacterial enteritis, and GM1 ganglioside with GBS.^{8-12,63} *C. jejuni* infection is an antecedent illness in 20%–36% of GBS patients.^{8,9,11,12,47}

Antibodies to GM1 were present in 52% of patients with, compared to 15% of those without, evidence of recent Cj infection.¹² Anti-GM1 antibodies recognize surface epitopes on Cj, suggesting molecular mimicry.^{8,10,63} There is also evidence of molecular mimicry between Cj and the ganglioside GQ1B in FS.⁶⁴ An animal model of GBS associated with Cj infection is limited to chickens fed Cj that were isolated from a patient with GBS.⁶⁵ Rabbits injected with Cj lipopolysaccharides develop antibodies that react with gangliosides but not EAN.⁸

Recent studies suggest a possible role of $\gamma\delta$ T cells in the pathogenesis of GBS. $\gamma\delta$ T cells participate in microbial defense, are prevalent in intestinal epithelia, and are activated in autoimmune diseases. In EAN, $\gamma\delta$ T cells express CD45RC⁺CD8⁺ markers in root lesions, suggesting a cytotoxic or suppressor role.⁶⁶ In one patient with GBS and Cj infection, a sural nerve T-lymphocyte culture consisted entirely of $\gamma\delta$ T lymphocytes.⁶⁷ The $\gamma\delta$ T cells cultured from the sural nerve of another patient with GBS and Cj infection were predominantly of the V δ 1 subset.⁶⁸ Patients with GBS were recently shown to have an expanded V δ 1 subset with elevated expression of NKR1A.⁶⁹ NKR1A is a receptor expressed on activated natural killer cells. A minority of GBS patients have elevated levels of V δ 1/CD8⁺ cells, possibly associated with elevated Cj or GM1 titers.¹³ $\gamma\delta$ T cells may have a cytotoxic (or suppressor) role in the disease.

TREATMENT

Immunosuppression

Plasma exchange and intravenous immunoglobulin (IVIG) are equally efficacious treatments for patients with functional deficits that limit motor function or gait. The choice depends on the availability and ease of administration of either treatment. Since IVIG has fewer serious adverse effects, generally does not require a central intravenous port, and is administered in a shorter period of time (5 versus 7–14 days), it is often the treatment of choice. Unstable cardiovascular disease and coagulopathy are contraindications for plasma exchange. Patients with more advanced GBS characteristically have autonomic instability with wide swings in blood pressure. Neither treatment is

proven to prevent significant residual disability after 1 year, but both increase the rate of recovery and likely improve the functional motor outcomes in most patients.^{70–72} The dose of IVIG is 2 g/kg total, usually given as 400 mg/kg daily for 5 days. The total plasma volume exchanged by plasma exchange is not standardized but is usually 200–250 mL/kg.

If patients relapse within several days of completing immune-modulating therapy, additional IVIG or plasmapheresis may be given. Optimal dosing of IVIG in this setting is not established. The relapse rate is similar after both treatments (5%).⁷³ There is no added benefit of sequential treatment with plasmapheresis followed by IVIG.⁷³ Plasmapheresis is generally not performed following IVIG administration, but it may be considered if the patient does not respond to an initial course of IVIG. Oral prednisolone and intravenous corticosteroids, alone or in combination with IVIG, are ineffective.^{74,75} Whether mild cases with little or no weakness should be treated is controversial. Since recovery may begin sooner with immunosuppression, and since there are no distinguishing features to separate mild from more progressive cases, we suggest IVIG treatment in most patients. One exception may be patients who have minimal weakness and are no worse by day 8 of the appearance of neurologic symptoms, since these patients tend to have a benign course.⁷⁶

In children with AIDP, treatment with IVIG before the loss of unaided ambulation did not affect the functional outcome, but recovery was faster.⁷⁷ Additionally, the effectiveness of treatment was similar whether the total dose of 2 g/kg was administered over 2 or 5 days, although relapses occurred with the shorter regimen.⁷⁷

Respiratory Treatment

Patients who present within the first few weeks of neurologic symptom onset and are not improving should be admitted to the hospital even with mild deficits (i.e., ambulatory without assistive devices), since weakness and dysautonomia may progress considerably overnight. Patients who cannot ambulate without assistance or have respiratory weakness on admission (forced vital capacity [FVC] <20 mL/kg or peak inspiratory pressure [PI_{max}]

<30) should be observed initially in a monitored unit.⁷⁸ Blood pressure, heart rate and rhythm, and the ability to cough and swallow should be closely monitored. Forced vital capacity and, if available, PI_{max} are followed at the bedside every 8 hours. Pulse O₂ saturation is monitored during sleep.

The need for intubation is determined by clinical parameters—respiratory rate, use of accessory muscles, weak cough, hypophonia—and FVC. Prominent weakness of neck flexors and shoulder girdle muscles is associated with respiratory muscle weakness. An FVC measurement may not be reliable if there is significant bifacial weakness. Intubation should be considered for patients with dyspnea at rest, obvious bulbar dysfunction, FVC <15 mL/kg, a >30% drop in FVC, or partial pressure of oxygen (pO₂) <70 mm.^{78,79} Respiratory failure needing emergency intubation can rarely lead to anoxic encephalopathy.⁷⁹ Cough assist devices can facilitate sputum production and help prevent atelectasis in nonintubated patients with compromised respiratory muscles. Aggressive suctioning should be avoided because of dysautonomia. In patients with less severe, stable, or improving respiratory weakness, noninvasive positive pressure ventilation may be tried. However, this is contraindicated in patients with significant bulbar dysfunction because of reduced efficacy and lack of airway protection.

Intubated patients who are quadriplegic may be “locked in.” Although most such patients are sedated for comfort, every effort should be made to communicate with them through eye blinking or some other form of preserved motor function.

Autonomic System Treatment

Autonomic instability in GBS is common, even in mild cases. Resting tachycardia is a useful bedside sign. Mild swings in blood pressure are common. In more severe cases of GBS, wide swings in blood pressure may occur, accompanied by brady- or tachyarrhythmias. Daily systolic blood pressure variation of >85 mmHg may predict bradycardia.¹⁷ Other causes of autonomic dysfunction in the intensive care unit (ICU) setting should be excluded, such as hypoxia, dehydration, pulmonary embolus, and gastrointestinal hemorrhage. Hypotension is treated with intravenous hydration; pressor

agents are generally avoided. Ileus and urinary retention may also occur. Urinary retention may occur secondary to autonomic dysfunction, abdominal wall weakness, and external urinary sphincter dysfunction. Catheterization is necessary for postvoid urine volumes greater than 100 mL. The corneas may require protection with lubricants and taping of the lids closed. In mild GBS, tests of autonomic function often improve after 3 months.⁸⁰

Pain

Pain is relatively common in GBS, occurring in about 30% of patients.⁶ It often begins with the onset of neurologic symptoms, though it may develop later in the disease course. Deep, aching, symmetric pain in the lower back, buttocks, and thighs (often posterior) is characteristic. Acral dysesthesias or stabbing interscapular pain may also develop. Bedbound patients may develop musculoskeletal pain related to immobility. More than mild pain requires tramadol or narcotics. Gabapentin, carbamazepine, or pregabalin may reduce the dysesthetic pain.⁸¹ Amitriptyline may act as an analgesic adjuvant and facilitate sleep. Positioning changes and range-of-motion exercise are also essential.

Chronic Supportive Care

Nutritional requirements, the need for nasogastric feeds, positioning changes, and deep venous thrombosis prophylaxis are addressed in the hospitalized GBS patient. Range-of-motion exercises and stretching are essential to maintain joint mobility. This is particularly true of muscle groups that are only antigravity or weaker. Bedbound patients should be turned about every 2 hours, and pressure-sensitive areas should be inspected for skin breakdown. Slight leg elevation, about 30 degrees, or pneumatic stockings can limit leg edema and distal skin breakdown. Passive range-of-motion exercise of all joints, three to five repetitions, twice daily are suggested. Between sessions, the limbs are positioned to allow mild stretch from gravity in prone muscle groups.

Splinting may help prevent joint deformities and may provide support and functional benefits by substituting for weak muscles. Encouraging patient activity and endurance exercises in less functionally impaired patients

cannot be overemphasized. Fatigability can be severe in the early recovery period, and it must be differentiated from depression. Depression may be treated with antidepressant medication and psychiatric counseling if it persists. Patient and caregiver support groups are valuable resources for accepting patients.

It is generally considered safe to administer vaccinations to patients with prior GBS, although they should probably be avoided during the acute period and the first year of recovery.⁸¹ Additionally, any specific immunization that was temporally related to GBS in a given patient should probably be avoided indefinitely.

COURSE AND PROGNOSIS

Within 4 weeks of the onset of neurologic symptoms, 90% of patients reach a maximal deficit. Recovery begins in 1 to 4 weeks after the deficit stabilizes. Progression beyond 2 months suggests chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). It is controversial whether there is a separate entity of subacute inflammatory demyelinating polyneuropathy with a nadir of 4 to 8 weeks.⁸² These patients generally resemble patients with AIDP, except that the majority of patients improve after prednisone treatment and 17% relapse months later, consistent with CIDP.⁸² The majority of patients with GBS have an excellent functional recovery. Within 6 months, about 80% of patients are ambulatory. At 1 year, about 45%–60% of patients have recovered fully, 17% are unable to run, 9% are unable to walk unassisted, and 4% remain bedbound or ventilator dependent.^{2,83} However, the extent of the recovery depends on the degree of motor axon loss. Most patients with quadriplegia have a significant degree of motor axon degeneration and recover poorly, although there are remarkable exceptions. A rapid progression to quadriplegia, advanced age, and the need for mechanical ventilation further worsen the prognosis. Inexcitable motor nerves predict considerable motor axon degeneration. Mortality is about 2%–8% overall and is 20% in ventilated patients.^{2,3,83,84}

Treatment-related fluctuations occur in 6%–16% of patients days to a few of weeks after completing plasmapheresis or IVIG therapy.⁸⁵ It is likely that the initial immune attack is still active and that the treatment has only

temporarily arrested its progression. Fatigue is very common after paresis from GBS and can last for years after patients' strength recovers. It may be associated with persistent electrophysiologic abnormalities and improves with bicycle exercise training.⁸⁶

Recurrent cases of GBS, months to years following recovery, are unusual, occurring in about 1%–5% of patients.^{85,87} Recurrence after 8 weeks or more than two times suggests CIDP, although some recurrent cases resemble a typical course of GBS.⁸⁵

In children, the course of GBS is generally better than that in adults, with long-term muscle weakness in one or more muscles in 23% of patients with maintained functional independence; long-term muscle weakness is predicted by young age and rapid progression.⁸⁸

AXONAL IMMUNE-MEDIATED NEUROPATHIES

Acute Motor Axonal Neuropathy (AMAN) and Acute Motor and Sensory Axonal Neuropathy (AMSAN)

INTRODUCTION

In August 1990, epidemics of a GBS-like illness in rural parts of northern China were investigated by McKhann et al.⁹⁰ A distinctive axonal form of GBS was shown to be common in this region. The syndrome was characterized by rapidly ascending quadriparesis, respiratory failure, reduced reflexes, albuminocytologic dissociation, and evidence of motor axon degeneration electrophysiologically and pathologically. This prevalent form of GBS in northern China was termed *acute motor axonal neuropathy* (AMAN). A subset of patients had additional sensory axon degeneration, termed *acute motor and sensory axonal neuropathy* (AMSAN). AMSAN otherwise resembles AMAN clinically and pathologically. These axonal forms of GBS rarely occur in the United States and Europe.

CLINICAL FEATURES

Epidemiology

There are no studies of the prevalence or incidence of AMAN in China, Europe, or the

United States. A summer epidemic was noted in a 2-week period of August 1991 in rural northern China.⁹¹ In 1991 and 1992, 129 patients from China with GBS were studied electrophysiologically. AMAN was present in 65% and AIDP in 24%; 11% of cases were unclassifiable.⁹¹ The disease occurs in children and young adults in rural areas around Hebei, China, and the surrounding provinces. The mean age of patients in two hospitals in China was 4.5 and 19 years.⁹² The ratio of males to females was 3:2.⁹² The disease did not cluster in specific schools or families. In Beijing, China, between June 1991 and June 1993, 20 of 27 (74%) children with GBS had AMAN.⁹³ Of 167 patients with GBS studied in Taiwan, 82 (49%) had AIDP, 32 (19%) had FS, and only 6 (4%) had "axonal" GBS.⁹⁴ In Buenos Aires, Argentina, 18 of 61 (30%) patients had AMAN; 90% of children with AMAN resided in suburban or rural regions without running water, compared to 50% of AIDP patients who resided in a metropolitan area.⁹⁵ AMAN developed more acutely, and the children were younger. By contrast, in Greece between January 1989 and December 2001, 6% of 105 patients with GBS had axonal electrophysiologic findings.⁹⁶ In the authors' experience, fewer than 1 in 30 patients have clinical and electrophysiologic features suggestive of AMAN in the United States.¹³

The frequency of AMSAN is unclear. It was found in 3 of 12 autopsied GBS patients from Hebei province, China.⁹⁷

Antecedent Illnesses

The only studies of antecedent illness in AMAN assessed the frequency of Cj infection. There is a strong correlation of Cj infection with AMAN in China. Positive Cj titers occur in 76%–81% of AMAN patients in China but in less than 50% of patients in Japan.^{91,98} This compares to positive Cj titers in only 44% of AIDP patients in China and 20%–36% of AIDP patients in the United States and Europe.⁹¹ Conversely, of 22 Cj-positive patients in one Japanese series, 16 (73%) had AMAN and 5 (23%) had AIDP.⁹⁹ None of 14 cytomegalovirus/Epstein-Barr virus (CMV/EBV)-positive patients had AMAN. AMSAN may also be associated with elevated Cj titers, but the number of patients reported is small.¹⁰⁰

Approximately 30% of AMAN patients had a “viral prodrome” with fever preceding the onset of paralysis.⁹² Diarrhea occurred in 10%–30% of patients, and 20% had an upper respiratory infection.⁹²

Symptoms and Signs

In patients in rural China, weakness typically presents acutely in the legs with gait difficulty and falls. Patients are afebrile at neurologic symptom onset. Ascending symmetric paralysis is very characteristic, leading to dysphagia, hoarseness, facial diparesis, and dysarthria.⁹⁰ Quadriparesis and respiratory failure develop in the most severe cases. Pain and stiffness of the spine is common, though radicular pain is rare. About 10% of patients develop acral paresthesias. On exam, patients have symmetric weakness, hypotonia, and areflexia. Symmetric weakness of the face, jaw, tongue, and pharynx is frequent, with relative sparing of extraocular muscles. Tongue weakness is more common than in AIDP. Neck flexors are characteristically weak, with spasm of neck extensors resembling meningismus, particularly in the young. Large- and small-fiber sensory functions are normal. Some patients have autonomic dysfunction with arrhythmias, blood pressure alterations, and patchy hyperhydrosis.

Clinical descriptions of AMSAN are sparse. AMSAN resembles AMAN clinically except that sensory symptoms in the limbs may occur. Weakness may begin in the limbs or lower cranial nerves and spread to become quadriparesis.^{97,100} Areflexia, respiratory failure, and autonomic features may occur.

During recovery, deep tendon reflexes return in weak muscles and may become brisk. Approximately 50% of patients have mild hyperreflexia upon recovery. In Japan, 7 (13%) of 54 patients had hyperreflexia with spread in the early recovery phase; 1 of these patients had hyperreflexia early in the progressive phase of the illness.¹⁰¹

Differential Diagnosis

For AMAN, the differential diagnosis is similar to that of AIDP, excluding disorders with prominent sensory symptoms such as myelitis and arsenic poisoning. A polio-like illness, including West Nile virus infection, is a

consideration, particularly if weakness onset occurs with fever. Porphyric polyneuropathy may be a predominantly motor syndrome.

LABORATORY STUDIES

Blood Tests

Routine blood cell counts, electrolytes, and renal and hepatic function are typically normal.⁹⁰ GM1 titers are associated with AMAN, occurring in 24%–60% of patients, depending on the titer cutoff.⁹⁸ Elevated GM1, GM1b, and GD1a antibody titers were significantly more frequent in 21 AMAN patients than in 19 AIDP patients.¹⁰² GD1a antibodies are more specific for AMAN, occurring in 21%–24% of AMAN patients and 0% of AIDP patients at a high-titer cutoff.^{103,104} GD1b antibodies may also be more common in AMAN patients (32%) than in AIDP (11%) patients. AMSAN also has antibodies against GM1, GM1b, and GD1a, similar to AMAN.¹⁰²

Electrodiagnostic Studies

In AMAN, sensory nerve conduction is generally normal. Mild median or ulnar sensory conduction abnormalities are rarely reported.^{90,92} Median sensory involvement may represent superimposed entrapment neuropathy. The main nerve conduction abnormalities are motor, with reductions in CMAP amplitudes and normal or absent F-waves (absent when CMAP reductions are marked). Motor nerve conduction velocities are normal or show mild slowing proportional to CMAP amplitude reduction. Needle EMG shows diffuse fibrillation potentials with reduced recruitment of normal configuration motor unit potentials. Fibrillations tend to occur earlier than in AIDP.

In AMSAN, electrodiagnostic studies are limited. One of two patients in China had reduced CMAP and sensory potential amplitudes with “preserved” conduction velocities.¹⁰⁰ The other patient had a mild decrease in CMAP amplitude.

Cerebrospinal Fluid

White blood cell counts in CSF are typically normal (<10 cells) in AMAN. Protein elevations in CSF occur in about two-thirds of

patients, with a trend toward higher elevations later in the course of the illness. Glucose is typically normal. Studies of CSF are not reported in AMSAN in the China series.

Imaging

Magnetic resonance imaging of the spine in an adolescent with AMAN showed enhancement of the cauda equina, but MRI studies are limited.¹⁰⁵ Cerebral white matter lesions may occur.¹⁰⁶

Genetics

Unlike AIDP, there are no clear class II human leukocyte antigen (HLA) associations with AMAN.¹⁰⁷

PATHOLOGY

Sural nerve biopsies are essentially normal in AMAN, consistent with the predominant motor involvement in this disorder. Motor nerve terminal biopsies show denervated neuromuscular junctions and a reduced number of intramuscular nerve fibers. In AMSAN the sural nerve may show Wallerian-like degeneration of large and, to a lesser degree, small myelinated fibers.⁹⁷

The pathology of AMAN is distinct from that of AIDP. There is Wallerian-like degeneration of ventral roots and motor fibers. Macrophages are seen in the periaxonal space, displacing or surrounding the axon, and are beneath an intact myelin sheath.⁹⁷ There is a paucity of lymphocytic infiltration; a few CD-45-positive cells may be present. Immunoglobulin G (IgG) and complement activation product C3d bind to the nodal axolemma and appear within the periaxonal space beneath internodal myelin in more severe cases.¹⁰⁸ Teased fiber preparations show some paranodal changes, nodal lengthening, and only rare paranodal demyelination.⁹⁷ There are also cases with severe quadriplegia that have minimal pathology at autopsy; Wallerian-like degeneration is minimal. There are rare macrophages in paranodes and internodes, as well as paranodal changes.⁹⁷

The pathology in AMSAN resembles that in AMAN except that there are varying degrees of Wallerian-like degeneration in both motor and sensory fibers.¹⁰⁰ Wallerian-like degeneration

occurs in dorsal and ventral roots and, to a lesser degree, in mixed nerves and the posterior columns. Periaxonal macrophages beneath intact myelin also occur in AMSAN, but in both ventral and dorsal roots. In rare instances, a macrophage process can be identified within an axon. Inflammatory infiltrates of lymphocytes are sparse in dorsal root ganglia and ventral roots. Anterior horn cells show chromatolysis. Peripheral nerves may show loss of myelinated fibers, particularly large fibers.

PATHOGENESIS

It is unknown whether antigenic stimuli in AMAN differ from those in AIDP or whether differences reflect immunologic factors of the host.⁹⁷ The antigenic target is also undefined; possibilities include the motor axon, the motor nerve terminal, and the motor neuron.¹⁰⁸ Rapid recovery suggests either a physiologic block of motor axons or motor terminal involvement. In more severe cases, there is pathologic evidence of periaxonal macrophages that are thought to play a role in the pathogenesis. The association of GM1 and GD1a antibodies with AMAN and Cj infection raises the possibility of molecular mimicry between an axonal antigen and an infectious agent. GD1a antibodies may account for motor axonal involvement because GD1a is present in the axon at the nodes of Ranvier, in the nerve terminals, and its structure differs in motor and sensory fibers.¹⁰⁹ There is also weaker evidence of molecular mimicry of *Haemophilus influenzae* and GM1, as well as *Mycoplasma pneumoniae*, in patients with AMAN.^{110,111} Some patients in Europe who received commercial ganglioside preparations for pain developed AMAN. GD1A antibodies from patients with AMAN may bind to motor, but not sensory, nodes of Ranvier.¹¹²

Rabbits injected with bovine brain ganglioside or GM1 develop flaccid limb weakness, IgG deposition on nerve roots, periaxonal macrophage infiltration, and, in some cases, mild Wallerian-like degeneration.^{113,114} Other investigators showed mild axonal polyneuropathy in mice when gangliosides were passively transferred by intraperitoneal hybridoma implantation; however, this did not occur following systemic administration despite similar serum ganglioside levels.¹¹⁵ The investigators

suggested that the hybridoma may cause more leakage of the blood-nerve barrier. Treatment with IVIG in the mouse model reduces weakness and axonal degeneration.¹¹⁶

AMSAN is considered part of a continuum with AMAN, with additional sensory involvement. In both AMAN and AMSAN, macrophages may play a role in the pathogenesis, considering their abundance in the periaxonal spaces beneath intact myelin sheaths by day 18 of neurologic disease.⁹⁷

TREATMENT

Immunosuppression

There are no controlled trials of immunosuppressive therapy in AMAN. In the rabbit model of AMAN, there was earlier recovery of strength and less axonal degeneration pathologically with immunoglobulin treatment, although the level of GM1 titers was unaffected.¹¹⁶ Patients with AMAN who are treated with plasma exchange or IVIG improve, although it is unclear if that reflects the natural course of the disease, since improvement is the norm.¹¹⁷ A study of GBS in Turkey showed delayed, but similar, recovery of children with AMAN and AMSAN compared to those with AIDP at 12 months.¹¹⁸ In view of the infectious triggers and an association with ganglioside antibodies similar to that in AIDP, as well as an animal model of AMAN that responds to immunoglobulin, we recommend IVIG or plasma exchange in patients with AMAN or AMSAN and functionally significant motor deficits.

The management of acute respiratory dysfunction, dysautonomia, pain, and chronic supportive care is similar to that of AIDP. Chronic dysesthetic pain is not an issue in AMAN.

COURSE AND PROGNOSIS

In China, recovery often starts within a few weeks (mean, 16 days), with quicker recovery (days) in younger patients. One year after onset, the vast majority of patients are ambulatory, although about 75% have mild distal limb weakness and atrophy.⁹² Reflexes tend to recover early as strength improves. Hyperreflexia occasionally occurs during the recovery period. Remote relapse occurs in 5%–7% of patients; overall mortality is 3%–5%.^{90,92}

NEURONOPATHIES

Sensory (Idiopathic, Sjögren Syndrome, Paraneoplastic) and Motor (Paraneoplastic) Neuronopathies and Autoimmune Autonomic Ganglionopathy (AAG)

INTRODUCTION

Neuronopathy refers to conditions in which the initial morphologic or biochemical changes occur in the neuronal cell body. Sensory neuronopathies (or ganglionopathies) are caused by various inflammatory, paraneoplastic, toxic, and infectious disorders. Regardless of the cause, the clinical and electrophysiologic features are characteristic. Onset is acute, subacute, or chronic, with acral or diffuse paresthesias often involving the face. Ataxia relates to proprioceptive impairment from loss of sensory neurons and associated large, myelinated nerve fibers. Anterior horn cells and strength are spared. Tendon reflexes are absent or reduced, and recovery is variable (reflecting degeneration of sensory nerve cell bodies). Nerve conduction studies mimic a severe sensory polyneuropathy with diffusely absent or low-amplitude sensory responses, preserved motor conduction, and normal needle EMG. An acute sensory neuronopathy syndrome may occur after a viral prodrome.¹¹⁹ Sensory neuronopathies are also associated with Sjögren syndrome (SS) and malignancy, particularly small cell carcinoma of the lung.

Inflammatory motor neuronopathies are rare. Some paraneoplastic cases of sensory neuronopathy with or without encephalomyelitis have additional motor neuron involvement; motor neuron dysfunction rarely dominates the clinical picture. A subacute, isolated motor neuronopathy is associated with lymphoma and, rarely, with thymoma and other cancers.^{120,121} Infection with HIV has been associated with both a lower motor neuron and an amyotrophic lateral sclerosis (ALS)-like syndrome that may respond to antiretroviral therapy.^{122,123} Autoimmune autonomic ganglionopathy (AAG) presents with panautonomic failure over days or weeks following an antecedent illness.

This section will discuss neuropathies related to inflammatory (including idiopathic) and paraneoplastic conditions.

CLINICAL FEATURES

Epidemiology

Epidemiologic studies of the incidence and prevalence of sensory and motor neuropathies are lacking. Paraneoplastic sensory neuropathies typically affect patients over 50 years of age (mean, 60 years) and are subacute or chronic. Cases related to SS may occur at any age (mean, 49 years) and may be acute or indolent.^{124,125} One study found sensory neuropathy in 2 of 46 (4%) patients with SS.¹²⁶ Of patients with anti-Hu antibodies, 20%–62% have a sensory neuropathy, depending on patient selection.^{127,128} There is a strong female predominance in SS.¹²⁴ Motor neuropathy occurred in 1% of a series of patients with positive anti-Hu antibodies.¹²⁹ There is a 2:1 female predominance in AAG.¹³⁰

Symptoms and Signs

Sensory neuropathies present with profound sensory loss and ataxia. The onset may be acute, subacute, or chronic progressive. Numbness and paresthesias may begin in the limbs or face and spread to other regions, including the trunk, or may begin more diffusely. Ataxia and gait difficulty are usually early and prominent complaints. The upper limbs may be affected first (in about 50% of patients), in contrast to a length-dependent sensory polyneuropathy.¹²⁴ Paraneoplastic cases often have concurrent small-fiber sensory involvement with shooting or aching limb pains, burning, and dysesthesias. Sensory symptoms and signs occasionally have marked asymmetries. The loss of position sense in the arms leads to pseudoathetosis and inability to localize the limb with the vision shielded. Impairment of proprioception is marked in both proximal and distal joints. Tendon reflexes are reduced or absent.

Autonomic dysfunction also occurs. In paraneoplastic cases, pseudo-obstruction from ileus and blood pressure instability are common; constipation and urinary retention also occur.¹²⁷ In SS, sicca symptoms, alterations in blood pressure and pulse, and Adie pupils occur; however, autonomic dysfunction, in addition to sicca symptoms, is often

subclinical and is evident only with autonomic testing (i.e., abnormal R-R interval).¹³¹

The diagnosis of paraneoplastic sensory neuropathy may be complicated by concurrent, clinically symptomatic encephalomyelitis in 40% of patients with anti-Hu antibodies and a paraneoplastic syndrome.¹³¹ Attentional/behavioral dysfunction, ataxia, and cranial neuropathies may occur as a result of central nervous system dysfunction. Motor neuron dysfunction also occurs but is rarely predominant.^{127,128} Small cell carcinoma of the lung is the most common associated malignancy, but rare patients have other lung tumors, lymphoma, breast cancer, adenocarcinoma (colon or prostate), and sarcoma.^{125,129}

Motor neuropathy rarely occurs in association with lymphoma and also with anti-Hu antibodies.^{120,129} The presentation is subacute, painless, and progressive, with asymmetric lower motor neuron dysfunction that usually affects the legs.¹²⁰ Sensory symptoms may be present, though sensory signs are typically absent. This syndrome also occurs with thymoma and, rarely, with other neoplasms.¹²¹ A lower motor neuropathy and ALS have been associated with anti-Hu antibodies, usually in association with other features of encephalomyelitis such as seizures, ataxia, and sensory neuropathy.¹³² One such patient had prostate cancer. Pure motor neuropathy with anti-Hu antibodies and small cell carcinoma is exceptional.¹³³ Subacute onset of lower motor neuron disease or an ALS-like illness rarely occurs in HIV infection.^{122,123} This may respond to antiretroviral therapy and is not associated with other features of HIV myelopathy.

In patients with SS, about 75% have sicca symptoms.¹²⁴ Involvement of other organ systems is unusual, and neuropathy is often a presenting symptom.¹³⁴

Sensory neuropathy may also occur as an acute postviral syndrome (idiopathic) without any associated disease and after acute EBV infection.^{119,135} Patients progressed over 1 week with ataxia, kinesthetic sensory loss, and a subsequent stable functional deficit.¹¹⁹ However, the idiopathic cases were described before the recognized association with SS, and the patients were not tested for anti-Ro antibodies or lip biopsies, although some had normal antinuclear antibodies or sedimentation rates.¹¹⁹ In addition, SS patients may plateau after an acute onset. Toxic causes include pyridoxine excess and cisplatin chemotherapy.^{136,137}

Autoimmune autonomic ganglionopathy typically presents with acute or subacute pandysautonomia over days or weeks with an antecedent (often viral) illness, reminiscent of GBS, although more chronic presentations are seen.¹³⁸ Patients typically present with orthostatic hypotension and gastrointestinal dysmotility.¹³⁰ Both sympathetic (orthostatic hypotension, anhidrosis) and parasympathetic (sicca complex, sexual dysfunction, urinary retention, impaired pupillary responses, fixed heart rate, early satiety, anorexia, postprandial abdominal pain, vomiting, constipation, and diarrhea) dysfunction occur.¹³⁰ Chronic AAG, like the more typical acute form, is suggested by the presence of elevated ganglionic acetylcholine receptor (AChR) antibodies.^{138,139} In chronic AAG, patients with high titers have sicca complex, pupillary abnormalities, neurogenic bladder, and gastrointestinal dysmotility, while patients with low titers have few cholinergic symptoms and resemble pure autonomic failure.¹³⁸ Strength, sensation, and tendon reflexes are normal, but 25% of patients have minor paresthesias.¹³⁰

Differential Diagnosis

When patients present with profound kinesthetic sensory loss and ataxia, the reflexes are a key exam finding to differentiate a central nervous system

(CNS) from a peripheral nervous system (PNS) cause. Brainstem and spinal cord lesions are typically associated with corticospinal tract involvement and hyperreflexia, and may have posterior column involvement. Cerebellar disease may cause hyporeflexia and ataxia, though it does not cause sensory loss. As such, profound proprioceptive sensory loss, ataxia, and hyperreflexia should raise the possibility of a brainstem or spinal cord disorder such as myelitis, brainstem encephalitis, or subacute combined degeneration with involvement of the posterior columns. Rarely, isolated ataxia without pain may be the initial manifestation of neoplastic spinal cord compression.¹⁴⁰ Tabes dorsalis usually involves reduced reflexes in the legs (dorsal root involvement), but not the arms, whereas in sensory neuronopathy, hyporeflexia is generalized.¹⁴¹

If the patient with sensory loss and ataxia has reduced reflexes, other possibilities besides sensory neuronopathy include FS, ataxic GBS (hyporeflexia, sensory loss, ataxia, positive GD1B antibodies without weakness), sensory CIDP, IgM gammopathies, and, if chronic, Friedreich ataxia. Sensory neuronopathy patients have more profound proprioceptive loss on exam and lack motor nerve conduction abnormalities. The differential diagnosis of acquired, sensory, ataxic neuropathies/neuronopathies is provided in Table 6–3.

Table 6–3 **Acquired, Sensory, Large-Fiber, Ataxic Neuropathies/Neuronopathies**

Sensory neuronopathy (ganglionopathy)	SS Paraneoplastic Idiopathic Toxic: pyridoxine hypervitaminosis, cisplatin, thalidomide, linezolid, metronidazole, podophyllotoxin, taxanes HIV (rare) Epstein-Barr virus	
	Acute: Ataxic GBS FS Diphtheritic neuropathy	Chronic: Sensory CIDP Anti-MAG/IgM MGUS CANOMAD CISP
Demyelinating or mixed neuropathies		
Miscellaneous	Tabes dorsalis (dorsal root/posterior columns)	
	Anti-sulfatide antibodies (axonal or demyelinating)	
	Celiac disease	
	HTLV-1 or -2 (tropical ataxic neuropathy)	
	Vitamin deficiencies: B ₁₂ , B ₁ , E	

CANOMAD: chronic ataxic neuropathy with ophthalmoplegia, IgM paraprotein, cold agglutinins, and anti-GD1b disialosyl antibodies; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; CISP: chronic immune sensory polyradiculopathy; FS: Fisher syndrome; GBS: Guillain-Barré syndrome; HTLV: human T-cell lymphotropic virus; MAG: myelin-associated glycoprotein; MGUS: monoclonal gammopathy of undetermined significance; SS: Sjögren syndrome.

Motor neuronopathy must be distinguished from direct effects of lymphoma and radiation injury. Progressive muscular atrophy is a consideration in more progressive cases of asymmetric weakness and those with bulbar dysfunction.

Subacute autonomic dysfunction with gastrointestinal dysmotility also occurs in paraneoplastic disease associated with small cell carcinoma or thymoma.¹³⁰ Chronic forms of autoimmune autonomic ganglionopathy may be confused with pure autonomic failure, a neurodegenerative disease.

LABORATORY STUDIES

Blood Tests

Paraneoplastic sensory neuronopathy is associated with anti-Hu (antineuronal nuclear antibodies [ANNA] type 1) antibodies in about 80% of patients.¹⁴² Rare patients also have antibodies to crossveinless-2 (CV-2) and amphiphysin. Fourteen percent of patients with amphiphysin antibodies have sensory neuropathy.^{133,143} These are usually associated with an axonal sensorimotor polyneuropathy.^{144,145} An immunofixation is a simple but insensitive screen for lymphoma, showing an M-protein in about 20% of cases.¹⁴⁶ Anti-Hu antibodies are typically negative in patients with isolated motor neuronopathy and cancer.¹³²

In SS, anti-Ro antibodies are more sensitive than anti-La antibodies but were positive in only 30% of patients with sensory neuronopathy,¹⁴⁷ 30% of those with distal sensory neuropathy, and 40% of those with any neurologic involvement.^{124,148} Either RF or ANA antibodies are positive in about 30% of patients with SS and sensory neuronopathy. Anti-Ro and La antibodies are more frequent in patients less than 45 years old. Epstein-Barr virus titers should be tested in patients who present with an acute viral syndrome, particularly if adenopathy is present.¹³⁵

Ganglionic acetylcholine receptor binding antibodies are present in 50% of patients with AAG and about 25% of patients with paraneoplastic autonomic neuropathy.^{130,138,149} Postural tachycardia syndrome (POTS), a milder form of dysautonomia, is associated with ganglionic AchR antibodies in 10%–15% of patients.¹³⁰ Supine catecholamine levels are low in AAG.¹⁵⁰

Electrodiagnostic Studies

The electrophysiologic findings of most sensory neuropathies are identical to those of a more severe sensory polyneuropathy. Sensory response amplitudes are reduced or absent throughout, with normal motor conduction and F wave studies. H reflexes are typically absent. Needle EMG is normal.¹⁵¹ One exception is paraneoplastic sensory neuronopathy, which may have motor axon or neuron involvement in terms of low CMAP amplitudes, mild motor conduction slowing, prolonged F waves, and fibrillations and increased motor unit potential size on needle EMG. Rare cases of sensory neuronopathy with SS show asymmetric, unilateral absence of sensory responses.¹⁵² Somatosensory evoked responses are often absent.^{148,153} Blink reflexes are abnormal in about 50% of patients with sensory neuronopathy and SS and only rarely in those with paraneoplastic disease.¹⁵⁴

In motor neuronopathy, the electrophysiology resembles that of motor neuron disease, with normal or low-amplitude motor conduction, sparing of sensory conduction, and active and chronic denervation changes on needle EMG. Nerve conduction/EMG studies in AAG are normal. Autonomic testing shows orthostatic hypotension, as well as baroreflex-sympathoneural and cardiovascular impairment.¹³⁰

Cerebrospinal Fluid

Spinal fluid protein may be normal or moderately elevated in paraneoplastic and SS-related sensory neuronopathy. Spinal fluid protein is typically elevated in motor neuronopathy associated with cancer.¹³² While typically absent, pleocytosis occurs in a minority of paraneoplastic cases, even in the absence of encephalomyelitis.¹⁵⁵

Imaging

An MRI scan of the cervical and thoracic spine may show increased T2 signal in the posterior columns secondary to Wallerian degeneration of the central sensory neuronal processes.^{156,157} Imaging the chest with MRI is essential for patients at risk of small cell carcinoma.

In contrast to pure autonomic failure, cardiac sympathetic neuroimaging with thoracic 6-[(18)F] fluorodopamine scanning suggests intact myocardial sympathetic innervation in AAG.¹⁵⁰

Genetics

Genetic studies are unavailable.

PATHOLOGY

Nerve

Sural nerve biopsies typically show Wallerian-like degeneration affecting both large- and small-diameter myelinated fibers. Inflammatory infiltrates are characteristically absent. However, some individuals have evidence of lymphocytic, epineurial, blood vessel infiltrates without vessel wall necrosis.^{134,155,158} In SS, inflammatory infiltrates were reported in 1 of 22 sural nerve biopsies in one series and in 6 of 12 biopsies in another.^{124,159} Rare mononuclear cells stain with anti-Leu-2a, suggesting that the cells are cytotoxic/suppressor T cells.¹²⁴

Salivary Gland

Sjögren syndrome is confirmed by lip biopsy showing more than one focus of lymphocytes per 4 mm² of minor salivary gland tissue.¹⁶⁰ A false negative result may occur, is more likely after immunosuppressive treatment, and may be remedied by parotid biopsy.^{161,162}

Dorsal Root Ganglia/CNS

The dorsal root ganglia (DRG) show mononuclear cell infiltrates enveloping degenerating sensory neurons. In more evolved lesions, satellite cells proliferate and form bundles of cells called *Nageotte nodules*; inflammatory cells are less prominent.^{124,155} In SS, most of the mononuclear cells are lymphocytes, and immunohistochemistry suggests that most are cytotoxic/suppressor T cells. In paraneoplastic cases, the DRG also shows evidence of IgG deposits, but there is a paucity of evidence of anti-Hu antibody deposition.^{163,164} Cytotoxic CD8 cells are found adjacent to vessels and sensory neurons and sometime penetrate the capsule of associated satellite cells.¹³⁴ CD8+

T cells may attach to and indent both IgG-positive and IgG-negative neurons, favoring a cell-mediated response.¹⁶⁵ Macrophages are not found in contact with neurons.¹³⁴ Most intralesional lymphocytes in paraneoplastic cases are CD45RO+ memory cells, suggesting T-cell-mediated immunity. These cells also predominate in exocrine glands in SS.¹⁶⁶

In SS, dorsal roots and dorsal columns of the spinal cord undergo Wallerian degeneration, and inflammatory cells are frequently found within the dorsal roots.¹²⁴ In paraneoplastic cases, there is degeneration of posterior columns and roots with macrophage infiltration, astrogliosis, and Wallerian degeneration.

In more advanced cases, there is myelinated fiber loss and gliosis.¹⁵⁵ In patients with pseudo-obstruction, the myenteric plexus may show neuronal loss, Schwann cell proliferation, and lymphohistiocytic infiltration.¹²⁵

In motor neuronopathy and lymphoma, there is prominent anterior horn cell degeneration in the spinal cord and demyelination in the ventral roots and posterior columns.¹²⁰ Hyperchromatic Schwann cells are also present. Patients with motor neuron disease, cancer, and anti-Hu antibodies may show anterior horn cell degeneration associated with inflammatory cells in the spinal cord gray matter. Neuronal loss and inflammatory infiltrates may also occur in the hippocampus, medulla, and DRG.¹³²

Epidermal Nerve Fibers

In patients with SS and sensory neuronopathy, epidermal nerve fiber densities are not length-dependent, with epidermal nerve fiber loss in the thigh similar to that in the distal leg.¹⁶⁷ Patients with SS or celiac disease and what resembles a small-fiber polyneuropathy clinically also show epidermal nerve fiber loss that is not length-dependent, suggesting that these cases may be part of a spectrum of sensory neuronopathies.^{168,169}

PATHOGENESIS

Anti-Hu antibody does not appear to be pathogenic, since immunized SJL/J mice, Lewis rats, and Hartley guinea pigs with purified recombinant HuD fusion protein develop high anti-Hu antibodies, but the clinical and pathologic findings in the nervous system are unremarkable.¹⁷⁰

Anti-Hu antibodies react to a family of proteins that bind to mRNA that are expressed in neural tissue during development: HuD, HuC, and Hel-N1.¹⁷¹ HuD is expressed in small cell carcinoma cells and by many classes of neurons.¹⁶⁴ As such, HuD expression is not specific to sensory neurons. Anti-Hu serum is toxic to sensory neurons but it appears to be independent of IgG.¹⁷² Tumors frequently express both Hu and Class 1 MHC proteins, suggesting a T-cell-dependent response.¹³¹ Intrathecal synthesis of anti-Hu antibodies occurs in 88% of patients with paraneoplastic encephalomyelitis but in only 7% of patients with sensory neuronopathy.¹⁷³

Inflammatory infiltrates are common in all forms of neuropathy related to SS, though necrotizing vasculitis is rare.¹²⁶ Antiganglion neuron antibodies recognizing proteins of several different molecular weights were detected in patients with SS and sensory neuropathy.¹⁷⁴

Rabbits immunized with ganglionic AChR subunit proteins develop experimental autoimmune autonomic ganglionopathy (EAAG) characterized by autonomic failure similar to that of AAG patients. Passive transfer of ganglionic AChR IgG to mice also results in autonomic dysfunction.¹⁷⁵ Ganglionic AChR IgG antibody causes internalization and depletion of cell surface AChR (antigenic modulation) and some immediate current blocking similar to that of myasthenia gravis.^{149,175}

TREATMENT

Immunosuppression

Sensory neuronopathy is generally poorly responsive to immunosuppressive treatment regardless of the type, probably because of considerable and frequent sensory axon loss. Sensory neuronopathies tend to be the most severe form of a spectrum of sensory neuropathies. In paraneoplastic cases of sensory neuronopathy, immunosuppressive treatments such as prednisone, cyclophosphamide, plasma exchange and IVIG are largely ineffective.^{128,176} In one series of 18 patient with sensory neuronopathy or encephalomyelitis and anti-Hu antibodies, only 1 patient improved and 1 stabilized after initiation of IVIG therapy.¹⁷⁷ Removal of the associated tumor rarely results in neurologic improvement.¹⁷⁸ Tumor removal was the only treatment

significantly associated with clinical improvement of various paraneoplastic syndromes in one study.¹⁷⁹

There has been variable success in treating sensory neuronopathy with immunosuppressive agents. In one series of sensory neuronopathy patients with SS, three of five patients treated with IVIG showed improvement in gait and ataxia (in an additional patient who was said to have improved, the data were unconvincing).¹⁸⁰ One patient report showed marked clinical and electrophysiologic improvement after 3 months with repeated infusions of infliximab.¹⁸¹ Two patients who were poorly responsive to other immunosuppressive agents were reported to improve with alpha-interferon, 3 million units three times weekly, after 2 months. Gait or the ability to perform activities of daily living improved, and sural response amplitudes increased.¹⁸² We have observed sustained functional improvement in gait ataxia, small- and large-fiber sensory loss, and upper extremity sensory potentials in a patient with SS-associated sensory neuronopathy treated with a combination of plasma exchange, azathioprine, and plaquenil.

Case reports and small, uncontrolled series suggest that plasma exchange (PE), with or without additional immunosuppressive drugs, and intravenous immunoglobulin improves autonomic dysfunction in patients with AAG.¹³⁰ However, protracted and combined immunosuppressive treatment may be necessary to advance and maintain improvement.¹⁸³ Prednisone and mycophenolate mofetil in combination with PE show promise in patients unresponsive to PE or IVIG alone.¹⁸⁴ Azathioprine and rituximab have each been associated with improvement in individual patients, in combination with PE, IVIG, or prednisone.¹⁸³ A small placebo-controlled trial suggests that pyridostigmine, with or without midodrine, improves orthostatic hypotension.¹³⁰

COURSE AND PROGNOSIS

Patients with sensory neuronopathy are frequently left with significant gait ataxia and kinesthetic sensory loss regardless of the cause. Paraneoplastic sensory neuronopathy tends to have a more subacute and progressive course than that related to SS.¹²⁴ In SS, the course is more variable and may be acute or

chronic. Both types may plateau after weeks or months, but sensory neuropathy in SS is more likely to stabilize or improve. Paraneoplastic patients with isolated sensory neuropathy are more likely to stabilize than those with CNS involvement.¹⁷⁷ There are rare reports of spontaneous tumor regression in patients with paraneoplastic sensory neuropathy with anti-Hu antibodies and small cell carcinoma.¹⁸⁵ One-year survival is about 40% for patients with paraneoplastic sensory neuropathy or encephalomyelitis. Median survival in various paraneoplastic syndromes is about 43 months.¹⁷⁹ In contrast, the mean survival of small cell carcinoma patients treated with chemotherapy is about 10 months when extensive and 25 months when limited.¹⁸⁶ Early diagnosis and tumor treatment are associated with lower disability and mortality; older age and a higher Rankin scale score (greater disability) are associated with a poorer functional outcome.¹⁸⁷

One series of patients with motor neuropathy and lymphoma described spontaneous improvement in 7 of 10 patients; 3 became neurologically normal, independent of the activity of the underlying neoplasm.¹²⁰

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Chronic Immune-Mediated Neuropathies

**CHRONIC INFLAMMATORY
DEMYELINATING
POLYRADICULONEUROPATHY (CIDP)
AND ITS VARIANTS**

Multifocal Motor Neuropathy with Conduction Block (MMN), Lewis-Sumner Syndrome (LSS)/Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM), Distal Acquired Demyelinating Symmetric Neuropathy (DADS), CIDP with CNS Features, Chronic Immune Sensory Polyradiculopathy (CISP), Chronic Sensory Demyelinating Polyneuropathy

- Introduction
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**CHRONIC INFLAMMATORY
DEMYELINATING
POLYRADICULONEUROPATHY
(CIDP) AND ITS VARIANTS**

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired multifocal neuropathy that commonly has symmetric, proximal, and distal limb weakness, distal sensory loss and progresses over more than 2 months.¹ The clinical and immunopathologic features suggest an autoimmune disease, analogous to acute inflammatory demyelinating polyradiculoneuropathy (AIDP), and CIDP characteristically responds to

immunosuppressive therapies. The diagnosis is supported by nerve conduction or sensory nerve biopsy findings suggestive of multifocal demyelination. Since the 1980s, several phenotypic variations of chronic, presumably inflammatory, demyelinating polyneuropathies have been characterized. These variants include multifocal motor neuropathy with conduction block, Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy, MADSAM) and distal acquired demyelinating symmetric neuropathy (DADS).^{2,3} Although these syndromes may be part of a spectrum of a common disease (CIDP), the distinction has clinical utility because different variants respond to different immunosuppressive regimens (Table 7–1).

Table 7–1 Comparison of Clinically Defined, Chronic, Acquired, Demyelinating Neuropathies

Clinical/Lab Feature	CIDP	MMN	LSS/MADSAM	DADS
Weakness	Symmetric, generalized	Multifocal Arms > legs Distal > proximal	Multifocal Arms > legs Distal > proximal	Symmetric, mild, distal
Pin/touch loss	Symmetric, distal	Absent	Multifocal, nerve distribution	Mostly symmetric, distal
Deep tendon reflexes	Reduced or absent Generalized	Reduced or absent, may be spared	Reduced or absent, multifocal or diffuse	Reduced or absent, distal and symmetric
EMG/NCS Motor slowing, ↓ amplitudes	Asymmetric	Multifocal	Multifocal	Mostly symmetric May be multifocal
Conduction block, temporal dispersion	Common	Common	Common	Less common, esp. IgM-MGUS
Sensory slowing, ↓ amplitudes	Mostly symmetric	Absent	Multifocal	Mostly symmetric
Laboratory M-protein	IgA, IgG, ~25%	Rare	Rare	IgM-kappa, ~60%
GM1 titers	Rare	~50%	Rare	Absent
CSF protein	Mostly elevated	Normal or mild↑	Mostly elevated	Mostly elevated
Sensory nerve biopsy	Demyelination/ remyelination	Minimal demyelination	Demyelination/ remyelination	Demyelination/ remyelination
Treatment response				
Prednisone	Yes	No	Yes	Poor (IgM)*
IV Immunoglobulin	Yes	Yes	Yes	Poor (IgM)*
Plasma exchange	Yes	May worsen	?	Poor (IgM)*
Cyclophosphamide	Yes	Yes	?	Poor (IgM)*

CIDP: chronic inflammatory demyelinating polyradiculoneuropathy; CSF: cerebrospinal fluid; DADS: distal acquired demyelinating symmetric neuropathy; EMG/NCS: electromyography/nerve conduction studies; LSS/MADSAM: Lewis-Sumner syndrome/multifocal acquired demyelinating sensory and motor neuropathy; MGUS: monoclonal gammopathy of undetermined significance; MMN: multifocal motor neuropathy with conduction block.

*Without IgM similar to CIDP, possibly less responsive.

Source: From Saperstein DS et al.: Clinical Spectrum of Chronic Acquired Demyelinating Polyneuropathies. *Muscle Nerve* 24:311-324, 2001. Reprinted with permission of John Wiley & Sons, Inc.

Clinical Features

EPIDEMIOLOGY

Epidemiologic studies of CIDP are limited. In the South East Thames Region of Great Britain, the prevalence of probable or definite cases of CIDP was 1/100,000.⁴ On the day they were examined, 87% of CIDP patients could walk independently. A prevalence study in South Wales, Australia, found a slightly higher estimated CIDP prevalence of 1.9/100,000.⁵ The prevalence was greater in male than in female patients and reached a maximum of 6.7/100,000

in the 70- to 79-year age group. The estimated incidence was only 0.15/100,000. The mean age of onset was 47.6 years. A relapsing-remitting course occurred in 51% of patients. The incidence of CIDP in children is about 0.5/100,000.⁶ The mean age of onset is older in chronic progressive than relapsing cases.⁷

There are no epidemiologic studies of multifocal motor neuropathy or Lewis-Sumner syndrome. However, 1.6% of patients initially thought to have amyotrophic lateral sclerosis (ALS) in the Irish ALS registry were found to have multifocal motor neuropathy during the follow-up period.⁸

ASSOCIATED DISEASES

CIDP is usually idiopathic but may be associated with other systemic metabolic, inflammatory, neoplastic, and infectious diseases. Most common are diabetes mellitus and monoclonal gammopathy of undetermined significance (MGUS). Other diseases include human immunodeficiency virus (HIV) infection, hepatitis C infection, Sjögren syndrome, lymphoma, and melanoma. CIDP with diabetes mellitus occurs equally in Type 1 and Type 2 diabetes and may be more frequent than idiopathic CIDP.⁹ One study of the clinical course of and response to treatment of CIDP subtypes (isolated, diabetes, IgG, IgA, or IgM monoclonal gammopathies) found CIDP with diabetes mellitus to be a more severe disease with fewer relapses and a better response to intravenous immunoglobulin (IVIG).¹⁰ Autonomic dysfunction may be more frequent in CIDP with diabetes mellitus.¹¹ In some cases, it may be difficult to differentiate advanced axonal diabetic polyneuropathy from true CIDP because there is secondary demyelination and slowing of conduction in diabetic polyneuropathy. Other investigators have shown that patients with CIDP and diabetes have lower motor and sensory nerve response amplitudes on conduction studies, as well as a response rate similar to that of patients with idiopathic CIDP but a poorer functional recovery.¹² This likely reflects the greater axonal polyneuropathy in diabetic patients. Another study showed an 81% response rate of CIDP and diabetes to IVIG, and the presence of conduction block favored responsiveness.¹³ Conduction block may favor concurrent CIDP over advanced, axonal, diabetic polyneuropathy. Controlled studies of IVIG in patients with CIDP and diabetes are lacking.

In the majority of patients with CIDP and an associated monoclonal gammopathy, the gammopathy is of undetermined significance (i.e., limited monoclonal plasma cell expansion in bone marrow without detectable organ damage). Patients with CIDP and IgA or IgG monoclonal gammopathies typically have proximal and distal weakness, and respond to IVIG and immunosuppressive treatment similarly to patients with idiopathic CIDP. Patients with an IgM kappa paraproteinemia, however, frequently have associated anti-myelin-

associated glycoprotein (MAG) antibodies (about two-thirds of patients) and the clinical features of a DADS phenotype.¹⁴ This is characterized by distal sensory loss, mild distal weakness, ataxia, marked distal motor latency prolongation, and a poor response to prednisone, immunoglobulin, and other immunosuppressive treatments. About two-thirds of patients with DADS have a IgM monoclonal gammopathy.¹⁴

CIDP associated with hematologic malignancies characteristically involves plasma cells such as plasmacytoma or osteosclerotic myeloma.¹⁵ Waldenström macroglobulinemia is a low-grade lymphoplasmacytoid lymphoma with an associated monoclonal IgM protein. Associated polyneuropathy is characteristically demyelinating and may be associated with POEMS syndrome, although axonal neuropathies also occur.¹⁶ POEMS syndrome is characterized by **P**olyneuropathy, **O**rganomegaly (hepatosplenomegaly), **E**ndocrine changes (gynecomastia), **M** (monoclonal)-protein, and **S**kin changes (hypertrichosis and hyperpigmentation).¹⁷ Most cases are associated with osteosclerotic myeloma or Castleman disease. Other frequent manifestations include edema, ascites, thrombocytosis, and papilledema.¹⁸ Castleman disease is a rare lymphoproliferative disorder characterized by enlarged, hyperplastic lymph nodes with prominent proliferative vascular changes. Identification of an associated plasma cell dyscrasia is important because the treatment is directed to the underlying neoplasm. CIDP with T-cell lymphoma is rare.¹⁹ Most CIDP cases with lymphoma are refractory to treatment. However, osteosclerotic myeloma is a hematologic malignancy that is important to recognize because it is responsive to focal radiation therapy directed against the tumor.

In HIV infection, CIDP typically occurs with an established infection when CD4 counts are relatively normal, and it responds to immunosuppressive treatments similar to those of idiopathic CIDP.²⁰ Prednisone is generally avoided in HIV infection. There are only case reports of CIDP in association with collagen vascular disease, inflammatory bowel disease, hepatitis C, hepatitis B, bone marrow and solid organ transplantation, T-cell lymphoma, and melanoma.^{21–24} Hepatitis C treatment with peg-interferon-alpha-2b and ribavirin in a

patient with concurrent CIDP led to clinical and electrophysiologic improvement of the neuropathy.²⁵ However, another patient developed CIDP after interferon-alpha-2b therapy was initiated for chronic hepatitis C infection.²⁶ The association of melanoma and CIDP has been postulated to be related to shared surface antigens between Schwann cells and melanoma cells, as both originate from neuroectoderm.²⁷

SYMPTOMS AND SIGNS

Classic idiopathic CIDP presents with progressive weakness and predominantly distal sensory symptoms over more than 2 months. Weakness is characteristically symmetric and generalized (proximal and distal). The presence of proximal weakness clinically differentiates CIDP from the more common length-dependent axonal polyneuropathies. Distal predominance of motor and sensory findings is present in about 17% of patients. Most of these patients have DADS. Pure motor variants occur in about 10% of patients.²⁴ These patients frequently have a multifocal presentation, specifically multifocal motor neuropathy with conduction block.

Cranial nerve dysfunction is uncommon and often subclinical, occurring in 5%–30% of patients.²⁸ Enlarged cranial nerves, facial numbness, facial weakness (usually bilateral), and papilledema are most frequent. Rarely, optic neuritis, oculomotor palsies (including pupillary involvement), or vestibulopathy occur.^{29,30} Hypoglossal neuropathies rarely occur in the multifocal, motor variant and in Lewis-Sumner syndrome. Most CIDP patients have distal large-fiber and small-fiber sensory loss on exam. A postural tremor occurs in CIDP in about 10% of patients and is more frequent in CIDP with MGUS, particularly IgM.²⁴ Reflexes are generally reduced or absent, often earlier and more diffusely than in axonal polyneuropathies. Preservation of reflexes may occur, particularly when strength is relatively preserved. Respiratory failure from diaphragmatic weakness and micturition disturbance are rare.³¹ Occasional patients have mild autonomic dysfunction, though it is usually subclinical.³² Children often have a more acute onset and present with gait difficulty. Minor sensory symptoms in isolation are uncommon.³³

CIDP VARIANTS

Multifocal Motor Neuropathy

The most written about and least commonly seen variant of CIDP is multifocal motor neuropathy with conduction block. This typically presents with insidious onset of weakness and, in more advanced cases, atrophy of muscles in multiple nerve distributions, in one or both arms.³⁴ Weakness begins to overlap with other, less affected nerves in the arm, and leg weakness may ensue (Table 7–1). Problems with grip strength or wrist drop are common presentations.³⁵ Intrinsic hand muscles are most affected (70% of patients).³⁶ Less common presentations include brachial plexus-like weakness, foot drop, and, more rarely, trapezius weakness and diaphragmatic paralysis.^{37–39} Very rare cases have an acute onset, occasionally progressing to quadriplegia or respiratory failure, but they differ from AIDP by having more chronic symptoms and persistent conduction block.⁴⁰ Some of the more acute cases have been associated with *Campylobacter jejuni* infection.^{40,41} Cramps and fasciculations occasionally occur but are not characteristically prominent.³⁴ Cranial nerves are typically spared, but unilateral hypoglossal neuropathies rarely occur. Bulbar ALS differs by consistent bilateral involvement and worse dysarthria. Reflexes are generally reduced or absent, though they are occasionally preserved. Sensory and upper motor neuron signs are absent, although there may be subclinical sensory fiber degeneration pathologically.⁴² Minor sensory symptoms may be present. Rarely, a similar clinical presentation occurs without the electrophysiologic finding of conduction block or other demyelinating changes. This has been referred to as *axonal multifocal motor neuropathy without conduction block* and is often less responsive to IVIG and other immunosuppressive treatments.⁴³

Lewis-Sumner Syndrome (LSS)/Multifocal Acquired Demyelinating Sensory and Motor (MADSAM) Neuropathy

In 1982, R.A. Lewis, A.J. Sumner, and their colleagues reported a multifocal variant of CIDP with a mononeuropathy multiplex-like presentation that was characterized by

multifocal conduction block electrophysiologically and responsiveness to prednisone.² Two of their five patients also had optic neuritis. The illness closely resembles multifocal motor neuropathy with conduction block, but the sensory symptoms and signs and nerve conduction abnormalities in LSS parallel motor conduction abnormalities in a multifocal nerve distribution. A brachial plexus presentation also occurs in LSS.⁴⁴ There are other important differences from multifocal motor neuropathy, including elevated cerebrospinal fluid (CSF) protein, lack of GM1 antibodies, and responsiveness to prednisone in LSS.³ Lower limb involvement at onset is more frequent at presentation than in multifocal motor neuropathy.⁴⁵ Unlike a vasculitic, axonal mononeuropathy multiplex, the condition is often insidiously progressive (71%), with less intense complaints of pain. Dysesthesias do occur.² The terms *Lewis-Sumner syndrome* and *multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy* are both widely used in the literature.⁴⁶

Distal Acquired Demyelinating Symmetric Neuropathy (DADS)

DADS is an important category because it can clinically mimic the more common distal, length-dependent, axonal, sensorimotor polyneuropathy. Patients present with distal sensory or sensorimotor symptoms, but weakness is usually mild. DADS with an IgM monoclonal protein affects men 90% of the time, and most are over 50 years old.³ Tremor and ataxia are more common than in other CIDP variants.⁴⁷ DADS without an IgM monoclonal protein affects younger patients as well, and a greater percentage of women. Cases not associated with an IgM kappa monoclonal protein and anti-MAG often respond to immunosuppressive treatments similar to those for CIDP. However, some cases in the literature are difficult to distinguish from hereditary demyelinating polyneuropathies with intermediate degrees of motor slowing on nerve conduction studies (such as the myelin protein zero [MPZ], lipopolysaccharide induced tumor necrosis factor alpha [LITAF] or connexin mutations) because motor slowing is relatively uniform and conduction block is characteristically absent.

CIDP with Central Nervous System Features

Rarely, patients with CIDP present with both peripheral and central nervous system (CNS) symptoms and signs. Most patients have classic CIDP with asymptomatic white matter changes on brain magnetic resonance imaging (MRI), or abnormal visual evoked responses or central motor conduction time.⁴⁸⁻⁵⁰ Rare patients develop superimposed CNS lesions in the brain or spinal cord causing encephalopathy, optic neuritis, or other multiple sclerosis (MS)-like presentations.⁵¹ Mass-like demyelinating changes in the brain also occur.⁵² We have seen an LSS-like syndrome in a patient with relapsing paraparesis from MS-like lesions in the spinal cord, and two of Lewis and Sumner's original cases had optic neuritis.²

Chronic Immune Sensory Polyradiculopathy (CISP)

CISP may be a form of CIDP with demyelination of the dorsal roots.⁵³ Patients present with chronic gait ataxia, paresthesias, large-fiber sensory loss, and hyporeflexia. The CSF protein is usually elevated without cells, nerve conduction studies are normal (except for absent H-reflexes), somatosensory evoked potentials (SSEPs) are often prolonged or absent, and occasional patients have enlarged lumbar roots on MRI.⁵³ Patients often respond to intravenous (IV) corticosteroids or IVIG.

Chronic Sensory Demyelinating Polyneuropathy

Also referred to as *sensory CIDP*, this is a variant of CIDP with pure (at least at presentation) sensory involvement.⁵⁴ Many of these patients have DADS. Some have multifocal disease, and functionally significant weakness may occur subsequently.^{55,56}

DIFFERENTIAL DIAGNOSIS

CIDP may have an acute presentation, causing early confusion with AIDP. The diagnosis may only become obvious when progression of weakness continues or when the patient relapses weeks after recovery. Cranial nerve dysfunction is less common in CIDP than in AIDP. If reflexes are spared in patients with

considerable quadriparesis, myelopathy may be a consideration, though normal or brisk reflexes in CIDP are quite rare. One of the principal difficulties is differentiating CIDP, particularly in DADS cases, from a hereditary demyelinating polyneuropathy with uniform and an intermediate degree of motor slowing on nerve conduction studies (i.e., median motor 38–45 m/s). Genetic testing for MPZ, connexin, LITAF, NEFL (neurofilament protein, light peptide), EGR2 (early growth responses 2), GDAP1 (ganglioside-induced differentiation-associated protein 1), and DNM2 (dynamin 2) may help to confirm a hereditary polyneuropathy. Additionally, hereditary polyneuropathy with liability to pressure palsies may mimic CIDP.⁵⁷ If the presentation is more acute or subacute and the diagnosis is uncertain, a sural nerve biopsy or an empiric trial of an immunosuppressive agent may be warranted. In infants or young children, it may be difficult to differentiate Dejerine-Sottas disease from CIDP; genetic testing for PMP-22 or MPZ may be diagnostic for Dejerine-Sottas disease. Rare cases of Charcot-Marie-Tooth (CMT) disease may be responsive to immunosuppressive agents such as prednisone, suggesting either a superimposed acquired demyelinating polyneuropathy or a prednisone-responsive hereditary nerve disorder.⁵⁸ Sensory neuronopathies (secondary to Sjögren syndrome, paraneoplastic, idiopathic, or toxic) present with ataxic gait, sensory loss, and areflexia, mimicking DADS cases or CIDP with an IgM MGUS. However, large-fiber sensory loss and ataxia are generally more profound, and distal weakness is absent in sensory neuronopathy. Familial amyloid polyneuropathy associated with the transthyretin mutation is often misdiagnosed as CIDP, particularly in late-onset, isolated, non-familial cases (see Chapter 15).

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) polyneuropathy may resemble CIDP with symmetric weakness, hyporeflexia, a relapsing course, elevated CSF protein, and demyelinating electrophysiology including conduction block.⁵⁹ MNGIE polyneuropathy may be distinguished by more distal weakness, ophthalmoparesis, bowel dysmotility symptoms, and a positive family history in some cases.

Certain toxic polyneuropathies, such as those caused by amiodarone treatment or n-hexane exposure (solvent inhalation), can

mimic CIDP in terms of quadriparesis and demyelinating electrophysiology such as motor conduction slowing and conduction block.^{60–63} However, the pathology is predominantly axonal, with secondary demyelination pathologically with either toxin.^{60,63} Procainamide and tacrolimus may also cause a chronic demyelinating polyneuropathy.^{64,65}

Laboratory Studies

BLOOD TESTS

Liver function, blood cell counts, and the sedimentation rate are generally normal. Checking a serum immunofixation for a monoclonal protein and quantitative immunoglobulins are important in screening for a hematologic malignancy. The presence of an IgM M-protein has treatment implications. Quantitative immunoglobulins are also relevant in screening for IgA deficiency, since this is a contraindication to IVIG. An antinuclear antibody (ANA) test can screen for an associated collagen vascular disease or malignancy, but a low titer may occur in healthy persons. Elevated GM1 IgG titers are occasionally present in CIDP (23% in one series).⁴⁴ GM1 antibody titer elevations are uncommon in LSS.⁴⁶ GM1 IgM titers occur in about 50% of patients with multifocal motor neuropathy with conduction block but are a poor predictor of the response to immunosuppressive treatment.⁶⁶ Diabetes mellitus, uremia, and, rarely, cryoglobulinemia may have demyelinating features and should be screened for by the relevant blood tests. In DADS cases, genetic testing for hereditary demyelinating disorders should be considered, particularly if there is pes cavus, a positive family history of neuropathy or a foot deformity, or uniform slowing on nerve conduction studies.

ELECTRODIAGNOSTIC STUDIES

Chronic Inflammatory Demyelinating Polyradiculoneuropathy

The electrophysiologic hallmark of CIDP is multifocal slowing of motor conduction velocities, prolonged distal motor latencies, motor conduction block, temporal dispersion, and prolonged F wave minimal latencies. Criteria differ in terms of the degree of slowing considered suggestive of demyelination or the degree of amplitude drop that constitutes conduction

block.^{2,3,28,67–70} Generally, stricter criteria sacrifice sensitivity for specificity. Inclusion of measurements of distal compound muscle action potential (CMAP) durations, assessing distal temporal dispersion, may increase sensitivity without sacrificing specificity.^{71,72} Sensory responses are generally of low amplitude or absent; sensory slowing is generally mild. Unlike AIDP, sensory responses may be affected to a greater extent in longer nerves (i.e., the sural nerve).⁷³ F wave latencies may also show increased range between the minimal and maximal latencies. Similar to AIDP, motor slowing is not uniform, unlike demyelinating hereditary neuropathies. Motor slowing predominantly at entrapment sites raises the possibility of a hereditary neuropathy with liability to pressure palsies. Fibrillation potentials on electromyography (EMG) are often distally accentuated but may be multifocal.

Multifocal Motor Neuropathy

Multifocal motor neuropathy has multifocal motor conduction block, generally less motor slowing and prolongation of distal motor latencies than CIDP, with sparing of sensory nerve conduction.⁷⁴ Sensory fibers are spared electrophysiologically, even across sites of motor conduction block. Individual motor nerves are often involved rather than diffuse or segmental disease.

Conduction block tends to affect the ulnar and, to a lesser extent, the median nerves³⁶ (see Fig. 4–4, Chapter 4). F wave latencies are often prolonged in nerves with conduction block. Active denervation changes are typical in the more affected nerves.

Lewis-Sumner Syndrome/Multifocal Acquired Demyelinating Sensory and Motor Neuropathy

Lewis-Sumner syndrome resembles multifocal motor neuropathy electrophysiologically, except that there is additional multifocal reduction of sensory response amplitudes (Fig. 7–1). Similar to the clinical findings, leg involvement is more common than in multifocal motor neuropathy, and brachial plexus presentations occur, particularly early in the course.⁷⁵

Distal Acquired Demyelinating Symmetric Neuropathy

In DADS, demyelinating features are usually symmetric, distal motor latencies are prolonged (especially with an IgM monoclonal gammopathy), conduction block is uncommon, and sensory response amplitudes are often symmetrically reduced (Table 7–1). In IgM monoclonal cases with anti-MAG, distal motor latencies are often disproportionately

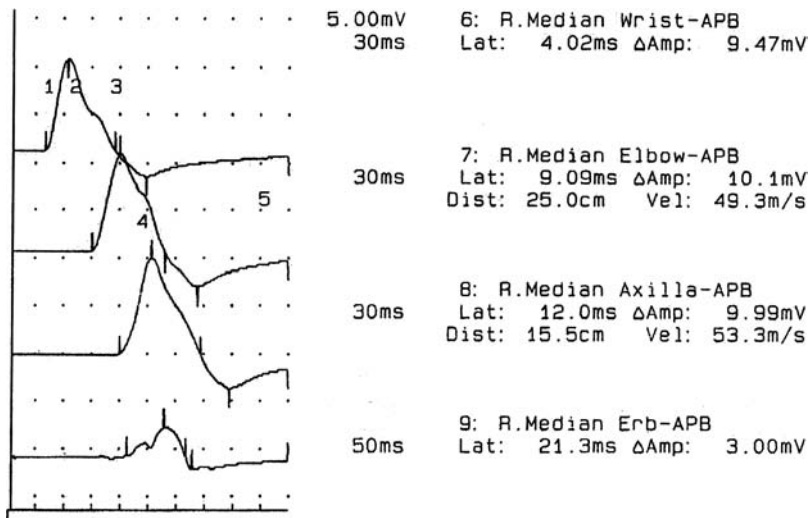


Figure 7–1. Partial conduction block/temporal dispersion between the axilla and Erb point stimulation sites for the median nerve in a patient with the LSS/MADSAM variant of CIDP.

prolonged, with a reduced terminal latency index. The terminal latency index is the distance of the recording electrode from the distal stimulation site, divided by the motor conduction velocity times the distal motor latency. In IgG and IgA monoclonal gammopathies the electrophysiology usually mimics typical CIDP.

CEREBROSPINAL FLUID

The CSF protein is generally elevated in CIDP during some stage of the illness but fluctuates in severity. Elevations may be marked (>100 mg/dL). In one series, the CSF protein was increased in 86% of patients and ranged from 50 to 800 mg/dL.⁷⁶ The CSF protein is also elevated in LSS and DADS neuropathy, but to a lesser extent (<100 mg/dL).⁴⁵ In LSS, mild protein elevations occur in 33% of patients and the remainder are normal.⁴⁶ The CSF protein is often normal in multifocal motor neuropathy. A mononuclear pleocytosis (>10 cells per mm³) is generally absent in these neuropathies but may be present with concurrent HIV infection.

IMAGING

In CIDP, MRI may show cervical or lumbosacral root or plexus hypertrophy, increased signal intensity on proton or T2-weighted images, or gadolinium enhancement.^{77,78} These MRI findings correlate with areas of focal conduction block and temporal dispersion on nerve conduction studies; gadolinium enhancement may resolve with immunosuppression.⁷⁹ An MRI scan of the spinal cord may show spinal cord atrophy, thought to reflect axonal loss.⁸⁰ Ultrasound may also demonstrate cervical root enlargement.⁸¹

The MRI findings are likely similar in patients with LSS, multifocal motor neuropathy, and IgG/IgM monoclonal antibody-related cases, possibly with a predilection for the brachial plexus.^{82,83}

GENETICS

An association of human leukocyte antigens (HLAs) with CIDP has been found by some⁸⁴ but not other authors.⁸⁵ Rare patients with CMT may develop superimposed CIDP, which responds to immunosuppression.⁵⁸

Pathology

NERVE BIOPSY

The hallmark of CIDP on nerve biopsy is evidence of demyelination and remyelination on either teased fiber studies ($>12\%$ of 50 teased fibers, at least four internodes each) or electron microscopy (>5 fibers).⁸⁶ Mononuclear cell infiltration, subperineural or endoneurial edema, onion bulb formation, and variation in the degree of myelination between fascicles further support the diagnosis, but in isolation they are nonspecific.⁸⁷ Sural nerve biopsy in CIDP has been suggested when electrodiagnostic studies do not meet criteria for demyelination,⁶⁷ but the specificity of sural nerve biopsy findings for CIDP has been questioned, as these findings overlap with those in chronic axonal polyneuropathies.^{88,89}

Inflammatory infiltrates are generally present in less than one-third of patients and consist largely of T cells and macrophages.^{87,90} However, while the presence of T cells in sural nerves is nonspecific for CIDP, also occurring less frequently in chronic idiopathic axonal neuropathies, the presence of macrophages clustered around endoneurial vessels may have greater specificity (72%)^{91,92} (Fig. 7–2). CIDP with diabetes may show expression of metalloproteinase-9, a product of inflammatory cells that is involved in tissue remodeling.¹⁰

In anti-MAG, IgM-associated CIDP, IgM antibodies bind to myelin sheaths that display widening⁹³ (Fig. 8–1, Chapter 8). It is unclear if complement plays a role in the widening of myelin sheaths.⁹³ Myelin-associated glycoprotein may be involved in neurofilament spacing by sidearm phosphorylation.⁹⁴ Anti-MAG antibodies are also deposited in dermal myelinated fibers associated with loss of epidermal nerve fibers.⁹⁵

In multifocal motor neuropathy there is mild sural sensory nerve pathology, despite the lack of clinical and electrophysiologic evidence of sensory nerve involvement.⁴² Sural biopsies show minimal demyelinating changes, namely, thinly myelinated, large-diameter fibers with rare onion bulbs on electron microscopy; active demyelination is rare.⁴²

Rootlet biopsies of patients with CISP show thickened rootlets, decreased density of large myelinated fibers, segmental demyelination, onion bulb formation, and endoneurial inflammation.⁵³

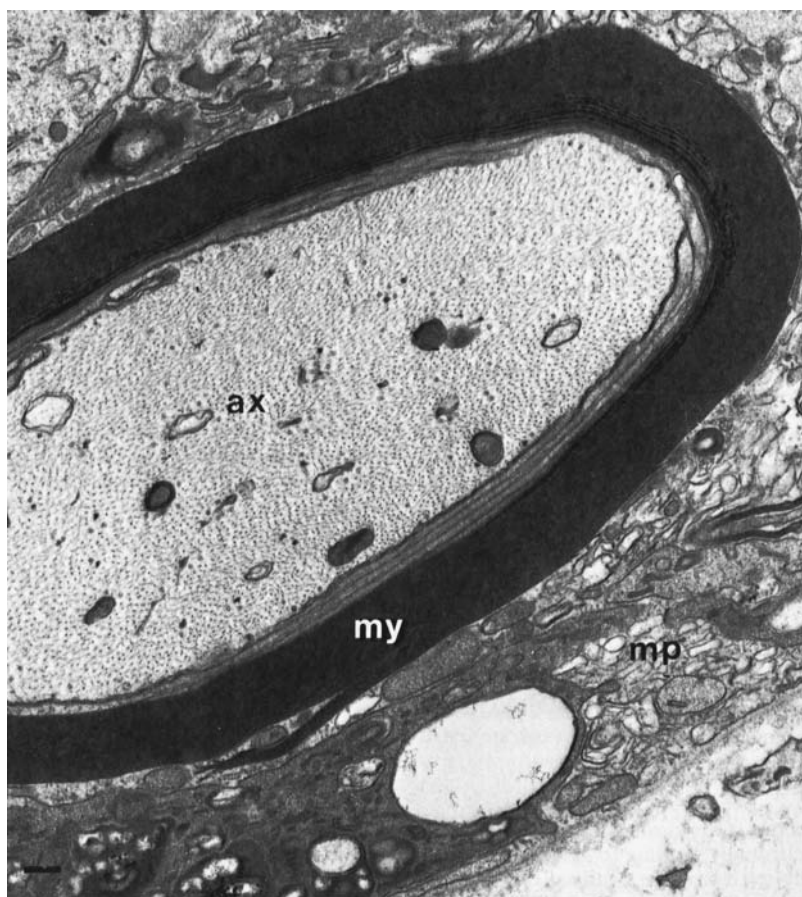


Figure 7–2. Electron micrograph from a nerve biopsy performed in a patient with CIDP. An intact axon (ax) is surrounded by a myelin sheath (my) that is being stripped off by a macrophage (mp) containing myelin debris. Bar = 0.2 μ m.

AUTOPSY

Autopsy studies of CIDP are rare, since it is rarely fatal. One autopsy study showed demyelinated or thinly myelinated axons in lumbar spinal nerves, the abducens and facial nerves, the axolemma displaced by infiltrating cells, and invading macrophages between the myelin lamella and axon (on electron microscopy).⁹⁶ Some myelinated fibers had C3d deposition, but this did not correlate with axon loss or macrophage infiltration.

An autopsy of a patient with a multifocal motor neuropathy with conduction block showed inflammatory infiltrates and macrophages in ventral roots, cranial nerves, and the meninges, segmental demyelination of lumbosacral ventral roots, deposition of IgG and IgM in motor roots, and loss of motor neurons.^{96a} However,

the presence of Bunina bodies raised the possibility of concurrent motor neuron disease. Another case, by contrast, showed multifocal IgG and IgM deposits on nerve fibers, as well as loss and central chromatolysis of spinal motor neurons without inflammatory cells or histologic evidence of demyelination.⁹⁷ A brachial plexus biopsy of a patient with LSS showed prominent infiltrates of T-cell and some B-cell lymphocytes and macrophages.⁷⁵ Autopsy of two patients with LSS was reported.⁵⁶ One patient had rapid quadriplegia, and a few Bunina bodies were found at autopsy, suggesting ALS. However, this patient had a prominent inflammatory response in the oculomotor nerve, roots, and peripheral nerves. The other patient showed patchy, asymmetric demyelination of motor and sensory nerves. Both patients showed variable myelinated fiber loss within and between fascicles.

Pathogenesis

The primary animal model for AIDP is experimental allergic neuritis (EAN) in rabbits and rats. This is generally a monophasic illness analogous to AIDP. However, depending on the species and age of the animals and the antigen used, a more chronic or relapsing illness resembling CIDP may develop. Guinea pigs inoculated with bovine peripheral nerve are relatively resistant to EAN, but juvenile guinea pigs occasionally develop chronic or relapsing EAN with paresis, demyelination, and onion bulb formation.^{98,99} Inoculation of rabbits or juvenile rats with bovine dorsal root or peripheral nerve in adjuvant results in chronic or relapsing paresis, motor slowing, temporal dispersion electrophysiologically, and demyelination and onion bulb formation, resembling CIDP.^{100,101} Chronic EAN also occurs in rabbits injected with glycolipid galactocerebroside.¹⁰² Various immunosuppressive regimens have been tested in animal models. EAN is predominantly T-cell mediated because passive transfer of T cells can induce disease, but antibodies likely contribute to demyelination. Interestingly, another potential animal model for CIDP appears to be P0 heterozygous knockout mice.¹⁰³ By 1 year, these mice develop asymmetric motor slowing, conduction block, and, pathologically, focal demyelination and inflammatory cells. This demonstrates that a genetic abnormality of myelin may lead to an immune-mediated polyneuropathy.

Sural nerve immunohistochemical studies (see above) show more frequent T cells in CIDP than axonal neuropathies or normal controls.^{104,105} Most T cells express $\alpha\beta$ -receptor chains, and both CD4 and CD8 cells are present in varying proportions. T cells in CIDP secrete matrix metalloproteinases (MMPs) that disrupt endoneurial proteins and the blood-nerve barrier.¹⁰⁵ In addition, MMPs are secreted in other inflammatory conditions and vasculitic neuropathies. A transcription factor that stimulates macrophage activation (NF- κ B), is increased in Guillain-Barré syndrome (GBS) and CIDP; the cytokines interleukin (IL)-1 β and IL-6 are also increased.¹⁰⁵ Macrophages and endothelial cells may act as presenting cells.¹⁰⁶ Schwann cells express I κ B, which binds NF- κ B and may modulate the

immune response.¹⁰⁷ CIDP is also suggested by increased circulating T cells that express DR antigen, increased activated CD4+ cells, increased cytokines IL-2R and IL-2, and increased tumor necrosis factor- α (TNF- α).¹⁰⁵

Cholera toxin, which binds to GM1, is concentrated around paranodal regions after injection into rat sciatic nerves.¹⁰⁸ Anti-GM1 antibodies targeted to rat sciatic nerve by the injection of the B-subunit of cholera toxin into rat sciatic nerve showed conduction block and axon loss electrophysiologically. This study raised the possibility that GM1 antibodies cause axonal neuropathy with conduction block analogous to multifocal motor neuropathy.¹⁰⁹ Galactocerebroside antibodies cross-react with glycolipids and glycoproteins and may cause demyelination.¹¹⁰ Fifty-seven percent of patients with CIDP have beta-tubulin IgM or IgG antibodies, though these also occur in 20% of patients with GBS and 2% of controls.¹¹¹ Beta-tubulin is an axonal antigen. Beta-tubulin IgM antibodies that recognize the 301 to 314 amino acid epitope may be more specific for CIDP.¹¹² An elevated panel of antibodies to GM-1, histone H3, and NP-9 may have greater specificity to multifocal motor neuropathy than GM1 titers alone.¹¹³ Peripheral nerve myelin protein antibodies, possibly against P0, are present in 25% of CIDP patients, 32% percent of GBS patients, and 5% of controls.¹¹⁴ Elevated GM1 titers in CIDP have been associated with predominantly motor involvement, though they do not predict the response to treatment.⁴⁴ Antibodies to P0, and to a lesser extent PMP22 and P2, occur in a minority of patients with CIDP.¹¹⁴

Ganglioside IgG titers (GM1, GD1a, and GD1b) are occasionally elevated in LSS.¹¹⁵ GM1 IgM antibodies are more commonly associated with multifocal motor neuropathy, occurring in about 50% of patients.⁶⁶ Sensitivity may be increased to 85% of patients with multifocal motor neuropathy using GM1 covalently bound to secondary amino groups on enzyme-linked immunosorbent assay (ELISA) plates (Co-GM1); however, these antibodies are also increased in acute motor axonal neuropathy (AMAN).¹¹⁶ Overall, antibodies to gangliosides and other neural glycolipids and proteins have not been very useful clinically because they do not, with sufficient specificity, predict a particular

demyelinating neuropathy syndrome and, more importantly, they do not appear to predict the responsiveness to immunosuppressive treatment.

Treatment

IMMUNOSUPPRESSION

It is controversial whether the first-line treatment for CIDP is IVIG or corticosteroids. Oral corticosteroids and IVIG are similarly effective, although IVIG is widely used as initial treatment because of its better side effect profile.^{117,118} Prednisone is considerably less costly. Intravenous high-dose solumedrol (1 g daily for 3–5 days) given at monthly intervals (or followed by 1-g doses at weekly or longer intervals) may lessen the adverse effects of corticosteroids while providing similar efficacy, but it is less well studied.^{119,120} The authors suggest prednisone or prednisolone as the first-line treatment in milder, predominantly sensory cases. We usually start with prednisone, 60 mg daily, with a gradual alternate-day taper over the next 4 to 6 months.

Different dosing regimens of IVIG have been employed, but most give an induction of 2 g/kg over 2 to 5 days with a maintenance dose of 800 mg to 1 g/kg monthly, reducing the interdose interval if there is a wearing-off effect.^{121–123} Doses of 2 g/kg every 4 to 8 weeks has been proposed as an alternative.¹ In cases with waning efficacy of IVIG over time, a course of plasma exchange may help restore IVIG efficacy.¹²⁴

Plasma exchange is as effective as prednisone and IVIG, but it is generally reserved for refractory cases because of the need for central venous access and hospital administration in most centers.^{117,121}

Azathioprine has been used as a steroid-sparing agent and in refractory cases of CIDP, but there is little data to support its efficacy.^{125,126} Other immunosuppressive agents of uncertain efficacy used in CIDP include beta-interferon, alpha-interferon, cyclophosphamide, cyclosporine A, mycophenolate mofetil, etanercept, and rituximab.^{127–131} All reports of the efficacy of these drugs involve small, uncontrolled series. Clinical response rates are most impressive for

cyclophosphamide and cyclosporine, but both agents have considerable toxicity. One patient with CIDP developed chronic nephrotoxicity requiring hemodialysis after cyclosporine A treatment.¹³² CIDP has developed following etanercept treatment in rheumatoid arthritis, so it may be unsafe for treating CIDP. Rituximab may be effective in anti-MAG-associated polyneuropathy, which is generally refractory to IVIG.¹³³

CIDP in children responds very favorably to prednisone and IVIG.^{134–136} However, intravenous high-dose methylprednisolone may be associated with clinical deterioration and loss of strength.¹³⁷ In children with features of both MS and CIDP, the CIDP may respond to IVIG but not to interferon-beta.¹³⁵

Multifocal motor neuropathy differs from other variants of CIDP with sensory nerve involvement by a lack of response to prednisone and plasmapheresis^{3,139} (Table 7-1). Plasma exchange may even be detrimental.¹⁴⁰ It is unclear whether IVIG prevents progression of weakness and disability in patients with multifocal motor neuropathy, even when there is initial improvement in function.¹⁴¹

LSS and DADS respond to treatment similar to that of typical CIDP, except for the DADS patients with an associated IgM monoclonal gammopathy, who generally do not respond to any immunosuppressive treatment.³ Additionally, patients with LSS may respond better to IVIG (a 54% response rate) than to oral corticosteroids (a 33% response rate).⁴⁶ Overall, 73% of patients with LSS respond to immunosuppressive therapy. The authors have had success using combined IVIG and prednisone in refractory cases.

CIDP with an associated IgG or IgA monoclonal gammopathy responds similarly to classic CIDP. It is unclear how diabetes affects the treatment response in CIDP; it may have a similar response rate but poorer functional recovery.¹² Our experience suggests that CIDP with diabetes is more likely to respond in acute or subacute onset cases than in chronic, slowly progressive cases; conduction block and marked motor slowing may also predict the response to treatment. Rituximab shows promise in IgM MGUS-associated CIDP.¹³³ In POEMS syndrome, local irradiation or resection of an isolated plasmacytoma is indicated if it is accessible. Melphalan, with or without corticosteroids,

and hematology assistance should also be considered.¹⁴²

SUPPORTIVE THERAPIES

Neuropathic pain may be associated with CIDP, usually in the form of acral dysesthesias. These may be treated with gabapentin, pregabalin, duloxetine, tramadol or other narcotics. Passive range-of-motion exercise is essential for joints that do not offer resistance against gravity. Resistance and cardiovascular exercise on alternate days is important to help maintain strength and endurance. Distal weakness that interferes with ambulation may be aided by an ankle foot orthosis.

Course and Prognosis

Patients with relapsing CIDP (with or without diabetes mellitus) tend to respond better to immunosuppressive therapies than those with a chronic, progressive course.^{143,144} About 65% of patients have a relapsing course and 35% have a progressive or monophasic course.⁷ Approximately 16% of CIDP patients present acutely.⁷ Progression of neurologic symptoms beyond 2 months differentiates CIDP from AIDP.

An improved prognosis in CIDP is suggested by subacute onset, younger age (particularly children), symmetric symptoms, proximal weakness, less motor axon loss (preserved CMAP amplitudes), and distally accentuated motor slowing on electrophysiologic testing.^{33,143–146}

About 73%–87% of patients with CIDP have a good functional recovery.^{7,144,146} Severe disabilities (leaving the patient wheelchair-bound) or death occur in 8%–13%.^{7,146} Complete remission occurs in 13%–26% of patients with CIDP, some without treatment; remission may occur within 1 to 5 years.^{144,146}

Patients with multifocal motor neuropathy characteristically have a protracted course, with gradual loss of motor function over years; more acute relapses may occur. Patients with LSS also tend to have a more chronic progressive course, occurring in 73% of patients.⁴⁶ Some LSS patients progress to a more diffuse neuropathy similar to classic CIDP.⁴⁶

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Neuropathies Associated with Monoclonal Gammopathies and Cancer

**MULTIPLE MYELOMA,
OSTEOSCLEROTIC MYELOMA,
PRIMARY SYSTEMIC AMYLOIDOSIS
(AL AMYLOIDOSIS), WALDENSTRÖM
MACROGLOBULINEMIA,
MONOCLONAL GAMMOPATHY OF
UNDETERMINED SIGNIFICANCE**
Introduction

Clinical Features
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**MULTIPLE MYELOMA,
OSTEOSCLEROTIC MYELOMA,
PRIMARY SYSTEMIC
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SIGNIFICANCE**

Introduction

Polyneuropathy in multiple myeloma (MM) is relatively rare, occurring in 3%–13% of patients.¹ Spinal cord compression and radiculopathy are more common clinical problems in MM. Polyneuropathy in MM can be divided into those with typical myeloma and those with osteosclerotic myeloma (OM).¹ Cases with typical

myeloma can be further divided into those with and without amyloidosis. Polyneuropathy with myeloma but without amyloid is associated with typical length-dependent, predominantly axonal sensorimotor polyneuropathy. Concurrent radiculopathy may give the appearance of asymmetric polyneuropathy or multiple mononeuropathies. Rare patients may have progressive muscular atrophy (motor neuron or nerve disease) and even amyotrophic lateral sclerosis (ALS).^{1,2} Neuropathic pain and autonomic symptoms are generally absent. In patients with MM and amyloidosis, the polyneuropathy resembles polyneuropathy associated with systemic AL amyloidosis (primary systemic amyloidosis). The neuropathy is distal, symmetric, axonal, predominantly small-fiber, and sensory, with neuropathic pain and autonomic dysfunction. Autonomic dysfunction includes orthostatic hypotension, diarrhea or constipation, and male impotence. There may be associated carpal tunnel syndrome.

Polyneuropathy associated with osteosclerotic myeloma resembles chronic inflammatory demyelinating polyneuropathy (CIDP) except for the association of sclerotic bone lesions (plasmacytoma), Castleman disease (a lymphoproliferative disorder with hyperplastic nodes and proliferative vascular changes), and other systemic features of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) syndrome (see the discussion of CIDP and associated diseases in Chapter 7).

Primary systemic amyloidosis (AL [amyloid light chain] amyloidosis) is associated with a distal, painful, predominantly small-fiber, axonal sensory polyneuropathy similar to familial amyloid polyneuropathy (see Chapter 15).³ Systemic involvement includes nephrotic syndrome, restrictive cardiomyopathy, macroglossia, and purpura.^{4,5} A monoclonal protein is present in 90% of patients.⁵ If MM is associated, one of the two disorders usually predominates.⁵

Waldenström macroglobulinemia (WM) is usually associated with a demyelinating, predominantly sensory polyneuropathy, DADS (distal acquired demyelinating symmetric) phenotype, similar to other immunoglobulin M (IgM) polyneuropathies with MAG (myelin-associated glycoprotein) antibodies. In 50% of these patients, MAG antibodies are present. Waldenström macroglobulinemia with anti-sulfatide antibodies is associated with an axonal sensory polyneuropathy.⁶

Both axonal and demyelinating polyneuropathies are associated with monoclonal gammopathy of undetermined significance (MGUS), although the relationship of the monoclonal protein to the pathogenesis of the polyneuropathy is most clear in IgM monoclonal gammopathies with demyelinating polyneuropathy (see Chapter 7). Polyneuropathies with MGUS tend to be distal, symmetric, and predominantly sensory. The features of polyneuropathy in these disorders are outlined in Table 8–1.

Clinical Features

EPIDEMIOLOGY

Monoclonal Gammopathy of Undetermined Significance

MGUS is the most common type of plasma cell dyscrasia, occurring in 3% of the general population over 50 years of age and in 5% of the

population over 70 years.⁷ The mean age of patients with any MGUS in southeastern Minnesota is 74 years at diagnosis, and that of patients with an IgM monoclonal gammopathy and polyneuropathy is about 59 years (range, 37–82 years).^{8,9} MGUS is more prevalent in men than in women and in blacks than in whites. The rate of patients with MGUS developing a hematologic malignancy is about 1% per year.⁵ The rate of progression to hematologic malignancy in patients with MGUS and polyneuropathy is 22% after 1 month to 11 years of follow-up (mean, 3 years).¹⁰ Independent risk factors for malignancy are weight loss, progression of the neuropathy, and an M-protein level >1 g/L.¹⁰ Patients with an abnormal serum free light-chain ratio, an immunoglobulin A (IgA) or IgM monoclonal protein, and a serum protein concentration >1.5 g/dL have a considerable risk of progression (58% at 20 years) to a plasma cell malignancy.^{11,12}

Multiple Myeloma

The annual incidence rate of MM, age-adjusted to the 2000 U.S. population, is 4.3 per 100,000.¹³ In one series, polyneuropathy was seen in 8 of 29 patients with MM, 2 associated with and 6 without amyloidosis.¹⁴

Osteosclerotic Myeloma

Osteosclerotic myeloma with polyneuropathy or POEMS syndrome occurs in 1.4% of patients with a plasma cell dyscrasia.¹⁵ The mean age for development of OM is younger (49 years) than that for typical MM (62 years).¹

Amyloid Light Chain (AL) Amyloidosis

For AL amyloidosis with polyneuropathy, the average age of patients is 63 years and 87% are men.³ Thirty-five percent of patients with AL amyloidosis develop polyneuropathy.¹⁶ Epidemiologic studies of polyneuropathy and hematologic malignancies or AL amyloidosis are generally lacking.

Waldenström Macroglobulinemia

Waldenström macroglobulinemia has an age-adjusted incidence of 3.4 for men and 1.7 for

Table 8–1 **Features of Polyneuropathy in MGUS and Hematologic Malignancies**

Feature	Multiple Myeloma Amyloid (-)	Multiple Myeloma Amyloid (+)	Sclerotic Myeloma	Primary Systemic (AL) Amyloidosis	Waldenström Macroglobulinemia	MGUS
Neurologic symptoms at presentation	Rare	Occasional	Frequent	Frequent	Rare	Frequent
Pain	None	Marked	Occasional	Marked	No	Occasional
Autonomic features	None	Moderate	None	Moderate	No	Rare
Sensory/motor	Mixed	Sensory or mixed	Motor or mixed	Sensory or mixed	Sensory or mixed	Sensory
Axonal/demyelinating	Axonal	Axonal	Demyelinating	Axonal	Demyelinating, rare axonal	Demyelinating or axonal
Carpal tunnel syndrome	No	Yes	No	Yes	No	No
Skeletal x-rays	Lytic	Lytic	Sclerotic or mixed	Normal	Normal	Normal
CSF protein	Normal	Normal	Increased	Normal	Increased or normal	Increased or normal
Monoclonal protein	IgM- κ , IgG- κ , IgA- κ , >3 g	IgM- κ , IgG- κ , IgA- κ , >3 g	IgG- λ , IgA- λ , λ light chain	IgG- λ , IgA- λ , urine light chain	IgM- κ	Any
Clinical course	Slow progression	Progressive	Progressive-no treatment	Progressive	Slowly progressive	Mostly stable

women per 1 million person-years.¹⁷ The disease is less common in black than in white patients.¹⁷ It develops in 17% of patients with IgM monoclonal gammopathy who are followed for 4 to 9 years.¹⁸

SYMPTOMS AND SIGNS

Multiple Myeloma

Polyneuropathy in typical MM without amyloidosis presents as a length-dependent axonal sensorimotor neuropathy.¹ Polyneuropathy may be a presenting feature, but it usually occurs in patients with established myeloma. There is usually slow progression of distal numbness or paresthesias in the legs more than the arms over months or years, which may be associated with mild distal weakness.¹ Neuropathic pain and autonomic symptoms and signs are typically lacking. Bone pain and weight loss are frequent systemic symptoms in MM. Cervical or lumbosacral radicular pain frequently occurs with polyneuropathy from myeloma involving the spine. Both pin and vibration sense are involved in a stocking-glove distribution. Ankle reflexes are depressed or absent.¹ Occasionally, myelopathic signs are present (knee hyperreflexia, Babinski signs, and ataxia), even in the absence of spinal cord compression.¹ A picture of progressive muscular atrophy with quadriparesis, bifacial weakness, tongue fasciculations, and hyporeflexia is reported in isolated cases with additional “shooting pains” in the limbs and acral paresthesias.¹ Upper and lower motor neuron signs resembling those of ALS may occur, but treatment of myeloma with chemotherapy does not affect the progressive and fatal course.¹⁹ When typical MM is associated with amyloidosis, the resulting polyneuropathy resembles that seen with AL amyloidosis—a painful, distal, small-fiber, predominantly sensory polyneuropathy. Patients often present with burning pain in the feet or nocturnal hand paresthesias (carpal tunnel syndrome).¹ Carpal tunnel syndrome may occur in isolation or may be a presenting feature.¹ Distal paresthesias and numbness are characteristically symmetric, but mild asymmetries may occur. Autonomic symptoms (impotence, syncope) occur, but not invariably. There may be mild distal weakness greater in the leg than in the

hand. Thenar weakness may be disproportionate, with concurrent median nerve entrapment at the wrist. Polyneuropathy and amyloidosis may develop years after the onset of MM. The average age of patients with MM and polyneuropathy is similar with (64 years) and without (62 years) associated amyloidosis.¹

Osteosclerotic Myeloma

Patients with OM develop a predominantly demyelinating, motor-predominant polyneuropathy resembling CIDP.²⁰ In one series, polyneuropathy was the presenting feature in 15 of 16 patients by months to years (median, 20 months).²⁰ Weakness of distal limb muscles greater than that in proximal limb muscles is usually the predominant complaint.²⁰ However, numbness and paresthesias of the feet and legs are often appreciated first and accompany the weakness.²¹ Shooting, aching, or burning pains are infrequent. Functionally significant weakness occurs in 62% of patients, impairing the ability to climb steps, rise from a chair, or grip objects.²⁰ Distal and proximal or distally accentuated limb weakness is evident on exam. Vibration and proprioception are often more affected than pin and temperature sense. Areflexia is common in the legs, with hypo- or areflexia in the arms. Areflexia is associated with a greater degree of weakness. Cranial nerves are spared except for papilledema in about one-third of patients and rare, mild bifacial weakness.^{15,20}

Osteosclerotic myeloma may be isolated (solitary plasmacytoma) or may be associated with POEMS syndrome (also called *Crow-Fukase syndrome*; Table 8–2). Solitary plasmacytomas may be sclerotic or lytic.²² POEMS syndrome is a systemic disease defined by the presence of a monoclonal plasma cell disorder, polyneuropathy, and at least one of the following features: OM, Castleman disease, organomegaly (hepatosplenomegaly), endocrinopathy (excluding diabetes mellitus or hypothyroidism), edema, typical skin changes (hypertrichosis and hyperpigmentation), and papilledema.^{5,15} The absence of OM or Castleman disease raises doubt about the diagnosis. Castleman disease is a lymphoproliferative disorder characterized by enlarged, hyperplastic lymph nodes with prominent proliferative vascular changes. In POEMS

Table 8–2 Features of POEMS Syndrome

Acronym Letter	System Involved	Clinical Features	Symptom Frequency
P	Polyneuropathy	Sensorimotor > motor Demyelinating	100% (by definition)
O	Organomegaly	Hepatomegaly Splenomegaly Lymphadenopathy	24% 21% 42%
E	Endocrinopathy	Gynecomastia Impotence, testicular atrophy Amenorrhea Hypothyroidism Diabetes mellitus	50%
M	Monoclonal gammopathy	IgA λ or IgG κ	87%
S	Skin changes	Hyperpigmentation Hypertrichosis Hyperhidrosis Scleroderma-like Papillary angiomas	58% (overall)

syndrome, lymphadenopathy occurs in 42%, peripheral edema in 29%, and ascites in 11% of cases.^{5,15}

Amyloid Light Chain (AL) Amyloidosis

The neuropathy associated with AL amyloidosis is a distal, painful, predominantly small-fiber, axonal sensory polyneuropathy. The polyneuropathy resembles that seen in trans-thyretin-related familial amyloid polyneuropathy. In one series of polyneuropathy in AL amyloidosis, 42% of patients presented with progressive neurologic symptoms in isolation (sensory, motor, or autonomic symptoms), and the remainder had systemic symptoms that dominated the clinical presentation.³ Sensory symptoms predominated, occurring a median of 13 months prior to diagnosis and presenting in a length-dependent fashion. Numbness occurred in the feet in 94% and in the hands in 84% of patients, and was usually associated with neuropathic pain that was burning, stabbing, or shock-like in quality. Numbness was present in the hands in 19% of patients and was attributed to associated carpal tunnel syndrome. Autonomic dysfunction was present in 74% of patients. Postural hypotension was most frequent, occurring in 55% of patients. Thirty percent of men had

impotence, 35% of all patients had constipation or diarrhea, and 29% of all patients had bladder dysfunction (weak stream or incontinence).

Common systemic symptoms include weight loss, fatigue, and lightheadedness (52%), edema (35%), and dyspnea (23%).³ Abdominal complaints and purpura are less frequent. Each of the following is present in about 20% of patients: congestive heart failure, nephrotic syndrome, and carpal tunnel syndrome. On examination, sensory loss is length-dependent, worse in the feet, and affects pin and temperature more than vibration and position senses.³ Dissociated sensory loss (small- greater than large-fiber) is present in about 50% of patients. Weakness is common (84%) and tends to be distal and symmetric. More severe weakness was reported in 25% of patients and was worse distally. Orthostatic hypotension was noted in 74% of patients tested, and sluggish pupils were found in 13%.³ Proximal limb-girdle weakness suggests concurrent myopathy.³ Macroglossia occurred in 10%.²³

Waldenström Macroglobulinemia

In WM, patients may develop a demyelinating, sensory- greater than motor polyneuropathy,

with or without anti-MAG, resembling demyelinating polyneuropathy associated with an IgM MGUS.⁶ Sensory symptoms and ataxia often predominate. Numbness and dysesthesias occurred in 47% of patients in a prospective series of patients with WM.^{6,24} Distal pin loss, gait disorders, and abnormal quantitative vibration scores are more frequent than in normal controls.⁶ A distal, axonal, sensorimotor polyneuropathy has also rarely been reported in WM; we have also observed this association in isolated patients.²⁵ Cranial nerve and focal or multifocal neuropathies also occur. Systemic symptoms usually precede and accompany neurologic symptoms.²⁵ Hyperviscosity causes fatigue, bleeding from the gums and nose, visual blurring, and encephalopathy.²⁵ Direct tumor invasion results in weight loss, hepatosplenomegaly, and lymphadenopathy.²⁶ Amyloidosis and cryoglobulinemia, which also cause axonal neuropathies, are also rarely associated with WM.²⁶

Monoclonal Gammopathy of Undetermined Significance

MGUS may occur with axonal or demyelinating polyneuropathies. The clinical presentation will vary, depending on whether the monoclonal protein is IgM compared to IgG or IgA²⁷ (Table 8–3). Polyneuropathies associated with IgM MGUS are distal, predominantly sensory, and usually demyelinating. In IgM MGUS, the symptoms develop gradually in 90% of patients.⁸ About 88% of patients present with paresthesias, including tingling, prickling, cold, band-like, or sand-like sensations in the feet.^{8,28} Only 18% of patients have burning or painful electric sensations in the legs. Gait ataxia is common (70%). A postural 4–5-Hz tremor of the arms is present in about 30% of patients.^{28,29} On examination, 82% of

patients have impaired vibration, proprioception, and pin sensation; in 28% of patients the distal arms are involved (both large- and small-fiber senses).⁸ Distal weakness may be present but tends not to dominate the clinical picture. A motor deficit occurs in 58%, mostly limited to the distal legs.⁸ Proximal leg weakness is rare and was noted in only 1 of 40 patients.⁸ Areflexia occurs in about 82% of patients; in two-thirds of patients it is generalized, and in one-third it is limited to the legs.⁸ An IgG- or IgA-associated MGUS may be associated either with a demyelinating sensorimotor polyneuropathy that otherwise resembles CIDP or with a distal axonal, sensorimotor polyneuropathy. The relationship between the MGUS and the polyneuropathy is uncertain in these instances, particularly in axonal cases. The demyelinating forms are characteristic of typical CIDP.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis differs for each of the categories discussed in this chapter. For patients with MM and no amyloidosis, the possibilities are numerous, as in idiopathic axonal neuropathies. However, weight loss and systemic symptoms raise the possibility of MM or another malignancy, particularly if the patient is over 60 years of age. The presence of a MGUS should raise the possibility of MM, AL amyloidosis, WM (IgM), or cryoglobulinemia. In patients with MM and amyloidosis or in those with AL amyloidosis, the differential diagnosis is that of a small-fiber, painful, axonal, sensorimotor polyneuropathy with autonomic features, which may also be caused by diabetes mellitus, human immunodeficiency virus (HIV) infection, hereditary sensory neuropathies, paraneoplastic syndromes, Sjögren syndrome, sarcoidosis, cryoglobulinemia, and acute panautonomic neuropathy.

POEMS syndrome may be mistaken for typical CIDP, missing the opportunity to treat the associated plasmacytoma. The associated MGUS, systemic signs, and skeletal survey results help to differentiate the two conditions. Since the polyneuropathy associated with IgM monoclonal gammopathy is distal, symmetric, and predominantly sensory, it may be confused with an idiopathic axonal polyneuropathy

Table 8–3 Criteria for MGUS

Serum monoclonal protein level <3 g/dL
Bone marrow plasma cells <10%
Absence of end organ damage attributable to a plasma cell disorder (lytic bone lesions, anemia, hypercalcemia, or renal insufficiency)

clinically. As discussed in Chapter 7 in relation to CIDP, some hereditary polyneuropathies with intermediate degrees of motor conduction slowing (myelin protein zero [MPZ], lipopolysaccharide induced tumor necrosis factor alpha [LITAF], or connexin mutations) may mimic DADS with an IgM/anti-MAG MGUS. Pes cavus and more uniform motor slowing on nerve conduction studies favor a hereditary polyneuropathy. An IgG or IgA MGUS with polyneuropathy resembles either CIDP or idiopathic axonal polyneuropathies. The association of an IgG or IgA MGUS with a polyneuropathy in elderly patients may be due to chance because of the increased frequency of MGUS in the otherwise healthy elderly. Patients with a MGUS should be screened for a malignant plasma cell dyscrasia, perhaps annually, depending on the risk factors.

Laboratory Studies

BLOOD TESTS

The key screening test is a serum protein immunofixation electrophoresis (IFE) to check for a MGUS. A serum protein electrophoresis (SPEP) is less sensitive and can miss a smaller monoclonal protein spike. Rarely, only a urine protein electrophoresis (UPEP) or urine immunofixation may show a monoclonal protein. Antibodies for MAG should be checked in patients with a DADS presentation, or with demyelinating polyneuropathies with prolonged distal latencies, or when an IgM MGUS is present. In the presence of a monoclonal gammopathy, liver function tests, blood urea nitrogen (BUN)/creatinine, serum calcium, a complete blood cell count, quantitative immunoglobulin tests, cryoglobulin tests, and a urinalysis are appropriate. Systemic involvement would suggest MM or AL amyloidosis. If POEMS is suspected, glucose, thyroid stimulating hormone (TSH), and serum testosterone levels may also be tested. A skeletal survey should be performed on all patients with a chronic, acquired, demyelinating polyneuropathy and MGUS or another feature suggesting a plasma cell disorder (bone pain, POEMS syndrome features, anemia, or proteinemia) to screen for OM or typical

myeloma. Diagnosis of AL amyloidosis is accomplished by showing amyloid deposition consisting of immunoglobulin light chains in biopsied tissue. The majority of patients have free kappa or lambda light chains in the urine, and 90% have a monoclonal protein in the serum or urine.^{3,5} An abnormal free light chain ratio (the ratio of free kappa to free lambda chains) is defined as one below 0.26 or above 1.65 and suggests clonal expansion.¹¹ An abnormal value increases the risk of MM or a related hematologic malignancy and is present in most MM patients with a negative immunofixation.^{5,11}

A bone marrow aspirate is indicated when the monoclonal protein is ≥ 1.5 g/dL or when there are abnormalities of the complete blood cell count, serum creatinine, calcium, or skeletal survey.⁵ In the setting of an IgM monoclonal protein, bone marrow infiltration by lymphoplasmacytoid cells suggests WM.²⁶ Fifty percent of patients with WM have MAG antibodies.³⁰ There may be an association between WM and cryoglobulinemia or amyloidosis. Sensory axon loss is associated with anti-sulfatide antibody in 4% of patients with WM.⁶ In MM, bone marrow studies show $>10\%$ plasma cells, atypical malignant plasma cells, or both; bone marrow findings are normal or nonspecific in OM.

ELECTRODIAGNOSTIC STUDIES

Multiple Myeloma/Amyloid Light Chain (AL) Amyloidosis

In polyneuropathy associated with typical myeloma, myeloma with amyloidosis, and AL amyloidosis, the nerve conduction studies show characteristic findings of a distal, axonal, sensorimotor polyneuropathy with low sensory nerve action potential (SNAP) amplitudes, worse in the legs than in the arms, low compound muscle action potential (CMAP) amplitudes in more advanced cases, mild or no slowing, and modest prolongation of late response latencies. Electromyography (EMG) shows a distal pattern of fibrillations, long-duration motor unit potentials, and reduced recruitment. Patients with amyloidosis may have focal slowing of sensory or motor nerve conduction across the wrist because of superimposed carpal tunnel syndrome.³ Patients

with MM may also have asymmetric CMAP amplitudes, late response latencies, and a myotomal pattern of fibrillation potentials because of superimposed radiculopathy from spine involvement. Rare motor neuronopathies associated with MM resemble motor neuron disease with generalized fibrillations and reinnervation changes on EMG. In AL amyloidosis, there may be an associated myopathy, as suggested by proximal weakness, proximal fibrillations, and short-duration, low-amplitude motor unit potentials with increased recruitment. Rare presentations in AL amyloidosis include a mononeuropathy multiplex and a predominantly demyelinating polyneuropathy.³¹

Osteosclerotic Myeloma

The electrophysiology of OM and POEMS syndrome resembles that of CIDP, with multifocal motor conduction slowing, prolonged distal latencies, and proximal temporal dispersion, suggesting a predominantly demyelinating polyneuropathy.²⁰ Needle EMG shows distal or distal and proximal fibrillation potentials. In IgM MGUS, more diffuse demyelinating features are present, as in DADS.

Waldenström Macroglobulinemia

In WM, the electrophysiology resembles that of CIDP associated with an IgM MGUS, with marked slowing of distal motor latencies and motor conduction slowing. This is evident both with and without MAG antibodies.⁶ Patients with WM and sulfatide antibodies have axonal polyneuropathies with low-amplitude sensory and motor potentials.⁶ As already discussed, IgG and IgA MGUS may be associated with axonal or demyelinating changes. Demyelinating neuropathies with an IgA or IgG MGUS resemble typical CIDP.

CEREBROSPINAL FLUID

In patients with MM and polyneuropathy, cerebrospinal fluid (CSF) findings are generally normal.¹ However, in POEMS syndrome and OM with polyneuropathy, the CSF shows elevated protein (median, 166; range, 68–441 mg/dL), generally no cells, and normal glucose, similar to CIDP.²⁰ In one small series, CSF showed abnormalities of protein

electrophoresis or immunoelectrophoresis in 9 of the 11 patients with MGUS (IgG and IgM).³²

IMAGING

In OM, a skeletal survey may show sclerotic or mixed lytic and sclerotic lesions predominantly involving the spine, pelvis, and ribs. Magnetic resonance imaging (MRI) of the spine and pelvis is also sensitive to screen for sclerotic lesions.⁵ In typical myeloma, MRI of the spine is important in the presence of radicular or myelopathic features to assess for spinal cord or root compression. Bone scan is generally less sensitive and specific in detecting skeletal involvement in MM and OM, but it may have utility in select cases and may correlate with disease activity.^{33,34}

GENETICS

Familial amyloidosis also causes axonal polyneuropathy, carpal tunnel syndrome, autonomic dysfunction, and constitutional symptoms, and most families have autosomal dominant inheritance. In the majority of cases, the offending protein is variant transthyretin (TTR).³⁵ However, the diseases discussed in this chapter are sporadic. In MGUS, molecular genetic testing shows evidence of genomic instability with primary chromosomal translocations at the immunoglobulin heavy chain locus 14q32 (50%), hyperdiploidy (40%), or other conditions (10%).⁵

NERVE BIOPSY

Multiple Myeloma

Sural nerve biopsy in MM without amyloidosis shows axonal degeneration and slight segmental demyelination.^{1,36} Nonspecific axonal changes occur. In about 50% of cases of plasma cell dyscrasias, there are inflammatory infiltrates of CD4- and CD8-positive T cells.³⁷

Amyloid Light Chain (AL) Amyloidosis

In AL amyloidosis, amyloid deposits occur predominantly around capillaries in the endoneurium and around the walls of small blood vessels in the epineurium.³ Most nerves show severe loss of myelinated fibers, cellular

infiltrates are sparse, and axonal degeneration is the predominant finding on teased fiber preparations. Segmental demyelination occurs in about 10%–20% of patients.^{3,38} Complement deposition occurs on sural nerve amyloid deposits in both acquired and familial cases, including deposition of C5b-9 neoantigen.³⁹

Osteosclerotic Myeloma

In OM and POEMS syndrome, sural nerve biopsies show small perivascular infiltrates in the epineurium, and decreased myelinated fiber density. On teased fiber preparations, demyelination, remyelination, and axonal degeneration are present to varying degrees.²⁰ Endoneurial deposits of immunoglobulins are commonly present.⁴⁰ Occasional deposits of M-protein are present in the myelin sheath or between Schwann cells.

Monoclonal Gammopathy of Undetermined Significance

In IgM MGUS associated with anti-MAG, IgM antibodies bind to myelin sheaths, which display widening (Figs. 8–1, 8–2, see also

Chapter 7).⁴¹ In IgG and IgA MGUS, sural nerve biopsy findings resemble those of either typical CIDP or idiopathic sensorimotor polyneuropathies. Elevated numbers of sural nerve T cells occur more commonly in IgG MGUS than in controls.⁴²

Waldenström Macroglobulinemia

Sural nerve biopsies in WM show demyelination and IgM deposits on the myelin sheath in the presence of anti-MAG.³⁰ In the absence of MAG, endoneurial deposits of IgM are frequent; rarely, sural nerve biopsies show binding of IgM to myelin by indirect immunofluorescence and several protein bands by immunoblot.³⁰

Pathology

In AL amyloidosis and myeloma-associated amyloidosis, there appear to be three types of nerve lesions at autopsy: endoneurial deposition of amyloid, with loss of unmyelinated and small myelinated fibers; vessel wall deposition of amyloid in the vasa nervorum, with loss of

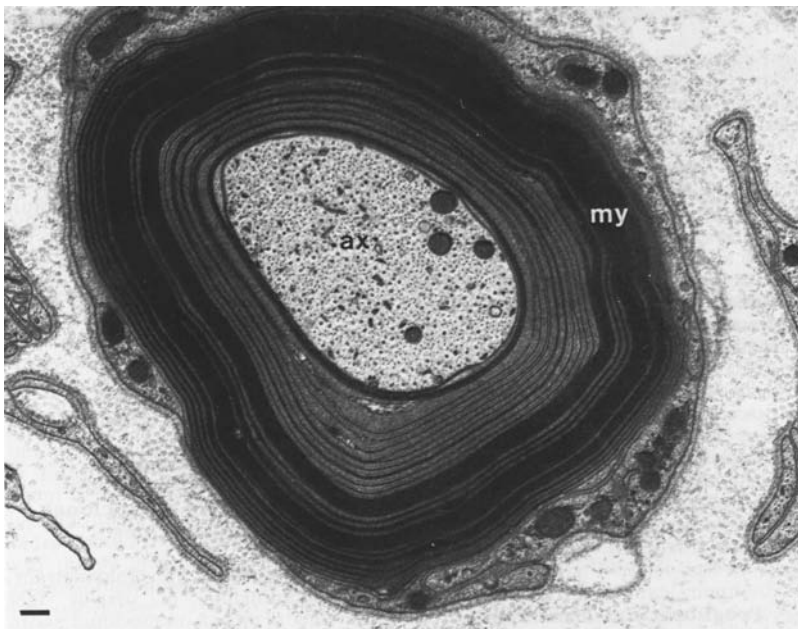


Figure 8–1. Electron micrograph of a transverse section through a myelinated nerve fiber from a patient with an IgM kappa, anti-MAG, antibody-associated paraproteinemic polyneuropathy. The axon (ax) is surrounded by a myelin sheath (my) that possesses alternating zones with both normal and abnormally widened periodicity. Bar = 0.2 μ m.

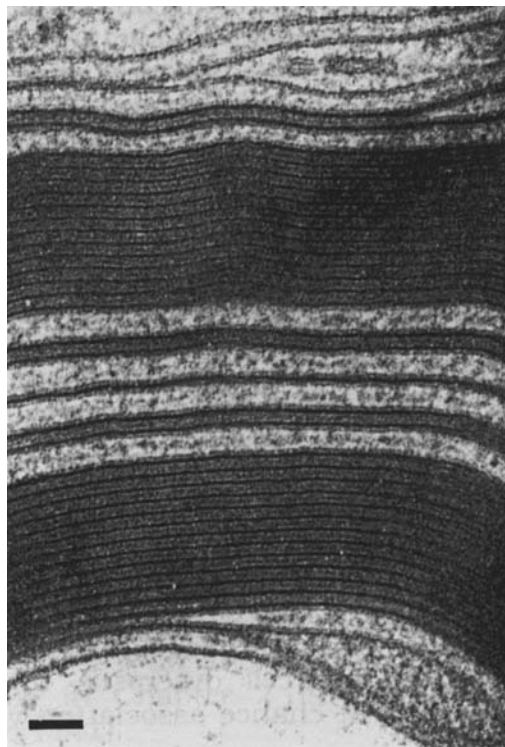


Figure 8-2. Detail of myelin from the same case showing darker areas in which myelin periodicity is normal, separated by zones with abnormally wide spacing. Bar = 0.1 μm .

large myelinated fibers; and a mixed type.⁴³ Often amyloid deposits are too small for adequate immunohistochemical classification; additionally, the type of amyloidosis cannot be determined by the features or severity of the neuropathy or the location or extent of amyloid deposits in nerve.⁴⁴ In POEMS syndrome, peripheral nerve lesions at autopsy include both segmental demyelination and axonal degeneration, with uncompacted myelin lamellae.⁴⁵

Pathogenesis

Patients with POEMS syndrome have higher serum levels of interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF)-alpha (inflammatory cytokines) than patients with MM.⁴⁶ Serum, but not CSF, levels of vascular endothelial growth factor (VEGF) are elevated in patients with POEMS syndrome.⁴⁷ This may

contribute to the observed increase in vascular permeability and microangiopathy. Passive transfer of the IgM fractions from patients with WM to mice results in IgM immunostaining in the perineurium and the endoneurial space, but not in myelin lamellae or axons.⁴⁸

There is electrophysiologic evidence of a length-dependent process in IgM monoclonal gammopathy, with greater distal slowing of motor conduction and greater distal axon loss.⁴⁹ Although this raises the possibility of axonal pathology, the degree of slowing electrophysiologically and the association of IgM binding to myelin sheaths, which display widening of the lamellae, suggest primary demyelination. It is possible that the blood-nerve barrier is more impaired distally. There is evidence of complement-mediated demyelination.⁵⁰ Injection of serum from patients with MAG-reactive IgM MGUS into cat sciatic nerve causes demyelination that is complement and M-protein dependent.⁵¹ Immunoglobulin gene analysis in IgM monoclonal gammopathy shows somatic mutation and intraclonal variation in about 50% of patients, suggesting that an immune response to bacterial antigens may recruit somatically mutated autoreactive B cells.⁵²

In WM, there may be direct tumor infiltration of the leptomeninges, causing cranial neuropathies or radiculopathy.⁵³ Patients with IgM >3 g/dL may develop hyperviscosity syndrome.²⁶ A direct immune attack against myelin sheath proteins is best demonstrated in cases associated with anti-MAG antibody.

Treatment, Course, and Prognosis

Multiple Myeloma

Treatment for polyneuropathy with MM in the absence of amyloid is directed at the myeloma. Treatment for MM varies based on the severity of disease. Most physicians use thalidomide plus dexamethasone or dexamethasone alone for induction. Vincristine, doxorubicin (Adriamycin), and dexamethasone (VAD) have been used previously.⁵⁴ Close observation of the clinical signs of polyneuropathy is needed, as both thalidomide and vincristine are neurotoxic. Patients should be considered possible candidates for an autologous stem cell transplantation.⁵⁴ Optimal chemotherapy

regimens in patients with MM and amyloidosis are unclear. Focal spine lesions causing compressive radiculopathy are treated with focal spine radiation. The polyneuropathy in MM without amyloidosis tends to stabilize or progress slowly independent of myeloma progression or the response to chemotherapy.¹ When MM is associated with amyloidosis, it tends to have a more rapidly progressive course over months. If carpal tunnel syndrome is associated, it may respond to bracing or transcarpal ligament release.

Amyloid light chain (AL) Amyloidosis

In patients with AL (and myeloma-associated) amyloidosis, polyneuropathy usually progresses despite chemotherapy.¹ The principal treatment for AL amyloidosis has been melphalan and prednisone for years.⁵ Patients with less severe disease have been offered autologous stem cell transplantation based on anecdotal evidence of a more prolonged response with stem cell transplantation.⁵ However, a recent randomized trial comparing high-dose intravenous melphalan followed by autologous hematopoietic stem cell rescue with standard-dose melphalan plus high-dose dexamethasone showed greater survival in the melphalan/dexamethasone group.⁵⁵ Thalidomide plus dexamethasone has also been used, but thalidomide is neurotoxic. In AL amyloidosis, death usually is due to cardiac or renal failure. The 1-year survival is about 60% and 3-year survival is 22%.³ Patients with longer survival note slow progression of polyneuropathy over months and have less cardiac and renal involvement.³ With progression, distal neuropathic pain subsides and distal extremity numbness increases. Weakness progresses, impairing gait to the point that assistive devices or a wheelchair are required.³ Autonomic dysfunction also becomes severe, with frequent urinary incontinence or retention.³

Osteosclerotic Myeloma

Placebo-controlled trials in OM are lacking. In patients with a CIDP-like presentation and unrecognized OM, treatment with prednisone, 60 mg daily, with or without azathioprine

resulted in only mild, transient, subjective improvement.²⁰ About 50% of patients with solitary OM treated with localized irradiation (3000–5000 rads) show considerable functional improvement in polyneuropathy; mild improvement occurs in most remaining patients.²⁰ Improvement begins insidiously within 3 months and may continue for 1–2 years. Evidence of improvement by clinical and electrophysiologic examination is usually clear by 6 months. Various combinations of therapies have been tried for patients unresponsive to radiation therapy. Rapidly progressing polyneuropathy associated with OM may respond to intravenous immunoglobulin combined with local irradiation.⁵⁶ Patients unresponsive to irradiation may respond to more aggressive therapy with surgical resection and combination chemotherapy with chlorambucil, danazol, and corticosteroids.⁵⁷ Lack of improvement with localized irradiation may raise the possibility of multiple lesions.

Multiple osteosclerotic lesions treated with melphalan (15 mg/kg) and prednisone (60 mg) for 1 week every 6 weeks resulted in slight improvement in three, stabilization in two, and continued progression in two patients.²⁰ A more complete response to melphalan and prednisone has also been reported.⁵⁸ Polyneuropathy in OM may also respond to strontium-89 and prednisone in combination.⁵⁹ Plasma exchange may be ineffective.⁶⁰ Patients with multiple lesions generally respond less well to treatment than those with solitary lesions.

Patients with more advanced disease may be considered for stem cell therapy similar to that of patients with MM.⁵ Four patients with POEMS syndrome treated with high-dose chemotherapy and autologous peripheral blood stem cell transplantation showed rapid normalization of serum VEGF levels with improvement in symptoms over 6 months.⁶¹

Waldenström Macroglobulinemia

Randomized studies in WM are lacking. Initial therapy involves single agents (rituximab, fludarabine, cladribine, or chlorambucil) or combination chemotherapy (fludarabine plus rituximab, fludarabine plus cyclophosphamide and rituximab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and

prednisone).^{5,62} Refractory cases may be treated with autologous bone marrow transplantation, which produces 5-year survival in about 40% of patients, or alpha-interferon.^{63,64} Hyperviscosity syndrome requires plasma exchange.⁵

Monoclonal Gammopathy of Undetermined Significance

Immunoglobulin G or IgA MGUS associated with CIDP is treated like classic CIDP (see Chapter 7). Immunoglobulin M MGUS associated with a demyelinating polyneuropathy is typically refractory to treatment with intravenous immunoglobulin (IVIG), although this may be tried.⁶⁵ Mild cases with sensory predominance may be treated symptomatically and followed clinically without immunosuppression. Placebo-controlled trials of immunosuppressive drugs in IgM MGUS are lacking. In uncontrolled series, rituximab appears to have the best response rates, though it doesn't lessen IVIG dependence.^{66,67} Other treatments with possible benefits include chlorambucil, plasma exchange, cyclophosphamide plus prednisone, alpha-interferon, and antibody-based immunoadsorption.^{68–72}

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INTRODUCTION

Infectious and granulomatous neuropathies cause focal, multifocal, and, similar to vasculitic neuropathies, more confluent, distal, symmetric axonal sensorimotor polyneuropathies. Focal neuropathies include cranial neuropathies, particularly of the facial nerve in Lyme disease, sarcoidosis, herpes simplex, and human

immunodeficiency virus (HIV) infection, as well as ulnar and superficial radial neuropathies in leprosy. Human immunodeficiency virus infection is also associated with acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), as well as superinfection with cytomegalovirus (CMV) causing a severe lumbosacral polyradiculopathy or

mononeuropathy multiplex. In infectious cases, direct infection of peripheral nerve is limited to dorsal root and cranial ganglia neurons in varicella-zoster infection and to Schwann cells and macrophages in lepromatous leprosy.^{1,2} Most neuropathies in infectious and granulomatous diseases relate to local and systemic inflammatory responses. Treatment in infectious cases is directed at the underlying infection, often with concurrent immunosuppressive treatment to lessen a resulting or primary inflammatory response. Sarcoidosis and immune-mediated HIV neuropathies (AIDP, CIDP, and mild multiple mononeuropathies) are treated with immunosuppression.

HERPES ZOSTER/HERPES SIMPLEX

Clinical Features

EPIDEMIOLOGY

Herpes zoster can occur at any age, is more common in elderly patients, has a slight female predominance, and has an annual incidence of 0.9–4.0 per 1000 patient-years. However, the incidence can be as high as 14.6 per 1000 in elderly patients (over 80 years of age) or those with rheumatoid arthritis.^{3–6} Immunosuppressive drug use is a significant predictor of herpes zoster.⁵ Malignancy, especially lymphoma, HIV infection, and transplantation are also common risk factors.⁷

Herpes simplex has an annual prevalence 14.8%, is significantly more frequent in women than in men ($P < .001$), and decreases with age ($P < .001$).⁸

SYMPTOMS AND SIGNS

Herpes zoster presents with pain and paresthesias in a dermatomal or trigeminal nerve distribution 2–14 days (usually 2–4 days) prior to the onset of eruption of a vesicular rash.⁹ The vesicles are usually confined to one dermatome, usually thoracic (T5–10), but two or more dermatomes may be affected, particularly in limb cases¹⁰ (Fig. 9–1). Zoster infection of the trigeminal (usually V1, herpes zoster ophthalmicus), facial (Ramsay-Hunt syndrome), and, rarely, other cranial nerves



Figure 9–1. Healed lesions of herpes zoster covering adjacent dermatomes.

may also occur. Vesicles become cloudy in a few days and crusted in 5–10 days, with subsequent hyperpigmentation and scarring. Although the rash typically affects one dermatome, the associated dysesthetic pain and allodynia usually span two or more dermatomes. Neuropathic pain usually improves after 1 month but may persist for months or years. Segmental motor paralysis of the limbs occurs in 2%–5% of cutaneous herpes zoster cases.^{11,12} Paralysis is myotomal (segmental zoster paresis) and usually mild. The cervical and lumbar spinal segments are equally affected.¹¹ Rarely, diaphragmatic or bladder paralysis occurs. The facial nerve may be affected, characteristically in association with a vesicular eruption of the external auditory meatus and tympanic membrane; tinnitus, vertigo, loss of taste in the anterior two-thirds of the tongue, and hearing loss may be associated. Herpes zoster may also cause a central nervous

system (CNS) vaculitis, a meningoencephalomyelitis, or a myelitis.

Zoster sine herpette refers to neuropathic radicular pain related to herpes zoster reactivation without rash. The best evidence for this is a small series of patients with recurrent radicular pain who had positive varicella-zoster DNA by polymerase chain reaction (PCR) in CSF, blood, or both and responded to herpes antiviral treatment.¹³ One prospective series of patients with Ramsay-Hunt syndrome showed that 14% of patients develop the vesicular rash after the development of facial paralysis.¹⁴ Therefore, some patients with “Bell’s palsy” may have the beginning of Ramsay-Hunt syndrome and zoster sine herpette.

Herpes simplex has been associated with cranial neuropathies of the trigeminal, facial, and, rarely, optic nerves.^{15–19} The finding of herpes simplex virus 1 (HSV1) DNA in 79% of patients with severe idiopathic facial palsy and no controls or in patients with Ramsay-Hunt syndrome suggests an association of herpes simplex with Bell’s palsy.¹⁹ However, this finding has been questioned, since another group found a high percentage of herpes simplex DNA by PCR in geniculate ganglion of control preparations.²⁰

LABORATORY STUDIES

Elevated serum titers of immunoglobulin M (IgM) or immunoglobulin A (IgA) against varicella-zoster suggest recent infection or reactivation.⁹ However, positive varicella-zoster DNA by PCR in CSF, blood, or both is more specific for zoster reactivation.¹³ The CSF displays a variable lymphocytic pleocytosis and a moderate protein elevation.

ELECTRODIAGNOSTIC STUDIES

In thoracic disease, paraspinal fibrillations are frequent at two or more contiguous myotomal levels or bilaterally, despite unilateral neuropathic symptoms and rash.²¹ Electrophysiologic studies in zoster paresis characteristically suggest ventral root or focal anterior horn cell disease with a myotomal pattern of fibrillations. Proximal myotomes (C5–7) and (L2–5) may be preferentially affected, although an L5, S1/sciatic distribution has also been reported.¹² In more severe cases, sensory nerve action potential

amplitudes (i.e., superficial peroneal) may be reduced, suggesting dorsal ganglia or peripheral nerve involvement as well. In Ramsay-Hunt syndrome, blink reflexes are prolonged or absent in an efferent pattern, facial compound muscular action potentials (CMAPs) may be reduced or absent, and facial nerve innervated muscles may develop fibrillations.

Pathology

In dorsal root ganglia, varicella-zoster DNA is present in both neuronal and satellite cells in latent infection. In spinal segments associated with active infection, varicella-zoster DNA and gpI, a late viral protein, are present in ganglia neurons.¹ In trigeminal ganglia studied at autopsy, varicella-zoster DNA was found in neuronal nuclei and only rarely in glial cells.²² There are rare patient reports of brachial neuritis related to herpes zoster. The brachial plexus at autopsy showed extensive lymphocytic infiltration, myelin degeneration, preserved axons, and no vasculitis. The cervical spinal cord showed perivascular lymphocytic cuffing without anterior horn necrosis.²³

Treatment, Course, and Prognosis

Prognosis for recovery of strength is generally good, particularly when patients are treated within the first few days of rash onset with antiviral medications. In zoster paresis, functional motor recovery occurs in about 75% of cases, generally within 1 to 2 years, similar to Bell’s palsy.¹² Patients with Ramsay-Hunt syndrome tend to have a poorer recovery than those with idiopathic Bell’s palsy. However, 75% of patients with Ramsay-Hunt syndrome recover fully when treated within 3 days with prednisone and acyclovir compared to 30% of patients treated after 7 days.²⁴

Neuropathic pain usually improves after 4–8 weeks, but pain may resolve more slowly over months or become chronic. *Postherpetic neuralgia* refers to persistent neuropathic pain, typically lasting for more than 2 months. Pain is typically described as sharp, unpleasant paresthesias or burning; allodynia is frequent. Risk factors for developing postherpetic neuralgia include older age, female sex, presence of a

prodrome, greater rash severity, and greater acute pain severity.²⁵ Effective treatments for persistent pain include gabapentin, pregabalin, tricyclic antidepressants, lidocaine patches, opioids, and nerve blocks. Intrathecal methylprednisolone may also be an option for refractory postherpetic neuralgia.²⁶ Spinal myelomeningocele is a rare complication of herpes zoster.²⁷

The treatment for acute zoster infection is valacyclovir 1000 mg PO tid, famciclovir 500 mg PO tid, or acyclovir 800 mg five times daily for 7 days. The addition of prednisone to antiviral drugs improves acute neuropathic pain but does not lessen the frequency of postherpetic neuralgia. Analgesic medications used to treat postherpetic neuralgia are often required to treat acute pain as well.^{28,29} Idiopathic Bell's palsy is usually treated with a prednisone taper for 7–10 days; a role for antiviral therapy is still *sub judice* despite a number of reports, some supporting its use and others suggesting that it is ineffective³⁰ (see Chapter 18).

LEPROSY

Clinical Features

EPIDEMIOLOGY

Globally, leprosy is one of the most common treatable causes of neuropathy. However, it remains rare in Western medicine. Only isolated cases of secondary exposure have been documented in the United States.³¹

The introduction of multidrug therapy and public health measures in India led to a decline in the prevalence of leprosy in certain regions of India from 15–20 per 10,000 between 1970 and 1980 to 1 per 10,000 in 2005.³² In Hong Kong, the incidence of leprosy decreased from 3.2 per 100,000 in 1970 to 0.088 per 100,000 in 2004.³³ There is a male predominance after puberty, with a male-to-female ratio of 1.5–2.0 to 1.³⁴

SYMPTOMS AND SIGNS

Leprosy affects the skin, nerves, and eyes and has systemic manifestations in lepromatous disease. The initial lesion in leprosy is characteristically a hypopigmented macule or plaque that is anesthetic, representing local skin infection with *Mycobacterium leprae*. Sensory loss over the skin is the presenting

neurologic feature, regardless of the type of leprosy, and reflects intradermal nerve damage. Pain and temperature sensation are the initial sensory modalities affected, likely reflecting early involvement of Schwann cells of small myelinated and unmyelinated fibers in superficial nerves. Anhidrosis in affected areas is an early feature. The overall distribution and timing of the lesions are determined by the host's immune response and the type of leprosy. There are tuberculoid, lepromatous, borderline, and primary neuritic forms of the disease. Differences in the clinical presentation reflect the patient's immunologic response.

Tuberculoid Leprosy

In tuberculoid leprosy, a robust cell-mediated immune response restricts the disease to a few circumscribed patches of skin or nerve trunks. Generally only one or two well-demarcated anesthetic skin lesions develop. A mixed nerve trunk beneath the patch may become affected. The most commonly affected nerves are superficial, allowing for lower temperature, and include the greater auricular, ulnar (elbow), superficial radial (wrist), median (wrist), tibial (medial malleolus), common peroneal (fibular head), facial (zygomatic branch), and sural nerves.³⁴ Affected nerves are palpably swollen and may be tender. Nerve enlargement may lead to secondary entrapment neuropathies. Autonomic dysfunction causes frequent anhidrosis in skin lesions (dermal nerves) and nerve trunks.

Lepromatous Leprosy

Lepromatous leprosy is characterized by the absence of immunity to *M. leprae*, which results in widespread infiltration of the skin and peripheral nerves with multiple lesions. Skin lesions are often not anesthetic. Diffuse hematogenous spread results in deposition of *M. leprae* in cool regions, first affecting temperature and pin loss over the ears, the dorsal surface of the hands and forearms, the feet, and the lateral legs. Over a period of years, sensory loss evolves into a more stocking-glove-like distribution, but with palmar and sole sparing, and involvement of the nasal, malar, and eyebrow regions.³⁵ Further progression results in more diffuse small-fiber

sensory loss and later motor weakness in the distribution of susceptible nerves. The ulnar nerve at the elbow is often affected before other nerves. In more advanced cases, sensory loss spreads to the palms and face, and weakness may involve facial, median, and common peroneal innervated muscles.

Borderline Leprosy

Borderline leprosy is an intermediate form of leprosy in which there is progressive reduction of cell-mediated immunity resulting in an increased bacillary load, more frequent and generalized skin and nerve lesions, higher antibody titers, and clinical instability.³⁴ Patients may present with neuropathic pain, more acute neuropathies, many new skin lesions, fever, and eye pain. Skin lesions may be larger than in tuberculoid leprosy and coalesce. Nerve involvement generally resembles that of lepromatous or tuberculoid forms of leprosy. However, more atypical focal neuropathies may develop, such as total facial paralysis, brachial plexopathy, or median neuropathy.³⁶ Mononeuropathies may progress to more diffuse polyneuropathy. Type 1, or reversal, reactions occur in one-third of borderline patients due to increases in T-cell-mediated immunity against *M. leprae* and cytokines. An “upgrading” reaction (toward the tuberculoid form) may develop in borderline cases during the first year of treatment or occasionally in untreated cases. Skin lesions and focal neuropathies worsen acutely with inflammatory signs. Tissue necrosis may occur with the formation of nerve abscesses. A “downgrading” reaction occurs rarely in ineffectually treated or untreated cases, involving a greater bacillary burden and lepromatous disease. A Type 2 reaction, or erythema nodosum leprosum, is a systemic inflammatory response related to extravascular immune-complex deposition associated with fever, malaise, and nodular, red skin lesions.

Primary Neuritic Leprosy

Primary neuritic leprosy presents with asymmetric peripheral nerve involvement in the absence of skin lesions. This represents 10% of leprosy cases in India.³⁷ A mononeuritis

multiplex presentation is common.³⁷ The cellular response on nerve biopsies ranges from lepromatous to tuberculoid; bacilli are often present, however, on skin and nasal mucosa biopsy specimens.

Laboratory Studies

The initial diagnostic test is a skin smear to detect acid-fast bacilli; it has high specificity but low sensitivity (30%).³⁴ The sides of small slits cut over skin lesions are scraped to prepare smears for acid-fast staining. The gold standard for the diagnosis is histologic. The diagnosis can often be made by skin biopsy. Fite-faraco staining is preferable in skin biopsies.³⁷ Nerve biopsy is often necessary in primary neuritic leprosy. The histology may not correlate with the clinical staging, and the bacillary load may differ between nerve and skin biopsies. Polymerase chain reaction studies may increase the sensitivity of nerve biopsies, although the sensitivity is generally low and is especially poor when the bacillary burden is low (i.e., in tuberculoid disease).³⁵

Serologic testing, using antibodies to phenolic glycolipid-1 (PGL-1), also has low sensitivity (about 50% in primary neuritic disease) and is rarely used to confirm the diagnosis.^{34,37}

ELECTRODIAGNOSTIC STUDIES

Early in the course of disease, nerve conduction studies show focal slowing or conduction block, particularly across vulnerable segments of the nerve (i.e., the ulnar nerve at the elbow or the peroneal nerve at the fibular head).³⁹ This is especially true in tuberculoid cases. Sensory conduction slowing also occurs, particularly in the superficial radial nerve.⁴⁰ Distal motor latencies are prolonged at vulnerable sites such as the median nerve in the distal forearm or tibial nerve at the ankle.³⁷ Neuropathy may be restricted to the ulnar nerve or may be multifocal. As the disease progresses, findings of axonal neuropathy predominate in terms of motor and sensory amplitude reduction, although asymmetries are characteristic. Late responses may have prolonged latencies.

Nerve Biopsy/Pathology

Nerve biopsies are rarely necessary for confirmation of leprosy except in primary neuritic leprosy and to exclude other diseases. The nerve of choice is a palpably enlarged sensory nerve. In tuberculoid leprosy, enlarged nerves are usually adjacent to skin lesions. Granulomas are present in the perineurium and the endoneurium with epithelioid cells, giant cells, and scattered mononuclear cells; the nerve architecture is typically disrupted, and bacilli are sparse.³⁷ In lepromatous leprosy, the nerve architecture is better preserved, the endo- and perineurium are infiltrated by foamy macrophages, and lymphocytes and plasma cells may be present in the endoneurium. Acid-fast bacilli are often abundant in macrophages, in Schwann cells, and, more rarely, in endothelial cells or vessels.³⁷ Unmyelinated axons are affected initially. Eventually, there is diffuse, near-total fiber loss. Cutaneous nerves are converted to bundles of connective tissue. In borderline leprosy there may be more widespread nerve involvement (as in lepromatous disease), with degeneration of the nerve architecture (as in tuberculoid disease). The degree of nerve destruction, granuloma formation, and bacillary load varies. Most patients with primary neuritic leprosy have tuberculoid or borderline tuberculoid pathology.⁴¹

Pathogenesis

M. leprae enters the nerve through the Schwann cell. An *M. leprae* glycolipid, PGL-1, binds to laminin-2 of the Schwann cell extracellular basement membrane, allowing for bacilli entry.⁴² The attachment of PGL-1 to the Schwann cell results in demyelination.⁴³ Nonmyelinating Schwann cells are more susceptible to bacillary invasion, explaining the predilection toward small nerve fiber involvement.⁴³ The immune system likely plays a more important role in more established infection and the tuberculoid form, as *M. leprae* causes nerve damage in immunodeficient mice.⁴⁴

Differences in the pathology and type of leprosy reflect differences in the host's immune response. The more robust response in tuberculoid leprosy limits the extent of

M. leprae proliferation but, because of granuloma formation, causes greater tissue destruction. In lepromatous leprosy, the less effective immune response results in a greater and more widespread bacillary load. In tuberculoid leprosy, skin and nerve lesions are infiltrated by Th1-like (T-cell and macrophage activator) T cells that secrete interferon γ , tumor necrosis factor alpha (TNF α), and interleukins-2 and -15.⁴⁵ T cells express interleukin-12 receptors, and transcripts for interleukins-12 and -18 are abundant.^{34,46} In lepromatous leprosy, the T-cell and cytokine repertoire differs. T cells produce Th2-like (B-cell activator) cytokines and interleukins-4 and -10, and lesions contain the related mRNA transcripts.^{34,47} Some lepromatous patients show Th0-like (uncommitted T cells) cytokine expression with mixed patterns.

Some patients show no T-cell responsiveness to *M. leprae*, suggesting a T-cell deletion.³⁴ Suppressor CD4+ T-cell clones may also be present in lepromatous cases.³⁴ $\gamma\delta$ T cells, which play a role in the early host defense against invading microorganisms through recognition of nonpeptide antigens, may also be present in skin lesions.⁴⁸

Treatment

Leprosy should be managed by clinicians experienced with this disease. Patients often require care by internists as well as neurologists, orthopedic surgeons, ophthalmologists, dermatologists, and rehabilitation physicians. Dapsone, clofazimine, and rifampin are the most widely used drugs. Modified World Health Organization (WHO)-recommended antibiotic regimens are listed in Table 9-1.³⁴ In the United States, the recommended treatment for paucibacillary (tuberculoid) patients is dapsone 100 mg plus rifampin 600 mg daily for 1 year. Multibacillary (lepromatous) patients are treated with the above regimen plus clofazimine 50 mg daily for 2 years.⁴⁹

Hepatotoxicity is a major and uncommon side effect of rifampin. Hemolysis with mild anemia is common with dapsone. Agranulocytosis and serious skin eruptions are rare. Dapsone also causes an axonal motor polyneuropathy as a direct toxicity. Clofazimine causes red-black skin discoloration and may produce gastrointestinal discomfort.⁴⁹ Missense mutations of the *folP1* gene

Table 9–1 **Modified WHO-Recommended Multidrug Treatment Regimens for Leprosy**

Leprosy Type*	Drug Treatment		Treatment Duration (months)
	Monthly Supervised	Daily Self-Administered	
Paucibacillary	Rifampin 600 mg	Dapsone 100 mg	6 months
Multibacillary	Rifampin 600 mg and clofazimine 300 mg	Clofazimine 50 mg Dapsone 100 mg	24 months
Paucibacillary; single lesion	Rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg		Single dose

* WHO classification for field use when slit skin smears are unavailable. In field control programs, WHO recommends treatment of multibacillary patients for only 12 months. From Britton and Lockwood³⁴ and modified with permission from the World Health Organization.

predict dapsone resistance and can be detected by PCR of skin biopsy specimens.⁵⁰ Minocycline, ofloxacin, clarithromycin, and streptomycin are second-line drugs used if side effects of or resistance to standard regimens occur. Nerve dysfunction may worsen during treatment and should be monitored clinically and by nerve conduction studies when available.

Reversal reactions (Type 1) are treated with prednisone 40–60 mg daily, decreasing 5 mg every 2–4 weeks following clinical improvement.⁵¹ Attempts to prevent the reversal reaction with lower doses of prednisone have not been very successful. Type 2 reactions can be treated with prednisone, clofazimine (through an anti-inflammatory effect), or thalidomide 400 mg daily.^{34,52} Thalidomide may worsen the polyneuropathy.

An important supportive measure is to prevent trauma to anesthetic limbs, such as accidental burns, habitual limb compression, or damage caused by ill-fitting shoes. Avoidance of weight bearing assists in healing of plantar ulcerations.³⁴ Splinting may provide symptomatic relief. Surgical excision of nerve abscesses, ulnar nerve transposition, and nerve grafting may relieve neuropathic pain, but recovery of sensory or motor function is limited in advanced cases.^{53,54} Cosmetic surgeries may lessen facial deformities. Tenodesis (tendon anchoring), arthrodesis (joint fusion), and tendon transfers may be used to partially restore or stabilize joint function.

Course and Prognosis

Morbidity in leprosy is secondary to nerve damage. The prognosis for recovery from individual peripheral nerve lesions in tuberculoid leprosy is poor because of the extensive destruction of the nerve architecture that characterizes even the early lesions. Early peripheral nerve lesions in lepromatous leprosy may be stabilized by antibacterial treatment, and considerable function may be preserved. Later stages of lepromatous leprosy neuropathy carry a poor prognosis secondary to greater axonal loss.⁵⁵

SARCOIDOSIS

Clinical Features

EPIDEMIOLOGY

The incidence of sarcoidosis in Europe in persons over 15 years of age is 19 per 100,000 per year, with a female predominance of 1.3:1.⁵⁶ Incidence peaks between 20 and 34 years of age with a second lower, broader peak in older women.⁵⁶ In Oslo, Norway, the incidence of sarcoid arthritis is 2.9 per 100,000 persons between 18 and 60 years of age. The incidence of neurosarcoidosis is unknown, but it occurs in about 5%–15% of patients with sarcoidosis.⁵⁷ In patients with neurosarcoidosis, about 9%–24% have polyneuropathy.^{58,59}

Women are more likely to have neurologic and ocular involvement and erythema nodosum.⁶⁰ First- and second-degree relatives of patients with sarcoidosis have a significantly elevated risk of sarcoidosis (odds ratio of 5.8 in siblings).⁶¹ The prevalence of spondyloarthropathy in sarcoidosis patients is 7% versus 2% in the general population.⁶² Potential occupational risk factors for developing sarcoidosis include metal exposures and high humidity.⁶³

SYMPTOMS AND SIGNS

Sarcoidosis commonly causes acute sensory symptoms that are more frequently multifocal or focal rather than distal and symmetric.⁶⁴ Neuropathic pain is often a dominant symptom, with a dysesthetic or sharp quality.⁶⁵ Cervical and lumbosacral radicular pain, often accompanied by dermatomal dysesthesias, is a particularly common presentation. Concurrent thoracic radicular sensory symptoms, present in 17% of sarcoid neuropathy patients, often distinguish sarcoidosis from degenerative spine disease.⁶⁵ Polyradiculoneuropathy is most common, occurring in 39% of sarcoid neuropathy patients. A severe form of polyradiculopathy may present as a cauda equina syndrome with paraparesis, sensory loss, and sphincter involvement with or without thoracic radicular symptoms.⁶⁶ Lumbar radicular pain, back pain, and absent leg reflexes are frequently associated. Distal, symmetric, small-fiber polyneuropathies may be more common than was previously recognized.^{67,68} Gastroparesis and subclinical autonomic dysfunction may occur. Chronic, symmetric, axonal sensorimotor polyneuropathies were relatively frequent in one series, but our experience and recent data favor multifocal onset of sensory symptoms.^{58,65,69}

Cranial neuropathies also occur in sarcoidosis, and facial nerve involvement is most frequent. The clinical features resemble those of Bell's palsy, although sequential, bilateral facial palsies are a distinguishing feature. Simultaneous bilateral involvement is rare. Facial nerve palsies may be a presenting feature. Optic neuritis and, more rarely, VIIIth nerve dysfunction are also reported.⁷⁰ The latter may be bilateral.⁷¹

There are reports of sarcoidosis patients with AIDP, mononeuritis multiplex, lumbosacral plexopathy (with distal polyneuropathy),

and multifocal motor conduction block with sensory involvement.^{58,72}

Systemic symptoms of sarcoidosis are commonly associated with peripheral nervous system disease in sarcoidosis, although neurologic disease may be a presenting feature, particularly facial palsy, radiculopathy, or mononeuropathies. Systemic features may include lymphadenopathy, asymptomatic hilar adenopathy, dyspnea or nonproductive cough, uveitis, arthritis (with a predilection for the ankles, knees, and spine), erythema nodosum, violet-red skin lesions, and scar granulomas. Spondyloarthropathy in sarcoidosis may be more common than in the general population.⁶² In one series, CNS disease was present in about 20% and myopathy in about 10% of patients with sarcoid neuropathy.⁶⁵

Laboratory Studies

BLOOD TESTS

An elevated angiotensin converting enzyme (ACE) level is a very insensitive indicator, occurring in only 25% of patients with sarcoid polyneuropathy.^{64,65} Hypercalcemia and sedimentation rate elevations occur in about 20% of patients or less.⁶⁵

ELECTRODIAGNOSTIC STUDIES

Most patients with multifocal sensory symptoms and neuropathic pain have normal nerve conduction studies and electromyography (EMG) because of predominant small-fiber involvement. In more severe neuropathies and polyneuropathies, evidence of axonal loss is suggested by low sensory and motor response amplitudes, relatively preserved conduction velocities, and active denervation changes. Asymmetries between sides and individual nerves are often evident. In one series, axonal degeneration predominated over demyelinating changes in 43 of 49 sarcoid neuropathy patients.⁶⁵ Proximal fibrillations on EMG, often affecting paraspinal muscles, occur in approximately 50% of cases.⁶⁵ Polyradiculopathy may show fibrillations in a myotomal pattern with normal nerve conduction studies.⁶⁶ Multifocal motor conduction block is rare and likely represents

pseudoconduction block from acute, focal axonal lesions in some cases.^{64,72}

CEREBROSPINAL FLUID

The presence of CSF lymphocytic pleocytosis or protein elevation suggests CNS or radicular disease. In patients with multifocal sensory symptoms, protein elevations occur in about 90% and pleocytosis in about 30%.⁶⁵ Glucose reduction is rare (10%).⁶⁵ A CSF ACE level may be helpful if CNS involvement is suspected, but the serum assay cannot be used because of a much lower CSF concentration.⁷³ Elevated CSF ACE levels also occur in malignant CNS tumors and bacterial meningitis, but extreme elevations may be specific for neurosarcoidosis.^{74,75}

IMAGING

Evidence of pulmonary involvement on chest radiographs is found in about 50% to 80% of patients with sarcoid neuropathy.^{59,64,65} Chest imaging, preferably computed tomography (CT), should be performed in all patients suspected of having sarcoidosis. Bilateral hilar adenopathy supports the diagnosis and should prompt tissue biopsy. A gallium scan, with 85% sensitivity, may be helpful to support the diagnosis when attempts at a tissue diagnosis are unsuccessful.⁵⁹ Magnetic resonance imaging (MRI) of the cervical or lumbosacral spine or the brachial or lumbosacral plexus may show diffuse or nodular thickening of nerves or roots with increased T2 signal.^{65,66} Meningeal enhancement and multiple white matter lesions also occur in about 40% of neurosarcoidosis patients.^{76,77}

Nerve Biopsy/Pathology

Sural or superficial peroneal sensory nerve biopsies show epineurial granulomas, perineurial inflammatory infiltrates, and asymmetric involvement of nerve fascicles and axon degeneration^{64,72} (Fig. 9-2; see also Color Fig. 9-2). In one series, approximately one-third of patients had endoneurial granulomas (largely perivascular) and inflammatory infiltrates; about 50% of patients developed a necrotizing lymphocytic vasculitis.^{64,72} On electron microscopy, both unmyelinated and

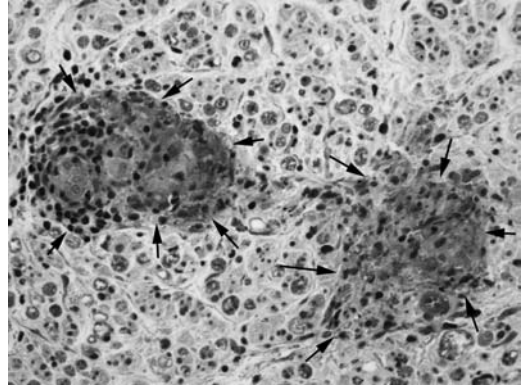


Figure 9-2. Sarcoid neuropathy. Two noncaseating granulomas composed of epithelioid histiocytes and a few adjacent small, round lymphocytes are marked with arrows and seen within a peripheral nerve fascicle. The round lymphocytes are seen at the left edge of the granuloma on the left. There is marked loss of axons within the nerve itself. Luxol fast blue. Original magnification x400. Courtesy of Dr. Karen M. Weidenheim M.D. (See Color Plate 9-2.)

myelinated fiber loss is apparent. Inflammatory infiltrates consist of CD68+ macrophages, particularly in association with granulomas, and T cells; T cells are CD4+ predominant.^{64,72}

Muscle biopsy may show granulomas, multinucleated giant cells, and necrotizing vasculitis with fibrinoid necrosis.^{64,72} In sarcoid myopathy, macrophages and CD4+ T cells are diffusely distributed; CD8+ T cells are scattered in the granulomatous infiltrate early and confined to the surrounding mantle in later stages of granuloma formation.⁷⁸ Inflammatory cells in granulomas express interleukin-1, which is thought to contribute to granuloma formation, and interleukin-2 receptor and activated human leukocyte antigen-DR (HLA-DR).^{78,79} The lack of muscle fiber atrophy and perifascicular atrophy, expression of proteases by invading macrophages, and expression of cytoskeletal proteins (i.e., desmin, dystrophin, and merosin) along the surface of granulomas, suggest a direct attack of inflammatory cells rather than compression or ischemia by granulomas.⁸⁰

Pathogenesis

Sarcoidosis is considered an inflammatory disease that is caused by a combination of still-undefined genetic and environmental factors.

Various specific polymorphisms are associated with an increased risk of disease or a modification of the disease presentation.⁸¹ Polymorphisms affect various major histocompatibility complex (MHC) molecules and cytokines, including TNF- α .⁸¹ A deficiency of CD1d-restricted natural killer cells, which protect against disorders with an increased CD4+ Th1 (cell-mediated) response, is present in the blood, lungs, and lymph nodes of patients with sarcoidosis.⁸²

Treatment, Course, and Prognosis

Pathologic confirmation of sarcoidosis can be obtained by biopsy of a variety of tissues, including lung (bronchoscopy), mediastinal nodes (mediastinoscopy), scar granulomas, lacrimal gland, muscle, or nerve. Sensory polyneuropathy or polyradiculopathy with mild, relapsing/remitting sensory symptoms may be followed for signs of progression or treated symptomatically with neuropathic pain medications. In more progressive disease, prednisone is the first-line immunosuppressive treatment.

Patients with sarcoid neuropathy frequently progress for weeks or sometimes months, plateau, and show variable improvement.⁶⁵ The rate of spontaneous remission in sarcoid neuropathy is unknown but occurs in two-thirds of patients with pulmonary disease, making it difficult to interpret the response to treatments. Most patients report complete relief of pain and sensory symptoms with corticosteroid treatment.⁶⁵ Doses of 20–60 mg daily are typically used for a couple of weeks to months, depending on disease severity. A positive response to treatment is predicted by a shorter duration of symptoms, greater disability at presentation, and a CSF pleocytosis.⁶⁵ Isolated facial neuropathy is treated with a 7- to 10-day taper of prednisone beginning with 60–80 mg daily; recovery is generally good if the patient is treated early. Intravenous solumedrol may be beneficial in more severe presentations.⁸³

Second-line treatments for neurosarcoidosis include chloroquine, hydroxychloroquine, and, in more severe, refractory disease, cyclophosphamide.^{59,84} Chloroquine and thalidomide (used for cutaneous sarcoidosis) should probably be avoided in patients with sensory neuropathies because of peripheral nerve toxicity.⁸⁵ One patient with sensory

polyneuropathy refractory to prednisone responded to intravenous immunoglobulin (IVIG), although associated arthritis did not respond to IVIG.⁸⁶

LYME DISEASE

Clinical Features

EPIDEMIOLOGY

Lyme disease (LD), or Lyme borreliosis, occurs where the causative vector-borne spirochete, *Borrelia burgdorferi* (Bb), is endemic. In the United States, endemic areas include the Northeast, the upper Midwest, and, to a lesser extent, northern California. It is also prevalent throughout much of Europe and parts of Asia (including Russia, China, and Japan).⁸⁷ Lyme disease most commonly presents in the spring and summer months, when ticks are most active, but cases are reported year round.⁸⁸ The median age of patients is 39 years, with a bimodal distribution. The highest reported incidence occurs in children 5–9 years old and in adults aged 50–59 years.⁸⁹ In 2002, 57% of the cases reported to the Centers for Disease Control (CDC) in the United States had symptom onset in June or July.

SYMPTOMS AND SIGNS

Systemic Disease

After inoculation of Bb into the skin by an infected tick, approximately 60% of patients develop the pathognomonic skin rash, erythema migrans (EM), within 3–30 days.^{88,90} The lesion is a centrifugally expanding, erythematous, annular macule or papule, often with a target appearance. Satellite lesions may appear, representing local spread of the spirochetes. Multiple EM lesions may result from hematogenous spread. Often, as EM is evolving, there are non-specific flu-like symptoms, including headache, fever, fatigue, neck stiffness, myalgias, and arthralgias.⁹¹ A flu-like syndrome in *summer months*, in Lyme endemic regions, should raise the possibility of acute LD. Within days to weeks of infection the spirochete disseminates widely, and can be isolated from blood and multiple tissues.⁸⁸ Approximately 8% of untreated patients develop cardiac

abnormalities, especially varying degrees of atrioventricular block.^{92,93} Arthritis is common, occurring in 50%–60% of untreated patients.⁹² Arthritis may be episodic or chronic, monoarticular or asymmetric oligoarticular, and typically involves large joints, especially the knee. In children, arthritis may be an isolated manifestation, and EM is a presenting feature in 90% of cases.^{94,95}

Central Nervous System

Involvement of the CNS varies and includes meningitis, mild encephalopathy, and encephalomyelitis with focal brain or spinal cord lesions.^{96–98} Meningitis is more common with early infection. Fatigue is common and often prominent.⁸⁸ Central nervous system LD in children often presents as a mild encephalopathy or meningitis; a “pseudotumor-like” syndrome more rarely occurs.⁹⁹

Peripheral Nervous System: Cranial Neuropathies

Facial nerve dysfunction is most common and occurs in 10% of patients with untreated LD.^{88,100,101} Facial palsy is usually unilateral, but bilateral presentations occur in up to one-third of patients.^{101,102} Bilateral facial palsy in endemic areas strongly suggests LD. Dysgeusia may be associated.¹⁰³ In a Lyme endemic county in New York State, it was estimated that about 25% of patients presenting with isolated facial palsies had LD.¹⁰⁴ Most of these patients (75% or more) did not have intrathecal synthesis of *Borrelia*-specific antibody.^{104,105} Patients with facial palsy due to LD who are not treated with antibiotics in the early stages of the disease are at greater risk for subsequent peripheral nervous system (PNS) and possible CNS sequelae.¹⁰⁶

Involvement of other cranial nerves, including nerves III, IV, V, VI, and VIII, may rarely occur, alone or in combination.^{107–113} There is an association of LD with papillitis but not with retrobulbar optic neuritis.¹⁰⁸

Peripheral Nervous System: Noncranial Neuropathies

The PNS is involved in 30%–50% of patients with neurologic abnormalities^{114–118} (Table 9–2). In the United States, the most

Table 9–2 Clinical Manifestations of LD Affecting the PNS

Neuropathies

Monoradiculopathy/polyradiculopathy
Brachial/lumbosacral plexopathy
Chronic, mild, sensorimotor polyneuropathy (generally symmetric)
Multiple mononeuropathies
Acute motor-predominant polyneuropathy (AIDP-like)
Carpal tunnel syndrome?
AIDP?

Cranial Neuropathies

Facial palsies (common)
Others (cranial nerves III, IV, V, VI, VIII); papillitis?

common presentations are radiculopathy (cervical, lumbosacral, or thoracic) or a distal axonal sensory polyneuropathy, which may have asymmetric features.^{119,120} Symptoms tend to develop months or more after acute infection. Of patients with LD and chronic peripheral neuropathy, about 50% have symmetric, distal, painless paresthesias and 50% have asymmetric radicular pain; asymptomatic polyneuropathy is rare.¹¹⁹ Cervical and thoracolumbosacral radicular symptoms are more common than isolated lumbar radicular symptoms.¹¹⁹ Another group of investigators found less frequent painful radiculopathy in 8% of patients.¹⁰⁴ Preceding erythema migrans (84%), arthritis (50%), and facial palsy (25%) during acute infection often suggest the diagnosis in an endemic area.¹¹⁹ Sensory loss to pin and vibration occurs predominantly in patients with a distal polyneuropathy, in a stocking-glove distribution and is less common in patients with radicular pain. Distal or segmental weakness and areflexia are rare.

We have observed a few patients with serologically confirmed LD, often subacute, with a brachial plexus neuropathy (neuralgic amyotrophy)-like presentation, who develop shoulder pain followed by scapular or other shoulder girdle muscle weakness consistent with a mononeuropathy (e.g., of the long thoracic nerve) or multiple mononeuropathies. Long thoracic neuropathy has been reported in Europe.¹²¹ Phrenic nerve palsy may also occur.¹²² It is possible that some instances of Lyme “radiculitis” have a

peripheral nerve, rather than root, localization, considering the multifocal axonal pathology and electrophysiologic findings (see the discussion of electrodiagnostic findings below).

The association of carpal tunnel syndrome and LD is unclear. One group showed a frequency of carpal tunnel syndrome as high as 25%, but this was not confirmed by other investigators.^{104,119,123,124} There are rare reports of AIDP with LD, but the relationship is unclear.¹⁰⁴

In the United States, an acute, predominantly motor, polyradiculoneuropathy with cranial neuropathy (bilateral facial palsies) and lymphocytic meningitis occurs more rarely. These cases may resemble AIDP, and although the electrophysiology is predominantly axonal, some cases have equivocal demyelinating electrophysiologic changes.^{125–127} Myositis, which may be focal or resemble polymyositis, is an infrequent feature of LD.^{128,129} Both the rare acute and more common chronic polyneuropathies in LD have preceding systemic features suggestive of the disease such as flu-like symptoms, EM, or oligoarticular arthritis.

Laboratory Studies

BLOOD TESTS

Nonspecific abnormalities include mild elevation of the erythrocyte sedimentation rate, serum IgM, cryoglobulins, circulating immune complexes, and abnormal liver function tests.⁸⁸ Specific diagnosis by culture or histology is limited. High-volume blood and skin biopsy cultures may show a positive result in about 50% of patients with EM, but the mean recovery time is more than 3 weeks and the sensitivity is far lower in patients with chronic symptoms.¹³⁰ Screening serology by indirect immunofluorescent assay (IFA) or enzyme-linked immunosorbent assay (ELISA; whole sonicated organisms) demonstrates antibodies to Bb in about 90% of patients with LD symptoms of greater than 1-month duration.¹³¹ However, the ELISA has limited specificity, particularly in controls with syphilis or oral infections.¹³¹ A false negative test may occur in patients with acute infection (<4–6 weeks) or with early, inadequate antibiotic treatment. A positive ELISA finding should be confirmed with an immunoblot for LD. The CDC criteria

attempt to optimize the discriminatory ability of the immunoblot and require at least 2 of the 3 IgM bands in early disease (23, 39, and 41 kDa) and at least 5 of the 10 most frequent IgG bands after the first month of infection (18, 23, 28 30, 39, 41, 45, 60, 66, and 93 kDa).¹³² The 23-kDa (OspC) and 41-kDa (flagellar) IgM antibodies are frequent early on and remain detectable for long periods; IgM to antigens 39, 58, 60, 66, and 93 kDa is usually positive only within the first month and is therefore more indicative of acute infection.

Detection of Bb DNA by PCR in serum has little diagnostic utility in neurologic LD, even in acute infection, because of its low sensitivity.^{130,133} This likely reflects the small number of spirochetes and spirochetal DNA in blood in early and late neurologic LD. The sensitivity of PCR is considerably higher in skin (92%) and synovial fluid (up to >90%) in untreated disease compared to plasma (28%).^{130,134,135} A positive PCR (from any fluid) in seronegative patients with late manifestations of LD usually represents a false positive. Additionally, PCR assays are poorly standardized.

ELECTRODIAGNOSTIC STUDIES

Nerve conduction studies and EMG show focal or multifocal, predominantly axonal abnormalities in patterns suggesting monoradiculopathy, polyradiculopathy, polyneuropathy, multiple mononeuropathies, mononeuropathy, or plexopathy.^{97,104,119,120} Electrophysiologic abnormalities are often mild but are typically more widespread than the clinical features.¹⁰⁴ Mildly prolonged distal motor, sensory, and F-wave latencies are frequent, with relative sparing of sural response amplitudes.¹¹⁹ Nerve conduction abnormalities are more frequent in patients with distal paresthesias than in those with radiculopathy.¹¹⁹ Focal demyelinating changes are rare.^{104,119,127} The association of LD with carpal tunnel syndrome is unclear.^{119,123,124} Patients with LD and carpal tunnel syndrome have systemic features of LD.¹²³

CEREBROSPINAL FLUID

In patients with meningitis, or occasionally encephalomyelitis, there is a moderate

lymphocytic pleocytosis and elevated protein.^{101,116} Glucose is usually normal. Patients with peripheral neuropathies or facial palsies may have normal CSF. Fewer than 10% of patients with Lyme meningitis have positive CSF cultures for Bb.¹³⁶ The presence of intrathecal synthesis of Bb IgG or IgM antibodies (antibody index) strongly suggests active CNS infection, occurring in about 66% of patients with CNS involvement overall and in 85% of patients with meningitis or encephalomyelitis.^{96,137} The frequency of intrathecal synthesis of Bb antibody in PNS disease is much lower, occurring in about 8% of patients.⁹⁶ Detection of *Borrelia*-specific DNA by PCR in the CSF of patients with neurologic LD has low sensitivity (5%–50%).^{133,138,139,140} The sensitivity of CSF PCR is higher in patients with acute neuroborreliosis.^{139,141} Specificity is high, with negative results in 97%–100% of controls.^{133,138–141}

IMAGING

Brain MRI scans are abnormal in about 40% of patients with encephalopathy and evidence of CNS *Borrelia* infection.⁹⁶ Small areas of increased signal on proton density and T2-weighted images in the subcortical white matter are characteristic. Rare myelitis-like lesions are reported in the spinal cord. Gadolinium enhancement of the meninges, cranial nerves, and cervical roots may be observed.^{142,143} The MRI scans are characteristically normal in patients with polyneuropathy.

Nerve Biopsy/Pathology

Pathologic studies of LD are rare. Sensory nerve biopsies show infiltration of epineurial vessels and endoneurial capillaries with lymphocytes, macrophages, and plasma cells, degeneration of myelinated axons, and no vessel wall necrosis.^{115,144} Perineurial thickening and neovascularization are more common in *Borrelia*-associated neuropathy than in idiopathic (and possibly vasculitic) axonal polyneuropathies.¹⁴⁵ Small unmyelinated fibers are unaffected; segmental demyelination on teased fiber preparations is rare.¹²⁰ Immunofluorescent staining for Bb is absent, with occasional positive staining for IgM and

C3.¹²⁰ Perineurial C5b-9 deposition and T-cell infiltrates are more common in *Borrelia*-associated neuropathy than in axonal polyneuropathies.¹⁴⁵ Polymerase chain reaction detected Bb flagellin DNA in homogenized nerve sections.¹⁴⁶

Rhesus monkeys with chronic Bb infection develop an axonal mononeuropathy multiplex that improves after antibiotic treatment, resembling human disease.¹⁴⁷ The pathologic sural nerve findings are also similar, with multifocal axonal degeneration, occasional perivascular inflammatory cell infiltrates, lack of vessel wall necrosis, and absent spirochetes. Dogs bitten by infected ticks also show perivascular inflammatory cells.¹⁴⁸ In nonhuman primates, T cells and plasma cells are more prominent in nerve roots and dorsal root ganglia than in the spinal cord; spirochetal DNA is also evident by PCR.¹⁴⁹

Pathogenesis

It remains unclear whether direct spirochetal infection or the resulting immune response is primarily responsible for the peripheral nerve manifestations of the disease, although the frequent clinical improvement with antibiotic treatment alone suggests that active infection is necessary to cause tissue damage. However, the paucity of observed spirochetes pathologically, frequent inflammatory cell infiltrates, the binding of Bb anti-flagellin monoclonal antibodies to axonal cytoplasm, and the development of anti-ganglioside antibodies in animals and patients with LD suggest that polyneuropathy and radiculopathy may be immune-mediated.¹¹²

Treatment, Course, and Prognosis

Attached ticks, observed in as few as 50% of adults with LD, should be removed immediately with a fine-tipped forceps if available.^{112,150} Any embedded tick mouth parts may be left in the skin with application of a disinfectant, since the risk of LD is not increased. Tick bite prophylaxis against LD with a single 200-mg dose of oral doxycycline is indicated if the bite occurred in an LD-endemic region, the tick is *Ixodes scapularis* and is engorged or attached for ≥ 36 hours,

prophylaxis can be given within ≤ 72 hours of tick removal, and there is no contraindication to doxycycline.¹⁵⁰ For early LD with erythema migrans and no neurologic or cardiac (heart block) manifestations, doxycycline 100 mg bid, amoxicillin 500 mg tid, or cefuroxime axetil 500 mg bid for 14–21 days is recommended.¹⁵⁰ Doxycycline is contraindicated in children below 8 years of age and in women during lactation.

In early neurologic syndromes such as meningitis, radiculopathy, or facial palsy, ceftriaxone 2 g intravenously (50–75 mg/kg in children) per day for 14 days is suggested (range, 10–28 days).¹⁵⁰ Alternative treatments include cefotaxime, 2 g every 8 hours, or penicillin G, 3–4 million units every 4 hours. Doxycycline 100–200 mg po bid for 10–28 days may be a reasonable alternative for β -lactam antibiotic allergy or intolerance, particularly for PNS disease.^{112,150} For late neurologic manifestations of LD, ceftriaxone 2 g intravenously daily for 2–4 weeks is suggested. Cefotaxime 2 g every 8 hours or penicillin G 3–4 million units every 4 hours for 2–4 weeks are alternatives. A Jarisch-Herxheimer reaction may occur in 10%–20% of cases.¹¹⁴

Although there is little data to suggest that a 4-week course of antibiotics is more efficacious than a 2-week course, 3 to 4 weeks of antibiotic treatment is routinely administered; this is done to prevent relapses based on anecdotal observations.¹¹² Occasionally, treatment failures occur, as suggested by recurrent neurologic and systemic symptoms and signs, warranting an additional course of antibiotics. Recurrent or persistent symptoms may result from true treatment failure, reinfection, irreversible tissue damage, or possibly an associated immunologic disorder. Serologic testing is often not useful in this setting, as Lyme titers may remain positive years after effective treatment. Persistent flu-like or encephalomyelitis symptoms may result from *erlichiosis* or *babesiosis* coinfection; these infections are resistant to ceftriaxone.

Recovery from neurologic disease with antibiotic treatment is generally satisfactory and gradual over weeks to months.¹¹² In neuropathies, a greater degree of initial axonal degeneration is associated with a more prolonged and incomplete recovery. Facial palsy may resolve even without antibiotic treatment.^{88,101} Persistent, nonspecific symptoms after a

complete course of treatment, such as fatigue, myalgias, and subjective memory and cognitive difficulties (often attentional), occur with sufficient frequency to raise the possibility of some postinfectious inflammatory disorder (“post-Lyme syndrome”).¹¹² However, several studies have shown that additional prolonged courses of antibiotics do not help this disorder, making persistent infection an unlikely cause.^{151–154} Psychiatric illness may play a role in some cases. Symptomatic treatment of post-Lyme syndrome is recommended.¹⁵⁵

The U.S. Lyme vaccine was taken off the market because of financial concerns. It appeared to offer protection to only 76% of subjects after three injections, and because of waning immunity, booster injections were considered necessary every 1 to 3 years.¹⁵⁶

HUMAN IMMUNODEFICIENCY VIRUS (HIV)–RELATED PERIPHERAL NEUROPATHIES

Clinical Features

EPIDEMIOLOGY

Peripheral nervous system disease is a frequent complication of infection with HIV. The 1-year incidence of symptomatic distal sensory polyneuropathy (DSP) in the pre-HAART (highly active antiretroviral therapy) era was 36%, and in the post-HAART era it was 21%.^{157,158} In the pre-HAART era, DSP was associated with a history of acquired immunodeficiency syndrome (AIDS) and a lower CD4 count.¹⁵⁷ In the post-HAART era, the association with a lower CD4 count disappeared, and DSP has more recently been associated with stavudine (d4T) and didanosine (ddI) exposure, baseline CSF macrophage colony-stimulating factor, drug use (including alcohol and opiates), and distal epidermal denervation.^{158–161} A very low CD4 nadir may predict the neurologic complications of polyneuropathy and dementia.¹⁶² Polyneuropathy also occurs in about 14%–34% of mostly older children with HIV infection.^{163,164} Nerve biopsy findings of polyneuropathy in patients with AIDS are present in nearly 100% of patients. Intravenous drug use may be a risk factor for polyneuropathy independent of HIV infection.¹⁶⁵

SYMPTOMS AND SIGNS

An HIV infection may cause dysfunction at most levels of the nervous system. Polyneuropathy is a particularly frequent PNS manifestation (Table 9–3). Other PNS manifestations include motor neuron disease and inflammatory myopathy. Recognition of HIV-related peripheral nerve disease is important since such disease may (1) herald HIV infection (as in AIDP and motor neuron disease), (2) indicate a more severe stage of HIV infection, (3) be potentially treatable, or (4) predispose to toxic neuropathies as an adverse effect of nucleoside therapy.

Distal Symmetric Sensorimotor Polyneuropathy

Early studies of HIV patients suggested that the type of polyneuropathy varies based on the patient's immune status, viral load, and stage of disease. However, in the post-HAART era this is less clear, possibly because there are far fewer patients with advanced immunodeficiency. The HIV-related neuropathies include a distal, sensory greater than motor polyneuropathy, AIDP, CIDP, cranial neuropathies, mononeuropathy multiplex, progressive polyradiculopathy, sensory neuronopathy, vasculitic polyneuropathy, and autonomic neuropathy.^{166–174} By far the most common polyneuropathy is a distal sensory polyneuropathy (DSP) with axonal features. Burning or dysesthetic pain in the soles of both feet, usually symmetric but occasionally starting in one foot, is the most common presenting symptom.¹⁶⁶ Symptoms of allodynia and hyperpathia are present, and patients often complain of a sensation resembling a pebble stuck in their shoe or avoid wearing shoes. Paresthesias are also frequent and often involve the entire feet. Complaints of distal leg weakness, such as problems moving the toes, and hand symptoms are unusual. On examination, the most common signs, in descending frequency, are distal stocking or stocking-glove pin or vibratory loss, reduced or absent ankle jerks, and foot muscle weakness.¹⁶⁶ Arm reflexes are usually normal. Trophic changes such as hair loss, thinning of the skin, and dependent rubor may be present in the legs. A minority of patients have associated myelopathic signs such as knee hyperreflexia and Babinski responses. In addition,

DSP occurs in children with HIV infection, with milder features and less neuropathic pain.¹⁶⁴

Toxic Polyneuropathy from Antiretroviral Drugs

A distal, symmetric, sensory greater than motor polyneuropathy caused by certain antiretroviral drugs may be difficult to differentiate from DSP due to HIV infection. Antiretroviral drugs that are neurotoxic in a dose-dependent manner include ddI, zalcitabine (ddC, discontinued in the United States in December 2006), and stavudine.^{169,175,176} The mean ddI dose associated with polyneuropathy is 27 mg/kg; a dose of <12.5 mg/kg/day is recommended to prevent the development of polyneuropathy.^{176,177} The risk of stavudine-induced polyneuropathy increases with doses >0.5 mg/kg/day.¹⁷⁶

Clinical symptoms and signs mimic those of DSP from HIV infection. Many patients have subclinical polyneuropathy, which is exacerbated by one of the above drugs. The temporal relation of HAART initiation to the onset of neuropathic symptoms, namely, foot dysesthesias and numbness, provides the best evidence that a given drug is causative in an individual patient. Improvement of sensory symptoms after stopping the drug may be delayed for months. There is less clear evidence that the protease inhibitors indinavir, saquinavir, and ritonavir increase the risk of DSP.^{169,178}

Inflammatory Demyelinating Polyneuropathies

Both AIDP and CIDP occur in patients with HIV infection, although it is unclear if the frequency is higher than in the general population. Symptoms and signs are similar to those seen in patients without HIV infection, except that lymphadenopathy may suggest HIV positivity. In the pre-HAART era, both AIDP and CIDP were considered more common early in the course of infection.¹⁷⁹ However, this notion has been challenged post-HAART.¹⁷⁰ Another distinguishing feature is that patients with HIV infection occasionally have a CSF lymphocytosis, although this feature is often absent.¹⁷⁰ Both AIDP and CIDP are generally not seen in the setting of severe immunosuppression (CD4 <50).¹⁷⁰ Recurrent weakness (relapses)

Table 9–3 **Major Neuropathic Syndromes in HIV Disease**

Diagnosis	Disease Stage	Initial Symptoms	Neurologic Signs	Diagnostic Studies	Therapy
Distal Sensory Polyneuropathy	Late	Distal numbness Distal paresthesias Burning pain	Stocking-glove sensory loss Absent ankle jerks	EMG: distal axonopathy	Neurotoxin withdrawal, analgesics, anticonvulsants, antidepressants
AIDP/CIDP	Early >> late	Quadriparesis Acral paresthesia	Quadriparesis Diffuse hyporeflexia Mild sensory loss	CSF: ↑wbc, ↑↑ protein EMG: demyelinating	Early: IVIG, plasma exchange Late: gancyclovir, foscarnet, cidofovir
Mononeuropathy Multiplex	Early (limited) Late (progressive)	Facial weakness Foot or wrist drop Focal pain	Multifocal cranial/ peripheral nerve weakness/ sensory loss	EMG: multifocal axonal Nerve: inflammatory cells, vasculitis, CMV inclusions	Early: none or prednisone Late: gancyclovir, foscarnet, cidofovir
Progressive Polyradiculopathy	Late	Paraparesis Paresthesias Bladder dysfunction	Flaccid paraparesis Saddle anesthesia Leg hyporeflexia	CSF: ↑wbc (PMNs), ↑↑ protein, CMV PCR/Cx EMG: LE/ps denervation	Gancyclovir, foscarnet, cidofovir
Diffuse Inflammatory Lymphocytosis Syndrome	Late > early	Paresthesias Burning pain Sicca syndrome	Sensory loss Mild weakness Symmetric > asymmetric	EMG: axonal > demyelinating Nerve: CD8 T cells	Prednisone, zidovudine
ALS-Like Syndrome	Early > late	Mono- or quadriparesis Dysarthria	Limb atrophy/fascic Tongue atrophy/fascic Hyperreflexia	EMG: generalized fibs Pathology: motor neuron loss	HAART: Indinavir, zidovudine, lamivudine, nefinavir

AIDP: acute inflammatory demyelinating polyneuropathy; CIDP: chronic inflammatory demyelinating polyneuropathy; CMV: cytomegalovirus; Cx: culture; fascic: fasciculations; fibs: fibrillations; IVIG: intravenous immunoglobulin; LE: lower extremity; PCR: polymerase chain reaction; PMNs: polymorphonuclear leukocytes; ps: paraspinal; wbc: white blood cells. From Simpson¹⁷⁶ with permission.

may be more frequent in inflammatory demyelinating polyneuropathies with HIV infection.¹⁷⁰

Guillain-Barré syndrome may occur within several weeks of initiating HAART, which is thought to relate to immune reconstitution.^{180,181} Immune reconstitution is associated with the appearance of autoimmune disease after starting HAART, associated with rises in the CD4 counts and reduced viral loads. It is thought to relate to a specific immune response against an opportunistic infection or increased susceptibility to immune dysregulation.^{182,183}

Progressive Polyradiculopathy

An acute or subacute polyradiculopathy occurs in patients with low CD4 counts (usually <50), usually in association with CMV infection.^{171,172} Patients present with a progressive cauda equina syndrome characterized by asymmetric, ascending flaccid paraparesis, early sacral numbness, bladder retention, and lower back and radicular pain.^{171,172} Motor and sensory deficits begin in caudal lumbosacral segments and ascend with marked proximal and distal leg weakness, impairing ambulation. However, there may also be involvement of thoracic segments and, in advanced cases, of the arms and cranial nerves. On examination, the legs are found to be hypo- or areflexic, there is small- and large-fiber sensory loss in the legs, and a thoracic level to pin may be evident.¹⁷¹ Cytomegalovirus retinitis may be evident prior to or concurrent with polyradicular symptoms. Corticospinal tract signs are generally absent. Other causes of polyradiculopathy include herpes zoster and lymphomatous meningitis, and possibly tuberculosis and syphilis.^{169,172}

Mononeuropathies (Cranial and Peripheral) and Mononeuropathy Multiplex

Isolated cranial neuropathies are relatively rare. Facial palsy may occur alone, typically at the time of seroconversion.¹⁸⁴ Trigeminal and laryngeal neuropathies occur more rarely, frequently as part of a mononeuropathy multiplex. Cranial nerve involvement should prompt CSF examination to assess for opportunistic infection and lymphomatous

meningitis. Mononeuropathies occur in about 3% of HIV-positive patients.¹⁸⁵ There are two forms of mononeuropathy multiplex associated with HIV infection. One is mild, predominantly sensory, often initially presenting as a mononeuropathy, and self-limited. The second is more severe and progressive, with multifocal weakness and sensory symptoms, often associated with CMV infection.^{186–188} A CD4 count <50 predicts a more severe course and possible CMV infection.¹⁸⁹ Facial, recurrent laryngeal, sciatic nerve branch, and ulnar and radial neuropathies have been reported.^{189,190} More severe cases are distinguished from CMV lumbosacral polyradiculopathy by greater arm involvement or onset in the arms. More confluent sensorimotor symptoms may develop in the legs as the disease progresses.

Vasculitis

Vasculitic polyneuropathy may occur in HIV infection without associated disease or in the setting of CMV infection (see the discussion of mononeuropathy multiplex above). Vasculitis occurs in only 0.3%–1.0% of patients with AIDS.¹⁸⁵ A frequent clue is asymmetry in sensory symptoms or signs, particularly in the legs, and asymmetric ankle jerks. Sensory and motor response amplitudes in the legs may also be asymmetric. More severe cases present as a mononeuropathy multiplex and may be associated with CMV infection or herpes zoster.¹⁸⁷ Coinfection with hepatitis C virus may be associated with cryoglobulinemia and vasculitic polyneuropathy, as seen in cryoglobulinemia.^{191,192} Polyneuropathy in this setting often presents with asymmetric, distal sensory symptoms and signs in the legs, mild, often unilateral weakness of peroneal muscles, and depressed, asymmetric ankle jerks. Rarely, vasculitis in HIV infection may mimic DSP.^{168,193,194}

Dorsal Root Ganglionitis

There is a case report of sensory neuronopathy (dorsal root ganglionitis) in HIV infection resulting in an ataxic neuropathy with prominent proprioceptive sensory loss. The CSF protein was normal, and sural nerve biopsy showed degeneration of large myelinated fibers without inflammatory infiltrates. Autopsy showed inflammatory infiltrates and

loss of sensory neurons in the dorsal root ganglia.^{166,195} Patients with HIV without clinical evidence of peripheral nerve disease, particularly those with AIDS, may show a sensory ganglionitis at autopsy with HIV-1 gp41 envelope protein expression in intraganglionic macrophages.¹⁹⁶ Human immunodeficiency virus DNA and RNA sequences are present in DRG satellite cells, mononuclear cells, and possibly neurons in patients with and without polyneuropathy.^{197,198}

Diffuse Infiltrative Lymphocytosis Syndrome

Diffuse infiltrative lymphocytosis syndrome (DILS) is the result of a polyclonal increase in CD8 cells with infiltration of salivary glands, lungs, kidneys, gastrointestinal tract, and peripheral nerves. Infiltration of the salivary glands commonly causes sicca syndrome. Peripheral neuropathy presents as an acute or subacute, painful, symmetrical (but occasionally asymmetrical), sensory greater than motor, axonal polyneuropathy.¹⁹⁹ Patients typically have higher CD4 counts and fewer opportunistic infections. Sural nerve biopsies show angiocentric CD8 infiltrates with abundant expression of HIV p24 protein in macrophages, suggesting that HIV protein expression may incite clonal expansion of CD8 cells.¹⁹⁹ Aseptic meningitis, facial palsies (uni- or bilateral), and a motor neuropathy may also occur.^{200,201}

Motor Neuron Disease

Rare patients with HIV infection develop an amyotrophic lateral sclerosis (ALS)-like illness, which may be self-limited or progressive. It is important to recognize, since it may improve or remit completely with antiretroviral therapy.^{202,203} It can be a presenting symptom of HIV infection and may differ from classical ALS by the presence of lymphadenopathy and a CSF pleocytosis.²⁰³

Laboratory Studies

BLOOD TESTS

Anemia is evident in HIV infection in 1.3%–95% of patients, depending on the severity of disease.²⁰⁴ In the HAART era, symptomatic

DSP correlates less clearly with reduced CD4 counts, except possibly in older patients.^{157,158,160,205} The ELISA, which detects either HIV-1 or HIV-2 antibodies, is the standard screening test for HIV infection. The Western blot is the most commonly used confirmatory test. As antibodies to HIV take 4–8 weeks to develop, patients suspected of having recent exposure should have the ELISA repeated in 3 months or testing for HIV-1 p24 antigen on HIV RNA may be performed. In DSP, it is reasonable to screen for associated conditions by testing blood glucose and blood urea nitrogen (BUN)/creatinine, as well as performing liver function tests and determining the vitamin B₁₂ level.

Elevated lactate levels may predict polyneuropathy associated with nucleoside analogues.²⁰⁶ If vasculitis is suspected by exam asymmetries or systemic symptoms, an erythrocyte sedimentation rate (ESR), hepatitis C virus (HCV) titers, cryoglobulins, rheumatoid factor (RF), antinuclear antibody (ANA), immunofixation, and CMV titers should be sent to screen for associated conditions; progressive cases require sensory nerve and muscle biopsy.

ELECTRODIAGNOSTIC STUDIES

Distal sensory polyneuropathy is characterized by reduced distal, sensory more than motor, response amplitudes and late response abnormalities typical of a distal axonopathy.²⁰⁷ There may be distal active denervation changes on EMG. The findings in toxic polyneuropathy from antiretroviral drugs are identical. Nerve conduction changes consistent with DSP occur in about 25% of children, most of whom are older; isolated median nerve entrapment may also occur in children.¹⁶³

The electrophysiology in HIV patients with AIDP or CIDP resembles that found in patients without HIV infection (see Chapters 6 and 7). Lumbosacral polyradiculopathy typically shows low motor response amplitudes in both legs, which may be asymmetric, late response abnormalities, occasional low sensory response amplitudes (from associated polyneuropathy), and prominent fibrillation potentials throughout the muscles of both legs and paraspinal muscles.^{171,172}

The characteristic findings in mononeuropathy multiplex or vasculitic neuropathies are either reduced sensory and motor amplitudes

in the distribution of two or more nerves or asymmetries in response amplitudes between right and left limbs or between nerves.^{185,186} However, occasionally, the findings are more symmetric, resembling those of DSP. Needle EMG may show a greater degree of fibrillation potentials in proximal muscles in confluent cases compared to DSP and in muscles of individual nerves in more focal cases.

In dorsal root ganglionitis, sensory responses are globally absent or reduced with sparing of motor conduction. In motor neuron disease cases, EMG shows generalized fibrillation and fasciculation potentials as in classical ALS, but there may be normal rather than long duration motor potentials, reflecting a more acute process in HIV.²⁰³ Nerve conduction studies in DILS are usually consistent with a distal, symmetric, axonal polyneuropathy, but occasional cases are demyelinating or asymmetric.¹⁹⁹

CEREBROSPINAL FLUID

In progressive polyradiculopathy due to CMV, there is marked CSF pleocytosis with a predominance of polymorphonuclear cells (about 70%) and mean protein elevations >200 mg/dL.^{171,172} Cytomegalovirus infection of the CSF can be detected by PCR of CMV DNA or can be confirmed by culture.^{169,171,172} Other causes of polyradiculopathy, such as lymphoma, varicella, syphilis, and tuberculosis, should be excluded.¹⁶⁹ In mononeuropathy multiplex with CMV infection, CSF protein is typically normal.¹⁸⁹

In DILS, a mild pleocytosis (<40 lymphocytes) and a mild to moderate protein elevation (<227 mg/dL) are frequent.¹⁹⁹ In HIV-infected individuals without symptomatic polyneuropathy, the CSF may show a mild lymphocytic pleocytosis (<20 cells) and mild protein elevation (<60 mg/dL).²⁰⁸

In inflammatory demyelinating polyneuropathy, a CSF pleocytosis of 10–50 cells should raise the possibility of HIV infection.²⁰⁹ In AIDP with HIV, the CSF protein range was 72–388 mg/dL in one series.¹⁷⁰

Nerve Biopsy/Pathology

Sural nerve and autopsy studies in DSP show distally accentuated axonal degeneration

suggesting a dying-back pattern, loss of unmyelinated and occasionally large myelinated fibers, and a variable degree of macrophage or CD8+ T-cell infiltration of peripheral nerves and dorsal root ganglia.^{210–213} Some studies have revealed segmental demyelination even in DSP cases.²¹³

On EM, axonal loss predominates. There are plasmacytoid cells in the endoneurium, tubuloreticular inclusions in endothelial cells, and thickened basement membranes around small blood vessels and Schwann cells.^{212,214} Epidermal skin biopsy specimens show reduced fiber density, increased fiber varicosities (swellings), and fiber fragmentation suggesting the presence of a small-fiber sensory polyneuropathy.^{210,215,216} Epidermal fiber loss can be used to monitor disease progression and can predict symptomatic DSP.²¹⁶

There is expression of monocyte-macrophage markers and upregulation of histocompatibility complex antigens on endothelial cells, mononuclear inflammatory cells, occasional Schwann cells, and nerve fibers.^{211,213} Occasionally, HIV has been cultured from sural nerve, and HIV mRNA and viral proteins have been identified in endoneurial mononuclear cells.^{211,213} However, HIV antigen has not been identified in nerve fibers or Schwann cells by immunohistochemical staining.²¹³ Dorsal root ganglia may show ganglion cell loss, fibrosis, and variable inflammatory cells.²¹³

Vasculitic neuropathy and mononeuropathy multiplex in HIV infection show findings typical of vasculitis, with fibrinoid necrosis of epineurial arterioles, perivascular inflammatory cells, and focal loss of nerve fascicles.¹⁶⁹ In severe cases, CMV inclusions in inflammatory cells are occasionally evident in peripheral nerve by immunohistochemistry.^{187,189} In progressive polyradiculopathy, the predominant finding at autopsy is acute and chronic inflammation in the ventral and dorsal roots, worse caudally.¹⁷¹ In more severe cases, there is necrosis and hemorrhage of the cauda equina. Immunocytochemically positive inclusion-bearing cells for CMV are present in areas of inflammation. In DILS, nerve biopsy shows an angiocentric pattern of CD8+ T cells in the endo- and epineurium and loss of myelinated fibers, without fibrinoid necrosis or fascicular fiber loss; EM additionally shows loss of unmyelinated fibers without viral particles.¹⁹⁹

Pathogenesis

The findings of upregulation of histocompatibility complex and monocyte-macrophage markers associated with HIV-related proteins and RNA in endoneurial cells suggest that HIV enters the PNS through macrophage/monocytes, and macrophage activation may play a role in polyneuropathy development.²¹¹ In rodent dorsal root ganglia cultures, the HIV viral envelope protein gp120 causes axonal degeneration and neuronal apoptosis.²¹⁷ Local axonal toxicity may be the result of caspase pathway activation and is dependent on gp120 binding to axonal chemokine receptors; Schwann cell-dependent apoptosis at the cell body level may also occur.²¹⁷

A cat model of HIV polyneuropathy, induced by feline immunodeficiency virus infection of neonatal cats, is characterized by loss of epidermal nerve fibers and macrophage infiltration of dorsal root ganglia.²¹⁸ A rodent model, induced by the administration of didanosine to transgenic mice expressing gp120, is characterized by degeneration of distal, unmyelinated, sensory axons.²¹⁹

Neurotoxic dideoxynucleoside analogues show direct mitochondrial toxicity in vitro, probably independent of DNA polymerase- γ inhibition and caspase cascade activation.^{220,221} Dorsal root ganglia cultures exposed to indinavir show neuronal atrophy, neurite process loss, and macrophage toxicity (apoptosis).¹⁷⁸

Treatment

Since the introduction of HAART has altered the natural history and risk factors of polyneuropathy in HIV infection, it is probable that HAART slows disease progression.^{158,161} While there is no known disease-modifying treatment for HIV patients with DSP, it is reasonable to treat HIV infection with HAART when dictated by the viral load, CD4 counts, or the presence of opportunistic infections. Nerve growth factor and peptide T failed to improve measures of nerve function in DSP.^{222,223} Nerve growth factor and prosap- tide, a polypeptide analgesic, may reduce neuropathic pain, but neither is used clinically.^{169,224} Neurotoxic drugs such as

didanosine and stavudine should be avoided if possible. If HIV infection is well controlled with one of these neurotoxic drugs, the decision to replace the drug with another agent will depend on the severity of the polyneuropathy and the patient's tolerance of other antiretroviral agents. Vitamin deficiencies (thiamine, vitamin B₁₂) should be screened for and treated.

Neuropathic pain may be treated with gabapentin, pregabalin, tricyclic antidepressants, duloxetine, tramadol, or lamotrigine. Lamotrigine was efficacious in HIV patients with DSP who were on neurotoxic antiretroviral medications in a placebo-controlled trial.²²⁵ Lidocaine 5% gel, memantine, mexiletene, and amitriptyline were ineffective in treating neuropathic pain in DSP associated with HIV infection.^{226–228} Narcotics are useful in refractory patients.

Progressive polyradiculopathy and severe mononeuropathy multiplex due to CMV infection should be treated urgently with gancyclovir, considering the high morbidity and mortality.¹⁷¹ In cases of CMV resistance (progression >1 week after gancyclovir initiation) or those that develop during gancyclovir treatment (i.e., for CMV retinitis), foscarnet may be added.¹⁷² In mononeuropathy multiplex associated with vasculitis, high-dose corticosteroids are used. In milder cases of mononeuropathy multiplex or mononeuropathies, a short course of oral prednisone may be tried, particularly in the setting of weakness. DILS may respond to zidovudine or corticosteroids.¹⁹⁹ In AIDP and CIDP, IVIG may be preferable to prednisone, since there is less risk of infection with IVIG. However, controlled data are lacking.

Amyotrophic lateral sclerosis in HIV infection should be treated with HAART to determine if the motor neuron disease is a reversible form. Supportive measures used to treat patients with classic ALS may also be used, including noninvasive positive pressure ventilation (NIPPV), gastrostomy tubes, occupational therapy, physical therapy, and pharmacologic treatment of depression, sialorrhea, emotional lability, spasticity, and cramps.

Course and Prognosis

It is unclear if treatment with HAART to lower the viral load is beneficial in DSP, although this was suggested by a pilot study.²²⁹ The institution

of HAART has led to fewer patients with HIV infection and AIDS and a less apparent association of reduced CD4 counts and high viral loads with polyneuropathy. Many patients with HIV-associated DSP have normal CD4 counts. Most patients with asymptomatic polyneuropathy develop symptomatic DSP.²³⁰ Neuropathic pain is typically the most disabling symptom. Although pain can usually be controlled with analgesic medication, it may be refractory.

Cytomegalovirus polyradiculopathy has a high mortality that approaches 100% when not treated with gancyclovir or if treatment is delayed >48 hours after admission.^{171,172} With gancyclovir treatment the majority of patients stabilize within 2 weeks.¹⁷² Slow improvement in leg strength is characteristic in patients who survive for more than 3 months. However, in one series, only 1 of 14 patients regained independent ambulation with treatment.¹⁷² Mononeuropathy multiplex associated with CMV infection may have a poor prognosis, with generalized weakness and high mortality that approaches that of progressive polyradiculopathy, particularly when CD4 counts are <50.¹⁸⁹ Mild cases of mononeuropathies and mononeuropathy multiplex are self-limited, typically resolving over several weeks.

The course of AIDP and CIDP in HIV infection resembles that in patients without HIV. With treatment, DILS resolves completely in two-third of patients and partially in about 17% of patients.¹⁹⁹ Despite CD8+ T-cell proliferation in DILS, there is a propensity to develop B-cell lymphomas.

In the authors' experience, patients with HIV and motor neuron disease may have a progressive fatal course similar to that of classic ALS or they may rarely have a remarkable, reversible illness with complete recovery from bulbar dysfunction and quadriplegia over a several-month period following HAART.²⁰³

CRYOGLOBULINEMIA AND HEPATITIS C

Clinical Features

EPIDEMIOLOGY

In patients with hepatitis C infection, clinical signs of polyneuropathy occur in about 11%

and electrophysiologic signs in 15%.²³¹ In one study, polyneuropathy occurred in 18 of 40 hepatitis C patients with cryoglobulinemia and in 1 of 11 patients without cryoglobulinemia.²³² However, in another study, there was only a nonsignificant trend toward a greater frequency of polyneuropathy in patients with (21%) compared to those without (13%) cryoglobulinemia; increased age was an independent predictor of polyneuropathy.²³¹ The presence of cryoglobulinemia predicts the development of necrotizing arteritis.²³³ A female predominance in patients with cryoglobulinemia and hepatitis C has been shown in some^{233,234} but not other studies.²³² The mean age of patients with hepatitis C with cryoglobulinemia is 60 years.^{232,234}

SYMPTOMS AND SIGNS

Monoclonal cryoglobulins (Type 1, often IgM) are usually associated with hematologic malignancies such as lymphoma, multiple myeloma, and Waldenström macroglobulinemia. Essential mixed cryoglobulinemia is polyclonal with (Type 2) or without (Type 3) a monoclonal component and is associated with hepatitis C infection in about 80% of patients. In patients with hepatitis C virus infection, cryoglobulinemia and polyneuropathy, distal paresthesias, particularly in the legs, are the most common presenting complaints, occurring in two-thirds of patients.²³⁴ Asymmetric presentations and multiple mononeuropathies with sensory loss and weakness in individual nerve distributions also occur and raise the possibility of a vasculitic polyneuropathy. Burning dysesthesias and sharp pain in the feet also occur in about 40% of patients, often in those with less severe disease.^{234,235} Less common features include sensory gait ataxia in 10%–35% and cranial neuropathies in <10% of patients.^{233,234} On examination, distal, asymmetric large- and small-fiber sensory loss and mild, asymmetric weakness of toe extensors are common findings. Weakness may be multifocal or involve all four limbs in more severe cases of vasculitis. Absent ankle jerks are more frequent in patients with systemic disease (purpura, higher cryocrits).²³⁴

Polyneuropathy is more common in hepatitis C virus patients with cryoglobulinemia than in those without cryoglobulinemia.^{232,233} In patients with hepatitis C virus without

cryoglobulinemia, mononeuropathy multiplex may be less frequent, but the data are conflicting.^{232,233} Patients with hepatitis C virus may have greater motor deficits.²³⁶ Vasculitic neuropathy tends to be less severe and neuropathic pain less frequent in patients without cryoglobulinemia.^{232,233} Studies comparing hepatitis C virus patients with and without cryoglobulinemia are complicated by the fact that cryoglobulin levels in sera fluctuate and collected sera should clot at body temperature.

Purpura (cutaneous vasculitis) is present in about 23% of patients with hepatitis C infection and polyneuropathy; most of these patients have a distal symmetric polyneuropathy.²³³ The rash is purple, macular, or palpable without blanching and involves the distal legs. Renal disease (glomerulonephritis) occurs in 10%–30% of patients with cryoglobulinemia but is unusual in patients with polyneuropathy.²³⁷ Vasculitis of the CNS, gastrointestinal tract, and heart also occurs infrequently.

Coinfection with hepatitis C virus and HIV is associated with similar vasculitic polyneuropathy, except that patients are more frequently younger, male, intravenous drug users, and have higher hepatitis C viremia and liver inflammation/necrosis.¹⁹²

Laboratory Studies

BLOOD TESTS

The fundamental finding in essential mixed (polyclonal) cryoglobulinemia is the presence of circulating cryoglobulins. A qualitative measure—a cryocrit—is usually performed, which indicates whether cryoglobulins are present or absent, although quantitative measures are available. Rheumatoid factor is frequent and may be a useful clue to the disease as a screening test or when cryoglobulins are initially absent. Reduced complement levels occur in 90% of patients.²³⁷ An elevated ESR, low positive ANA, and anemia are frequent. Evidence of hepatitis C infection must be sought in all patients by testing for hepatitis C antibodies and hepatitis C RNA. An immunofixation is more important to screen for a hematologic malignancy when testing for hepatitis C is negative.

ELECTRODIAGNOSTIC STUDIES

Nerve conduction studies show reduced sensory and motor response amplitudes, often worse in the legs, with asymmetric features.^{232,233,238} Such findings suggest axonopathy and raise the possibility of a vasculitic polyneuropathy. Multiple mononeuropathies also occur, but there is often some confluence of abnormalities.^{231,239,240} Mild demyelinating changes may be associated, but demyelinating polyneuropathy with conduction block is rare.^{240–242} Sensory conduction abnormalities predominate, though a pure motor variant has been described.²⁴³ F wave latencies are generally mildly prolonged.

Needle EMG characteristically shows multifocal or asymmetric fibrillations and chronic reinnervation changes. However, distal symmetric and L5/S1 radicular patterns may occur. In patients with cryoglobulinemia, compared to those without, electrophysiologic findings tend to be more multifocal and severe.²³²

CEREBROSPINAL FLUID

The CSF is characteristically normal in polyneuropathy associated with cryoglobulinemia.²⁴¹

Nerve Biopsy/Pathology

In patients with hepatitis C and cryoglobulinemia, sural nerve biopsies show axonal degeneration, loss of large myelinated fibers, and a spectrum of inflammatory infiltrates of small and medium-sized vessels ranging from perivascular infiltrates in 27% of patients to lymphocytic vasculitis (30%), leukocytoclastic angiitis (10%), and necrotizing arteritis (20%).²³³ Lymphocytic infiltrates predominate, but granulocytes are present in vessel walls in leukocytoclastic angiitis and necrotizing arteritis. More severe forms of vasculitis are associated with asymmetric nerve fiber loss between fascicles and mixed cryoglobulinemia.²³³ This occurs in 26%–40% of patients with hepatitis C and cryoglobulinemia.¹⁴² Immunohistochemistry may demonstrate IgM and complement component staining of epineurial venules and endoneurial vessels.^{239,244} The teased fiber preparation shows Wallerian degeneration without focal

demyelination.^{232,244} Electron microscopy reveals multifocal swelling and hyperplasia of endothelial cells, basement membrane duplication, and absence of dense material suggestive of cryoprecipitate.²⁴⁴ Genomic hepatitis C virus RNA, but not negative-stranded (replicative) RNA, was detected in 10% of nerve samples and 30% of muscle samples.²³³ Hepatitis C RNA was associated with inflammatory infiltrates and vasculitis in nerve but not in muscle.²³³

Autopsy cases of patients with cryoglobulinemia, hepatitis C, and polyneuropathy are rare. However, one case in a patient with a severe mononeuropathy multiplex showed a severe necrotizing vasculitis of small and medium-sized vessels with fibrinoid necrosis in multiple organs, including peripheral nerves, muscle, liver, kidneys, pancreas, and intestines.²⁴⁵

Pathogenesis

Polyneuropathy in hepatitis C and cryoglobulinemia is likely related to vasculitis or a less established inflammatory response and immune complex deposition. A clonal expansion of B cells may occur in the liver in response to hepatitis C virus antigens, with deposition of mixed cryoglobulins and rheumatoid factor.^{233,246} The contribution of humeral mechanisms is supported by IgM and complement deposition in microvessels, and T-cell-mediated injury is supported by the presence of perivascular T cells, monocytes, and upregulation of ICAM-1 (intracellular adhesion molecules).²⁴⁴ The absence of negative-stranded RNA in inflammatory nerve and muscle is evidence against *in situ* viral replication. Compared to patients with polyarteritis nodosa, those with hepatitis C virus and cryoglobulinemic vasculitis have greater expression of certain metalloproteinases, as well as oxidative stress-derived and pro-inflammatory molecules.²⁴⁷

Treatment

Prior to the discovery of hepatitis C infection as a cause of cryoglobulinemia, vasculitic polyneuropathy with cryoglobulinemia was treated with corticosteroids, plasmapheresis,

cyclophosphamide, or other immunosuppressive drugs based on improvement of systemic vasculitis and polyneuropathy in small, uncontrolled series.^{248,249} When the association with hepatitis C was identified, α -interferon treatment of hepatitis C was noted to improve the polyneuropathy in isolated patients, even in those refractory to prednisone.²⁵⁰ A small trial even suggested superior clinical efficacy of α -interferon compared to deflazacort.²⁵¹ However, reports followed suggesting that, in some patients, α -interferon may lead to an acute exacerbation of mononeuropathy multiplex,^{252,253} and that concurrent administration of prednisone may prevent worsening of and improve polyneuropathy.^{240,252} Additionally, prednisone and other immunosuppressants may worsen hepatic dysfunction.^{240,254,255} Current treatment for hepatitis C infection with systemic vasculitis and polyneuropathy involves the combination of PEGylated interferon alpha-2b (1.5 μ g/kg/week subcutaneously) and ribavirin (800–1200 mg/day orally) for a minimum of 6 months to 1 year.^{255,256} We advocate the addition of a prednisone taper of at least 2–3 weeks duration, beginning with 60 mg daily, in patients with a more severe mononeuropathy multiplex or at the first sign of acute exacerbation of polyneuropathy. In refractory cases of hepatitis C vasculitis with cryoglobulinemia, plasmapheresis or rituximab may be considered.^{248,257,258}

Course and Prognosis

Small-fiber neuropathy symptoms tend to occur in milder cryoglobulinemic syndromes and are generally self-limited.²³⁴ Treatment of cryoglobulinemic vasculitis and polyneuropathy due to hepatitis C infection with PEGylated interferon alpha-2b and ribavirin results in a positive treatment response in about 75% of patients.²⁵⁵ Clinical and electrophysiologic parameters, hepatitis C virus RNA, and cryoglobulin levels may all improve.^{255,256} Reappearance of hepatitis C virus RNA may be associated with clinical relapse. Mononeuropathy multiplex with more significant weakness and motor axon loss often results in more permanent functional deficits. Rituximab may have a similar response rate. However, as monotherapy, rituximab, like

prednisone, may worsen the hepatitis C viral load and hepatitis.^{257,258}

DIPHTHERIA

Clinical Features

Since the advent of diphtheria/tetanus/pertussis vaccine, diphtheria infection and resulting polyneuropathy are exceedingly rare in developed countries. However, isolated cases of diphtheric polyneuropathy resembling Guillain-Barré syndrome (GBS) have been reported, mostly in Eastern Europe.^{258,260} There was an outbreak of diphtheria in Latvia and St. Petersburg, Russia, in the mid-1990s, affecting adults between 40 and 60 years with waning immunity.²⁵⁹ Patients characteristically present with a sore throat associated with a marked tonsillar exudate.²⁶⁰ Early localized infection presents as acute tonsillitis, laryngitis, or nasopharyngitis with pseudomembranes.²⁵⁹ Bulbar paralysis from involvement of lower cranial nerves occurs a median of 10 days (range, 2–50 days) and limb paralysis 37 days (range, 12–63 days) after the initial throat infection.²⁵⁹ Acral paresthesias may precede the limb paralysis by a few days or a week.^{260,261} More severe cases of diphtheria are associated with neck edema, hypotension, acute renal failure, or myocarditis.²⁵⁹ Polyneuropathy occurs in about 15%–20% of patients but is much more frequent with severe infection.^{259,262} Bulbar paralysis is more common in diphtheric polyneuropathy (98%; one-third of patients require a nasogastric tube) than in GBS (10%).²⁵⁹ Early respiratory failure, bladder dysfunction, and optic neuropathies are also more common in diphtheric polyneuropathy than in GBS, although optic nerve dysfunction is rare (6%) in diphtheria.²⁵⁹ About 50% of patients develop cardiac vagal dysfunction on autonomic testing with a sinus tachycardia, but many patients have concurrent myocarditis.²⁶³

Laboratory Studies

DIAGNOSIS

During the acute throat phase of the infection, *Corynebacterium diphtheriae* can

be diagnosed by a methylene blue smear of the membrane or by Gram stain or fluorescent antibody stain of a swabbed pharyngeal exudate.²⁶⁰ Cultures of throat swabs require special media. If the patient received antibiotics or if the pharyngeal phase is missed, serologic determination of specific antibodies may be diagnostic.

ELECTRODIAGNOSTIC STUDIES AND CEREBROSPINAL FLUID

Findings of nerve conduction studies are consistent with an acquired demyelinating sensorimotor polyneuropathy similar to AIDP, with motor slowing, prolonged distal motor latencies, conduction block, and an early abnormal median-normal sural pattern.^{259,260} However, the degree of motor slowing and demyelinating electrophysiologic findings peak much later in diphtheric polyneuropathy (2–3 months after the onset of weakness).²⁶⁰ Cerebrospinal fluid pleocytosis may be more frequent in diphtheric polyneuropathy than in GBS, but an albuminocytologic dissociation also occurs.^{259,260}

Pathology

Injection of diphtheria toxin into nerve induces demyelination and axonal changes; the toxin inhibits synthesis of various myelin proteins in Schwann cells.²⁶⁰ The toxin may also interfere with ribosomal translocation, polypeptide synthesis, and axonal transport.²⁶⁰ In experimental diphtheric polyneuropathy in guinea pigs, there was early presymptomatic widening of the nodes of Ranvier.²⁶¹

Sural nerve biopsy shows signs of demyelination with short internodes and thin myelin sheaths, reduced fiber densities, no or small inflammatory infiltrates, and HLA-DR antigen expression on Schwann cells and macrophages.^{260,261}

Treatment, Course, and Prognosis

Prompt initiation of antibiotic treatment and diphtheria antitoxin (immunoglobulin), within 48 hours, may help prevent systemic and neurologic sequelae.^{259,260} Both bulbar and neuropathic features generally resolve gradually over weeks to months, with

electrophysiologic improvement generally lagging by several months.^{260,262} At 1-year follow-up in one series, 6% of patients required an aid to walk, and 80% had persistent motor or sensory limb symptoms.²⁵⁹ Mortality in diphtheria is approximately 2% and usually relates to cardiac arrhythmias or septic complications.²⁵⁹

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Diabetic and Other Endocrine Neuropathies

THE DIABETIC NEUROPATHIES

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Distal Symmetric Sensorimotor/Autonomic Polyneuropathy (DSP/A)

Autonomic Neuropathy

Proximal Multifocal Neuropathies (Diabetic Lumbosacral Radiculoplexus Neuropathy and Thoracolumbar Truncal Neuropathy)

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THE DIABETIC NEUROPATHIES

Introduction

Neuropathies of various types are among the most common and disabling complications of diabetes, and diabetes is the most common cause of neuropathy worldwide. Type 2 diabetes is far more common than type 1, and type 2 is becoming increasingly prevalent. Approximately 66% of type 1 and 59% of type 2 diabetics will develop symptomatic neuropathy during their lifetime; subclinical neuropathy and neuropathy associated with the prediabetic state of impaired glucose tolerance affect even more individuals.^{1–4} One study suggests that 60% of adolescents with type 1 or 2

diabetes display abnormalities on careful autonomic examination.⁴

Classification has proven difficult; it varies, whether based on pathologic features, topography, or presumed etiology.^{5,6} Our simplified scheme (Table 10–1) is based on the premise that the diabetic neuropathies are not unitary, but represent a number of hyperglycemia-related disturbances of nerves. Autonomic neuropathy is unusual in other metabolic neuropathies, except for porphyria, and is a distinctive feature of diabetes. Although listed separately from distal symmetric sensorimotor polyneuropathy (DSP) in most classifications, it is combined with it here; the two conditions co-occur, progress together, and likely have a similar pathogenesis.^{7,8}

Table 10–1 **Classification of the Diabetic Neuropathies**

Common Forms

- Distal symmetric sensorimotor/autonomic neuropathy
- Proximal multifocal neuropathies (lumbosacral radiculoplexus; thoracolumbar truncal)
- Focal limb neuropathies (entrapment neuropathies)
- Isolated cranial neuropathies (oculomotor, abducens, trochlear)

Uncommon Forms

- Acute painful neuropathy (diabetic neuropathic cachexia)
 - Diabetic motor-predominant neuropathies
 - Treatment-induced neuropathy (insulin neuritis)
 - Hyperglycemic neuropathy
-

**Distal Symmetric Sensorimotor/
Autonomic Polyneuropathy (DSP/A)**

DSP/A, length-dependent diabetic polyneuropathy, is the most common diabetic neuropathy; more than 80% of persons with diabetic neuropathy have DSP/A.⁹ In type 1 diabetes, symptomatic neuropathy usually appears only after years of hyperglycemia. In type 2, symptomatic DSP/A has a variable onset and may be a presenting symptom, although it is likely that these persons have had antecedent hyperglycemia. DSP/A often appears in concert with diabetic retinopathy and nephropathy. An occasional type 2 patient is asymptomatic, and neurologic deficits are discerned only at random physical examination.⁶ Risk factors for neuropathy in both types include poor glycemic control, hypertension, smoking, and cardiovascular disease.

Persons with mildly impaired glucose tolerance (IGT) without frank diabetes are also at risk for neuropathy and stroke. These prediabetic individuals may experience both acral pain and subtle autonomic dysfunction.⁴ Early identification of such persons is critical since aggressive management of hypertension and hyperglycemia, as well as lifestyle change, can lessen discomfort.

CLINICAL FEATURES

In frank diabetics with DSP/A, sensory symptoms commence in the feet and advance proximally in the gradual length-dependent manner associated with distal axonopathy. Eventually, legs to the knees and hands are involved.

Numbness, tingling, or discomfort (hot and cold or burning sensations) in the toes are frequent initial complaints, followed by unsteady gait.

Pain is widely held to be a hallmark of DSP/A and is helpful in distinguishing it from other length-dependent neuropathies; however, since many persons with DSP/A never experience significant discomfort, it is unreliable (when absent) in the differential diagnosis. Pain in DSP/A, is variable; it may be fleeting or persistent and can be mild and annoying or severe and disabling. Common complaints are cold, boring, burning, sticking, or lightning-like sensations in the feet and distal legs. Treatment of pain in DSP/A is frequently difficult and may become a major management issue. Pain may gradually dissipate and be replaced by numbness as neuropathy progresses.

Cramping sensations in the legs are common, as is nocturnal allodynia evoked by rubbing the feet against bedclothes; symptomatic weakness is rare. Autonomic symptoms (see the section Autonomic Neuropathy below) or subtle evidence of autonomic dysfunction frequently are present from the beginning.

Early physical findings are symmetrically impaired vibratory, position, touch, thermal, and pain senses in the distal lower limbs that slowly move proximally over time; impaired vibratory sense is often a heralding sign.¹⁰ Eventually, there is a stocking-glove distribution of sensory loss that may include the midline of the chest and abdomen in very advanced cases (*cuirass sign*); it is sometimes confused as representing a sensory level from spinal involvement. Impairment of small-fiber sensation

may be profound, with ulceration of the soles and joint deformities. The degree of this *pseudosyringomyelic* profile often is augmented by diabetic vascular compromise of the distal limbs. Selective impairment of large-fiber modalities can cause a *pseudotabetic syndrome* of sensory ataxia, bladder atony, and abnormal pupillary responses. Weakness, if present, is mild and distal; wasting of the extensor digitorum brevis is occasionally present.

Differential diagnosis is not difficult when pain is a prominent feature, hyperglycemia is long-standing, and there is evidence of retinopathy and nephropathy. *Diabetes is a common disorder, and diabetics who develop distal symmetric sensory neuropathies unaccompanied by renal or retinal changes should not be assumed to have DSP/A.* These individuals should be evaluated for coincident metabolic/toxic, hereditary, or dysimmune conditions associated with polyneuropathy, as well as for disorders of the lumbar spine and spinal cord. Conspicuous “red flags” in diagnosis include profound weakness, normal autonomic tests, markedly slowed nerve conductions, pure large-fiber sensory loss, and bladder symptoms (Table 10–2).

It is likely that the diagnosis of distal symmetric neuropathy will be made earlier by internists as they become more aware of the implications of the mild impairment in glucose metabolism characteristic of the IGT/prediabetic syndrome.⁴ This condition is applied to persons having either fasting blood glucose of 100–125 mg/dL or, preferably, a 2-hour oral glucose tolerance test of 140–199 mg/dL. Many also display features of the metabolic syndrome. A mild, predominantly small-fiber,

sometimes painful neuropathy may accompany IGT. Skin punch biopsy studies for intraepidermal nerve fiber density determination suggest that diet therapy, counseling, and weight loss can induce some reinnervation of epidermal nerve branches, correlating with lessened acral discomfort.¹¹

LABORATORY STUDIES

Electrodiagnostic studies disclose similar findings for types 1 and 2 diabetics; the extent of electrophysiologic impairment correlates poorly with clinical disease severity. Sensory amplitudes in distal leg nerves are generally reduced more than conduction velocities in a manner similar to that of most length-dependent axonal neuropathies. Progression of neuropathy is reflected by gradual loss of sensory potentials in the plantar nerves and profound amplitude reduction in the sural and peroneal sensory nerves.¹² A similar but less pronounced profile is present in distal arm nerves unless there are superimposed entrapments. Advanced cases are associated with reduced motor amplitudes in the lower limbs. Nerve conduction velocities are frequently in the 30–40 m/s range in the legs. Focal slowing at entrapment sites is common. Conduction block over long nerve segments is unusual. Late response abnormalities are frequent and early, as is denervation of intrinsic foot muscles on needle electromyography (EMG). Mild paraspinal denervation may be seen in diabetics without radicular symptoms.

Cerebrospinal fluid (CSF) usually displays a variably elevated protein level; in one study, it was elevated in 68% of diabetics with

Table 10–2 Diagnostic Pitfalls in Diabetic Neuropathy

Superimposed neuropathies
Severe weakness or demyelination: chronic inflammatory demyelinating polyneuropathy
Severe proprioceptive loss: sensory neuronopathy
Superimposed entrapments
Thoracic/abdominal/spinal disorders mimicking truncal neuropathy
Structural/neoplastic spinal or plexus disease mimicking diabetic lumbosacral radiculoplexus neuropathy
Diabetic muscle infarction mimicking diabetic lumbosacral radiculoplexus neuropathy
Aneurysmal versus diabetic third nerve palsy
Cuirass confused with spinal level

neuropathy (range: 51–224 mg/dL, mean: 77 mg/dL), and in another, the highest CSF protein level was 440 mg/dL.¹³ Lumbar puncture is unhelpful in diagnosis, as are nerve biopsies. The histopathologic changes on nerve biopsy (see below) are so diffuse and intense that other conditions would likely be unrecognizable. Skin punch biopsies in symptomatic persons display diminished numbers of intraepidermal nerve fibers, but there are no characteristic findings. Since it can be performed repeatedly in the same patient, this procedure has great promise as a quantitative measure of treatment efficacy.

PATHOLOGY AND PATHOGENESIS

There are two cardinal histopathologic features in diabetic neuropathic lower limb nerves: distal myelinated and unmyelinated fiber loss and microangiopathy. Nerve fiber degeneration and attempted regeneration is accompanied by secondary demyelination and onion bulb formation.¹⁴ It is unclear if there is also primary demyelination. Microangiopathy of endoneurial vessels is an early finding and, in advanced cases, is a striking and characteristic feature. Reduplication of the vessel basement membrane, with thickening of the vessel wall and pericyte degeneration, appear to be the initial events (Fig. 10–1). These changes are present to a mild degree in asymptomatic patients. As neuropathy becomes more symptomatic, the degree of microangiopathic change grows more severe. The blood-nerve barrier is altered, with leakage of protein into the endoneurial space, and occasional thickened capillaries are collapsed.¹⁵

All agree that hyperglycemia is the underlying force in the pathogenesis of DSP/A. While the length-dependent nature of DSP/A suggests to some that metabolic perturbation of neuronal function is primary, others emphasize a crucial role for hemodynamic compromise secondary to the abundant and striking microangiopathic changes. It seems likely that both mechanisms are operant and complementary.

Advocates of the metabolic theory have largely relied on findings in experimental animal studies, primarily utilizing the streptozotocin-treated or the spontaneously diabetic BB rat. These short-lived animals develop slowing of nerve conduction and axonal atrophy but do

not display microangiopathy. This limits their validity as models. Proposed metabolic dysfunctions include, *inter alia*, an elevated polyol pathway, diminished myo-inositol, nerve hypoxia, elevated protein kinase c, low levels of neurotrophic growth factors, diminished metabolism of long chain fatty acids, increased nonenzymatic glycation, and mitochondrial dysfunction.^{16–19} Most of these hypothetical mechanisms have been examined and specific therapies tried in experimental animals; some have received clinical trials. None has proven effective in humans.

TREATMENT, COURSE, AND PROGNOSIS

The course of DSP/A is variable. A population-based study states that 10% of patients had worsened over 2 years, 81% were unchanged, and 9% had improved.²⁰ Many never progress beyond a stage of numb feet, mildly unsteady gait, and occasional discomfort. A few eventually become severely disabled by a constellation of conditions, including severe sensory loss in the hands as well as the feet, inability to walk, severe pain, foot ulcers, traumatic joint deformity, and autonomic dysfunction. There may be factors that, when modified, can lower the risk of developing neuropathy.²¹

There is no specific treatment for DSP/A.^{22–24} Alphaipoic acid, 600 mg daily, may be of marginal benefit.²⁴ Strict glycemic control can slow the progression of established neuropathy and delay the onset of DSP/A in type 1 diabetics; it has little discernible effect on neuropathy in type 2 patients. Neuropathy, once established, is not significantly improved by strict glycemic control. Pancreatic transplantation has also halted its progression, but is a formidable undertaking and carries the burden of immunosuppressive therapy. Foot care and shoe selection are compelling issues in DSP/A, and ulceration in older patients is accelerated by large-vessel ischemia. Many agents are available for relief of chronic pain, including antiepileptics (gabapentin, pregabalin), tricyclics (nortriptyline, desipramine, amitriptyline), selective serotonin-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), lidocaine patch, tramadol, and opioids (see Chapter 3, Table 3–4).

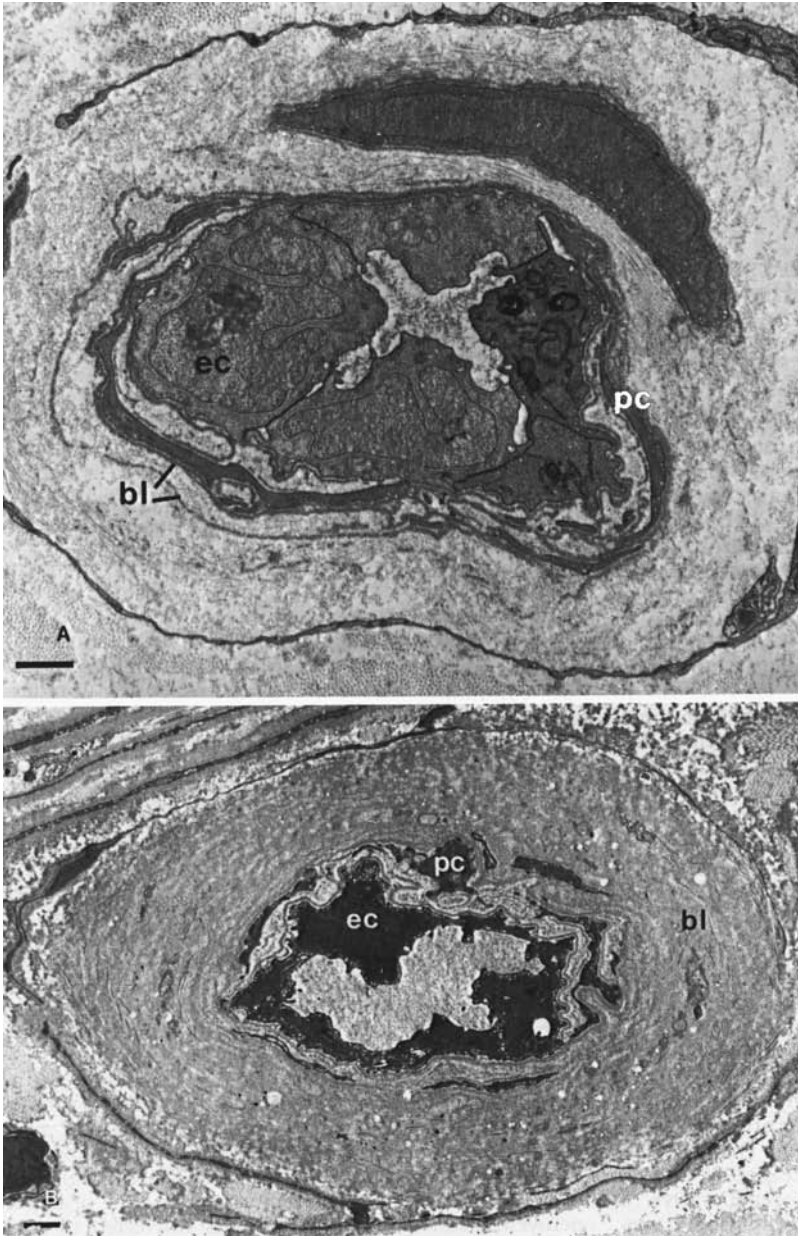


Figure 10-1. (A) Electron micrograph of an endoneurial capillary from a normal subject. The endothelial cells (ec) are surrounded by pericytes (pc), and both are enclosed by basal lamina (bl). Bar = 1 μ m. (B) Electron micrograph of an endoneurial capillary from a patient with diabetic polyneuropathy. The endothelial cells (ec) and pericytes (pc) are surrounded by a wide zone of reduplicated basal lamina (bl). Bar = 1 μ m.

Autonomic Neuropathy

Autonomic neuropathy is almost always accompanied by symptomatic or asymptomatic somatic neuropathy.²⁻⁹ The occurrence of symptomatic autonomic neuropathy is

especially difficult to assess since many of the symptoms attributed to autonomic dysfunction are vague and physicians' questions are often not targeted. Autonomic tests, if performed in a dedicated laboratory, are often abnormal at the time of diagnosis; worsening is correlated

with poor control of hyperglycemia. Most longitudinal studies strongly suggest that, once established, autonomic dysfunction steadily progresses; this phenomenon is enhanced in the aged patient. Experimental animal studies, except for those of the splanchnic nerves, have provided only modest insight into the pathogenesis or treatment of diabetic autonomic neuropathy. Interpretation of human postmortem autonomic ganglia and nerves has also been unhelpful, largely because of the abundant vascular compromise of these tissues in elderly diabetics.

Clinical manifestations appear in the following areas: cardiovascular, gastrointestinal, urogenital, sudomotor, respiratory, and pupillary. Cardiovascular autonomic neuropathy has received widespread attention, probably because it is readily detected at an asymptomatic stage by simple, noninvasive tests.³ It likely contributes significantly to mortality in elderly diabetics. Two abnormalities, a resting tachycardia and a fixed heart rate (unaffected by standing, breathing, or mild exercise), are characteristic. These appear before obvious symptoms of tachycardia or postural syncope. Postural hypotension, when mild, is relieved by behavioral and dietary modification (e.g., slowed rising and a high-salt diet). Pharmacologic intervention is best delayed until behavioral interventions fail.

Gastrointestinal symptoms are common in diabetic persons and include dysfunction of every segment of the primary digestive tract and the gallbladder. Disorders of gastric and intestinal motility are common and two, gastroparesis and diarrhea, are held to be characteristic. These problems were previously attributed to combinations of sympathetic and parasympathetic dysfunction; current studies indicate a more prominent role for hyperglycemia. The streptozotocin diabetic rat consistently develops megacolon, and axonal dystrophic change is present in splanchnic nerves. This axonal change, abundantly present in the absence of significant neural vasculopathy, is some of the most compelling evidence that metabolic features alone can induce axonopathy in the hyperglycemic state.²⁵

Urogenital dysfunction is especially distressing in males; erectile dysfunction prevalence increases with age and is hastened by diabetes. Almost one-half of diabetic males over age 50 are significantly impaired. Once it commences,

impotence is almost always permanent and is not ameliorated by rigid glycemic control. Treatment is best left to urologists; pharmacologic agents (sildenafil) and intracavernous injections with vasodilators may help those without severe vascular compromise. Signs of diabetic bladder dysfunction include incomplete emptying, reduced urinary flow, and recurrent infections.

Proximal Multifocal Neuropathies (Diabetic Lumbosacral Radiculoplexus Neuropathy and Thoracolumbar Truncal Neuropathy)

Previously, these two conditions were considered distinct pathogenetic entities. Recent studies demonstrate not only considerable co-occurrence and overlap, but also strikingly vasculopathic histologic changes in the lumbosacral condition. The two conditions are best considered to exemplify the same disorder occurring at slightly different levels of the neuraxis.

DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY (DLRPN; DIABETIC AMYOTROPHY; BRUNS-GARLAND SYNDROME)

Clinical Features

The cardinal feature of this condition is painful, asymmetric onset of weakness in the proximal lower limbs. It is most common in middle-aged and elderly type 2 diabetic males with good glycemic control; often it is associated with weight loss, sometimes profound. It often occurs early after a diagnosis of diabetes and, in contrast to DSP/A, is rarely accompanied by retinopathy or nephropathy.^{26–28}

Aching pain, often severe, is frequently the initial symptom; pain is initially confined to one side of the hip and thigh proximally but may rarely affect the distal leg; it frequently spreads to affect the other limb. Some patients experience piercing, sharp pain and allodynia. This is followed by asymmetric, progressively spreading weakness of one or both proximal lower extremities (predominantly anterior thigh muscles). Initially proximal, weakness eventually is present in almost all patients in

the distal lower limbs as well; it is accompanied by variable, usually mild sensory and autonomic involvement. Some cases may even begin with distal limb weakness and pain in lower back and distal muscles. Patellar reflexes are absent on one or both sides, and ankle jerks are depressed or absent if there is coexistent polyneuropathy or involvement of lower spinal root segments. Uncommonly, there is lower cervical brachial involvement as well. DLRPN probably is the cause of the condition previously labeled *diabetic femoral neuropathy*. The clinical spectrum of DLRPN probably also includes an occasional patient with a more symmetric, insidious, and painless phenotype.

Evolution of weakness in DLRPN may take place in a week, or over 6–9 months, and is disabling. Many persons with bilateral involvement are confined to a wheelchair; a few become paraplegic.²⁹

This is a monophasic illness. Recovery is variable, and is probably dependent on the age of the patient and the degree of axonal degeneration. Most patients improve slowly, and those with unilateral involvement usually have a better prognosis. Pain usually subsides after several weeks/months, and rehabilitation becomes easier. There is no established treatment; some uncontrolled trials of early immunotherapy (intravenous immunoglobulin [IVIG], pulsed corticosteroids) report improvement, but this therapy needs to be explored further.³⁰ Intravenous administration of corticosteroids, if commenced soon after onset of DLRPN, considerably alleviates pain. Physical therapy, control of hyperglycemia, and pain management are the mainstays of therapy.

Electrodiagnostic studies indicate multifocal axonal dysfunction in lower limb motor and sensory nerves and spinal roots. The electrophysiologic pattern suggests a poly-radiculopathy/plexopathy or a pure radiculopathy; there may also be evidence of an associated distal polyneuropathy. Quantitative sensory and autonomic testing, although seldom performed in these persons, indicate dysfunction of multiple nerve fiber modalities.

Differential diagnosis includes pelvic malignancies, retroperitoneal hemorrhage, necrotizing vasculitis, lumbar spine and hip diseases, and diabetic muscle infarction. Lumbar spine and plexus magnetic resonance imaging (MRI) and a vasculitis laboratory screen are indicated

in most cases. Cerebrospinal fluid analysis may be helpful; nerve biopsy is rarely useful.

Pathology and Pathogenesis

Several clinical features suggest that this condition has a different pathogenesis from DSP: the absence of retinopathy/nephropathy, a good glycemic control history, predominance in type 2, and onset soon after diagnosis of diabetes. Histopathologic studies of sural nerve or intermediate cutaneous nerve of the thigh biopsies and postmortem plexus sections support this notion; they indicate that DLRPN is secondary to a nonnecrotizing (without fibrinoid degeneration of arterial wall), multifocal, inflammatory microvasculitis with evidence of ischemic injury.^{31–34} Some suggest that the inflammatory infiltrate reflects an immune-mediated disorder; others maintain that the inflammatory cells are secondary. The demonstration of abundant microvasculopathy in DLRPN and in the corresponding syndrome in nondiabetic persons is strong evidence in favor of an ischemic, as opposed to a purely hyperglycemic/metabolic, etiology for this condition.

DIABETIC THORACOLUMBAR TRUNCAL RADICULONEUROPATHY

This painful intercostal/lumbar radiculoneuropathy may appear alone or in concert with DLRPN; the striking similarities and co-occurrence suggest a common pathogenesis. Both are more common in older type 2 diabetics and are frequently associated with weight loss. A thoracic syndrome predominates in most instances; lumbar nerve dysfunction is often undetected. Onset is sudden or subacute. Local thoracic or abdominal pain is a hallmark; it is occasionally bilateral. Symptoms may mimic those of pulmonary, cardiac, gastrointestinal, or spinal disease; occasionally, persons are considered to have herpes zoster or Lyme radiculoneuropathy. Pain is described as knife-like, burning, or band-like around the abdomen; some persons refuse to wear undergarments because of intolerable allodynia. Examination may disclose loss of sensation in the affected dermatomes. Rarely, a disfiguring abdominal protuberance develops when abdominal wall musculature is denervated (*pseudohernia*). Most patients improve after 2–5 months; uncommonly, the condition recurs.

Electromyography may show denervation in paraspinal and/or abdominal wall and intercostal muscles.^{35,36}

Diagnosis is straightforward when there is a characteristic dermatomal sensory loss, and no further work-up is indicated. Atypical or persistent/progressive disease may warrant a spinal MRI study. A cautionary note is indicated by the authors' experience of two persons with unclear sensory loss erroneously subjected to laparotomy for suspected abdominal malignancy or adhesions.

Focal Limb Neuropathies (Entrapment Neuropathies)

Clinical carpal tunnel syndrome is present in about 14% of diabetics without DSP and in 30% if DSP is present; by comparison, there is a 2% prevalence in a reference population.³⁷ It is widely assumed, but unproven by population-based studies, that there is an increased incidence of peroneal, ulnar, and lateral femoral cutaneous nerve entrapment in diabetics. Diabetic mononeuropathy at nonentrapment appendicular sites and/or mononeuropathy multiplex syndromes are unusual. Electrophysiologic diagnosis of median nerve entrapment in diabetics may be challenging because of effects attributable to coexistent polyneuropathy. Treatment and operative decisions concerning median nerve compression in diabetes are the same as those for the general population. Surgery is indicated if splinting and local corticosteroid injections fail or if thenar muscles become weak; the results may not be as gratifying as those for nondiabetics.

Isolated Cranial Neuropathies

The abducens (sixth) and oculomotor (third) nerves are most commonly affected. Almost all cases occur in persons over 50 years of age. Trochlear (fourth) nerve dysfunction may accompany oculomotor neuropathy. It is unclear if other cranial nerves, with the possible exception of the seventh, are ever affected in isolation.³⁸

Onset is usually abrupt; oculomotor neuropathy is often painful, but abducens palsy may be painless. Orbital discomfort, sometimes severe, often precedes oculomotor neuropathy

by several days; this may suggest the presence of an aneurysm of the posterior communicating artery. Paralysis of extraocular muscles is near total. Pupillary function is unaffected in about 80% of oculomotor diabetic mononeuropathies; this helps to make the bedside distinction from an aneurysmal leak or enlargement. Cranial magnetic resonance (MR) angiography is indicated in younger persons, or if there is any evidence of pupillary dysfunction or lack of improvement within 3 months. Most patients experience a good or complete recovery in 3–6 months. Rarely, cranial neuropathies are recurrent or multiple. The sudden, painful onset of third nerve dysfunction suggests a vascular pathogenesis, and postmortem studies support this notion.³⁹ Ischemic lesions may be present in either the extraaxial oculomotor nerve or, as demonstrated on MRI, in fascicular fibers in the midbrain.⁴⁰

Acute Painful Neuropathy (Diabetic Neuropathic Cachexia)

Severe, precipitous weight loss and poor glycemic control are associated with a disabling, painful neuropathy, more often in men than in women. This was originally termed *diabetic neuropathic cachexia*. Rarely, it appears unaccompanied by weight loss.⁴¹ Gradual onset of intolerable burning pain over the soles of the feet and legs accompanied by allodynia are the hallmarks of this condition; pain may be diffuse in the limbs and trunk. There is often a distal stocking loss of pin, thermal, and vibration sensation, and normal or diminished ankle jerks, but no weakness. This is a monophasic illness, rarely recurrent; restoration of glycemic control and weight gain are associated with diminished pain and gradual recovery over many months. A similar condition may occur in anorectic females.

Diabetic Motor-Predominant Neuropathies

Several studies depict a rare acute neuropathy that accompanies diabetes. Diabetes is a very common condition in adulthood, and it is likely that these are coincident instances of acute inflammatory demyelinating polyradiculoneuropathy (AIDP). There are also reports

of an uncommon progressive motor-predominant neuropathy resembling chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and some suggest that there is a genuine association between diabetes and chronic or subacute immune-mediated demyelination of peripheral nerve and roots. This notion receives some support from histopathologic studies of sural nerve biopsies and autopsy study of the proximal diabetic neuropathies. This entity should be considered in cases associated with severe weakness and large-fiber sensory dysfunction, with prominent demyelinating features on electrodiagnostic studies. The subject of CIDP and diabetic neuropathy, and the issue of possible immunosuppressive treatment, are discussed in Chapter 7.

Treatment-Induced Neuropathy (Insulin Neuritis)

This nebulous, poorly documented entity is an acute acral painful syndrome that is coincident within weeks of commencement of insulin therapy.⁴² Its pathogenesis is unclear and its existence has been challenged.⁴³ There may be mild stocking-glove sensory loss and allodynia, or no findings on either physical examination or electrodiagnostic tests. Pain gradually dissipates within a year of onset.

Hyperglycemic Neuropathy

Newly diagnosed, poorly controlled diabetics may experience an episode of transient acral pain and paresthesias. Allodynia may occur. There are few physical signs despite the severe acral pain. Most patients gradually improve following establishment of consistent glycemic control. At the other extreme, the question of whether neuropathy may result from recurrent or prolonged hypoglycemia is raised by rare cases associated with insulinoma.⁴⁴

ACROMEGALIC NEUROPATHY

Introduction

Acromegaly is usually caused by growth hormone-secreting tumors developing in the

pituitary gland. Two types of peripheral nervous system (PNS) involvement may develop: an entrapment mononeuropathy, usually carpal tunnel syndrome, and a distal symmetric polyneuropathy.⁴⁵ Proximal muscle weakness (acromegalic myopathy) occurs independently and may confuse the clinical profile.

Mononeuropathy

Compression of the median nerve at the wrist is a well-known complication of acromegaly and is present in about one third of cases (Fig. 10-2).⁴⁶⁻⁴⁸ It seems likely that acroparesthesias, which are common in acromegalics, arise from this cause. The lesion or lesions responsible for median nerve compression have not been determined with certainty. It is likely that the following have roles: synovial edema, hyperplasia of the ligaments, and enlargement of the nerve (as demonstrated in one MRI study).⁴⁹ Most are relieved by correction of the underlying endocrine disorder; surgery of the carpal ligament is usually unnecessary.

Distal Symmetric Polyneuropathy

Symmetric polyneuropathy may develop at any time in the course of acromegaly, but most cases occur late in the illness. Initial symptoms are paresthesias in the feet and hands followed by the insidious development of weakness. Decreased touch, vibration, and position sense in the lower extremities is characteristic. Tendon reflexes are usually absent in the lower limbs. Most patients experience only mild distal weakness, but an occasional patient becomes disabled and unable to walk.⁴⁵ Thickening of peripheral nerves is an inconsistent finding.⁵⁰ Motor and sensory nerve conduction in limb nerves is abnormal, with moderately reduced motor conduction velocity and depressed or absent sensory nerve action potentials.^{51,52} Nerve biopsy studies have shown both fiber loss and changes consistent with segmental demyelination suggesting a mixture of distal axonopathy and Schwann cell dysfunction.⁵³ Some aspects of the nerve biopsies appear to conflict with the nerve conduction studies that report change consistent with purely axonal disease. The cause of symmetric neuropathy is suggested to be

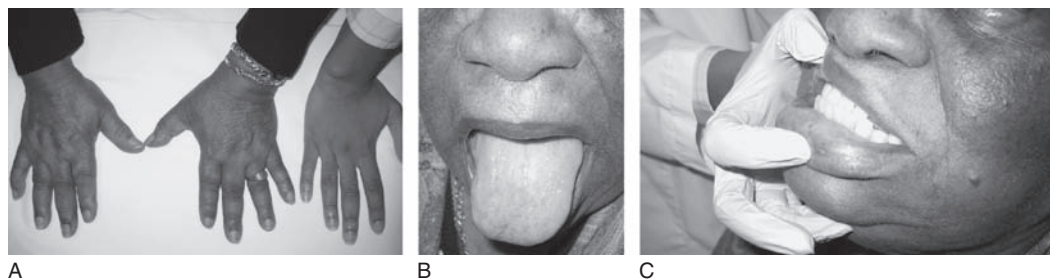


Figure 10-2. Patient with acromegaly and carpal tunnel syndrome demonstrating enlarged hands compared to the examiner (A), an enlarged tongue (B), and prognathia (C).

multifactorial and to reflect hypertrophic changes within the endoneurium, cellular proliferation, and endoneurial accumulation of water and electrolytes.⁴⁵

HYPOTHYROID NEUROPATHY

Introduction

Myxedema is now rare in North American medical practice, and many mild cases of hypothyroidism are treated following detection on routine office medical evaluation laboratory profiles. Two types of peripheral nerve disease may occur in hypothyroidism: compression mononeuropathy and distal symmetric polyneuropathy.⁵⁴ The former is most common and usually consists of carpal tunnel syndrome; dysfunction of the lateral femoral cutaneous nerve (meralgia paresthetica) may occasionally occur. Bilateral sensory neural hearing loss and deafness may rarely develop; their etiology is unclear, and recovery following treatment is usual.

Mononeuropathy

Symptomatic carpal tunnel syndrome is present in about 15% of persons with hypothyroidism, and it is likely that subclinical electrophysiologic abnormalities exist in many more with severe disease.⁵⁵ The severity of carpal tunnel syndrome correlates poorly with either the degree or the duration of thyroid dysfunction. The clinical syndrome of carpal tunnel syndrome in hypothyroidism is almost identical to the more common idiopathic

syndrome; the principal difference is that the carpal tunnel syndrome associated with hypothyroidism is more commonly bilateral. Intermittent paresthesias in the hands, especially at night, are the heralding feature of carpal tunnel syndrome. Median sensory loss is common; weakness is present only in advanced cases.

Electrodiagnostic testing of individuals with carpal tunnel syndrome is valuable, both in establishing the site of the lesion and in excluding a more diffuse neuropathy. Prolonged latencies of motor and sensory potentials at the wrist and diminished amplitudes of sensory nerve action potentials are usually present. Electromyography of the thenar muscles reveals denervation changes in advanced cases.⁵⁶

Most patients gradually improve following thyroid hormone replacement therapy; decompressive surgery is rarely necessary. The pathogenesis is likely a combination of median nerve compression by carpal ligaments, tendons, and synovial sheaths thickened by deposits of mucopolysaccharides.⁵⁷

Distal Symmetric Polyneuropathy

This now unusual entity has a symptomatic profile identical to those of many toxic/metabolic distal axonopathies. Initial symptoms of acral lower limb paresthesia are occasionally accompanied by pain and muscle cramps. Numbness of the hands appears within weeks. Unsteady gait is common and reflects proprioceptive dysfunction in the lower limbs. Many patients complain of fatigue; this usually reflects the underlying endocrinopathy. Severe muscle weakness from nerve

involvement is unusual except in advanced cases.^{58,59} There may be a coexistent myopathy causing a puzzling profile that includes proximal weakness. Diminished senses of touch, vibration, and position in the distal extremities are present in most patients; abnormalities of pain and thermal appreciation are rare. Tendon reflexes are depressed in the arms and often absent in the lower limbs. There may be prolonged relaxation of tendon reflexes ("hung-up"), a characteristic of hypothyroidism. Clumsiness may be extreme in some cases; it has been attributed to hypothyroid cerebellar dysfunction.

Electrophysiologic studies have yielded an unusual range of possible abnormalities. Several patients clearly have evidence of a distal demyelinating neuropathy with slowed conduction velocities and delayed latencies. Others have diminished sensory amplitudes and near-normal velocities, which are more consistent with an axonopathy.^{60,61}

Sural nerve biopsies reveal axonal loss and accumulations of glycogen granules but not frank axonal degeneration. There is a shift in the spectrum toward smaller fiber sizes that might reflect a demyelinative process.^{60,61} There are no descriptions of endoneurial deposition of mucopolysaccharides.

Once thyroid hormone replacement therapy commences, the prognosis is generally excellent. Most patients experience near-total recovery within 9 months.

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Neuropathies Associated with Vitamin and Essential Mineral Deficiencies and Malabsorption

INTRODUCTION

VITAMIN B₁₂ (COBALAMIN) DEFICIENCY

Clinical Features
Laboratory Studies
Nerve Biopsy/Pathology
Pathogenesis
Treatment, Course, and Prognosis

VITAMIN B₁ (THIAMINE) DEFICIENCY

Clinical Features
Laboratory Studies
Nerve Biopsy/Pathology
Pathogenesis
Treatment, Course, and Prognosis

CELIAC DISEASE

Clinical Features
Laboratory Studies
Nerve Biopsy/Pathology
Pathogenesis
Treatment, Course, and Prognosis

VITAMIN E (α-TOCOPHEROL) DEFICIENCY

Clinical Features
Laboratory Studies
Nerve Biopsy/Pathology
Pathogenesis
Treatment, Course, and Prognosis

COPPER DEFICIENCY

Clinical Features
Laboratory Studies
Nerve Biopsy/Pathology
Pathogenesis
Treatment, Course, and Prognosis

OTHER: CUBAN EPIDEMIC OPTIC AND PERIPHERAL NEUROPATHY; DEFICIENCIES: RIBOFLAVIN (VITAMIN B₂), PYRIDOXINE (VITAMIN B₆), FOLATE, ZINC; BARIATRIC SURGERY

INTRODUCTION

Few vitamin and essential mineral deficiencies cause polyneuropathy, namely, vitamin B₁₂ (cobalamin), vitamin B₁ (thiamine), copper, and probably vitamin E (α-tocopherol). Celiac disease is an autoimmune disorder which may be associated with malabsorption symptoms and mimics a vitamin deficiency affecting the nervous system. Polyneuropathy in all these conditions is usually mild, distal, sensory, and axonal; associated central nervous system (CNS) features

are common and often predominate. Ataxia is common to all of these disorders. Vitamin B₁₂, vitamin E, and copper deficiencies are associated with myelopathic signs (Table 11–1). Vitamin B₁₂ and thiamine deficiencies are associated with cognitive changes. The association of vitamin E deficiency and polyneuropathy is less certain in humans. It is based on a few case reports, the finding of low α-tocopherol in sural nerves of patients with vitamin E deficiency, and the finding of a myeloradiculoneuropathy in vitamin E-deficient rats and monkeys.^{1–5} Copper

Table 11–1 Vitamin Deficiencies, Malnutrition, and Polyneuropathies: Distinguishing Features

Clinical Feature	Vitamin B ₁₂ Deficiency	Vitamin B ₁ Deficiency	Celiac Disease	Vitamin E Deficiency	Copper Deficiency
Truncal ataxia	+	+/-	++	++	+
Limb dysmetria	-	-	+/-	+	-
Muscle weakness	+/-, distal	+, distal	+, distal*	+/-	-
Spasticity	+	-	-	-	+/-
Babinski responses	+	-	-	+/-	+/-
Sensory loss					
Pin/temperature	+	+	++	-	+
Vibration/ position	++	++	++	++	++
Absent ankle jerks	+/-	++	+	++	+/-
Ophthalmoplegia	-	+/-, Wernicke	-	+/-	-
Dysarthria	-	+/-, Wernicke	-	+	-
Cognitive deficits	+/-	+/-, Wernicke	-	-	-
Myelopathy	++	-	-	+	++
Polyneuropathy (axonal)	+	++	+	+/-	+
Treatment response	90% partial response rate over days to months; response begins in 3–6 months	Gradual recovery over a few weeks to several months	Little to no response with gluten restriction or immunosuppression	Recovery in several months to a few years (if <15 years' duration)	Mild, subjective improvement; stabilization common

* May be multifocal or asymmetric.

deficiency causes a myeloneuropathy mimicking subacute combined degeneration due to vitamin B₁₂ deficiency without cognitive dysfunction.^{6,7} Bariatric surgery can cause vitamin and mineral deficiencies through malabsorption, compressive mononeuropathies, and inflammatory neuropathies.^{8,9} The Cuban epidemic optic and peripheral neuropathy is an axonopathy thought to be related to nutritional deficiencies and exposure to toxins such as tobacco.^{10–12}

VITAMIN B₁₂ (COBALAMIN) DEFICIENCY

Clinical Features

EPIDEMIOLOGY

Pernicious anemia generally occurs in patients over 40 years of age and may be present in up to 1.9% of persons over age 60; it occurs earlier

in black women than in white women.¹³ The incidence of vitamin B₁₂ deficiency after gastric bypass is about 4%.¹⁴ A prevalence of 14.5% was noted for vitamin B₁₂ deficiency in a geriatric outpatient clinic in Denver.¹⁵ In an academic neuromuscular clinic in Kansas, 8% of cryptogenic polyneuropathy patients had cobalamin deficiency; of these, 44% had normal vitamin B₁₂ levels.¹⁶ The frequency of polyneuropathy in patients with vitamin B₁₂ deficiency ranges from 16% to 44%, although patients with concurrent diabetes mellitus were not excluded in the study showing more frequent polyneuropathy (44%).^{17,18}

SOURCES, REQUIREMENTS, AND ABSORPTION

Vitamin B₁₂ deficiency is usually related to malabsorption. Dietary deficiency is rare but may result from a strict vegetarian diet.

Malabsorption usually results from either inadequate gastric production of intrinsic factor (pernicious anemia, gastrectomy, or *Helicobacter pylori* infection) or from disorders of the terminal ileum (intestinal resection or Crohn disease). The principal dietary sources of vitamin B₁₂ are meat, dairy products, and fish. The minimum daily adult requirement is 2.4 µg.¹⁹ Hydrochloric acid releases vitamin B₁₂ from proteins during digestion (proton pump inhibitors may inhibit its release). Dietary vitamin B₁₂ combines with intrinsic factor (IF), a glycoprotein that is produced by stomach parietal cells. The B₁₂-IF complex is absorbed in the distal ileum. Vitamin B₁₂ deficiency may also occur in conditions that increase vitamin B₁₂ consumption, such as pregnancy, thyrotoxicosis, hemolytic anemia, hemorrhage, malignancy, and liver or kidney disease, or with the use of drugs that inhibit vitamin B₁₂-dependent enzymes (nitrous oxide) or that affect vitamin B₁₂ absorption (metformin).

SYMPTOMS AND SIGNS

Myelopathy or myeloneuropathy from subacute combined degeneration of the spinal cord is the classic neurologic presentation of vitamin B₁₂ deficiency.^{20,21} It is unclear whether polyneuropathy occurs as commonly without, as compared to with, concurrent myelopathy. Studies that screen for vitamin B₁₂ deficiency in patients with myelopathy or any vitamin B₁₂ deficiency neurologic syndrome find polyneuropathy in 44%–55% of patients, and 93%–100% of these have myelopathic signs.^{20,21} By contrast, only 11% of patients in an electromyography (EMG) lab population had hyperreflexia and no patients had spasticity or upper motor neuron signs.¹⁶ The authors' experience is that the majority of patients with polyneuropathy have associated myelopathic signs, although polyneuropathy alone may occur.

Polyneuropathy characteristically presents with painless paresthesias in the feet. However, paresthesias begin in the hands or hands and feet simultaneously more frequently than in idiopathic sensory polyneuropathies.^{16,22} In an EMG lab population, approximately 78% of patients have involvement of both the hands and feet.¹⁶ Over 80% of patients have distal pin or large-fiber sensory loss.¹⁶ Distal leg weakness is unusual, occurring in 15% of patients.

In studies that are likely biased toward screening for vitamin B₁₂ deficiency in CNS syndromes, myelopathy symptoms and signs often predominate, with gait disturbance (ataxia and later spasticity), distal large-fiber sensory loss (particularly vibratory loss in the feet), and variable, mild corticospinal tract signs^{20,23} (Table 11–1). Gait unsteadiness occurs in about one-third of patients.^{21,24} Reduced or absent ankle jerks may suggest concurrent polyneuropathy.^{16,20} The combination of absent ankle jerks and hyperreflexic knee jerks is a useful clinical clue to a myeloneuropathy syndrome.

Cognitive impairment ranges from 0% to 48%.^{16,20,21,24} Quadriparesis, paraparesis, and bladder incontinence are unusual.²⁰ There is a questionable association of optic neuropathy with vitamin B₁₂ deficiency.^{9,25} One patient developed optic neuropathy associated with vitamin B₁₂ deficiency following bariatric surgery that improved with B₁₂ supplementation.⁹ However, the patient also had oligoclonal bands, an increased immunoglobulin G (IgG) index, and an increased IgG synthesis rate in the cerebrospinal fluid (CSF) with cerebral white matter lesions on a brain magnetic resonance imaging (MRI) scan, suggesting multiple sclerosis.

Laboratory Studies

BLOOD TESTS

Serum vitamin B₁₂ levels are probably an adequate screen for B₁₂ deficiency. Vitamin B₁₂ levels <200 pg/mL are generally considered abnormal. If there is a low-normal vitamin B₁₂ level, 250–300 pg/mL or perhaps even higher, and either malabsorption, a high clinical suspicion (i.e., polyneuropathy with corticospinal tract signs), or a macrocytic anemia, it is reasonable to screen for impaired vitamin B₁₂ metabolism with serum methylmalonic acid and homocysteine levels.¹⁶ If methylmalonic acid or homocysteine levels are elevated, IF, parietal cell antibodies, and gastrin levels are checked to assess for pernicious anemia. Elevated homocysteine levels are less specific for vitamin B₁₂ deficiency. Pernicious anemia is diagnosed by IF antibodies or parietal cell antibodies with an elevated serum gastrin level.¹⁶ Schilling tests are rarely necessary. A macrocytic anemia is present in about 10%–67% of patients with vitamin B₁₂

deficiency and polyneuropathy or myelopathy.^{16,18,20} Hypersegmented neutrophils are more sensitive than other hematologic parameters for vitamin B₁₂ deficiency.²⁶

ELECTRODIAGNOSTIC STUDIES

In vitamin B₁₂ deficiency, prolonged tibial somatosensory evoked potentials are more frequent than nerve conduction study abnormalities, reflecting posterior column dysfunction.^{21,27} On nerve conduction studies, sensory response amplitudes are often reduced in the legs, consistent with an axonal sensory polyneuropathy, although conduction may be normal.¹⁶ Moderate sensory conduction slowing, suggesting sensory nerve demyelination, and distal fibrillations in the legs on needle EMG, suggesting mild motor axon loss, may also occur.^{20,21,23}

CEREBROSPINAL FLUID

The CSF is usually normal in subacute combined degeneration, although a moderate increase in protein may occur. Methylmalonic acid CSF concentrations may be elevated in patients with vitamin B₁₂ deficiency, with or without associated CNS disease.^{28,29}

IMAGING

In subacute combined degeneration, MRI of the cervical spine shows hyperintense T2 lesions in the dorsal columns in about 50% of patients that usually improve with vitamin B₁₂ supplementation in 8–12 months^{20,21} (Fig. 11–1). Cord atrophy occurs less frequently, and gadolinium enhancement may occur.^{21,30} An MRI scan of the brain in patients with cognitive dysfunction may show increased signal in the periventricular white matter (cerebrum and brainstem) and the

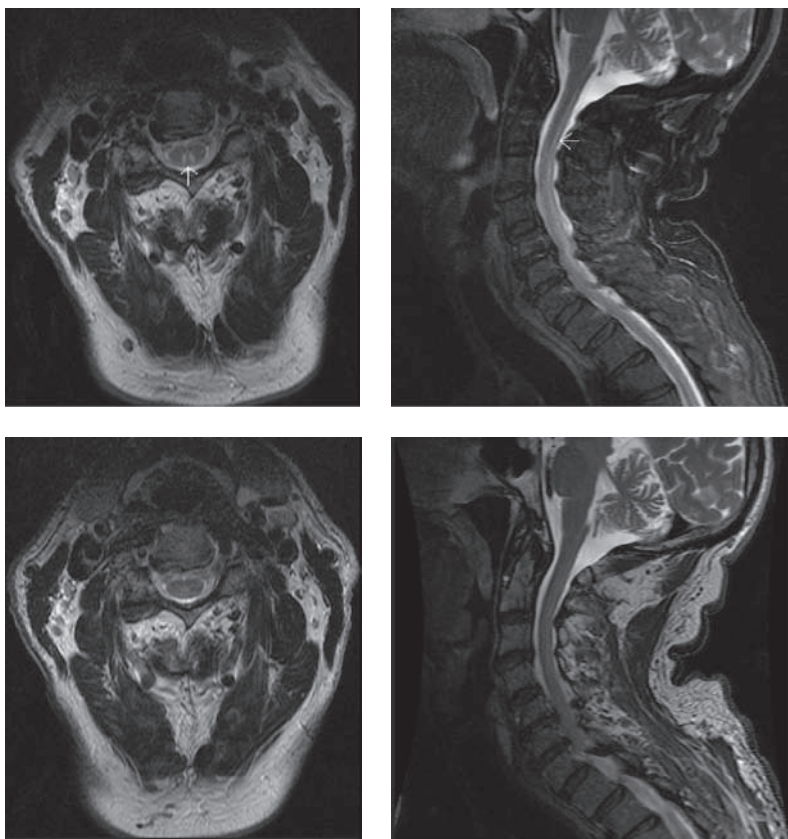


Figure 11–1. Axial (A) and sagittal (B) T2-weighted cervical MRI scan showing hyperintensity of the dorsal columns (arrow) in a patient with severe vitamin B₁₂ deficiency. Clinical and imaging (C and D) improvement followed several months of parenteral treatment.

corpus callosum.^{20,31} Diffusion tensor imaging shows reduced anisotropy and more extensive periventricular white matter involvement.³²

Nerve Biopsy/Pathology

Limited studies of sensory nerves show axonal degeneration with loss of myelinated fibers.^{33–35} Rare autopsy studies of subacute combined degeneration (or combined system disease) show patchy degeneration of white matter in the spinal cord and occasionally in the brain and optic nerves.³⁶ There is a predilection for the posterior columns and corticospinal tracts of the cervical and upper thoracic regions. Both myelin and axonal degeneration occurs, with late marked gliosis.³⁶

Rhesus monkeys deprived of vitamin B₁₂ show early lesions of the posterior columns characterized by separation of myelin lamellae and formation of intramyelinic vacuoles, leading eventually to complete destruction of myelin sheaths.³⁷ With more advanced disease, there is degeneration of axons and marked gliosis.³⁷ Unlike in humans, there is early and prominent retrobulbar optic nerve and chiasm involvement without peripheral nerve involvement.³⁸

Pathogenesis

It is unclear if the classic explanation for subacute combined degeneration of the CNS, inhibition of methylmalonyl coenzyme A (CoA) mutase with deficiency of succinyl CoA, plays a role. It was proposed that succinyl CoA is replaced by propionyl CoA, impairing membrane lipid and myelin synthesis. However, this has been challenged by the finding that methylmalonyl CoA mutase was normal in a hereditary form of cobalamin deficiency that showed characteristic CNS lesions of subacute combined degeneration.³⁹ It has been suggested that inhibition of methionine synthetase, which converts homocysteine to methionine, is the mechanism. This is also supported by the occurrence of hematologic and neurologic features of vitamin B₁₂ deficiency in nitrous oxide toxicity, which also inhibits methionine synthetase.⁴⁰

Treatment, Course, and Prognosis

The usual recommendation for vitamin B₁₂ replacement in both neurologic and hematologic disease is 1000 µg of cyanocobalamin or hydroxycobalamin IM daily for a few days, once weekly for 1 month, and then monthly for life. This regimen may be necessary in patients with pernicious anemia. However, recent studies suggest that oral administration of cobalamin, 500 to 1000 µg daily, may be sufficient as maintenance therapy in elderly patients with mild absorption impairment or nutritional deficiency.¹⁸

The severity of the myeloneuropathy before treatment correlates with symptom duration and the hematocrit.²³ Rarely, patients worsen with the initiation of vitamin B₁₂ treatment. About 47% of patients recover completely with vitamin B₁₂ replacement.²³ In one series, a 50 % reduction of symptom severity was reported in 91% of patients and residual, moderate to severe, long-term disability in 6% of patients.²³ The response to treatment usually begins within the first 3–6 months, with more gradual recovery over the next year or more.⁴¹

VITAMIN B₁ (THIAMINE) DEFICIENCY

Clinical Features

EPIDEMIOLOGY

Historically, thiamine deficiency in developed countries has usually been associated with alcoholism.⁴² However, bariatric surgery has become an increasingly common cause.⁴³ Other causes include hepatitis C infection, chronic hemodialysis, colonic surgery, protracted vomiting, and drastic weight reduction.^{42,44} The incidence or prevalence of thiamine deficiency, and of polyneuropathy due to thiamine deficiency, is unknown. In a large cohort of elderly persons in Taiwan, thiamine deficiency was observed in 16% of men and 14% of women.⁴⁵ Following gastric bypass surgery, thiamine deficiency occurs in about 18% of patients and is more common in blacks than in whites.¹⁴ Wernicke encephalopathy occurs in about 8%–9%, typically 4–12 weeks following bariatric surgery.^{9,43}

SOURCES, REQUIREMENTS, AND ABSORPTION

Thiamine is found in fortified breads/rice, cereals, pasta, whole grains, lean meats (pork, beef), fish, legumes, nuts, oats, and soybeans. The minimum daily requirement is 1.1 mg for women and 1.2 mg for men. Only about 25 mg is stored in the body. Daily gastrointestinal absorption capacity is limited to 5–10 mg, so oral administration in excess of this amount is excreted in the feces (an important issue in treating neurologic deficiency syndromes). Ethanol decreases thiamine absorption, reduces hepatic stores, and diminishes phosphorylation of thiamine to its active form.⁴⁶

SYMPTOMS AND SIGNS

Alcoholic polyneuropathy without thiamine deficiency causes slowly progressive, symmetric dysesthesias, burning pain, loss of pin and temperature sense in the feet, and reduced or absent ankle jerks, with relative preservation of autonomic function.^{47–49} Symptoms progress proximally in the legs and may involve the hands.⁴⁸ By contrast, patients with thiamine deficiency unrelated to alcohol dependency have more frequent distal weakness, less neuropathic pain, and greater large-fiber sensory loss, although distal sensory loss remains a common early feature⁴⁸ (Table 11–1). Acute progression, over 1 month, is more frequent in patients with thiamine deficiency alone; many of these patients have an acute nutritional status change following gastric (but not bariatric) surgery.⁴⁸

In patients with thiamine deficiency neuropathy, associated conditions include gastrectomy (36% of patients with compared to 56% without alcoholism), Wernicke encephalopathy (32% with compared to 22% without alcoholism), and heart failure (50% with compared to 69% without alcoholism).⁴⁸ These conditions are absent in alcoholic neuropathy patients without thiamine deficiency.

Laboratory Studies

BLOOD TESTS

Thiamine deficiency is best assessed by measurement of transketolase activity before and

after the addition of thiamine pyrophosphate. An activity coefficient of >1.25 is considered abnormal. Thiamine or the phosphorylated esters of thiamine in serum or blood may also be measured by high-performance liquid chromatography (HPLC) to detect deficiency.^{50,51}

ELECTRODIAGNOSTIC STUDIES

In patients with thiamine deficiency, conduction abnormalities are greater in the legs than in the arms and sural response amplitudes are often reduced, with lesser reductions in tibial compound muscle action potential (CMAP) amplitudes and conduction velocities.⁴⁸ These findings are consistent with a length-dependent axonal process.

CEREBROSPINAL FLUID

The CSF studies typically show normal protein and no cells in thiamine deficiency with CNS disease. However, false positive oligoclonal bands and 14-3-3 protein are reported in isolated cases of Wernicke encephalopathy.^{52,53}

IMAGING

Brain MRI in Wernicke disease shows increased signal on T2 and diffusion-weighted images in the bilateral paramedian thalamus, mamillary bodies, and periaqueductal gray matter.^{54,55} The apparent diffusion coefficient (ADC) values are decreased in corresponding lesions.^{54,55}

Nerve Biopsy/Pathology

Sural nerve biopsies in thiamine deficiency and alcoholism both show features of axonal neuropathy.⁴⁸ However, patients with nonalcoholic thiamine deficiency show greater large-fiber loss, more subperineurial edema, and less myelin irregularity, demyelination, and remyelination than those with alcoholic polyneuropathy.⁴⁸ In recent-onset cases of alcoholic polyneuropathy, small-fiber loss predominates.^{48,49} Chickens deprived of thiamine develop polyneuropathy characterized by axonal loss and minimal secondary segmental demyelination.⁵⁶

Pathogenesis

The pathogenesis of thiamine deficiency neuropathy is largely unstudied. Thiamine diphosphate, the active form of thiamine, serves as a cofactor for several enzymes involved in carbohydrate metabolism and is important in neurotransmitter synthesis, oxidative stress defense mechanisms, and biosynthesis of nucleic acid precursors.⁵⁷ The CNS in thiamine-deficient rats shows a reduction in the mitochondrial enzyme alpha-ketoglutarate dehydrogenase complex, possibly compromising mitochondrial oxidation.⁵⁸ Increased gene expression in the inferior colliculus and thalamus of thiamine-deficient rats involves transcripts associated with inflammation, cellular stress, cell death and repair, and metabolism.⁵⁹ In the thalamus and inferior colliculus of thiamine-deficient mice, pathologic effects in CNS regions, neuronal loss, and an increase in microglia begin in 8–9 days and reach a nadir by day 11; thiamine reverses the pathologic changes only if given by day 9.⁶⁰

Treatment, Course, and Prognosis

In acute thiamine deficiency with neurologic disease, parenteral thiamine, 100 mg daily for 1 week (to overcome any malabsorption), is followed by 100 mg/day orally until symptoms resolve.⁵⁰ Thiamine is available in an oral form over the counter. In nonalcoholic thiamine deficiency polyneuropathy, patients have greater distal motor deficits and, as a result, greater impairment in activities of daily living than patients with alcoholic polyneuropathy.⁴⁸ Additionally, up to 84% of patients with thiamine deficiency lose the ability to ambulate compared to only 25% of those with alcoholic polyneuropathy.⁴⁸ Recovery from polyneuropathy in thiamine deficiency is gradual, occurring over a few weeks to a few years.³⁶

CELIAC DISEASE

Clinical Features

EPIDEMIOLOGY

Celiac disease (CD) is a chronic inflammatory small bowel enteropathy with gluten sensitivity.

The prevalence of CD in Europe and North America is 1 in 120 to 300 persons.^{61,62} Celiac disease is more common in Caucasians, particularly those of European descent, than in blacks or Asians. There is a slight female predominance. In a polyneuropathy treatment center in the United States, 2.5% of patients with polyneuropathy had biopsy-proven CD.⁶³ The average age of symptom onset in CD-associated polyneuropathy is 55 years.⁶⁴

There is an association with specific human leukocyte antigen (HLA) class 2 haplotypes, a 26 times greater risk in first-degree relatives with CD (13%) compared to the general population (0.5%), and a significantly higher pairwise concordance of 75% in monozygotic compared to 11% in dizygotic twin pairs.⁶⁵ This suggests a strong genetic predisposition.

SYMPTOMS AND SIGNS

Patients with CD and polyneuropathy present with distal acral paresthesias, dysesthesias, and numbness. Sensory symptoms are usually symmetric, although about one-third of patients have multifocal dysesthesias involving the trunk, thighs, and buttocks.⁶³ Facial dysesthesias also occur in about one-third of patients and gait ataxia in about one-fourth of patients.⁶³ Foot drop is rare. A mononeuropathy multiplex-like presentation also occurs with sensorimotor deficits that usually begin in the legs.⁶⁶ On examination, most patients have symmetric pin, vibration, and light touch loss in the feet⁶³ (Table 11–1). About one-third of patients have either an unsteady tandem gait or a positive Romberg test. Distal leg weakness is rare in distal symmetric cases and frequent in multifocal cases.^{63,66} Tendon reflexes are reduced or absent in more severe cases.⁶⁶ In addition, CD is associated with sporadic ataxia due to cerebellar disease.^{67–70} About 50% of patients have gastrointestinal symptoms including diarrhea, loose stools, obstipation, bloating, and weight loss.^{63,66}

Laboratory Studies

BLOOD TESTS

Anti-gliadin antibodies (IgG and IgA) are a sensitive screening test that reveals abnormalities in 88%–100 of patients with

CD-associated polyneuropathy.^{63,64,71} Up to one-third of patients with idiopathic axonal polyneuropathies have positive anti-gliadin antibodies, but far fewer, 0%–9% of such patients, have biopsy-proven CD.^{63,64,72} Immunoglobulin A antibodies may be more specific for CD than IgG antibodies. Anti-tissue transglutaminase antibodies are more specific for CD but are less sensitive for CD polyneuropathy, occurring in 50%–75% of patients.^{63,64,71} Ganglioside antibodies may be present in 30% of patients.⁶³

ELECTRODIAGNOSTIC STUDIES

Nerve conduction studies may be normal in up to 50% of patients, consistent with frequent small-fiber, sensory polyneuropathy.⁶³ There may be mild late response abnormalities and sensorimotor conduction abnormalities in the legs, including low sural response amplitudes.^{63,71,73} A blink reflex is rarely prolonged, despite frequent facial paresthesias.^{63,71} In patients with a multifocal polyneuropathy, about 80% have asymmetric reductions in sensory response amplitudes without conduction slowing.⁶⁶ In patients with CD and predominantly small-fiber symptoms, conduction studies are usually normal, except for an occasional reduced sural amplitude.⁷¹

CEREBROSPINAL FLUID

The CSF is typically normal in patients with CD and cerebellar ataxia with or without polyneuropathy, except for an increase in the IgG index.^{66,68}

IMAGING

Cerebellar atrophy is common in CD patients with ataxia.⁶⁸ Bilateral white matter lesions occur in 20% of pediatric and adult patients with ataxia.^{74,75}

Nerve Biopsy/Pathology

Sural nerve biopsy in CD-associated polyneuropathy shows chronic axonopathy with loss of myelinated fibers, regenerative clusters, a few thinly myelinated fibers, and no onion bulbs, inflammatory cells, or immunoglobulin deposits by immunofluorescence.⁶³ The findings are

similar in distal, symmetric, and multifocal axonal polyneuropathies.⁶⁶ Occasional biopsies show focal epineurial and perivascular endoneurial inflammatory infiltrates.⁶⁴ Teased fiber preparations show Wallerian degeneration.⁶⁴ About two-thirds of patients have reduced epidermal nerve fiber densities, often not in a length-dependent manner.⁷¹

In CD-associated ataxia there is perivascular cuffing of CD4 and CD8 T cells in cerebellar white matter, loss of Purkinje cells, deposition of IgG on Purkinje cells, and immunocytochemical staining of Purkinje cells with anti-gliadin antibodies.^{67,70}

Pathogenesis

The pathogenesis of CD-associated polyneuropathy is unclear, but an immune-mediated neuropathy or ganglionopathy is suspected.^{63,64,66,71} An immune-mediated pathogenesis is suggested by an association of CD with certain HLA types, cross-reactivity of anti-gliadin antibodies with Purkinje cells in CD-associated ataxia, association with other autoimmune diseases (thyroid disease and dermatitis herpetiformis),⁶³ and rare perivascular inflammatory deposits in sural nerve biopsies in CD-associated polyneuropathy.⁶⁴ Additionally, vitamin B₁, B₁₂, and vitamin E deficiencies are not associated features.⁶³ The possibility of a ganglionopathy is speculative based on the frequent lack of inflammatory infiltrates in sural nerve biopsies, frequent facial paresthesias, and lack of length-dependent epidermal nerve fiber loss.⁷¹

Treatment, Course, and Prognosis

The management of CD-associated polyneuropathy involves a gluten-free diet, although there is limited data supporting diet efficacy. An unblinded, prospective trial of patients with a distal, large-fiber, sensory polyneuropathy and positive anti-gliadin antibodies showed a statistically significant difference in sural amplitudes at 1 year in patients with (+0.76 μ V) compared to those without (−0.42 μ V) a gluten-free diet ($p < 0.03$).⁷³ A response to treatment was associated with a shorter disease duration but not with reduction of anti-gliadin

antibodies.⁷³ There was subjective improvement of symptoms. However, on examination, objective evidence of neurologic improvement with gluten restriction has not been observed.^{63,73}

Immunosuppressive treatments such as intravenous immunoglobulin (IVIG), plasma exchange, prednisone, azathioprine, mycophenolate mofetil, and etanercept have been largely ineffective in small, uncontrolled series.^{63,66} However, a minority of patients treated with IVIG have reported modest improvement in gait, strength, and sensation.^{63,66} One patient with a multifocal axonal polyneuropathy had reduced hand weakness with IVIG, but weakness recurred 2 months after cessation of therapy.⁶⁶

Patients with CD and a distal, symmetric, sensory polyneuropathy progress gradually, over months to years, and patients with multifocal polyneuropathy may have a more acute presentation.^{63,64,66} The majority of patients with CD polyneuropathy do not improve with gluten restriction or immunosuppressive therapy. Follow-up is limited.

VITAMIN E (α -TOCOPHEROL) DEFICIENCY

Clinical Features

EPIDEMIOLOGY

Serum α -tocopherol levels are higher in women than in men.⁷⁶ Serum levels increase with age and blood lipids. The prevalence of α -tocopherol deficiency in Taiwan is 1.0% in adults and is similar in Europe.^{76,77}

SOURCES, REQUIREMENTS, AND ABSORPTION

Vitamin E refers to the 2R stereoisomers of tocopherol. After small bowel absorption, vitamin E is extracted from chylomicrons by the liver, and a hepatic tocopherol transport protein integrates it into very low density lipoprotein (VLDL).⁵⁰ Vitamin E is widely distributed in food, and dietary deficiency is exceedingly rare. Sunflower, safflower, and wheat germ oils are high in vitamin E. It is also present in meats, nuts, and cereal grains,

with lesser amounts in fruits and vegetables.⁵⁰ Serum levels increase with age and blood lipids. Vitamin E deficiency occurs in malabsorption syndromes, small bowel resection, cystic fibrosis, prolonged cholestasis, abetalipoproteinemia, and a genetic defect in the tocopherol transport protein.^{50,76} A mutation in the tocopherol transfer protein gene, located on chromosome 8q, results in impaired tocopherol insertion in VLDL. This causes a spinocerebellar degeneration resembling Friedreich ataxia, but it responds to high-dose vitamin E supplementation.^{78–80}

SYMPTOMS AND SIGNS

Patients with vitamin E deficiency from either malabsorption or a mutation in the tocopherol transfer protein affecting the nervous system present with gait ataxia with variable acral paresthesias, ankle weakness, dysarthria, and visual disturbances^{4,81–83} (Table 11–1). Examination may show a combination of cerebellar, myelopathic, and neuropathic signs including gait and limb ataxia, marked proprioceptive loss, hyporeflexia, variable plantar responses, tremor, dysarthria, gaze palsies, and occasional visual loss.^{4,81–83} Pin and temperature senses are spared.^{4,83} Cognitive impairment is not reported in vitamin E–deficient patients with myeloneuropathy. However, encephalopathy rarely occurs in α -tocopherol transfer protein deficiency with ataxia, and infants with cystic fibrosis and nutritional vitamin E deficiency may show cognitive impairment.^{84,85}

Laboratory Studies

BLOOD TESTS

Complete blood cell counts (CBC), lipid levels, and electrolytes are normal in isolated vitamin E deficiency. Liver function tests are normal unless the cause of vitamin E deficiency is hepatobiliary disease. Fat malabsorption can also be screened for with a 72-hour fecal fat determination, vitamin A, K, and D levels, and an amylase level.⁴ The α -tocopherol levels are reduced.^{2,4,83} Abetalipoproteinemia is screened for with a CBC for acanthocytes, a lipid panel, an apolipoprotein B level, and a quantitative beta low-density lipoprotein (LDL) level.

ELECTRODIAGNOSTIC STUDIES

Nerve conduction studies in vitamin E deficiency show low sensory more than low motor response amplitudes, relatively preserved conduction velocities, and absent H reflexes.^{2,4,83,86} Fibrillations may be present in distal limb muscles.² Somatosensory evoked responses may show delayed central conduction time.^{81,83,86}

CEREBROSPINAL FLUID

The CSF findings are generally normal.⁸³

IMAGING

An MRI scan of the cervical spine may show increased signal in the posterior columns on T2-weighted images without gadolinium enhancement.⁸⁷

Nerve Biopsy/Pathology

Sural nerve biopsy findings are rare in patients with vitamin E deficiency and polyneuropathy. One patient had rare degenerating, large, myelinated axons on electron microscopy, while others were normal.⁸⁶ The tocopherol content in sural nerves was significantly lower in patients with familial vitamin E deficiency than in controls, and in some patients this preceded nerve fiber degeneration.¹

Pathogenesis

Vitamin E is an antioxidant that is an efficient pyroxyl radical scavenger. This protects LDLs and polyunsaturated fats in membranes from oxidation. Rats maintained on a vitamin E-deficient diet develop ataxia, muscle wasting, and axonal dystrophic changes in the rostral dorsal columns, particularly the gracile fasciculi; these consist of axonal swellings of both normal and abnormal organelles, including mitochondria and smooth endoplasmic reticulum.⁸⁸ Peripheral nerve axons show similar but less prominent changes. More prominent axonal degeneration in muscle spindles and cutaneous

sensory corpuscles (distal nerve segments) than in proximal nerve trunks suggests a “dying back” process.⁸⁹ Lipofuscin accumulates in dorsal root ganglia.^{5,89}

Monkeys maintained on a vitamin E-deficient diet for over 30 months develop similar degeneration of distal-to-proximal sensory axons in the posterior columns, dorsal roots, and peripheral nerves, with proportionally less degeneration of dorsal root ganglia and anterior horn cell neurons.⁹⁰ A necrotizing myopathy is also frequent. There is additional evidence in rats of interrupted fast anterograde and retrograde transport.⁸⁸ Mitochondria generate free radicals continuously, and the membranes of mitochondria and smooth endoplasmic reticulum may be more susceptible to damage from vitamin E deficiency because they contain a high proportion of polyunsaturated fatty acyl chains.⁹⁰ A disturbance of the axonal mitochondria could then lead to the reported abnormalities in fast retrograde transport, with a resulting dying-back axonal neuropathy.⁹⁰

Treatment, Course, and Prognosis

Vitamin E is started at 800 mg daily (α -tocopherol) and may be increased to 100 mg/kg/day until blood levels normalize.^{4,86} In patients unresponsive to oral therapy, vitamin E may be given parenterally at a dose of 100 mg/week. Vitamin E also protects against the development of cisplatin- and paclitaxel-induced polyneuropathy at a dose of 300 mg po bid.⁹¹

The polyneuropathy and ataxia associated with vitamin E deficiency may improve in terms of symptoms, clinical signs, and nerve conduction parameters (sensory response amplitudes), particularly when treatment is started within 15 years of onset.^{2,4,83,92} Tremor and ataxia tend to improve more than posterior column and reflex function.⁹² When neurologic improvement occurs, it is gradual, occurring over several months to a few years.^{2,83} In patients with clinical improvement, sensory response amplitudes may improve, suggesting reinnervation.^{2,83} Other patients may only stabilize neurologically with vitamin E supplementation.⁴

COPPER DEFICIENCY

Clinical Features

EPIDEMIOLOGY

The incidence of copper deficiency is unknown. It occurs as an acquired deficiency or a hereditary defect in copper metabolism (Menkes disease).⁹³ The mean age of onset is about 56 years in copper-deficient patients with myeloneuropathy.⁶

SOURCES, REQUIREMENTS, AND ABSORPTION

Copper is an essential trace element that is a component of critical metalloenzymes that play a role in the structure and function of the nervous system, iron metabolism, melanin synthesis, superoxide free radical scavenging, and collagen synthesis.^{6,50} It is a component of the following enzymes: amine oxidases, ferroxidase (ceruloplasmin), cytochrome-c oxidase, superoxide dismutase, and dopamine hydroxylase.⁵⁰ Dietary sources of copper include shellfish, liver, nuts, legumes, and bran.⁵⁰ The site of copper absorption in humans is unclear, although animal studies suggest absorption along the entire upper gastrointestinal tract, and hypocupremia does occur postgastrectomy.⁶ Copper deficiency was historically reported in malnourished children.⁹³ More recent recognized causes include gastric surgery, malabsorption, parenteral alimentation, zinc ingestion (including long-term use of zinc-containing denture cream), and nephrotic syndrome.^{6,94}

SYMPTOMS AND SIGNS

In copper deficiency, the chief complaint is typically gait difficulty or ataxia; lower limb paresthesias are also very common at presentation.^{6,95} The gait is typically ataxic, with a variable degree of stiff-leggedness and spasticity⁶ (Table 11–1). Weakness is variably present, typically mild, and found in an upper motor neuron pattern, although more significant foot drop may occur.^{6,7,95,96} Knee jerks are generally increased, and ankle jerks may be brisk or reduced.^{6,7,96} The majority of patients have extensor plantar responses.^{6,96}

Vibration or position sense is decreased in the limbs, sometimes markedly, and about two-thirds of patients have stocking pin and touch loss.⁶ A Lhermitte sign may rarely be present.^{94,95} Some patients have a sensory level to the upper thighs.⁹⁵

Laboratory Studies

BLOOD TESTS

Hypocupremia is diagnosed by the combination of reduced serum copper levels ($<0.75 \mu\text{g/mL}$) and reduced ceruloplasmin (normal, 22.9–43.1 mg/dL).⁹⁴ Zinc excess causes secondary copper deficiency and should be checked by measuring serum zinc levels (normal, 0.66–1.10 $\mu\text{g/mL}$).⁶ A 24-hour urinary zinc level test is probably oversensitive for zinc excess.⁶ About 50% of patients with copper deficiency have associated anemia. Other associated findings include leukopenia (neutropenia) and vitamin B₁₂ deficiency in about one-third of patients.^{94,96} Thrombocytopenia is rare.⁹⁴ Iron excess may also result in hypocupremia.⁹⁴ Bone marrow biopsy findings are characteristic and include an increase in immature and vacuolization of granulocytic and erythroid precursor cells and ringed sideroblasts (from iron deposition).

ELECTRODIAGNOSTIC STUDIES

In the largest series of patients with copper deficiency myeloneuropathy, 21 of 24 patients had an axonal polyneuropathy.⁹⁴ The neuropathy is usually sensorimotor, although about one-third of patients with polyneuropathy have predominant motor involvement, occasionally affecting the posterior interosseous nerve.⁹⁴ About one-half of patients have moderate to severe disease with low or absent sensory and motor response amplitudes and fibrillations on EMG.^{7,94} Somatosensory evoked responses show central conduction delay in about one-third of patients.^{7,94} Somatosensory conduction abnormalities suggesting dorsal column and possibly radicular dysfunction may better explain the prominent large-fiber sensory loss than the relatively mild nerve conduction abnormalities.⁹⁵ Visual evoked potentials are occasionally abnormal.⁹⁴

CEREBROSPINAL FLUID

In hypocupremia, CSF protein is typically normal but may be elevated in some patients.^{6,7}

IMAGING

Similar to vitamin E and B₁₂ deficiencies, copper deficiency may show increased T2 signal in the spinal cord, most commonly in the dorsal midline cervical and thoracic segments.⁹⁷ Resolution of abnormal signal can follow copper supplementation.⁹⁷ Cord atrophy may be present in chronic cases.⁹⁴ Cerebral white matter may show nonspecific increased T2 signal foci.⁶

Nerve Biopsy/Pathology

In copper deficiency myeloneuropathy, sensory nerve biopsy shows axonal degeneration and rare inflammatory infiltrates.⁶ Muscle biopsy in one patient showed vacuolar changes.^{6,95}

Pathogenesis

The cause of myelopathy and neuropathy in acquired copper deficiency is unknown. Menkes disease is a genetic cause of copper deficiency since birth, and mutations in ATP7A cause many of the neurologic and systemic manifestations.⁹⁸ ATP7A encodes a copper-transporting adenosine triphosphate. Loss of ATP7A function results in impaired copper transport in the gastrointestinal tract, placenta, and blood-brain barrier and copper deficiency.⁹⁴ High-affinity transporters Ctr1 and Ctr3 transport copper into mammalian cells to critical copper-containing enzymes such as cytochrome C oxidase and copper-zinc superoxide dismutase.⁹⁴ A speculative cause of myeloneuropathy in copper deficiency may be impaired mitochondrial function in dorsal column and peripheral nerve axons, similar to that proposed for vitamin E deficiency.

Zinc excess also causes copper deficiency. Zinc increases metallothionein synthesis in gut epithelium.⁶ Copper binds metallothionein with a higher affinity than zinc and remains bound in the gastrointestinal tract.^{6,96}

Treatment, Course, and Prognosis

When copper deficiency is diagnosed in adults, the usual treatment is 2 mg daily of copper sulfate or acetate solution for several months with periodic monitoring of serum copper levels.^{41,96,99} If copper absorption is problematic, higher doses of copper may be required: up to 8 mg daily.⁷ Copper chloride at a dose of 1 or 2 mg may be given parenterally.¹⁰⁰

With oral or parenteral copper supplementation, about 90% of patients with copper deficiency myeloneuropathy achieve normal copper levels.⁹⁴ Hematologic abnormalities reverse rapidly, while neurologic improvement is the exception and is mostly subjective.^{94,99} A minority of patients show improved proprioception and vibration sense, but most patients merely stabilize.^{6,7} Occasional patients have had reversal of increased T2 signal abnormalities in the dorsal column, improved central conduction time on somatosensory evoked potentials, or improved sensory nerve conduction.^{6,94,96}

OTHER: CUBAN EPIDEMIC OPTIC AND PERIPHERAL NEUROPATHY; DEFICIENCIES: RIBOFLAVIN (VITAMIN B₂), PYRIDOXINE (VITAMIN B₆), FOLATE, ZINC; BARIATRIC SURGERY

The **Cuban epidemic optic and peripheral neuropathy** was associated with nutritional deficiencies (possibly a combination of vitamin B₁₂, thiamine, riboflavin, niacin, and methionine) and exposure to toxins (especially tobacco).^{10–12,101} There were patients with optic and peripheral neuropathy forms; both demonstrated weight loss and fatigability.¹⁰¹ The optic features were subacute (3–30 days), painless, symmetric loss of visual acuity and color vision with central or cecocentral scotomata. The neuropathy was characterized by stocking-glove sensory loss (suggesting a distal axonopathy), leg cramps, hearing loss, sensory ataxia, and hyperactive or absent reflexes.^{11,101} The epidemic did not appear to relate to mitochondrial DNA mutations associated with Leber hereditary optic neuropathy.^{102,103}

Riboflavin (vitamin B₂) deficiency causes a demyelinating sensorimotor polyneuropathy with tomacula (focal paranodal myelin swellings) in chickens.^{104–106} However, there is no definitive evidence that riboflavin deficiency causes neuropathy in humans. Riboflavin and possibly thiamine deficiencies are reported in patients with Nigerian tropical ataxic polyneuropathy.¹⁰⁷ However, the cause is unknown and B-vitamin deficiencies are not considered a major factor in disease pathogenesis.^{107,108} Additionally, exposure to cyanide and cassava is not associated with Nigerian ataxic polyneuropathy.¹⁰⁸

Pyridoxine (vitamin B₆) deficiency is rare and is not associated with polyneuropathy in humans; however, it may cause a mild polyneuropathy in rats deprived of vitamin B₆.¹⁰⁹ Pyridoxine supplementation may protect against toxic polyneuropathy caused by isoniazid or hydralazine.^{110,111} Isoniazid increases urinary excretion of vitamin B₆ and interferes with its action as a coenzyme.¹¹² Pyridoxine excess is a greater concern, since patients who ingest high daily doses of pyridoxine (200 mg to 10 g) may develop a distal sensory axonopathy or neuronopathy in a dose-dependent manner.¹¹³

Folate deficiency is reported to cause polyneuropathy and optic neuropathy in humans, but data are limited.^{114–116} Small series of patients suggest axonal polyneuropathy with or without subacute combined degeneration of the spinal cord.^{114,115} Vitamin B₁₂ levels in these patients were normal, but the reports preceded the era of methylmalonic acid testing to assess vitamin B₁₂ metabolism. The few patients with optic neuropathy had additional tobacco and alcohol exposure.¹¹⁶ The main support for the association is that optic and peripheral nerve function may improve with folate administration.

Zinc deficiency causes a mild axonal polyneuropathy in chicks and guinea pigs; in guinea pigs, it is characterized by abnormal posture and gait, hyperesthesia, motor and sensory conduction slowing, prolonged somatosensory evoked potentials, normal myelinated fiber densities, and reduced nerve sodium, potassium adenosine triphosphatase (Na, K-ATPase) activity and simple sugar concentrations.^{117,118} However, in humans, zinc deficiency is a rare, usually genetic disorder in children (acrodermatitis enteropathica)

that has not been associated with polyneuropathy. Zinc excess from supplement use or excessive use of denture cream is more problematic and causes myeloneuropathy from secondary copper deficiency.^{6,119} There may be an association of zinc deficiency with optic neuropathy.^{120,121} Optic nerves of zinc-deficient rats show loss of myelinated fibers, myelin thinning, and glial cell proliferation.¹²² Toxic optic neuropathy from ethambutol, clioquinol, or cimetidine may relate to zinc chelation and secondary deficiency.^{122–124}

Neurologic complications following **bariatric surgery** are common. Some are due to malabsorption resulting in nutritional deficiencies discussed above (thiamine, vitamin B₁₂, and copper deficiencies). These include myelopathy, polyneuropathy, and encephalopathy.^{6,9,43,125} It is unclear if thiamine deficiency causes optic neuropathy; patients cited had other nutritional deficiencies and toxic exposure (alcohol, tobacco).⁴³ Acute neurologic syndromes after bariatric surgery include encephalopathy (Wernicke disease), mononeuropathies, radiculoplexus neuropathy, Guillain-Barré syndrome, and rhabdomyolysis.^{8,9,125} Mononeuropathies (radial, peroneal at the fibular head, sciatic, lateral femoral cutaneous neuropathies) often occur as a postoperative complication.⁸ Carpal and cubital tunnel syndromes develop subacutely, and median nerve entrapment is relatively frequent.⁸ Radiculoplexus neuropathy is likely an inflammatory disorder; this and carpal tunnel syndrome were associated with diabetes mellitus.⁸ Myelopathy, polyneuropathy, and optic neuropathy are late complications.⁹ Myelopathy may occur a decade after surgery.⁹ Sural nerve biopsies in patients with polyneuropathy show axonal degeneration and mononuclear inflammatory cells.⁸

Risk factors for peripheral neuropathies after bariatric surgery include rate of weight loss and total weight loss, prolonged gastrointestinal symptoms, not attending a nutritional clinic, low serum albumin, surgical complications, and jejunioileal bypass.⁸ Vitamin B₁₂ deficiency is present in 25%–42% of bariatric surgery patients with neurologic complications.^{9,125} In one series, copper deficiency occurred in 15% of patients.⁹ Both vitamin B₁₂ and copper deficiencies are associated with myelopathy in this population.⁹

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Vascular/Ischemic Neuropathies

VASCULITIC NEUROPATHIES

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VASCULITIC NEUROPATHIES

Introduction

Vasculitis refers to inflammatory destruction of blood vessel walls with resultant ischemic tissue injury. Vasculitides affecting small to medium-sized arteries commonly cause neuropathy by involvement of the epineurial vasa nervorum. An entirely satisfactory classification of the vasculitides awaits further developments in pathogenetic and etiologic understanding. In 1994, an international consensus conference (the Chapel Hill Consensus Conference) adopted the following nomenclature based on vessel size and histopathology, although not nerve pathology: large vessel vasculitis: giant cell (temporal) arteritis (GCA), Takayasu arteritis; medium-sized vessel vasculitis: classic polyarteritis nodosa (cPAN), Kawasaki disease; small vessel vasculitis: Wegener granulomatosis (WG), Churg-Strauss syndrome (CSS), microscopic polyangiitis (MPA), Henoch-Schönlein purpura (HSP), essential cryoglobulinemic vasculitis, and cutaneous leukocytoclastic angiitis.¹ Collins and Kissel

provide a comprehensive classification of those vasculitides associated with neuropathy, first distinguishing those resulting from direct vessel wall infection from those with an immunologic mechanism; the latter are then divided into systemic necrotizing vasculitides, hypersensitivity vasculitides, giant cell arteritides, and localized vasculitides (nonsystemic vasculitic neuropathy).² Many authors divide the vasculitides initially into systemic and nonsystemic types.³⁻⁵ The systemic forms are either primary, with no established cause (cPAN, WG, CSS, MPA), or secondary, associated with a variety of disorders (connective tissue diseases, sarcoidosis, infections, drugs, malignancies). The nonsystemic form confined clinically to nerve is referred to as *nonsystemic vasculitic neuropathy* (NSVN).⁶⁻⁹ Tables 12-1 to 12-4 summarize the vasculitides associated with neuropathy. The radiculoplexus neuropathies are included; they have been conceptualized as monophasic, restricted forms of NSVN since microvasculitis is demonstrable.³ For the connective tissue disorders, both vasculitic and nonvasculitic neuropathy types are listed.

Table 12–1 Primary Systemic Vasculitides^{2,3,5,12,22}

Disorder	Vessels Involved/Clinical Features	Neuropathy Frequency/Phenotypes
Classic polyarteritis nodosa (cPAN)	Medium-sized and small arteries; multi-organ, especially kidney, gastrointestinal tract, skin, and peripheral nerve; hepatitis B virus (HBV) antibody ~30%–50 %; arteriography: microaneurysms, stenoses	~38%–72%; mononeuropathy multiplex, asymmetric polyneuropathy, distal symmetric polyneuropathy
Wegener granulomatosis (WG)	Small to medium-sized vessels; granulomatous inflammation in upper and lower respiratory tracts, glomerulonephritis; cANCA (sensitivity ~28%–92%, specificity ~80%–100%)	~40%–50%; mononeuropathy multiplex, asymmetric polyneuropathy, distal symmetric polyneuropathy
Churg-Strauss syndrome (CSS)	Small to medium-sized vessels; granulomatous, eosinophilic tissue infiltrates; fever, eosinophilia, asthma, pulmonary infiltrates; cANCA or pANCA ~2%–50%	~70%–80%; mononeuropathy multiplex, asymmetric polyneuropathy, distal symmetric polyneuropathy
Microscopic polyangiitis (MPA)	Small vessels; no granulomas; glomerulonephritis; pulmonary hemorrhage; pANCA ~50%–80%, cANCA ~10%–50%	~60%–70%; mononeuropathy multiplex, asymmetric polyneuropathy, distal symmetric polyneuropathy
Giant cell arteritis ^{61,62} (GCA) (Temporal arteritis)	Most common systemic vasculitis; granulomatous, large and medium-sized arteries; onset after age 50; female:male ratio ~2:1; headache, jaw claudication, constitutional symptoms; polymyalgia rheumatica (~50%); ischemic optic neuropathy; elevated ESR/CRP	~15%; polyneuropathy, mononeuropathy multiplex, mononeuropathies, brachial plexopathy, midcervical radiculopathy

Table 12–2 Secondary Systemic Vasculitides: Connective Tissue Disorders^{3,63,64}

Disorder	Vessels Involved/Clinical Features	Neuropathy Frequency/Phenotypes
Rheumatoid arthritis ⁶⁵ (RA)	Small to medium-sized arteries; symmetrical distal synovitis; constitutional symptoms; +RF (~90%); +CCP (cyclic citrullinated peptides); rheumatoid vasculitis seen late in severe seropositive RA	~50% of patients with rheumatoid vasculitis; vasculitic mononeuropathy multiplex or sensory polyneuropathy; nonvasculitic, mild, symmetric sensory or sensorimotor polyneuropathy and entrapment neuropathies common
Systemic lupus erythematosus (SLE)	Small to medium-sized arteries; multi-system, relapsing-remitting; malar or discoid rash, nephropathy, arthritis, serositis, cerebritis, myelosuppression; +ANA (>95%), anti-Sm (~30%–40%), anti-dsDNA (~60%–70%)	~10% clinical neuropathy; asymmetric or multifocal neuropathy, sensorimotor polyneuropathy, lumbosacral polyradiculopathy, small-fiber neuropathy or fulminant Guillain-Barré syndrome-like presentations
Sjögren syndrome ^{66,67,68} (SS)	Diagnosis usually follows appearance of neuropathy; primary or secondary (associated with RA or SLE); exocrine gland lymphocytic infiltrates; sicca syndrome; multisystem extraglandular involvement; focal or multifocal brain or spinal cord disease mimicking multiple sclerosis; anti-RNP ~40%–75% (Ro/SS-A > La/SS-B)	~25%; vasculitic patterns: distal sensory neuropathy, mononeuropathy multiplex, multiple cranial neuropathy; ganglioneuropathic patterns: sensory ataxic, painful small-fiber, autonomic, trigeminal neuropathies

(continued)

Table 12–2 (continued)

Disorder	Vessels Involved/Clinical Features	Neuropathy Frequency/Phenotypes
Progressive systemic sclerosis ^{68–71} (PSS) (scleroderma)	Diffuse multiorgan fibrosis; limited variant: CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia); ANA (~100%), anti-Scl-70 (scleroderma) (~40%), anti-centromere (CREST) (~70%)	~20%–25% with electrodiagnosis; trigeminal sensory neuropathy, brachial plexopathy, mononeuropathy multiplex, sensorimotor polyneuropathy, autonomic neuropathy, carpal tunnel syndrome (CTS), subclinical form common
Mixed connective tissue disease ^{68,69,72,73} (MCTD)	Overlapping clinical features of SLE, scleroderma, and myositis; anti-U1-RNP antibodies, also ANA and RF	Trigeminal sensory neuropathy, CTS, rare report of vasculitic neuropathy
Undifferentiated connective tissue disease ^{69,74} (UCTD)	Patients with symptoms and signs of, but not yet fulfilling criteria for, a defined CTD; ~30% develop a defined CTD	Trigeminal sensory neuropathy, rare report of vasculitic neuropathy
Behçet disease ⁷⁵ (BD)	All vessels; young adults; Eastern Mediterranean and Asian descent; relapsing-remitting; oral and genital ulcers, meningoencephalitis/myelitis, uveitis, cerebral venous thrombosis, gastrointestinal inflammation and ulceration, cutaneous lesions; pathergy	Uncommon; sensorimotor polyneuropathy, mononeuropathy multiplex, recurrent facial palsy, motor-predominant polyradiculoneuropathy

Table 12–3 Secondary Systemic Vasculitides: Hypersensitivity Vasculitis

Disorder	Vessels Involved/Clinical Features	Neuropathy Frequency/Phenotypes
Henoch-Schönlein purpura ⁷⁶ (HSP)	Small vessels; predominantly children; often antecedent respiratory infection; palpable purpura, glomerulonephritis, arthritis, gastrointestinal involvement; skin biopsy: leukocytoclastic vasculitis with blood vessel wall IgA deposits	Rare reports of mononeuropathy multiplex, brachial plexopathy, or Guillain-Barré syndrome
Mixed cryoglobulinemia ^{77,78,79,80} (MC)	Small vessels; associated with hepatitis C in ~80%–90%; also lymphoproliferative and connective tissue diseases; RF (~70%–80%); type II cryoglobulins—mixture of monoclonal and polyclonal immunoglobulins; palpable purpura, arthralgia, glomerulonephritis, hepatitis, edema, cerebrovascular	Neuropathy common (~20%–90%); mononeuropathy multiplex, small-fiber sensory neuropathy, sensory or sensorimotor polyneuropathy (symmetric or asymmetric), few mixed axonal/demyelinating, CTS
Sarcoidosis ⁸¹	Discussed in Chapter 9; noncaseating granulomatous angiitis observed on biopsy or autopsy of some cases	Mononeuropathy, mononeuropathy multiplex, sensorimotor polyneuropathy, Guillain-Barré syndrome, CIDP, cranial neuropathies

(continued)

Table 12–3 (Continued)

Disorder	Vessels Involved/Clinical Features	Neuropathy Frequency/ Phenotypes
Infections ⁸²	Many agents; direct infection or immunologic mechanisms; common viral agents: HIV, HTLV-1, CMV, hepatitis B and C, varicella-zoster, parvovirus B19	Varied
Paraneoplastic ^{27,83}	Small vessels; small cell lung cancer and lymphoma most common; elevated ESR and CSF protein; anti-Hu antibody occ.	Symmetric or asymmetric polyneuropathy, mononeuropathy multiplex, sensory neuronopathy
Drugs ⁸⁴	Many reported; most common: antibiotics, propylthiouracil, hydralazine, colony-stimulating factors, allopurinol, D-penicillamine, phenytoin, isotretinoin, methotrexate; illicit drugs: cocaine, heroin, amphetamines	Mononeuropathy multiplex, plexopathy (heroin)
Eosinophilia-myalgia syndrome ^{85,86,87,88} (EMS)	Eosinophilia, myalgia, fasciitis, scleroderma-like skin changes associated with contaminated L-tryptophan ingestion	Axonal mononeuropathy multiplex, demyelinating polyneuropathy

Table 12–4 Nonsystemic Vasculitic Neuropathies

Disorder	Vessels Involved/Clinical Features	Neuropathy Frequency/ Phenotypes
Generalized		
Nonsystemic vasculitic neuropathy ¹¹ (NSVN)	Small vessels; most common peripheral nervous system (PNS) vasculitis; clinically restricted to peripheral nerve, but pathologically muscle often involved; constitutional symptoms and laboratory abnormalities, including ESR, milder and less frequent than in SVN, do occur	100%, by definition; mononeuropathy multiplex, asymmetric polyneuropathy, distal symmetric polyneuropathy
Regional, Monophasic, or Recurrent		
Diabetic/non-diabetic lumbosacral radiculoplexus neuropathy ^{89,90,91,92} (DLRPN,LRPN)	Nerve microvasculitis; acute/subacute, painful, asymmetric upper lumbosacral radiculoplexus dysfunction	Lumbosacral radiculoplexopathy
Immune brachial plexus neuropathy ⁹³ (IBPN) (neuralgic amyotrophy)	Nerve microvasculitis; painful, multifocal brachial plexopathy favoring upper plexus elements	Multifocal cervicobrachial radiculoplexopathy
Hereditary brachial plexus neuropathy ⁹⁴ (HBPN)(hereditary neuralgic amyotrophy - HNA)	Nerve microvasculitis; clinical features similar to those in IBPN; recurrent, dysmorphic features, autosomal dominant	Multifocal cervicobrachial radiculoplexopathy

Clinical Features

EPIDEMIOLOGY

The vasculitides are uncommon, but neuropathy is a common feature in many; MPA, NSVN, and rheumatoid vasculitic neuropathy are the most commonly encountered.^{2,10} Neuropathy is rare in GCA, and is not associated with Kawasaki disease or Takayasu arteritis. Vasculitic neuropathy usually develops in the sixth through eighth decades.^{2,8}

SYMPTOMS AND SIGNS

Systemic vasculitic neuropathy (SVN) and NSVN have similar clinical presentations, aside from multiorgan dysfunction in the former.^{2,5,6,11–13} Typically, symptoms develop over weeks to months, with stepwise, acute to subacute, painful sensory loss and weakness in the distribution of individual peripheral nerves. While this mononeuropathy multiplex (also termed *mononeuritis multiplex*, *multiple mononeuropathies* or *multifocal neuropathy*) is characteristic, a substantial number of patients, and probably the majority, present with a more confluent picture of a generalized but asymmetric/multifocal/ “overlapping” distal-predominant polyneuropathy, or least frequently a symmetric polyneuropathy. Extracting asymmetric, multifocal, and stepwise features from the history and clinical exam is critical to suggesting a possible vasculitic etiology. When restricted to the legs, the clinical and electrophysiologic pattern may be construed as that of an asymmetric lumbosacral plexopathy, and in the arms, brachial plexopathy. Rarely, the temporal course is rapid, with a painful quadriparesis mimicking Guillain-Barré syndrome.^{14,15} A slowly progressive, indolent course may occur particularly in the elderly.^{5,10,16}

Almost any nerve may be involved, but distal ones are affected more commonly than proximal ones, and the legs (peroneal > tibial > femoral) are involved more frequently than the arms (ulnar > median > radial).^{2,5,8,11} Neuropathic pain, related to nerve infarction, is characteristic, although not invariable; its absence should cast some doubt on the diagnosis. Pain is present in 96% of patients with NSVN.¹¹ Similarly, a case with purely motor involvement is unlikely to be vasculitic. Pure or primarily sensory neuropathy occurs in a minority of patients, regardless of symmetry.¹⁷

Cranial neuropathy and autonomic dysfunction occur infrequently. Trigeminal sensory neuropathy occurs characteristically in several connective tissue disorders (UCTD, MCTD, PSS, SS; see Table 12–2). Small-fiber neuropathy is infrequently reported.^{11,18,19}

Constitutional symptoms such as low-grade fever, weight loss, fatigue, malaise, anorexia or arthralgias, and, of course, clinical or laboratory evidence of involvement of other organs (most commonly skin), suggest SVN. Clinical involvement of other organs is absent in NSVN (pathologic involvement of muscle falls within the definition of NSVN), but constitutional symptoms occur in a smaller percentage.

DIFFERENTIAL DIAGNOSIS

In multifocal and asymmetric sensorimotor presentations, other clinical considerations may include multiple entrapments, demyelinating neuropathies (the multifocal acquired demyelinating sensory and motor neuropathy [MADSAM] variant of chronic inflammatory demyelinating polyradiculoneuropathy [CIDP]; hereditary neuropathy with liability to pressure palsy [HNPP]; rarely, acute inflammatory demyelinating polyradiculoneuropathy [AIDP] in acute, fulminant cases), inflammatory/infectious/granulomatous disorders (Lyme borreliosis, leprosy, human immunodeficiency virus/cytomegalovirus [HIV/CMV], herpes zoster, sarcoidosis), and neoplasms (neurolymphomatosis, neurofibromatosis). Multifocal pure sensory presentations may also suggest sensory perineuritis or Wartenberg migrant sensory neuropathy. A multifocal pure motor presentation is unlikely to be vasculitic, and a more likely diagnosis is multifocal motor neuropathy; the absence of pain in such cases is also strong evidence against vasculitis. In those cases with a subacute symmetric polyneuropathy, the broad range of axonopathies will need to be considered. Acute, fulminant, symmetric sensorimotor polyneuropathy is occasionally not Guillain-Barré syndrome but rather vasculitic.^{14,15} Associated systemic symptoms and signs along with inflammatory markers on laboratory testing point to possible SVN but are absent or minor in NSVN. Cholesterol emboli neuropathy is an interesting syndrome mimicking cPAN, with a polyneuropathy or multifocal neuropathy and similar systemic manifestations, often following intravascular procedures.²⁰

Laboratory Studies

BLOOD TESTS

Clinical clues should guide directed testing; otherwise, a thorough laboratory evaluation in cases of suspected vasculitic neuropathy may include some or most of the following: complete blood count (CBC) including eosinophil count, comprehensive metabolic panel for glucose, renal and liver function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibody (ANA), complement, extractable nuclear antigens (ENA; Ro, La, Sm, RNP, Scl-70), cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA; anti-proteinase 3), and p-ANCA (anti-myeloperoxidase), serum protein immunofixation electrophoresis, hepatitis panel, cryoglobulins, HIV, human T-cell lymphotropic virus-1 (HTLV-1), angiotensin converting enzyme (ACE), Lyme enzyme-linked immunosorbent assay (ELISA)/Western blot. Urinalysis and a chest x-ray (CXR) are also routine. Angiography (cPAN), minor salivary gland biopsy (SS), chest computed tomography (CT) or magnetic resonance imaging (MRI; sarcoidosis, neoplasia), and paraneoplastic antibodies (anti-Hu) may be appropriate in individual cases.

Elevated ESR (85%), leukocytosis (70%), and positive RF (45%) may be the best, although nonspecific, predictors of biopsy-confirmed systemic necrotizing vasculitis, with other of the more common abnormalities including anemia, positive ANA, or hypocomplementemia.² NSVN has less frequent and less pronounced abnormalities, except for mild elevation of the ESR in about 71% of patients.¹¹ An ESR > 75 mm/h is associated with systemic vasculitis.²¹

Two types of ANCA are found in the primary systemic vasculitides.²² ANCA directed at the neutrophil serine protease proteinase 3 (PR3) causes a cytoplasmic immunofluorescence pattern (c-ANCA), which is strongly associated with WG, but also occurs in some cases of CSS and MPA. ANCA directed at the neutrophil enzyme myeloperoxidase (MPO) causes a perinuclear pattern (p-ANCA), and is found predominantly in MPA and less often in CSS and WG.

ELECTRODIAGNOSTIC STUDIES

Extensive electrodiagnostic studies of bilateral upper and lower extremities are usually

required to demonstrate side-to-side asymmetries, major differences between nerves in the same limb, and non-length-dependent nerve conduction and needle electromyography (EMG) abnormalities. Characteristically, the studies demonstrate asymmetric, patchy, multifocal, sensory and motor axon loss reflected in reduced sensory and motor amplitudes, and active denervation with reduced motor unit recruitment in weak muscles.^{21,23} Advanced and confluent cases may look symmetric electrophysiologically, as they do clinically. A minority have mixed axonal-demyelinating features. Predominant demyelinating features are not present. Partial motor conduction block may occasionally be observed at nonentrapment sites, either *pseudoconduction block* caused by noncontinuity of acutely infarcted nerve undergoing Wallerian degeneration (this phenomenon will disappear as the distal stump loses conductivity within a few days)²⁴ or, more rarely, transient true conduction block related to ischemia.²⁵ The diagnostic yield of sural nerve biopsy may be enhanced by using sural nerve conduction abnormalities as a guide.²⁶ Isolated upper extremity nerve conduction abnormalities may occur.

CEREBROSPINAL FLUID

The cerebrospinal fluid (CSF) is often normal but may show mild protein elevation in 50% of cases.^{5,21} It is commonly elevated in paraneoplastic neuropathy.²⁷ It may be helpful in excluding infectious, inflammatory, or malignant mimics.

IMAGING

One report describes gadolinium enhancement on MRI of the cauda equina in a patient with SLE and a vasculitic polyradiculopathy.²⁸ Ultrasonography of the tibial nerve at the ankle in vasculitic neuropathy demonstrates enlargement and hypoechoic signal.²⁹ Magnetic resonance angiography (MRA) in one patient with necrotizing vasculitic neuropathy revealed occlusions of the distal peroneal and tibial arteries, collaterals from the femoral artery, and resolution of the abnormalities along with clinical improvement after 6 weeks of corticosteroid treatment.³⁰

Pathology/Nerve Biopsy

Histopathologically, Dyck and colleagues separate necrotizing vasculitis of nerve into two groups: large arteriole vasculitis (cPAN, WG, CSS, RA) and nerve microvasculitis (MPA, NSVN, Sjögren syndrome, paraneoplastic and virus-associated neuropathies, diabetic and nondiabetic radiculoplexus neuropathy).^{3,10,31,32} Large arteriole vasculitis involves predominantly small arteries and large arterioles mainly in the epineurium, with vessel wall mixed inflammatory infiltrates, fibrinoid necrosis of the tunica media, and occlusion of the vessel lumen (Fig. 12-1; see also Color Fig. 12-1). Nerve microvasculitis involves the smallest arterioles (few smooth muscles and no internal elastic lamina), microvessels, and venules, usually without fibrinoid necrosis but with vessel wall inflammation, and separation, fragmentation, and necrosis of the thin tunica media. Ischemic nerve injury is apparent in both types, with multifocal fiber degeneration and loss, perineurial injury, and signs of regeneration (injury neuroma, angioneogenesis). A centrofascicular-predominant pattern of axon loss is also suggestive of ischemia.⁵ Additional features may include perivascular hemosiderin deposits suggesting hemorrhage and immune complex deposition. Perivascular inflammation alone is nonspecific

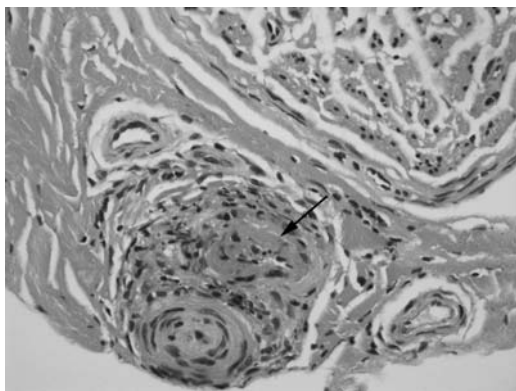


Figure 12-1. Vasculitis of the sural nerve. A small perineurial vessel at the lower left, adjacent to a peripheral nerve fascicle, contains bright pink fibrinoid material in its wall (arrow), together with adjacent inflammation. The lumen is no longer visible. H&E, original magnification $\times 200$. Courtesy of Karen M. Weidenheim, M.D. (See Color Plate 12-1.)

but supports a diagnosis of probable vasculitis when associated with other features; the most significant associations are with asymmetric nerve fiber loss, Wallerian-like degeneration, predominant axonal pathology, and myofiber necrosis or regeneration.²¹

Nerve biopsy is required to establish a diagnosis of suspected vasculitic neuropathy, but it may not be necessary when characteristic neuropathy develops in a well-established systemic vasculitic disorder or when vasculitis is demonstrated in another organ, including skin lesions, when present. Combined nerve and muscle biopsy is often recommended; superficial peroneal nerve/peroneus brevis muscle biopsy is a popular choice when the peroneal nerve distribution is involved, given the need for only a single incision.^{5,33} It has a sensitivity of about 60% with strict pathologic criteria (transmural inflammatory cell infiltrates along with signs of vascular injury such as fibrinoid necrosis) and 86% in suspicious/probable cases (no vascular destruction, but perivascular inflammation and other signs such as asymmetric nerve fiber loss).^{5,10,21,33} Muscle biopsy improves the yield by about 27%–28%^{5,10} (Fig. 12-2; see also Color Fig. 12-2). The sural nerve and gastrocnemius or vastus lateralis muscles are alternatives, and in some cases the radial sensory or intermediate cutaneous nerve of the thigh has been biopsied based on the distribution of clinical involvement. In the most recent retrospective study of nerve and muscle biopsy for vasculitis, a vastus lateralis muscle biopsy did not significantly increase the diagnostic yield compared with sural nerve biopsy alone, which showed 36% definite and 62% probable vasculitis.³⁴ Analysis of serial sections may be necessary, as the lesions are segmental. A negative biopsy does not entirely rule out a diagnosis of vasculitis. Whole nerve rather than fascicular biopsy is important since epineurial arterioles are preferentially involved.⁵

The likelihood of a nerve biopsy disclosing vasculitis in undiagnosed neuropathies is highest in acute and subacute asymmetric forms and lowest in chronic symmetric forms.^{35,36} Some studies suggest a substantial contribution of nerve biopsy to the diagnosis of disabling (impaired ambulation and/or disturbing pains or sensory loss) idiopathic neuropathy in the elderly; 35% of patients over age 65 had one form or another of vasculitic neuropathy.¹⁶ This included two diabetic patients with a multifocal neuropathy.

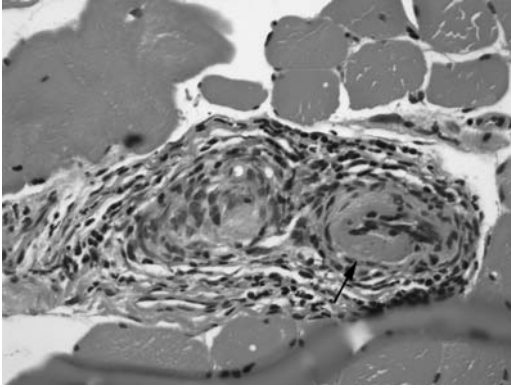


Figure 12–2. Vasculitis of muscle. A blood vessel in the perimysium shows bright pink fibrinoid necrosis (arrow) and mononuclear inflammatory cells within its walls. H&E, original magnification $\times 400$. Courtesy of Karen M. Weidenheim, M.D. (See Color Plate 12–2.)

Skin biopsies, even in skin without clinically active lesions, may show reduced epidermal nerve fiber density indicating small-fiber loss, as well as vascular infiltration by T cells and macrophages, but this is not specific for vasculitis.³⁷

Perineuritis is a pathologic disorder characterized by perineurial thickening, inflammatory infiltrates, and degeneration of perineurial cells.³⁸ It appears to be a nonspecific, likely autoimmune process, as it is associated with a variety of systemic illnesses (diabetes, rheumatologic disorders, malignancy, sepsis with multiorgan failure, nutritional deficiency) and neuropathic patterns (mononeuropathy multiplex, demyelinating neuropathy, sensory or sensorimotor polyneuropathy, polyradiculoneuropathy). The CSF protein in these cases has ranged from normal to 875 mg/dL, and the response to immunosuppressive treatment has been variable.

Pathogenesis

The antigenic agent that triggers autoimmune vasculitis is apparent in some cases (e.g., infections, drugs, malignancies) but not in many others.³⁹ Pathologic studies suggest a primary T-cell-mediated immunopathogenesis resulting in vessel injury in most types of vasculitis. In other cases, mainly those associated with various infections (hepatitis B and C), drugs, malignancies, cryoglobulinemia, and connective tissue

disorders, immune complex-mediated mechanisms are likely important. Antibody mechanisms may be in play in ANCA-related vasculitides (WG, CSS, MPA), and anti-endothelial cell antibodies may also have a role. This subject is reviewed comprehensively by Collins and Kissel.²

Vessel wall inflammation and necrosis with luminal compromise result in nerve ischemic injury, large myelinated fibers being more susceptible than unmyelinated fibers. Axonal degeneration is the major pathologic process, occurring in a multifocal fashion because of the random nature of vasculitic lesions. Watershed regions between the distributions of nutrient arteries of proximal nerves in the arm and thigh are particularly vulnerable.³¹

Treatment, Course, and Prognosis

Untreated SVN has a poor prognosis in terms of morbidity and mortality; therefore, early, aggressive immunosuppressive treatment is indicated. Where possible, the inciting antigen is removed (drug, tumor) or treated (infection). The generally accepted regimen to induce remission, based on retrospective analyses and trials in patients with systemic vasculitis without neuropathy, is a combination of corticosteroids (prednisone 1–2 mg/kg/day orally, or in very severe cases, IV pulse methylprednisolone, 1000 mg/day for the initial 3–5 days) and cyclophosphamide (CTX; 1–2 mg/kg/day orally, or IV pulse dosing, 1 g/m² monthly).^{2–5,40,41} Steroid treatment is continued at a high dose for weeks to months, depending on disease severity and course, response to treatment, and adverse effects, and then is tapered very gradually over at least many months. The transition to alternate-day steroid dosing may follow the clinical response. Azathioprine, methotrexate, mycophenolate mofetil, leflunomide, cyclosporine, etoposide, rituximab, infliximab, or plasmapheresis has been used in some cases as an alternative to CTX or for remission maintenance. Withdrawal of CTX and substitution of azathioprine after remission does not increase the relapse rate.^{2,3,42} After remission, maintenance therapy is usually required for at least 6–12 months. Inflammatory disease markers may be utilized as treatment guides. Relapses may occur during tapering or after treatment is

discontinued in 20%–60% of SVN cases and 46% of NSVN cases.^{2,3,5,11} Based on case series, intravenous immunoglobulin (IVIG) may be beneficial in cases of resistant vasculitic neuropathy.⁴³

More controversy exists regarding steroid monotherapy versus combination therapy for NSVN. A Cochrane review of immunosuppressive treatment for NSVN in 2007 revealed no adequate randomized, controlled trials.⁴⁴ In the most recent large retrospective study of NSVN, combination therapy appeared to be superior.¹¹ Milder improving cases may be managed with corticosteroids alone. Giant cell arteritis is generally treated with corticosteroids alone. The treatment of infection-related vasculitis (HIV, CMV, HCV/cyoglobulinemia) is discussed in Chapter 9; the distinction is important because of the need to add antiviral therapies. Hepatitis B-associated PAN is treated with corticosteroids, interferon- α or lamivudine, and adjunctive plasmapheresis. Drug-related vasculitis usually improves within a few weeks of discontinuing the drug but may require corticosteroids. Paraneoplastic vasculitic neuropathy often responds to anticancer therapy; in refractory cases, immunosuppression is attempted.²⁷ Severe, active cases of radiculoplexus neuropathy associated with significant pain and disability may be treated with intravenous methylprednisolone or IVIG, but further studies are required to establish efficacy and a regimen. Management of the individual connective tissue diseases is beyond the scope of this review and is done in conjunction with rheumatology.

In a recent retrospective analysis of a large series of patients with SVN and NSVN, 72% of 100 patients were reported to have a good outcome, aggressive early treatment with CTX in addition to corticosteroids appeared to prevent relapses (relapse rate 10%), and 1-year survival was about 90%.⁴⁵ NSVN generally has a more benign prognosis than SVN. About 6% of patients with NSVN develop vasculitis in non-neural, nonmuscular sites on long-term follow-up, and only in the skin (asymptomatic muscle involvement on biopsy is common in NSVN).¹¹ The experience of another large study was different, finding that 37% of patients developed systemic manifestations after an average of 6 years.⁵ Residual neuropathic pain is

common.^{5,11} Deficits result from axonal degeneration and when severe recovery may be incomplete, with patients taking months to 1–2 years to recover with axonal regeneration. About 15% of patients develop various malignancies within 2 years of onset of vasculitic neuropathy.²³

Steroid side effects are protean and must be anticipated, with prophylaxis and treatment. Among the more common and morbid side effects are hypertension, glucose intolerance, weight gain/edema, osteoporosis with compression fractures, cataracts, opportunistic infections, impaired wound healing, avascular necrosis of the hip, and mood disturbances. Concurrent use of vitamin D (800–1000 units daily) and calcium carbonate or citrate (750 mg bid), with periodic bone density measurements, is important to prevent osteoporosis. The development of steroid myopathy or spinal epidural lipomatosis with radiculopathy or myelopathy may complicate the clinical picture. Cytoxan is associated with hemorrhagic cystitis, pulmonary toxicity, myelosuppression, ovarian failure, alopecia, and a substantial increase in the risk of developing bladder cancer or lymphoma.⁴⁶ Current treatment options, recommendations, and drug side effects are reviewed comprehensively by Gorson⁴¹ and by Schaublin et al.⁴⁷

NEUROPATHIES ASSOCIATED WITH PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

Ischemic neuropathy related to acute or chronic large vessel occlusion secondary to atherosclerotic thrombotic or embolic disease, or to arteriovenous shunting, is uncommon, probably due to the extensive collateral circulation of peripheral nerve.⁴⁸ Nerve, however, is more vulnerable than muscle to acute limb ischemia, and signs of muscle involvement are usually lacking.⁴⁹ Axons appear to be more vulnerable to ischemia than Schwann cells or myelin.⁴⁸

Neuropathy caused by acute ischemia is termed *ischemic monomelic neuropathy* (IMN).⁴⁹ This occurs most commonly following arteriovenous fistula placement for dialysis in the brachiocephalic or antecubital location in diabetic patients, who often have

associated polyneuropathy and peripheral vascular disease. Multiple axon-loss mononeuropathies occur distal to the site of occlusion or shunting, beginning within minutes to hours, probably first in the distribution of terminal arterial branches or in watershed zones of perfusion. A more insidious, chronic vascular steal syndrome that includes ischemic signs in the hand may result from shunt-related retrograde flow from the digits. This subject is discussed in further detail in Chapter 13. In the upper extremity, rare reports describe acute brachial plexopathy associated with axillary artery cardioembolism.⁴⁶ In the lower extremity, IMN may follow thromboembolic disease (aortoiliac embolus, acute superficial femoral artery or iliofemoral thrombosis) or intraaortic balloon pump placement.^{49,50} Burning neuropathic pain is characteristic, and deficits depend on the nerves involved and the locus of infarction.

Whether chronic large vessel ischemia leads to a monomelic or polyneuropathic pattern of nerve dysfunction has been more controversial. Recent studies of chronic and critically ischemic limbs compared to less affected contralateral limbs in nondiabetic patients show clear asymmetries in neuropathic symptoms, clinical findings, and electrophysiologic abnormalities, correlating with measures of blood flow and suggesting a predominantly sensory neuropathy.⁵¹ Histologic evidence of denervation was shown in gastrocnemius muscle biopsies from symptomatic limbs.⁵² Patients have presented with subacute to chronic cumulative deficits in roots, plexus, or individual nerves before ischemic skin signs led to the discovery of aortic occlusion.⁵³ Such cases remind the reader that evaluation of neuropathy should routinely include checking pedal pulses and occasionally considering vascular studies. Similarly, an axonal sensorimotor polyneuropathy is demonstrable electrophysiologically and clinically in chronic bilateral peripheral arterial disease, the severity correlating with the duration and severity of the ischemia.^{54,55} Clinically, these cases are predominantly sensory, with very few showing distal leg weakness. Chronic ischemic neuropathy may improve with therapeutic angiogenesis with vascular endothelial growth factor.⁵⁶ Animal models of chronic endoneurial ischemia can show morphologic and functional abnormalities in peripheral nerves.⁵⁷

NEUROPATHIES ASSOCIATED WITH COMPARTMENT SYNDROMES

Acute compartment syndromes can injure major peripheral nerves traversing the involved compartment, as well as the muscles contained within.^{58–60} Compartments are closed spaces bounded usually by fascia, bone, external bandaging/casting, or other structures. Elevated intracompartmental pressure results from an increase in compartment contents (edema or blood), usually related to trauma or external restriction. The capillary circulation is compromised, leading to tissue ischemia. The major compartments involved include the forearm volar and medial brachial fascial in the arms and the anterior tibial, deep posterior, psoas, iliacus, and gluteal in the legs. Clinical features begin with localized pain, swelling, and tenderness if the compartment is superficial; pain with passive muscle stretch; and, as the process progresses, sensory followed by motor dysfunction in the nerves involved. Pulses are typically normal. Creatine kinase is often elevated, and rhabdomyolysis may occur. Compartment pressures can be measured, and emergent decompression with fasciotomy is usually indicated, preferably within hours of onset. Delayed treatment may result in permanent nerve dysfunction and muscle fibrosis with contractures. Chronic compartment syndrome is generally related to muscle exertion or overuse, with localized pain provoked by exercise and relieved with rest.

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Neuropathies Associated with Organ Failure

PULMONARY FAILURE

HEPATIC FAILURE

RENAL FAILURE

Uremic Polyneuropathy

Mononeuropathies

Ischemic Monomelic Neuropathy

ORGAN TRANSPLANTATION

CRITICAL ILLNESS POLYNEUROPATHY

Differential Diagnosis

PULMONARY FAILURE

Whether primary pulmonary insufficiency with chronic or intermittent hypoxia/hypercapnia can be the proximate cause of polyneuropathy has been investigated in patients with chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea (OSA).

In COPD, electrodiagnostic evidence of a predominantly sensory axonal polyneuropathy is variably reported in 15%–94% of patients.^{1–11} Most cases are subclinical; a minority of patients have clinical signs and fewer have clinical symptoms, usually mild. The majority of studies show the presence of neuropathy to be associated with cigarette consumption, older age, duration of illness, and severity of hypoxemia. One report suggests that improvement in symptoms and electrophysiologic parameters can follow treatment intervention that results in improved respiratory function.⁴ Nerve biopsies in five reports to date describe axonal degeneration and segmental demyelination, thickened perineurium and capillary basement membrane, endothelial cell hyperplasia and hypertrophy, narrowing of microvessel lumens, and mural pericytic debris deposits; muscle biopsies show

neurogenic atrophy and endomysial capillary basement membrane thickening.^{9,11–14} Subclinical cardiovascular autonomic neuropathy may be common in COPD.¹⁵

Case-control studies demonstrate an increased prevalence of axonal sensory polyneuropathy in patients with OSA.^{16,17} About 71% of these patients have mild symptomatic or asymptomatic clinical signs of polyneuropathy. Sural sensory nerve action potential (SNAP) amplitudes are decreased relative to controls and correlate with the severity of nocturnal intermittent hypoxemia. Treatment with nasal continuous positive airway pressure (nCPAP) appears to significantly improve the sural SNAP amplitude at 6-month follow-up, and this effect correlates with treatment compliance. Nasal CPAP also reverses the resistance to ischemic conduction failure (RICF) seen in some patients with OSA.¹⁸

These clinical studies are supported by experimental data showing that normal rats subjected to chronic hypoxia develop slowing of nerve conduction velocity and RICF by 4 weeks.¹⁹ How often cases of chronic cryptogenic polyneuropathy may be attributed to OSA is not known. Interpretation is

confounded by the high estimated prevalence of OSA in the general population (2%–5%).²⁰

The association of symptomatic polyneuropathy and respiratory insufficiency is less clear than that of polyneuropathy and renal or hepatic failure.

HEPATIC FAILURE

Many disorders—genetic, acquired, or toxic—simultaneously target the liver and peripheral nerves (e.g., alcoholism, viral hepatitis including hepatitis B and C, cytomegalovirus [CMV] and Epstein-Barr virus [EBV], cholestatic hepatobiliary disease and vitamin E deficiency, amyloidosis, Navajo neurohepatopathy). These are discussed in other chapters of this book. It has been more of a challenge to establish chronic hepatic failure as an independent cause of neuropathy (hepatic neuropathy), but the bulk of evidence suggests that a mild, usually asymptomatic, axonal, sensorimotor, and autonomic polyneuropathy is common in end-stage liver disease of various etiologies, including cryptogenic causes. Prevalence varies widely, but in several of the largest and most recent series administering batteries of tests, 71%–93% of patients with cirrhosis were found to have electrophysiologic evidence of somatic neuropathy and 36%–80% were found to have autonomic neuropathy.^{21–24} The severity of neuropathy correlates with the severity of liver dysfunction as measured by the Child-Pugh classification, although not in all studies.²³ Most patients are asymptomatic and, when symptomatic, mildly so, with distal numbness, paresthesias, or cramps. There may be distal small- or large-fiber sensory loss and depressed ankle reflexes; if any weakness is present, it is distal and mild. Autonomic dysfunction is predominantly parasympathetic. While some earlier reports suggested demyelinating electrophysiology, recent series point to a length-dependent axonal neuropathy. Conduction velocities may be reduced, but generally not in the demyelinating range. Median neuropathy at the wrist may be common (33%).²³ Pathology reports are few and appear to emphasize demyelinating features, although this has been questioned.²³ A few studies report improvement in clinical signs or electrophysiology after liver transplantation, particularly with return of normal hepatic function.^{24–26}

The pathophysiology of hepatic neuropathy is not established. While suggested by some studies, it is probably not related to portosystemic shunting; hepatocellular failure is favored as a mechanism in experimental studies in rats.^{23,27–29}

A sensory polyneuropathy may accompany primary biliary cirrhosis (PBC), with unique pathology of xanthomatous infiltration within peripheral nerve fascicles.³⁰ Other cases show axonal loss without xanthomas.³¹ Neuropathy may be the presenting feature in some instances.³² Autonomic dysfunction may accompany somatic neuropathy.³³ About 44%–64% of patients with PBC have a reduced serum vitamin E concentration.³⁴ Association of PBC with a number of autoimmune disorders suggests an immune-mediated pathogenesis for neuropathy in some cases.

RENAL FAILURE

Neuropathies are frequent in chronic renal failure (CRF) and include uremic polyneuropathy, mononeuropathies, and ischemic monomelic neuropathy related to arteriovenous (A-V) fistulas.

Uremic Polyneuropathy

Asbury, Victor, and Adams first used the term *uremic polyneuropathy* (UP) in 1962 in their clinical and pathological description of four men with a length-dependent, axonal, sensorimotor polyneuropathy attributable to CRF.^{35,36} Prevalence rates for UP in CRF vary widely, depending on the diagnostic criteria used; most range from about 50% to 100%.^{37,38} The disorder is more common in males. Generally, UP is seen with glomerular filtration rates below about 12 mL/min and creatinine levels greater than 5–6 mg/dL.³⁹

Clinical features are similar to those described for most distal axonopathies and include slowly progressive, distal, length-dependent, symmetric loss of sensory and motor function.⁴⁰ Initially, sensory symptoms often predominate, and tingling paresthesias of the legs are especially frequent. A minority of patients experience burning feet. Weakness appears later; foot dorsiflexion weakness is the usual first motor complaint. Muscle

cramps and restless legs syndrome are common.⁴¹ Early signs are loss of ankle reflexes and distal vibratory sense. Sensory loss mainly involves large-fiber function. Distal atrophy and weakness are less common but can be severe in untreated cases. Autonomic abnormalities are often demonstrable by neurophysiologic testing but are usually subclinical. Rarely, patients may have an acute ("accelerated"), subacute or chronic motor-predominant neuropathy with demyelinating or axonal features and elevated cerebrospinal fluid (CSF) protein simulating Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).⁴²⁻⁴⁴ Improvement is reported in individual cases with more frequent or high-flux dialysis or renal transplantation.

Neurophysiologic and pathologic studies are consistent with predominant large-fiber axonal dysfunction with secondary demyelination.^{36,44-46} Lower extremity F-wave and H-reflex latencies, sural sensory amplitudes, and vibration detection thresholds are the most sensitive electrophysiologic parameters.⁴⁷⁻⁴⁹ Paradoxical heat sensation in response to cold stimuli is common and early and correlates with the creatinine level.⁵⁰ Spinal fluid protein is elevated, usually to less than 100 mg/dL, in about 60% of uremic patients, but occurs in those with or without neuropathy.⁵¹

The prognosis for untreated UP is poor. Successful renal transplantation is unquestionably effective in the prevention and reversal of UP. Patients with mild cases display prompt relief of paresthesias and a steady return of strength and sensibility; recovery is more prolonged in advanced cases and not always complete.^{44,52} Hemodialysis and peritoneal dialysis are considerably less effective in ameliorating UP, although they tend to retard its progression.³⁷ The prevalent pathophysiologic hypothesis, as yet unproven, posits that a poorly dialyzable toxin in the middle molecular weight range is responsible for UP (middle molecule hypothesis).^{37,53} More recently, nerve excitability studies in CRF show a predialysis chronically depolarized state that correlates with the serum K^+ level, suggesting that chronic hyperkalemic depolarization may underlie the development of UP and that maintenance of a strictly normal serum K^+ level may be an effective treatment strategy.³⁷

Mononeuropathies

Entrapment neuropathies at the wrist (median), elbow (ulnar), and fibular head (peroneal) are commonly encountered, particularly carpal tunnel syndrome (CTS), whose incidence correlates with the duration of dialysis.^{37,54} β_2 -microglobulin amyloidosis is an important factor in the development of CTS in uremic patients on chronic hemodialysis.^{55,56} Amyloid deposits are demonstrated in about two-thirds of dialysis patients undergoing surgery for CTS with microscopic examination of the epineurium, flexor retinaculum, synovium, and flexor tendon sheaths.⁵⁷ Osteoarthropathy is a commonly associated feature. Conventional dialysis membranes do not filter β_2 -microglobulin; rates of CTS are reduced with the use of high-flux membranes or β_2 -microglobulin adsorption columns. Median nerve decompression may be successful, but results tend to be less favorable than in idiopathic CTS and recurrence rates higher. Focal median entrapment at the wrist can be difficult to demonstrate with certainty in the presence of a substantial polyneuropathy; the second lumbrical-interossei latency difference can be an aid in this circumstance.⁵⁸ Presumably related to vascular steal or venous congestion/edema, CTS also occurs more commonly in an arm harboring an A-V fistula, correlating with the age and the flow rate of the fistula.^{59,60} Uremic tumoral calcinosis (calcified periarticular soft tissue masses) is an additional mechanism for the development of CTS.⁶¹ Uncommonly, a compression neuropathy may result from a forearm shunt itself, and about 2% of patients undergoing renal transplantation surgery sustain a femoral neuropathy from retraction or hematoma, generally with good recovery.⁶² The lateral femoral cutaneous nerve may also be a victim of self-retaining retractors.⁶³ Ulnar or common peroneal entrapments are often associated with cachexia and a bedridden state.

Ischemic Monomelic Neuropathy

Limb ischemia consequent to placement of an A-V fistula in the arm may result in two clinically distinct syndromes.^{37,64-68} In the vascular steal syndrome, reversal of arterial blood flow

(retrograde flow) from the digits results in mild to severe ischemic changes affecting all tissues of the hand. Onset is insidious over days to months. Numbness, painful paresthesias, and digital stiffness and swelling occur; symptoms may be precipitated or exacerbated by hemodialysis. Digital pressures are reduced. Symptoms improve with correction of ischemia. In severe cases there are prominent ischemic signs, with development of ulcers, trophic changes, and dry gangrene.

Ischemic monomelic neuropathy (IMN) is a rarer presentation and begins within minutes to hours of A-V shunt placement in the brachiocephalic or antecubital location.^{69,70} Almost all of these patients are diabetic, most with associated polyneuropathy and peripheral vascular disease, these factors constituting clear risk factors for this condition. Signs of vascular insufficiency or muscle infarction are usually absent, with selective vulnerability of peripheral nerves, likely in watershed zones of perfusion, as demonstrated in experimental animal models.⁷¹ Only multiple mononeuropathies are present clinically and electrophysiologically, with evidence of axonal loss in median, ulnar, and radial sensory and motor nerve territories distal to the fistula. The median nerve may be preferentially involved, with reversible conduction block demonstrable in the forearm.⁷² Diagnostic delay is common, since this condition is often attributed to surgical trauma, positioning, or anesthetic complication.⁶⁵ Early recognition and immediate fistula ligation or revision are critical; significant improvement may result if IMN is treated within perhaps 2 weeks of onset, but many patients have permanent motor dysfunction.

ORGAN TRANSPLANTATION

Neuropathies developing in organ transplant recipients are often complex to unravel. One has to consider the relative contributions of the underlying disorder that led to organ dysfunction, neurotoxic medications, metabolic and nutritional issues, opportunistic infections, surgical complications, critical illness, and immune-mediated mechanisms. A severe sensorimotor or motor-predominant polyneuropathy simulating GBS or CIDP rarely follows various solid organ or bone marrow

transplantations, with or without other signs of acute or chronic graft-versus-host disease (GVHD).^{73–77} Electrophysiologic studies may or may not meet the criteria for demyelination. There is proximal and distal weakness, hypo- or areflexia, and usually elevated CSF protein; improvement follows immunosuppressive treatment, resolution of GVHD, or tissue rejection. Cytomegalovirus infection may be the trigger in many cases of GBS with solid organ transplantation and some following bone marrow transplantation.^{78–80} Rarely, a vasculitic mononeuropathy multiplex is associated with chronic GVHD.⁸¹ To confound matters, for those patients on tacrolimus immunosuppression, a neurotoxic mechanism must be considered since a handful of reports appear to connect this drug to an acute or chronic demyelinating or axonal polyneuropathy.^{82–85}

Almost 50% of lung transplant recipients have restless legs syndrome.⁸⁶ Patients undergoing open heart surgery can sustain a variety of mononeuropathies, most commonly a reversible lower trunk brachial plexopathy that may be related to chest wall retraction or traumatic jugular vein cannulation.⁸⁷ Traumatic brachial plexopathy also occasionally complicates liver transplantation. The focal neuropathies associated with renal transplantation are discussed in the prior section.

CRITICAL ILLNESS POLYNEUROPATHY

Bolton et al. first characterized critical illness polyneuropathy (CIP) in 1984, and Bolton provided a comprehensive review of the subject in 2005.^{88,89} Commonly, CIP occurs in the intensive care unit (ICU) setting within days to weeks, occurring in 50%–70% of patients with the systemic inflammatory response syndrome (SIRS), defined as a severe systemic response to various infections or trauma (including burns) and multiple organ failure. Concurrent septic encephalopathy often obscures recognition of neuromuscular weakness until the sensorium improves and flaccid weakness is appreciated or difficulty in weaning the patient from the ventilator is noted with no cardiac or pulmonary explanation. Motor findings predominate; weakness varies from mild, with a

distal predilection, to severe quadriparesis with respiratory failure. Cranial nerves are relatively spared. Reflexes are usually diminished or absent. Distal sensory loss is present but difficult to demonstrate reliably.

Electrophysiologic studies demonstrate an axonal sensorimotor polyneuropathy with reduced motor and sensory amplitudes, active denervation distally or diffusely on needle electromyography (EMG) after an appropriate period of time, and abnormal phrenic nerve conduction studies and diaphragmatic EMG accounting for respiratory muscle weakness. Abnormalities of sensory potentials help distinguish CIP from myopathy, but they may be normal in the early stage of CIP. Nerve biopsy and autopsy studies confirm primary axonal degeneration; the findings are nonspecific, and nerve biopsy is generally not indicated in making a diagnosis of CIP.^{88,90–92} The mortality rate in these critically ill patients is high, but if they survive their underlying illness, recovery can be substantial over weeks to months, except for the more severe cases with marked axon loss. The pathogenesis of CIP remains to be established. Recent studies suggest a relationship to endotoxin,⁹³ or note that motor axons in CIP patients are chronically depolarized and that this may be related to endoneurial hypokalemia and/or hypoxia.⁹⁴ Management at this time involves mainly treatment of SIRS and its attendant complications, avoidance of neuromuscular blocking agents and steroids, and physical therapy. Some studies have suggested that intensive insulin therapy in critically ill medical patients appears to reduce the incidence of CIP/critical illness myopathy as well as mortality.^{95–97} A recent meta-analysis suggested no significant effect on mortality and an increased risk of hypoglycemia,⁹⁸ while a large international randomized trial found that intensive glucose control actually increased mortality.⁹⁹

Differential Diagnosis

It is important to differentiate CIP from other neuromuscular disorders in the critical illness setting (Table 13–1); clinical features are often overlapping, and ancillary investigations are very helpful. First, consideration is given to unrecognized preceding neuromuscular disorders that may be associated with respiratory insufficiency and lead to infection and

hospitalization (e.g., motor neuron disease, myasthenia gravis, inflammatory myopathy or neuropathy). An acute high cervical myelopathy with spinal shock could explain the findings of flaccid quadriparesis and areflexia; involvement above the neck, if clearly demonstrable, excludes this possibility. Epidural abscess with spinal cord compression is a particular concern with septic patients. Neurotoxic or myotoxic drugs may play a contributory or confounding role in the clinical picture (e.g., statins, colchicine). The acute inflammatory demyelinating form of GBS is distinguished by demyelinating neurophysiology; the axonal variants (acute motor axonal neuropathy [AMAN], acute motor sensory axonal neuropathy [AMSAN]) may look similar to CIP but develop prior to ICU admission, and CSF protein is elevated.

Critical illness myopathy (CIM; previously known by numerous other designations) is also common and occurs independently of or concurrently with CIP, with similar clinical features of diffuse flaccid weakness, atrophy, diaphragm weakness, and depressed reflexes, more often with neck flexor and facial muscle weakness if testable; a proximal pattern may not readily be discernible.^{89,100–102} Some authors suggest that CIM is more common than CIP;^{103–105} some prefer the term *critical illness polyneuropathy and myopathy* (CIPNM) to reflect the difficulties in differentiation and the frequent presence of features of both conditions.¹⁰⁶ Several clinicopathologic forms fall under the rubric of CIM, including thick filament myosin loss (particularly associated with high-dose steroids and neuromuscular blocking agents in status asthmaticus, although sometimes sepsis alone), rhabdomyolysis with very high creatine kinase (CK) elevation, acute necrotizing myopathy (severe widespread muscle necrosis), and cachectic myopathy or disuse atrophy (type 2 fiber atrophy). Compound muscle action potential (CMAP) amplitudes are reduced, as in CIP, but SNAPs should be preserved if they can be relied upon given the technical difficulties of the ICU setting, including frequent edema. Prolonged CMAP duration (“synchronized dispersion”) is a characteristic and useful electrophysiologic clue, as is impaired direct muscle stimulation in severe CIM, although interpretation of the latter study is only semi-quantitative and difficult.^{105,107–109} Neurophysiologic studies show impaired

Table 13–1 **Neuromuscular Disorders of Critical Illness**

Disorder	Electrodiagnostic	Creatine Kinase	Pathology	Associations
Critical illness polyneuropathy	Axonal neuropathy, motor and sensory	Normal	Axonal degeneration	SIRS, multiple organ failure
Guillain-Barré syndrome	Demyelinating (AIDP) or axonal (AMAN/AMSAN) neuropathy	Normal	Demyelination Inflammation Axonal degeneration	Elevated CSF protein
Critical illness myopathy: thick filament myosin loss	Low CMAPs, normal SNAPs, prolonged CMAP duration, myopathic EMG with/without spontaneous activity, direct muscle inexcitability	Normal to mildly elevated	Thick filament myosin loss	Neuromuscular blocking agents, steroids, sepsis
Critical illness myopathy: rhabdomyolysis	Mostly unremarkable, may have fibrillations	Very high	Normal or variable myofiber necrosis	Myoglobinuria
Critical illness myopathy: acute necrotizing myopathy of intensive care	Severe myopathic	Very high	Severe myo-fiber necrosis	Myoglobinuria
Critical illness myopathy: cachectic/disuse atrophy	Normal	Normal	Normal or type 2 myofiber atrophy	Immobility, malnutrition
Neuromuscular junction blockade	Repetitive nerve stimulation studies: decrement	Normal	Normal	Neuromuscular blocking agents and renal/hepatic dysfunction

AIDP: acute inflammatory demyelinating polyradiculoneuropathy; AMAN: acute motor axonal neuropathy; AMSAN: acute motor sensory axonal neuropathy; CMAP: compound muscle action potential; CSF: cerebrospinal fluid; EMG: electromyography; SIRS: systemic inflammatory response syndrome; SNAP: sensory nerve action potential.

muscle fiber excitability in CIM.¹⁰⁵ Needle EMG may or may not show diffuse spontaneous activity; myopathic motor unit recruitment and morphology will be apparent in muscles that retain some degree of movement. Substantially elevated CK, if present, favors CIM over CIP. The prognosis for recovery in acute necrotizing myopathy may be poor, but it is more favorable in the other CIM subtypes if patients survive their underlying illness and is generally better than in severe CIP.¹¹⁰ For practical purposes, until specific treatments become available, other than some prognostic differences, differentiating CIP from CIM or a combination is not more useful than just establishing the presence of either.¹¹¹ Glucocorticoid excess in adult rats induces preferential depletion of

myosin in denervated skeletal muscles fibers, reproducing the thick filament myosin loss subtype of CIM seen in patients with the functional denervation of neuromuscular blockade and exposure to steroids.¹¹² An additional important consideration in the differential diagnosis is persistent neuromuscular blockade due to impaired hepatic or renal metabolism of administered neuromuscular blocking agents.¹¹³ This effect may be identified by repetitive stimulation studies and generally clears within days. Hopkins syndrome (asthmatic amyotrophy) is a severe, idiopathic, acute poliomyelitis-like motor neuron disorder with a poor prognosis, occurring mostly in children after asthmatic exacerbations and characterized by usually monomelic flaccid paralysis.^{114,115}

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The Hereditary Neuropathies

HEREDITARY MOTOR AND SENSORY NEUROPATHY (HMSN)/CHARCOT-MARIE-TOOTH DISEASE (CMT)

Introduction

Charcot-Marie-Tooth Disease, Type 1 (CMT1/HMSN I)

Hereditary Neuropathy with Liability to Pressure Palsy (HNPP)

Charcot-Marie-Tooth Disease, Type 2 (CMT2/HMSN II)

Additional Autosomal Recessive Axonal Neuropathies

Dejerine-Sottas Disease and Congenital Hypomyelinating Neuropathy (HMSN III)

Charcot-Marie-Tooth Disease, Type 4 (CMT4, Autosomal Recessive CMT1, ARCT1, HMSN IV)

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HEREDITARY PERIPHERAL NERVE CHANNELOPATHIES

Sodium Channelopathies

Potassium Channelopathies

In considering and classifying the hereditary neuropathies, it is useful to first distinguish those related to primary or isolated degeneration of peripheral neural elements, either alone or in association with other parts of the nervous

system (system atrophies), from those where neuropathy is part of a more generalized systemic/metabolic process (also called *syndromic* hereditary neuropathies). For the nonsystemic inherited neuropathies, classification follows

Table 14–1 Primary Hereditary Neuropathies or System Atrophies with Nerve Involvement without Systemic Features

Hereditary motor and sensory neuropathies/Charcot-Marie-Tooth Disease (HMSN/CMT)
Hereditary sensory and autonomic neuropathies (HSAN)
Distal hereditary motor neuropathies/neuronopathies (dHMN)
Hereditary ataxia with neuropathy (SCA)
Hereditary spastic paraplegia with neuropathy (HSP or SPG)
Hereditary brachial plexus neuropathy/hereditary neuralgic amyotrophy (HBPN/HNA)
Hereditary peripheral nerve channelopathies

involvement of specific neuron or nerve fiber types: motor and sensory nerves (HMSN or CMT), sensory and autonomic nerves (HSAN), lower motor neurons or nerves (dHMN), cerebellum and large-diameter sensory neurons (SCA), and spinal pyramidal tracts and lower motor neurons or nerves (HSP or SPG) (Table 14–1).¹

HEREDITARY MOTOR AND SENSORY NEUROPATHIES (HMSN)/CHARCOT-MARIE-TOOTH DISEASE (CMT)

Introduction

The hereditary motor and sensory neuropathies are a phenotypically and genetically heterogeneous group of peripheral nerve disorders affecting axons and/or Schwann cells. They are among the most common inherited neurologic disorders. A hereditary neuropathy may be the most common diagnosis when patients with idiopathic, unclassified neuropathy undergo extensive evaluation, with a careful family history and examination of family members being critical.² In the last two decades, remarkable advances in molecular genetics have identified the genetic causes of many of these disorders, beginning with CMT1A in 1989. More than 40 causative genes have been identified. Some of these genes, their phenotypes, and their putative protein functions are outlined in Table 14–2. A similar disease phenotype may result from mutations in different genes, while varied phenotypes can result from different mutations involving the same gene. For up-to-date information on this complex and rapidly evolving

area, the reader is referred to three excellent Web site databases: Online Mendelian Inheritance in Man (OMIM) at <http://www.ncbi.nlm.nih.gov/OMIM>; Inherited Peripheral Neuropathies Mutation Database (IPNMD) at <http://www.molgen.ua.ac.be/CMTMutations/>; and Genetests at <http://www.genetests.org/>.

In 1886, Jean Martin Charcot and Pierre Marie in France and Henry Tooth in England independently described a peroneal muscular atrophy syndrome ascribed to disease of peripheral nerve and later called *Charcot-Marie-Tooth disease*. Roussy and Lévy described a similar phenotype associated with tremor, and Dejerine and Sottas described a severe form with onset in infancy. In 1968 and subsequently, Dyck and Lambert developed a classification system based on electrophysiologic and pathologic criteria, dividing the hereditary motor and sensory neuropathies (HMSN, synonymous with CMT) into two main groups, one with slow nerve conduction velocities and hypertrophic demyelinating pathology (HMSN I, CMT1) and the other with relatively normal nerve conduction velocities and axonal pathology (HMSN II, CMT2). HMSN III was designated as the hypertrophic neuropathy of infancy (Dejerine-Sottas disease), HMSN IV as Refsum disease associated with phytanic acid excess, HMSN V was associated with spastic paraplegia, HMSN VI with optic atrophy, and HMSN VII with retinitis pigmentosa.³ Though used interchangeably, in more recent years *Charcot-Marie-Tooth disease* rather than *hereditary motor and sensory neuropathy* has become the preferred designation, particularly in the genetic literature. In 1980, Harding and Thomas described the clinical, electrophysiologic,

Table 14–2 CMT Genes, Related Phenotypes, and Protein Functions²¹⁶

Gene	Phenotypes	Putative Protein Function
Demyelinating Forms		
PMP22	CMT1A, DSD/CHN, HNPP	Compact myelin structure
MPZ	CMT1B, DSD/CHN, CMT2I, J, DI-CMTD	Compact myelin structure
EGR2	CMT1D, DSD/CHN, CMT4E	Transcription regulation
GJB1/ CX32	CMTX	Gap junction transport; noncompact myelin
MTMR2	CMT4B1 CMT4B2	Protein degradation; vesicle/membrane transport
MTMR13 (SBF2)		
PRX	CMT4F, DSD/CHN	Myelin structure—connection to basal lamina
SIMPLE/LITAF	CMT1C	Endosomal protein trafficking and degradation
GDAP1	CMT4A/2K	Signal transduction pathways in neuronal development; mitochondrial dysfunction
NDRG1	CMT4D (HMSNL), DSD/CHN	Vesicle/membrane trafficking; lipid distribution regulation
KIAA1985 (SH3TC2)	CMT4C, DSD/CHN	Assembly of protein complexes
FGD4 (FRABIN)	CMT4H	Actin filament binding protein
PRPS1	CMTX5	Purine and pyrimidine biosynthesis
FIG4	CMT4J	Vesicle trafficking
Axonal Forms		
KIF1B	CMT2A1	Axonal transport of mitochondria
MFN2	CMT2A2/HMSN VI/HMSNV	Mitochondrial membrane fusion; apoptosis regulation
RAB7	CMT2B/HSANI	Vesicular transport, late endocytic pathway
GARS	CMT2D/dHMNV	tRNA synthetase
NEFL	CMT2E/1F	Neurofilament assembly and axonal transport
HSPB1	CMT2F/dHMNIIB	Heat shock protein; alterations of the neurofilament network
HSPB8	CMT2L/dHMNIIA	Heat shock protein; alterations of the neurofilament network
DNM2	DI-CMTB; DI-CMTB + neutropenia; centronuclear myopathy; CMT2 phenotype	Endocytosis and cell motility
YARS	DI-CMTC	tRNA transferase
LMNA	CMT2B1; multiple laminopathies	Intermediate filament structural proteins underlying the inner nuclear membrane
BSCL2 [†]	CMT2D-like; dHMNV; Silver syndrome; congenital generalized lipodystrophy	Seipin—integral membrane protein of the endoplasmic reticulum
MED25	CMT2B2 (ARCMT2B)	Transcription regulation

^{*} Recently described, not yet classified.

[†] Not yet subtyped on OMIM.

AD: autosomal dominant; AR: autosomal recessive; BSCL2: Berardinelli-Seip congenital lipodystrophy type 2; CHN: congenital hypomyelinating neuropathy; Cx32: connexin 32; dHMN: distal hereditary motor neuropathy; DMN2: dynamin 2; DSD: Dejerine-Sottas disease; EGR2: early growth response 2; FGD4: frabin; GARS: glycyl t-RNA synthetase; GDAP1: ganglioside-induced differentiation-associated protein 1; GJB1: gap junction protein, beta 1; HMSNL: hereditary motor sensory neuropathy, LOM type; HMSN-P: hereditary motor sensory neuropathy—proximal; HSAN: hereditary sensory autonomic neuropathy; HSPB1: heat shock 27-kD protein 1; HSPB8: heat shock 22-kD protein 8; KIAA1985 (SH3TC2): SH3 domain and tetratricopeptide repeat domain 2; KIF1B: kinesin family member 1B; LITAF: lipopolysaccharide induced tumor necrosis factor alpha; LMNA: lamin A/C; MED25: mediator of RNA polymerase II transcription, subunit 25; MFN2: mitofusin-2; MPZ: myelin protein zero; MTMR2/MTMR13: myotubularin-related protein; NDRG1: NMYC downstream-regulated gene 1; NEFL: neurofilament protein, light polypeptide; PMP22: peripheral myelin protein 22; PRPS1: phosphoribosylpyrophosphate synthetase I; PRX: periaxin; RAB7: RAS-associated protein RAB7; SBF2: set-binding factor; SIMPLE: small integral membrane protein of lysosome; YARS: tyrosyl-tRNA synthetase.

and genetic characteristics of a large cohort of CMT1 and CMT2 patients, and were able to separate them based on whether the median forearm motor conduction velocity was above or below 38 m/s.⁴

The current classification system reflects the evolving identification of causative genes and is a work in progress (Table 14–3); variations will be seen in the work of different authors. Tables are likely to be out of date as soon as they are published. Classification is based on inheritance and electrodiagnostic features, and is further subdivided based on molecular genetics. The realization that some genes can be expressed as axonal or demyelinating confounds easy classification. CMT1 includes autosomal dominant demyelinating neuropathies caused by genes expressed mostly in Schwann cells, CMT2 includes mostly autosomal dominant axonal neuropathies associated with mostly neuronally expressed genes (a few recessive subtypes are included), and CMT4 includes autosomal recessive demyelinating forms. Dejerine-Sottas disease (DSD) and congenital hypomyelinating neuropathy (CHN), rather than CMT3, were reserved for the severe early-onset demyelinating form, although some authors regard these as severe phenotypic expressions of

CMT1. *X-linked dominant forms* (CMTX) and *hereditary neuropathy with liability to pressure palsy* (HNPP) are additional designations. *Dominant intermediate CMT* (DI-CMT) refers to classic CMT cases with intermediate motor nerve conduction velocities, between those of typical CMT1 and CMT2.

**Charcot-Marie-Tooth Disease,
Type 1 (CMT1/HMSN I)**

CLINICAL FEATURES

Epidemiology

Estimates of the overall prevalence of hereditary neuropathies are about 10–36 per 100,000 population.^{5,6} While CMT1 reportedly accounts for the majority of CMT cases, perhaps 50%, problems with ascertainment and as yet undiscovered gene mutations leave some doubt. It remains to be determined how many of the cases we currently diagnose as chronic idiopathic axonal neuropathy are actually examples of CMT2. The six current subtypes of CMT1, A–F, are listed in Table 14–4. CMT1A accounts for about 70%–80% of CMT1 and is associated with a

Table 14–3 **Classification of Charcot-Marie-Tooth Disease (CMT/HMSN)**^{215,216}

Disorder	Inheritance	Physiology/Pathology	Approximate Proportion of CMT
CMT1 (HMSN I), subtypes A–F	AD	Demyelinating	50%
HNPP	AD	Demyelinating	?
CMT2 (HMSN II), subtypes A–L	AD/few AR	Axonal	20%–40%
DSD/CHN [*] (HMSN III)	AD/AR	Demyelinating	Rare
CMT4 (HMSN IV), subtypes A–H	AR	Demyelinating	Rare
CMTX (HMSN X), subtypes 1–5	XLD/XLR	Mixed	10%–20%
DI-CMT, subtypes A–D	AD	Mixed	Rare

^{*} In some classifications, regarded as a severe phenotypic expression of CMT1 and the category eliminated.
AD: autosomal dominant; AR: autosomal recessive; CHN: congenital hypomyelinating neuropathy; DI-CMT: dominant intermediate CMT; DSD: Dejerine-Sottas disease; XLD: X-linked dominant; XLR: X-linked recessive.

Table 14–4 Charcot-Marie-Tooth Disease, Type 1 (CMT1) Subtypes^{215,216}

Subtype	Gene	Locus	Inheritance	Proportion of CMT1	Phenotypes
CMT1A	PMP22 duplication (98%)	17p11.2	AD	~70%–80%	Classic CMT; rare point mutation with DSD/CHN phenotype
CMT1B	MPZ mutation	1q22-23	AD	~5%–10%	Classic CMT; early onset, severe (DSD/CHN); adult onset, axonal, CMT2 type
CMT1C	SIMPLE/LITAF mutation	16p13.1-12.3	AD	Uncommon	Classic CMT
CMT1D	EGR2 mutation	10q21-22	AD	Uncommon	Classic CMT, DSD, CHN; multiple cranial neuropathies
CMT1E	PMP22 point mutation	17p11.2	AD	Uncommon	Classic CMT and deafness
CMT1F/ CMT2E	NEFL mutation	8p21	AD	Uncommon	Classic CMT with early onset, severe; axonal phenotype designated CMT2E more common

AD: autosomal dominant; CHN: congenital hypomyelinating neuropathy; DSD: Dejerine-Sottas disease; EGR2: early growth response 2; LITAF: lipopolysaccharide induced tumor necrosis factor alpha; MPZ: myelin protein zero; NEFL: neurofilament protein, light polypeptide; PMP22: peripheral myelin protein 22; SIMPLE: small integral membrane protein of lysosome.

1.4-Mb duplication in the PMP22 gene on chromosome 17p11.2.

Symptoms and Signs

The CMT1 subtypes are often clinically indistinguishable. The majority of patients with CMT1 have the classic CMT phenotype, with a slowly progressive, symmetric, motor more than sensory polyneuropathy, associated with distal atrophy and weakness of legs more than arms, reflex loss, and foot deformity.^{3,4,7} Symptoms typically begin in the first two decades of life (75% in the first decade) but have a wide range of onset, at least partly because the indolent progression eludes recognition of a problem.⁴ The clinical severity is extremely variable, from significant disability to complete unawareness by both the patient and the physician of a deficit. We've had the experience of first making this diagnosis in elderly patients hospitalized for unrelated reasons. The clinical picture of minor patient complaints or a vague recollection of onset and significant physical findings is a useful clinical clue that a chronic neuropathy is likely to be hereditary. Patients

may complain of motor delay or toe walking in infancy/childhood cases, abnormal (steppage) gait, foot deformity, ankle instability, imbalance, or foot drop. They may report high arches (pes cavus), hammer toes or difficulty with heel walking, and slow or clumsy running all of their lives. Cramps and fasciculations may be present. Sensory or autonomic symptoms are usually not the presenting complaints. While sensory abnormalities are present, patients do not typically complain of positive sensory symptoms (pain, paresthesias) as often as those with acquired neuropathies, and this too is a helpful clinical clue. Some studies, however, suggest that positive sensory symptoms and pain (either neuropathic or nociceptive) may be more frequent than is generally appreciated (54% overall), more so in CMT2 than in CMT1, where it is rarely the presenting or main feature.⁸ Nociceptive pain was particularly frequent (71%) in CMT1A patients, perhaps related to more severe foot abnormalities and ankle weakness.

Initial weakness is displayed in the peroneal muscles subserving toe and ankle dorsiflexion and eversion. Foot drop and contracture of

calf muscles may result from the unopposed flexor action of posterior compartment muscles; eventually, these muscles too undergo atrophy, sometimes resulting in a stork-legged or “inverted champagne bottle” appearance and impaired toe walking. The pes cavus/hammer toes deformity is a foreshortened, high-arched foot attributable to weakness and atrophy of the intrinsic foot muscles and the unequal action of long toe flexors and extensors (Fig. 14–1). Calluses and occasionally ulcers may develop at points of excessive mechanical pressure. Atrophy seldom extends beyond the mid-thigh, and weakness only very rarely involves the girdle muscles. Absence of the ankle reflex is an early sign, and generalized hypo- or areflexia is usual in established cases. In a large series of CMT1A patients, 75% were areflexic, 21% hyporeflexic, and 4% normal.⁷ Large- and small-fiber sensory involvement of some or all modalities in a stocking-glove distribution is present in all cases, but may be mild and difficult to demonstrate with certainty; nerve conduction studies (NCS) or quantitative sensory testing (QST) may help establish sensory involvement. Loss of distal vibration sensation is the most sensitive sign. Discolored skin, edema, and cold extremities probably result from inactivity, loss of muscle strength and bulk, and diminished blood flow, although small-fiber autonomic dysfunction may be an alternative explanation. The hands usually do not become weak until some years after the condition has become advanced in the legs, but hand involvement is present in the majority.⁷ Occasionally, the intrinsic hand muscles may atrophy to an extreme degree, resulting in a claw hand deformity, and forearm atrophy may also be apparent. Mild sensory loss may accompany the hand weakness; prominent sensory complaints in the hands may reflect superimposed entrapments. There is considerable variation in atrophy, weakness, and distal skeletal deformity in this disorder, and some individuals may be profoundly weak, with only slight atrophy and minimal or no pes cavus and even pes planus (flat feet). Foot difficulties are present from the earliest stages of this disease.⁹

Hypertrophic nerves are reportedly observed in 25%–50% of patients with CMT1.^{3,4} Greater auricular, cervical plexus, and upper extremity nerves seem to be the most useful to demonstrate nerve enlargement. Postural hand tremor, with features of

essential tremor, was described by Roussy and Levy, and this family has since been characterized as having an MPZ mutation (CMT1B);¹⁰ a similar tremor is described with CMT1A and PMP22 point mutations.⁷ Foot deformities occur in nearly three-quarters of CMT1A patients;⁷ the stress of misalignment may result in nociceptive pain. In one study, the probability that children with bilateral pes cavus will have a diagnosis of CMT based on NCS and /or the PMP22 duplication was 78%.¹¹ It should be noted that foot anomalies can also be associated with developmental central nervous system (CNS) disorders, and pes cavus also occurs in multiple endocrine neoplasia, type 2B. Hip dysplasia, often asymptomatic initially, may be a radiographic observation, particularly in CMT1.¹² Scoliosis may occur in approximately one-third of CMT patients and thoracic hyperkyphosis is common, particularly in severe cases with early onset, and more so in CMT1.^{13,14}

Some clinical variations include calf hypertrophy with CMT1A and B,^{15,17} severe proximal leg weakness late in the course of CMT1A¹⁸ or in CMT1B,¹⁹ and myelopathy or cauda equina syndrome from nerve root hypertrophy in CMT1A.^{20,21} Davidenkow syndrome (neuropathic scapulooperoneal syndrome) may be associated with the CMT1 phenotype and a chromosome 17p11.2/PMP22 deletion.²² Occasional CMT1A, CMT1B, or CMTX patients with atypical features of acute or subacute deterioration and positive sensory symptoms have been judged to have coexistent inflammatory neuropathy and have responded to immunotherapy with steroids and/or intravenous immunoglobulin (IVIG).²³ Dyck et al. described similar prednisone-responsive HMSN in 1982.²⁴ The role of the immune system in hereditary neuropathies remains to be elucidated. Other issues may include restless legs syndrome (more so in CMT2), restrictive lung disease (phrenic/diaphragmatic dysfunction in severe cases), sleep apnea, and vocal cord dysfunction.^{25,26} A few men with CMT1 have reported impotence,²⁷ but in general, symptomatic autonomic dysfunction is not a feature. Hearing loss may be associated with several subtypes, including CMT1B, D and E, and can be the initial feature in some CMT1B mutations. CMT with optic atrophy was

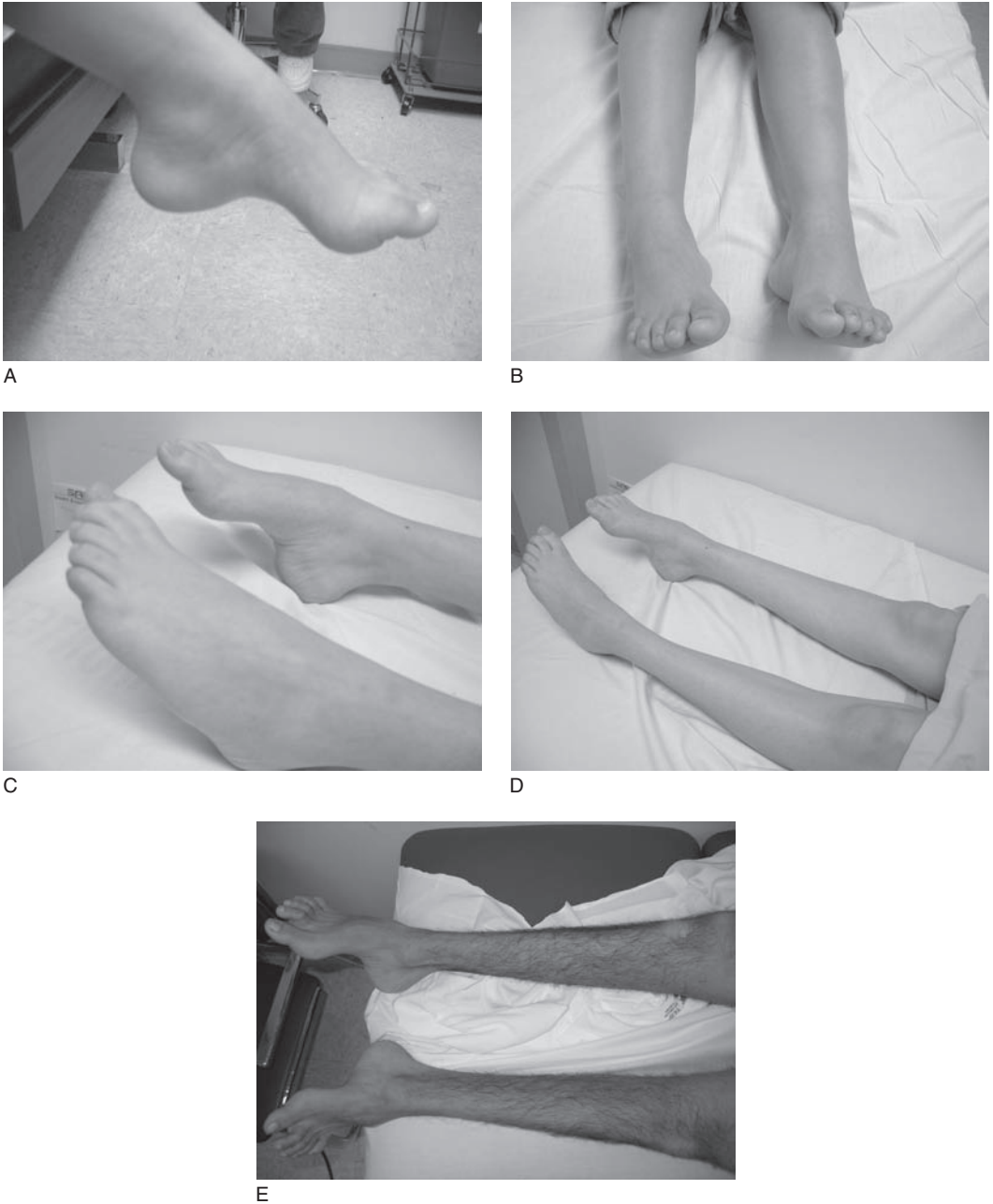


Figure 14-1. A child (A, B) and an adult (C, D) with CMT1a displaying pes cavus, calf muscle atrophy, and slight hammer toes. An advanced case of CMT2 with severe pes cavus, hammer toes and calf atrophy (E).

designated HMSN VI in the Dyck and Lambert classification.

CMT1B/MPZ mutations have a wide spectrum of phenotypic expression, including the classic CMT phenotype, early-onset severe

neuropathy fitting the rubric of DSD/CHN or late/adult-onset with an axonal/CMT2-type phenotype, including some with pupillary abnormalities and hearing loss (Thr95Met mutation).²⁸ One variant with late onset (age

45–55 years) and rapid progression to complete foot drop within a few years is associated with a Pro70Ser substitution in the extracellular domain of MPZ.²⁹ CMT1C-F are uncommon and are outlined in Table 14–4. CMT1F associated with (NEFL) mutations has an early onset and a severe phenotype with moderate to severely slowed nerve conduction, but the axonal CMT2E phenotype is more common.³⁰

Differential Diagnosis

Prior to categorization by NCS, CMT1 cannot readily be clinically differentiated from many cases of CMT2 or the other CMT types. Compared to CMT2, CMT1 tends to have an earlier age of onset, and patients are more likely to have hand weakness, tremor, tendon areflexia, foot and spinal deformities, nerve thickening, and more extensive distal sensory loss.^{4,31} Peripheral neuropathy may be a presenting feature of fragile X-associated tremor ataxia syndrome (FXTAS) and may be confused with CMT.³² Rare genetically verified cases of Friedreich ataxia (FRDA) are described with clinical features of both CMT and FRDA, including demyelinating nerve conduction.³³

Ankle dorsiflexors are always weaker than plantar flexors in CMT1. Therefore, finding the opposite pattern with selective calf weakness should suggest intraspinal pathology, such as spinal stenosis, tumor, meningeal carcinomatosis, or spinal muscular atrophy, or distal myopathy.³⁴

Differentiation from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) may occasionally be challenging, particularly when there is no clear family history or foot deformity and none of the more characteristic features of CIDP, such as a fluctuating course and proximal as well as distal weakness. Electrodiagnostic features of severe uniform conduction slowing without conduction block or substantial dispersion in CMT1, as well as moderately to severely elevated cerebrospinal fluid (CSF) protein in CIDP, will then be helpful. Rare cases of CMT1 (CMT1C), as well as HNPP and CMTX, may have multifocal conduction block or temporal dispersion mimicking CIDP. Occasionally, a nerve biopsy will be contemplated to help sort out the issue, but even this

has limitations. Onions bulbs may be seen in either condition; focal abnormalities, inflammatory infiltrates and edema, if present, suggest CIDP. When genetic testing is negative but the diagnosis remains unclear, we have occasionally resorted to a trial of empiric immunosuppression. Anti–myelin-associated glycoprotein (MAG) neuropathy will be associated with a demyelinating neuropathy with strikingly prolonged distal motor latencies and usually an immunoglobulin M (IgM) monoclonal gammopathy.

Prior to electrodiagnostic and neuroimaging evaluation, additional diagnostic considerations may include distal myopathies, lower motor neuron disorders, distal hereditary motor neuropathy, and spinal dysraphism.

LABORATORY STUDIES

Electrodiagnostic Studies

Nerve conduction studies are characterized by marked demyelinating changes, with prolonged distal motor latencies, slowed conduction velocities, and prolonged or absent late responses; sensory and motor potentials are often low amplitude or absent, particularly in the legs.^{35–37} Motor conduction velocity slowing tends to be uniform between nerves and between proximal and distal nerve segments. Segmental amplitude reductions suggesting conduction block or substantial temporal dispersion of waveforms are uncommon, and when present are often associated with low amplitudes wherein phase cancellation or superimposed focal compression are alternative explanations. Difficulty with supramaximal stimulation due to high stimulation thresholds may also be an issue. Uniformity tends to hold true for CMT1A, but asymmetric multifocal features may be seen in HNPP, CMTX, and some missense mutations of PMP22, MPZ, SIMPLE, and EGR2; some mutations have not been adequately characterized electrophysiologically. Care must be taken in differentiating hereditary from acquired neuropathies based on these criteria alone. Dispersion of the compound muscle action potential (CMAP) is more common in CIDP than in hereditary neuropathies, but it occurs often enough that it cannot be used in isolation as a distinguishing point.³⁸ Needle electromyography (EMG)

typically shows distal chronic reinnervation changes. Additionally, CMT with superimposed acquired demyelinating polyneuropathy may rarely develop.

Nerve conduction abnormalities can be detected in the first months of life; conduction slowing evolves over the first few years of life, and there is little change subsequently.^{39–41} Median forearm conduction velocities in CMT1A/PMP22 duplication tend to be in the low to mid 20 m/s range, with a range of under 10 to the low 40s.^{17,31,42,43} Conduction velocities can vary widely, as much as 27 m/s, within the same family.⁴⁴ CMT1B conduction velocities are bimodal, with early-onset cases in the CMT1A range and later-onset cases with near-normal values.^{17,28} In CMT1C, nerve conduction velocities (NCVs) range from 7.5 to 27 m/s in the peroneal nerve and may show temporal dispersion and nonuniform slowing;⁴⁵ in another study, median NCVs ranged from 16 to 33 m/s.⁴⁶ Progressive clinical disability in CMT over time correlates not with the degree of slowing but with loss of CMAP amplitudes indicating axon loss.⁴⁷ Slow NCVs are demonstrable before clinical deficits are apparent.

Cerebrospinal Fluid

The CSF protein is normal or moderately elevated, usually under 100 mg/dL.¹⁷ In a series of 13 patients with CMT1A, the mean CSF protein level was 58 mg/dL (range, 20–122 mg/dL).⁴⁸

Imaging

Magnetic resonance imaging (MRI) of the lumbosacral or cervical spine may show nerve root hypertrophy, and can be confused with other pathology such as neurofibromatosis or CIDP.^{20,21} Nerve root enhancement may be more frequent and pronounced in CIDP.⁴⁹

Genetics

An accurate family history is critical and is not always easy to obtain. Accuracy may require examination of relatives and review of medical records. Inheritance in CMT1 is autosomal dominant, conferring a 50% risk of inheriting the altered gene in each offspring. Penetrance is nearly 100%, but the range in age of onset

and severity is wide.³⁹ This wide variability has even been observed in monozygotic twins.⁵⁰ Striking variability of disease expression within some families suggests unestablished effects of modifier genes or epigenetic factors. In different reports, from 10% to about one-third of CMT1A results from a de novo gene mutations.⁵¹

CMT1A is associated with a 1.4-Mb duplication in the PMP22 gene on chromosome 17p11.2. PMP22 is a glycoprotein and constitutes 2%–5% of the protein content of compact myelin. The duplication results from an unequal meiotic crossover that is relatively frequent. The disease is the result of overexpression of PMP22. Deletion at this site causes decreased PMP22 gene dosage and the HNPP phenotype. Point mutations of PMP22, classified as CMT1E or under CMT1A, tend to confer a more severe phenotype than duplications. CMT1B is associated with more than 95 MPZ mutations.²⁸ Myelin protein zero is the major myelin protein expressed by Schwann cells, comprises about half of all peripheral nervous system (PNS) myelin proteins, is an adhesion molecule involved in myelin structure (compact myelin) and function, and is a member of the immunoglobulin supergene family. About half of the cases present as sporadic disorders. SIMPLE mutations are responsible for CMT1C, and the protein product may be involved in protein degradation.⁵² The rare EGR2 mutations are involved in transcription regulation and are associated with varied demyelinating phenotypes, including CMT1D, DSD/CHN, and the autosomal recessive CMT4E. NEFL mutations have either an axonal (CMT2E) or a demyelinating (CMT1F) phenotype, and the pathophysiology is probably related to disruption of neurofilament assembly and axonal transport.

Commercial molecular genetic testing is available for all of the CMT1 subtypes. It should be emphasized that negative molecular genetic testing does not entirely exclude a diagnosis of CMT while the full spectrum of involved genes and mutations remains unknown.

GUIDELINES FOR TESTING

Decisions regarding which molecular genetic tests to order should be guided by the clinical

and electrodiagnostic features and by the relative frequencies of known gene defects, and not by resorting indiscriminately to large *panels* of tests (Table 14–5). Based on the frequency distribution of genes contributing to the CMT phenotype, a molecular diagnosis can be established in approximately

45%–50% of all cases by testing for the CMT1A duplication, HNPP deletion, and GJB1 point mutation; specifying the CMT as demyelinating (CMT1) yields a diagnosis in 75%–80% of cases.⁵³ Testing for mutations of MFN2, GJB1, and MPZ yields a diagnosis in an estimated 20%–25% of cases of CMT2.⁵³

Table 14–5 **Clinical and Electrodiagnostic Clues to Guide Testing in CMT**

Inheritance	
No male to male; severity, male > female	CMTX
Multiple generations; male to male	AD forms
Parents unaffected, consanguinity	AR forms
No FH, ~ sporadic, demyelinating	Best yield: PMP22, MPZ, GJB1
No FH, ~ sporadic, axonal	Best yield: MFN2, MPZ, GJB1
Age of Onset	
Infancy	DSD, CHN, CMT4F
Childhood	CMT1, DSD
Adolescence	CMT1, CMTX
Adulthood	CMT2 > CMT1
Late adulthood	MPZ mutations
Physical Findings	
Areflexia	CMT1 > CMT2
Preserved proximal reflexes	CMT2, CMTX, DI-CMT
Brisk reflexes	CMT2A, HMSN V, CMT2H, BSCL2
Pes cavus	CMT1 > CMT2
Pupillary abnormalities	MPZ mutations
Hearing loss	CMT1B, D, E; CMTX, CMT2J, CMT4D
Tremor	CMT1 > CMT2
Hypertrophic nerves	CMT1
Prominent hand > foot wasting/weakness	CMT2D, dHMN V
Severe distal and proximal, wheelchair-bound	DI-CMT B, CMT2A2 early-onset
Scoliosis, hip dysplasia	CMT1 > CMT2; CMT4C
Prominent sensory	CMT2B; also consider HSAN1; CMT4F
Respiratory or vocal cord	CMT2C, CMT2K/4A, CMT1D, CMT4C
Multiple cranial neuropathies	CMT1D; CMT4B
Early-onset glaucoma	CMT4B2
Optic atrophy	CMT2A (MFN2)
Neutropenia	DI-CMTB
Late onset, rapid progression	MPZ
Electrodiagnosis	
NCV:	
<10 m/s	DSD, CHN (PMP22, MPZ, EGR2, PRX)
20–25 m/s (<38–42 m/s)	CMT1
25–45 m/s	CMTX, DI-CMT; NEFL, MPZ, GDAP
>38 m/s	CMT2
Nonuniform, multifocal features	CMTX, HNPP, CMT1C
Central Features	CMTX, HNPP, CMT2A (MFN2)

CHN: congenital hypomyelinating neuropathy; CMTX: X-linked CMT; dHMN V: distal hereditary motor neuropathy, type V; DI-CMT: dominant intermediate CMT; DSD: Dejerine-Sottas disease; EGR2: early growth response 2; FH: family history; GDAP: ganglioside-induced differentiation-associated protein; GJB1: gap junction protein, beta 1; HMSNV: hereditary motor and sensory neuropathy, type V; HNPP: hereditary neuropathy with liability to pressure palsies; HSAN: hereditary sensory autonomic neuropathy; MFN: mitofusin; MPZ: myelin protein zero; NCV: nerve conduction velocities; NEFL: neurofilament protein, light peptide; PMP22: peripheral myelin protein 22.

PATHOLOGY

Sural nerve biopsies in CMT1A reveal large- and small-diameter myelinated fiber loss, segmental demyelination, and Schwann cell proliferation forming onion bulbs, which are made up of circumferentially directed cytoplasmic processes of Schwann cells (Fig. 14–2). Onion bulbs are not pathognomonic of CMT1 since they may occur in other chronic neuropathies characterized by repeated episodes of segmental demyelination and remyelination (i.e., CIDP).^{3,54} Axon loss correlates with disease severity. In CMT1B, cases with early onset and severe nerve conduction slowing tend to show severe demyelinating features, whereas axonal pathology characterizes those with more normal conduction velocities.¹⁷ Tomacula, focal sausage-like thickenings of the myelin sheath, may occur, but not to the extent seen in HNPP. CMT1F/2E may be associated with axonal swellings due to focal accumulation of neurofilaments;⁵⁵ it is likely that, similar to hexacarbon neuropathy, paranodal axonal swelling causes retraction of the myelin sheath with paranodal demyelination accounting for the demyelinating electrophysiology. With the availability of molecular genetic testing, nerve

biopsies are now rarely necessary in clinical practice to support a diagnosis of CMT.

PATHOGENESIS

A variety of genes and their protein products are capable of resulting in the common distal neuropathy phenotype we recognize as CMT (Table 14–2). These include proteins involved in myelin or axonal structure, transcription regulation, apoptosis, axonal transport, and others.^{1,56} The final common pathway is axonal degeneration. Although the hallmark of CMT1 is demyelination, disrupting interactions between Schwann cells and axons results in significant dysfunction of axonal physiology, including changes in neurofilament packing density and phosphorylation, and axonal transport.⁵⁷ Axonal atrophy precedes fiber degeneration.³ The exact nature of the neuroprotective effect of Schwann cells on axons remains to be established. Myelin-associated glycoprotein, located in the adaxonal plasmalemma of myelin-producing cells, appears to promote resistance to axonal injury and prevent axonal degeneration in cell culture and in vivo.⁵⁸

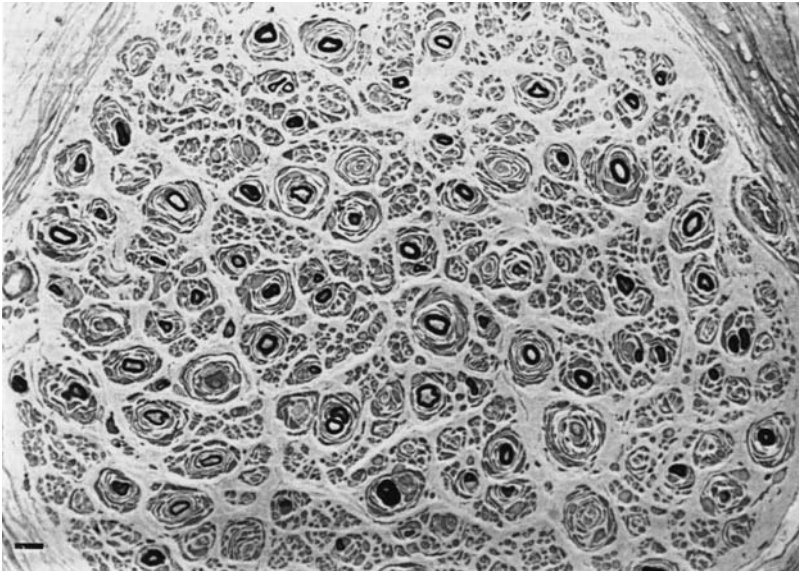


Figure 14–2. A low-power photomicrograph of myelinated nerve fibers from a sural nerve biopsy in a case of CMT1. The myelinated nerve fiber population is reduced. Many of the surviving fibers are surrounded by an onion bulb proliferation of Schwann cells. Some of the onion bulbs do not contain myelinated fibers or contain a demyelinated axon. These appearances indicate a chronic process with repeated demyelination and remyelination. Bar = 10 μ m.

TREATMENT, COURSE, AND PROGNOSIS

Men and women are equally disabled by CMT1A, suggesting that gender, pregnancy, or progesterone levels do not contribute significantly to the severity of neuropathy in women.⁵⁹ There is no decrease in lifespan. Severity varies from minimal disability to wheelchair bound, and the course is generally not entirely predictable in an individual case or within families. The vast majority of patients remain ambulatory.

Pregnancy may worsen CMT1 symptoms during or after gestation in about half of patients,⁶⁰ or the presence of CMT may complicate delivery.⁶¹

Exposure to peripheral neurotoxic agents, in particular vincristine or cisplatin, even after a few doses, can result in a severe, rapidly progressive polyneuropathy and should be avoided.⁶²⁻⁶⁴ A proposed list of medications of concern was recently compiled based on limited data.⁶⁵

Treatment of CMT currently is symptomatic and preventive. Management may include appropriate physical therapy, including therapy to prevent Achilles tendon contracture, special shoes or ankle-foot orthoses (AFO) for foot drop as needed, orthopedic tendon or joint surgery in selected cases, occupational therapy if there is significant hand involvement, and occasionally pain management. Foot reconstruction for disabling pes cavus is controversial. Obesity is best avoided, and regular inspection of the feet for injury is advisable. Genetic counseling is important. Rare patients with atypical CIDP-like presentations or deterioration may benefit from a trial of immunosuppression.

A number of promising pharmacologic approaches for therapy have emerged in recent years, targeting the effects of CMT mutations. In a transgenic rat model of CMT1A, PMP22 gene overexpression can be downregulated and the phenotype improved with the use of a progesterone antagonist.⁶⁶ Ascorbic acid inhibits PMP22 expression by reducing cyclic adenosine monophosphate (cAMP) levels and is efficacious in the transgenic mouse model; human studies are ongoing.⁶⁷ Neurotrophins are another avenue of investigation; recombinant neurotrophin-3 promoted improvement in a mouse model and in a small trial of patients with CMT1A.⁶⁸ Erythropoietin is suggested as a

neuroprotective agent and curcumin, a compound derived from the curry spice tumeric, as an antiapoptotic agent.^{69,70} Gene transfer and stem cell therapies are impractical at this time and will await future developments.

Hereditary Neuropathy with Liability to Pressure Palsy (HNPP)

INTRODUCTION

HNPP, previously called *tomaculous neuropathy* among other designations, is an autosomal dominant demyelinating neuropathy characterized by recurrent transient, painless mononeuropathies or brachial plexopathy often related to minor trauma. Features include nonuniform nerve conduction abnormalities localized to distal nerve segments and entrapment sites, focal myelin thickenings (tomacula) on nerve pathology, and, in most cases, a 1.4-Mb deletion of the PMP22 gene on chromosome 17p11.2.

CLINICAL FEATURES

Epidemiology

HNPP is likely to be underdiagnosed because of a mild or asymptomatic phenotype and a negative family history in many cases. Estimates of prevalence have included 2–5/100,000⁷¹ and at least 16/100,000 in Finland.⁷² The ratio of men to women is perhaps 4:3, with an earlier age of onset in men and a higher prevalence of brachial palsy in women.⁷³

Symptoms and Signs

Most patients with HNPP present with recurrent, acute, transient, focal, painless motor and/or sensory neuropathies in the distribution of individual nerves or plexi, related to mild trauma in the form of compression, traction, or repetitive use (Fig. 14–3).^{73,74} A substantial number of patients recall no obvious trigger. The mean age at onset is around 20 years, with presentation at around 40 years, but with a wide range. Symptoms last for minutes to years, but in the majority for hours to days. Sensory symptoms do not always fit neatly into a single nerve distribution but are focal.

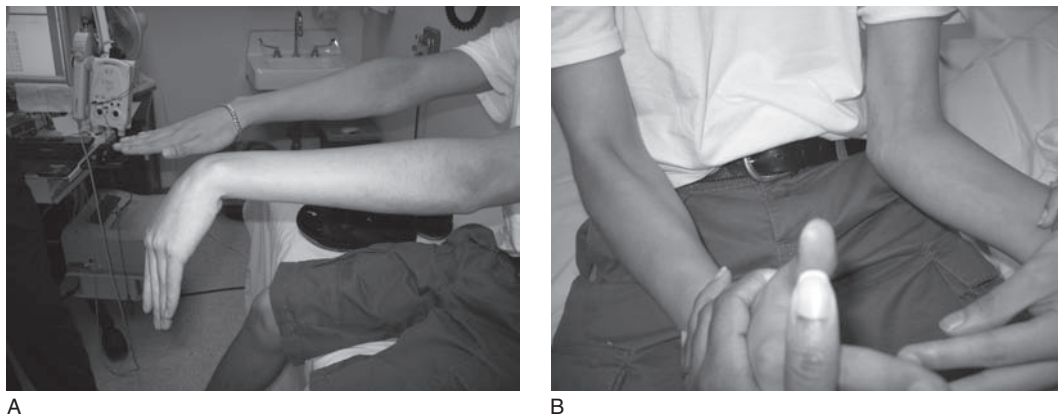


Figure 14-3. An adolescent with HNPP developed a radial neuropathy and complete left wrist and finger drop (A) after holding his arm around his girlfriend at a movie theater. (B) The weak left brachioradialis muscle does not appear upon resisted elbow flexion, while the right is normal.

Of 143 acute palsies in 70 patients, the most common nerves involved were: peroneal (36%), ulnar (28%), brachial plexus (20%), radial (13%), and median (4%).⁷³ Recurrent brachial plexopathy may be the only clinical expression of HNPP.⁷³ Muscle cramps are not uncommon. About 18% of symptomatic patients have pes cavus, and almost 50% have absent ankle jerks or generalized areflexia.⁷³ Weakness is most often found in a peroneal or ulnar distribution, and many patients have mild reduction of pinprick and vibration sensation in the feet.⁷⁴ The neurologic examination can be normal.

The broad phenotypic spectrum of presentation is displayed in many asymptomatic cases, as well as in reported cases with recurrent short-lived positional sensory symptoms, progressive rather than acute mononeuropathy, CMT-like polyneuropathy, chronic sensory polyneuropathy, CIDP-like recurrent subacute polyneuropathy, or indolent bilateral hand amyotrophy.^{73,76,77} Rare cases can be quite fulminant and severe, with axon loss related to intense physical activity, as reported in a young military recruit with severe bilateral brachial plexopathies beginning on her first day of training.⁷⁸ The uncommon presentation of a diffuse, symmetric, length-dependent CMT-like sensorimotor polyneuropathy appears to occur in an older age group.^{74,79} Neuropathic scapulo-peroneal syndrome (Davidenkow syndrome) can be associated with the PMP22

deletion.^{22,80} A few patients have been reported with facial, trigeminal, hypoglossal, phrenic, laryngeal, axillary, anterior interosseous, or femoral neuropathies.

A few cases and one large family have been associated with imaging abnormalities, with or more often without symptoms, suggesting concomitant CNS demyelination.^{81–83}

Differential Diagnosis

The brachial plexopathy presentation of HNPP is distinguished from that of hereditary brachial plexus neuropathy (hereditary neuralgic amyotrophy [HNA]) by the presence of pain, absence of a generalized neuropathy, dysmorphic features in some pedigrees, and linkage to 17q25 in HNA. Immune brachial plexus neuropathy (neuralgic amyotrophy; Parsonage Turner syndrome) is also associated with pain and no generalized neuropathy on electrodiagnostic testing. Recurrent focal neuropathies with minimal or no symptoms of a generalized neuropathy would help to distinguish HNPP patients from those with a generalized acquired neuropathy who may have superimposed entrapments. Unlike HNPP, the multiple mononeuropathies of vasculitic disorders tend to be painful, do not occur specifically around entrapment sites, and show less slowing on NCS.

HNPP should be considered in patients with multiple entrapments or a CMT1 phenotype, although the yield will be low. Screening for the disease appears not to be

a fruitful endeavor in the large population of patients with entrapment neuropathies. No cases of HNPP were identified in a series of 50 unrelated patients with idiopathic carpal tunnel syndrome screened for the HNPP deletion.⁸⁴ Likewise, none were identified in 59 patients with a history of surgery for more than one entrapment neuropathy.⁸⁵ Perhaps HNPP would be more likely to be picked up in children with carpal tunnel syndrome (CTS) since this entrapment is unusual in this age group. Alternatively, in another study, 30% of patients referred for electrodiagnostic testing for an acute painless mononeuropathy or brachial plexopathy of undetermined origin turned out to have the HNPP deletion, suggesting a high yield with this clinical presentation.⁸⁶ The deletion was detected in about half of the patients in another large series of undiagnosed multifocal neuropathies.⁸⁰

An IgM monoclonal gammopathy with anti-MAG antibodies may electrophysiologically mimic HNPP to some degree but should otherwise be distinguishable. Cases without sensory symptoms or an acute onset may occasionally suggest multifocal motor neuropathy or motor neuron disease.

LABORATORY STUDIES

Blood Tests

Commercial molecular genetic testing is available for the HNPP deletion and for rarer point mutations of PMP22.

Electrodiagnostic Studies

The characteristic electrodiagnostic features of this disorder are a generalized, nonuniform, distally accentuated sensorimotor polyneuropathy with superimposed focal conduction abnormalities preferentially located at common entrapment sites. There is diffuse sensory NCV slowing, prolonged distal motor and F-wave latencies, relatively minor effects on motor conduction velocities, and variable reduction of sensory or motor amplitudes, suggesting disproportionate distal conduction slowing in this disease.^{73,74,80,87–89} Dispersion of the CMAP may be seen in about 10% of nerves in HNPP.³⁸ These characteristic electrophysiologic abnormalities are reliably present in all deletion carriers,

both symptomatic and asymptomatic. Slowly progressive axonal loss may occur over time with declining CMAP amplitudes, as also demonstrated in heterozygous PMP22 knockout mice.^{79,90}

Studies of the blink reflex, jaw-opening reflex, and acoustic evoked potentials suggest subclinical functional myelin impairment in the brainstem.⁸³ Audiograms in HNPP show progressive sensorineural hearing impairment with normal speech recognition.⁹¹

Cerebrospinal Fluid

Reports are few, with CSF protein ranging from normal to modestly elevated (under 100 mg/dL), without pleocytosis.^{73,76,92}

Imaging

Fluid-attenuated inversion recovery (FLAIR) or T2-weighted brain MRI occasionally shows multifocal hyperintensities in the subcortical white matter.^{81–83}

Genetics

The inheritance is autosomal dominant. About 21% of cases are de novo deletions.⁸⁹ The penetrance is unknown; many patients have no or few symptoms and are unrecognized. The majority of patients with HNPP have a 1.4-Mb deletion at 17p11.2 that includes the PMP22 gene;⁹³ the others have a variety of PMP22 sequence mutations or deletions of a different size.⁹⁴ The reciprocal duplication causes CMT1A. PMP22 is the only gene known to cause HNPP. Of 156 unrelated HNPP patients, 84% had the 17p11.2 deletion.⁷¹

PATHOLOGY

Sural nerve biopsy specimens are characterized by segmental demyelination and remyelination, tomacula (sausage-shaped perinodal or internodal focal myelin thickenings), and a variable degree of axon loss (Fig. 14–4).⁹⁵ Tomacula, however, are nonspecific and are not present in all cases. They may also be seen in several other hereditary and acquired neuropathies.⁹⁵ Sural nerve biopsies may be useful in the approximately 16% of patients

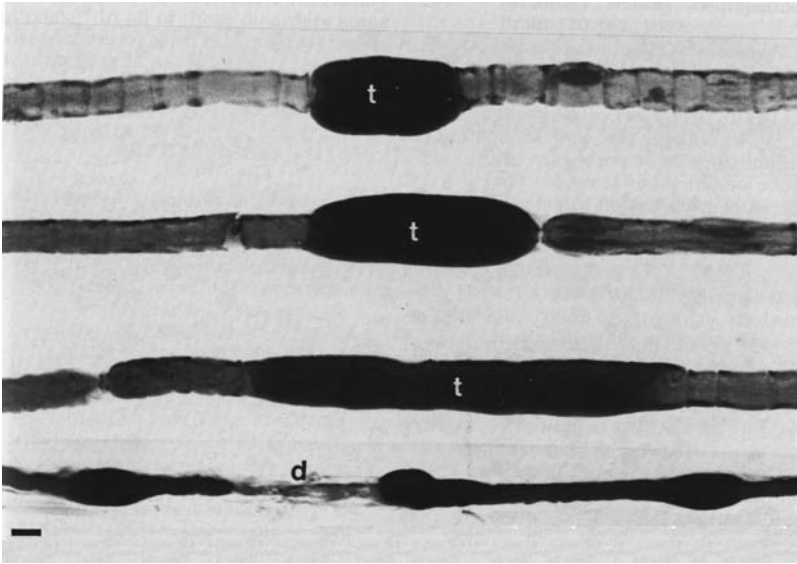


Figure 14-4. HNPP. Portions of isolated nerve fibers stained with osmium tetroxide showing focal sausage-shaped expansions (tomaculi, t). The lowermost fiber possesses a short region of demyelination (d).

with suspected HNPP without the 17p11.2 deletion.

PATHOGENESIS

The disease is related to a gene dosage effect with a predicted 50% of the normal expression of the PMP22 gene with the deletion. Underexpression of PMP22 mRNA in sural biopsy specimens of HNPP patients supports the notion of a gene dosage effect as the pathogenetic mechanism.⁹⁶⁻⁹⁸ This has also been demonstrated in skin biopsy specimens of patients with the *Leu7fs* mutation who have a phenotype identical to that of the PMP22 deletion.⁷⁹ HNPP nerve xenograft studies from a patient with another PMP22 point mutation demonstrated a marked delay in the onset of myelination, impairment of regenerative capacity, and increased neurofilament density, showing that this mutation interferes with the ability of Schwann cells to myelinate and that the axonal cytoskeleton is affected by impaired Schwann cell-axon interaction.⁹⁴ An animal model of HNPP, at least analogous to the more uncommon length-dependent neuropathy phenotype presentation in older patients, is provided by the heterozygous PMP22-deficient mouse, which develops a progressive

demyelinating tomaculous neuropathy.⁹⁰ The homozygous deletion knockout mouse develops a more severe demyelinating neuropathy.

It appears that decreased PMP22 in HNPP makes peripheral myelin susceptible to repetitive minor trauma, suggesting that at least part of the function of PMP22 is to stabilize myelin.⁷⁴

TREATMENT, COURSE, AND PROGNOSIS

Patients are advised to avoid activities that place nerves at risk for stretch or compression. This may apply to issues concerning occupation, lifestyle, positioning during operative procedures, and other situations. Protective pads may be appropriate for some activities. An AFO is helpful for a significant foot drop until recovery proceeds. Vincristine is to be avoided; one patient with undiagnosed HNPP developed a severe, mostly reversible tetraparesis after receiving 4 mg of vincristine.⁹² A few women have experienced nerve palsy during pregnancy or postpartum. The vast majority of patients make a complete or substantial clinical recovery from individual nerve palsies, with an occasional exception. When

formally assessed as a group, quality-of-life measures appear not to be impaired.⁹⁹ The life span is normal. No clear guidelines exist as to the advisability of surgery for entrapments in this disorder, given the favorable natural history and concern regarding the vulnerability of nerves to trauma.

Charcot-Marie-Tooth Disease, Type 2 (CMT2/HMSN II)

INTRODUCTION

CMT2 is designated as mostly autosomal dominant axonal neuropathies associated with mostly neuronally expressed genes (a few recessive subtypes have also been included, also referred to as ARCMT2, and some Schwann cell gene mutations may show an axonal phenotype). Motor conduction velocities are only mildly abnormal or normal, and pathology is consistent with an axonopathy. CMT2 turns out to have tremendous genetic heterogeneity. At least 10 genes and more loci have been identified in recent years, accounting currently for only a small proportion (less than one-third) of all cases of CMT2. Current subtypes A–L are outlined in Table 14–6.

CLINICAL FEATURES

Epidemiology

CMT2 may account for 20%–40% of all CMT, although the true prevalence is uncertain since all the causative genes have not been identified. MFN2 mutations are the most common cause of CMT2 identified to date, accounting for 9%–33% of cases in various studies.^{100–105}

Symptoms and Signs

Compared to CMT1, CMT2 cases as a whole tend to have a later age of onset, and are less likely to have hand weakness, tremor, tendon areflexia, foot and spinal deformities or nerve thickening, and less extensive distal sensory loss (with the exception of CMT2B).^{4,31} The peak age of onset is in the second decade, but many patients develop symptoms much later; some families have individuals with symptom onset in their mid-80s.¹⁰⁶ CMT2A with MFN2 mutations tends to show the classic CMT

phenotype, as described for CMT1, characterized by distal, symmetric, length-dependent weakness and wasting, more pronounced in the legs than in the arms, accompanied by varying degrees of distal sensory loss, depressed distal reflexes, and skeletal deformity. Phenotypes are different in early-onset and late-onset cases, with early-onset cases (<10 years) associated with severe functional disability.¹⁰⁴ The early-onset severe phenotype may include optic atrophy and appears to be responsible for cases designated as HMSN VI.^{104,107} In addition, CMT with pyramidal signs (HMSN V) but without frank spasticity, as in the hereditary spastic paraplegias, is genetically heterogeneous, including MFN2 mutations.¹⁰⁸ Variable clinical or imaging features of CNS involvement may accompany MFN mutations.^{104,109}

CMT2B associated with RAB7 mutations has the CMT phenotype but with prominent sensory loss and distal ulceration.¹¹⁰ Occasionally, there seem to be no motor features with a phenotype closely mimicking HSAN1, which is associated with the SPTLC1 mutation and more commonly positive sensory symptoms of lancinating neuropathic pain.¹¹¹ CMT2C may begin in infancy, childhood, or adult years, and in addition to limb weakness, there is vocal cord and respiratory muscle paresis;^{112,113} clinical overlap exists with dHMN VII. The CMT2D phenotype associated with GARS mutations is characterized by teenage or early-adult onset, early hand involvement with weakness and atrophy of predominantly thenar and first dorsal interosseous muscles, later hypothenar muscle involvement, and variable distal lower extremity muscle and sensory involvement.¹¹⁴ In the absence of sensory findings, this phenotype is designated allelic dHMN V or dSMA V. Features of the other CMT2 subtypes are summarized in Table 14–6; details are available in OMIM. Note that the autosomal recessive subtypes are also referred to as ARCMT2 in some publications.

Additional features in occasional CMT2 patients as a whole include proximal weakness, asymmetric weakness and atrophy, calf hypertrophy, normal or brisk knee reflexes, and extensor plantar responses without spasticity.¹¹⁵ In a series of 44 patients with CMT, restless legs syndrome was found in 37% with CMT2 and in none with CMT1.¹¹⁶

Table 14–6 Charcot-Marie-Tooth, Type 2 (CMT2) Subtypes²¹⁶

Subtype	Gene* / Locus	AD/ AR	Proportion of CMT2	Phenotypes and Ancestry
CMT2A1	KIF1B/ 1p36.2	AD	Rare	Classic CMT; single Japanese family
CMT2A2	MFN2/ 1p36.2	AD	~10%–30%	Classic CMT; occ. optic atrophy (HMSN VI), or pyramidal signs (HMSN V), or SNHL; early-onset severe, later-onset milder
CMT2B	RAB7/3q21	AD	Rare	Prominent sensory; similar to HSAN1 [‡]
CMT2B1 (ARCM2A)	LMNA/ 1q21.2	AR	Rare	Algerian/Moroccan; variable phenotypes; related disorders (laminopathies)
CMT2B2 (ARCM2B)	MED25/ 19q13.3	AR	Rare	Costa Rican; adult onset; milder than others
CMT2C	Unknown/ 12q23-q24	AD	Rare	Vocal cord and diaphragmatic paresis; similar to dHMN VII, with sensory involvement
CMT2D	GARS (?BSCL2) [†] /7p15	AD	Rare	Early hand >LE weakness/wasting; allelic dHMN V
CMT2E/1F	NEFL/8p21	AD	~2%	CMT1F with slow NCV
CMT2F	HSPB1 (HSP27)/ 7q11-q21	AD/ AR	Rare	Russian, Chinese; allelic dHMN IIB
CMT2G	Unknown/ 12q12-q13.3	AD	Rare	Spanish; very slow progression
CMT2H	Unknown (?GDAP1) /8q21.3	AR	Rare	Tunisian; pyramidal features
CMT2I	MPZ/1q22	AD	Rare	Late onset, axonal
CMT2J	MPZ/1q22	AD	Rare	Late onset, pupillary abnormalities, deafness
CMT2K/4A	GDAP1/ 8q13-q21.1	AR	Rare	Early onset; vocal cord and diaphragmatic paresis
CMT2L	HSPB8 (HSP22)/ 12q24	AD	Rare	Chinese; allelic dHMN IIA
HMSN-P	Unknown/ 3q13.1	AD	Rare	Okinawa, Japan; proximal involvement

* Additionally, two recent mutations of DNM2 pleckstrin homology have been found to cause a CMT2 phenotype as yet unclassified.²⁶²

[†] Phenotypically overlapping diseases associated with BSCL2 mutations include dHMN V, Silver syndrome (dHMN V phenotype with spasticity), and CMT2 (where on the subtype chart this fits is still unclear).^{115,263}

[‡] HSAN1 (SPTLC1 gene mutation) has lancinating neuropathic pain and less motor involvement.

AD: autosomal dominant; AR: autosomal recessive; BSCL2: Berardinelli-Seip congenital lipodystrophy type 2; dHMN: distal hereditary motor neuropathy; DMN2: dynamin-2; GARS: glycyl t-RNA synthetase; GDAP1: ganglioside-induced differentiation-associated protein 1; HMSN-P: hereditary motor sensory neuropathy—proximal; HSAN: hereditary sensory autonomic neuropathy; HSPB1: heat shock 27-kD protein 1; HSPB8: heat shock 22-kD protein 8; KIF1B: kinesin family member 1B; LMNA: lamin A/C; MED25: mediator of RNA polymerase II transcription, subunit 25; MFN2: mitofusin-2; MPZ: myelin protein zero; NCV: nerve conduction velocities; NEFL: neurofilament protein, light polypeptide; RAB7: RAS-associated protein RAB7.

Differential Diagnosis

Until electrodiagnostic studies are performed, there are no absolute distinguishing features between CMT1 and CMT2, but a combination of onset in the first decade of life, areflexia, and pes cavus makes CMT1 more likely.³¹ CMT1A patients tend to have greater distal weakness and foot drop, but there is considerable

overlap. Sporadic CMT2 must be differentiated from chronic acquired axonal polyneuropathies; early onset, a very careful family history including examination of family members, and foot deformity are helpful. When sensory symptoms or signs are difficult to demonstrate, dHMN, distal myopathies, lower motor neuron disorders, and spinal dysraphism should be considered. Acquired

chronic, predominantly sensory polyneuropathies may be an issue in cases of CMT2B. Early stages of CMT2D with hand amyotrophy may be confused with multiple entrapments, neurogenic thoracic outlet syndrome, multifocal motor neuropathy, or motor neuron disease.

LABORATORY STUDIES

Electrodiagnostic Studies

Classic CMT2 shows electrodiagnostic features consistent with an axonopathy involving sensory and motor fibers, with a predominance of abnormalities in the legs. Nerve conduction studies show reduced CMAP amplitudes with normal or mild to moderately reduced conduction velocities (>38 m/s in the median forearm, by definition, but this is not invariable within families). Sensory nerve action potential (SNAP) amplitudes are usually reduced or absent but may be normal. Needle EMG shows distal chronic and less frequent active denervation and distal neurogenic motor unit recruitment.^{4,115}

Cerebrospinal Fluid

Insufficient information is available.

Imaging

Eight of 21 patients (38%) with MFN mutations had T2 and FLAIR hyperintense lesions in the centrum semiovale, periventricular white matter, and subcortical white matter; some showed possible related symptoms or signs, while others were subclinical.¹⁰⁴ Brain magnetic resonance spectroscopy has revealed mitochondrial dysfunction in one studied family.¹⁰⁹ MFN2 is abundant in brain.

Genetics

Inheritance is autosomal dominant in all subtypes except CMT2B1, CMT2B2, CMT2H, and CMT2K, which are autosomal recessive. De novo mutations are common with MFN2,¹⁰⁴ and in some families approximately 25% of individuals with the mutation may be subclinical.¹⁰¹ Commercial molecular genetic testing is available for the following related genes: KIF1B, MFN2, RAB7, LMNA, GARS, NEFL, MPZ, GDAP1, HSPB1.

GUIDELINES FOR TESTING

For the classic CMT2 phenotype, one should test for MFN2 first, followed by NEFL and MPZ and possibly the other listed genes as available, although they are all rare. Since the electrodiagnostic features of CMTX may overlap and since it is common, adding GJB1 may be fruitful. In CMT2 with prominent sensory involvement, one should test for RAB7 and, if there is prominent neuropathic pain, for SPTCL1. With upper limb onset, one should test for GARS and BSCL2.^{53,101,117}

PATHOLOGY

Nerve biopsies in patients with CMT2A show an axonopathy without distinguishing features. There is loss of large myelinated fibers, more so at distal sites, and regenerating clusters, with occasional small onion bulbs or degenerative mitochondrial changes.^{100,118} CMT2E/1F associated with NEFL mutations may show giant axons, with axonal swellings containing accumulations of disorganized neurofilaments.¹¹⁹

PATHOGENESIS

Most of the gene products associated with CMT2 are involved with critical cellular processes in the demanding environment of neuronal tissue, including mitochondrial function (MFN2, HSP22, HSP27, GDAP1), endosomal trafficking (NEFL, KIF1B, RAB7), or RNA processing (GARS).¹²⁰ Additionally, Lamin A/C (LMNA) is a structural protein component of the inner nuclear membrane, and infrequently some mutations of Schwann cell proteins primarily associated with CMT1 (MPZ) may present an axonal phenotype. MFN is a mitochondrial transmembrane guanosine triphosphatase (GTPase), regulates mitochondrial network architecture by fusion of mitochondria, and is expressed ubiquitously. MFN2 mutations result in diminished axonal mitochondrial transport, which may explain the vulnerability of the longest peripheral axons.¹²¹ Studies of fibroblasts from MFN2-related CMT2A showing altered mitochondrial energy metabolism offer another mechanism for axonal degeneration.¹²² All the involved genes and their putative protein functions are listed in Table 14-2;

several reviews discuss potential mechanisms of axonal dysfunction.⁵⁶

TREATMENT, COURSE, AND PROGNOSIS

Management is symptomatic and preventive, as outlined for CMT1, and involves genetic counseling. Progression of weakness is slow,¹²³ with exceptions in some late-onset MPZ mutations.²⁹ Life expectancy is generally not affected, although in severely affected patients with CMT2C it may be shortened due to respiratory failure.¹¹²

Additional Autosomal Recessive Axonal Neuropathies

Three additional complex hereditary disorders are included here; these have not been part of the CMT classification but have features of the CMT2 phenotype and are autosomal recessive.

AGENESIS OF THE CORPUS CALLOSUM WITH PERIPHERAL NEUROPATHY (ACCPN); ANDERMANN SYNDROME; CHARLEVOIX DISEASE; HMSN/ACC)

Described with highest prevalence in French Canadians of Quebec, this severe, early-onset, autosomal recessive, axonal, sensorimotor neuropathy is associated with variable degrees of agenesis of the corpus callosum, mental retardation, and dysmorphic features. It results from mutations of the SLC12A6 gene encoding the K-Cl cotransporter KCC3.^{124,125}

SEVERE INFANTILE AXONAL NEUROPATHY WITH RESPIRATORY FAILURE (SIANRF; SPINAL MUSCULAR ATROPHY WITH RESPIRATORY DISTRESS [SMARD1] OR DISTAL HEREDITARY MOTOR NEUROPATHY, TYPE VI [dHMN VI])

This disorder is characterized by very early onset, with intrauterine growth retardation, weak cry and foot deformities, predominantly distal lower extremity weakness, and severe respiratory compromise presenting at age 1 to 6 months, leading to ventilator

dependence or death. When sensory abnormalities are absent, this condition is designated SMARD or dHMN VI. SMARD1 is linked to the gene IGHMBP2 (immunoglobulin mu-binding protein 2).¹²⁶

GIANT AXONAL NEUROPATHY (GAN)

Giant axonal neuropathy is a childhood autosomal recessive disorder of generalized intermediate filament organization resulting from mutations of the gigaxonin gene on chromosome 16q24.1. In the PNS, accumulations of densely packed neurofilaments result in giant axonal swellings or spheroids with segregation of other axoplasmic organelles and a severe, axonal sensorimotor neuropathy. Similar aggregates are seen in NEFL mutations and with some toxins such as n-hexane. Diffuse CNS involvement may result in cognitive decline and cerebellar dysfunction. Abnormalities may be seen on the electroencephalogram (EEG), in evoked potentials, and in the cerebral and cerebellar white matter on MRI. Altered keratin intermediate filaments cause the characteristic kinky, curly hair seen in most patients; scanning EM shows longitudinal grooves in the hairs. Additional clinical features may include cranial neuropathies and skeletal abnormalities. The disorder often progresses to death, usually by the third decade.^{127–130}

Dejerine-Sottas Disease and Congenital Hypomyelinating Neuropathy (HMSN III)

Dejerine-Sottas disease (DSD; also called *Dejerine-Sottas syndrome* [DSS], *Dejerine-Sottas neuropathy* [DSN], or *hypertrophic neuropathy of infancy*), first described in 1893 by Dejerine and Sottas as an early-onset, autosomal recessive, hypertrophic demyelinating neuropathy, is best regarded as a severe phenotypic expression of CMT1 or CMT4. It is now known to be associated with several autosomal dominant or recessive gene mutations, including PMP22, MPZ, EGR2 and PRX.^{131–136} Many cases occur as de novo mutations. The term *Dejerine-Sottas disease* has

been abandoned in some classifications but is still widely used to indicate a clinical phenotype, although not a specific genetic mutation or inheritance pattern.

Criteria that have been used for the DSD designation include onset in infancy or early childhood (by age 2–3), delayed motor development, severe motor (including proximal extension) and sensory deficits with ataxia, areflexia, skeletal deformity including pes cavus and scoliosis, palpable nerve hypertrophy, elevated CSF protein, markedly slowed motor conduction velocities, and pathology showing severe demyelination, onion bulb formation, and nerve fiber loss.^{3,135,137} To complicate matters further, because some axonal forms of CMT can also be severe and present in infancy, some use the DSD designation for any early-onset, severe phenotype, whether axonal or demyelinating.

Electrophysiologic findings in DSD are characteristic, with uniquely and remarkably slowed upper extremity motor conduction, usually under 10–12 m/s and often less than 6 m/s, very prolonged distal motor latencies, and often unobtainable sensory potentials.^{138,139} While motor velocities are uniform between nerves, marked temporal dispersion of waveforms may be seen, causing diagnostic confusion with acquired demyelinating neuropathies. High stimulation thresholds are typical. The CSF protein levels ranged from 0.72 to 2.12 g/L in one series.¹³⁹ An MRI scan may show spinal nerve root enlargement or enhancement.¹⁴⁰ At autopsy, the first patient of Dejerine and Sottas showed prominent hypertrophy of the anterior and posterior roots.¹³⁷

Prior to electrodiagnostic testing, diagnostic considerations for a weak, floppy, areflexic infant/child include spinal muscular atrophy, congenital and distal myopathies, congenital myasthenic syndromes, combined central/peripheral disorders such as the leukodystrophies, and CIDP. The difficulties in making a diagnostic differentiation from childhood CIDP are apparent when one considers that DSD also has proximal weakness, areflexia, elevated CSF protein, and waveform temporal dispersion and may occur as *de novo* mutations without a family history. However, the severe degree and uniformity of motor slowing would favor DSD. In select cases without a

demonstrable mutation and no genealogical clues, nerve biopsy may be appropriate, as might an empiric trial of IVIG. Unlike CIDP, nerve biopsy in DSD will show no inflammatory infiltrate or myelin-laden macrophages.¹³⁷

While often associated with severe disability, DSD does not invariably imply wheelchair dependence in adult life.¹⁴¹

Congenital hypomyelinating neuropathy (CHN) is generally regarded as a more severe variant of DSD, pathologically defined, showing axons with no myelin or remarkably thin myelin sheaths (amyelination or hypomyelination), and onion bulbs composed mainly of basal membranes. The pathology, including lack of myelin breakdown products, has led to CHN being considered by some as a congenital impairment of myelin formation distinct from DSD.¹⁴² Cases receiving the designation of CHN have had mutations in *PMP22*, *MPZ*, *EGR2*, and *MTMR2*.^{143–146}

Charcot-Marie-Tooth Disease, Type 4 (CMT4, Autosomal Recessive CMT1, ARCMT1, HMSN IV)

CMT4 is designated as autosomal recessive, demyelinating neuropathies, typically with a more severe phenotype than classic CMT. Some authors place a few autosomal recessive axonal phenotypes in this category rather than as subtypes of CMT2 or ARCMT2. While rare, CMT4 may be frequent in populations with high rates of consanguinity, accounting for 30%–50% of all CMT in those ethnic groups.^{147,148} Nine genes and 10 loci are classified in CMT4 subtypes A to J (Table 14–7). The genes include *GDAP1*, *MTMR2*, *MTMR13* (*SBF2*), *SH3TC2* (*KIAA1985*), *NDRG1*, *EGR2*, *PRX*, *FGD4*, and *FIG4*. Putative protein functions are listed in Table 14–2.

In general, autosomal recessive CMT tends to be more severe and earlier in onset than autosomal dominant forms.¹⁴⁹ Conduction velocity slowing is moderate to severe. Several subtypes may fit the rubric of DSD or CHN. Specific subtype diagnosis is aided by a combination of knowing the ethnic background and phenotypic features; also, more than in other CMT types, pathologic features can be

Table 14–7 Charcot-Marie-Tooth, Type 4 (CMT4) Subtypes²¹⁶

Subtype	Gene/Locus	AD/AR	Phenotypes and Ancestry
CMT4A	GDAP1/8q13-q21.1	AR	Tunisia, Turkey, Europe; early onset, severe, patients often wheelchair bound; occ. laryngeal and diaphragmatic paresis; hypomyelination with basal lamina onion bulbs
CMT4B1	MTMR2/11q22	AR	Italy, Turkey, United Kingdom, India, Saudi Arabia; early onset, severe, patients often wheelchair bound; cranial neuropathies in CMT4B1; focally folded myelin sheaths, no onion bulbs; early-onset glaucoma in CMT4B2
CMT4B2	MTMR13/SBF2/11p15	AR	
CMT4C	SH3TC2 (KIAA1985)/5q32	AR	Algeria, Turkey, Europe, Gypsies; variable phenotype; less severe; childhood onset; severe scoliosis; basal lamina onion bulbs, cytoplasmic extensions of Schwann cells, giant axons
CMT4D (HMSN-Lom)	NDRG1/8q24.3	AR	Gypsies (originally in Lom, Bulgaria); SNHL; severe axon loss, hypomyelination, onion bulbs early, curvilinear axonal inclusions
CMT4E	EGR2/10q21.1-q22.1	AR	CHN clinical, electrophysiologic, and pathologic phenotypes
CMT4F	PRX/19q13.1-q13.2	AR	Lebanon, Japan, Turkey; DSD; severe weakness, ataxia, pain; severe axon loss, onion bulbs
CMT4G (HMSN-Russe)	Unknown/10q22	AR	Gypsies; similar to CMT4D without SNHL; severe weakness, prominent sensory loss
CMT4H	FGD4/12p11.2-q13.1	AR	Lebanese, Algerian; onset by age 2; severe axon loss, features of congenital hypomyelination with some onion bulbs
CMT4J	FIG4/6q21	AR	Severe childhood-onset demyelinating neuropathy

AD: autosomal dominant; AR: autosomal recessive; CHN: congenital hypomyelinating neuropathy; DSD: Dejerine-Sottas disease; EGR2: early growth response 2; FDG4: frabin; FIG4: factor-induced gene 4; GDAP1: ganglioside-induced differentiation-associated protein 1; KIAA1985(SH3TC2): SH3 domain and tetratricopeptide repeat domain 2; MTMR2/MTMR13: myotubularin-related protein; NDRG1: NYMC downstream-regulated gene 1; PRX: periaxin; SBF2: set-binding factor; SNHL: sensorineural hearing loss.

characteristic.¹⁵⁰ The reader is referred to Table 14–7 and several recent reviews for more details.^{130,137}

Charcot-Marie-Tooth Disease, X-Linked (CMTX/HMSN X)

INTRODUCTION

CMTX is the second most common form of demyelinating CMT after CMT1A. Five subtypes are outlined in Table 14–8, with CMTX1 accounting for the majority. It is caused by mutations of GJB1, the gene encoding the gap junction protein connexin32 (Cx32), and is characterized by a classic CMT phenotype along with a mixed demyelinating and axonal

electrophysiologic and pathologic picture, with intermediate conduction velocities.

CLINICAL FEATURES

Epidemiology

CMTX1 accounts for about 10%–20% of CMT overall and for 90% of X-linked CMT. About 40%–44% of CMT families with a median motor nerve conduction velocity in the intermediate range of 30–40 m/s had CMTX1.^{151,152}

Symptoms and Signs

The features are those of the classic CMT phenotype. Symptoms typically begin in the first two decades, generally later than in CMT1A, but onset can be variable. Males tend to be severely

Table 14–8 **Charcot-Marie-Tooth Disease, Type X (CMTX) Subtypes**²¹⁶

Subtype	Gene	Locus	Inheritance	Proportion of CMTX	Phenotypes
CMTX1	GJB1	Xq13.1	XLD	90%	Classic CMT; occ. CNS
CMTX2	Unknown	Xp22.2	XLR	?	Infancy; mental retardation
CMTX3	Unknown	Xq26	XLR	?	Juvenile onset; spastic paraparesis
CMTX4 [°]	Unknown	Xq24-q26.1	XLR	?	Early onset; deafness, mental retardation
CMTX5 [†]	PRPS1	Xq21.3-q24	XLR	?	Early onset; deafness, optic neuropathy

[°]Cowchock syndrome.

[†]Rosenberg – Chutorian syndrome.

GJB1: gap junction protein, beta-1; PRPS1: phosphoribosylpyrophosphate synthetase I; XLD: X-linked dominant; XLR: X-linked recessive.

affected, while females usually have mild or sub-clinical involvement (probably due to X-inactivation), with a later onset than males. Some females, however, are severely disabled.¹⁵³ Clinical features are analogous to those described for CMT1, with a slowly progressive, length-dependent sensorimotor polyneuropathy, with foot deformity, initial distal atrophy and peroneal weakness, intrinsic hand weakness and atrophy, with particular thenar involvement and distal sensory loss.^{154–157} Ankle reflexes are typically absent, and other reflexes are generally depressed but more often retained than in CMT1. Pain and autonomic dysfunction are not important features. Occasionally, there is kyphoscoliosis, hearing loss, or tremor.^{157,158} Respiratory dysfunction is rare.

Transient, recurrent, CNS T2-hyperintense white matter lesions, often symmetric and nonenhancing on MRI and associated with restricted diffusion, may accompany some Cx32 mutations.¹⁵⁹ Patients may present in an ADEM (acute disseminated encephalomyelitis) or stroke-like fashion, with deficits depending on the location.¹⁶⁰ Lesions are predominantly in the posterior centrum semiovale, splenium of the corpus callosum, or middle cerebellar peduncles, and those involving the deep white matter spare the subcortical U fibers.¹⁶⁰ Return from a high-altitude trip (above 8000 ft) is suggested as a precipitant,¹⁶¹ or attacks may be related to fever/infection, physical exertion, respiratory distress, or hyperventilation, or may be unprovoked.¹⁶² Some mutations are associated with extensor plantar responses.

A rare patient with CMTX may appear to have a coexistent inflammatory neuropathy. This can be suspected in patients with acute or subacute deterioration.²³

The rare CMTX2 through CMTX5 subtypes are outlined in Table 14–8.

Differential Diagnosis

In general, CMTX is clinically indistinguishable from CMT1, except for the inheritance pattern. Compared to males with CMT1A, those with CMTX tend to have more severe disease, more frequent hand weakness and wasting of thenar muscles, and more frequent sensory abnormalities.^{154,155} The lack of male-to-male transmission and the fact that males are more severely affected than females suggest CMTX. The CNS features suggest CMTX. Conduction velocities are faster in CMTX, but values may overlap; nonuniform electrophysiologic features favor CMTX. Differentiation from CMT2 or dominant intermediate CMT forms may also be difficult, particularly in females. Overlap of clinical and electrophysiologic features in childhood CIDP and CMTX demands consideration of a hereditary neuropathy in all children with suspected CIDP.¹⁵⁸

LABORATORY STUDIES

Electrodiagnostic Studies

While there has been some controversy in the literature about whether CMTX is a primarily axonal or demyelinating neuropathy,

demyelinating features are clearly present. Intermediate NCVs characterize CMTX families, with the majority between 30 and 40 m/s for upper extremity motor conduction but ranging from 20 m/s to normal, being slower in males than in carrier females.^{153,155} Unlike CMT1A, there may be nonuniform slowing of conduction velocities and temporal dispersion within and between nerves.^{158,163} Although distal and proximal-distal CMAP dispersion are more common in CIDP, about 10% of nerves in CMTX may show distal CMAP dispersion (duration > or = 9 ms), and proximal-distal CMAP dispersion is similar (~20%), making distinction difficult based on these criteria alone.³⁸ SNAP and CMAP amplitudes may be low or absent, particularly in the lower extremities, and needle EMG shows chronic denervation-reinnervation.

Subclinical CNS involvement may be demonstrated with visual evoked potentials (VEP), brainstem auditory evoked potentials (BAEP), and central motor evoked potentials, with or without associated MRI abnormalities.^{164,165}

Cerebrospinal Fluid

A few reports have CSF protein ranging from normal to 107 mg/dL.^{38,160}

Imaging

Magnetic resonance imaging in the occasional patient with CNS features is described above under Symptoms and Signs. Brain MRI has occasionally shown subclinical bilateral corticospinal tract hyperintensities.¹⁶⁶

Genetics

Inheritance of CMTX1 is X-linked dominant. As sporadic cases do occur, a negative family history does not exclude CMTX. Definite male-to-male transmission excludes CMTX as a diagnostic possibility. Carrier females usually have mild or no symptoms. Some children with the mutation are normal clinically and electrophysiologically.¹⁵³ Over 200 different mutations are described in the GJB1 gene responsible for CMTX1 in OMIM. No specific mutation of GJB1 appears to be more severe than a deletion of the entire protein,¹⁶⁷ with perhaps an exception being a particularly

severe phenotype in a girl with a specific missense mutation associated with leaky Cx32 hemichannels.¹⁶⁸ A few kindreds are reported with recessive CMTX.

GUIDELINES FOR TESTING

It is important to test for GJB1 mutations in any patient with the classic CMT phenotype and a family history suggesting no male-to-male transmission and male severity exceeding female severity. Along with PMP22 and MPZ for demyelinating forms and MFN and MPZ for axonal forms, GJB1 testing will have a reasonable yield with a wide range of NCVs in sporadic cases or with an unclear family history. Additionally, consider CMTX when there are nonuniform electrodiagnostic features or CNS involvement.

PATHOLOGY

Although some investigators describe only axonal pathology, with loss of myelinated fibers and regenerating clusters, most describe features of both demyelination and axonal degeneration.¹⁵⁶ In a detailed study of 14 CMTX nerve biopsies, findings included prominent changes in paranodal myelin with widened nodes of Ranvier, less common segmental demyelination, early axonal cytoskeletal abnormalities and later axonal atrophy, degeneration and loss of myelinated fibers, prominent regenerative sprouting, dilatation of adaxonal spaces, prominence of adaxonal Schwann cell cytoplasm, and widening of Schmidt-Lanterman incisures.¹⁶⁹ Compared to CMT1A, CMTX biopsies show higher myelinated fiber density, thinner myelin sheaths, more regenerated clusters, fewer onion bulbs, and less teased fiber demyelinating changes.^{54,163,170} Demyelination is the first pathologic finding in GJB1/Cx32-null mice.¹⁷¹

PATHOGENESIS

The gap junction protein Cx32, one of about 20 mammalian connexins, is located in the paranodal loops of noncompact myelin and in the Schmidt-Lanterman incisures. Cx32 is widely expressed by the Schwann cells of peripheral nerve and mainly by oligodendrocytes in brain. It is also widely expressed by many other tissues, especially the liver, but without clinical

involvement. Connexins form channels providing a low-resistance pathway for the intercellular diffusion of ions and small molecules (<1000 Da).¹⁷² Most GJB1 mutations cause simple loss of function.¹⁶⁷ Mutations may lead to impaired functional channel assembly, changes in channel permeability, or altered trafficking of Cx32 protein to junctional sites.^{173–175} Compromised Schwann cell functions likely lead to impaired Schwann cell–axon interactions and both myelin and axonal pathology.¹⁶⁹ Disrupted oligodendrocyte–astrocyte gap junction communication may underly CNS dysfunction with some mutations.¹⁶⁰

TREATMENT, COURSE, AND PROGNOSIS

Treatment is supportive, as outlined for CMT1. Disability increases with age and best correlates with length-dependent axonal degeneration.¹⁶⁷ The lifespan is normal. Care

must be exercised in administering potentially neurotoxic medications, although single patients are reported to have received vincristine¹⁷⁶ or cisplatin¹⁷⁷ uneventfully.

Charcot-Marie-Tooth Disease, Dominant Intermediate (DI-CMT)

The designation *dominant intermediate* CMT was born of the observation that in some families with the dominant CMT phenotype, upper extremity NCVs in affected members do not fit neatly into either CMT1 or CMT2, but rather span the intermediate range (~25–45 m/s).^{178–182} Sural nerve biopsies show a mixture of axonal and demyelinating features, with or without onion bulbs. Characteristics of the four subtypes described to date are outlined in Table 14–9. Two newly described mutated genes, DN2 (dynamin2) and YARS (tyrosyl-tRNA synthetase), account for DI-CMTB and DI-CMTC, respectively.

Table 14–9 **Charcot-Marie-Tooth Disease, Dominant Intermediate (DI-CMT) Subtypes**²¹⁶

Subtype	Gene	Protein	Locus	AD/AR	Phenotypes and Ancestry
DI-CMTA	Unknown	Unknown	10q24.1-q25.1	AD	Italian family; begins in second decade; median NCVs 25–45 m/s; mixed path with onion bulbs
DI-CMTB	DNM2	Dynamin2	19p12-p13.2	AD	Three families: Australia (NCVs 24–54 m/s, axonal > demyelinating, onion bulbs). Belgium, North America; may be associated with neutropenia; also CMT2 phenotype
DI-CMTC	YARS	Tyrosyl-tRNA synthetase	1p34-p35	AD	Two families: American (German/Polish origin), onset in first/second decade, NCVs 30–40 m/s, no onion bulbs; Bulgarian: onset at 7–59 years, NCVs 33 m/s to normal, motor predominant
DI-CMTD	MPZ	Myelin protein zero	1q22	AD	Macedonian family; UE NCVs 24–48 m/s; axonal > demyelinating pathology, without onion bulbs

AD: autosomal dominant; AR: autosomal recessive; DI-CMT: dominant intermediate CMT; DN2: dynamin2; MPZ: myelin protein zero; NCVs: nerve conduction velocities; UE: upper extremity; YARS: tyrosyl-tRNA synthetase.

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES (HSAN)

Introduction

The hereditary sensory and autonomic neuropathies (HSAN) are a phenotypically and genetically heterogeneous group of disorders affecting primarily, although not exclusively, sensory or autonomic axons or neurons. The term *hereditary sensory neuropathy* (HSN) is used synonymously, mostly for HSAN I (HSN I) or HSAN II (HSN II), which have few if any autonomic features; it was first used by Hicks in 1922 in describing a family with perforating foot ulcers, shooting pains, and deafness with

onset from 15 to 36 years of age.¹⁸³ The earliest descriptions of these disorders are credited to the French literature in the mid-1800s. Five types (one autosomal dominant, four autosomal recessive), several subtypes, six genes, and eight loci are currently classified (Table 14–10).^{184–186}

Clinical Features

EPIDEMIOLOGY

The HSANs are rare. Clustering of SPTLC1 (serine palmitoyltransferase, long-chain base unit 1)-associated HSAN I in Australian and English families appears to be related to a common British founder.¹⁸⁶ A higher prevalence of HSAN II is reported in eastern

Table 14–10 Hereditary Sensory and Autonomic Neuropathies (HSAN)²¹⁶

Type	AD/AR	Gene/Locus	Phenotype
HSAN I (HSN I; AD hereditary sensory radicular neuropathy)	AD	SPTLC1/9q22.2	Predominant small-fiber sensory loss; variable motor symptoms—can be severe; lancinating pain; acromutilation; occasional SNHL
CMT2B	AD	RAB7/3q21	HSAN I without lancinating pain
HSAN IB	AD	Unknown/ 3p22-p24	HSAN I + cough and gastroesophageal reflux
HSAN	AD	Unknown	HSAN I
HSAN II (HSN II) [*]	AR	HSN2/ 12p13.3	Infancy, childhood onset; severe sensory loss; acromutilation
HSAN IIB	AR	Unknown	Congenital
HSAN with spastic paraplegia	AR	Unknown/ 5p15.31–14.1	Infancy; ulcero-mutilating sensory neuropathy with spastic paraplegia
HSAN III (familial dysautonomia; Riley-Day syndrome)	AR	IKBKAP/ 9q31	Congenital; severe dysautonomia, less profound sensory loss; alacrima; orthostatic hypotension; absent lingual fungiform papillae; Ashkenazi Jews
HSAN IV (congenital insensitivity to pain and anhidrosis [CIPA]; familial dysautonomia type II)	AR	NTRK1/ 1q21-q22	Congenital; anhidrosis; recurrent hyperpyrexia; insensitivity to pain with self-mutilation; mental retardation
HSAN V (congenital insensitivity to pain)	AR	NTRK1/ 1q21-q22;NGFB/1p13.1	Congenital; HSAN IV with less severe or no anhidrosis and no mental retardation

^{*} Multiple other names: Morvan disease; syringomyelia of infancy; congenital sensory neuropathy; neurogenic acroosteolysis; hereditary autosomal recessive sensory radicular neuropathy; progressive sensory neuropathy of children; painless whitlows. AD: autosomal dominant; AR: autosomal recessive; HSN: hereditary sensory neuropathy; IKBKAP: inhibitor of kappa light polypeptide enhancer in B cells, kinase complex associated protein; NGFB: nerve growth factor beta; NTRK1: neurotrophic tyrosine kinase receptor, type 1; RAB7: RAS-associated protein RAB7; SNHL: sensorineural hearing loss; SPTLC1: serine palmitoyltransferase, long-chain base unit 1.

Canada, where two founder mutations are described.^{187,188} HSAN III occurs almost exclusively in persons of Ashkenazi Jewish descent, with an incidence of 1 per 3600 live births.¹⁸⁹

SYMPTOMS AND SIGNS

HSAN I

HSAN I is autosomal dominant and slowly progressive. Onset is usually in the second to fourth decade but is variable, with a range of 12 to 70 years.^{184,190–192} Severity is also variable, even within the same family. A distal, symmetric, sensory polyneuropathy predominates, involving feet more than hands; all modalities may be involved or early, dissociated, and severe involvement of pain and temperature sensation. Positive sensory symptoms with lancinating, shooting, or burning pain are frequent; persistent paresthesia is not. Painless injuries or burns may lead to slowly healing ulcers, osteomyelitis, amputations, and neuropathic arthropathy. Distal, predominantly peroneal, motor involvement is more variable but can be prominent, even early, and cause diagnostic confusion with CMT. Autonomic features are absent or minimal, usually present only in more severe cases, and involve sweating disturbance. Distal reflexes can be diminished or absent. The CNS is usually not affected. Additional features may occasionally include sensorineural hearing loss (SNHL), dementia, restless legs, pupillary abnormalities, and foot deformity.

CMT2B associated with the RAB7 mutation is essentially indistinguishable from HSAN I except for the absence of lancinating pain. HSAN IB is a rare autosomal dominant adult-onset variant with distal sensory loss without motor involvement and associated with paroxysmal cough (triggered by noxious odors or pressure in the external auditory canal), gastroesophageal reflux, throat clearing, hoarse voice, cough syncope, and SNHL.¹⁹³ Chronic cough and gastroesophageal reflux are also reported with a Thr124Met mutation of the MPZ gene.¹⁹⁴ SPTLC1 mutations appear to account for only a small proportion of HSAN I, and additional genetic causes remain to be identified.¹⁹⁵ These cases are more commonly found in British families because of a common founder effect.¹⁹⁰

HSAN II

HSAN II is autosomal recessive, with onset in infancy or childhood, and may be progressive or nonprogressive. Clinical features include severe, glove-stocking, pan-sensory loss (involving the trunk in some), ulceromutilating complications due to loss of pain sensation, minimal autonomic dysfunction, and depressed or absent reflexes, but no weakness, ataxia, or mental changes.^{184–187,191}

HSAN III

Known as *familial dysautonomia* or *Riley-Day syndrome*, this autosomal recessive, congenital, and progressive disorder occurs almost exclusively among Ashkenazi Jews.^{184,189} There is striking sympathetic and parasympathetic autonomic dysfunction; sensory abnormalities are present but are not as profound as in the other HSAN disorders. Features include feeding difficulties and gastroesophageal reflux in infants, recurrent aspiration pneumonia, defective temperature control, alacrima, dysautonomic crises with episodic nausea and vomiting, hypertension, tachycardia, skin blotching and hyperhidrosis, and orthostatic hypotension. There is hypotonia and delayed motor milestones, and later progressive gait ataxia, but muscle strength is good. Reflexes are depressed or absent. Scoliosis or kyphosis is common. There is insensitivity to pain, but rarely self-mutilation. The lingual fungiform papillae are characteristically absent, with associated dysgeusia, and there is corneal insensitivity.

HSAN IV

Also known as *congenital insensitivity to pain with anhidrosis* (CIPA), HSAN IV is present at birth, autosomal recessive, and characterized by generalized anhidrosis resulting in recurrent hyperpyrexia (occasionally leading to seizures or death) and thickened, calloused skin, insensitivity to pain with self-mutilation, and mental retardation.^{184,189} Other autonomic features are not notable. Muscle strength, reflexes, and lacrimation are normal.

HSAN V

This has a similar phenotype to HSAN IV, but with less severe anhidrosis or normal sweating, no mental retardation, and a different pattern of fiber loss. Neuropathic arthropathy and fractures are common due to markedly impaired deep pain sensation.^{184,186,196}

DIFFERENTIAL DIAGNOSIS

HSAN I/SPTLC1 is essentially indistinguishable clinically from CMT2B associated with the RAB7 mutation, except perhaps for the absence of lancinating pain in the latter. Occasionally, CMT1A may have similar features.¹⁹² Acquired disorders potentially associated with small-fiber neuropathy or ulceromutilating complications may need to be considered in sporadic cases and older patients; these might include diabetes, amyloidosis, some neurotoxins, tabes dorsalis, leprosy, and syringomyelia. However, no known SPTLC1 or RAB7 mutations were discovered in 92 patients screened with idiopathic sensory neuropathy in one study,¹⁹⁵ and only one SPTLC1 mutation was found in 60 individuals with sporadic sensory neuropathy in another.¹⁹⁰ HSAN II-V is usually sufficiently distinguishable clinically. Alacrima and frequent orthostatic hypotension are characteristic of HSAN III, and widespread anhidrosis is a hallmark of HSAN IV.

Insensitivity to pain and painless injuries are striking features of these disorders. While rare, there have been occasional persons in whom, unlike those with HSAN, no anatomic or electrophysiologic abnormalities were detected in sensory pathways; these were labeled as having *congenital indifference* (as opposed to *insensitivity*) to pain. The implication was that pain perception was perhaps impaired due to dysfunction of central cognitive or emotional processing of pain, although abnormalities of mechanoreceptors or pain neurotransmitters remained possibilities.¹⁹⁷ Very recently, such persons in multiple families around the world have been shown to harbor loss-of-function mutations in the SCN9A gene encoding the voltage-gated sodium channel Na_v1.7, which is strongly expressed in nociceptive neurons.^{198,199} Cox et al. proposed the term *channelopathy-associated insensitivity to pain* as a

more appropriate designation for this disorder.¹⁹⁸ This is discussed further at the end of this chapter.

Laboratory Studies

ELECTRODIAGNOSTIC STUDIES

Overall, neurophysiologic testing in HSAN I suggests an axonal sensorimotor polyneuropathy, with occasional studies suggesting some demyelinating features.^{184,190,192} In HSAN II, sensory potentials are absent; any motor involvement is minor. There is little information on nerve conductions in HSAN III; thermal perception is impaired.²⁰⁰ The few reports on HSAN IV suggest normal nerve conduction studies but abnormal small-fiber studies.²⁰¹ Nerve conduction studies are also normal in HSAN V, but thermal thresholds are increased.¹⁹⁶

The sympathetic skin response is preserved in HSAN III and absent in HSAN IV, aiding in their differentiation.²⁰²

All of the HSANs (except some mild cases of HSAN II or HSAN V) show no axon flare after intradermal histamine administration, indicating unmyelinated C-fiber dysfunction. Denervation hypersensitivity to sympathomimetic and parasympathomimetic agents is present in HSAN III.¹⁸⁹

CEREBROSPINAL FLUID

Insufficient information is available.

IMAGING

Insufficient information is available.

GENETICS

Currently identified genes for the HSANs are listed in Table 14–10. They include SPTCL1 and RAB7 (also CMT2B) for HSAN I, HSN2 for HSAN II, IKBKAP for HSAN III, NTRK1 for HSAN IV, and NTRK1 and NGFB for HSAN V. Genetic testing is commercially available currently only for the IKBKAP gene causing HSAN III. The carrier frequency of IKBKAP mutations in the Ashkenazi Jewish population is reported as 1 in 27–32.^{184,189}

Pathology

HSAN I

Sural nerve biopsy studies show severe loss of all fiber types, small more than large, with fibers undergoing atrophy, myelin wrinkling, demyelination and remyelination, and axonal degeneration, with changes possibly more severe at distal sites.¹⁸⁴ A member of the family reported by Hicks underwent an autopsy by Denny-Brown, showing marked loss of ganglion cells in the sacral and lumbar dorsal root ganglia with degeneration of their central and peripheral axons and secondary amyloid deposits.²⁰³ Several other patients have since been described, and the most recent autopsy of a late-onset SPTLC1-associated HSAN I patient showed moderate loss of dorsal root ganglion cells, moderate loss of dorsal column myelinated fibers (particularly gracile fasciculi), loss of posterior root myelinated fibers, very severe loss of myelinated fibers and fibrosis in radial and sural sensory nerves, and less severe involvement of unmyelinated fibers; sympathetic ganglia were normal.²⁰⁴

HSAN II

There is severe loss of myelinated fibers and some loss of unmyelinated fibers in sural biopsy specimens, as well as absence of cutaneous sensory receptors and nerve fibers.^{184,187}

HSAN III

There is severe neuronal loss in sensory and sympathetic ganglia, less so in parasympathetic ganglia. The sural nerve shows severe loss of predominantly unmyelinated and small myelinated fibers.^{184,189} Epidermal nerve fiber density is severely reduced.²⁰⁰

HSAN IV

There is severe loss of unmyelinated fibers in sural biopsy specimens and lack of innervation of epidermis and eccrine sweat glands in skin biopsy specimens.^{184,189,205}

HSAN V

Sural nerve biopsies show a moderate loss of A delta fibers and severe reduction of C fibers.¹⁹⁶

Pathophysiology

Based on the genes involved and their putative protein functions, the pathophysiologic mechanisms implicated in HSAN include sphingolipid metabolism (SPTCL1), vesicular transport (SPTCL1, RAB7, IKBKAP, NTRK1, NGFB), and interactions between neurotrophic factors and their ligands (NTRK1, NGFB), the end result being degeneration of sensory or autonomic neurons.¹⁸⁵ SPTCL1 codes for serine palmitoyltransferase, the rate-limiting enzyme for sphingolipid biosynthesis, with the regulatory molecule ceramide being a sphingolipid metabolite. The function of the HSN II gene is unknown. IKBKAP and its protein product IKAP may be involved in transcription regulation. NGF and its signaling receptor, the tyrosine kinase NTRK1, are involved in the development and function of dorsal root, sympathetic, and trigeminal neurons; mice with a disrupted NTRK/NGF receptor gene develop severe sensory and sympathetic dysfunction.²⁰⁶

Treatment, Course, and Prognosis

This group of disorders can be associated with severe morbidity. No specific therapy is currently available; theoretical genetic or growth factor therapies must await future developments. Drugs that increase the expression of wild-type relative to mutant IKBKAP are being explored for HSAN III. Genetic counseling is conducted regarding inheritance and the nature of the illness. Management is supportive, including prevention of injury, self-mutilation, and infection, frequent inspection for unrecognized injury, avoidance and control of hyperthermia, and pain management. Particularly challenging is the medical treatment of the multiple dysautonomic features of HSAN III, especially blood pressure lability, gastrointestinal and pulmonary dysfunction, and alacrima; with careful attention to these issues, about half of the children with HSAN III now reach adulthood.^{184,185,189} Hyperthermia can be the cause of death in HSAN IV.

DISTAL HEREDITARY MOTOR NEUROPATHIES/ NEURONOPATHIES (dHMN)

The terms *distal hereditary motor neuropathy* (dHMN), *distal spinal muscular atrophy* (dSMA), *distal hereditary motor neuronopathy*, *distal hereditary motor neuropathy/neuronopathy* and the *spinal form of CMT* are all used interchangeably in the literature. Harding suggested that *hereditary motor neuronopathy* is perhaps the most apt term, arguing that the primary pathologic process is likely to occur in the anterior horn cell body, rather than in the distal axon, and that bulbar involvement in some make the term *spinal muscular atrophy* inaccurate.^{207,208} These disorders are characterized by very slowly progressive predominant degeneration of the lower motor neuron, in most cases in a distal symmetric pattern of atrophy and weakness, justifying their inclusion in a chapter on neuropathies rather than, or in addition to, motor neuron disorders/spinal muscular atrophies. That some dHMN subtypes are allelic to CMT2 subtypes further connects these disorders. In northeast England, dHMN accounts for about 10% of persons with a peroneal muscular atrophy phenotype.²⁰⁹

While phenotypically very much like CMT, particularly CMT2, dHMN is distinguished by the absence of clinical sensory involvement. This is confirmed by normal sensory nerve action potentials, quantitative sensory testing, and sural nerve biopsies in most cases, low-amplitude CMAPs, normal conduction velocities except as affected by loss of fast fibers in very severe cases, and chronic denervation on needle EMG.²¹⁰ In addition, as a group, the dHMNs differ from CMT1 and CMT2 by featuring less upper limb weakness (except dHMN V and dHMN VII), less ataxia and tremor, and relative preservation of reflexes.²⁰⁸ Pes cavus is very common, and scoliosis is found in about one-quarter of patients. Creatine kinase may be modestly raised. There is little autopsy data on this group of disorders; one patient with a dHMN VII phenotype and a dynactin mutation showed motor neuron degeneration and axonal loss in the ventral horn of the spinal cord and hypoglossal nucleus, with inclusions of dynactin and dynein.²¹¹ Aside from some severe infantile and autosomal recessive subtypes, the prognosis tends to be good in regard to ambulation.²⁰⁷

Table 14–11 lists the current dHMN subtypes, including their inheritance, known

Table 14–11 **Distal Hereditary Motor Neuropathies/Neuronopathies (dHMN)**^{207,212,213,216}

Subtype	Inher.	Gene	Locus	Onset	Phenotype
dHMN I	AD	Unknown	7q34-q36	Juvenile	Distal atrophy and weakness
dHMN IIA	AD	HSP22/ HSPB8	12q24	Adult	Distal atrophy and weakness; allelic CMT2L
dHMN IIB	AD/ AR	HSP27/ HSPB1	7q11-q21	Juvenile to adult	Distal atrophy and weakness; allelic CMT2F
dHMN III	AR	Unknown	11q13	Juvenile to early adult	Milder, distal atrophy and weakness
dHMN IV	AR	Unknown	11q13	Juvenile	More severe; diaphragmatic weakness
dHMN IV	AR	PLEKHG5	1p36	Juvenile	More severe; diaphragmatic weakness
dHMN V	AD	GARS	7p15	Juvenile	Allelic CMT2D; upper limb predominance; occ. pyramidal
dHMN V	AD	BSCL2	11q12-q14	Juvenile	Upper limb predominance; Silver syndrome (SPG17); dHMN V + spasticity

(continued)

Table 14–11 (Continued)

Subtype	Inher.	Gene	Locus	Onset	Phenotype
dHMN VI (SMARD1)	AR	IGHMBP2	11q 13.2-13.4	Infantile	Severe; diaphragmatic weakness
dHMN VII	AD	Unknown	2q14	Adult	Vocal cord paralysis; hand before leg weakness; similar to CMT2C
dHMN VII	AD	DCTN1	2p13	Adult	Early bilateral vocal cord paralysis; later hand (esp. thenar) > leg and bulbar (facial, dysarthria, dysphagia) weakness
X-linked dHMN (DSMAX)	XLR	Unknown	Xq13.1-q21	Juvenile	Distal atrophy and weakness; foot deformity; slow course; ambulation maintained
dHMN/ALS4	AD	SETX	9q34	Juvenile	Distal atrophy and weakness with pyramidal signs; normal life expectancy
dHMN-J	AR	Unknown	9p21.1-p12	Juvenile	Jordan; distal atrophy and weakness; initial pyramidal signs
Congenital distal SMA	AD	Unknown	12q23-q24	Congenital	Nonprogressive; weakness/atrophy in legs; arthrogryposis

AD: autosomal dominant; ALS4: amyotrophic lateral sclerosis 4; AR: autosomal recessive; BSCL2: Berardinelli-Seip congenital lipodystrophy type 2; DCTN1: dynactin; dHMN: distal hereditary neuropathy or neuronopathy; dHMN-J: distal hereditary neuropathy-Jerash type; DSMAX: X-linked distal spinal muscular atrophy; GARS: glycyl t-RNA synthetase; HSP: heat shock protein; IGHMBP2: immunoglobulin μ binding protein 2; PLEKHG5: pleckstrin homology domain-containing protein, family G member 5; SETX: senataxin; SMA: spinal muscular atrophy; SMARD1: spinal muscular atrophy with respiratory distress 1; XLR: X-linked recessive.

genes, age of onset, and phenotypic features. Subtypes are recognized by additional features such as diaphragmatic weakness (dHMN IV and VI), upper limb predominance (dHMN V), vocal cord paralysis (dHMN VII), pyramidal signs (dHMN/ALS4, dHMN-J, dHMN V), or nonprogressive/arthrogryposis (congenital distal SMA). The genes involved subserve diverse functions and are reviewed by Irobi et al.^{212,213}

HEREDITARY ATAXIA WITH NEUROPATHY

Autosomal Dominant

The autosomal dominant cerebellar ataxias (ADCAs) or spinocerebellar ataxias (SCAs) are a heterogeneous group of disorders characterized by cerebellar ataxia as the predominant feature, but often associated with involvement of other central and peripheral

systems.²¹⁴ Many are associated with trinucleotide (CAG, CTG) or pentanucleotide (ATTCT) repeats. At least several of the 28 SCA subtypes described to date may have associated peripheral neuropathy; these include SCA1, SCA2, SCA3 (Machado-Joseph disease), SCA4, SCA7, SCA25, and SCA27.^{215,216} The neuropathy is axonal, sensory, or sensorimotor, with the highest frequency in SCA2.²¹⁷ It may be symptomatic but is often subclinical, reflected only in depressed or absent reflexes and associated with low-amplitude or absent SNAPs.^{217,218} In an analysis of the distal to proximal gradient of electrophysiologic abnormalities in a large series of patients with SCA, 70% of whom had electrophysiologic neuropathy, 30% were judged to be compatible with a dying-back axonopathy pattern and 40% with neuronopathy (sensory and/or motor).²¹⁹ SCA1 and SCA2 displayed mostly features of neuronopathy, and SCA3 and SCA7 both displayed features of axonopathy and neuronopathy. Neuropathology of these subtypes in other studies has shown neuronal loss in dorsal root ganglia and/or anterior

horns.^{219–221} The primary event is likely dysfunction at the sensory or motor neuronal level.²¹⁹

Autosomal Recessive

Most of the autosomal recessive cerebellar ataxias are associated with sensory neuropathy or neuronopathy, with vibratory and proprioceptive loss and areflexia. Many also have signs of amyotrophy, weakness, and pes cavus. A recent review of this subject helpfully categorizes these disorders into: (1) Friedreich ataxia-like: Friedreich ataxia (FRDA), ataxia with vitamin E deficiency, abetalipoproteinemia, Refsum disease; (2) Friedreich ataxia-like with cerebellar atrophy: late-onset Tay-Sachs disease (hexosaminidase A deficiency), cerebrotendinous xanthomatosis, DNA polymerase disorders, spinocerebellar ataxia with axonal neuropathy; and (3) early-onset ataxia with cerebellar atrophy: ataxia telangiectasia, ataxia telangiectasia-like disorder, ataxia with oculomotor apraxia types 1 and 2, autosomal recessive spastic ataxia of Charlevoix-Saguenay, infantile-onset SCA, Cayman ataxia, and Marinesco-Sjögren syndrome.²²² Aside from Cayman ataxia, all have some features of neuropathy. Many other unclassified ataxias are described in individual families around the world, many with neuropathic features.

FRDA is the most common hereditary ataxia and is caused in most cases by a triplet GAA expansion of the frataxin gene on chromosome 9q13; the size of the repeat is correlated with disease severity. Onset is usually before age 25, with early loss of large dorsal root ganglia neurons and subsequent degeneration of the dorsal columns, peripheral sensory axons, and spinocerebellar and pyramidal tracts.^{214,223–226} There is progressive gait and appendicular ataxia, dysarthria, gaze fixation instability, vibratory and proprioceptive loss, areflexia, pyramidal signs, pes cavus, scoliosis, hearing loss, cardiomyopathy, and diabetes. SNAPs are absent in almost all cases, with normal or only slightly decreased motor conduction velocities.²²⁷ Rare genetically verified cases are described with clinical features of both CMT and FRDA, with demyelinating nerve

conductions.²²⁸ A late-onset (over age 25) presentation of FRDA is associated more often with retained reflexes and lower limb spasticity.²²⁹

X-Linked

Of the X-linked hereditary ataxias, signs of peripheral neuropathy (usually axonal sensorimotor, occasionally demyelinating features on NCS) are present in about 60% of cases of fragile X-associated tremor ataxia syndrome (FXTAS) and may be a presenting feature.^{230,231} Sensory symptoms are generally lacking.²³²

HEREDITARY SPASTIC PARAPLEGIA WITH NEUROPATHY (HSP)

The hereditary spastic paraplegias (HSP) are a heterogeneous group of disorders wherein lower extremity spasticity and weakness are the predominant features.^{214,233,234} Over 30 chromosomal loci and 16 genes are currently classified, including AD, AR, and X-linked recessive forms, designated as SPG (spastic gait) followed by the assigned number in order of discovery.^{216,235} Harding classified HSP into uncomplicated, or pure, and complicated forms.^{214,233,234}

In uncomplicated HSP, there is a wide range of onset and slow progression of lower extremity spastic paraparesis, which may be accompanied by mild sensory disturbance with impaired vibration sensation and urinary symptoms. A pattern of severe spasticity and only mild or no weakness is characteristic.²³⁶ Upper limb involvement, aside from hyperreflexia, is uncommon; cranial nerves and corticobulbar tracts are spared. Nerve conductions are normal in most cases. Postmortem pathology shows axonal degeneration predominantly in the longest spinal tracts, the distal corticospinal tracts, and gracile fasciculi.²³⁷ Life expectancy can be normal.

Complicated HSP shows additional neurologic involvement in many areas, including amyotrophy or peripheral neuropathy in many cases. At least the following subtypes are associated with either a pattern of distal amyotrophy/motor neuronopathy in most cases or sensory or sensorimotor

polyneuropathy: autosomal dominant—SPG3A, SPG4, SPG9, SPG10, SPG17; autosomal recessive—SPG7, SPG11, SPG14, SPG15, SPG20, SPG26, SPG30; X-linked recessive—SPG2.^{216,235} SPG17 has an unusual phenotype with spastic paraparesis and amyotrophy of hand muscles (Silver syndrome), phenotypically overlapping with dHMNV and CMT2D.

HEREDITARY BRACHIAL PLEXUS NEUROPATHY (HBPN)/HEREDITARY NEURALGIC AMYOTROPHY (HNA)

Introduction

Hereditary brachial plexus neuropathy (HBPN) or hereditary neuralgic amyotrophy (HNA) is a rare autosomal dominant, recurrent, painful, multifocal neuropathy involving combinations of nerves arising from the brachial plexus.²³⁸ It is unusual among the inherited neuropathies by virtue of the episodic attacks, focal signs, and environmental triggers.²³⁹ The clinical and electrodiagnostic picture is similar to that of immune brachial plexus neuropathy (neuralgic amyotrophy; Parsonage-Turner syndrome). Recently, mutations in the SEPT9 gene on chromosome 17q25 were found to cause HNA; SEPT9 is involved in cellular structure, cell division, and tumorigenesis.²⁴⁰

Clinical Features

SYMPTOMS AND SIGNS

Onset is usually in the second or third decade but may occur in childhood or later.²⁴¹ There is a slight male predominance.^{238,242} The course can be *classic relapsing-remitting*, with acute to subacute onset of severe pain lasting for a few days to several weeks, concomitant or subsequent evolution of paresis and atrophy, and gradual recovery over months to about 2 years, or *chronic undulating*, with pain more gradual in onset, and pain and weakness improving but not resolving before the next attack. An average of four to five attacks occurred during a 26-year follow-up period.²³⁹ Cases are described with attacks consisting of pain alone lasting only for

hours, so-called *abortive attacks*.^{238,242} Intervals between attacks can be very long, and attack frequency declines with advancing age.²³⁸ There is a predilection for the right brachial plexus. Attacks may occasionally involve both arms asymmetrically, or even cranial nerves (most commonly recurrent laryngeal and facial), the phrenic nerve, lumbosacral plexus, or focal autonomic dysfunction (usually sudomotor). Horner's syndrome was reported in one case, but it should always trigger a search to exclude a structural plexopathy.²⁴² Pain is invariably present in the first attack and almost always in subsequent attacks. It is typically severe and continuous (lasting an average of 4 weeks), with a neuropathic quality and mechanical sensitivity, and is located in or radiates from the shoulder or the cervical spine down into the arm.²⁴² Later in the course, various musculoskeletal-type pains may persist. Motor deficits predominate but sensory abnormalities are common, with a variable distribution but most commonly hypoesthesia and/or paresthesia over the deltoid and lateral upper arm region. Two patients are described in a family with HNA who also had features of Wartenberg migrant sensory neuropathy.²⁴³ Paresis involves any part of the brachial plexus and any muscle but predominates in the distribution of the upper plexus, with the spinati and serratus anterior most commonly affected. A single isolated nerve may be involved, such as the long thoracic with scapular winging.²⁴⁴ Acute scapular winging is always a good clue to this diagnosis, whether the hereditary or the immune/sporadic variety.

As in the sporadic form of neuralgic amyotrophy, several preceding events are implicated in attacks including infection, immunization, pregnancy, puerperium, cold weather, strenuous exercise of the affected limb, trauma, surgery, or stress, although most often no precipitating event is reported.^{239,242} Exercise, trauma, and cold weather are followed by an attack within hours, while infection and childbirth precede an attack by days to weeks.²³⁹ Craniofacial and cutaneous features may include hypotelorism, epicanthal folds, cleft palate, and unusual skin folds or creases (the neck in women; the forearms in infants and toddlers; cutis verticis gyrata, scalp folds, or furrows running in an anterior to posterior direction, described in one man).²⁴⁵

DIFFERENTIAL DIAGNOSIS

There is frequently a delay in making the proper diagnosis.²⁴² It is the temporal course and patchy clinical and electrophysiologic features in the distribution of individual nerves arising from the brachial plexus and roots that suggest this diagnosis. In individual cases, differential diagnosis may include cervical radiculopathy, orthopedic or rheumatologic disorders of the shoulder, malignant compression or infiltration of roots or plexus, and inflammatory/infectious plexopathies. The brachial plexopathy presentation of HNPP, the other multifocal inherited neuropathy, is distinguished by the absence of pain and the presence of a more generalized neuropathy; atrophy is also uncommon in this disorder. The clinical features of HNA are essentially indistinguishable from those of immune brachial plexus neuropathy, except that HNA patients tend to have an earlier onset, more attacks, more frequent involvement of nonbrachial plexus nerves, more severe maximum weakness, and a poorer functional outcome.²⁴² It is mostly the family history that allows the distinction, as well as dysmorphic features when present.

Laboratory Studies

Electromyography shows signs of axonal damage in the distribution of involved portions of the brachial plexus or individual nerves.²³⁸ This is also reflected in diminished sensory or motor amplitudes if appropriately affected distributions are examined and the lesions are severe enough, but there are no signs of a generalized neuropathy. Subclinical denervation may be found in muscles of the involved or opposite limb. Paraspinal denervation does not exclude this diagnosis. An MRI scan of the brachial plexus may occasionally show T2 hyperintensities or focal thickening, or T2 signal changes in individual muscles can indicate neurogenic changes.^{238,242} The CSF is normal or shows a mild protein elevation, typically acellular; rare cases show slight pleocytosis, one case with reported 38 mononuclear cells.^{242,246} It may be helpful to check for a PMP22 deletion to screen for HNPP.²⁴⁷

Pathology/Pathophysiology

In one study of four patients, upper extremity nerve biopsies (superficial radial or proximal median fascicular) during attacks of HNA showed prominent perivascular inflammation with vessel wall disruption (although no fibrinoid necrosis and no tomacula), suggesting that in at least some cases, altered immunity with multifocal inflammation is pathogenic in this genetic disorder.²⁴⁸ Pain was ameliorated in two of these patients with intravenous methylprednisolone. One additional patient has been reported with an anecdotal response to IVIG.²⁴⁶

Other authors have failed to demonstrate histologic inflammation, but have confirmed the multifocal, fascicular nature of nerve injury in this disorder. They have suggested that there is more generalized, subclinical involvement in sural biopsy studies.^{249,250}

Treatment, Course, and Prognosis

Management involves counseling regarding the genetic issues and the known risk factors for attacks, pain treatment, and physical therapy. The most effective symptomatic pain relief is reported with a combination of a non-steroidal anti-inflammatory drug (NSAID) and an opiate.²⁴² Intravenous methylprednisolone ameliorated pain in two reported cases²⁴⁸ and is often tried to abort attacks and lessen pain. Corticosteroids are generally thought to shorten acute attacks of pain, but it is less clear that their use prevents arm weakness and disability. Clinical trials are needed to establish the possible role of immunosuppression with steroids or IVIG, as reported in a few patients.^{246,248} While many authors report an overall favorable prognosis for recovery, which can be full, this is not invariable; a substantial proportion of patients have residual symptoms, signs, and functional impairment.^{239,242} There is no effect on the lifespan.

HEREDITARY PERIPHERAL NERVE CHANNELOPATHIES

In recent years, a newly recognized category of genetic disorders has emerged involving the

Table 14–12 **Hereditary Peripheral Nerve Channelopathies**²⁵¹

Disorder	AD/ AR	Gene	Channel	Phenotype
Sodium Channelopathies				
Erythromelalgia	AD	SCN9A	Nav1.7	Heat-provoked attacks of acral burning pain, redness, swelling
Paroxysmal extreme pain disorder (PEPD)	AD	SCN9A	Nav1.7	Neonatal or infantile-onset dysautonomic events followed by attacks of severe rectal, ocular, or jaw pain
Channelopathy-associated insensitivity to pain (CAIP)	AR	SCN9A	Nav1.7	Isolated loss of pain perception
Potassium Channelopathies				
Peripheral nerve hyperexcitability +/- benign familial neonatal convulsions (BFNC)	AD	KCNQ2	Kv7.2	Myokymia and exercise-induced cramps; some with neonatal seizures
Episodic ataxia with myokymia (EA-1)	AD	KCNA1	Kv1.1	Brief attacks of cerebellar ataxia and continuous interictal myokymia

AD: autosomal dominant; AR: autosomal recessive; KCNA1: voltage-gated potassium channel, Shaker-related subfamily, member 1; KCNQ2: voltage-gated potassium channel, KQT-like subfamily, member 2; Kv: voltage-gated potassium channel; Nav: voltage-gated sodium channel; SCN9A: sodium channel, voltage gated, type IX, alpha subunit.

sodium and potassium channels responsible for the depolarization and repolarization phases of the axonal action potential. Mutations in specific ion channels result in axonal hyperexcitability or inexcitability²⁵¹ (Table 14–12).

Sodium Channelopathies

There are at least 10 different sodium channel isoforms, with varied properties and distributions in the nervous system.²⁵² The Nav1.7 isoform, encoded by the SCN9A gene (sodium channel, voltage gated, type IX, alpha subunit), is highly expressed in nociceptive DRG neurons but not in the CNS, is also present in sympathetic neurons, and is associated with three clinical syndromes to date.

ERYTHROMELALGIA

Gain-of-function mutations of SCN9A cause enhanced activity of Nav1.7 channels and hyperexcitability, and result in autosomal dominant primary or familial

erythromelalgia (also called *erythromalgia*).^{252,253} Secondary or acquired erythromelalgia is associated mostly with myeloproliferative disorders, particularly thrombocythemia, and appears to be a platelet-mediated disorder of arteriolar inflammation and thrombosis, responsive to aspirin.²⁵⁴ Primary erythromelalgia usually has a childhood or adolescence onset and is characterized by episodic attacks of symmetric, acral, burning pain, erythema, warmth, and swelling, precipitated by heat and exercise and relieved by rest, elevation, and cold. In severe cases, patients are quite miserable and debilitated; their painful, erythematous feet are held high in the air or immersed in ice water to the point of maceration. Treatment has been elusive, although there are anecdotal reports of some success with the sodium channel blockers lidocaine and mexiletine, as well as many other drugs or interventions.^{253,255} Treatment targeted at the Nav1.7 sodium channel is clearly the goal of future research, and this disorder may provide a model for the understanding of other pain syndromes.²⁵³

PAROXYSMAL EXTREME PAIN DISORDER (PEPD)

Formerly called *familial rectal pain syndrome*, PEPD is also an autosomal dominant disorder associated with gain-of-function SCN9A/Nav1.7 mutations.²⁵⁶ This rare disorder is characterized by neonatal or infantile onset of autonomic features including skin flushing, harlequin color change, syncope with bradycardia or asystole, and tonic nonepileptic seizures. These are followed by attacks of severe rectal, ocular, or jaw pain, occasionally more diffuse. Attacks last for seconds to minutes, up to 2 hours. Provoking factors may include defecation, wiping the perineum, eating, taking medication, cold wind, emotion, and others. Carbamazepine is at least partially effective in reducing attack frequency and severity. While this disorder is lifelong, attack frequency declines with age.

CHANNELOPATHY-ASSOCIATED INSENSITIVITY TO PAIN (CAIP)

Loss-of-function mutations of SCN9A cause CAIP, formerly called *congenital indifference to pain*.^{198,199} Inheritance is autosomal recessive. These patients do not perceive painful stimuli, but all other sensory modalities remain intact. They are at great risk for painless injuries, fractures, and burns. Patients described in the literature with this condition have had such occupations as human pin-cushion act or street performer placing knives through his arms and walking on burning coals.^{198,257} Nerve conductions and sural biopsies are normal. Knockout mice lacking Nav1.7 have elevated thresholds for pain.

Potassium Channelopathies

Impaired function of voltage-gated potassium channels (VGKCs) results in a decreased potassium outward current, preventing repolarization and manifesting as hyperexcitability.²⁵¹ An autoimmune mechanism of peripheral nerve hyperexcitability (PNH) is present in acquired neuromyotonia (Isaacs syndrome), with demonstrable VGKC antibodies in almost half of the cases; patients have predominant lower motor neuron hyperexcitability, some with additional sensory or

autonomic symptoms.^{258,259} Inherited disorders of VGKCs manifest varied phenotypes, depending on the specific gene and mutations involved in either the CNS and/or the PNS. Mutations of the KCNQ2 (VGKC, KQT-like subfamily, member 2) gene encoding the potassium channel K_v7.2 cause autosomal dominant benign familial neonatal convulsions (BFNC), occasionally with myokymia appearing later in life. A novel KCNQ2 mutation within the voltage sensor region of K_v7.2 can cause idiopathic, sporadic PNH alone without neonatal seizures.²⁶⁰ Patients have typical clinical and electrophysiologic myokymia in the hands and exercise-induced cramps. Retigabine, an anticonvulsant that facilitates K_v7.2 opening, restores balance to membrane excitability and may be a treatment option for PNH.²⁶⁰ Mutations in the gene KCNA1 (VGKC, Shaker-related subfamily, member 1), encoding K_v1.1, are associated with autosomal dominant episodic ataxia with myokymia (EA-1).²⁶¹ These patients have brief attacks of cerebellar ataxia and continuous interictal myokymia.

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Hereditary Metabolic/Multisystem Disorders with Neuropathy

**FAMILIAL AMYLOID
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**FAMILIAL AMYLOID
POLYNEUROPATHIES**

Introduction

The amyloidoses comprise a heterogeneous group of protein-misfolding disorders

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characterized by the extracellular deposition of aggregates of insoluble, nonbranching, 7.5- to 10-nm-wide and indefinite-length fibrils, as seen on electron microscopy. Congo red staining produces a characteristic apple-green birefringence under polarized light, attributed to the β -pleated sheet configuration of the polypeptide chains comprising the fibrils.

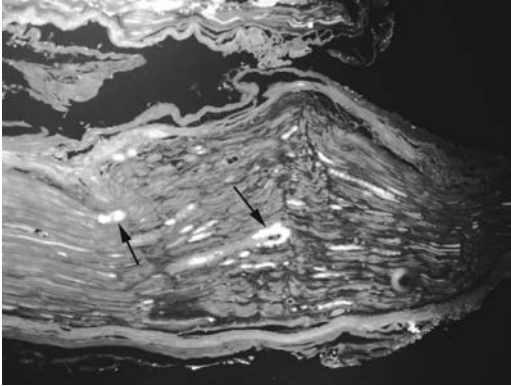


Figure 15-1. Transthyretin amyloidosis. Amyloid fluoresces yellow using thioflavin S stain. The bright yellow amyloid deposits (arrows), usually perivascular, are seen against the green background of the peripheral nerve in longitudinal section. Original magnification $\times 100$. Courtesy of Karen M. Weidenheim, M.D. (See Color Plate 15-1.)

With hematoxylin and eosin (H&E) staining, amyloid appears pink and amorphous. A sensitive method for amyloid detection is fluorescence using thioflavin S stain (Fig. 15-1; see also Color Fig. 15-1). Many unrelated proteins can form amyloid, and three amyloid types are associated with neuropathy. AL, or *primary*, immunoglobulin light chain amyloidosis, with or without multiple myeloma, is the most common cause of amyloid neuropathy; AA, or

secondary, reactive amyloidosis associated with chronic inflammatory conditions, typically does not have neuropathy. A localized form of amyloidotic neuropathy is the carpal tunnel syndrome frequently associated with $A\beta_2M$, β_2 -microglobulin-related amyloidosis in chronic hemodialysis (dialysis arthropathy).¹ Inherited or familial amyloid polyneuropathy (FAP) is associated with *amyloidogenic transthyretin protein* (ATTR), *apolipoprotein AI* (AApoAI), or *gelsolin* (AGel) and is addressed in this subchapter. The prior FAP classification based on ethnic origin and clinical presentation has been supplanted by one based on the involved mutant protein (Table 15-1). Familial amyloid polyneuropathy is the subject of several recent reviews.^{2,3}

Clinical Features

EPIDEMIOLOGY

ATTR-FAP has a wide geographic distribution, but is uncommon aside from three endemic foci for the most common mutation, Val30Met (methionine substituted for valine at position 30), in northern Portugal, northern Sweden, and Japan. It was first reported in Portugal, where the estimated prevalence is 1/1000.^{4,5} AApoAI is described in few kindreds, and most cases of AGel are Finnish.

Table 15-1 Familial Amyloid Polyneuropathies

Mutated Protein	Symbol	AD/AR	Gene Locus	Phenotype
Transthyretin	ATTR	AD	18q11.2-q12.1	Onset in third/fourth decade but wide range; Val30Met mutation most common; progressive, predominant small-fiber and autonomic neuropathy; CTS; cardiac / renal dysfunction; vitreous opacities; scalloped pupils ; oculoleptomeningeal form; ~10-year course
Apolipoprotein AI	AApoAI	AD	11q23	Similar, except often early weakness; Gly26Arg mutation only; predominant nephropathy , limited proteinuria; peptic ulcer
Gelsolin	AGel	AD	9q34	Early lattice corneal dystrophy, progressive cranial polyneuropathy (begins with upper facial paresis), cutis laxa and usually mild distal sensory and autonomic polyneuropathy; mostly found in Finland

AApoAI: amyloidogenic apolipoprotein AI; AD/AR: autosomal dominant/autosomal recessive; AGel: amyloidogenic gelsolin; ATTR: amyloidogenic transthyretin; CTS: carpal tunnel syndrome.

SYMPTOMS AND SIGNS

ATTR-FAP has varied presentations, depending on the mutation and geographic location.⁶ Val30Met is the most common mutation. Symptoms begin in the third or fourth decade but have a wide range of onset, including in the elderly. The age at onset shows anticipation. The course is slowly progressive. Sensory symptoms predominate early, with painful, burning feet and dissociated sensory loss (predominant loss of pain and temperature sensation), but large-fiber function is also progressively impaired. Distal weakness appears later. Autonomic dysfunction is frequent, although not invariable, may occur early and precede sensory abnormalities, and can be severe. Manifestations include orthostatic hypotension, gastrointestinal dysmotility, bladder retention, impotence, and dyshydrosis. Ocular involvement includes visual loss, vitreous opacities, glaucoma, keratoconjunctivitis sicca, and pupillary abnormalities including virtually pathognomonic bilateral scalloped pupils, most apparent on miosis, due to amyloid deposition in the terminal branches of the ciliary nerves of the eye.⁷ Carpal tunnel syndrome (CTS) can be an early and sometimes isolated feature.⁸ Occasional cranial neuropathies include vocal cord paralysis or hypoglossal neuropathy.^{3,5,6} Constitutional signs include anemia, weight loss, and edema. Cardiac dysfunction is a common accompaniment; less frequently, nephropathy develops. A few transthyretin protein (TTR) mutations (including Val30Met) are associated with an oculoleptomeningeal form of FAP, with cerebral amyloid angiopathy and ocular amyloidosis, presenting with central symptoms and signs including stroke and hemorrhage.⁶ In late-onset (over age 50) cases of ATTR-Val30Met, a family history and autonomic dysfunction are less frequent, while organ involvement and severe neuropathic pain are more frequent.⁹

AApoAI-FAP has a phenotype similar to that described for ATTR-Val30Met, except for often early leg weakness, prominent renal dysfunction with limited proteinuria, frequent peptic ulcer disease and hearing loss, less prominent dysautonomia and CTS, and no vitreous opacities.^{3,10}

AGel-FAP has early lattice corneal dystrophy, progressive cranial polyneuropathy (beginning with upper facial paresis), variable involvement of cranial nerves VIII–XII, cutis

laxa, and usually mild distal sensory and autonomic polyneuropathy.¹¹ The facial appearance is characteristic due to the facial paresis and skin laxity.

DIFFERENTIAL DIAGNOSIS

In the presentation of FAP as a predominantly small-fiber sensory neuropathy with or without prominent dysautonomia, differential diagnostic considerations may include a number of hereditary (hereditary sensory autonomic neuropathy [HSAN], Fabry disease, Tangier disease) or acquired (AL amyloidosis, diabetes, human immunodeficiency virus [HIV], some toxins, leprosy, hypertriglyceridemia, idiopathic small-fiber neuropathy) disorders.

ATTR-FAP is often misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), particularly in late-onset, isolated, nonfamilial cases.⁵ Occasional demyelinating features on nerve conduction studies, elevated cerebrospinal fluid (CSF) protein, misleadingly negative biopsies, or incidental monoclonal gammopathies lead to diagnostic confusion. Often overlooked are the dysautonomia and cardiac manifestations, which are not features of CIDP. The most common clinical pattern of presentation in this group of patients is a length-dependent sensorimotor polyneuropathy with postural hypotension, intermittent diarrhea, weight loss, and impotence.⁵ Late-onset cases may have less frequent autonomic dysfunction.⁹ AGel-FAP has a rather unique phenotype.

Laboratory Studies

ELECTRODIAGNOSTIC STUDIES

Nerve conduction studies and needle electromyography (EMG) in most cases are consistent with an axonal sensory or sensorimotor polyneuropathy. In early cases with only small-fiber involvement, nerve conduction studies can be normal, and only thermal quantitative sensory testing (QST), autonomic testing, or skin biopsy may be abnormal. Median entrapment at the wrists is common and may be an isolated finding.³ Mixed axonal-demyelinating electrophysiologic features can be seen and cause diagnostic confusion with CIDP.⁵

CEREBROSPINAL FLUID

The CSF protein may be normal or mildly to moderately elevated.⁵

IMAGING

Some TTR mutations are associated with magnetic resonance imaging (MRI) abnormalities, including leptomeningeal and CSF enhancement (Tyr114Cys; Val30Met) or multifocal white matter lesions (Tyr77).^{12–14}

GENETICS

In ATTR-FAP, the Val30Met mutation is most common and has been detected worldwide, with over 100 other mutations described.^{2,3} The TTR gene is located on chromosome 18q11.2-q12.1. Inheritance is autosomal dominant with varied penetrance, depending on the mutation and location. There is an equal sex ratio. Molecular genetic testing by sequence analysis is highly sensitive, more so than tissue biopsy, and is commercially available (genetests.org). AApoAI is associated with a Gly26Arg mutation in the apolipoprotein AI gene on chromosome 11; two known mutations of the gelsolin gene on chromosome 9 cause AGel.³ AApoAI and AGel DNA testing is not commercially available and would require the aid of an amyloidosis research lab.

Pathology

Diagnosis can be achieved by demonstrating amyloid on tissue biopsy (in the abdominal fat pad, rectum, minor salivary gland, skin, muscle, and sural nerve), with the protein component being established by immunohistochemistry. Molecular genetic testing for TTR, however, is more sensitive, specific, and expeditious.

Autopsies in ATTR-FAP show widespread amyloid deposits throughout the length of peripheral nerves, dorsal and ventral roots, sensory and autonomic ganglia, and choroid plexus, in addition to the heart, kidneys, gastrointestinal tract, thyroid, and other organs.^{15,16} Similar findings occur in AApoAI and AGel, with the latter showing severe involvement of cranial nerves.

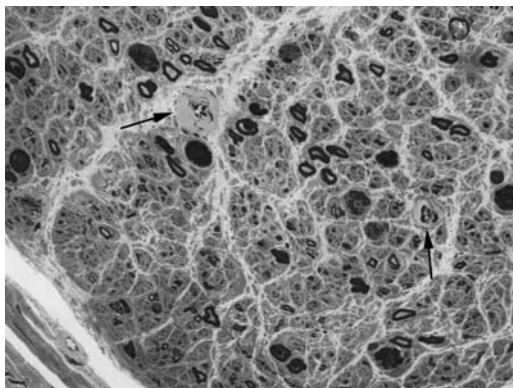


Figure 15–2. Transthyretin amyloidosis. This toluidine blue-stained, 1- μ m-thick plastic-embedded section shows light-staining, amorphous amyloid deposits in the endoneurial blood vessel walls (arrows) of a sural nerve biopsy specimen. There is marked loss of myelinated axons. Original magnification $\times 400$. Courtesy of Karen M. Weidenheim, M.D. (See Color Plate 15–2.)

On sural biopsies, amyloid deposits accumulate in the subperineurial area and around endoneurial blood vessels, some of which are occluded or destroyed (Fig. 15–2; see also Color Fig. 15–2).^{3,5} Large globular deposits of amyloid may displace nerve fibers. In addition to axonal degeneration, teased fiber studies may show distortion of the myelin sheath in contact with amyloid, segmental demyelination, and remyelination. The patchy nature of the amyloid deposits may elude detection on sural biopsies. Early-stage FAP shows predominantly small-fiber loss, with large-fiber loss in more advanced cases^{15–17} (Fig. 15–2).

Pathophysiology

Transthyretin (formerly called *prealbumin*) is a transport protein for thyroid hormone and retinol-binding protein, with a tetrameric structure. Almost all plasma TTR is synthesized in the liver, with additional expression in brain choroid plexus and retinal pigment epithelium. Mutations are thought to destabilize the native TTR structure, resulting in amyloid fibrils. The mechanisms of TTR amyloidogenesis, toxicity, and tissue-specific pattern of TTR deposition remain to be clarified; current understanding has been reviewed recently by Hou et al.¹⁸ The finding

that TTR participates in nerve physiology and enhances nerve regeneration may explain its deposition in mutated form in peripheral nerve.¹⁹ ApoAI is the major apoprotein of high-density lipoprotein (HDL) and is synthesized in the liver and small intestine. Gelsolin, largely derived from muscle, severs actin filaments.

Treatment, Course, and Prognosis

Orthotopic liver transplantation (cadaveric or living donor) is an accepted treatment option for ATTR-FAP since TTR is mostly synthesized in the liver. It may improve or, more commonly, just halt progression of the neurologic features, but not invariably.^{3,20,21} It may also be helpful in AApoAI; it is not useful in AGel since gelsolin is not derived primarily from liver. Patients with the ATTR-Val30Met mutation are most likely to benefit. Results are improved with early transplantation in symptomatic patients with a good nutritional status.²² Cardiac dysfunction may, unfortunately, progress due to continued deposition of wild-type TTR. Given the scarcity of livers for transplantation, sequential or domino procedures have been performed wherein the livers of ATTR patients are donated to those awaiting transplants for chronic liver disorders; the hope has been that the presumably inevitable symptomatic amyloid deposition will not appear for many years. Unfortunately, reports have suggested amyloid deposition in gastroduodenal mucosal biopsies in some cases within 4 years and symptoms within 5–8 years.^{23,24}

Some nonsteroidal anti-inflammatory drugs (NSAIDs; diflunisal) or metal ions (Cr^{3+}) increase tetrameric TTR stability and may offer a future treatment approach by preventing amyloid deposition.^{6,25} Genetic approaches to suppressing hepatic TTR expression, including antisense oligonucleotides or ribozymes, are being explored.³ Neuropathic pain, as well as cardiac, renal, ocular, and autonomic problems, require assessment and management. Vitrectomy can be effective for ocular amyloid. Lattice corneal dystrophy in AGel can be treated with corneal transplantation. Restrictive cardiomyopathy is a major cause of morbidity and mortality in ATTR-FAP; in AApoAI-FAP, it is renal failure. Average life

expectancy for patients with ATTR-FAP is about 10 years, a bit longer for those with AApoAI; AGel has a more benign course.

DISORDERS OF LIPID METABOLISM

Lysosomal Disorders

FABRY DISEASE

Introduction

Fabry disease (FD) is an X-linked recessive multisystem disorder caused by mutations in the GLA gene on chromosome Xq22 encoding the lysosomal enzyme α -galactosidase A. Accumulation of glycosphingolipids, predominantly globotriaosylceramide (Gb3), results in multiple organ involvement, most prominently in the nervous system, skin, eyes, kidneys, and heart. Classic FD is a childhood- or adolescence-onset disorder with painful acroparesthesias, angiokeratomas, hypohidrosis, corneal and lenticular opacities, and proteinuria, progressing to end-stage renal, cardiac, and cerebrovascular disease in middle age. Described independently in 1898 by Fabry and Anderson, alternative terms have included *angiokeratoma corporis diffusum*, *Anderson-Fabry disease*, *hereditary dystopic lipidosis*, *α -galactosidase A deficiency*, *GLA deficiency*, and *ceramide trihexosidase deficiency*.²⁶

Clinical Features

Epidemiology The classic FD phenotype has an estimated incidence of approximately 1:50,000 males, although a recent large newborn screening study uncovered mutations predicting later-onset FD with an incidence of 1:4600, suggesting that this disease is underdiagnosed.^{27,28} Various screening studies in cohorts with cryptogenic stroke, nephropathy/hemodialysis, or hypertrophic cardiomyopathy have detected previously undiagnosed FD in under 1% up to 5% of cases.²⁸

Symptoms and Signs Symptoms begin in hemizygous males in late childhood or adolescence. In the Fabry Registry, one of two large FD databases, the median ages at symptom onset are 9 for males and 13 for females, with

Table 15–2 Disorders of Lipid Metabolism

Disease	Inheritance/ Gene/Locus	Enzyme or Protein Deficiency/Accumulated or Deficient Substrates	Neuropathy Patterns
Lysosomal disorders			
Fabry disease (FD)	XLR/GLA/ Xq22	α -Galactosidase A/ ↑ glycosphingolipids	Small-fiber sensory and autonomic
Metachromatic leukodystrophy (MLD)	AR/ARSA/ 22q13	Arylsulfatase A/ ↑ sulfatides	Sensorimotor polyneuropathy, demyelinating—uniform or nonuniform
Krabbe disease (KD)	AR/GALC/ 14q31	Galactosylceramidase/ ↑ galactosylceramide, ↑ psychosine	Sensorimotor polyneuropathy, demyelinating—uniform
Peroxisomal disorders			
Refsum disease (RD)	AR/PHYH/ 10p	Phytanoyl-CoA hydroxylase/ ↑ phytanic acid	Sensorimotor polyneuropathy, demyelinating > axonal— nonuniform
Adrenomyelo- neuropathy (AMN)	XLR/ ABCD1/Xq28	Adrenoleukodystrophy protein/ ↑ very long chain fatty acids	Sensorimotor polyneuropathy, axonal or mixed
Lipoprotein deficiencies			
Tangier disease (TD)	AR/ABCA1/ 9q31	Cholesterol efflux regulatory protein/ ↓ HDL-cholesterol	Mononeuropathy multiplex; syringomyelia-like; sensorimotor polyneuropathy; mixed axonal/demyelinating features
Abetalipo- proteinemia	AR/MTP/ 4q22-24	Microsomal triglyceride transfer protein/ ↓ apo B-containing lipoproteins	Sensory or sensorimotor polyneuropathy, axonal
Familial hypobeta- lipoproteinemia	Codominant/ apo B/ 2p23-24	Apo B/ ↓ apo B-containing lipoproteins	Sensory or sensorimotor polyneuropathy, axonal
Miscellaneous disorders			
Cerebrotendinous xanthomatosis	AR/ CYP27A1/ 2q33-qter	Sterol 27-hydroxylase/ ↑ cholestanol	Sensorimotor polyneuropathy, axonal or mixed > demyelinating

ABCA1: ATP-binding cassette, subfamily A, member 1; ABCD: ATP-binding cassette, subfamily D (ALD); AR: autosomal recessive; ARSA1: arylsulfatase A1; ATTR: amyloidogenic transthyretin; CYP27 A1: cytochrome p450, subfamily XXVIA, polypeptide 1; GALC: galactosylceramide β -galactosidase; GLA: galactosidase, alpha; MTP: microsomal triglyceride transfer protein; PHYH: phytanoyl-CoA hydroxylase; XLR: X-linked recessive.

a delay to diagnosis of 14 and 19 years, respectively.²⁹ In the Fabry Outcome Survey (FOS) database, the delay is 13.7 and 16.3 years, respectively.³⁰ Although females heterozygous for FD may have a later onset, more variable

features, and a slower rate of progression, they are usually and often severely affected and should not be considered asymptomatic “carriers.” The initial and most characteristic symptom is acral paresthesias (acroparesthesias)

punctuated by episodic severe burning or shooting pain (Fabry crises) in the toes or fingers lasting for minutes to days.^{30,31} The pain may be more generalized;³² on the torso, it may mimic appendicitis or nephrolithiasis. Crises may be precipitated by exercise, stress, fatigue, febrile illness, and temperature or humidity change. They can be associated with low-grade fever and an elevated erythrocyte sedimentation rate (ESR). Hypohidrosis is the only notable clinical autonomic feature. The neurologic exam in FD is often unremarkable, but may show distal impairment of pain, temperature, or light touch in older patients.³³

Skin manifestations include angiokeratoma, hypohidrosis, telangiectasia, and lymphedema.³⁴ Angiokeratomas are macular or papular, dark red to blue lesions occurring mostly in a bathing trunk distribution; they represent ectatic vessels and hyperkeratosis due to lipid accumulation in vessel walls. These lesions are also described in other storage diseases. Gastrointestinal symptoms occur in about one-half of patients, with abdominal pain and diarrhea being most frequent.³⁵ Cornea verticillata is the most frequent ophthalmic abnormality and is often present at the time of diagnosis; conjunctival and retinal vessel tortuosity and Fabry cataract are additional features.³⁶ Renal, cardiovascular, and cerebrovascular diseases become significant in the third to fifth decade of life. Cerebral vasculopathy results in large- and small-vessel ischemic strokes.³⁷ Renal involvement results in proteinuria and azotemia and progresses to end-stage renal disease in middle age. Cardiovascular features include arrhythmias, cardiac hypertrophy, valvular insufficiency, and myocardial infarction.

An adult variant is described presenting with a painful, activity-induced cramp-fasciculation syndrome, without identifiable small-fiber neuropathy.³⁸ Late-onset cardiac and renal variants have residual α -galactosidase A activity and lack the classic (including neurologic) FD features.

Differential Diagnosis In its classic, fully expressed form, FD is reasonably characteristic. The protean manifestations, however, can lead to misdiagnosis. In the FOS database, 25% of cases were previously misdiagnosed; diagnoses included rheumatologic disease, rheumatic fever, arthritis, fibromyalgia, dermatomyositis, erythromelalgia, Osler's disease (hereditary

hemorrhagic telangiectasis), neuropsychologic disease, and a variety of others, including "growing pains."³⁰ Most often, FD arises as a diagnostic possibility in the relatively young patient with a painful small-fiber neuropathy. The seemingly bizarre and intermittent nature of the symptoms, along with the unremarkable neurologic exam, poses a diagnostic challenge. Even more challenging perhaps is the high index of suspicion necessary to pick up the late-onset variants hiding within the large populations of patients with stroke, cardiac disease, and renal disease. Some cases have been misdiagnosed as multiple sclerosis.³⁹ Angiokeratoma, while characteristic, is not entirely sensitive or specific.

Laboratory Studies

Blood Tests/Genetics In males, demonstrating deficient plasma or leukocyte α -galactosidase A activity (<1% in the classic form) is diagnostic. Molecular genetic testing of the GLA gene, located at chromosomeXq22, can then identify a specific mutation by sequence analysis. Several hundred mutations have been described to date. Males with the cardiac or renal variant of FD have residual enzyme activity greater than 1%. Heterozygous females may have markedly decreased enzyme activity, but many are in the normal range because of X-chromosome inactivation, making detection problematic; in these cases, mutation analysis is necessary. Prenatal testing is feasible on fetal cells from chorionic villus sampling or amniocentesis.

Electrodiagnostic Studies Nerve conduction studies are unremarkable in most reported series, aside from median nerve entrapment in about one-quarter of cases.⁴⁰ Some studies describe axonal changes.⁴¹ Quantitative sensory testing shows predominant involvement of small-fiber function, with loss of thermal sensation, cold more so than warm.^{33,40,42} The sympathetic skin response is usually preserved; the respiratory rate interval variation (RRIV) may be abnormal.^{33,40} Other quantitative autonomic tests may show abnormalities.⁴³ Hearing loss is common, and impairment on audiograms is more pronounced at higher frequencies.³³

Imaging Brain MRI findings are present in about one-half of patients in the FOS database,

including ischemic infarcts (posterior circulation more commonly), less frequent hemorrhagic events, commonly nonspecific white matter lesions (lesion load correlating with age), subcortical gray matter ischemic lesions, and dolichoectasia.^{33,44} Up to one-quarter of patients have symmetric T1 hyperintensity in the pulvinar, perhaps related to calcium deposition (*pulvinar sign*, not to be confused with the T2 hyperintensity of the pulvinar in variant CJD). Diffusion tensor imaging is sensitive in detecting and quantifying brain tissue changes in FD.⁴⁵

Pathology/Pathophysiology

In sural biopsies, small myelinated and unmyelinated fibers are selectively decreased, and dense, osmiophilic, lamellated bodies representing deposits of glycosphingolipids, predominantly Gb3, are present in endothelial cells, pericytes, smooth muscle cells, fibroblasts, and perineurial cells.^{31,46} Studies of dorsal root ganglia show selective loss of small neurons.³¹ Glycosphingolipid accumulation is present in neurons of dorsal root and autonomic ganglia, and especially in areas of the central nervous system (CNS) with a permeable blood-brain barrier.^{31,47–49} Neural compromise may be related to the associated vasculopathy or cellular deposits. Skin biopsy can be used to quantitate epidermal innervation, as well as to demonstrate lipid deposits.⁵⁰

Treatment, Course, and Prognosis

The mean age at death is about 45 years for men and 55 years for women.³⁰ Complications of renal, cardiac, and cerebrovascular disease result in morbidity and mortality; the primary cause of death is renal failure in men and cardiac disease in women.

Symptomatic therapy is directed at management of individual organ involvement, including treatment of neuropathic pain with the usual array of drugs, with patients reportedly responding to diphenylhydantoin, carbamazepine, and, more recently, gabapentin.⁵¹ Two preparations of α -galactosidase A (agalsidase alpha and beta) have been available for enzyme replacement therapy (ERT) since 2001. Agalsidase beta is approved for use in the United States. A comprehensive review of clinical trials of ERT in FD shows positive

effects on the nervous system, kidneys, and heart and on the quality of life, but further studies are needed to confirm its long-term benefits, effects on women, and results with early initiation of therapy.⁵² More specifically, studies have suggested some improvement in pain and measures of small-fiber function,^{32,53} although one study failed to show epidermal nerve fiber regeneration.⁵⁴ Ongoing research in this area includes enzyme enhancement (chaperone) therapy, designed to enhance residual enzyme activity by protecting mutant enzyme from misfolding and degradation, and gene replacement therapy.⁵⁵

LEUKODYSTROPHIES

Metachromatic Leukodystrophy (Sulfatide Lipidosis)

Introduction Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disease caused by deficiency of the enzyme arylsulfatase A (ARSA). The disorder is characterized by clinical, electrodiagnostic, and imaging features of diffuse central and peripheral demyelination.

Clinical Features Metachromatic leukodystrophy is rare except in some consanguineous populations. Three MLD types are recognized: late infantile (most common, onset at ages 1–3), juvenile (early and late, onset at ages 4–13), and adult (onset after age 13).⁵⁶ In the late infantile form, following an initial period of apparently normal development, motor abnormalities predominate early, with hypotonic weakness and hyporeflexia, evolving to cognitive deterioration, quadriparesis, spasticity, appendicular pain, visual and hearing loss, and seizures. Juvenile-onset cases have features of both the late infantile and adult forms. Adult-onset MLD may begin with cognitive and behavioral changes or gait disturbance, the phenotype correlating with the genotype; schizophrenia or depression may be initial diagnoses.^{57,58}

While central features tend to predominate in all forms, peripheral neuropathy is a cardinal finding, and occasionally the presenting and even an isolated feature.^{56,59–64} Rare adult-onset mutations appear to have no significant peripheral nerve involvement.⁶⁵ Pes cavus is described in one adult-onset case of MLD.⁶⁶

Two rare variants of MLD also have peripheral nervous system (PNS) involvement. Multiple sulfatase deficiency has features similar to those of late infantile MLD, with additional ichthyosis, hepatosplenomegaly, skeletal deformities, and coarse facial features. Sulfatide activator protein-B (saposin B) deficiency has few reported cases. Other differential diagnostic considerations with MLD might include Krabbe disease, adrenoleukodystrophy, Pelizaeus-Mertzbacher disease, Canavan disease, Alexander disease, and GM1 and GM2 gangliosidosis, among others. In some cases, CIDP or hereditary motor and sensory neuropathy (HMSN, Dejerine-Sottas disease/congenital hypomyelinating neuropathy [DSD/CHN]) will be differential diagnostic possibilities.

Laboratory Studies Electrodiagnostic studies demonstrate a demyelinating sensorimotor polyneuropathy. Conductions are slowed in a uniform manner in some studies;^{56,67} multifocal demyelinating abnormalities are described in others, mimicking acquired conditions.^{59,68} Conduction velocities are severely reduced, often in the 10–30 m/s range. Severe demyelination may result in a high stimulation threshold. Sensory nerve action potential (SNAP) and compound muscle action potential (CMAP) amplitudes are frequently diminished or absent. Brain MRI shows symmetric and extensive T2 hyperintensity in periventricular and subcortical white matter, with predominant posterior involvement in late infantile cases, initial sparing of subcortical U fibers, and a “tigroid” or “leopard skin” pattern in the centrum semiovale.⁶⁹ The CSF protein is frequently elevated, but it can be normal.⁵⁹

The diagnosis is established by assay of ARSA in leukocytes and confirmed by mutational analysis of the ARSA gene, urinary sulfatide excretion, or metachromasia in a nerve biopsy. Pseudodeficiency of ARSA from common polymorphisms that do not result in sulfatide accumulation must be distinguished.⁵⁷

Pathology/Pathophysiology Metachromatic leukodystrophy is an autosomal recessive disorder caused by deficiency of the lysosomal enzyme arylsulfatase A resulting from mutations of the ARSA gene on chromosome 22q13. Sulfatides, mainly 3-O-sulfogalactosylceramide, accumulate in the nervous system as

intracellular, granular, metachromatic-staining deposits in the CNS (oligodendrocytes, microglia) and PNS (Schwann cells, macrophages, Remak cells, and in the vicinity of endoneurial capillaries).⁷⁰ Widespread central and peripheral demyelination ensues, although the mechanism remains unestablished. Sural biopsies show loss of large- and small-diameter axons, demyelination, and occasionally small onion bulbs; electron microscopy of the metachromatic granules reveals three types of inclusions: zebra bodies, tuffstone bodies, and prismatic inclusions.^{59,70}

Treatment, Course, and Prognosis This disorder progresses to complete disability and death within a few years in the late infantile-onset form, with a more protracted course in older patients. Management is symptomatic and supportive; some success has been reported with hematopoietic cell transplantation if performed in the early stage of later-onset disease.⁷¹ The search for enzyme, cell, and gene-based therapies for MLD is reviewed by Sevin et al.⁷²

Krabbe Disease (Globoid Cell Leukodystrophy)

Introduction Krabbe disease (KD), first described in 1916, is an autosomal recessive lysosomal storage disorder caused by deficiency of the enzyme galactosylceramidase (galactosylceramide β -galactosidase; GALC).^{73,74} The GALC gene is mapped to chromosome 14q31.

Clinical Features The estimated incidence is about 1:100,000.⁷⁵ Infantile, juvenile, and adult forms occur. The more common infantile KD (85%–90%) begins after a few months of apparently normal development and evolves with a rapidly progressive course, over weeks to months, in three stages.⁷⁶ Stage I, usually beginning at 3–6 months of age, is characterized by hyperirritability, stiffness, unexplained fever or vomiting, psychomotor deterioration, and seizures. In stage II there is rapid decline in mental and motor function, with hypertonicity, hyperreflexia, and optic atrophy. In stage III there is decerebrate posturing, blindness, and deafness. Peripheral neuropathy may manifest as depressed reflexes at about 6 months of illness.⁷⁷ It may be the single initial feature in infantile KD for a period of months.⁷⁸

Late-infantile, juvenile, and adult-onset (even elderly) forms of KD are much less common and have a more variable phenotype and course; features include cognitive deterioration, weakness, pyramidal signs, sensorimotor polyneuropathy, and visual loss.⁷⁹ Peripheral neuropathy is occasionally the presenting feature, but often is not apparent and nerve conductions can be normal. *Pes cavus* is described in some late-onset cases.⁷⁹ One patient with adult-onset KD is described with a spinocerebellar syndrome and demyelinating sensorimotor neuropathy.⁸⁰

Differential diagnostic considerations are similar to those discussed for MLD in the previous section.

Laboratory Studies Nerve conduction studies show a demyelinating sensorimotor polyneuropathy.^{79,81} In the largest cohort of KD studied to date, nerve conduction studies were found to be a highly sensitive modality for infantile KD. The studies were abnormal very early in the disease (1-day- and 3-week-old neonates), severity of demyelination correlated with clinical severity, and demyelinating features were uniform.⁸¹ Nerve conduction velocities varied, but many were in the 10–20 m/sec range. The electroencephalogram (EEG), brainstem auditory evoked response (BAER), and visual evoked potentials (VEP) are abnormal less often.⁸² The CSF protein is highly elevated in infantile KD, less so or not at all in later forms.⁷⁴ The MRI scan shows white matter T2 hyperintensity.⁸³ There may be cranial nerve and spinal root enhancement.^{84,85} The earliest MRI finding in adult-onset KD appears to be involvement of the upper corticospinal tracts.⁸⁶

GALC enzyme activity can be measured in leukocytes, cultured skin fibroblasts, amniocytes, or chorionic villus cells. Symptomatic individuals show 0%–5% of normal activity; carriers have a wide range of enzymatic activity and require molecular genetic testing for diagnosis.

Pathology/Pathophysiology GALC is a lysosomal enzyme that catalyzes galactosylceramide, localized in the myelin sheath, to ceramide and galactose. It also catalyzes psychosine (galactosylsphingosine) to sphingosine and galactose. Galactosylceramide, however,

does not accumulate in large quantities in the brain; psychosine does, and is thought to be the cytotoxic metabolite leading to death of oligodendrocytes.⁷⁴ Free galactosylceramide induces infiltration of multinucleated macrophages with periodic acid–Schiff (PAS)-positive tubular or filamentous inclusions called *globoid cells*, the pathologic hallmark of KD in the CNS. Additional pathologic features include loss of oligodendrocytes and myelin and fibrillary astrocytic gliosis. Peripheral nerves show segmental demyelination, myelinated fiber loss, endoneurial fibrosis, and tubular inclusions in Schwann cells and endoneurial macrophages but no globoid cells. Genetic defects in saposin A, a GALC activator protein, may be an additional cause of globoid cell leukodystrophy.⁷⁴

Treatment, Course, and Prognosis Infantile KD eventuates in death within about 2 years. Later-onset cases can have a more protracted course.⁸⁷

If performed early in later-onset cases or in infantile KD prior to the onset of neurologic symptoms, hematopoietic stem cell transplantation may slow disease progression and may reduce nerve conduction abnormalities, at least temporarily.⁸¹

Peroxisomal Disorders

Peroxisomes are cellular organelles containing enzymes involved in fatty acid anabolic and catabolic processes. Two single-enzyme deficiencies with prominent neuropathic involvement will be discussed here: Refsum disease and adrenoleukodystrophy. The peroxisomal biogenesis disorders, Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, and rhizomelic chondrodysplasia punctata, are complex disorders with early onset, rapid progression, and early death, with less common or less obvious peripheral nerve involvement.⁸⁸

REFSUM DISEASE

Introduction

Refsum disease (RD), also referred to as *classic* or *adult Refsum disease* and *heredopathia atactica polyneuritiformis*, is a rare autosomal

recessive disorder resulting from mutations in peroxisomal enzymes involved in the degradation of phytanic acid (PA).^{89–91} Cardinal features are retinitis pigmentosa, demyelinating sensorimotor polyneuropathy, ataxia, and elevated CSF protein.

Clinical Features

Symptoms typically begin in late childhood to under age 20, but onset can be as early as the first year or as late as the sixth decade.⁸⁹ The presentation may be acute, triggered by weight loss, stress, trauma, or infection, or may be chronic and progressive. Retinitis pigmentosa (atypical, patchy “salt and pepper” appearance) is a universal and early feature, beginning with night blindness and progressing to visual loss and constricted visual fields. Patients may also have cataracts, optic atrophy, vitreous opacities, and miotic, poorly reactive pupils. Electroretinography may be abnormal early in the course. Anosmia appears to be invariable and can be established by formal smell testing.⁹² Hearing loss is common and early. The polyneuropathy is distal, symmetric, and sensorimotor, with distal weakness and atrophy, stocking pan-sensory loss, hypo- or areflexia, and occasionally palpable hypertrophied nerves and pes cavus. A mild, clinically purely sensory neuropathy is described in a 40-year-old patient.⁹³ A chronic, slowly progressive course is usual, but a relapsing-remitting course may occur. Additional features include ataxia, ichthyosis in a minority, cardiomyopathy/cardiac arrhythmias, and skeletal abnormalities (multiple epiphyseal dysplasia, shortened metatarsals or metacarpals).⁹⁴ The neuropathy, as well as rash and cardiac arrhythmias, are linked to the plasma PA level.⁹⁵

Refsum disease must be considered in all patients presenting with retinitis pigmentosa, as it may account for 4%–5% of cases.⁹⁶ It is a rare cause of chronic demyelinating polyneuropathy in children, adolescents, and young adults. It may be confused with Charcot-Marie-Tooth disease (CMT), CIDP, or Friedreich ataxia. The rare case appearing in an older adult is a greater diagnostic challenge. It is important to check for pigmentary retinopathy; anosmia and hearing loss may also be helpful clinical clues. The PA level can be elevated in the peroxisomal biogenesis disorders but not in isolation.

Laboratory Studies

Electrodiagnostic studies show a nonuniform, demyelinating, sensorimotor polyneuropathy. The degree of conduction slowing is variable, but the rate may be as slow as 7 m/s.⁹⁷ Needle EMG shows distal chronic denervation. Axonal neuropathy is also described.⁹⁸ The CSF protein is elevated (100–700 mg/dL or higher), without pleocytosis.⁹⁷

Plasma PA levels are highly elevated (>200 $\mu\text{mol/L}$). Enzyme activity can be assessed by measuring α -oxidation of PA in cultured fibroblasts. Molecular genetic testing can establish the mutation by gene sequencing.

Pathology/Pathophysiology

Pathologic findings include nerve hypertrophy (particularly in proximal nerve segments), myelinated fiber loss, segmental demyelination, onion bulbs, and nonspecific Schwann cell osmiophilic and crystalline inclusions.^{70,99}

The cause of RD is defective α -oxidation of PA, due in about 90% of cases to mutations in PHYH (phytanoyl-CoA hydroxylase; also called PAHX) on chromosome 10p. In about 10% of cases, mutations in the PEX7 (peroxisome biogenesis factor 7) gene on chromosome 6q encoding the PTS2 receptor (peroxisome-targeting signal type 2) cause a similar phenotype. The designations *RD types 1 and 2* have been suggested.^{100,101} Symptoms of RD are presumably caused, at least partially, by accumulation of PA in tissues. This conclusion is supported by clinical improvement when PA blood levels are lowered, although the mechanism is not established.⁹¹

Treatment, Course, and Prognosis

Untreated, patients will do poorly, about one-half dying by age 30. Death may result from cardiac arrhythmia/cardiomyopathy. Fasting or low caloric intake is to be avoided since it mobilizes stored PA from adipose tissue into the plasma.⁹⁵ Exacerbations can also be related to intercurrent illness, stress, or pregnancy. Since PA is entirely exogenous in origin, treatment in all cases is dietary restriction (mostly meats of ruminants and dairy products). Plasmapheresis and lipapheresis will rapidly reduce plasma PA levels, and are employed as

an early adjunct and in severe or rapidly worsening cases.¹⁰² Plasma PA levels can be substantially reduced, and improvement or arrest can be expected in the ichthyosis, polyneuropathy, cardiac manifestations and ataxia; the effect on the retinitis pigmentosa, anosmia, and deafness is less certain.⁹¹ Early-treated, well-controlled RD may prevent clinical evolution for decades.^{103,104} Possible enzyme replacement and gene therapies await further developments.

ADRENOMYELONEUROPATHY

Introduction

Adrenoleukodystrophy (ALD) is an X-linked recessive peroxisomal disorder of the CNS, peripheral nervous system (PNS), adrenal cortex, and testes, with accumulation of very long chain fatty acids (VLCFAs). Several phenotypes have been described and recently reviewed by Moser et al., including childhood (ages 3–10) and adolescent (ages 11–21) cerebral ALD, adrenomyeloneuropathy (AMN), adult cerebral, olivoponto-cerebellar, Addison-only and asymptomatic forms.^{105–108} These variants can occur within the same kindred. The most common subtype is AMN; it involves predominantly the spinal cord and to a lesser extent peripheral nerves, and is reviewed here.

Clinical Features

Epidemiology. There is no ethnic or geographic predilection. The incidence of ALD in the United States is estimated at 1:17,000.¹⁰⁵

Symptoms and Signs. Typically, AMN presents in men in the third or fourth decade (mean age of onset, 28 years) as a slowly progressive (over decades), spastic paraparesis with urinary sphincter and sexual dysfunction.^{107,109} Occasional patients will show rapid progression.¹¹⁰ Cerebral involvement, clinically or by MRI, is evident in almost half of cases and in 10%–20% may be severe. Adrenal dysfunction is demonstrable in about 70%, and there may be skin hyperpigmentation, gynecomastia, testicular atrophy, and typical scanty scalp hair.¹⁰⁸ Clinical examination reveals mostly myelopathic features restricted to the

legs, with spasticity, weakness, gait impairment, distal sensory loss of all modalities (especially vibration), hyperreflexia, and extensor plantar responses. Peripheral neuropathy may be reflected in distal lower motor neuron weakness and relatively depressed ankle jerks, or is otherwise difficult to sort out from the effects of myelopathy.

About 50% of heterozygous women develop an AMN-like syndrome that is later in onset, somewhat milder and slower in progression than in men, and rarely with cerebral or adrenal involvement.¹⁰⁵

Differential Diagnosis Disorders mimicking the myeloneuropathy of AMN may include chronic progressive multiple sclerosis, hereditary spastic paraparesis, cervical spondylotic myelopathy, vitamin B₁₂ or copper deficiency, human T-cell lymphotropic virus-1 (HTLV-1) myelopathy, and spinal vascular malformations and tumors.

Laboratory Studies

Mutations in the ABCD1 (ATP-binding cassette, subfamily D [ALD], member 1) gene on chromosome Xq28, which encodes the adrenoleukodystrophy protein (ALDP), result in defective peroxisomal β -oxidation and the accumulation of VLCFAs. Diagnosis is established by demonstrating elevated plasma levels of VLCFAs (C26:0, and abnormally high ratios of C24:0 and C26:0 to C22:0), which are increased in all males with ALD and in about 80% of carrier females. Mutation analysis can identify false-negative carriers and provide prenatal diagnosis.

The two largest series of nerve conduction studies in AMN concluded that the neuropathy is due to primary axonal degeneration¹¹¹ or a mixture of axonopathy and multifocal demyelination.¹¹² Occasionally, electrophysiologic studies show no evidence of polyneuropathy.¹¹⁰ The BAER and somatosensory evoked potential (SSEP) studies are frequently abnormal, VEP less so.^{110,113}

The CSF protein is usually normal.¹⁰⁹

Thoracic spinal MRI commonly displays diffuse spinal cord atrophy.^{110,114,115} About half or more of brain MRI scans show varying degrees of demyelination; diffusion tensor or magnetization transfer imaging may be more

sensitive in detecting abnormalities.¹⁰⁵ Cerebral ALD in 80% of cases starts with a characteristic symmetric parieto-occipital white matter T2 hyperintensity; contrast enhancement on T1 images is associated with progression.¹¹⁴

Pathology/Pathophysiology

Unlike the cerebral form of ALD, where an inflammatory response is observed in the white matter, AMN is a noninflammatory distal axonopathy of the spinal cord long tracts and peripheral nerves with secondary demyelination.^{116–118} Sural biopsies in AMN show loss of myelinated axons, with or without involvement of unmyelinated axons, some onion bulbs, and Schwann cell lamellar inclusions.¹⁰⁹ A mouse model of ALD develops the AMN phenotype.¹¹⁹ The pathogenesis of ALD as it relates to accumulation of VLCFAs, possible immune perturbation in the cerebral form, or other mechanisms is not yet understood.

Treatment, Course, and Prognosis

Adrenal insufficiency is treated with corticosteroid replacement therapy. This does not substantially affect the neurologic status, but one study of AMN reports some improvement.¹²⁰ Hypogonadism may be treated. Symptomatic treatment of the typically neurogenic overactive bladder can be helpful.¹²¹ Dietary restriction of VLCFAs alone is not effective. Lorenzo's oil, a 4:1 mixture of glyceryl trioleate and glyceryl trierucate, in combination with dietary restriction lowers plasma VLCFA levels and may have some preventive effect on the development of MRI abnormalities in asymptomatic boys with ALD and normal MRI scans.¹²² Some encouraging open study results with Lorenzo's oil in AMN require further confirmation.¹⁰⁵ Hematopoietic stem cell transplantation appears to have a favorable effect in the early stage of childhood ALD; its utility in AMN is unknown. There are no data to support immunosuppression. Adrenomyeloneuropathy without cerebral involvement has a more favorable prognosis for longevity, and the lifespan can be almost normal.

Lipoprotein Deficiencies

TANGIER DISEASE

Introduction

Tangier disease (TD), also termed *high-density lipoprotein deficiency, type 1*, is a very rare autosomal recessive disorder caused by mutations of the ABCA1 gene and characterized by severe deficiency or absence of high-density lipoprotein (HDL)-cholesterol. First described in two siblings on Tangier Island in the Chesapeake Bay off the coast of Virginia in 1961, it has since been reported worldwide.¹²³ The characteristic clinical features include enlarged yellow-orange tonsils, hepatosplenomegaly with mild thrombocytopenia, and peripheral neuropathy.

Clinical Features

Tangier disease has been diagnosed in the first through seventh decades. About 50% of TD homozygotes develop neuropathy.¹²⁴ Three clinical phenotypes are described.¹²⁵ A relapsing-remitting sensorimotor mononeuropathy multiplex involves various appendicular and cranial nerves.^{126–129} Occasionally, the pattern may be that of a plexopathy. A recent reported case describes a 17-year-old male with six separate episodes including sciatic, posterior interosseous (twice), brachial plexus/ulnar, spinal accessory, and median neuropathies over about 8 years; the clinical picture is very reminiscent of hereditary neuropathy with liability to pressure palsy (HNPP), including some episodes possibly related to compression.¹²⁹ The syringomyelia-like syndrome is slowly progressive and more severe, involving predominantly the upper extremities with distal wasting and weakness, facial weakness, dissociated sensory loss of predominantly small-fiber function over the arms and trunk initially, and preserved or diminished reflexes.^{127,130–133} These patients may have pain and mutilating acropathy. The least common pattern is a distal, symmetric sensorimotor polyneuropathy involving all sensory modalities.¹³⁴ One patient is reported with a rapidly progressive Guillain-Barré-like illness.¹³⁵

Consider TD in the following clinical situations: undiagnosed relapsing-remitting mononeuropathy multiplex, including a picture

mimicking HNPP or leprosy; an upper extremity and bulbar syringomyelia-like presentation with no syrinx on spinal imaging; and distal, predominantly small-fiber or sensorimotor polyneuropathy (include a lipid profile in these neuropathy work-ups). Some overlapping features are noted in a recently described syndrome of unknown etiology in four patients with a syringomyelia-like presentation of facial onset sensory and motor neuronopathy (FOSMN syndrome).¹³⁶

Laboratory Studies

Lipid profiles will display the following: absence or severe deficiency of HDL and apo A-I, reduced low-density lipoprotein (LDL)-cholesterol, low or normal cholesterol, and elevated triglycerides.¹³⁷ Obligate heterozygotes for TD mutations have a 50% reduction of HDL-cholesterol but are asymptomatic.

Descriptions of electrodiagnostic studies are few and limited. The syringomyelia-like syndrome displays sensory and motor axon loss in predominantly the upper extremities and facial muscles, but some demyelinating features are also described, although in the context of markedly reduced amplitudes.^{130,138} The mononeuropathy multiplex pattern may show some demyelinating features, including conduction block, and entrapment neuropathy.^{127,129,139} The distal polyneuropathy pattern has mixed axonal/demyelinating features.¹³⁴

There are few reports of CSF findings. The CSF protein may be normal or mildly elevated. Cervical MRI showed cord atrophy in one syringomyelia-like case (as well as brain MRI with scattered T2 hyperintensities in cerebral white matter)¹⁴⁰ and was normal in another.¹³⁰

Pathology

Sural biopsies show axonal degeneration of myelinated and unmyelinated fibers, with some studies suggesting predominant reduction of smaller myelinated and unmyelinated fibers.^{125,131} Non-membrane-bound, lipid-laden vacuoles are present in Schwann cells and endoneurial fibroblasts, macrophages and perineurial cells, as well as in vasa nervorum.¹³⁴ Advanced cases may have complete endoneurial sclerosis of all fascicles in the sural

nerve.¹³⁰ In a carefully examined case of relapsing-remitting multifocal neuropathy, the non-compacted myelin region of the paranode appeared to be the preferential site of lipid storage in the myelinated Schwann cell with tomacula formation; this suggests that space-occupying effects of lipid accumulation lead to paranodal dysfunction and correlate nicely with the clinical characteristics of this syndrome.¹²⁹ Autopsy studies in the syringomyelia-like syndrome suggest sensory and motor neuronopathy with loss of small dorsal root ganglion cells, anterior horn cells (severe in the cervical cord), and facial nuclei neurons.^{141,142}

Deposits of cholesteryl esters in extra-neural tissues result in the other clinical features, including the large, lobulated yellow-orange tonsils, orange-brown spots on the rectal mucosa, splenomegaly and, less commonly, hepatomegaly, and corneal deposits.

Pathophysiology

Tangier disease is caused by mutations of the ABCA1 gene (ATP-binding cassette, subfamily A, member 1) on chromosome 9q3.¹⁴³ This gene encodes a cell membrane protein known as *cholesterol efflux regulatory protein* or *ATP-binding cassette transporter 1*, which functions as a cholesterol efflux pump, mediating the secretion of excess cholesterol from cells into the HDL metabolic pathway for elimination by the liver. The mechanisms by which lipid accumulation and neuronal loss ensue remain to be established. The ability of ABCA1 to deplete cells of cholesterol and raise plasma HDL levels may be a promising avenue of research into the prevention of atherosclerotic disease.¹⁴⁴

Treatment, Course, and Prognosis

No specific therapy is currently available. Possible gene therapies manipulating the ABCA1 gene await future developments. The course of the neuropathy may be relatively benign or severely debilitating. The neurologic features do not affect longevity but premature atherosclerosis may, with an estimated four- to sixfold elevated risk of cardiovascular disease.¹⁴⁵

ABETALIPOPROTEINEMIA

Introduction

Abetalipoproteinemia (ABL), also known as *Bassen-Kornzweig disease*, is a rare autosomal recessive disorder characterized by absence of apolipoprotein B-containing lipoproteins and caused by mutations of the MTP (microsomal triglyceride transfer protein) gene on chromosome 4q22-24.^{146–148} A founder mutation was identified in the Ashkenazi Jewish population in Israel, with a carrier frequency of 1:131.¹⁴⁹ Clinical features include gastrointestinal, hematologic, retinal, and neurologic abnormalities, the latter two likely related to secondary vitamin E deficiency.

Clinical Features

Gastrointestinal (malabsorption of fat and fat-soluble vitamins, steatorrhea, malnutrition, failure to thrive, intolerance to fatty meals) and hematologic (acanthocytes, hemolysis, anemia) abnormalities are present at birth. Retinal (retinitis pigmentosa with night blindness, visual loss, and constricted fields) and neurologic features appear later. A progressive, ataxic, combined spinocerebellar and peripheral neuropathic syndrome usually begins in early childhood. The clinical picture is similar to that of Friedreich ataxia, with features that may include cerebellar ataxia, dysarthria, intention and head tremor, large-fiber vibratory and proprioceptive loss, stocking-glove sensory loss for pain and touch, areflexia, foot dorsiflexor weakness, extensor plantar responses, occasional extraocular muscle weakness and ptosis, and skeletal deformities, including pes cavus and kyphoscoliosis. Hyporeflexia may be an early sign. Heterozygotes have no clinical or laboratory abnormalities.

Laboratory Studies

Patients with ABL have a characteristic profile with almost complete absence of apolipoprotein B-containing lipoproteins (chylomicrons, VLDL, and LDL), very low levels of triglycerides and cholesterol, and low levels of vitamins A, E, and K due to malabsorption. Occasionally, muscle enzymes are elevated, indicating associated

myopathic dysfunction, also likely related to vitamin E deficiency; this may also contribute to any observed weakness.¹⁵⁰ Acanthocytes, demonstrable on blood smear, constitute about one-half of circulating red blood cells.

Nerve conduction studies are consistent with either a sensory-predominant or sensorimotor axonal polyneuropathy.^{151–155} Somatosensory evoked potentials demonstrate dorsal column dysfunction.^{153,154}

Pathology

Sural nerve pathology, in a few reports, is characterized mostly by myelinated fiber loss.^{151,152} Few autopsy studies have suggested diffuse fiber loss in the dorsal columns and spinocerebellar tracts.^{151,156}

Pathophysiology

Mutations in the MTP gene lead to defects in the assembly of apolipoprotein B-containing lipoproteins. This results in disruption of intestinal absorption and transport of fat-soluble vitamins.¹⁵⁷ Vitamin E deficiency is felt to play the dominant role in the neurologic and retinal manifestations of ABL. This conclusion is supported by several observations. The neurologic and pathologic pictures in ABL are similar to those in other disorders associated with vitamin E deficiency, similar pathology is seen in experimental vitamin E deficiency in monkeys and rats, and there is a clear response to vitamin E supplementation.^{158,159}

Treatment, Course, and Prognosis

Untreated, patients are wheelchair dependent by the fourth decade. The malabsorption syndrome can be ameliorated by instituting a low-fat diet and eliminating long chain fatty acids. Early, very-high-dose oral vitamin E therapy can prevent or delay the appearance of neurologic and retinal disease, and arrest progression or improve established disease.^{150,159–161} Vitamin A is usually added to the regimen, as the level is low, but it does not seem to be effective as an isolated treatment for the retinopathy.¹⁶⁰

FAMILIAL HYPOBETALIPOPROTEINEMIA

Familial hypobetalipoproteinemia (FHBL) is a codominant disorder caused by mutations of the apo B gene on chromosome 2p23-24 in about 50% of subjects.¹⁶² The phenotype and biochemical profile in homozygotes are similar to those of ABL, described in the preceding section, although milder. Heterozygotes with FHBL have decreased LDL and apo B levels, unlike the normal levels in heterozygous ABL. They may have fatty liver disease and occasionally oral fat intolerance and intestinal fat malabsorption.

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis (CTX), also referred to as *cholestanolosis* or *cholestanol lipidosis*, is a rare autosomal recessive disorder of bile acid synthesis caused by mutations in the CYP27A1 gene on chromosome 2q33-qter encoding the mitochondrial enzyme sterol 27-hydroxylase.¹⁶³⁻¹⁶⁵ Excess production and massive accumulation of cholestanol and cholesterol in many tissues result in early bilateral cataracts and chronic diarrhea in children; tendon xanthomas (particularly of the Achilles tendon), osteoporosis, premature atherosclerosis, and neurologic dysfunction appear later. The CNS features include dementia, neuropsychiatric symptoms, seizures, and pyramidal, extrapyramidal, and cerebellar signs. T2-weighted MRI shows periventricular and characteristic cerebellar dentate (predominantly), globus pallidus, substantia nigra, and inferior olive signal hyperintensity; these areas correlate at autopsy with the presence of lipid crystal clefts, perivascular macrophages, neuronal loss, demyelination, fibrosis, and reactive astrocytosis.¹⁶⁶ A spinal form with chronic myelopathy is also described, and MRI may show increased T2-signal intensity in the lateral and dorsal columns.^{166,167} The CSF protein may be highly elevated.¹⁶⁸

A sensorimotor polyneuropathy is common, recognized clinically with lower extremity signs that may include weakness, distal atrophy, pes cavus, distal sensory loss, or areflexia.¹⁶⁷⁻¹⁶⁹ Reported nerve conduction and needle EMG studies are quite variable, the majority showing an axonal or mixed picture, but some

prominently demyelinating.^{168,170-173} Similarly, three pathologic types are described, with the demyelinating type including onion bulbs; lipid granules may be seen in Schwann cell cytoplasm.¹⁶⁸

Diagnosis can be established by demonstrating elevated cholestanol levels in plasma and molecular genetic testing by sequence analysis of the CYP27A1 gene. Replacement therapy with chenodeoxycholic acid inhibits abnormal bile acid synthesis and reduces plasma cholestanol levels. Early treatment significantly ameliorates the complications of CTX.^{165,169}

PORPHYRIA

Introduction

The porphyrias are a group of seven rare hereditary disorders, five hepatic and two erythropoietic, caused by mutations of enzymes involved in heme biosynthesis (Fig. 15-3). Partial enzymatic defects result in accumulation of heme precursors that are excreted in the urine, where oxidation results in pigmented porphyrins and a characteristic dark red discoloration. Historically, speculation has it that a number of luminaries may have suffered from this malady, including King George III of England, Mary, Queen of Scots, and Vincent van Gogh.¹⁷⁴ Four of the acute hepatic porphyrias— δ -aminolevulinic acid (ALA) dehydratase deficiency, acute intermittent porphyria (AIP; porphobilinogen deaminase deficiency), hereditary coproporphyria (HCP; coproporphyrinogen oxidase deficiency), and variegate porphyria (VP; protoporphyrinogen oxidase deficiency)—are associated with gastrointestinal, neuropsychiatric, and somatic and autonomic neuropathic manifestations and are discussed here (Table 15-3). The neuropathy is axonal, motor, and often predominant proximally. The erythropoietic protoporphyrias primarily manifest with skin sensitivity but occasionally, in the setting of hepatic failure, can have an acute neuropathy identical to that seen with AIP.¹⁷⁵ Porphyric neuropathy was recently reviewed in detail by Albers and Fink.¹⁷⁴

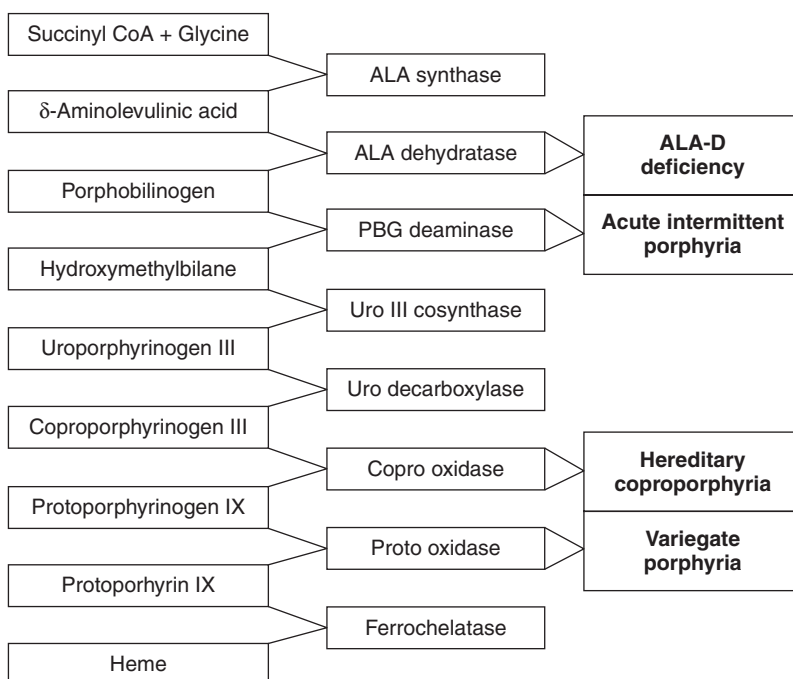


Figure 15–3. The heme biosynthetic pathway and hepatic neuropathy–associated porphyrias. ALA: δ-aminolevulinic acid; ALA-D: δ-aminolevulinic acid dehydratase; Copro: coproporphyrinogen; PBG: porphobilinogen; Proto: protoporphyrinogen; Uro: uroporphyrinogen.

Table 15–3 The Hepatic Porphyrias Associated with Neuropathy¹⁷⁴

Disease	Enzyme Deficiency	Inheritance/Locus	Elevated* Urine Porphyrins	Elevated* Fecal Porphyrins	Clinical Features
ALA dehydratase deficiency	ALA dehydratase	AR/9q34	ALA Copro	None	Presents in infancy; least common
Acute intermittent porphyria	PBG deaminase	AD/11q23-11qter	ALA PBG Uro	None	Most common; begins after puberty, second/third decade; ♀ > ♂
Hereditary coproporphyria	Copro-oxidase	AD/3q12	ALA PBG Uro Copro	Copro > proto	Photosensitive
Variegate porphyria	Proto-oxidase	AD/1q21-q23	ALA PBG Uro Copro	Proto > copro	Photosensitive; South Africa

* During acute attacks.

AD: autosomal dominant; ALA: δ-aminolevulinic acid; AR: autosomal recessive; Copro: coproporphyrinogen; PBG: porphobilinogen; Proto: protoporphyrinogen; Uro: uroporphyrinogen.

Clinical Features

EPIDEMIOLOGY

Acute intermittent porphyria, HCP, and VP are transmitted as autosomal dominant traits, while ALA dehydratase deficiency is autosomal recessive. Acute intermittent porphyria is probably the most common form; its prevalence in the white population is estimated as 1 in 10,000 to 1 in 100,000, and it is more common in Sweden.^{174,176} Penetrance is low; as many as 90% of persons with the gene mutation for AIP are asymptomatic and have no biochemical abnormalities. Attacks are more frequent in women, rarely occur before puberty, and may be associated with the luteal phase of the menstrual cycle. Variegate porphyria is most common in South Africa.

SYMPTOMS AND SIGNS

The triad of acute abdominal pain, psychosis, and neuropathy suggests porphyria.^{174,176–179} Acute neurologic attacks are similar in the various forms of hepatic porphyria, although less severe in HCP and VP than in AIP. Precipitants common to all include drugs, fasting, hormones, and stress. Formation of vesicles and bullae due to accumulation of photosensitive porphyrins in the skin is a feature of HCP and VP. The attacks usually begin with acute, severe abdominal pain, constipation, and tachycardia, likely related to dysautonomia, and may also include labile hypertension, episodic diaphoresis, nausea, vomiting, diarrhea, or urinary symptoms. An intra-abdominal catastrophe may be suspected. Pain may occur in other areas as well, including the back and extremities. Neuropsychiatric manifestations follow and may begin with anxiety, agitation, and insomnia progressing to delirium, psychosis, coma, and seizures. The syndrome of inappropriate antidiuretic hormone (SIADH) can be a complicating factor.

The neuropathy develops within 2–3 days of symptom onset and progresses rapidly over a few days, although it may evolve over several weeks.^{174,176–179} While the pattern of weakness may be distal or diffuse, there is a predilection for early proximal involvement, with onset in the arms in about 50%. Facial, bulbar, rarely extraocular, and, in severe cases, respiratory

muscles can be involved. Asymmetric weakness mimicking polyradiculopathy may occur. Reflexes are lost in proportion to weakness; a pattern of preserved ankle reflexes may be observed. Sensory symptoms and signs tend not to be prominent but may occur in either a distal, proximal/trunk (“bathing trunk”), or head/neck distribution.

DIFFERENTIAL DIAGNOSIS

Porphyria should be considered in all cases of acute flaccid paralysis where Guillain-Barré syndrome (GBS) is the major diagnostic consideration. Clinical clues to the diagnosis may include a history of prior attacks (uncommon with GBS), onset in the arms and predominant proximal weakness, asymmetric weakness, or preserved ankle reflexes. Abdominal pain, constipation, and abnormal mental status are helpful differentiating points. Lead neuropathy has clinical similarities, and it is of interest that acute lead intoxication affects the later stages of porphyrin metabolism. Arsenic and thallium toxicity may also be associated with abdominal pain, along with CNS features and neuropathy. Porphyria may be considered in the differential diagnosis of posterior reversible encephalopathy syndrome (vide infra). Tyrosinemia, an autosomal recessive disorder caused by deficiency of fumaryl acetoacetate hydrolase, has a clinical, biochemical, and pathologic picture similar to that of porphyria.

Laboratory Studies

TESTS OF BLOOD, URINE, AND FECES

Screening for porphyria can be done with high sensitivity by assessment of total 24-hour urine and fecal porphyrins and the Watson-Schwartz reaction on spot urine. Patterns of specific porphyrin precursor accumulation in urine and feces or specific enzyme determinations may help distinguish the various types, but they can be confusing (Table 15–3).^{180,181} It should be borne in mind, however, that increased excretion of porphyrin precursors may occur with other medical conditions unrelated to the hepatic porphyrias (alcoholic liver disease,

diabetes), with intoxications (lead, hexachlorobenzene), or in some individuals taking medications that induce the hepatic microsomal cytochrome P450 system.

ELECTRODIAGNOSTIC STUDIES

The electrophysiologic abnormalities are consistent with an acute axonal neuropathy.^{182,183} There are no demyelinating features, distinguishing this from the acute inflammatory demyelinating form of GBS, although not necessarily from axonal GBS. Motor amplitudes are diminished, and sensory amplitudes vary from normal to severe involvement. Needle EMG performed within a few weeks of onset shows prominent spontaneous activity, especially in proximal muscles, and is similar to the clinical pattern, occasionally more in the arms than in the legs. Sparing of sensory responses with non-length-dependent fibrillations mimics polyradicular disease. Chronic motor unit reinnervation follows with recovery. Electrophysiologic studies tend to be normal in asymptomatic patients between attacks.¹⁸⁴

CEREBROSPINAL FLUID

The CSF is acellular, usually with normal or mildly elevated protein.

IMAGING

Patients with AIP associated with seizures, hallucinations, and occasionally cortical blindness can have the MRI and clinical picture of posterior reversible encephalopathy syndrome (PRES).^{185,186} They may vary from the usual case of PRES by virtue of intense contrast enhancement. Since diffusion-weighted MRI and MR spectroscopy are normal, the lesions may be related to reversible vasogenic edema.¹⁸⁶

Pathology

While reports vary, the majority of neuropathologic biopsy and autopsy investigations suggest primary axonal degeneration, with occasional secondary demyelination.^{187–189}

Pathophysiology

The basis for physiologic perturbation and structural neuronal damage in the porphyrias is not established. Putative mechanisms are reviewed by Albers and Fink¹⁷⁴ and by Windebank and Bonkovsky.¹⁷⁶ Porphobilinogen (PBG) deaminase-deficient mice develop an axonal motor neuropathy closely resembling human porphyria; this occurs in the absence of high levels of ALA, suggesting that heme deficiency with subsequent dysfunction of heme proteins may be the cause of porphyric neuropathy.¹⁹⁰

Treatment, Course, and Prognosis

Preventing acute attacks centers on avoiding the common precipitants, which include fasting, stress, infections, and use of alcohol and numerous contraindicated drugs such as barbiturates and sex hormones; many of the problematic drugs are either inducers of the hepatic microsomal cytochrome P450 enzyme system or induce the rate-limiting enzyme of heme biosynthesis, ALA synthase. Current sources of drug information should be consulted before giving a patient with known porphyria any new drug. Patients with HCP and VP are photosensitive and should avoid sunlight.

Supportive care is similar to that for GBS, with additional attention to the choice of medications. Treatment of acute attacks includes carbohydrate loading and, if there is no prompt response, administration of intravenous hematin (4 mg/kg/day once daily or in two divided doses for 4–14 days), both of which inhibit ALA synthase activity. Early treatment appears to have a salutary effect on the neuropathy, but treatment after extensive axonal degeneration is unlikely to be helpful.^{191,192} Better therapies are needed; investigations of possible gene therapy in porphyria are ongoing.¹⁹³ A recombinant human PBG deaminase enzyme preparation was recently found to be safe and effective in removing PBG from plasma and urine, setting the stage for trials in AIP.¹⁹⁴

Once aborted, the prognosis for recovery from the autonomic and CNS features of an acute attack is generally good. The prognosis and time course for motor recovery from

individual attacks will depend on the degree of axonal loss; deficits may accrue with repeated events. Patients with AIP have an increased risk of developing hepatocellular carcinoma.

DISORDERS OF DEFECTIVE DNA REPAIR

Complex mechanisms exist for the recognition and repair of DNA damaged by endogenous (sources within a cell's metabolism, likely reactive oxygen species) or exogenous (chemicals, radiation) factors.^{174,195–197} The excision repair pathway is the predominant mechanism, with two forms, nucleotide excision repair (NER) and base excision repair (BER). The NER pathway removes ultraviolet (UV) light-induced DNA lesions. Additional mechanisms exist for repair of double-strand DNA breaks (DSB) and single-strand DNA breaks (SSB). Several disorders linked to DNA repair defects and having associated neuropathy include xeroderma pigmentosum and Cockayne syndrome (NER defects), ataxia telangiectasia and ataxia telangiectasia-like disorder (DSB repair defects), ataxia with oculomotor apraxia 1, and spinocerebellar ataxia with axonal neuropathy (SSB repair defects). All are associated with a predominantly axonal neuropathy, except for Cockayne syndrome, where the neuropathy is predominantly demyelinating or mixed. Features of these disorders are outlined in Table 15–4.

MITOCHONDRIAL DISORDERS

Mitochondria are essential for cellular aerobic metabolism. Dysfunction may arise from mutations of mitochondrial DNA (mtDNA), or nuclear DNA (nDNA) encoding electron transport chain components or intergenomic communication. The inheritance pattern of mtDNA mutations is maternal. Factors influencing the phenotypic expression and severity of mitochondrial disorders include variable tissue distribution of mtDNA mutations, varied proportion of mutant mtDNA within the many mitochondria in a cell (heteroplasmy), and the unique energy requirement of different tissues (threshold effect). While the CNS and muscle are often predominantly

affected in these multisystem disorders with protean manifestations, the PNS is often involved as well. Polyneuropathy may be subclinical, mildly symptomatic, or severe and a defining feature in some cases. Axonal neuropathy is more common than demyelinating neuropathy. Neuropathologically, abnormalities of mitochondrial cristae may be seen in axons or Schwann cell cytoplasm.¹⁹⁸ Associated endocrinopathies, in particular diabetes mellitus, may confound interpretation. How often mitochondrial disorders are the cause of isolated, chronic, idiopathic, axonal polyneuropathy is uncertain.

Neuropathy is a common or major feature of Leigh syndrome, MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), SANDO (sensory ataxic neuropathy, dysarthria, and ophthalmoparesis), NARP (neuropathy, ataxia, and retinitis pigmentosa), and NNH (Navajo neurohepatopathy); less common but of notable frequency in MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) and MERRF (myoclonus epilepsy with ragged-red fibers); and least often reported with KSS (Kearns-Sayre syndrome) and LHON (Leber hereditary optic neuropathy). This topic is reviewed in detail by Hanna and Cuddia.¹⁹⁸ Table 15–5 provides a summary of the major mitochondrial disorders and associated neuropathies.

NEUROACANTHOCYTOSIS SYNDROMES

Acanthocytes (from the Greek *acantha* = thorn) are abnormal, spike-shaped red blood cells (RBCs) seen in several rare disorders. They are a hallmark of ABL and familial hypobetalipoproteinemia (discussed previously under lipoprotein deficiencies), characterized by an ataxic spinocerebellar and peripheral neuropathic syndrome, and are also found in chorea-acanthocytosis and McLeod syndromes, neurodegenerative basal ganglia disorders with associated neuropathy. Acanthocytosis is also occasionally seen in pantothenate kinase-associated neurodegeneration (PKAN), Huntington disease-like 2 (HDL2), autosomal dominant familial acanthocytosis with paroxysmal exertion-

Table 15–4 Disorders of Defective DNA Repair ²³⁵

Disorder/DNA Repair Defect	Inheritance/ Gene/Locus	Onset (yrs)	Nonneurologic Features	Neurologic Features	Neuropathy (NCS/ Path)
Ataxia telangiectasia/DSB	AR/ATM/11q22.3	Early childhood	Oculocutaneous telangiectasia, endocrinopathies, radiosensitivity, impaired immunity, elevated α -fetoprotein, infections and malignancies; death in teens	Ataxia, oculomotor dyspraxia, choreoathetosis, sensorimotor polyneuropathy	Axonal
Ataxia telangiectasia-like disorder/DSB	AR/MRE11A/11q21	Later onset	Similar phenotype without telangiectasia, later onset, slower progression	Poorly described sensorimotor polyneuropathy	?
Xeroderma pigmentosum (XP)/NER	AR/multiple genes	1–2	Photosensitive dermatitis, 1000-fold increase in skin cancer risk	Microcephaly, MR, seizures, spasticity, SNHL, ataxia, movement disorders, sensorimotor polyneuropathy with hyporeflexia	Axonal or mixed
Cockayne syndrome (CS)/NER	AR/ERCC/5q12—type A; 10q11— type B; type C—CS + XP	2	Photosensitive dermatitis, cachectic dwarfism, progeroid appearance, normal skin cancer risk	Microcephaly, MR, SNHL, pigmentary retinopathy, ataxia; sensorimotor polyneuropathy with hyporeflexia; distal amyotrophy in adults	Demyelinating or mixed
Ataxia with oculomotor apraxia I (AOA1)/SSB	AR/aprataxin/9p13.3	Childhood	Hypoalbuminemia, hypercholesterolemia	Cerebellar ataxia, oculomotor apraxia, choreoathetosis, sensorimotor polyneuropathy	Axonal
Spinocerebellar ataxia with axonal neuropathy (SCAN1)/SSB	AR/tyrosyl-DNA phosphodiesterase-1/14q31-q32	Teens	Hypoalbuminemia, hypercholesterolemia, Saudi Arabian	Cerebellar ataxia, sensorimotor polyneuropathy, distal muscular atrophy, pes cavus, steppage gait	Axonal

AR: autosomal recessive; ATM: ataxia telangiectasia mutated gene; DSB: double-stranded DNA breaks; ERCC: excision-repair cross-complementing protein; MR: mental retardation; MRE11A: meiotic recombination 11, *S. cerevisiae*, homolog of A; NCS: nerve conduction study; NER: nucleotide excision repair; SNHL: sensorineural hearing loss; SSB: single-strand breaks.

Table 15–5 **Mitochondrial Disorders and Neuropathy**

Disorder	Inheritance/Gene/Locus	Clinical Features	Neuropathy Type
Leigh syndrome (subacute necrotizing encephalo- myelopathy) ^{236–239}	Maternal or AR/multiple mitochondrial or nuclear genes	Onset usually in first year, occasionally juvenile or adult, variable presentations, developmental regression, ataxia, movement disorders, hypotonia, spasticity, seizures; brainstem, respiratory, and spinal cord dysfunction; symmetric T2 hyperintensity in brainstem and basal ganglia; acute or chronic sensorimotor polyneuropathy	Demyelinating
MNGIE ^{240–243}	AR/ECGF1 (thymidine phosphorylase)/ 22q13.32-qter	Onset in second to fifth decade, PEO/ ptosis, cachexia, GI symptoms with dysmotility, SNHL; MRI shows leukoencephalopathy; sensorimotor polyneuropathy, mimics CMT or CIDP	Demyelinating (nonuniform) or mixed
SANDO ²⁴⁴	AR/POLG or C10ORF2/15q25, 10q24	Onset >30 years of age, severe sensory ataxic neuropathy, dysarthria, external ophthalmoplegia, migraine, depression	Axonal
MELAS ^{245–247}	Maternal/multiple mitochondrial tRNA genes (A3243G mutation in tRNA ^{Leu} gene most common)	Onset from childhood to <40 years of age, stroke-like episodes, encephalopathy (dementia, seizures), myopathic limb weakness, episodic vomiting, SNHL, lactic acidosis, short stature; acute, subacute, or chronic sensory or sensorimotor polyneuropathy (risk factors: male gender, older age)	Axonal or mixed (most), some demyelinating (uniform or nonuniform); single report of isolated small-fiber type

(continued)

Table 15–5 (Continued)

Disorder	Inheritance/Gene/Locus	Clinical Features	Neuropathy Type
NARP ²⁴⁸	Maternal/mitochondrial ATPase6	Late childhood or adult onset, sensory or sensorimotor polyneuropathy, areflexia, proximal neurogenic muscle weakness, retinitis pigmentosa, ataxia, developmental delay, dementia, seizures	Axonal
MERRF ^{249,250}	Maternal/mitochondrial gene MT-TK encoding tRNA ^{Lys} most common	Childhood to adult onset, myoclonus, seizures, ataxia, ragged-red fibers, SNHL, lactic acidosis, exercise intolerance, dementia, short stature, optic atrophy; sensorimotor polyneuropathy	Axonal or mixed
KSS ^{251,252}	Sporadic/single mtDNA deletions	Onset <20 years old, PEO, retinitis pigmentosa, ataxia, limb weakness, complete heart block, CSF protein >100 mg/dL, SNHL, impaired intellect, endocrinopathies; peripheral neuropathy	Axonal
LHON ^{253,254}	Maternal/several mtDNA mutations	Optic neuropathy; painless, subacute, bilateral visual loss, male > female, postural tremor, absent ankle reflexes; rarely reported sensorimotor neuropathy	Axonal; single report of demyelinating type
NNH ²⁵⁵	AR/MPV17 mutations	Navajo children of southwestern United States; hepatopathy, corneal anesthesia and scarring, acral mutilation, cerebral leukoencephalopathy, recurrent metabolic acidosis with intercurrent infections, failure to thrive, sensorimotor polyneuropathy	Demyelinating (?)

AR: autosomal recessive; C10ORF2: chromosome 10 open reading frame 2; ECGF1: endothelial cell growth factor, platelet derived; KSS: Kearns-Sayre syndrome; LHON: Leber hereditary optic neuropathy; MELAS: mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF: myoclonus epilepsy with ragged-red fibers; MNGIE: mitochondrial neurogastrointestinal encephalomyopathy; mtDNA: mitochondrial DNA; NARP: neuropathy, ataxia, and retinitis pigmentosa; NNH: Navajo neurohepatopathy; PEO: progressive external ophthalmoplegia; POLG: DNA polymerase-gamma; SANDO: sensory ataxic neuropathy, dysarthria, and ophthalmoplegia; SNHL: sensorineural hearing loss.

induced dyskinesias and epilepsy (FAPED), and MELAS.¹⁹⁹

Chorea-Acanthocytosis Syndrome (ChAc)

This autosomal recessive disorder is caused by mutations of the VPS13A gene on chromosome 9q21 encoding the protein chorein. The age range for onset is wide, with a mean of 35 years. Features include chorea and other varied movement disorders, orofaciolingual dyskinesias with involuntary tongue and lip biting, dysarthria, dysphagia, dementia, psychiatric symptoms, seizures, parkinsonian features, elevated creatine kinase, and peripheral neuropathy with depressed or absent reflexes. The CNS features resemble those of Huntington disease. Muscle wasting and weakness are commonly reported, distal sensory disturbance less often. Nerve conduction studies and needle EMG are consistent with an axonal motor or sensorimotor polyneuropathy. Muscle biopsies usually show neuropathic changes. Nerve biopsy and autopsy studies demonstrate predominant loss of large myelinated fibers, distally accentuated, and may show axonal swellings with accumulation of neurofilaments suggesting effects on axonal transport.^{199–203}

McLeod Neuroacanthocytosis Syndrome

This X-linked progressive neurodegenerative and neuromuscular disorder, named after the propositus, is caused by mutations of the XK gene on chromosome Xp21. In addition to the presence of acanthocytes, there is absent expression of the Kx RBC antigen and diminished expression of Kell glycoprotein RBC antigens. Onset is often difficult to determine, but most cases manifest by the fifth decade. Features are analogous to those described for ChAc, with much less frequent tongue/lip biting and parkinsonism and a significant incidence of progressive cardiomyopathy. Muscle biopsies show myopathic features more often than in ChAc, but neurophysiologic and muscle histology studies suggest predominant axonal neuropathic dysfunction, supported by nerve biopsy findings. While weakness or

neuropathic features in some of these patients may be mild or subclinical, they can be progressive, distal, and leg-predominant, leading to severe disability.^{200,204–206}

NEUROFIBROMATOUS NEUROPATHY

Neurofibromatosis 1 (NF1)

Neurofibromatosis 1 is a common (incidence approximately 1 in 3000) autosomal dominant, neurocutaneous syndrome caused by mutations of the neurofibromin gene on chromosome 17q11.2. Almost half of cases are de novo mutations. Diagnostic criteria for NF1 are any two or more of the following: six or more café au lait macules over 15 mm in diameter in postpubertal persons, two or more neurofibromas or one plexiform neurofibroma, intertriginous freckling (axillary or inguinal), optic glioma, Lisch nodules (iris hamartomas), sphenoid dysplasia or tibial pseudarthrosis, or a first-degree relative with NF1.²⁰⁷ Histologically, the neurofibroma is a complex tumor composed of axonal processes, Schwann cells, perineurial cells, fibroblasts, and mast cells within a collagen-rich extracellular matrix, without a cleavage plane between normal nerve and the tumor. The prevalence of peripheral nerve involvement in NF1 is considered low, but may include neurofibromas of subcutaneous nerves with associated pain and occasional malignant transformation, intradural spinal root neurofibromas with radiculopathy or spinal cord compression, mononeuropathy, or mononeuropathy multiplex.²⁰⁸ Plexiform neurofibroma of the cauda equina may clinically mimic CMT disease.²⁰⁹ The prominent hypertrophic changes of spinal roots that may accompany CIDP have been mistaken for neurofibromatosis.²¹⁰

In the two largest reported series, a diffuse, symmetric polyneuropathy occurred in 1.3%–2.3% of 1288 patients with NF1.^{208,211} Clinical patterns range from asymptomatic to mild, with moderate or severe sensory or sensorimotor features. Pes cavus can be seen. Peripheral nerves may be palpable, with diffuse nodular enlargement. The course is chronic in most

cases, subacute in a few. Superimposed radicular changes are common. Electrophysiologic studies may show predominantly axonal, mixed, or quite frequently demyelinating features. Biopsied nerves show diffuse neurofibromatous change. There is a strong association with early development of numerous subcutaneous neurofibromas and large, diffuse spinal root neurofibromas, as well as the appearance of malignant peripheral nerve sheath tumors.^{208,211,212}

Neurofibromatosis 2 (NF2)

Neurofibromatosis 2 is a more rare autosomal dominant disorder caused by mutations of the tumor suppressor NF2 gene on chromosome 22q12.2, encoding the protein product merlin or schwannomin. About 50% of cases are de novo mutations. Patients develop bilateral vestibular schwannomas by age 30, along with a variety of other tumors including schwannomas of other cranial or peripheral nerves, meningiomas, astrocytomas, ependymomas, or neurofibromas, as well as posterior subcapsular lenticular opacities. Café au lait spots occur in about one-half of patients; almost always, there are fewer than six, and skin tumors are common. Presenting symptoms are most often hearing loss, tinnitus, balance dysfunction, or focal weakness; children have an unusually high incidence of unilateral facial palsy or foot drop at presentation. Morbidity and mortality are substantial in this disorder, with an average age of death of 36 years.^{213–215}

Compressive mononeuropathies or radiculopathies may arise from tumor masses. Cases are also reported of mononeuritis multiplex or focal amyotrophy as presenting or preceding features to the diagnosis of NF2, without demonstrable discrete tumors.^{215–218} While prior reports suggested polyneuropathy to be rare in NF2, two recent reports suggest otherwise.^{219,220} A systematic investigation of 15 patients with NF2 found evidence of polyneuropathy electrophysiologically in 10 (7 axonal, 2 mixed, 1 demyelinating) and clinically in 7, ranging from mild (most) to severe, either sensory or sensorimotor.²¹⁹ A relationship was observed between the presence of skin tumors and polyneuropathy. Sural nerve histopathology showed fiber loss, “dedifferentiated” Schwann cells (schwannoma cells), either isolated or in complexes,

and increased collagen. The authors hypothesized that axonal polyneuropathy in NF2 is the result of compression effects of multiple tumorlets along the course of peripheral nerves, toxic or metabolic effects of endoneurial pathologic cells, or a consequence of defective cell–cell contact. Another study examined eight sural nerve biopsies in seven NF2 patients with slowly evolving sensorimotor polyneuropathy that progressed to disability.²²⁰ There was severe fiber loss, diffuse Schwann cell proliferation, small endoneurial tumorlets of schwannomas and perineuriomas, perivascular fibrous thickening of endo- and perineurial vessels, and some Schwann cell onion bulbs or onion bulb-like structures. The findings suggested that polyneuropathy in NF2 is a secondary axonopathy of multifactorial origin.

GLYCOGEN STORAGE DISEASES

Adult Polyglucosan Body Disease (APBD)

APBD is a very rare sporadic or autosomal recessive (primarily in the Ashkenazi Jewish population) glycogen storage disorder, although one may get a different impression from the frequency with which it is presented in neuromuscular case sessions at national meetings. It is caused by mutations in the glycogen branching enzyme (GBE) gene on chromosome 3p12 in most but not all cases; other mutations in the same gene cause type IV glycogen storage disease (GSD IV), an early childhood disorder with hepatic and multisystem dysfunction. Deficiency of GBE in leukocytes is found in many but not all cases of APBD. Polyglucosan bodies are nonmembrane-bound, round or ellipsoid cytoplasmic inclusions consisting primarily of glucose polymers in a homogeneous granular and amorphous matrix. They accumulate in CNS neuronal and astrocytic processes, PNS myelinated and unmyelinated axons and Schwann cells, visceral organs, and muscle; they are not, however, entirely specific for APBD.^{221–224}

APBD usually begins after age 40 and progresses to death over about 1–20 years.²²² In its fully expressed form, APBD is characterized by

a slowly progressive combination of upper and lower motor neuron symptoms and signs, with gait disturbance, dementia, urinary sphincter dysfunction, and sensorimotor polyneuropathy. Additional features or occasional presentations include cerebellar dysfunction, extrapyramidal syndrome, isolated frontal dementia, multiple entrapment neuropathies, and symmetric limb-girdle, distal, or asymmetric myopathy.^{225–228} The protean manifestations and partial presentations lead to diagnostic difficulty, many cases in particular being confused with amyotrophic lateral sclerosis.²²⁹ Urinary sphincter dysfunction and sensory loss are useful diagnostic clues. Depending on the constellation of features at the time of evaluation, differential diagnostic considerations may include multiple sclerosis, leukodystrophies, motor neuron disorders with dementia plus sensory neuropathy, spinocerebellar disorders, extrapyramidal disorders, degenerative dementias, and other chronic axonal neuropathies.

Electrodiagnostic studies typically demonstrate an axonal sensorimotor polyneuropathy or polyradiculoneuropathy, with patchy active and chronic denervation changes accentuated in the legs on EMG; occasionally, there are demyelinating features.^{222,223,226,230–234} Cases with myopathy show myopathic motor unit potentials on needle EMG and irritative features, including fibrillations, positive sharp waves, and complex repetitive discharges.²²⁷ The CSF protein may be mildly elevated, as may creatine kinase levels. The MRI scan often reveals extensive periventricular and subcortical white matter abnormalities, with involvement of the brainstem and cerebellum, along with diffuse brain and cervical cord atrophy. Diagnosis can be established by sural nerve biopsy showing many polyglucosan bodies in predominantly myelinated axons, or by axillary skin biopsy showing similar inclusions in myoepithelial cells of apocrine glands.^{231,232}

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The Toxic Neuropathies: Principles of General and Peripheral Neurotoxicology; Pharmaceutical Agents

**PRINCIPLES OF GENERAL
NEUROTOXICOLOGY**

**PRINCIPLES OF PERIPHERAL
NEUROTOXICOLOGY**

Mononeuropathy
Vasculitis/Fasciitis/Inflammation
Demyelinating Neuropathy
Sensory Neuronopathy
Toxic Channelopathy
Distal Axonopathy (Central-Peripheral Distal
Axonopathy)

**PERIPHERAL NEUROTOXICITY
ASSOCIATED WITH PHARMACEUTICAL
AGENTS**

Amiodarone
Bortezomib
Colchicine

Dapsone
Disulfiram
Ethambutol
Ethanol
Isoniazid
Metronidazole
Misonidazole
Nitrous Oxide
Nucleoside Analogues
Phenytoin
Platinum (Cisplatin and Oxaliplatin)
Pyridoxine
Suramin
Tacrolimus
Taxanes
Thalidomide
Vinca Alkaloids

**PRINCIPLES OF GENERAL
NEUROTOXICOLOGY¹**

1. **Strong dose-response relationship:**
Most chemicals that trigger structural damage to the nervous system produce a consistent pattern of disease, commensurate with the dose and duration of exposure. Significant exposure of the nervous system to a single neurotoxic agent will invariably produce similar

dysfunction in most individuals. Aside from endogenous factors that may modify the intensity of the disorder, such as age, sex, body weight, and renal/liver integrity, there are few genetic variations in the human response to neurotoxic substances. This phenomenon, in part, reflects the direct metabolic pathogenesis of most neurotoxic conditions; in addition, few of these syndromes have an indirect immunologic basis.

2. **Proximity to exposure:** Neurotoxic illness usually occurs concurrent with exposure or following a short latent period. The three most notorious exceptions—the 2- to 6-week delay following exposure to organophosphates, the occasional 2-month latency to onset of cisplatin neuropathy, and the 2-month delay of onset of symptoms of methylmercury intoxication—are not in the same league as the multiyear intervals characteristic of mesothelioma from asbestos exposure.
3. **Asymptomatic disease:** Asymptomatic toxic disease of the nervous system occurs and, under certain circumstances, may be widespread. Unless a person performs at an unusually skilled job or requires consistent, high-level physical activity, a modest decline in performance may go unnoticed by the individual. An analogous phenomenon has been described in workers with subclinical toxic neuropathies who deny having any disability, despite sensory dysfunction obvious to their spouses.
4. **Modulation by bystander chemicals:** An agent without known neurotoxic activity may enhance the toxicity of a known neurotoxin that is present at a “no-effect” level. The phenomenon of potentiation of a neurotoxic chemical by a second, apparently innocuous agent is best exemplified by a mini-epidemic of peripheral neuropathy among Berlin youths who abusively inhaled fumes from paint thinner. This solvent initially contained the neurotoxin *n*-hexane, but at a level that failed to produce neuropathy. However, after several years, the solvent was reformulated by lowering the concentration of *n*-hexane and introducing methyl ethyl ketone, whereupon severe cases of neuropathy developed. Experimental studies subsequently demonstrated that, while methyl ethyl ketone was unable to produce experimental neuropathy, the compound dramatically enhanced the neurotoxic property of *n*-hexane.
5. **The chemical formula may not predict toxicity:** The neurotoxic potential of a substance usually cannot reliably be predicted by its chemical formula. This has been an especially vexing issue in evaluating patients with occupational exposure to chemicals superficially similar to known neurotoxins. Workers who handle acrylamide polymer, an innocuous substance, have been needlessly alarmed by physicians familiar only with the side effects of acrylamide monomer, a potent neurotoxin. Unpredictability prevails, in part, because the biochemical mechanisms and active metabolites of most neurotoxins are unknown. Structure–activity relationships are clear for only a few classes of substances, such as organophosphates and hydrocarbons with a common gamma di-ketone metabolite. Hydrocarbons with two ketone groups at slightly different spacing may be harmless (for example, 2,5-heptanedione is neurotoxic; 2,6-heptanedione is not).
6. **Coasting:** Following withdrawal from toxic exposure, symptoms and signs may intensify for weeks before recovery commences. This does not imply a persistent body burden of toxin but likely reflects continued axonal degeneration and reconstitution.
7. **Pseudoneurotoxic neuropathy:** This is an issue in persons with axonal neuropathies of uncertain cause. Having eliminated all of the “usual suspects”—diabetes, nutritional disorders, pharmaceuticals, and those immune disorders readily detected on clinical laboratory testing—some clinicians then determine the body burdens of environmental heavy metals, despite the patient’s having no known unusual occupational or other environmental exposures. Some body burden determinations cast a wide net and detect not only minor elevations in the usual neurotoxic heavy metals (arsenic, lead, mercury, thallium), but also in some exotic substances such as antimony, manganese, molybdenum, cadmium, and selenium. It is the authors’ experience that, unless the patient displays other signs consistent with the toxicity of the implicated substance (e.g., anemia and gastrointestinal symptoms with arsenic, tremor with elemental mercury), such investigations are fruitless and often delay discovery of the etiology of the neuropathy.

PRINCIPLES OF PERIPHERAL NEUROTOXICOLOGY¹

Peripheral neuropathy of the distal axonopathy type is the most common form of neurotoxic disease. Most instances are caused by pharmaceutical agents or substance abuse; occupational neuropathies are relatively infrequent in North America. Except for sensory neuronopathy and toxic channelopathy, the other anatomic variants of peripheral neuropathy encountered in neurological practice (the mononeuropathy, vasculitis, demyelinating types) are rarely neurotoxic.

Mononeuropathy

Accidental injection of pharmaceutical agents (usually antibiotics, analgesics, or local anesthetics) directly into a peripheral nerve is an occasional event. The sciatic nerve in the buttocks of children or emaciated adults is the usual site. Severe pain is immediate and is followed by hamstring weakness and a flail foot. Severe axonal destruction and fibrosis are usual and most patients have disabling residual paralysis, sometimes accompanied by a complex regional pain syndrome.

Vasculitis/Fasciitis/Inflammation

Two epidemics of multifocal neuropathy in concert with connective tissue and muscle disease have occurred; one followed consumption of food cooked in adulterated rapeseed oil (Spanish oil syndrome), the other from self-medication with a tryptophan analog (eosinophilia myalgia syndrome). An episode of a variant of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) has been described in pork processors who inhaled an aerosol of pork brain. All three conditions are presumably immune-mediated.

Demyelinating Neuropathy

Several agents (diphtheria, arsenic) may be associated with an acute toxic demyelinating neuropathy (presumably not immune-mediated). Exposure to these agents can result

in a disabling acute or subacute diffuse, predominantly motor neuropathy with areflexia and cranial nerve dysfunction. This condition resembles the Guillain-Barré syndrome, a postinfectious polyradiculoneuropathy caused by an immune-mediated inflammatory demyelination of spinal roots and nerves. Recovery is usually satisfactory and can be rapid in mild cases.

Subacute or chronic, predominantly demyelinating neuropathy with moderate axonal degeneration is associated with therapy with a few pharmaceutical agents: perhexilene maleate, amiodarone, suramin, bortezomib, and tacrolimus.

Sensory Neuronopathy

The dorsal root and Gasserian ganglion neurons are believed to be particularly vulnerable to some circulating toxins because of the special permeability of their fenestrated blood vessels. Effects are diffuse or patchy, resulting in dysfunction or death of the neuronal cell body and limited or no recovery. Several agents may result in the pattern of a distal axonopathy or a sensory neuronopathy: cisplatin, pyridoxine, linezolid, metronidazole, podophyllotoxin, taxanes, and thalidomide.

Toxic Channelopathy

Neurotoxicity may involve sensory or motor peripheral nerve hyperexcitability (gold salts, oxaliplatin, marine biotoxins) caused by reversible effects on axonal sodium or potassium channels and characterized by paresthesias, cramps, stiffness, weakness, myokymia, neuro-myotonia, or fasciculations.

Distal Axonopathy (Central-Peripheral Distal Axonopathy)

This common morphologic reaction occurs after chronic or subacute exposure to many pharmaceutical and occupational agents. Some cause severe systemic illness (thallium), while others are well tolerated and patients feel well (acrylamide, pyridoxine). Most are associated with chronic low-level exposure, onset is

insidious, and sensory symptoms are prominent (Chapter 2). A few have rapid onset, and weakness is the dominant complaint (hexane sniffers, dapsone, organophosphates).

The neuropathologic substrate is nonspecific degeneration of distal regions of axons in the central nervous system (CNS) and peripheral nervous system (PNS; illustrated in Chapter 2). In the PNS, degeneration appears to advance proximally toward the nerve cell body as long as exposure lasts; its reversal allows the axon slowly to regenerate along the distal Schwann cell tube to the appropriate terminal. An identical sequence usually occurs in the distal ends of long CNS axons (dorsal column, corticospinal tract), although regeneration is poor.

PERIPHERAL NEUROTOXICITY ASSOCIATED WITH PHARMACEUTICAL AGENTS

New pharmaceutical agents are constantly being identified or implicated as causes of neuropathy; most appear to produce distal axonopathy, usually after prolonged use. There are few careful experimental studies of the neurotoxicity of these substances; clinical reports are often the sole basis for many of the alleged drug-induced peripheral neuropathies, and some instances doubtless reflect other coincident conditions. Drugs tend to be associated with one or several specific syndromes based on their mechanisms of action, which in many cases are not established. A careful history of all administered drugs is mandatory when faced with essentially any neurologic syndrome. Whether a neuropathy is in fact related to a drug requires recognition of known related effects, establishing a credible temporal relationship and seeing clinical improvement following removal from exposure. In only a few cases can toxicity be inferred from analyzing drug levels and even less frequently from tissue analysis. Disease severity should generally correlate with the level and duration of exposure, but vulnerability may depend on factors such as age, preexisting conditions (such as underlying hereditary neuropathy when receiving chemotherapy), or genetic variations in drug metabolism. A few selected, clinically relevant agents are reviewed here.

Amiodarone

Amiodarone is a diiodinated benzofuran derivative used as a cardiac antiarrhythmia agent. Common neurotoxic side effects, in order of declining frequency, are tremor, ataxia, and sensorimotor neuropathy; uncommonly, optic neuropathy, pseudotumor, myopathy, and basal ganglia dysfunction occur.^{2,3}

Both axonal and demyelinating neuropathies may accompany amiodarone therapy. Most appear following prolonged moderate- and high-dose regimens, but cases have appeared following only 1 month of low-level treatment. Most cases evolve in a gradual fashion with distal limb sensory and motor dysfunction.^{4,5} A few display the subacute appearance of a predominantly motor demyelinating neuropathy and are difficult to distinguish from Guillain-Barré syndrome. Electrodiagnostic and sural nerve biopsy studies have yielded findings consistent with axonal degeneration in some cases and predominantly demyelinating changes in others. Cytoplasmic lysosomal lamellar inclusions appear in Schwann cells, axoplasm, and perineurial cells, both in sural nerve biopsy specimens and in zones of weak blood-brain barrier in experimental animals.^{6,7} These inclusions are similar to those associated with the neuropathy of perhexilene maleate, another amphiphilic cationic drug. Both mild and severe cases of amiodarone neuropathy improve with lowering of the dose or stopping therapy.

Bortezomib

Bortezomib is a promising proteasome inhibitor used in the treatment of patients with multiple myeloma who have relapsed after initial therapy with another agent. It is a highly effective polycyclic derivative of boronic acid and inhibits the 26S proteasome, a part of the ubiquitin degradation pathway. Bortezomib downregulates the expression of proteins that promote cell division and proliferation.

Sensory neuropathy of the small-fiber type with severe neuropathic pain can be a disabling and daunting consequence of therapy with bortezomib. The neuropathy appears to be both dose-related and cumulative. It is especially common if persons have residual dysfunction

from previous thalidomide therapy, but it also occurs when bortezomib is used as a first-line agent. Most patients gradually improve following termination of treatment.^{8,9} Combination therapy with bortezomib and thalidomide is associated with a predominantly axonal, sensory > motor, large-fiber > small-fiber polyneuropathy, with a subset of patients showing demyelinating electrophysiology.¹⁰

Colchicine

Colchicine is a tricyclic anti-inflammatory alkaloid employed in the treatment of gouty arthritis. Chronic administration of colchicine at the usual dose of 0.6 mg twice daily can cause a mild sensory distal axonopathy. It is usually overshadowed by a coincident debilitating vacuolar myopathy with elevated serum creatine kinase.¹¹ The primary risk factor for colchicine myoneuropathy appears to be chronic renal dysfunction, which is common in gout. Symptoms usually include inability to rise readily from a seated position or to raise the arms above the head in concert with distal acral paresthesias. Neurologic findings include proximal myopathic weakness, distal symmetric sensory loss of large-fiber modalities, and hyporeflexia. Myopathic proximal weakness may so dominate the clinical profile that an erroneous diagnosis of polymyositis is entertained. Electromyography shows an irritative myopathy (often including myotonia) in proximal muscles, and nerve conduction studies display reduced amplitudes in distal sensory and motor nerves.¹² Sural nerve biopsy shows reduced numbers of large myelinated fibers and moderate axonal degeneration. Medication withdrawal is followed by a dramatic fall in creatine kinase and gradual improvement. The pathogenesis of neuropathy is widely held to result from defective axonal transport resulting from impaired microtubule assembly.¹³

Dapsone

Dapsone is a sulfone derivative and is used in treating leprosy, *Pneumocystis* pneumonia, and dermatologic conditions. Most instances of peripheral neuropathy have occurred following prolonged treatment for dermatologic conditions,

usually with 200–400 mg daily; the low doses used for leprosy and *Pneumocystis* therapies are not associated with neuropathy. Dapsone neuropathy is uncommon and not always dose dependent; slow acetylators may be more vulnerable.¹⁴ Uncommon for a toxic neuropathy, dapsone produces an axonal, primarily motor neuropathy. Weakness is symmetric and, surprisingly, may primarily involve the upper limbs. Tendon reflexes are usually spared or only the ankle reflexes are absent. Mild large-fiber sensory loss is occasionally detectable. Improvement follows drug withdrawal but may be delayed.¹⁵ Electrophysiologic studies show low-amplitude compound muscle action potentials with minimal slowing of conduction velocities. Sural nerve biopsy specimens may contain modest large myelinated fiber loss. There is no valid experimental animal model.¹⁶

Disulfiram

Disulfiram (Antabuse), an inhibitor of the enzymes acetaldehyde dehydrogenase and dopamine beta-hydroxylase, is used as aversion therapy in motivated alcoholics; it has also been suggested as possible therapy for cocaine addiction. The disulfiram-ethanol reaction can be severe and even fatal. Independent of this reaction, disulfiram has significant CNS and PNS toxicity, principally an axonal sensorimotor neuropathy.¹⁷ Most instances of neuropathy occur at standard therapeutic doses (250–500 mg daily) and commence within several months of starting treatment; one report describes an onset after 30 years of treatment with 250 mg daily. Tingling paresthesias in the feet, followed shortly by unsteady gait, are the initial complaints. Signs of diminished pain, temperature, and position sense in the feet, absent reflexes, and weakness of foot dorsiflexion are present in most cases.^{18,19} Eventually, the distal upper extremities are involved. Cranial nerve palsies are not a feature of the neuropathy; optic neuropathy may appear independently. Drug withdrawal is followed by gradual remission of signs in most cases. Mild slowing of motor nerve conduction, diminished amplitude of sensory nerve action potentials, and electromyographic evidence of denervation in distal muscles are characteristic findings. Sural nerve biopsies have disclosed axonal degeneration with

swellings composed of intermediate neurofilaments.²⁰ It has been suggested that carbon disulfide, a metabolite of disulfiram that produces axonal swellings, is the responsible agent. An experimental animal study, which has shown vacuolation in Schwann cells and demyelination, has challenged a role of carbon disulfide in the pathogenesis of the neuropathy.²¹

Ethambutol

Ethambutol, used in combination treatment for tuberculosis, may cause a severe chiasmal optic neuropathy and mild sensory-predominant distal axonopathy. These adverse effects are commonly associated with prolonged doses exceeding 15 mg/kg/day.²² The elderly may be at greater risk for neuropathy. Numbness of the feet and fingers is customary and is usually found in concert with mild large-fiber-type sensory loss; weakness is rare. Recovery from polyneuropathy follows withdrawal; recovery from optic neuropathy is variable, especially in advanced cases.²³ Sensory nerve action potentials are depressed or absent; motor conduction studies are often unremarkable. An experimental animal study has demonstrated axonal degeneration.²⁴ The pathogenesis of ethambutol neurotoxicity is unclear; one study suggests that binding of zinc may have a role.²⁵

Ethanol

Disabling alcoholic neuropathy, once common, is now unusual in North American clinical practice. In the past, most instances of alcoholic neuropathy appeared in persons with nutritional (thiamine/multivitamin) deficiencies, and many investigators believe that alcohol causes its neurotoxicity by producing a beriberi-like illness.²⁶ Others maintain that ethanol is a direct neurotoxin; they cite a few well-documented instances and one careful clinical study suggesting that well-nourished alcoholics can develop a painful sensory distal axonopathy.^{27,28} This issue is still unresolved. Experimental animal studies in several mammalian species have failed to cause axonal compromise.²⁹ Vitamin deficiency/alcoholic neuropathy is fully discussed in Chapter 11.

Isoniazid

Isoniazid (INH) is a primary drug used to treat tuberculosis. Peripheral neuropathy of the distal axonopathy type is the most common side effect. The primary route of INH metabolism is by acetylation. Persons genetically unable to acetylate normally (slow acetylators) maintain prolonged high blood levels of INH and are more susceptible to neuropathy than rapid acetylators.³⁰ Isoniazid inhibits pyridoxal phosphokinase, and neuropathy is due to depletion of pyridoxine; it can be prevented by coadministering pyridoxine in doses ranging from 10 to 50 mg daily.³¹

The INH neuropathy is dose-dependent. Common doses (3–5 mg/kg daily) are associated with a 2% incidence of neuropathy and 6 mg/kg daily with a 17% incidence; with higher doses, the incidence increases still more. Symptoms of neuropathy may appear within 3 weeks in the last group: conventional doses cause neuropathy after 6 months. Initial symptoms are tingling and numbness, usually followed by weakness and an unsteady gait. Loss of vibration, pain, and temperature sense is usually greater than loss of position sense and deep pain. Aching cutaneous pain in the calf muscles is an especially common complaint, and often accompanies distal leg weakness and reflex loss. The neuropathy evolves gradually with continued administration: in advanced cases, patients eventually develop distal muscle atrophy, ataxia, and profound sensory loss. Recovery usually commences within weeks of drug withdrawal.³⁰ Pyridoxine administration does not affect recovery. Sural nerve biopsies and a post-mortem study feature degeneration of myelinated fibers and axonal degeneration in the distal gracile nucleus.³² Peripheral neuropathy is readily produced in rats, and its pattern closely mimics that seen in humans.³³

Metronidazole

Metronidazole, a 5-nitroimidazole compound, is used as an antimicrobial in the treatment of protozoal and anaerobic bacterial infections and in Crohn disease.³⁴ Short-term treatment for protozoal disease is rarely associated with neuropathy. Longer-term therapy in excess of

1 g of cumulative therapy for anaerobic bacterial infections, and especially for Crohn disease, may cause a large-fiber sensory neuropathy of the distal axonopathy type. Paresthesias of the feet and later of the hands are characteristic.³⁵ These complaints are accompanied by findings of stocking-glove sensory loss of all modalities, diminished ankle jerks, and normal strength. Nerve conduction studies reveal diminished amplitude of sensory nerve action potentials and normal motor nerve conduction.³⁶ Sural nerve biopsy shows moderate axonal degeneration. The neuropathy in most instances is mild, and recovery is satisfactory. The mechanism of the neuropathy is unclear.

Misonidazole

Misonidazole, a 2-nitroimidazole, is used as a radiation sensitizer in the treatment of radiation-resistant neoplasms. Neurotoxicity includes dose-limiting, predominantly sensory polyneuropathy and, at high doses, encephalopathy.³⁷ The incidence of neuropathy correlates with the total dose; it is frequent at doses exceeding 18 g, and 39% of recipients of 11 g developed neuropathy. Clinical features are those of a predominantly sensory polyneuropathy affecting the legs more than the arms. Pain is common. There is a distal loss of touch, pain, vibration, and position sense to varying degrees, with preserved tendon reflexes. Improvement is gradual and takes months. Nerve conduction studies are compatible with a distal axonopathy, and sural nerve biopsies show axonal degeneration.^{38,39} Experimental animal studies in rats have produced distal axonal degeneration and multifocal necrotic changes in brainstem and cerebellar nuclei resembling those found in thiamine deficiency.⁴⁰ Coadministration of thiamine does not prevent neuropathy in rats or humans.

Nitrous Oxide

Nitrous oxide (NO) is an inorganic gas used as an anesthetic for brief procedures and as a propellant in food dispensers. Repeated self-administration abuse inactivates cobalamin and causes a myeloneuropathy syndrome similar to that in vitamin B₁₂ deficiency.⁴¹ Rarely, persons with subclinical vitamin B₁₂ deficiency have developed myeloneuropathy following NO general anesthesia. Most studies of abusers suggest a

strong dose–effect relationship. Inhalation daily of 100–200 cartridges for 3 months causes a mild myeloneuropathy syndrome, which worsens with continued abuse. Six months of this regimen results in disabling lower limb ataxia. Initial symptoms are acral paresthesia, unsteady gait, and the Lhermitte sign. Subsequently, hand clumsiness, leg weakness, and bladder dysfunction appear. Early signs are diminished proprioception and vibration sense in the distal lower limbs. Later, there is a mixture of upper and lower motor neuron signs (Babinski signs, hypo- and hyperreflexia) and severe lower limb sensory ataxia.⁴² Improvement follows withdrawal; in severe cases, there may be permanent position sense loss in the legs. Serum vitamin B₁₂ levels are usually normal since nutrition and absorption are unimpaired in the abusers. Treatment consists of abstinence from abuse; treatment with vitamin B₁₂ is often given but likely is of little help if abuse continues. Electrophysiologic studies are consistent with an axonal neuropathy. Spinal magnetic resonance imaging (MRI) may show increased signal intensity in the posterior columns. There are no human postmortem studies. Experimental studies in monkeys have convincingly demonstrated a vacuolar myelopathy in the spinal cord similar to that caused by human vitamin B₁₂ deficiency.⁴³ Nitrous oxide oxidizes the monovalent cobalt moiety of cobalamin (vitamin B₁₂) to an inactive trivalent state. This causes a reduction in cobalamin-dependent enzyme activity (methionine synthetase) in humans and in experimental animals.⁴⁴

Nucleoside Analogues

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) are an essential component of retroviral therapy. Three analogues—zalcitabine, didanosine, and stavudine—are used in treating human immunodeficiency virus (HIV) infection. Peripheral neuropathy is associated with each; zalcitabine (ddC) was the first NRTI used, and most studies have focused on its neurotoxic profile.⁴⁵ This analogue causes a painful sensory neuropathy that can be dose-limiting. Neuropathy is evident after 2 months in all HIV-positive patients taking the highest dose: 0.06 mg/kg every 4 hours for up to 12 weeks. The presenting symptom is abrupt onset of burning or shooting pain in the feet; discomfort

is extreme in some instances. Paresthesias and numbness of the feet follow, often accompanied by muscle cramps. On examination, there is symmetric loss of temperature and touch sensation in the feet, with relatively preserved vibration and strength. Most patients lose their ankle jerks, but other tendon reflexes remain intact. The incidence of neuropathy is less when the dose is lowered to its current level of 0.005 mg/kg. Significant recovery, after a period of coasting, occurs in 75% of patients receiving the highest dose.⁴⁶ Recovery helps distinguish nucleoside neuropathy from the painful neuropathy associated with HIV infection. Nerve conduction studies in persons receiving the highest dose reveal absent or reduced sensory amplitudes, with preservation of motor and F wave conduction. There is no satisfactory experimental animal model of nucleoside neuropathy. In vitro studies strongly support the notion that mitochondrial bioenergetic dysfunction is the fundamental mechanism of toxicity.⁴⁷

Phenytoin

Phenytoin (diphenylhydantoin) has been used as an anticonvulsant since 1938. Potential side effects are many and include, uncommonly, peripheral neuropathy. A clinical significant chronic axonal sensorimotor neuropathy or an acute reversible neuropathy may occur.⁴⁸ Slowing of nerve conduction has been associated with high blood levels, and an acute reversible sensory motor dysfunction may rarely occur within hours of administration of high-dose phenytoin.⁴⁹ More common is a subclinical, occasionally symptomatic axonal sensorimotor polyneuropathy after years of administration.⁵⁰ Subclinical patients have absent ankle reflexes with mild distal sensory loss and no weakness. Symptomatic individuals experience insidious development of distal paresthesias, unsteady gait, reduced tendon reflexes, sensory loss involving all modalities, and mild distal weakness. Gradual recovery follows withdrawal. Studies of asymptomatic adults and children receiving chronic phenytoin show mild effects on sensory amplitudes; symptomatic persons display characteristic features of a distal axonopathy.⁵¹ A sural nerve biopsy on a symptomatic person with 30 years of treatment displayed loss of large myelinated fibers and diminished axonal caliber.⁵¹ Experimental animals with high serum levels

develop slow conduction and reduced motor amplitudes within hours. The mechanism of phenytoin neuropathy is unknown.

Platinum (Cisplatin and Oxaliplatin)

Three platinum compounds are widely used as DNA-damaging agents in the treatment of a wide range of cancers. Cisplatin is a first-line drug for testicular cancer, and is used as adjunctive therapy for non-small cell lung cancer and some gastrointestinal tumors. Carboplatin is a first-line drug for ovarian cancer and an adjunct in metastatic non-small cell lung cancer and breast cancers. Oxaliplatin is a first-line treatment for colon cancer. Progressive, large-fiber, sensory distal axonopathy and sensory neuronopathy are associated with their use.⁵² The dorsal root ganglion cell is held to be the primary target of its action. The Lhermitte sign often heralds sensory symptoms in the distal extremities. Neuropathy is dose-limiting for many patients and may appear following cumulative doses of 250–600 mg/m². Local mononeuropathy and lumbar plexopathy can follow femoral intra-arterial administration of cisplatin.

Oxaliplatin produces an additional type of acute neurotoxicity characterized by cold-induced paresthesias, muscle tightness, and cramps, beginning during or soon after an infusion and resolving within about a week. These features of peripheral nerve hyperexcitability are associated electrophysiologically with repetitive compound muscle action potentials (CMAPs) and neuromyotonic discharges; they likely reflect transient axonal voltage-gated sodium channel dysfunction.^{53,54}

Initial symptoms of the sensory neuropathy are tingling and numbness in the fingers and toes with eventual spread to the more proximal limbs. Weakness is not a feature of this neuropathy. Some persons do not become symptomatic until a month or two following cessation of treatment; such delayed onset is very unusual in a toxic neuropathy, and it may be difficult to distinguish these persons from those with new-onset paraneoplastic sensory neuropathies. Examination of patients with cisplatin neuropathy reveals marked diminution or loss of vibration sense and severe impairment of position sense that may eventuate in pseudoathetosis in the upper limbs. Thermal and

touch sensation are only moderately impaired; strength is normal, but persons may feel weak because of impaired coordination of fine finger movements. Patients with paraneoplastic conditions, in contrast, generally experience discomfort and have equal impairment of all sensory modalities. As with many toxic axonopathies, symptoms of cisplatin axonopathy may progress for up to 8 weeks following removal from exposure before recovery commences. Most patients improve significantly if the medication is stopped at an early stage; recovery is less complete in those who develop pseudoathetosis.⁵⁵

Sensory nerve conduction velocity is not markedly altered; however, there are diminished sensory amplitudes and delayed sensory latencies. Abnormal lower limb somatosensory evoked potentials may appear early; motor conduction is near normal. Axonal loss is described in sural nerve biopsies and in the dorsal columns of the spinal cord at postmortem examination.

There is no robust experimental animal model of cisplatin neuropathy. Neuronal tissue culture studies have convincingly demonstrated apoptotic changes following cisplatin administration, indicating the DNA of dorsal root ganglion cytons as a primary site of dysfunction.⁵⁶ These cells are likely vulnerable because their fenestrated capillaries constitute a deficiency in the blood-nerve barrier.

Pyridoxine

Pyridoxine, an essential water-soluble vitamin (B_6), is a coenzyme for many decarboxylation and transamination reactions. The recommended human daily requirement of pyridoxine is 2.5 mg. Malnourished individuals, pregnant women, and persons taking INH are given 10–50 mg daily. An acute, diffuse, irreversible sensory neuronopathy syndrome follows massive intravenous administration, while a gradually progressive sensory distal axonopathy is associated with prolonged consumption of lower doses.

Acute sensory neuronopathy is described in two individuals receiving 180 g of pyridoxine intravenously over a period of 3 days as treatment for mushroom poisoning. One week following the injection, they experienced the onset of diffuse paresthesias and appendicular

ataxia. Progressive whole-body sensory loss, incapacitating four-limb ataxia, and autonomic dysfunction steadily developed. Strength was only slightly and transiently diminished. Nerve conduction studies disclosed absent sensory potentials and mildly diminished motor potentials of uncertain significance. Recovery from autonomic dysfunction was good; however, the patients remain disabled from upper limb sensory ataxia, and neither one can walk.⁵⁷

Gradually progressive, reversible sensory neuropathy is associated with oral consumption of high doses of pyridoxine (200 mg to 10 g daily), usually as part of a self-administration regimen for the premenstrual syndrome. The onset of symptoms and the course of the illness have been remarkably stereotyped; both are closely related to the dose and the duration of treatment. Levels of less than 1 g daily usually elicit symptoms after a year or longer, higher levels within months of commencement. Unsteady gait and numb feet herald the illness; most patients initially report the inability to wear high-heeled shoes. Numbness of the hands and impaired finger dexterity follow within months. All cases result in a stocking-glove distribution of sensory loss; large-fiber modalities appear to be especially affected, and strength is preserved. Distal limb tendon reflexes are absent. A study of deliberate, controlled administration to normal volunteers has demonstrated that subtle elevations in acral sensory thresholds precede symptoms. Nerve conduction studies indicate profoundly diminished sensory amplitudes and normal motor conduction and amplitudes. Sural nerve biopsy reveals widespread nonspecific axonal degeneration of myelinated fibers. The neurologic disability gradually improves following withdrawal; the patients examined after a prolonged follow-up period make a satisfactory recovery.⁵⁸

Both the acute neuronopathy and the chronic axonopathy syndromes are readily reproduced in experimental animals. Dogs, rats, and guinea pigs develop an acute sensory neuronopathy syndrome characterized by sensory limb ataxia days after administration of massive doses. Necrosis of dorsal root ganglion cells is accompanied by centrifugal axonal atrophy and degeneration of peripheral and central sensory fibers. Lower doses, chronically administered, have little effect on ganglion cell morphology but produce distal

axonal atrophy and degeneration.⁵⁹ The pathogenesis and biochemical basis of pyridoxine neurotoxicity are unknown. The purely sensory syndrome following megadoses may reflect the anatomic vulnerability of the dorsal root ganglion cells. A study of the spatiotemporal pattern of degeneration in rats dosed with 1200 mg/kg per day showed that accumulation of vesicular structures, mitochondria, and dense bodies appeared in the nodal and distal paranodal axons of large myelinated fibers in the L6 rat dorsal root ganglia on the second day; this preceded degeneration of both peripheral and central projections.⁶⁰ It is suggested that the accumulation of vesicular structures reflects a blockade of fast axonal transport in the proximal axon and cell body that caused degeneration of its projections. Several studies have convincingly demonstrated neurotrophic factor protection by neurotrophin-2 (NT-3) in rats given large doses (800 mg/kg for 8 days) of pyridoxine.⁶¹

Suramin

Suramin is a polysulphonated naphthylurea used for decades as an antiparasitic agent for the treatment of African trypanosomiasis and onchocerciasis. It was subsequently found to have efficacy in treating refractory prostate, ovarian, and renal carcinomas and non-Hodgkin lymphoma. Its use has been limited by myelosuppression and neurotoxicity.

Suramin, in antineoplastic doses much higher than those used for parasitic infections, has the unusual ability to cause either an axonal or a demyelinating neuropathy with distinctly different clinical profiles.⁶²

An acute or subacute demyelinating neuropathy appears in about 10% of patients soon after high-level infusions; it progresses for about 6 weeks and gradually improves. Distal paresthesias are followed by weakness, which may be profound, involve the bulbar musculature, and require ventilatory support. Like the Guillain-Barré syndrome, suramin demyelinating neuropathy is also associated with elevated cerebrospinal fluid (CSF) protein, slowed nerve conduction, and lymphocytic infiltration of nerves. Early treatment with plasma exchange is associated with improved recovery.⁶³

A moderate distal axonopathy is also associated with high-level suramin treatment.

This neuropathy is usually characterized by distal, length-dependent paresthesias, pin and vibratory sense impairment, mild extensor toe weakness, and absent ankle tendon reflexes. A few persons, who received exceptionally high doses, have developed markedly impaired position sense and severe gait ataxia and weakness. Physiologic changes in mild cases include reduced sensory and motor nerve amplitudes with relatively preserved conduction velocities. Most patients make a gradual satisfactory recovery after drug withdrawal; some severely involved patients are left with a disabling impairment of gait.⁶⁴

The demyelinating neuropathy is suggested to have an immune pathogenesis, but the mechanism is unclear. Rats given large doses of suramin develop an axonal neuropathy with accumulation of glycolipid lysosomal inclusions in dorsal root ganglion neurons and Schwann cells. Suramin is associated with inhibition of lysosomal enzymes involved in degradation of sphingolipids and mucopolysaccharides. This has been suggested as a possible mechanism for the axonopathy.⁶⁵

Tacrolimus

Tacrolimus (FK 506) is a macrolide antibiotic used as an immunosuppressant to prevent rejection following solid organ transplants. Serious CNS toxicity is common; it includes seizures, encephalopathy, tremor, and a posterior leukoencephalopathy syndrome. Demyelinating peripheral neuropathy is rare, with only three cases detected in one series of 1000 transplant recipients. Asymmetric sensory and motor dysfunction appeared within 10 weeks of treatment; paresthesias appeared first, followed by diffuse weakness and tendon reflex loss. The CSF protein was elevated (89–131 mg/dL). All three patients recovered slowly following immunoglobulin or plasma exchange treatments.⁶⁶ Another report describes a similar case commencing 2 months after treatment, with gradual improvement following withdrawal.⁶⁷ A third report concerned two patients with rapid onset of quadriparesis, which resolved following drug withdrawal. The quadriparesis was attributed to axonal dysfunction because nerve conduction studies showed low-amplitude motor responses.⁶⁸ However, the clinical course and limited data do not allow a clear assessment of

the pathophysiology, which may reflect demyelination at very proximal or distal nerve segments, or effects at axonal channels or neuromuscular junctions. The mechanism of tacrolimus demyelinating neuropathy is unknown.

Taxanes

The taxanes, paclitaxel and docetaxel, are novel antineoplastic agents used to treat several solid tumors; both cause an axonal sensorimotor polyneuropathy. Taxanes bind to tubulin; both paclitaxel and docetaxel promote polymerization and inhibit disassembly of microtubules. This causes cellular dysfunction with inhibition of mitosis and intracellular transport. Neuropathy is most likely caused by disruption of axonal transport.

Taxane neuropathy is dose-dependent, occurring with higher cumulative doses and higher doses per cycle. The frequency varies, yet more than half of the patients develop dose-limiting neuropathy when receiving more than 200 mg/m²; some experience mild symptoms at lower doses. The range for docetaxel is larger; some patients experience symptoms at doses of 60 mg/m². Persons with diabetes, another preexisting neuropathy, or prior treatment with cisplatin are especially vulnerable.⁶⁹ Symptoms often begin within 1 to 3 days of receiving a single large dose and progress after each subsequent treatment. Paresthesias and burning dysesthesias of the feet are initial symptoms, and the hands are involved soon afterward. Rarely, perioral and lingual paresthesias develop. Transient myalgias are common, but significant distal weakness is present usually only at high doses. Rarely, proximal weakness appears, suggesting a myopathic process. Some patients experience the Lhermitte phenomenon; autonomic dysfunction is rare. On examination, all acral sensory modalities (especially vibration) are found to be impaired, ankle reflexes are lost, and there is mild gait ataxia. Recovery from mild symptomatic neuropathy usually takes months following a coasting period of worsening.⁷⁰ Patients with more severe neuropathy experience considerable residual sensory and tendon reflex loss. There are no neuroprotective strategies other than dose reduction.

Electrophysiologic findings are consistent with a symmetric length-dependent distal axonopathy involving mostly sensory nerves. Electromyography (EMG) shows distal

denervation in persons with weakness.⁷¹ Sural nerve biopsies show axonal degeneration and atrophy with preferential involvement of large myelinated fibers.

There have been several in vivo and in vitro experimental studies of taxane neurotoxicity. Cultured sensory neurons show proliferation and aggregation of neurotubules; application of nerve growth factor inhibits this effect.⁷² Mice and rats develop axonal degeneration when given paclitaxel, and there is accumulation of neurotubules. An innovative in vitro study using taxane application to isolated dorsal root ganglion preparations suggests that the cells die by necrosis, not apoptosis.⁷³

Thalidomide

Thalidomide is an immunomodulating agent used in the treatment of, *inter alia*, multiple myeloma, recurrent aphthosis, and graft-versus-host disease. Sedation and sensory neuropathy are potential dose-limiting factors in thalidomide therapy. Females of childbearing age must follow strict guidelines for contraception to prevent having offspring with dysmelia.

Strong dose-effect and dose-duration relationships are unestablished for neuropathy.^{74,75} However, several recent studies suggest a convincing relationship among cumulative dose, symptoms, and electrophysiologic changes.⁷⁶ Initial symptoms are leg cramps, and tingling and numbness in the feet. Paresthesias spread up the legs and involve the hands after 2 months. All sensory modalities are impaired in a stocking-glove distribution. Tendon reflexes are affected late, and weakness, if it appears, is mild and often proximal.⁷⁷ Recovery is rapid, often with little coasting, if the drug is withdrawn soon after the onset of symptoms. The previous reports of poor recovery with long-lasting, painful paresthesias likely reflect the continuation of therapy long after the onset of neuropathy.⁷⁸

Electrodiagnostic studies show a loss or decline of sural nerve action potentials concurrent with the onset of symptoms; there are only minor motor nerve abnormalities. Nerve biopsies and one postmortem study showed Wallerian-like degenerative changes in nerves; the postmortem study also demonstrated loss of dorsal root ganglion cells and

spinal cord dorsal column fibers.⁷⁹ The pathogenesis of thalidomide neuropathy is unknown, and there is no convincing experimental animal model.

Vinca Alkaloids

Vincristine (VCR), vinblastine, vindesine, and vinorelbine are synthetic derivatives of the periwinkle plant; VCR is used extensively as a parenteral chemotherapeutic agent. Sensorimotor and autonomic neuropathies are major dose-limiting toxicities. Vincristine is often administered as one component of combination chemotherapy regimens. The other agents in the combination are selectively chosen to have little overlapping toxicity; this allows each to be given at a near-maximum dose. The maximum single dose of VCR in such regimens is 2 mg, regardless of the body area.⁸⁰

Neuropathy develops in a stereotyped manner in an unusual distribution for a distal axonopathy. Acral sensory symptoms are present by 2 months in 90% of persons receiving VCR; reduced or absent tendon reflexes are detected in all. High-dose protocols are associated with earlier onset and increased disability.⁸¹ Paresthesias herald the onset and are often appreciated in the fingers before the feet are affected. Small-fiber modalities, pin and touch, are more compromised than position and vibration. The sensory loss is usually confined to the feet and hands; progression to the knees and elbows is uncommon. Especially atypical for distal axonopathy, weakness and autonomic dysfunction are prominent and disabling features of VCR neuropathy. Leg cramps and clumsy fingers are initial motor complaints. These are followed by extensor wrist and foot dorsiflexor weakness, which can become disabling; some patients are unable to walk only 5–10 days following onset. Autonomic dysfunction (constipation, ileus, and urinary retention) often accompanies weakness. Jaw cramping is a common transient complaint following infusions. Cranial nerve palsies are rare in adults; bifacial palsies may occur in children.

Recovery generally occurs within 6 months except for extreme cases; in persons with mild or moderate disability, paresthesias abate within a month of ending treatment. Sensory and motor functions can recover rapidly if

therapy is stopped at an early stage of neuropathy. Tendon reflexes, except for the ankle jerk, eventually reappear. Despite success in experimental animal studies, at present there are no valid neuroprotective strategies.^{82–84}

Electrophysiologic studies demonstrate reduced amplitudes in sensory limb nerves commensurate with the dosage and modest decrements in conduction velocity. An EMG study of distal muscles shows evidence of denervation. Sural nerve biopsies demonstrate nonspecific axonal degenerative changes.⁸⁴

The pathogenesis of VCR neuropathy is held to stem from its inhibition of microtubules and its enhancement of their disassembly, the converse of the effect of taxanes. There is neuronal cytoskeletal damage with impaired anterograde and retrograde axonal transport. Experimental whole animal studies of VCR neuropathy have not yielded a convincing model of axonal degeneration but have displayed subtle changes in cytoskeletal architecture.⁸⁵ Focal in vivo application of VCR to axons causes both microtubular disorganization and focal accumulation of neurofilaments in ganglion cells that antedate axonal degeneration. Studies using in vitro application to segments of axons in an isolated chamber support the concept that VCR neuropathy reflects a direct effect upon the axon in addition to perturbation of cyton microtubular turnover.

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The Toxic Neuropathies: Industrial, Occupational, and Environmental Agents

PERIPHERAL NEUROTOXICITY ASSOCIATED WITH INDUSTRIAL, OCCUPATIONAL, AND ENVIRONMENTAL AGENTS

Arsenic (Inorganic)
Ethylene Oxide

Hexacarbons (n-Hexane)
Lead
Methyl Bromide
Organophosphates
Thallium

PERIPHERAL NEUROTOXICITY ASSOCIATED WITH INDUSTRIAL, OCCUPATIONAL, AND ENVIRONMENTAL AGENTS

Arsenic (Inorganic)

INTRODUCTION

Peripheral neuropathy from arsenic almost always follows ingestion or inhalation of trivalent arsenic (arsenic trioxide, arsenite). Arsenite (the +3 oxidation form of inorganic arsenic) is more toxic and tightly bound to keratin than arsenate (the +5 oxidation form).¹ Arsenic compounds are not mined as such, but arsenates occur as by-products of smelting of copper and lead ores. Inorganic arsenic compounds are usually highly charged and do not cross the blood-brain barrier readily; the inorganic salts are indefinitely stable and remain hazardous for 50 years. Transient encephalopathy occurs only

following ingestion of massive doses. Primary target organs are the gastrointestinal tract, skin, kidney, bone marrow, and peripheral nerve.

Orally ingested *organic* arsenic salts are not toxic and are widespread in the marine environment; many organisms (especially shellfish) contain large concentrations of arsenobetaine and small amounts of the less neurotoxic (arsenate) form of inorganic arsenic. Individuals consuming a diet high in seafood may display alarming elevations in urine arsenic levels.

CLINICAL FEATURES

Acute arsenic intoxication almost always causes a severe systemic illness and distal axonopathy; it is usually secondary to homicidal or suicidal attempts.^{2,3} Chronic low-level exposure produces a more subtle condition with prominent skin changes and mild anemia; often it is not associated with severe neuropathy. Although many in North America have mildly elevated

body burdens, clinically significant chronic arsenic intoxication is rare. Individuals potentially at risk include miners, smelter workers, persons with wells adjacent to mines, and inhalant drug abusers whose agents are diluted with arsenic. Arsenic trioxide, formed when treated marine wood is burned, is occasionally a source of accidental human exposure.

Acute Exposure

More than 0.5 g of an arsenic salt is sufficient to cause systemic intoxication. Manifestations appear within minutes or hours following ingestion; they include nausea, vomiting, diarrhea, confusion, delirium, and circulatory collapse. Death may occur within 24 hours. If the individual survives, manifestations of neuropathy appear within 7–10 days. Sensory symptoms appear first; usually these include numbness and intense distal limb paresthesias. Weakness in the lower limbs soon follows and may involve the upper extremities as well; in severe cases, respiratory muscles are involved. Tendon reflexes are diminished or absent.

Neuropathy has a subacute progression, sometimes for as long as 6 weeks, and the degree of impairment varies considerably. Stabilization usually is apparent after 1–2 months and is followed by a very prolonged, gradual recovery, which may be incomplete. Impairment of position and vibration senses may be profound in these persons, and those with profound atrophy may be permanently disabled.

Differential diagnosis based on the history may be surprisingly difficult if homicidal and suicidal persons are unwilling or unable to volunteer information. Other subacute-onset neuropathic possibilities associated with gastrointestinal symptoms are Guillain-Barré syndrome (GBS), thallium intoxication, and acute intermittent porphyria. Guillain-Barré syndrome may be suggested by electrodiagnostic studies that reflect a degree of proximal demyelination in this distal axonopathy.⁴ Anemia, hyperpigmentation, hyperkeratosis, and white nail striations (Mees lines) are not prominent early features of acute exposures (Fig. 17–1). As they do not appear for 1–2 months, they are usually of little help in the early stages. Mees lines, although characteristic, are not pathognomonic; they occur following thallium intoxication and with some chemotherapeutic agents. Diagnosis depends upon demonstration of excessive arsenic exposure (see Laboratory Studies).

Chronic Exposure

Chronic contact with inorganic arsenic, sufficient to cause symptomatic peripheral neuropathy, is rare in North America. There are no convincing reports of symptomatic disease in the United States or Canada. One study of smelter workers describes electrophysiologic changes as the sole evidence of dysfunction.⁵ In the authors' experience of two homicidal cases, low-level exposure produces a consistent chronologic



Figure 17–1. Mees lines in the fingernails of a patient with arsenic intoxication following a single acute exposure. Reproduced with permission from Albers, J.W. & Bromberg, M.B. (1992). Neuromuscular emergencies. In G.R. Schwartz (Ed.), *Principles and Practice of Emergency Medicine* (3rd ed.), p. 1564, Philadelphia: Lippincott Williams & Wilkins, 1992.

triad of conditions. The initial phase is characterized by malaise, loss of appetite, and vomiting. Hyperkeratosis, darkened skin, and Mees lines follow this stage. Eventually, mild distal lower limb paresthesias and numbness commence; diminished vibration and position senses dominate the neuropathic profile and may produce a tabetic gait. Continued exposure may result in severe distal stocking-glove sensorimotor neuropathy. Recovery was good in the mild case and less satisfactory in the case with severe involvement.

LABORATORY STUDIES

Body Burden

A single intravenous injection of inorganic arsenic is excreted slowly in the urine in a three-phase manner; the half-times are 2 hours, 8 hours, and 8 days.¹ Urine levels may be elevated for weeks following a massive acute exposure. Arsenic is rapidly cleared from the blood, and levels are of little clinical diagnostic use. The urine arsenic level should not exceed 25 µg/24 h in unexposed individuals. In the author's (HHS) experience, values as frighteningly high as 100–2000 µg are occasionally encountered in persons with no extraneural systemic symptoms. This usually reflects excretion of nontoxic organic arsenobetaine from seafood consumption (usually 100–200 µg) or other exotic sources. Reference laboratories can, in a series of expensive analyses, distinguish between the two forms. If high-level seafood consumption is suspected, the urine level can be retested after a month's abstinence. Hair and nail levels may provide evidence of past exposure, as trivalent arsenic is tightly bound to keratin. *Since prolonged low-level exposures rarely cause clinically significant neuropathy in North America, indiscriminate screening of urine is inappropriate in persons with a chronic progressive neuropathy unless there is strong suspicion of a source.*

Electrodiagnostic Studies

These studies usually indicate an axonal neuropathy with very depressed sensory and motor amplitudes and denervation in distal limbs on electromyography (EMG).^{2,3} Occasionally, a study performed early in the acute illness suggests proximal slowing and even conduction

block. This may reflect proximal demyelination and can further confound differentiation from GBS. In subsequent studies, such individuals display an electrodiagnostic profile compatible with an axonopathy.

A moderate elevation of cerebrospinal fluid (CSF) protein (<100 mg/dL) without pleocytosis may be present in acute cases; on occasion, the protein level is even higher.

PATHOLOGY

Axonal degeneration is the predominant change in nerve biopsy specimens from patients with arsenic neuropathy, and there is mild segmental demyelination; clusters of small regenerating axons are present in biopsy specimens from recovering individuals.^{2,3} One autopsy report of a severe case of neuropathy, utilizing limited histologic techniques, describes changes in peripheral nerves and in the dorsal columns of the spinal cord.⁶ Taken in concert with the clinical and electrophysiologic changes, the pathologic material indicates that inorganic arsenic produces distal axonopathy. Unfortunately, there is no valid animal model of inorganic arsenic neurotoxicity, and the nature and distribution of axonal changes remain to be elucidated.

PATHOGENESIS

The pathogenesis of arsenic neuropathy is unknown. It is suggested that arsenic, by linking to sulfhydryl-containing proteins, can disrupt or uncouple oxidative phosphorylation. Pentavalent arsenic (arsenate), the less toxic inorganic form found in shellfish, does not bind to thiol groups. Specifically, arsenic may act on the lipoic acid component of the pyruvate dehydrogenase complex, inhibiting the conversion of pyruvate to acetyl coenzyme A. The affinity of arsenic trioxide for keratin of hair and nail is attributed to similar thiol binding. British Anti Lewisite (BAL), an antidote, is dimercaptopropanol (a dithiol), which forms a nontoxic stable ring with arsenic and is then excreted.

TREATMENT, COURSE, AND PROGNOSIS

Treatment regimens include removal of the patient from exposure, maintaining circulatory

and renal function, increasing excretion, and preventing tissue binding. Chelation therapy with BAL is advocated for the acute form. If it is to have any effect, it should be commenced early. Chelation therapy appears unhelpful once the neuropathy is well established, probably because the metal binds so tightly to the target tissues. In the past, BAL, which must be given parenterally and has many side effects, was the agent of choice. Penicillamine has also been employed. Recently, a newer orally administered dithiol 2,3-dimercaptosuccinic acid, has been advocated for subacute and chronic cases.⁷ Since the acute neuropathy may progress for some time after commencement, there is a theoretical rationale for continued treatment in such instances. The prognosis is good in persons with only a mild stocking-glove sensory loss. In severe cases, recovery commences slowly; once progression ceases, it is often incomplete.

Ethylene Oxide

Ethylene oxide (EtO) is a gas widely used in industry. It is especially useful in sterilizing biomedical materials that cannot withstand heat sterilization. Most hospital sterilizing facilities now use a totally enclosed EtO delivery system with postdelivery fresh air purges to minimize human exposure. Several reports describe distal symmetric polyneuropathy in persons and experimental animals chronically exposed, by inhalation, to varying levels of EtO.⁸⁻¹³ One study of operating room nurses claims that they developed focal hand sensory neuropathy from wearing gowns whose cuffs contained high levels of EtO.¹⁴ It is also suggested that residual EtO in dialysis tubing may contribute to the peripheral neuropathy in patients on long-term hemodialysis.¹⁵

In the inhalation cases, symptoms of distal extremity numbness and weakness are accompanied by evidence of diminished sensation in the feet and hands. Tendon reflexes are diminished throughout, and ankle jerks are absent. Motor and sensory nerve conduction velocities are mildly diminished. Encephalopathic symptoms may accompany the peripheral neuropathy.¹⁶ Sural nerve biopsy reveals evidence of nonspecific axonal degeneration. There are no postmortem reports of individuals with EtO

intoxication. Gradual recovery commences within 2 months of withdrawal from exposure. Experimental animals chronically exposed to 250 ppm develop widespread sensory nerve fiber degeneration in the distribution of a length-dependent distal axonopathy.¹⁷

Hexacarbons (*n*-Hexane)

n-Hexane is widely used as an inexpensive solvent and is a component of lacquers, glues, glue thinners, and gasoline. Worldwide human neurologic disease was initially associated with occupational exposure and subsequently was encountered in persons who deliberately inhaled vapors containing *n*-hexane (glue sniffers).^{18,19} Methyl *n*-butyl ketone (MnBK), also metabolized to 2,5-hexanedione (2,5-HD), has a greater neurotoxic potential than *n*-hexane; it was enjoying increasing use as a solvent until it was implicated in the 1973 outbreak of peripheral neuropathy in Ohio. Methyl ethyl ketone (MEK) and methyl isobutyl ketone are also present in some neurotoxic solvent mixtures containing *n*-hexane, and they can cause central nervous system dysfunction. Although some reports of human neuropathy have identified them as causative agents, these solvents do not cause neuropathy in experimental animals, but they may accelerate the development of neurotoxicity in persons and experimental animals exposed to *n*-hexane.²⁰

Both males and females are affected, and the age of onset ranges from adolescence to late middle age. Individuals in different countries have been exposed to a wide variety of solvent mixtures and, in many instances, the contents and methods of chemical analysis are poorly described. The quality of the documentation of neurologic, clinical, electrophysiologic, and laboratory data varies considerably, and long-term follow-up examinations are few.

The most common initial complaint, both in industrial cases and among glue sniffers, is an insidious onset of numbness of the toes and fingers. This type of distal sensory neuropathy is generally the only clinical illness in the least severe industrial cases. The pattern of sensory abnormality is characteristically symmetric and involves only the hands and feet, rarely extending as high as the knees. Moderate loss of touch, pain, vibration, and thermal sensation

is usually prominent and may be accompanied by loss of the Achilles tendon reflexes; the other tendon reflexes are spared. In mild cases, there is preservation of position sense and no sensory ataxia, periosteal pain, cranial nerve abnormalities, or autonomic dysfunction. In more severe industrial cases, weakness and weight loss occur, occasionally accompanied by anorexia, abdominal pain, and cramps in the lower extremities. Reflex loss is usually less than that observed in other polyneuropathies and, even in moderate to severe cases, may be confined to the Achilles tendon reflexes and finger jerks. Weakness most commonly involves the intrinsic muscles of the hands and long extensors or flexors of the digits. A common complaint in these individuals is difficulty with pinching movements, grasping objects, and stepping over curbs. Instances of pure motor neuropathy are unusual in industrial cases. Vibration and position sense are only mildly impaired, and pinprick and tactile sensory loss is usually confined to the hands and feet. As the neuropathy becomes more severe, weakness and atrophy dominate the clinical picture and extend to involve proximal limb muscles. Glue-sniffing patients may display a subacute distal to proximal progression of weakness early in the course of the disease. In a few glue sniffers, blurred vision has been a symptom, but objective evidence of visual loss has not been documented. Seizures, toxic delirium, cerebellar ataxia, tremor, or cholinergic symptoms are not described.

No predisposing conditions exist for *n*-hexane neurotoxicity, although one report describes a high incidence of polyneuropathy in older workers and slowed motor nerve conduction in "normal" individuals in factories with documented cases of solvent neuropathy. This strengthens the notion that subclinical and readily reversible *n*-hexane nerve damage may be an unrecognized industrial problem.²¹

Autonomic disturbances are reported among glue sniffers but not in industrial cases. Prominent among these disturbances is hyperhidrosis of the hands and feet, occasionally followed by anhidrosis. Blue discoloration of the hands and feet, reduced extremity temperature, and Mees lines are sometimes present. Impotence occasionally occurs among glue sniffers with moderate or severe neuropathy, but its relationship to nervous system dysfunction is unestablished.²⁰

n-Hexane causes an axonal neuropathy characterized by focal paranodal accumulations of neurofilaments in distal axons, accompanied by focal retraction of myelin at the paranodes. This paranodal demyelination likely accounts for the profound slowing of nerve conduction in many cases. This phenomenon may lead to an erroneous diagnosis of a primary demyelinating neuropathy.^{19,22}

Slow progression is the hallmark of industrial cases. In most instances, this reflects low-level, intermittent exposure. In some glue sniffers, especially those with excessive abuse, a subacute course develops, leading, in severe cases, to quadriplegia within 2 months of onset of the first symptoms. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) has been a serious diagnostic consideration in some of these patients.

A universal feature of *n*-hexane neurotoxicity is the continuous progression of disability (*coasting*) after removal from exposure. Coasting usually lasts for 1–4 months. The degree of recovery in most cases correlates directly with the intensity of the neurologic deficit. Individuals with a mild or moderate sensorimotor neuropathy usually recover completely within 10 months of cessation of exposure. Severely affected patients with industrial exposure also improve; some retain mild to moderate residual neuropathy on follow-up examination as long as 3 years after exposure. Such individuals, on occasion, display hyperactive knee jerks. This reflex change may reflect the degeneration in the corticospinal tracts accompanying the peripheral axonal degeneration.²³

Differential diagnosis of *n*-hexane neuropathy is based upon clinical signs that indicate distal axonopathy, an unusual degree of slowing of peripheral nerve conduction, and, most importantly, a history of solvent exposure. Without a clear exposure history, peripheral neuropathy from other metabolic or toxic causes can be difficult to rule out. Routine clinical laboratory tests, including CSF examination, usually yield normal results. Tests of blood and urinary levels of 2,5-HD are now commercially available and can confirm current exposure. These tests are of little use in persons with *n*-hexane neuropathy whose exposure terminated months previously. A biological exposure index for occupational

n-hexane exposure has been determined based on urinary 2,5-HD levels.

Lead

Peripheral neuropathy from inorganic lead, once common, is now very rare in North American clinical practice.²⁴ There are no reports attributing neuropathy to organic (tetraethyl) lead exposure. There is an abundance of lead in the environment, but neuropathy is now largely encountered in adults with prolonged, *high-level* industrial (smelting, battery manufacture) or unusual (lead shot, illicit whisky) encounters. Children with lead encephalopathy rarely display evidence of peripheral nerve dysfunction. Inorganic lead is a multiorgan mitochondrial toxin.²⁵ Since neuropathy only occurs subsequent to high-level exposure, persons with neuropathy almost always additionally display signs of varying levels of systemic illness such as bone marrow depression, intestinal hypo- and hypermotility, renal dysfunction, hypertension, and gout.

Symptomatic lead neuropathy has a unique pattern among the toxic neuropathies, most of which present with symptoms of sensory dysfunction. The older classic descriptions of lead neuropathy indicated that the signs and symptoms were motor, featuring striking wrist drop, were often confined to the upper limbs, and were unaccompanied by sensory complaints. Reliable contemporary case descriptions confirm the upper limb distribution; some patients present with predominant wrist drop, others with more diffuse paralysis including mild pelvic girdle weakness. Several patients have developed atrophy, and a few have become quadriplegic.^{26–29} Bulbar dysfunction and sensory loss are not features of this illness; the latter condition can help distinguish lead from alcoholic neuropathy in moonshiners. Nerve conduction studies usually have diminished compound muscle action potential (CMAP) amplitudes with near-normal motor nerve conduction velocities, and needle EMG studies feature prominent fibrillation potentials. Several case reports, with normal sensory exams, have surprisingly displayed diminished sensory nerve amplitudes. Mildly and moderately affected patients have made a gradual recovery following removal of the source and chelation therapy.

Several epidemiologic studies of workers with prolonged *low-level* exposures claim that sensory nerve conduction abnormalities and subclinical or mild sensory loss occur without weakness.^{30,31} A meticulous study of Danish lead workers has challenged this notion.²⁹

Although there is general agreement that lead toxicity reflects mitochondrial dysfunction, the pathology and pathophysiology of lead neuropathy are unclear. The nerve biopsy studies, electrophysiologic findings, denervation atrophy, and recovery all indicate that it is an axonal disorder. Experimental animal studies indicate considerable interspecies variability; guinea pigs develop a predominantly demyelinating neuropathy, and rabbits display axonal degeneration.²⁵ Earlier suggestions that the human condition is a reversible form of motor neuron disease no longer appear credible.

There are widely different theories of the pathogenesis of lead neuropathy. One is that leakage of the blood-nerve barrier causes endoneurial edema with compromise of endoneurial capillary function. Another is that the motor neuropathy results from abnormal porphyrin metabolism, and the pattern of weakness is similar to that of porphyric neuropathy.

Diagnosis depends on measurement of blood lead (5–40 µg/dL) and erythrocyte protoporphyrin (15–30 µg/dL) levels, as well as increased urinary excretion of δ -aminolevulinic acid and coproporphyrins.

Treatment consists of termination of exposure and removal of lead by chelation. Three forms of Food and Drug Administration (FDA)-approved chelation are used. Ethylenediaminetetraacetic acid (EDTA) and BAL are the older parenteral form of treatment. They are best given by persons experienced in their use, as they are associated with considerable systemic toxicity. Meso-2-3-dimercaptosuccinic acid (succimer) is a newer, safer, orally administered agent; it is gradually supplanting EDTA and BAL.

Methyl Bromide

Methyl bromide is a colorless, nonflammable gas. It is used as an insecticidal fumigant, refrigerant, and fire extinguisher, as a solvent for oil extraction from nuts, flowers, and seeds, and as an industrial methylating agent.

Intoxication is usually through the lungs, but absorption is also possible via the gastrointestinal tract and skin.

Acute intoxication initially results in mucosal irritation followed by malaise and gastrointestinal distress. Within hours there are signs and symptoms of severe central nervous system (CNS) dysfunction, including headache, dizziness, dysarthria, visual impairment, delirium or psychosis, seizures, and myoclonus. Recovery is common after low-dose exposure, but high-dose intoxication may cause coma with eventual death.³²

Chronic high-level exposure may result in a syndrome characterized by dysfunction of pyramidal tracts, cerebellum, and peripheral nerves, along with behavioral abnormalities. Magnetic resonance imaging (MRI) scans during the acute cerebellar syndrome show strikingly increased signal intensity on T2 and Fluid Attenuated Inversion Recovery (FLAIR) sequences in the cerebellar dentate nuclei, periaqueductal region, dorsal midbrain and pons, and inferior olives.³³

There are few detailed reports of methyl bromide peripheral neuropathy. Most describe distal, symmetric sensorimotor neuropathy developing over 3–7 months of exposure. Neuropathy is heralded by acral paresthesias and pain, followed by distal leg weakness, hand clumsiness, and gait ataxia. Findings include a stocking distribution of pain and touch loss, distal leg weakness, and tender calf muscles. The Achilles tendon reflexes are lost. The overall clinical pattern most closely suggests a distal axonopathy. Electrophysiologic studies have shown a distal, predominantly motor axonopathy. A sural nerve biopsy showed loss of predominantly large myelinated fibers. Postmortem findings in a fatal case following high-dose acute exposure demonstrated neuronal loss in dorsal root ganglia, axonal degeneration in nerve roots and proximal nerve segments, and necrosis in the mammillary bodies and cerebellar dentate nuclei.³⁴ Gradual improvement, with complete recovery in milder cases, occurs within a year after withdrawal from exposure.

The mechanism of methyl bromide neurotoxicity remains uncertain. The rapid improvement in the CNS dysfunction, reversible findings on MRI, and elevated pyruvate in one case suggest that methyl bromide causes an energy deprivation syndrome analogous to

that of Wernicke encephalopathy, Leigh disease, and misonidazole/metronidazole intoxications.³³

Organophosphates

There are over 20,000 compounds classified as organophosphates. Their physicochemical properties are varied, and they exist in solid, liquid, and gaseous forms. Almost all organophosphorus esters (OPs) cause a cholinergic response, and some cause a distal axonopathy characterized by widespread CNS and peripheral nervous system (PNS) degeneration, organophosphate-induced delayed polyneuropathy (OPIDP).³⁵

Organophosphates are most commonly used as petroleum additives, insecticides, lubricants, antioxidants, flame retardants, and plastic modifiers. Intoxication may occur due to accidental pesticide exposure from agricultural spraying. Exposure may occur in individuals mixing or applying the pesticide or through dermal exposure of those working in the fields shortly after spraying. Organophosphorus ester pesticides are now restricted to professional application and are no longer available for use by homeowners. Most OPs are quickly degraded in the environment. The majority of epidemic triorthocresyl phosphate (TOCP) intoxications have resulted from inadvertent adulteration of food, drink, or cooking oil. Prominent outbreaks occurred in the United States from drinking contaminated Jamaica ginger extract (jake leg paralysis) and in Morocco from eating food cooked in contaminated oil. Acute OP intoxication and OPIDP are now rare in North American clinical practice.

The nature and severity of the acute neurologic symptoms following OP exposure is partly dependent upon the type of OP, the degree of exposure, and the extent of absorption. A transient, clinically heterogeneous cholinergic response usually occurs following a single OP exposure. This type I syndrome includes cholinergic symptoms due to excessive muscarinic receptor stimulation, which are evident shortly after exposure. Symptoms include gastrointestinal distress, miosis, lacrimation, salivation, diarrhea, and bradycardia. Weakness is not a component of the type I syndrome. A type II or intermediate syndrome, so named because of

its temporal appearance between the early type I syndrome 12–96 hours after exposure and the later OPIDP, is due to excessive nicotinic receptor stimulation.³⁶ The type II syndrome includes fasciculations, limb and respiratory muscle weakness, tachycardia, and hypertension. Patients may be symptom free between 1 and 4 days following OP exposure before type II symptoms occur. Respiratory distress may be the initial symptom, followed by weakness of proximal limb and neck flexor muscles. Sensory function is normal, but dystonic limb posturing may be present. Respiratory and cardiac failure may occur in severe cases. Occasionally, CNS signs appear, including anxiety, confusion, blurred vision, impaired memory, tremor, convulsions, respiratory depression, and coma. Recovery usually begins at about 5–15 days; the rate depends on the type of OP, the extent of exposure, and the manner of treatment.

OPIDP is much less common than cholinergic symptoms after OP exposure but results in considerable morbidity. The underlying pathology of OPIDP is central-peripheral axonal degeneration, with clinical symptoms appearing after a latent period of 7–21 days. The OPs capable of producing OPIDP almost invariably cause the preceding cholinergic symptoms, although these may be subtle and unappreciated. There is little evidence that low-level exposures, without cholinergic signs, cause OPIDP.³⁷ Peripheral neuropathy is heralded by early muscle cramping and calf pain, along with tingling and burning sensations in the feet and occasionally in the hands. Weakness is an early and invariable finding, and established cases may have predominant motor deficits with minimal sensory complaints. Distal muscles are the earliest and most severely affected, although proximal muscles may occasionally be involved in severe cases. The Achilles reflexes are depressed or absent; more proximal reflexes may be either depressed or even increased if central nervous system dysfunction is present. Cranial nerve and autonomic function is preserved. Neuropathy progression is subacute, being fully expressed within a few days.³⁸ Symptoms and signs of CNS dysfunction may be present in severe cases and represent damage to distal ends of motor and sensory tracts within the spinal cord. Central nervous system dysfunction is usually inapparent early in the

neuropathy, as signs of peripheral nerve damage predominate. As time passes and peripheral nerves recover, signs of CNS dysfunction may emerge, including hyperreflexia, increased motor tone, and spastic gait. In its most severe expression, OPIDP includes upper and lower motor neuron involvement. A common physical finding in a 30-year follow-up study of individuals with TOCP poisoning was the combination of spastic paraparesis and distal leg atrophy. Routine clinical laboratory studies in OPIDP are usually normal. Depressed erythrocyte acetylcholine esterase (AChE) levels suggest exposure to OPs, and early severe weakness appears to be associated with AChE levels less than 20% of normal. The AChE levels provide little information on the likelihood of developing OPIDP. Because erythrocyte AChE levels regenerate at the rate of about 1% per day, patients with previous exposure may have normal levels by the time they come to medical attention. Plasma pseudocholinesterase levels have little diagnostic value. The diagnosis of OP-related neuropathy is simple if there is a clear indication of ingestion occurring about 2 weeks before the illness, including the presence of cholinergic symptoms. If such evidence is lacking, this condition becomes almost impossible to establish with certainty.

The prognosis in mildly affected individuals is usually good, with most making a nearly complete recovery. Others with a more severe initial deficit are left with varying degrees of morbidity, which include sequelae of both PNS (atrophy, claw hands, foot drop) and CNS (spasticity, ataxia) damage. In severe cases, the ultimate prognosis depends more on the degree of CNS than PNS dysfunction. There is no specific treatment once the acute cholinergic crisis has resolved.

Thallium

Thallous salts were once widely employed as depilatories, rodenticides, and pesticides. These uses are now virtually unheard of in North America, and the rare instances of thallium poisoning are homicidal or suicidal.

There are two distinct clinical syndromes associated with thallium exposure. One follows consumption of >2 g. It is an acute, fulminating illness characterized by

abdominal pain and cardiovascular collapse that is fatal within 24 hours.³⁹ The other is a more subacute condition from consumption of <1 g with systemic symptoms of vomiting, abdominal pain, and diarrhea that commence within a day. Within 5 days to 2 weeks, severe burning paresthesias begin in the legs and feet, often accompanied by intense joint pain. Sensory symptoms next appear in the hands and sometimes in the trunk. All sensory modalities are affected. Weakness is not a prominent complaint in many instances but is usually detectable on examination.⁴⁰ Tendon reflexes are usually present in the early stages, and may assist in differentiating thallium neuropathy from GBS in the rare instances where limb and cranial nerves are affected. Lethargy, coma, and cardiac, renal, and respiratory failure may develop, and death can occur within a week. Recovery is gradual, and the extent varies with the dose. The diagnosis of subacute thallium neuropathy is extraordinarily difficult unless there is clear evidence of suicidal or homicidal intent. Alopecia, the classic indication of thallium poisoning, appears 15–39 days after ingestion. This characteristic sign, therefore, is not present in the early stages of the subacute neuropathy. Hair regrowth usually begins within 10 weeks of withdrawal. Typical Mees lines may appear in the fingernails and toenails.

Electrophysiologic and nerve biopsy studies suggest that thallium neuropathy is a distal axonopathy. Nerve conduction studies are often normal in the first 2 weeks but eventually disclose diminished sensory nerve amplitudes with near-normal distal latencies and velocities. Sural nerve biopsies have shown axonal degeneration across the entire spectrum of fiber diameters. Skin biopsies in one study disclosed loss of epidermal nerves and fragmentation of dermal fibers.⁴¹ Diagnosis depends upon demonstration of elevated thallium, usually in urine, but hair or other tissues (even cremation ash) may be used.

Treatment is supportive in unstable acute cases. Activated charcoal, cathartics, and Prussian blue are all widely employed.⁴² Hemodialysis is indicated in some specific instances. Chelating agents, peritoneal dialysis, and potassium therapies have not clearly proven useful.

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Focal Neuropathies: Nerve Injuries, Entrapments, and other Mononeuropathies

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FOCAL NEUROPATHIES: CRANIAL NEUROPATHIES

Idiopathic Facial Nerve Paralysis (Bell's Palsy)

Focal neuropathies result from trauma (laceration, stretch or traction, crush or compression, friction), ischemia (small or large vessel), infiltration (neoplastic, granulomatous, inflammatory/infectious), hemorrhage, chemical neuritis from injection of toxic agents, freezing, or radiation.

NERVE INJURIES

Anatomy and Pathophysiology of Nerve Injuries

The anatomy and pathophysiology of nerve injuries are reviewed comprehensively by a number of authors.¹⁻⁵ Several factors influence the

susceptibility of nerves to injury. Supporting epineurial and perineurial tissues protect nerves from compressive and traction forces, and this explains why nerve roots, which lack these structures, are more vulnerable. Nerves are particularly at risk when passing over hard, unyielding surfaces (ulnar nerve at the medial epicondyle) or through fixed compartments (median nerve in the carpal tunnel); chronic compression syndromes at these sites are called *entrapment neuropathies*. Underlying polyneuropathies may increase the vulnerability of nerves to compression; this is generally held to be true for metabolic neuropathies, such as diabetes, and is certainly the case with hereditary neuropathy with liability to pressure palsy (HNPP). Although we do see a substantial

number of patients who happen to have concurrent radiculopathy and distal entrapment (C6 or C7 and carpal tunnel syndrome [CTS]; C8 and ulnar neuropathy), the double crush hypothesis, the notion that a proximal nerve injury predisposes to a distal lesion, perhaps by affecting axoplasmic transport, has never been established.⁶ Large myelinated fibers are preferentially affected by compression, accounting for the more pronounced weakness compared to sensory loss in many cases.⁷ Fascicular injury can be selective; the outer fibers in a fascicle may be affected more than the inner ones.⁸

Nerve compression may be acute or chronic, intermittent or progressive, and the relative contributions of mechanical and ischemic factors are debated. Entrapped nerves observed at surgery show constriction at the entrapment site, with proximal swelling due either to edema or, more commonly, to fibrous thickening. Acute injury, modeled experimentally by tourniquet application, is characterized by mechanical deformation (invagination/intussusception of myelin) at the node of Ranvier, concentrated at the cuff edges, leading first to paranodal demyelination and then to segmental demyelination.^{7,9,10} More severe or prolonged compression results in axonal degeneration. Both experimental and human autopsy studies of chronic nerve compression also point to a mechanical mechanism, although the pathologic features differ. Bulbous expansions of redundant myelin (polarized, like tadpoles swimming away from the lesion in both directions) occur in the paranodal region as an early histologic feature in the entire area of the entrapment.^{11–13} Segmental demyelination and remyelination ensue, and in severe lesions, fiber loss occurs. There is endoneurial and perineurial connective tissue thickening just above the lesion. Sunderland has championed the role of ischemia, postulating that compression impairs venous return, which leads to increased intraneural pressure, capillary damage with leakage and edema, ischemia, and subsequent axonal loss.¹ In acute compression with suprasystolic pressure, which we have all experienced when falling asleep on an extremity, ischemia is likely responsible for the rapidly reversible physiologic block.

Clinical Classification of Nerve Injuries

The classification of nerve injury proposed by Seddon in 1943 is still in common use.¹⁴ *Neurapraxia* refers to a focal myelin dysfunction resulting in conduction slowing and block, with intact axon and connective tissue structure. *Axonotmesis* refers to axonal interruption with intact connective tissue structure. In *neurotmesis*, the entire nerve is disrupted. Sunderland's classification has five degrees of nerve injury, with the first degree corresponding to neurapraxia and the fifth degree to neurotmesis; axonotmesis is subclassified by whether endoneurial tubes, perineurium, and epineurium are all intact (second degree), endoneurial tubes are disrupted (third degree), or only the epineurium is intact (fourth degree).¹ A mixed lesion with both conduction block and axon loss is probably common and has been referred to as *sixth-degree injury*.¹⁵

Electrodiagnostic Features of Nerve Injuries

The timing of needle electromyography (EMG) and nerve conduction abnormalities must be considered in evaluating nerve injuries. If present, focal slowing or conduction block across a lesion site is demonstrable immediately. With axon loss, sensory nerve action potential (SNAP) and compound muscle action potential (CMAP) amplitudes recorded distal to the lesion will be unchanged for approximately the first 3 days, then rapidly decline as Wallerian degeneration ensues, but will not reach a nadir until about 9 days for the CMAP and 11 days for the SNAP.¹⁶ Therefore, neurapraxia cannot be distinguished from axonotmesis until Wallerian degeneration is complete. Axonotmesis and neurotmesis have the same electrophysiologic profile. The first abnormality detected on needle EMG after an acute axon-loss lesion develops is reduced motor unit recruitment, and if the lesion is incomplete, remaining motor units will be firing rapidly. Fibrillation potentials on needle EMG will develop in about 1–2 weeks, with a short distal nerve stump, and up to 3–4 weeks with a long stump. In incomplete

lesions, signs of reinnervation appear from collateral sprouting starting within about 3 weeks, with increased motor unit polyphasia, amplitude, and duration. With complete axon-loss lesions, axonal reinnervation is manifest first by small, polyphasic, unstable motor units (*nascent units*) appearing initially in those muscles closest to the lesion site. Side-to-side comparison of the CMAP amplitude, after sufficient time has elapsed for Wallerian degeneration to be complete, is the best electrophysiologic measure of axonal loss in focal nerve injury and is a guide to the prognosis.

Focal slowing of conduction and conduction block are the main electrophysiologic features of entrapment neuropathies, but many are pure axon-loss in type, commonly seen with ulnar and posterior tibial (tarsal tunnel) entrapments.

Nerve Regeneration and Repair

Recovery of motor function in neurapraxic lesions involves resolution of the conduction block in areas with segmental demyelination.³ Schwann cells proliferate and remyelinate denuded internodes, which are usually shorter than normal; therefore, conduction velocity is slower than normal. This can be accomplished successfully within a few weeks but may take up to several months (usually completed within 3 months). Recovery from partial axonotmesis involves first distal sprouting of intact axons to reinnervate denervated muscle fibers. This process begins within days, with electrophysiologic correlates appearing over weeks to months. Further axonal regeneration occurs from the proximal nerve stump. Force is also enhanced by hypertrophy of functioning muscle fibers. In complete axonotmesis, recovery depends solely on axonal regeneration, which proceeds at a rate of about 1–5 mm/day, faster in proximal than in distal nerve segments and slower after nerve laceration or suture injury compared to crush injury.¹ When the endoneurial basal lamina tubes are intact to guide the regenerating axons, effective reinnervation can ensue. A shorter distance to reinnervate confers a better prognosis. Effectiveness will also depend on muscle fiber viability, which wanes after 18–24 months of the

denervated state due to atrophy and fibrosis. Neurotmetic lesions with complete transection have a poor prognosis and will not recover without surgical intervention to either appose the two ends or place a graft; neuromas may occur. Severe lesions may be associated with aberrant reinnervation. Sensory function recovers by resolution of conduction block, redistribution of intact adjacent cutaneous fibers, and, ultimately, axonal regeneration.

The complex decision making in regard to the timing and approach of surgical management of nerve injury is detailed by Sunderland¹ and reviewed by Robinson.³

FOCAL NEUROPATHIES: THE UPPER EXTREMITY

Median Nerve

ANATOMY

The median nerve arises from the C6 to T1 roots and from branches of the lateral and medial cords of the brachial plexus (Fig. 18–1; see also Color Fig. 18–1). Sensory fibers arise primarily from the C6 and C7 segments through the upper and middle trunks, while motor fibers arise from C6–T1 through all three trunks. As the median nerve descends down the medial arm, it is intimately associated with the brachial artery as well as the ulnar and radial nerves. No muscles are innervated above the elbow. At the elbow, the median nerve passes under the bicipital aponeurosis, then usually between the superficial and deep heads of the pronator teres muscle and then under the flexor digitorum superficialis (FDS) muscle. In the forearm, the median nerve innervates the pronator teres, flexor carpi radialis, palmaris longus, and flexor digitorum superficialis muscles. The anterior interosseous branch comes off the median nerve 5–8 cm distal to the lateral epicondyle, usually distal to the pronator teres, innervating the flexor pollicis longus (FPL), flexor digitorum profundus (FDP; digits 2 and 3), and pronator quadratus muscles; it has no cutaneous sensory innervation. Anomalous communication between the median (frequently the anterior interosseous nerve) and ulnar nerves in the forearm is common (Martin-Gruber anastomosis) and can be a source of clinical and

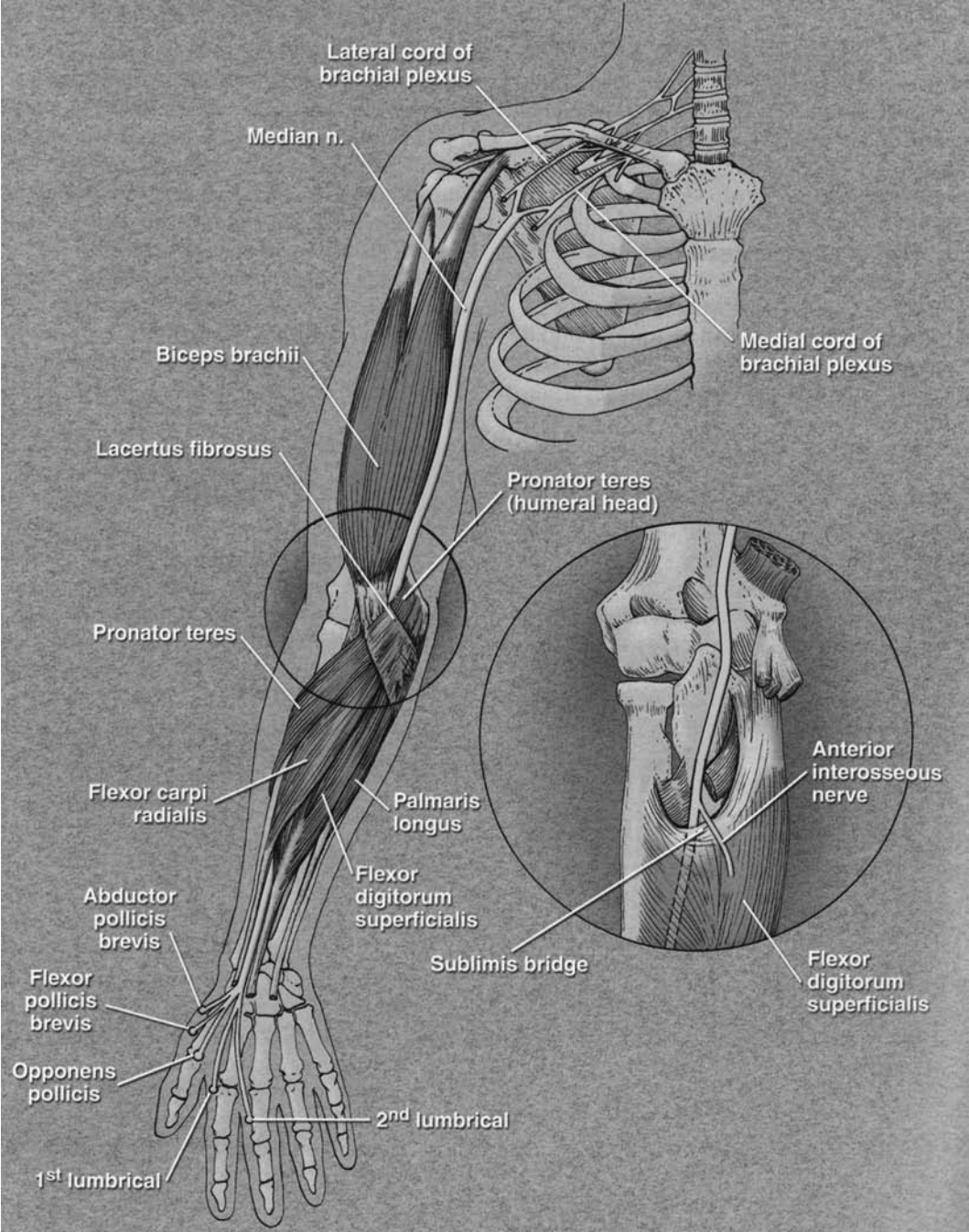


Figure 18-1. Anatomy of the median nerve. From Mendell^{16a} with permission (See Color Plate 18-1.)

electrodiagnostic confusion. Prior to entering the carpal tunnel at the wrist, the palmar cutaneous sensory branch is given off and supplies the skin over the thenar eminence (Fig. 18-2; see also Color Fig. 18-2). The carpal tunnel is

formed by the carpal bones as the floor and walls and the transverse carpal ligament (flexor retinaculum) as the roof. Within are nine flexor tendons (FPL, four FDPs, four FDSs) and the median nerve. In the hand, the recurrent

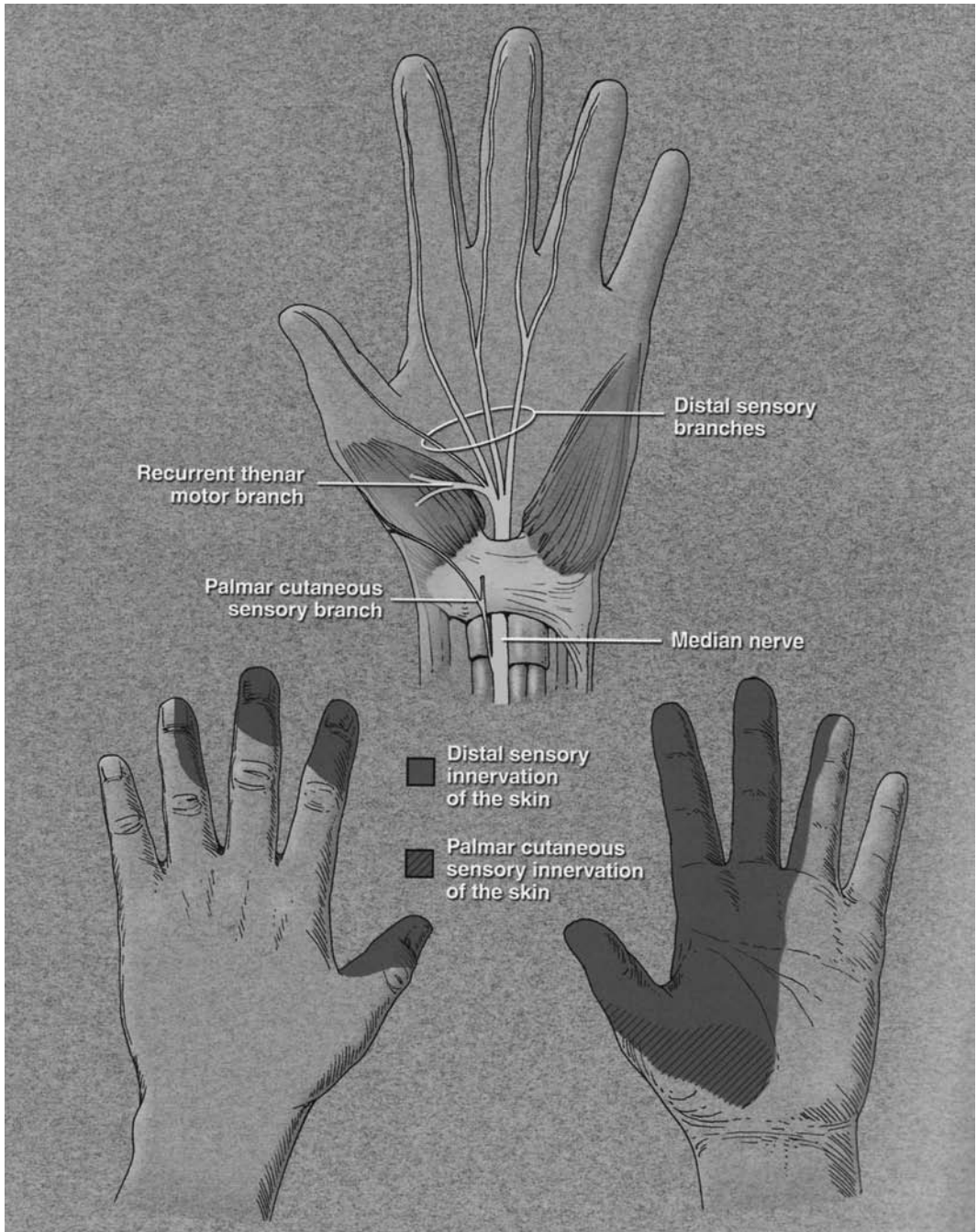


Figure 18-2. Anatomy of the median nerve in the wrist and hand, and cutaneous sensory innervation. From Mendell^{16a} with permission (See Color Plate 18-2.)

thenar motor branch supplies the abductor pollicis brevis, opponens pollicis, and superficial head of the flexor pollicis brevis muscles, and a separate branch supplies the first and second lumbricals. Sensory branches supply the palmar

and distal dorsal aspects of digits 1-3 and lateral digit 4, although there may be variations in innervation; in particular, either the median or ulnar nerve may exclusively supply digit 4. Anomalous communications

occasionally occur between the deep motor branches of the median and ulnar nerves (Riche-Cannieu anastomoses). Sudomotor and vasomotor sympathetic fibers to the skin and blood vessels accompany the median nerve into the hand.

PROXIMAL MEDIAN NEUROPATHIES

Median neuropathies in the axilla, upper arm, elbow, or forearm are uncommon (Table 18–1). The proximity to other nerves in the axilla and upper arm results in multineurite involvement in many cases. In differentiating proximal median lesions from CTS, while the distribution of sensory involvement may be similar, demonstrating sensory loss over the palmar cutaneous branch can be a helpful clue, as is involvement of median forearm flexor muscles. In an interesting anatomic study of cadavers, seven anatomic structures were encountered that may compress the median nerve between the axilla and the distal forearm: brachialis muscle, Struthers ligament, bicipital aponeurosis, pronator teres, FDS, accessory head of the flexor pollicis longus (Gantzer muscle), and vascular structures.¹⁷

The so-called *pronator syndrome* is a controversial issue as a pain syndrome attributed to median compression in the proximal

forearm, since in most such cases there are no supportive abnormalities on clinical examination or electrodiagnostic studies. The reliability of various provocative tests to elicit pain and localize median nerve compression in the forearm is uncertain. Anterior interosseous neuropathy (AIN) results in weakness of pinch, with inability to make the “O” sign due to weakness of the distal phalanx of the thumb (FPL) and index finger (FDP). While there is no cutaneous sensory loss, there may be forearm pain. Anterior interosseous neuropathy is a frequent accompaniment to immune brachial plexus neuropathy (neuralgic amyotrophy) and may be an isolated feature in some cases; other cases relate to compression. *Pseudo-AIN* may occur when more proximal median lesions affect only the AIN fascicles, which are grouped in the posterior portion of the median nerve. When partial and seemingly affecting only a single muscle such as the FPL, AIN may be confused with a tendon rupture; normal needle EMG in such cases will suggest tendon rupture.

The median SNAP amplitude may be decreased with axon-loss proximal median lesions (spared with AIN), but it does not localize the level of the lesion. Focal slowing of

Table 18–1 Proximal Median Neuropathies: Etiologies

Axilla/upper arm	Various traumatic injuries
	Compression in a stuporous state or during sleep
	Crutch palsy
	Medial brachial fascial compartment syndrome
	Brachiocephalic fistulas for hemodialysis—ischemic or compressive mechanisms
	Aneurysms
	Tumors
Elbow region	Focal demyelination (MMN, MADSAM)
	Injection injury
	Compression under ligament of Struthers/supracondylar spur
	Supracondylar fractures and elbow dislocations
	<i>Pronator syndrome</i> —compression under the bicipital aponeurosis (lacertus fibrosus), heads of pronator teres, or fibrous arch of the flexor digitorum superficialis
Forearm	Arteriovenous fistulas
	Anomalous vessels or muscles
	Compartment syndrome
	Anterior interosseous neuropathy—various anatomic anomalies may cause compression; more often forme fruste of IBPN
	Median palmar cutaneous sensory neuropathy—rare trauma or compression by anomalous muscle or ganglion

IBPN: immune brachial plexus neuropathy (neuralgic amyotrophy); MADSAM: multifocal acquired demyelinating sensory and motor neuropathy; MMN: multifocal motor neuropathy.

motor conduction or conduction block may be seen in some cases but is not common. The pattern of needle EMG involvement facilitates localization and excludes involvement of other nerves; it does not distinguish between median lesions more proximal than the pronator teres innervation since there are no other median-innervated muscles above the elbow. Motor nerve conduction studies of the anterior interosseous nerve are not well established.

CARPAL TUNNEL SYNDROME

Clinical Features

Epidemiology Carpal tunnel syndrome (CTS), the clinical syndrome related to median nerve entrapment at the wrist, is by far the most common entrapment neuropathy.^{18–20} It affects 3%–5% of adults in the United States²¹ and has a 10% lifetime risk.²² The highest incidence is between 40 and 60 years of age. The female-to-male ratio is about 2–3:1. At least half of these patients have bilateral symptoms, and approximately three-quarters have bilateral median entrapment that is demonstrable electrophysiologically.²³ The dominant hand is more frequently and severely affected. Risk factors for idiopathic CTS include female sex, increasing age, obesity, and high body mass index (BMI), small hand size and squarer wrist, prolonged, repetitive wrist flexion and extension, especially with forceful grip, and use of hand-held vibratory tools.^{19,24} Some occupations are particularly notorious in this regard (carpentry, butchering, meat packing). An association with computer use, while popularized with the lay public, has been more difficult to establish; there may be some association with mouse, not keyboard, use suggested in one study.^{25,26} In children, CTS is rare, often related to storage disorders, and rarely idiopathic.²⁷ Autosomal dominant familial cases of CTS are rarely reported.

Symptoms and Signs Symptoms begin with intermittent hand numbness, paresthesias, or pain in any combination. Nocturnal symptoms interrupting sleep or present upon awakening are characteristic, although not invariable. Symptoms are provoked by activities such as driving a car, holding a newspaper or phone, or prolonged gripping. Some patients find relief

by shaking the hand briefly (*flick sign*) or putting the arm in a dependent position. Symptoms confined to the median-innervated fingers occur in only about one-third to one-half of patients, as many perceive involvement of all the digits or sometimes the whole hand, although when asked, most say that the little finger is least involved.²⁸ Rarely, and inexplicably, some reported cases of CTS have symptoms displaced to the predominantly ulnar distribution. Occasional patients note splitting of the ring finger, but more often this is observed on examination. Most often, three or four fingers are involved, less often two fingers, very uncommonly only one finger; the middle finger tends to be most affected. About one-half of patients perceive pain and paresthesias extending proximally beyond the fingers to the wrist, forearm, and elbow, even as proximal as the shoulder. A description of pain radiating down the arm rather than up usually does not indicate CTS. Most patients feel that the symptoms are on the palmar aspect of the fingers, but about 10% say that they are more dorsal. With progression, sensory symptoms become more persistent, with perceived hand weakness or clumsiness in handling objects. Sensory examination may reveal hypesthesia or hyperesthesia in involved fingers. Weakness of the thenar muscles, along with thenar atrophy, represents more advanced median nerve compression; weakness of the abductor pollicis brevis is the most useful sign. Autonomic disturbances are common in CTS, occurring with increasing severity of electrophysiologic findings, and may include finger swelling, dry palms, Raynaud phenomenon or hand blanching/erythema, and, rarely, other trophic changes.²⁹

The wrist-flexion test (*Phalen sign*), maintained for 30–60 seconds, may reproduce or aggravate median-distribution sensory symptoms; it was elicited in 74% of Phalen's patients and is probably highly specific²⁰ (Fig. 18–3). Phalen did not find sustained wrist extension, which may also aggravate symptoms, a consistently reliable sign. A wrist-flexed position overnight may be one reason for nocturnal awakening. The *Tinel sign*, elicited by light percussion with a finger or reflex hammer over the median nerve at the wrist, was present in 73% of CTS cases described by Phalen, but we find that it is present all too often in normal, asymptomatic persons. Applying direct pressure over the median nerve at the wrist is another



Figure 18–3. The wrist-flexion test (Phalen sign).

described but seldom utilized method to reproduce symptoms. A sausage-shaped swelling, sometimes referred to as the *volar hot dog sign*, is occasionally seen on the volar aspect just proximal to the wrist, particularly in patients with rheumatoid arthritis and CTS.²⁰

Differential Diagnosis Associated tenosynovial disorders are common, including de Quervain disease, trigger finger, basal thumb joint arthritis, and lateral epicondylitis.²⁰ Disorders that cause diagnostic confusion in some cases may include myelopathies (cervical spondylotic myelopathy, multiple sclerosis plaques, vitamin B₁₂ deficiency), cervical radiculopathy (C6, C7), neurogenic thoracic outlet syndrome, polyneuropathy, proximal median neuropathies, and Raynaud phenomenon. The absence of paresthesias is rare in CTS, but when they are vague or absent and only weakness and atrophy are present, considerations may include motor neuron disease, multifocal motor neuropathy, a lesion of the recurrent thenar motor branch in the palm, or the rare congenital thenar hypoplasia. Pain alone as a symptom in the wrist or hand is always more uncertain because of the many possible etiologies, but aching in the ventral wrist and forearm is common.

Laboratory Studies

Electrodiagnostic Studies Nerve conduction studies are highly sensitive in establishing median nerve entrapment at the wrist, its severity, and its axonal versus demyelinating features. Sensory conduction is the most sensitive measure. Short segment studies across the carpal tunnel are particularly helpful, and many techniques have been described.³⁰ Motor conduction studies, in conjunction with needle EMG of the abductor pollicis brevis can establish focal motor slowing, conduction block, or axon loss involving motor fibers. Other nerves and proximal sites are typically sampled to confirm isolated involvement of the median nerve at or distal to the carpal tunnel and to exclude mimicking conditions.

While grading of severity electrophysiologically is not standardized, and not all practitioners feel it is appropriate, we find it useful. Mild median nerve entrapment is marked by prolonged sensory or mixed nerve latencies and slowed conduction velocities, with or without low-amplitude SNAPs. Prolonged distal motor latencies bring it into the moderate range. Severe median nerve entrapment includes low-amplitude or absent CMAPs and SNAPs, along with needle EMG evidence of acute and chronic denervation. The severity of

symptoms does not always correlate well with latencies. Nerve conduction studies after successful carpal tunnel release usually show improvement but often do not return to normal.

Imaging Both ultrasound and magnetic resonance imaging (MRI) can show flattening of the median nerve within the carpal tunnel and swelling proximal to the lesion site. They can also detect mass lesions and other anomalies and may be useful in evaluating failed surgery. Their accuracy and role in uncomplicated CTS, particularly in mild cases, remain to be clarified. Some studies suggest that the accuracy of ultrasonography is similar to that of EMG.³¹

Etiology, Pathology, and Pathogenesis

Identifiable etiologies include the chronic arthritides (particularly rheumatoid arthritis) with flexor tenosynovitis, infiltrative or endocrine diseases such as amyloidosis, myxedema, acromegaly and diabetes, crystal-induced synovitis (gout, pseudogout), pregnancy (presumably related to edema), infections (Lyme disease), space-occupying lesions such as tumors, ganglion cysts or bony spurs, acute or repeated trauma (following Colles fracture), arteriovenous fistulas, and anatomic variations such as muscle or ligamentous anomalies or congenitally narrow tunnels. The majority of cases, however, are idiopathic and probably due to nonspecific tenosynovitis with synovial thickening or fibrosis, as demonstrated at surgery.²⁰ Patients with HNPP frequently show median entrapment at the wrist, but screening for HNPP in idiopathic CTS is not fruitful.³² Likewise, in patients with otherwise typical CTS and no suggestion of an underlying disorder, screening blood work for diabetes, hypothyroidism, or connective tissue disease has a very low yield.³³

Treatment, Course, and Prognosis

A significant percentage (perhaps one-quarter or more) of untreated CTS will improve spontaneously by both clinical and neurophysiologic criteria.³⁴ Positive prognostic factors include short duration of symptoms and younger age; more severe initial impairment is also associated with improved odds for spontaneous improvement. If an underlying disorder is identified (e.g., rheumatoid arthritis, hypothyroidism),

specific treatment may help alleviate CTS. Acute median neuropathy at the wrist with rapid progression, usually following trauma (e.g., Colles fracture, hand/wrist contusion on a steering wheel or from an air bag deployment, hemorrhage into the carpal tunnel), requires emergent decompression before extensive damage ensues; electrophysiologic features may be more typical of conduction block and/or axon loss than of focal slowing. Pregnancy-related CTS tends to have a benign course.

Wrist splinting in a neutral position and activity modifications are often adequate in mild cases with intermittent symptoms and normal exams. About three-quarters of patients overall obtain some relief from splinting, but the long-term failure rate is high.³⁵

Controlled trials demonstrate the short-term benefit of local corticosteroid injection (~70%–77%) or low-dose, short-term oral corticosteroids;^{36–38} injection may be superior.³⁹ The response to injection may also be helpful diagnostically in some cases where the diagnosis is uncertain and may predict a response to carpal tunnel release (CTR).⁴⁰ Recurrence rates, however, are high, usually within weeks to months. Many authors recommend no more than a few local corticosteroid injections, although others report excellent tolerance without significant adverse effects even after multiple injections.³⁷ While generally safe, these injections do pose the potential danger of inadvertent direct or chemical nerve injury if misdirected, digital flexor tendon rupture, and focal adipose/subcutaneous atrophy, although these are rare.^{41,42} Carpal tunnel release results in better long-term symptomatic and electrophysiologic outcomes than local corticosteroid injection.⁴³

Patients with moderate to severe symptoms and signs of CTS, refractory symptoms despite bracing, and certainly those with clinical or electrophysiologic signs of axonal degeneration, are considered for CTR. Over ~70%–75% of patients report satisfaction with the results; 70%–90% report being free of nocturnal pain.^{42,44} Pain relief is rapid; weakness may take months to disappear. Patients with middle-grade nerve conduction abnormalities may have better results than those with either very severe or no abnormality.⁴² A workers compensation claim for CTS is associated with a poorer outcome.⁴⁵ Patients with CTS



Figure 18–4. This elderly patient first came to attention with CTS and advanced left thenar atrophy compared to the normal right thenar eminence.

and peripheral neuropathy can benefit from CTR.⁴⁶ Some practitioners may be reluctant to recommend CTR to patients with very severe CTS, including marked thenar atrophy and unelicitable sensory and motor potentials, and although they would not be expected to do as well as milder cases, a positive response is not precluded, particularly in regard to pain and nocturnal symptoms. The elderly tend to come to medical attention with more severe objective clinical and electrophysiologic CTS (Fig. 18–4).⁴⁷ Carpal tunnel release can be associated with good results in the elderly.⁴⁸

About 8% of patients report that they are worse after CTR.⁴² Adverse sequelae of CTR may include persistent symptoms (incomplete division of the transverse carpal ligament), increased or new symptoms (nerve injury, especially to the recurrent thenar branch), recurrent symptoms after initial benefit (reconstitution of the ligament or scar formation), or complex regional pain syndrome. Some “failures” are the result of misdiagnosis. Success rates for CTR are lower when decisions to perform CTR are based purely on clinical grounds, with normal electrodiagnostic studies.⁴²

There is no established evidence to support the use of nonsteroidal anti-inflammatory drugs (NSAIDs), diuretics, or vitamin B₆.^{49,50}

We observe, however, that NSAID use is widespread. Some practitioners also employ trials of neuropathic medications such as gabapentin; this symptomatic approach is just beginning to be studied. One study describes a maneuver wherein gently squeezing the distal metacarpal heads, and sometimes stretching the middle and ring fingers, relieves paresthesias.⁵¹

Ulnar Nerve

ANATOMY

The ulnar nerve derives from the C8 and T1 roots (occasionally also C7), lower trunk, and medial cord (Fig. 18–5; see also Color Fig. 18–5). It descends the proximal arm along with the brachial artery and median and radial nerves. No muscles are innervated above the elbow. It passes into the retrocondylar (ulnar) groove behind the medial epicondyle at the elbow and then (about 1.0–2.5 cm distal to the ulnar groove) under the humeroulnar arcade, the aponeurotic arch of the flexor carpi ulnaris (FCU), commonly referred to as the *cubital tunnel*. Two muscles are innervated in the proximal forearm: the FCU, whose branch

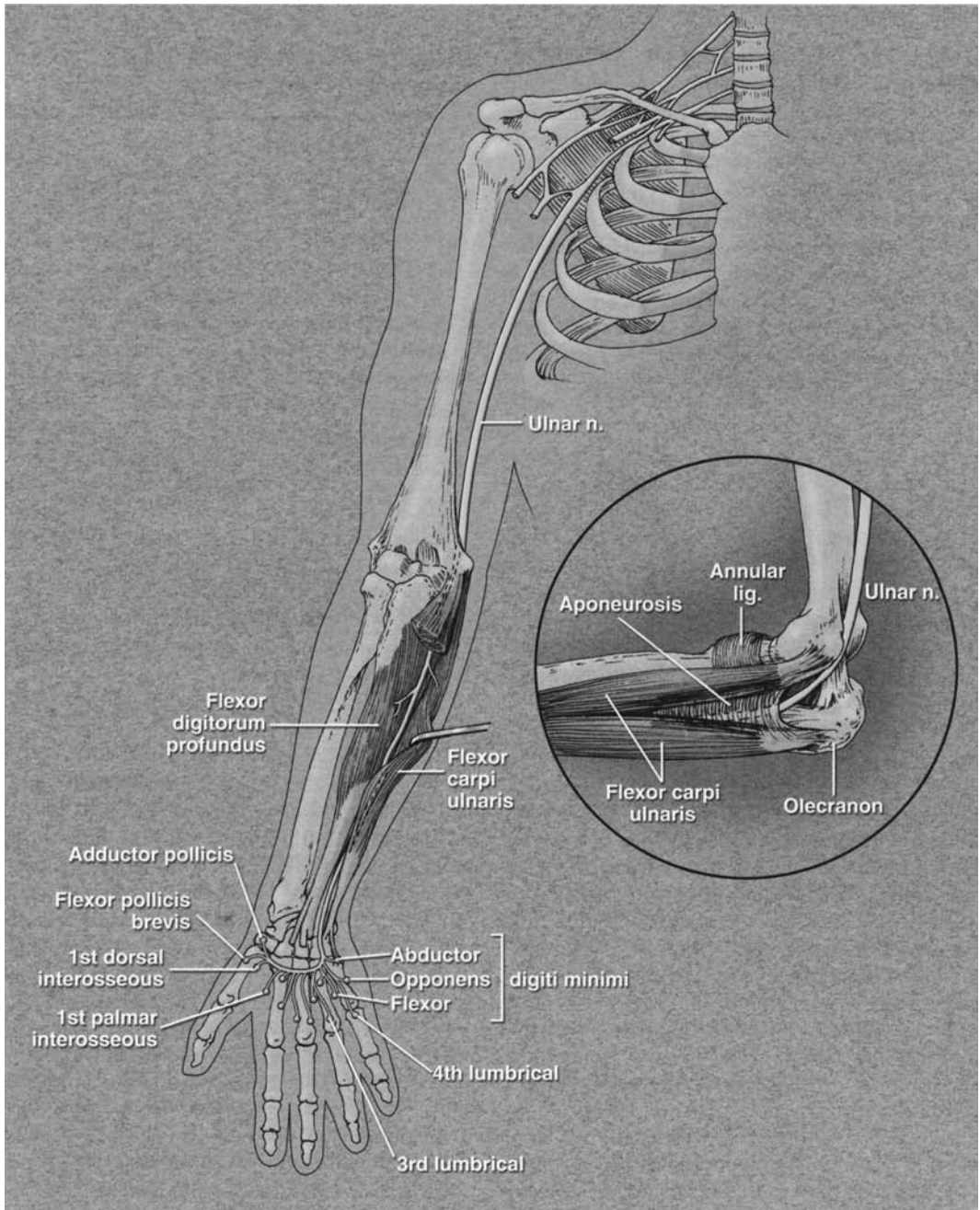


Figure 18-5. Anatomy of the ulnar nerve. The inset illustrates the retrocondylar (ulnar) groove and humeroulnar aponeurotic arcade (cubital tunnel). From Mendell^{16a} with permission (See Color Plate 18-5.)

may originate just proximal to or within the cubital tunnel, and the FDP to digits 4 and 5 (ulnar FDP) more distally. From 5 to 8 cm proximal to the wrist, the dorsal ulnar sensory branch leaves the main branch to supply the

dorsomedial hand, dorsal fifth finger, and dorsomedial fourth finger. The skin over the proximal part of the hypothenar area is supplied by the palmar cutaneous branch, which arises in the mid- to distal forearm and does not pass

through the *Guyon canal (ulnar tunnel)*. At the wrist, the ulnar nerve passes through the Guyon canal along with the ulnar artery but no tendons. The canal is formed by the hook of the hamate laterally, the pisiform bone medially, the transverse carpal and pisohamate ligaments posteriorly, and the volar carpal ligament anteriorly. Within the canal, the nerve divides into the superficial terminal branch, which supplies sensation to the fifth and medial fourth digits, and the deep palmar branch, which supplies the hypothenar muscles (abductor, opponens, and flexor digiti minimi), followed by the dorsal and ventral interossei, third and fourth lumbricals, adductor pollicis, and deep head of the flexor pollicis brevis.

PROXIMAL ULNAR NEUROPATHIES

Ulnar lesions in the axilla or upper arm are uncommon. Their etiologies are similar to those outlined above for the adjacent median nerve at those sites.

ULNAR NEUROPATHY AT THE ELBOW (UNE)

This is the second most common entrapment neuropathy. The nerve is particularly vulnerable to compression in its superficial location in the ulnar groove and under the aponeurotic arch of the cubital tunnel^{52,53} (Fig. 18-5; see also Color Fig. 18-5). Prolonged external pressure and prolonged flexion (the latter tightens the aponeurotic arch) are common mechanisms of injury. This is particularly true in anesthetized surgical, comatose, or bed- and wheelchair-bound patients. Sleeping with the elbow tightly flexed is a likely culprit in some cases. In some instances, the nerve is traumatized by repeated prolapse from the ulnar groove with elbow flexion. Compression may follow remote elbow trauma, including fractures (*tardy ulnar palsy*), or other pathology of the elbow joint such as rheumatoid synovitis and congenital bony abnormalities. Rarely, various masses may arise in this region, including the anomalous muscle anconeus epitrochlearis. Compression under the ligament of Struthers occurs but more commonly involves the median nerve. Leprosy has a predilection for the ulnar nerve. In many cases, a precipitating cause is not apparent. Many physicians use the term *cubital tunnel syndrome* to refer

to all ulnar neuropathies in the elbow region, but this should be reserved for those lesions referable to the tunnel; at least by neurophysiologic criteria using short-segment (inching) studies, many more lesions are probably at or just above the ulnar groove.⁵⁴⁻⁵⁶

Initial symptoms are usually intermittent numbness or paresthesias in the fourth and fifth digits (Fig. 18-6; see also Color Fig. 18-6). There may be pain in the medial hand or in the medial elbow radiating down the forearm. Symptoms may be aggravated by elbow flexion. Splitting of the fourth digit with involvement of the medial side is a classic sign, but often the entire fourth digit is involved; occasionally, only the fifth digit is affected or the fifth, fourth, and medial third digits. With increasing severity, intermittent sensory symptoms become persistent, and weakness and atrophy of intrinsic hand muscles ensue. Unlike CTS, it is weakness with impaired dexterity, and not sensory loss, that is the basis for disability in ulnar neuropathy. Signs may include pinky abduction due to weakness of ventral interossei resulting in the digit's getting caught when placing the hand in a pocket (*Wartenberg sign*), substitution of the flexor pollicis longus for weak thumb adduction in performing a pinch (*Froment sign*), claw deformity or *griffe* (due to weakness of ulnar lumbricals), a Tinel sign at the elbow (although this is neither very sensitive nor specific), and an area of thickening or tenderness over the course of the nerve (Fig. 18-7). Sensory loss over the dorsomedial hand places the lesion proximal to the takeoff of the dorsal ulnar cutaneous nerve and likely at the elbow, but this is often not demonstrable and cannot be relied upon. Sensory loss in the medial forearm, more than a few centimeters above the wrist, suggests involvement of the medial antebrachial cutaneous nerve and either the lower plexus or C8/T1 roots. Weakness of the FCU and ulnar FDP is helpful in suggesting that the lesion is at the elbow, but this too is often not reliably present except in severe cases; the latter muscle is more often involved.

The differential diagnosis of UNE includes ulnar neuropathy at the wrist, forearm, or proximal arm, C8/T1 radiculopathy, lower trunk or medial cord plexopathy (including neurogenic thoracic outlet syndrome), and, rarely, spinal cord or even well-placed cerebral lesions causing a *pseud-ulnar* pattern.⁵⁷ Apparent hand clawing due to finger drop has been described with lesions of the cervical cord,

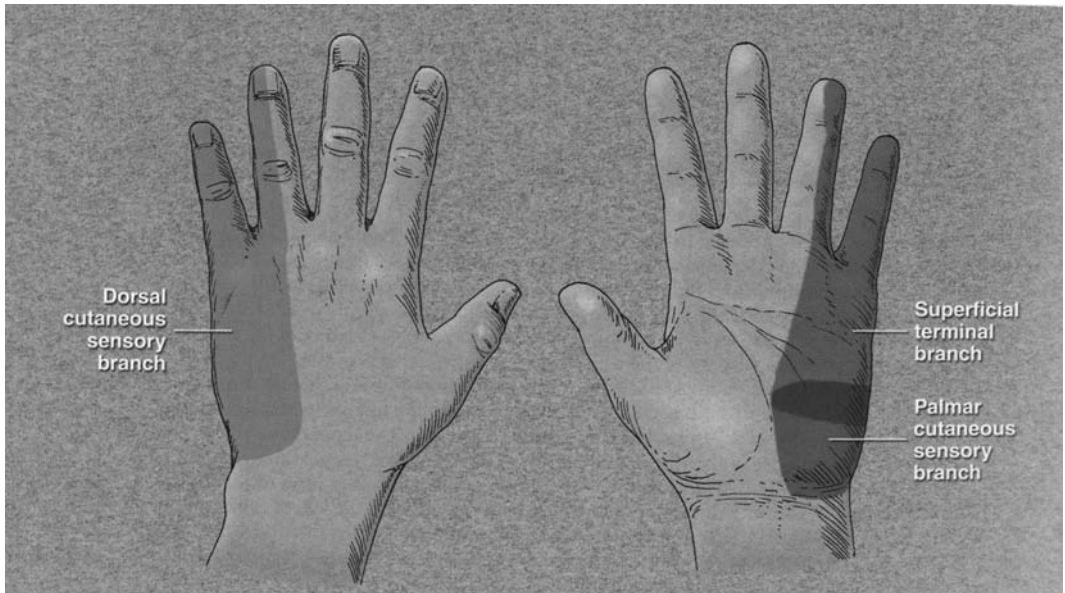


Figure 18-6. Cutaneous innervation of the ulnar nerve. From Mendell^{16a} with permission (See Color Plate 18-6.)



Figure 18-7. Ulnar neuropathy at the elbow illustrating claw-hand deformity and atrophy of dorsal interossei muscles.

lower cervical roots, radial nerve, and posterior interosseous nerve.⁵⁸

Electrodiagnostic studies are very helpful in sorting out these various localizations but, unlike CTS, are frustratingly more limited in their ability to establish an ulnar lesion and its exact location. Guidelines are provided in the American Association of Neuromuscular and Electrodiagnostic Medicine's (AANEM) practice parameters.⁵⁹ In mild cases with intermittent symptoms, the study may be normal. With focal demyelination, focal slowing of motor conduction (recording abductor digiti minimi

or first dorsal interosseous muscles), mixed or sensory conduction, or motor conduction block can be demonstrated across the elbow segment. In mild cases, a short-segment ("inching") study in 1- to 2-cm segments may be helpful.⁵⁵ In the subset of patients with UNE and conduction block, onset is usually acute to subacute and the site of conduction block is frequently proximal to the medial epicondyle.⁵⁶ Involvement of the dorsal ulnar cutaneous nerve favors a lesion at the elbow rather than at the wrist, but this nerve is not always involved in UNE. Pure axon-loss lesions involving sensory and/or motor fibers are not uncommon and are not definitively localizable. Denervation restricted to ulnar hand muscles and the FCU/ulnar FDP places the lesion at the elbow segment or above, but all too often the forearm muscles are spared with UNE, presumably related to fascicular sparing. Care must be taken regarding the technical aspects of an ulnar study, including elbow flexion at 70–90 degrees, avoiding an excessively cold elbow, and recognizing anomalous forearm anastomoses (including proximal Martin-Gruber anastomosis, which can simulate partial conduction block).^{60–62} High-resolution ultrasound and MRI may be useful adjuncts in the evaluation of UNE; ongoing studies will clarify their role in the near future.⁶³

There is little guidance on management from controlled trials. Patients with intermittent symptoms or mild, nonprogressive clinical and electrophysiologic findings are often initially managed conservatively for a few weeks to months, and many will do well.^{64,65} Conservative therapy consists of altering activities and habits to avoid direct elbow pressure and prolonged elbow flexion, as well as the use of elbow pads and nocturnal elbow splinting; some practitioners prescribe NSAIDs. Local corticosteroid injection does not appear to provide any benefit beyond splinting.⁶⁶ Careful follow-up is important, and surgical intervention is recommended before substantial axonal degeneration and weakness appear, at which point the prognosis for recovery worsens. Conduction block, indicating demyelination, is associated with a more favorable response to surgery.^{67,68} Surgical approaches include simple decompression, medial epicondylectomy, and anterior transposition (subcutaneous, intramuscular, or submuscular); the relative merits of each are debated. Intraoperative nerve conduction studies can help guide the choice of procedure.⁶⁹ Nerve transposition is more often associated with complications, including devascularization or scarring. A recent meta-analysis concluded that there is no significant difference in outcome between simple decompression and transposition (the two most commonly employed procedures) for UNE.⁷⁰

ULNAR NEUROPATHY IN THE FOREARM

Compression of the ulnar nerve in the forearm is rare but may occur in its intramuscular course in the FCU, at its point of exit from the FCU, and occasionally from compartment syndrome or tumor.⁷¹ Inflammatory or ischemic lesions at this site include multifocal motor neuropathy and ischemic monomelic neuropathy. Diabetics with severe polyneuropathy occasionally show disproportionate nerve conduction abnormalities on motor studies of this segment. A Martin-Gruber anastomosis sometimes mimics ulnar motor conduction block in the forearm.

ULNAR NEUROPATHY IN THE WRIST AND HAND

Wu et al. categorized these lesions into five types⁷² (Fig. 18–8; see also Color Fig. 18–8). Type I is most common and involves the ulnar nerve prior to its bifurcation into superficial terminal and deep palmar branches, just proximal to or within the Guyon canal. All intrinsic hand muscles are involved; sensory loss is in the fifth and medial fourth digits, sparing the dorsal and proximal ventral medial hand. Type II, in the Guyon canal, involves only the superficial terminal branch, resulting in only sensory loss. Types III to V are pure motor neuropathies involving the deep palmar branch, distal to the superficial terminal branch. Type III is proximal to the hypothenar branch, so all ulnar intrinsic hand muscles are involved. Type IV is distal to the hypothenar branch, sparing those muscles. Type V is a distal lesion involving only the first dorsal interosseous and adductor pollicis muscles.

These lesions are uncommon and can be difficult to recognize, particularly if there is no focal wrist or hand pain, swelling, mass, callus, or Tinel sign. Differential diagnostic considerations are similar to those in UNE. Symptoms, of course, overlap with those of UNE, but forearm ulnar muscles are spared, as is sensation in the medial hand, both ventrally and dorsally. Electrodiagnostic findings depend on the lesion site.⁷³ The dorsal ulnar cutaneous SNAP is always spared, and there is no denervation in ulnar forearm muscles. Proximal lesions often involve the ulnar SNAP along with prolonged distal motor latencies or reduced CMAP amplitudes and denervation in both hypothenar and first dorsal interosseous muscles. More distal lesions show severe involvement of the first dorsal interosseous muscle. The lumbrical/interosseous comparison study can be an additional helpful study in localizing ulnar dysfunction to the wrist.⁷⁴

Ulnar neuropathies at the wrist and hand may result from acute trauma. They are often the result of chronic external compression related to occupations (mechanics, pizza cutters) or hobbies (cyclists), and these will often respond to a change in activity. When no such history is apparent, a mass lesion is likely, most commonly a ganglion cyst, and surgery is required. Imaging with MRI or ultrasound is commonly employed.^{75,76} Idiopathic cases that

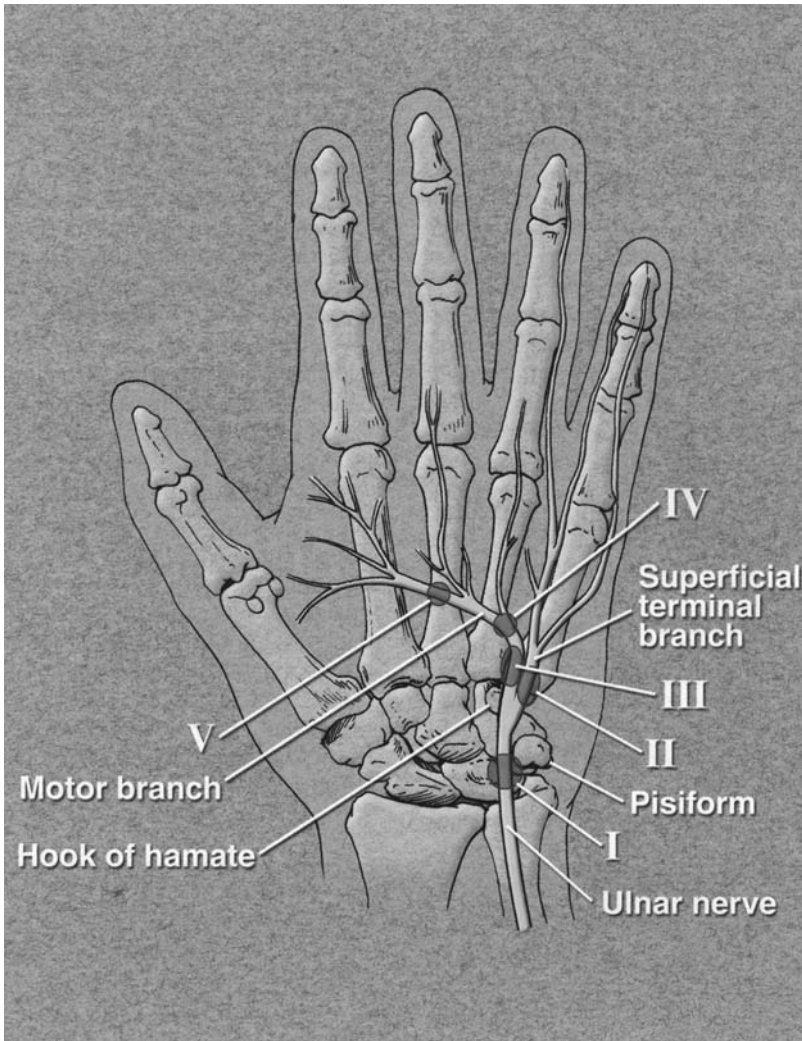


Figure 18–8. Ulnar nerve anatomy in the wrist (Guyon canal) and hand. Sites I–V depict the lesion types described in the text. From Mendell^{16a} with permission (See Color Plate 18–8.)

are severe or progressive, without a clear lesion, and traumatic lesions that do not respond to conservative therapy may need exploration.

Radial Nerve

ANATOMY

The radial nerve derives from the C5–C8 (T1) roots, all three trunks, posterior divisions, and posterior cord⁷⁷ (Fig. 18–9; see also Color Fig. 18–9). It courses along the medial side of the humerus giving off the posterior brachial and

antebrachial cutaneous nerves and branches to the triceps and anconeus muscles, then winds around the spiral groove into the distal lateral arm, where it supplies the brachioradialis (BR) and extensor carpi radialis longus/brevis (ECRL/B) muscles (the brachialis muscle also receives partial radial innervation). It should be recalled that the integrity of the BR must be determined clinically by visual inspection and palpation because the biceps will adequately flex the forearm even when the forearm is semipronated (see Chapter 14, Fig. 14–3B). About the elbow, the radial nerve

divides into a motor branch, the posterior interosseous nerve (PIN), and the superficial radial nerve. The PIN passes around the neck of the radius into the extensor forearm. The so-called *radial tunnel* is about 5 cm in length

along the proximal radius from the elbow joint to the fibrous proximal border of the superficial head of the supinator muscle (*arcade of Frohse*), bounded by the BR, ECRL/B, capsule of the radiocapitellar joint, and biceps tendon

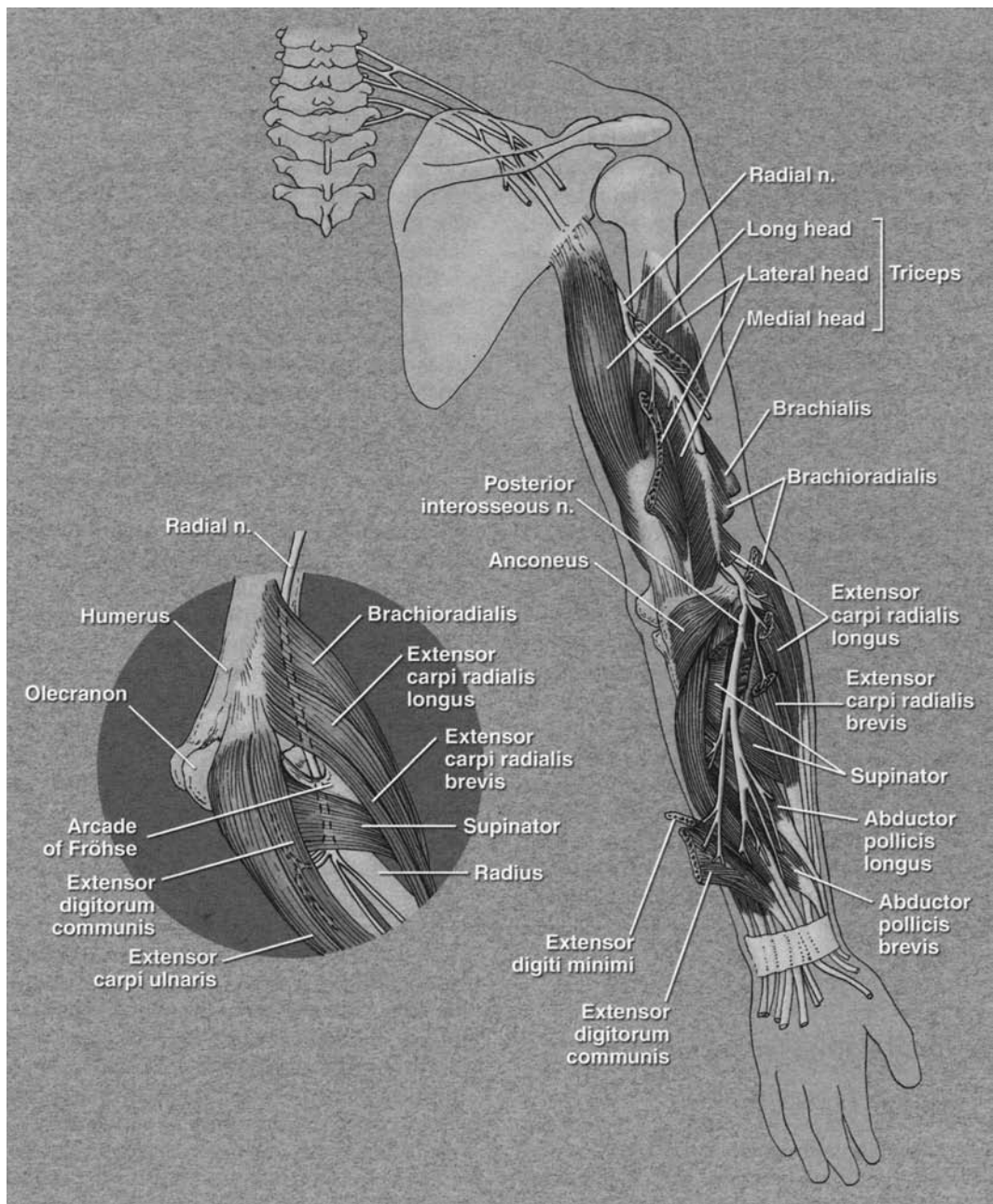


Figure 18–9. Anatomy of the radial nerve motor branches. The inset illustrates the anatomy of the radial tunnel. From Mendell^{16a} with permission (See Color Plate 18–9.)

and brachialis. The supinator muscle is innervated either before or after the arcade of Frohse. Distal to the supinator, branches in the forearm supply the extensor digitorum communis, extensor digiti minimi, extensor carpi ulnaris, extensor pollicis longus/brevis, abductor pollicis longus, and extensor indicis. Radial finger extension of digits 2–4 is at the metacarpophalangeal joints; extension at the interphalangeal joints is a median/ulnar nerve function. The superficial radial nerve becomes superficial in the distal radial third of the forearm and supplies sensation to the dorsolateral hand and dorsal first three digits.

RADIAL NEUROPATHIES IN THE AXILLA

Lesions at this site are uncommon and usually traumatic (*crutch palsy*, *lover's palsy*, or missile injuries), often involving the median or ulnar nerves as well. All radial muscles are affected, including the triceps. Sensory loss may occur in the distribution of the posterior brachial and antebrachial nerves, as well as the superficial radial nerve. A posterior cord lesion will involve the deltoid, teres minor, and latissimus dorsi muscles.

RADIAL NEUROPATHIES IN THE UPPER ARM

Acute strenuous muscular effort can injure the radial nerve within the triceps muscle; weakness is found in radial muscles distal to the triceps innervation.^{78,79} Ill-placed injections intended for the deltoid muscle may instead injure the radial nerve. This nerve can also be the victim of HNPP and multifocal motor neuropathy. The nerve is particularly vulnerable to injury at the spiral groove from external compression (*Saturday night palsy*) or humeral fractures acutely, or chronically from callus.⁸⁰ The triceps is spared with lesions at the humeral groove, and only the superficial radial sensory territory is involved. Focal conduction block may be demonstrable or the lesion may be of the axon-loss type.⁸¹ The radial SNAP is occasionally spared even with substantial motor axon loss. Lesions predominantly associated with conduction block can improve substantially within a few weeks; axon-loss lesions may take months to a year or more. Any

recordable CMAP amplitude from the extensor indicis and recruitment from the BR muscle predict a good prognosis, but even 65% of subjects with an absent radial CMAP will have a good outcome.⁸² Volume conduction from adjacent anterior interosseous-innervated muscles is common in complete radial nerve lesions.

Most radial neuropathies are treated conservatively with cock-up splinting (partial extension); some associated with humeral fractures require exploration, as may some that are progressive or do not improve after a few months of observation. There may be difficulty distinguishing a monoparesis related to stroke from a painless radial neuropathy when other clear upper motor neuron features are not apparent. Weakness of wrist and finger extension in radial neuropathy can alter the mechanics and stability of the hand such that it may be very difficult to convincingly demonstrate normal median and ulnar nerve function in the hand. We find that lack of visible BR activation is helpful in pointing to a radial lesion. Electrodiagnostic testing or brain imaging should clarify the issue. C7 radiculopathies have overlapping features, but involvement of nonradial C7 muscles clinically and electrophysiologically is diagnostic.

POSTERIOR INTEROSSEOUS NEUROPATHY (PIN)

Posterior interosseous neuropathy results in severe finger and thumb drop, with only partial wrist drop with radial deviation since the extensor carpi radialis is spared. Partial lesions may affect extension of one or combinations of fingers, more often digits 4 and 5. Extensor tendon rupture may have a similar appearance, but electrodiagnostic studies will be normal (Fig. 18–10). Sensation is not involved, but there may be pain in the forearm/elbow region in some cases. Due to selective fascicular involvement, a more proximal radial lesion may occasionally mimic a PIN. A variety of traumatic and nontraumatic (mass) lesions result in PIN. Compression or entrapment most often occurs under the arcade of Frohse, less commonly at the edge of the extensor carpi radialis. Occasionally, the posterior interosseous nerve is involved in an



Figure 18-10. Severe weakness of extension of the fourth and fifth digits, initially thought by some observers to reflect a partial posterior interosseous neuropathy or even the claw hand of an ulnar neuropathy. Electrodiagnostic studies were normal. This was the result of extensor tendon rupture.

otherwise typical case of immune brachial plexus neuropathy (neuralgic amyotrophy), and may be an isolated feature in some instances. Imaging of the elbow and proximal forearm by MRI and ultrasound is appropriate in many cases of PIN, particularly if it is progressive and not associated with simple trauma. Needle EMG shows findings restricted to the posterior interosseous nerve distribution; the CMAP recording from the extensor indicis will provide a measure of axonal loss. A period of observation may be appropriate, depending on the etiology, but many cases of idiopathic PIN will require surgical exploration if there is no improvement within a few months and certainly if there is progression.

The so-called *radial tunnel syndrome*, also referred to as *resistant tennis elbow*, is a more controversial entity.⁸³ It refers to a pain syndrome in the region of the extensor mass of the proximal forearm, attributed to dysfunction of the posterior interosseous nerve due to various structures of the radial tunnel. There is no weakness and usually there are no electrodiagnostic abnormalities, making it a difficult entity to pin down.⁸⁴ In addition to deep pain in the

extensor muscle mass, physical findings may include point tenderness in that area, a few centimeters distal to the lateral epicondyle, pain on resisted extension of the middle finger with the elbow extended and pronated, wrist neutral, and fingers extended (*middle finger test*), and pain on resisted forearm supination with the elbow extended.⁸⁵ Lateral epicondylitis, or *tennis elbow*, is distinguished by the point of tenderness being over the lateral epicondyle, and eliciting pain with wrist and finger flexion while the elbow is extended. The reliability of these tests in distinguishing these entities is not entirely clear, and some authors feel that both conditions may coexist. A prolonged period of conservative therapy is appropriate in all cases; some will receive operative therapy, with variable results.⁸⁶

SUPERFICIAL RADIAL NEUROPATHY (SRN)

The superficial radial nerve is usually damaged by compression (handcuffs, tight casts) or laceration (de Quervain tenosynovectomy, venipuncture, knives, glass) in its vulnerable

superficial location at the wrist. The extent of sensory loss over the dorsolateral hand and fingers varies, depending on the degree of injury and the extent of overlap from adjacent territories of the lateral antebrachial cutaneous and dorsal ulnar cutaneous nerves. While the sensory loss is usually trivial, the associated pain and paresthesias in some cases are troublesome; rarely, patients have developed complex regional pain syndrome. A true entrapment may uncommonly occur in the forearm between the tendons of the BR and extensor carpi radialis muscle as the nerve transits from deep to superficial.^{87,88} Symptoms may be induced or aggravated by

wrist ulnar flexion with the forearm pronated, but the pain elicited with this maneuver is indistinguishable from that seen with De Quervain extensor tenosynovitis. Wartenberg coined the term *cheiralgia paresthetica* for this entrapment.⁸⁹ Except for lacerations, SRN is usually initially managed conservatively before exploration is considered.

Other Upper Extremity Mononeuropathies

Less common mononeuropathies of the upper extremity are presented in Table 18–2.

Table 18–2 Less Common Mononeuropathies of the Upper Extremity

Nerve	Roots	Trunks/ cords	Muscles	Features	Etiologies*
Spinal accessory	C1-5	—	Trapezius, (sternocleidomastoid if lesion is proximal)	Shoulder drop and pain; weakness at >90° shoulder abduction; lateral scapular winging with shoulder abduction	Posterior triangle neck surgery, lymph node biopsy
Phrenic	C3, C4, C5	—	Diaphragm	Dyspnea	Frequently IBPN; trauma; tumor; MMN; CIP
Dorsal scapular	C5	—	Rhomboides major and minor; levator scapula	Scapular winging, inferior angle rotated laterally	Rarely isolated
Long thoracic	C5, C6, C7	—	Serratus anterior	Scapular winging, accentuated by forward flexion and pushing against a wall	Trauma; particularly associated with IBPN
Suprascapular	C5, C6	Upper	Supraspinatus, infraspinatus	Initial shoulder abduction (SSP), external rotation (ISP)	Suprascapular notch (SSP and ISP), spinoglenoid notch (ISP); ganglion
Axillary	C5, C6	Upper/ posterior	Deltoid, teres minor	Shoulder abduction weakness; sensory patch over deltoid	Shoulder dislocation, humeral fracture, injection injury, quadrilateral space syndrome
Musculocutaneous	C5, C6	Upper/ lateral	Biceps, coraco-brachialis, brachialis	Weakness in elbow flexion; sensory loss in LAC territory	Strenuous exercise (<i>effort neuropathy</i>); LAC is most commonly affected sensory nerve in IBPN; iatrogenic trauma
Digital sensory (palmar: median, ulnar; dorsal: SRN, DUC)	C6, C7, C8	All	—	Common digital nerve: adjacent sides of two fingers Proper digital nerve: side of one finger	Trauma, mass, vasculitis, diabetes, leprosy; tendency to form painful neuroma

(continued)

Table 18–2 (Continued)

Nerve	Roots	Trunk-s/cords	Muscles	Features	Etiologies*
Recurrent thenar motor	C8, T1	Lower/medial	Abductor pollicis brevis, opponens pollicis, flexor pollicis brevis	Thenar weakness, sparing sensory function	Trauma

*Any nerve may be involved in immune brachial plexus neuropathy (IBPN; neuralgic amyotrophy), either isolated or in combination, or may be otherwise idiopathic.

CIP: critical illness polyneuropathy; DUC: dorsal ulnar cutaneous; IBPN: immune brachial plexus neuropathy; ISP: infraspinatus; LAC: lateral antebrachial cutaneous; MMN: multifocal motor neuropathy; SRN: superficial radial nerve; SSP: supraspinatus.

FOCAL NEUROPATHIES: THE LOWER EXTREMITY

Sciatic Nerve

ANATOMY

The sciatic nerve originates from the L4-S3 roots. It is composed of two distinct trunks throughout its course. The lateral trunk arises from the posterior divisions of the ventral rami of L4-S2 and forms the common peroneal nerve; the medial trunk arises from the anterior divisions of the ventral rami of L4-S3 and forms the tibial nerve. The sciatic nerve leaves the pelvis into the buttock through the greater sciatic foramen (sciatic notch) and either under, through, or over the piriformis muscle. The gluteal nerves, as well as the posterior cutaneous nerve of the thigh (S1-3) and the pudendal nerve (S2-4), come off proximal to the formation of the sciatic nerve but also pass through the sciatic notch; the inferior gluteal nerve (L5-S2) passes under the piriformis muscle, while the superior gluteal nerve (L4-S1) does not. The sciatic nerve descends near the posterior aspect of the hip joint. In the posterior thigh it innervates the hamstring muscles and partially the adductor magnus; the medial trunk supplies the semimembranosis, semitendinosis, long head of the biceps femoris, and adductor muscles, while the lateral trunk supplies the short head of the biceps femoris muscle. It terminates as the common peroneal and tibial nerves just proximal to the popliteal fossa.

SCIATIC NEUROPATHIES IN THE SCIATIC NOTCH/GLUTEAL/THIGH AREAS

Most sciatic neuropathies are traumatic, either from external compression, missile injury, misplaced injections, or hip fracture/dislocation/arthroplasty. The incidence following hip arthroplasty ranges from 0.08% to 7.6%, most commonly with revision surgery.⁹⁰ Subclinical signs of denervation on postoperative needle EMG are even more common.⁹¹ The femoral or obturator nerves may be concomitantly or exclusively injured. Additional etiologies include hematomas, fibrosis, endometriosis (*cyclic, cyclical, or catamenial sciatica*), tumors (schwannoma, neurofibroma, lymphoma), aneurysms/pseudoaneurysms, compartment syndrome, vasculitic infarction, and ischemic monomelic neuropathy.

Compression/entrapment of the proximal sciatic nerve by the piriformis muscle (*piriformis syndrome, extraspinal sciatica, or sciatica of non-disc origin*) is a controversial entity, and its true frequency is uncertain.⁹² Purported features include buttock and radiating posterior thigh pain, sciatic notch tenderness, and pain on provocative maneuvers with hip flexion, adduction, and internal rotation, none of which are specific. A true neurogenic compression at this site would produce clinical and electrophysiologic evidence of a sciatic neuropathy, including possibly involving the inferior gluteal nerve, which also passes under the piriformis, sparing the superior gluteal nerve, which does not. Most reported cases, however, have normal exams

and electrodiagnostic studies, and are pain syndromes with diagnostic uncertainty. Many such cases may reflect L5 or S1 radiculopathy without lower back pain. Sometimes the syndrome appears to follow buttock trauma. Some reports suggest improvement with anesthetic, corticosteroid, or botulinum toxin injection, or surgical sectioning of the piriformis muscle. Two recent studies of magnetic resonance neurography demonstrate abnormal increased signal in the proximal sciatic nerve and lend some credence to the existence of this entity.^{93,94}

A complete sciatic neuropathy results in weakness of the hamstring muscles and all muscles below the knee, resulting in a flail foot; gluteal muscles are spared unless the process involved also affects the gluteal nerves separately.⁹⁵ Sensory loss involves the entire foot and calf, sparing the saphenous territory of the medial leg. Pain and features of complex regional pain syndrome (CRPS) may be present. The ankle reflex is lost. It is important to palpate the buttock or posterior thigh for masses or tenderness. The straight leg raising test may be positive but is a nonspecific sign. The lateral trunk/peroneal division tends to be more vulnerable in partial lesions and may mimic a more distal common peroneal lesion.⁹⁶ Electrodiagnostic studies commonly reflect axon-loss lesions affecting peroneal greater than tibial division.⁹⁷ Computed tomography (CT) or MRI of the pelvis, sciatic notch/buttock, or thigh is frequently employed. The differential diagnosis of sciatic neuropathy includes lumbosacral radiculopathy, lumbosacral plexopathy, and common peroneal neuropathy. Management depends on the etiology and severity of the lesion. Most partial lesions resulting from hip arthroplasty or misplaced injections are managed conservatively. The prognosis is guarded in severe axon-loss lesions; pain and features of CRPS may be very problematic.

Peroneal Nerve

ANATOMY

The common peroneal nerve originates from the posterior divisions of the ventral rami of the L4, L5, and S1 roots (Fig. 18–11; see also Color Fig. 18–11). It descends as the lateral trunk of the sciatic nerve until it separates

laterally from the tibial division in the upper popliteal fossa. In the distal thigh, it innervates the short head of the biceps femoris muscle, and gives off the lateral cutaneous nerve of the calf supplying sensation to the upper lateral calf and the sural communicating branch. It winds around the fibular head, through a tendinous arch of the peroneus longus muscle (fibular tunnel) into the anterior compartment of the calf, and divides into superficial (peroneus longus and brevis muscles; sensation over the proximal two-thirds of the anterolateral calf and most of the dorsal foot except the first web space) and deep (tibialis anterior, extensor digitorum longus, extensor hallucis longus, and peroneus tertius muscles) peroneal nerves. At the ankle, the deep peroneal nerve passes under the extensor retinaculum and supplies the extensor digitorum brevis muscle and sensation over the contiguous sides and web space of the first two toes. An accessory peroneal branch from the superficial peroneal nerve is a common anomaly supplying the extensor digitorum brevis muscle.

COMMON PERONEAL NEUROPATHY AT THE FIBULAR HEAD

This is the most common lower extremity mononeuropathy.⁹⁸ The superficial location and tethering of the common peroneal nerve abutting and just distal to the fibular neck make it vulnerable to compression or traction injury. Associations include weight loss resulting in reduced subcutaneous fat padding, direct trauma, ankle inversion injury, knee surgery or arthroscopy, habitual leg crossing or prolonged squatting, malpositioning or pressure applied during various surgical procedures or an obtunded state, and a variety of mass lesions. It is commonly involved in HNPP. True entrapment at the fibular tunnel is probably uncommon. Imaging should be considered in nontraumatic cases. An MRI scan of nontraumatic peroneal neuropathies may reveal a ganglion cyst, osteochondroma, synovial cyst, or aneurysm.⁹⁹ High-resolution ultrasound reveals an intraneural ganglion in 18% of nontraumatic peroneal neuropathies, confirmed by histology.¹⁰⁰ Compared to common peroneal neuropathies without a clear cause, those associated with an intraneural ganglion

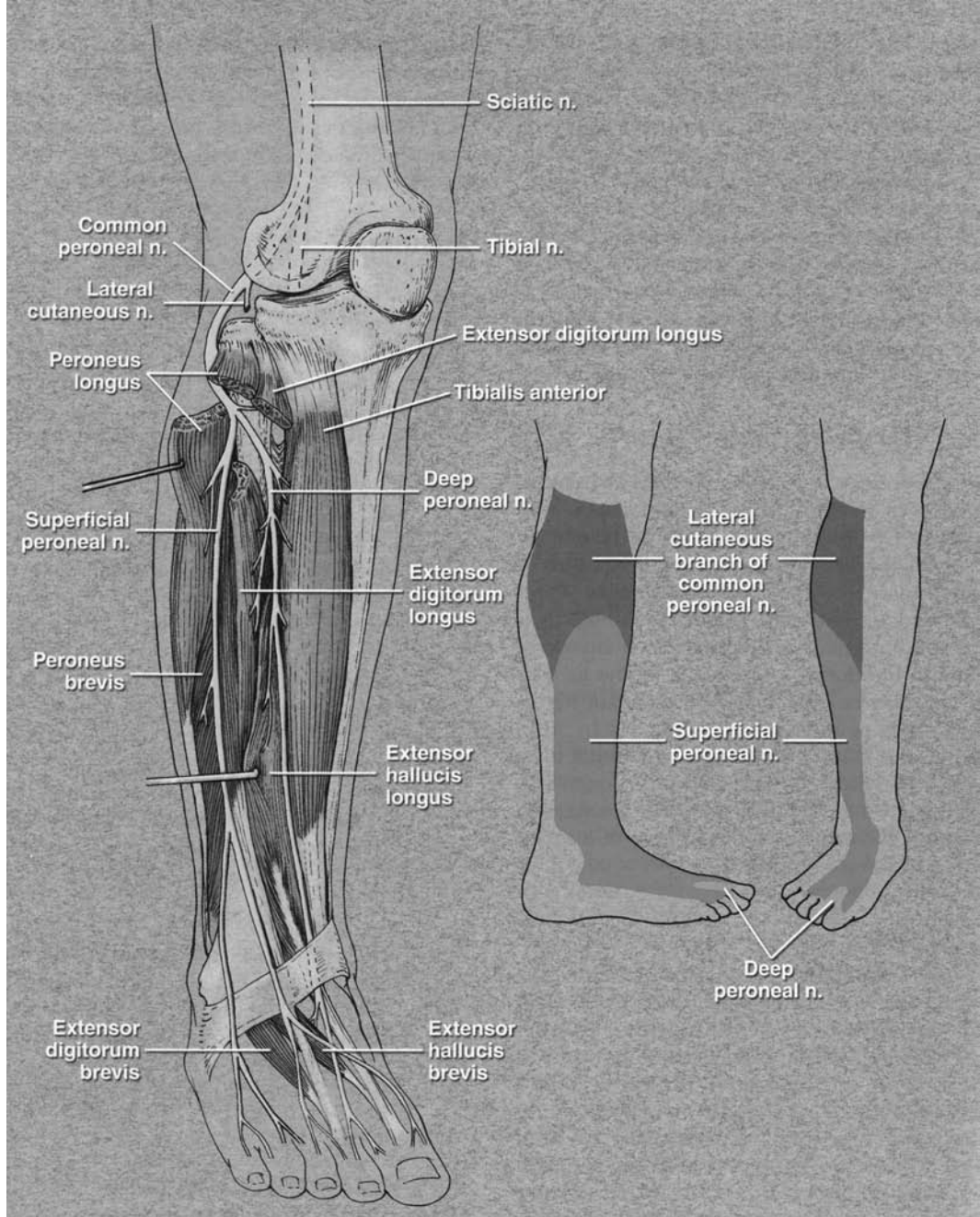


Figure 18–11. Anatomy of the common, deep, and superficial peroneal nerves and their cutaneous innervation. From Mendell^{16a} with permission (See Color Plate 18–11.)

tend to have a greater BMI, more knee or peroneal distribution pain, more fluctuating weakness with weight bearing, or a palpable mass at the fibular head.¹⁰¹ Many of these same etiologies, particularly trauma, apply

to the much less common individual deep peroneal or superficial peroneal neuropathies that may occur in the calf, with the addition of anterior or lateral compartment syndromes, respectively.

The clinical presentation is foot drop, with weakness of foot and toe dorsiflexion and eversion. Foot inversion is spared but may appear slightly weak when dorsiflexion weakness is severe. Sensory loss may be partial or over the entire distribution of the superficial peroneal nerve. Compressive lesions are often painless; those associated with a mass may be painful, as are vasculitic infarcts that can occur at various points along the nerve. A Tinel sign may be appreciated around the fibular head, and a mass may be palpated. Differential fascicular involvement is frequent in common peroneal neuropathies; muscles supplied by the deep peroneal nerve tend to be more frequently and severely affected, and the distribution of sensory involvement can be variable.¹⁰²

Nerve conduction studies can document focal slowing of motor conduction or conduction block at the fibular head in demyelinating lesions (recording from the extensor digitorum brevis and, importantly, the tibialis anterior muscles).¹⁰³ In pure axon-loss lesions, peroneal SNAP and CMAP amplitudes will be reduced without focal demyelinating abnormalities to localize the lesion; needle EMG will then aid localization by demonstrating denervation restricted to the common peroneal distribution, without involvement of muscles proximal to the knee, including the short head of the biceps femoris, and sparing of tibial muscles. Even in severe common peroneal neuropathies the SNAP amplitude may occasionally be preserved, again showing selective fascicular vulnerability.¹⁰⁴

Differential diagnosis depends on the specific clinical features, including whether unilateral or bilateral, and may include parasagittal lesions, motor neuron disease, L5 radiculopathy, lumbosacral plexopathy, sciatic neuropathy, polyneuropathy, and distal myopathy. L5 radiculopathy is the most common mimicker and, aside from radicular pain when present, may be distinguished clinically by involvement of foot inversion and muscles proximal to the knee (hamstrings, glutei), sensory loss that includes the upper lateral calf, and more severe weakness of the extensor hallucis relative to tibialis anterior muscles. Electrophysiologic features will generally distinguish these various localizations.

Management depends on the etiology and pathophysiology. Known external compressive lesions are managed conservatively. Those with predominantly conduction block can improve

within weeks; those associated with substantial axon loss will take many months, and recovery may be incomplete. Progressive lesions and those associated with a mass require surgical exploration. Ambulation is aided by an ankle foot orthosis until recovery occurs.

DEEP PERONEAL NEUROPATHY AT THE ANKLE

This condition is also referred to as *anterior tarsal tunnel syndrome* (although there is no true tunnel). The deep peroneal nerve may rarely be injured or entrapped under the extensor retinaculum at the ankle. There may be pain at the ankle and dorsal foot, numbness in the first web space, weakness and atrophy of the extensor digitorum brevis, and a Tinel sign at the ankle. Associations include ankle trauma, tight shoes, high-heeled shoes, and mass lesions.

Tibial Nerve

ANATOMY

The tibial nerve derives from the L4-S2 roots and medial division of the sciatic nerve, becoming independent just proximal to the popliteal fossa (Fig. 18–12; see also Color Fig. 18–12). In the popliteal fossa it gives off the medial sural cutaneous nerve, which joins the lateral sural cutaneous nerve from the common peroneal nerve to form the sural nerve. The tibial nerve travels deep to the gastrocnemius supplying the following calf muscles: gastrocnemius, popliteus, plantaris, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus. It passes posterior to the medial malleolus at the ankle, often first giving off the medial calcaneal branch that supplies sensation to the heel, although its origin is variable¹⁰⁵ (Fig. 18–13; see also Color Fig. 18–13). It then passes under the flexor retinaculum (tarsal tunnel) accompanied by tendons of the tibialis posterior, flexor hallucis longus, and flexor digitorum longus and the posterior tibial artery and vein. Either within the tarsal tunnel, or occasionally more proximal or distal, it divides into the medial and lateral plantar nerves. These supply sensation to the medial and lateral sole and toes,

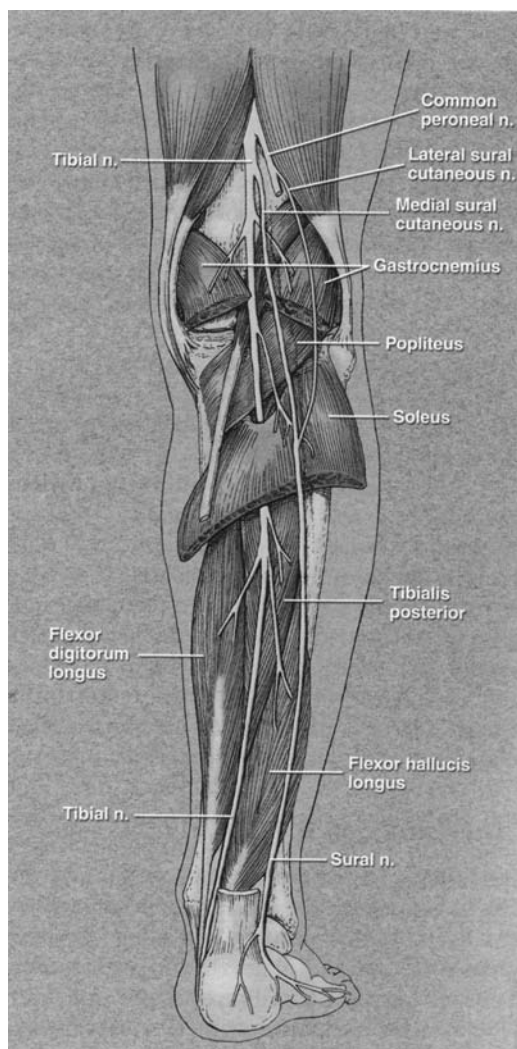


Figure 18-12. Anatomy of the tibial and sural nerves. From Mendell^{16a} with permission (See Color Plate 18-12.)

respectively, in a pattern analogous to that of the median and ulnar nerves in the hand, and innervate the intrinsic foot muscles.

PROXIMAL TIBIAL NEUROPATHY

Isolated tibial neuropathies in the popliteal fossa or calf are uncommon and may be associated with trauma, ischemia, neoplasm, Baker cyst, or compartment syndrome.¹⁰⁶ A rare tibial nerve entrapment in the popliteal fossa occurs under the tendinous arch of

origin of the soleus muscle.¹⁰⁷ Clinical and electrodiagnostic features reflect the level of tibial nerve involvement. It is important to palpate for a mass and check for a Tinel sign. Imaging studies may be helpful. Differential diagnostic considerations include S1/S2 radiculopathy, sacral plexopathy, sciatic neuropathy, and tarsal tunnel syndrome.

TARSAL TUNNEL SYNDROME

Tarsal tunnel syndrome (TTS), also called *posterior TTS*, is an entrapment neuropathy of the posterior tibial nerve under the flexor retinaculum at the medial ankle¹⁰⁸ (Fig. 18-13; see also Color Fig. 18-13). It is probably uncommon, but is both misdiagnosed and unrecognized because of the vagaries of the symptoms and signs and the difficulties in electrodiagnostic confirmation. It can be confused with many sources of neuropathic and non-neuropathic foot pain or paresthesias, including peripheral neuropathy, peripheral vascular disease, plantar fasciitis, tendonitis, bursitis, arthritis, stress fractures, partial sciatic or S1 radicular lesions, and more distal plantar neuropathies. Conditions associated with TTS include ankle injury, posttraumatic fibrosis, thick flexor retinaculum, tight footwear, and space-occupying lesions (ganglia, varicose veins, schwannoma, lipoma, abnormal muscles within the tunnel). Ultrasonography or MRI is often helpful for anatomic definition.

Typically, there is burning or sharp foot pain, numbness, or paresthesias in the distribution of one or more of the plantar nerves; the heel is often not involved, as the calcaneal branch may arise proximal to the tarsal tunnel. Symptoms are aggravated by weight bearing, are relieved with rest, and may be nocturnal. They may radiate proximally. Weakness of intrinsic foot muscles is difficult to demonstrate. Associated sensory loss on testing (most often in the medial plantar territory) and a Tinel sign or tenderness over the tarsal tunnel tend to be the most reliable signs. In the *nerve compression test*, gentle pressure over the tarsal tunnel for 30 seconds reproduces the symptoms.¹⁰⁹

Electrodiagnostic testing can be helpful, but may be limited and difficult to interpret in patients who are elderly and in those with calloused feet, bilateral symptoms, or underlying peripheral neuropathy. Nerve conduction tests include tibial motor, mixed plantar, and plantar

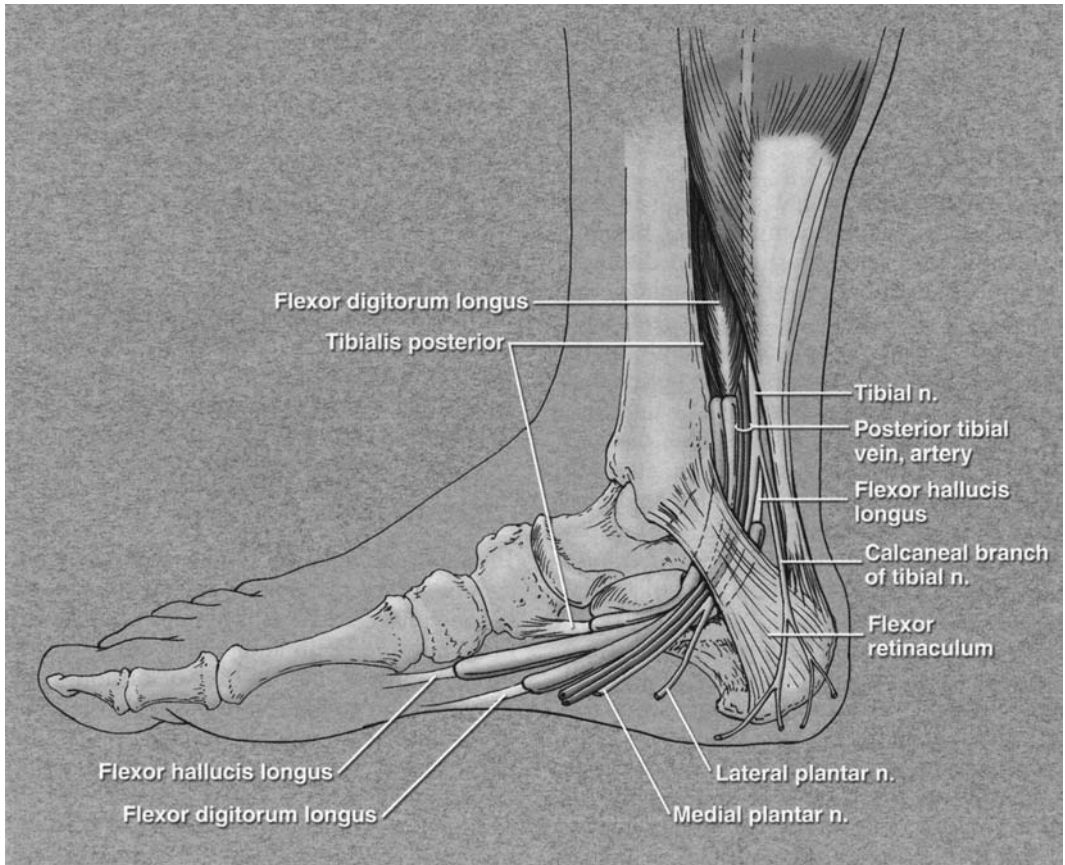


Figure 18–13. Posterior tibial nerve anatomy passing beneath the flexor retinaculum (tarsal tunnel) at the medial ankle. From Mendell^{16a} with permission (See Color Plate 18–13.)

sensory studies. Needle EMG may show denervation in intrinsic foot muscles, but this is non-specific and may be seen in normal subjects. Near-nerve conduction studies of the medial and lateral plantar nerves have been described to improve the yield of these studies, but they are not widely employed.¹¹⁰

Conservative therapy is initially employed in most cases without a space-occupying lesion, and may include avoiding external compression, anti-inflammatory/neuropathic medications, corticosteroid injection, and orthotics. Corticosteroid injection into the tarsal tunnel may be both diagnostic and therapeutic. Good clinical results are often reported with surgical release of the flexor retinaculum, including improvement in electrophysiologic parameters, but it is not uncommon to encounter apparent failures in the EMG lab.^{109,111}

PLANTAR AND DIGITAL NEUROPATHIES

Medial plantar neuropathy (also called *jogger's foot*) may occur from compression at the entrance to the fibromuscular tunnel (abductor tunnel) behind the navicular tuberosity distal to the tarsal tunnel, where a Tinel sign can be demonstrated to help distinguish it from TTS.¹¹² Distal medial plantar neuropathy occurs in infantry soldiers, likely due to repeated mechanical injury, and often resolves within weeks to months.¹¹³ Joplin neuroma, or *digitalgia paresthetica*, is a mononeuropathy of the medial plantar proper digital nerve supplying sensation to the medial big toe, usually associated with trauma, and is demonstrable electrophysiologically.¹¹⁴ Morton neuroma (*Morton metatarsalgia*) is an interdigital neuropathy with localized pain and a Tinel sign

most often on the plantar aspect between the third and fourth metatarsal heads.¹¹⁵ Isolated lateral plantar or medial calcaneal neuropathies are rare.

Femoral Nerve

ANATOMY

The femoral nerve derives from the L2-4 ventral rami and posterior division of the lumbar plexus (Fig. 18-14; see also Color Fig. 18-14). In the pelvis, it passes between and innervates the iliopsoas and iliacus muscles. It passes under the inguinal ligament, lateral to the femoral artery and vein. In the thigh, motor branches innervate the quadriceps (vastus lateralis, vastus medialis, vastus intermedius, rectus femoris) and sartorius muscles. The medial and intermediate cutaneous nerves of the thigh (anterior femoral cutaneous nerves) supply sensation to the anterior and anteromedial thigh. The saphenous nerve is the terminal sensory branch of the femoral nerve, descending in the adductor canal (subsartorial/Hunter canal) in the thigh, exiting above the knee, giving off the infrapatellar branch that supplies the skin over the knee, then innervating the skin over the medial leg, ankle, and foot.

FEMORAL NEUROPATHY

In the pelvis/retroperitoneum, femoral neuropathy may result from surgery, hematoma related to procedures, anticoagulation or blood dyscrasia, neoplasm, or ischemia.¹¹⁶ At the inguinal ligament, lesions are usually due to compression or stretching (e.g., the lithotomy position), surgical complications including hip arthroplasty, or femoral artery cannulation/hematoma. So-called *diabetic femoral neuropathy* is actually a forme fruste of diabetic lumbosacral radiculoplexus neuropathy; extensive needle EMG will show that abnormalities are not restricted to the femoral distribution. Rarely, isolated femoral mononeuropathy may involve a single branch to only one of the quadriceps muscles.

Clinical features include knee extensor weakness and atrophy, numbness over the anterior thigh and medial leg, depressed or absent patellar reflexes, and occasionally pain. Weakness of hip flexion (iliopsoas) implies that the lesion is intrapelvic/retroperitoneal.

Differential diagnostic considerations include L2-4 radiculopathies, lumbosacral plexopathy, and, rarely, diabetic muscle infarction. Pelvic MRI or CT is frequently employed. Electrodiagnostic studies in axon-loss lesions show involvement of the saphenous sensory potential, a reduced femoral CMAP, and denervation in femoral muscles, sparing the obturator (adductors), peroneal, and tibial distributions as well as the paraspinal muscles. The femoral CMAP is the best predictor of recovery, with an amplitude $\geq 50\%$ of the contralateral side predicting a good prognosis over 1 year.¹¹⁷ Most compressive, stretch, partial, and predominantly demyelinating lesions are managed conservatively. Masses are treated surgically. If hematomas are to be evacuated, a controversial subject, this must be done expeditiously before substantial axon loss has ensued.¹¹⁸

Lateral Femoral Cutaneous Nerve

The lateral femoral cutaneous nerve (LFCN), or lateral cutaneous nerve of the thigh, is a sensory nerve formed from the ventral rami of L2 and L3, travels along the lateral aspect of the pelvis, emerges under, through, or above the inguinal ligament adjacent to the anterior superior iliac spine, and innervates the skin of the anterolateral thigh (Fig. 18-14; see also Color Fig. 18-14). Variations in the course of the nerve in the groin are common. Neuropathy of the LFCN is not uncommon in neurologic practice and is generally referred to as *meralgia* (Greek, *meros* = thigh, *algo* = pain) *paresthetica* (MP). Lesions may occur in the pelvis or thigh, but most by far are related to compression at the inguinal ligament.^{119,120}

In the pelvis, lesions may be related to various surgical procedures, iliac bone graft, tumor, or hematoma. In the thigh, they are usually traumatic. At the inguinal ligament, they are related to trauma, surgery, chronic external compression (tight belts or jeans, equipment belts, seat belts), or, most often, idiopathic entrapment. Routine autopsy studies of the LFCN often show changes typical of focal compression at the inguinal ligament.¹²¹ There is a common association with obesity or pregnancy; diabetes is frequently held to be an association, but this is unestablished.

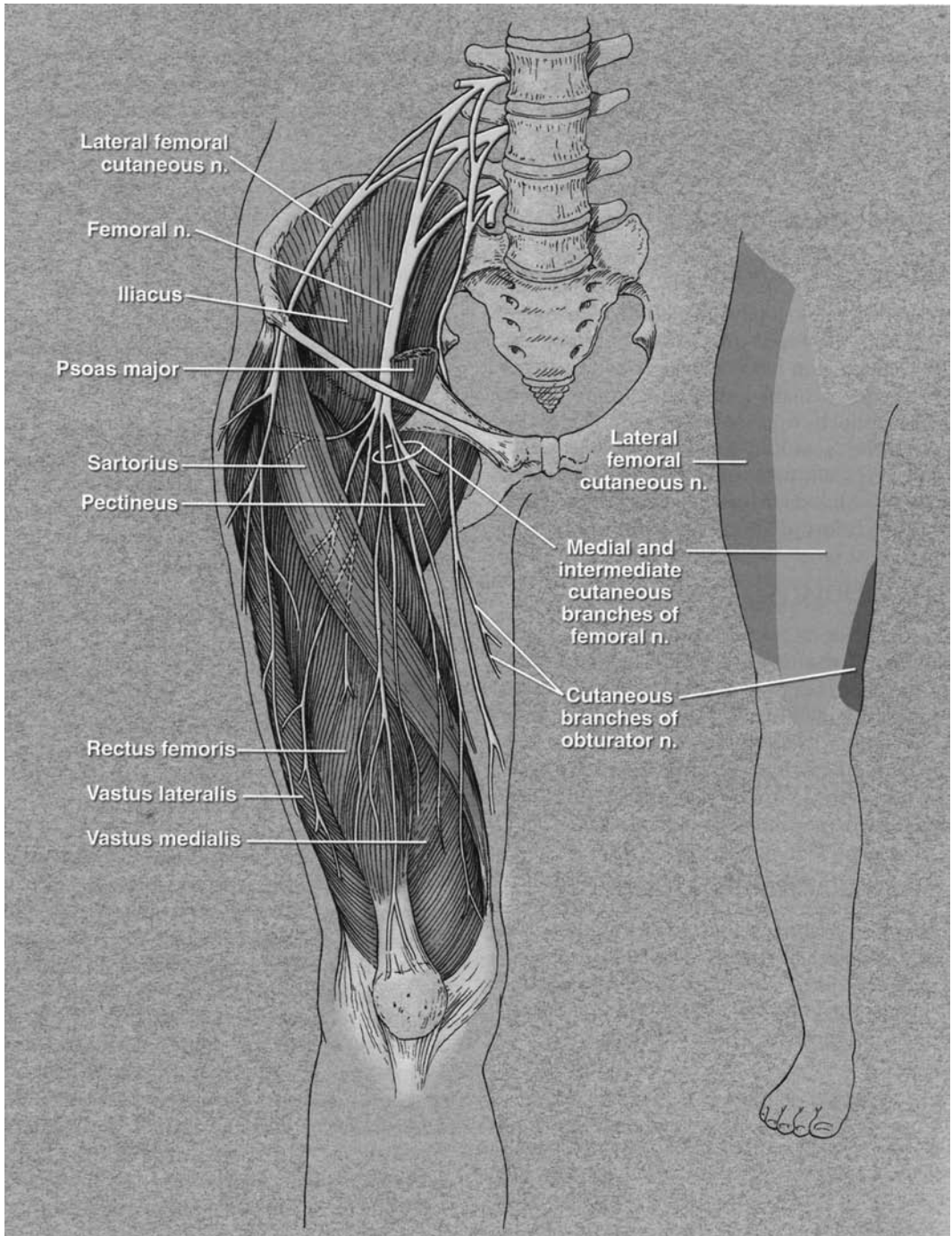


Figure 18-14. Anatomy of the femoral, obturator, and lateral femoral cutaneous nerves and their cutaneous innervation. From Mendell^{16a} with permission (See Color Plate 18-14.)

Patients have intermittent or persistent burning or aching pain, paresthesias, or numbness of varying severity over the anterolateral thigh.¹¹⁹ The extent of involvement is variable,

from the entire territory of the nerve to a small patch, never extends over the knee, and in about 27% of cases has an atypical distribution that includes the anterior thigh. There may be

allodynia. Standing or walking can be aggravating factors. A Tinel sign may be appreciated over the lateral inguinal ligament. Meralgia paresthetica may be bilateral in about 10% of cases, but symptoms on one side predominate¹¹⁹

In most cases, the diagnosis can be confidently established clinically. Differential diagnostic considerations include L2-L4 radiculopathy, lumbar plexopathy, and femoral neuropathy, which can be sorted out by electrodiagnostic testing and occasional imaging. Pelvic imaging can be limited to those cases where a pelvic mass is suspected. Side-to-side comparison of the LFCN SNAP can support the diagnosis by demonstrating axon loss. Unfortunately, the SNAP is all too often not elicited on either side in healthy subjects and particularly in obese patients. A local anesthetic/corticosteroid nerve block at the inguinal ligament in patients with pain can be diagnostic as well as therapeutic. Ultrasound-guided blockade of the LFCN can improve the success rate.¹²² The *pelvic compression test* has been suggested as a sensitive and specific test for MP, helping to distinguish it from lumbosacral radiculopathy.¹²³ With the patient lying in the lateral position on the asymptomatic side, lateral compressive force is applied to

the pelvis for 45 seconds; this is thought to relax the inguinal ligament, resulting in relief of pressure on the nerve and temporary alleviation of symptoms.

Most patients can be managed conservatively, with avoidance of precipitating and aggravating factors, weight loss if obese, and analgesia with neuropathic medications. Those who do not respond or who have severe pain can benefit from corticosteroid injection. Based on observational studies, the natural history of MP appears to be quite favorable, with 69% of patients showing spontaneous improvement.¹²⁴ Cure or improvement follows injection of corticosteroids and local anesthetics in 83%. When necessary in recalcitrant cases, surgical treatment is beneficial in up to 88% of patients with decompression and 94% of those with neurectomy.^{124,125} In iatrogenic MP, 97% of patients recover completely.

Other Lower Extremity Mononeuropathies

Less common mononeuropathies of the lower extremity are presented in Table 18–3.

Table 18–3 **Less Common Mononeuropathies of the Lower Extremity**

Nerve	Roots	Cutaneous Innervation	Muscles	Features	Etiologies
Sural	S1	Posterolateral leg, dorsolateral foot	—	Pain, paresthesias, sensory loss in dorsolateral foot	Trauma, Baker cyst, arthroscopic surgery, biopsy
Saphenous	L3, L4	Medial calf and foot	—	Pain, paresthesias, sensory loss in medial leg	Trauma, surgical iatrogenic damage; possibly entrapment at exit from adductor canal
Infrapatellar branch of saphenous	L4	Small patch over/below knee	—	Pain mimicking other knee pathology	Arthroscopy, other medial knee trauma; <i>gonyalgia paresthetica</i>
Superficial peroneal sensory	L5	Distal two-thirds of lateral leg, dorsal foot	—	Pain, paresthesias, sensory loss in dorsal foot, lateral leg	Trauma, rare entrapment in lower leg as exits deep fascia
Posterior femoral cutaneous	S1-3	Posterior thigh, lower buttock, parts of scrotum/labia	—	Sciatic and inferior gluteal nerves often also involved	Trauma, prolonged buttock pressure, pelvic neoplasm

(continued)

Table 18–3 (Continued)

Nerve	Roots	Cutaneous Innervation	Muscles	Features	Etiologies
Superior gluteal	L4, L5, S1	—	Gluteus medius, minimus; tensor fascia lata	Exits sciatic notch superior to piriformis muscle; hip abductor weakness, waddling gait	Misplaced intramuscular injections, compartment syndrome
Inferior gluteal	L5, S1, S2	—	Gluteus maximus	Exits inferior to piriformis muscle; often associated sciatic, posterior femoral cutaneous, or pudendal involvement; weakness of hip extension	Pelvic masses, misplaced intramuscular injections, compartment syndrome
Obturator	L2-4; anterior division of lumbar plexus	Lower medial thigh	Adductor brevis, magnus, longus; gracilis; obturator externus	Medial thigh pain, paresthesias or sensory loss; thigh adductor weakness	Trauma, childbirth, pelvic neoplasm, hip arthroplasty, obturator hernia, endometriosis
Pudendal	S2-4	Genitalia, perineum	Bulbospongiosus, ischiocavernosus	Numbness in penis, labia, perineum; erectile dysfunction; vulvodynia	Pelvic masses, misplaced intramuscular injections, long bicycle rides, childbirth
Ilio-hypogastric	T12, L1	Small patches in upper buttock and above pubis	Lower abdominal	Minor sensory deficit; bulging lower quadrant	Iatrogenic/surgery in inguinal/lower quadrant area, retroperitoneal tumors or surgery
Ilioinguinal	L1	Inguinal ligament, upper medial thigh, base of penis/ upper scrotum, mons pubis/ labium majus	Lower abdominal	Difficult to distinguish from genitofemoral; bulging lower quadrant with ilioinguinal; <i>inguinal neuralgia</i> —burning, stabbing pain; tenderness, Tinel sign; aggravated by walking, standing, hip extension; diagnostic/therapeutic selective nerve block; neurectomy occasionally needed	Iatrogenic/surgery in inguinal/lower quadrant area (herniorrhaphy, appendectomy), blunt trauma, retroperitoneal tumors or surgery, rarely entrapment
Genitofemoral	L1, L2	Small patch of anterior thigh, scrotum, mons pubis/labium majus	Cremaster	Similar to ilioinguinal	Iatrogenic/surgery in inguinal/lower quadrant area (herniorrhaphy, appendectomy), blunt trauma, psoas abscess

**FOCAL NEUROPATHIES:
CRANIAL NEUROPATHIES**

**Idiopathic Facial Nerve Paralysis
(Bell's Palsy)**

INTRODUCTION

Bell's palsy is common; the incidence in the United States is 25 per 100,000, and it accounts for about 66% of persons with unilateral facial paralysis.^{126,127} Although the condition was initially described over 150 years ago and has been exhaustively investigated, its pathology, pathogenesis, and optimal treatment are still uncertain.

CLINICAL FEATURES

All age groups are affected; it is rare in children under age 10 and is more common in older persons. Both sides of the face are equally involved. Rarely, the disorder is recurrent or familial. Unilateral facial paralysis usually develops within a few hours or evolves over 1 or 2 days; it is often accompanied by

retroauricular pain and lacrimation disturbance.^{128,129} *Facial numbness* is a common complaint, but some patients use this term to refer to immobility, and generally there is no objective sensory deficit. Rarely are hyperacusis and diminished taste significant to the patient. Global unilateral facial muscle weakness is the hallmark of this condition; it is partial in 40% of cases. Hyperacusis, diminished lacrimation, and abnormal taste sensation are present to varying degrees, depending upon the level of the lesion. Figure 18–15 delineates the putative levels of involvement of the facial nerve in the common Bell's palsy syndromes. Topographic localization is frequently both unhelpful and inaccurate.

Other reported associations with acute unilateral facial palsy include trauma, Lyme disease, human immunodeficiency virus (HIV) infection, hypertension/diabetes, preeclampsia, parotid gland neoplasm, sarcoidosis, amyloidosis, pontine infarct, Sjögren syndrome, inactivated intranasal influenza vaccine (Swiss), and herpes zoster oticus or cephalicus (Ramsay Hunt syndrome).¹³⁰ Bilateral acute facial paralysis in a child is usually Lyme

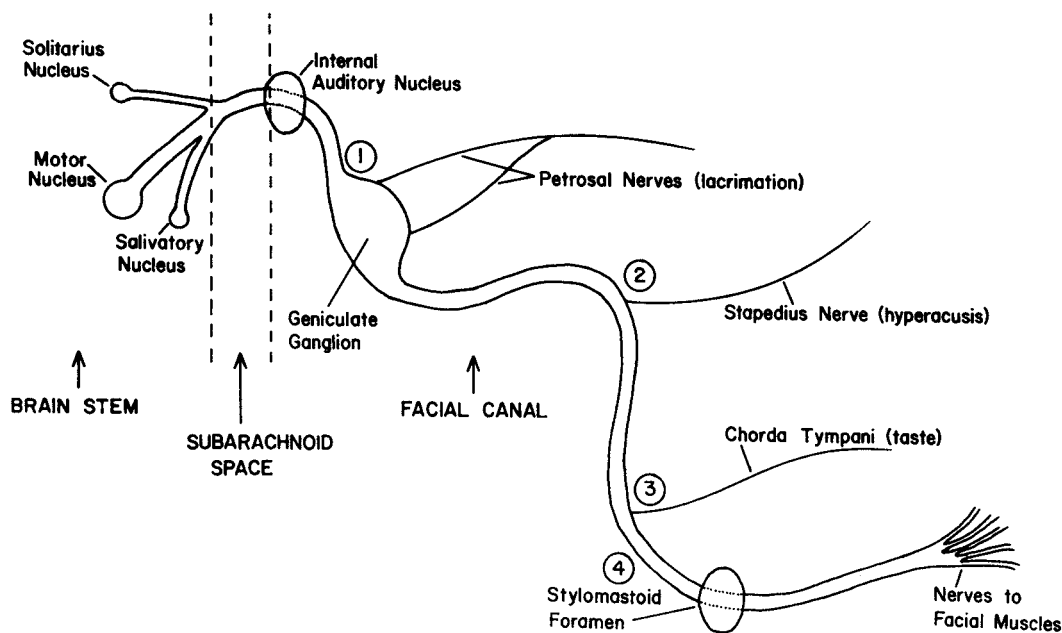


Figure 18–15. Diagram of four putative facial canal lesion sites in the various Bell's palsy syndromes. *Site 1:* impaired lacrimation, hyperacusis, impaired taste, facial paralysis. *Site 2:* hyperacusis, impaired taste, facial paralysis. *Site 3:* impaired taste, facial paralysis. *Site 4:* facial paralysis.

disease, and in an adult it is acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or Lyme disease, in the appropriate endemic setting.

LABORATORY AND IMAGING STUDIES

Cerebrospinal fluid is not routinely examined. When done, the fluid is usually acellular and the protein is normal. Pleocytosis suggests a more diffuse inflammatory meningeal lesion, as seen with HIV, Lyme disease, or sarcoidosis. Electrodiagnostic studies (blink reflex and facial CMAPs) can establish localization and severity, and aid in predicting the outcome, although patients don't always seem to obey the apparent rules; it is best performed after at least 4–5 days of onset of weakness, preferably later, in order to detect evidence of axonal damage. As a measure of axonal integrity, the CMAP amplitude recorded from involved facial muscles and compared to the normal side provides the best electrophysiologic guide to the prognosis. Within the first 3 weeks, persons with evidence of 90% or more fiber degeneration have only a 50% chance of making a satisfactory recovery. If no response is obtained, recovery is seldom satisfactory.¹³¹ A good prognosis is portended by facial motor potential amplitude of at least 50%. Brain MRI studies are not usually indicated unless a pontine infarct is suspected. The most common abnormality is contrast enhancement of the intracranial and labyrinthine segments of the facial nerve.¹³²

PATHOLOGY AND PATHOGENESIS

The underlying pathology of Bell's palsy is unclear; surgeons' reports of swollen nerves during decompression procedures have suggested roles for ischemia or inflammation.¹³³ Contrast enhancement of the facial nerve on MRI scans within 3 weeks of onset supports these notions. It is likely that persons with rapid recovery and conduction block on nerve conduction studies have sustained focal demyelination, while those with poor recovery and denervation of facial muscles have axonal injury. Ischemic mononeuropathy from diabetes or atherosclerosis may cause both demyelination and axonal injury, depending on the degree of vascular compromise. Following the demonstration of herpes simplex virus type 1

(HSV-1) DNA in endoneurial fluid recovered during decompression surgery, the inflammatory lesion in Bell's palsy is now widely held to stem from HSV-1 infection.¹³⁴ The precise role of the virus in disease pathogenesis is unclear.

TREATMENT, COURSE, AND PROGNOSIS

In patients without risk factors, 75%–80% make a satisfactory recovery.^{127–129,131} Treatment is targeted at the 25% who do not do well. In occasional cases, motor recovery fails completely. Aberrant regeneration may occur, leading to embarrassing synkinetic movements or excessive lacrimation, sometimes related to gustatory stimulation (*crocodile tears*). Patients destined to recover completely usually begin to improve within the first 3 weeks, while those with permanent residual disability remain unchanged for approximately 3 months. Prognostic decisions rely heavily upon the results of electrophysiological studies.

A 10-day course of oral corticosteroids administered in the first 72 hours after onset of Bell's palsy significantly improves the chances of complete recovery and is the current treatment standard.^{135,136} Since the role of HSV-1 infection has emerged, in recent years many practitioners have added antiviral treatment to the regimen. A role for antiviral therapy is still *sub judice* despite a number of reports; some support its use, while others suggest that it is ineffective.^{135–139} The two largest studies to date suggest no added benefit of acyclovir or valacyclovir given alone or in combination with corticosteroids.^{135,136} Although advocated by some when paralysis is total and recovery delayed, we have never referred a patient for decompression or vascular repositioning surgery.¹⁴⁰

Male patients frequently choose to grow a beard to lessen the cosmetic impact of facial paralysis. An eye patch and lubricant may be necessary to avoid exposure keratitis. Hypoglossal-facial nerve anastomosis can restore facial tone; a surgeon experienced in this procedure does it best. Gold implantation in the upper eyelid helps improve closure. Facial slings from the temporalis fascia to the angle of the mouth are generally unsatisfactory. Radical facial plastic surgery (face lift) may produce considerable improvement in facial symmetry in persistent cases of bilateral facial palsy following AIDP. Patients with eye closure weakness may develop

exposure keratitis or conjunctivitis from lagophthalmos, and a lateral tarsorrhaphy may be necessary. There is no definitive treatment for synkinetic movements; botulinum toxin injection may provide some relief.

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Plexopathies

BRACHIAL PLEXOPATHY

Anatomy

Etiology

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Thoracic Outlet Syndromes (TOS)

Neoplastic Brachial Plexopathy

Radiation-Induced Brachial Plexopathy

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(Neuralgic Amyotrophy)

LUMBOSACRAL PLEXOPATHY

Anatomy

Etiology

Trauma And Ischemia

Retroperitoneal Hemorrhage

Neoplastic Lumbosacral Plexopathy

Radiation-Induced Lumbosacral
Plexopathy

Nondiabetic Lumbosacral Radiculoplexus
Neuropathy

BRACHIAL PLEXOPATHY

Anatomy

An authoritative review of brachial plexopathies is provided by Wilbourn¹ and others.^{2,3} The brachial plexus (BP) is a complex web of nerves composed of five roots, three trunks, six divisions, three cords, and several terminal nerves (Fig. 19–1). In the most widely utilized schema, the clavicle separates the BP into anatomic regions: the supraclavicular plexus is composed of the roots and trunks, the retroclavicular plexus of the divisions, and the infraclavicular plexus of the cords and terminal nerves. In the supraclavicular plexus, the C5/6 roots/upper trunk, C7 root/middle trunk, and C8/T1 roots/lower trunk are referred to as the *upper plexus*, *middle plexus*, and *lower plexus*, respectively. The anatomy at the supraclavicular plexus level maintains a segmental pattern, while at the infraclavicular level it has sorted into nerve patterns; lesions at these sites will reflect this anatomy. Isolated lesions at the retroclavicular/divisional level are rare.

The vascular supply of the BP comes from the subclavian artery and its branches.

The dorsal and ventral roots are intraspinal and combine to form mixed spinal nerves intraforaminally, which then divide into dorsal (posterior) primary rami innervating the paraspinal muscles and ventral (anterior) primary rami. The ventral rami of C5–T1 pass between the anterior and middle scalene muscles, along with the subclavian artery; the subclavian vein lies anterior to the anterior scalene muscle. Nerves arising at this level include the long thoracic to the serratus anterior (C5–7), the dorsal scapular to the rhomboids (C5), and the nerve to the subclavius (C5, C6); C5 also contributes to the phrenic nerve (C3–5). Occasionally, the BP may anomalously receive a significant contribution from C4 (*prefixed*) or T2 (*postfixed*). Postganglionic sympathetic fibers supplying the arm join the BP at the ventral rami.

C5 and C6 unite to form the upper trunk, C7 continues as the middle trunk, and C8 and T1 unite to form the lower trunk. Off the upper trunk comes the suprascapular nerve to the supra- and infraspinatus (C5, C6); no nerves

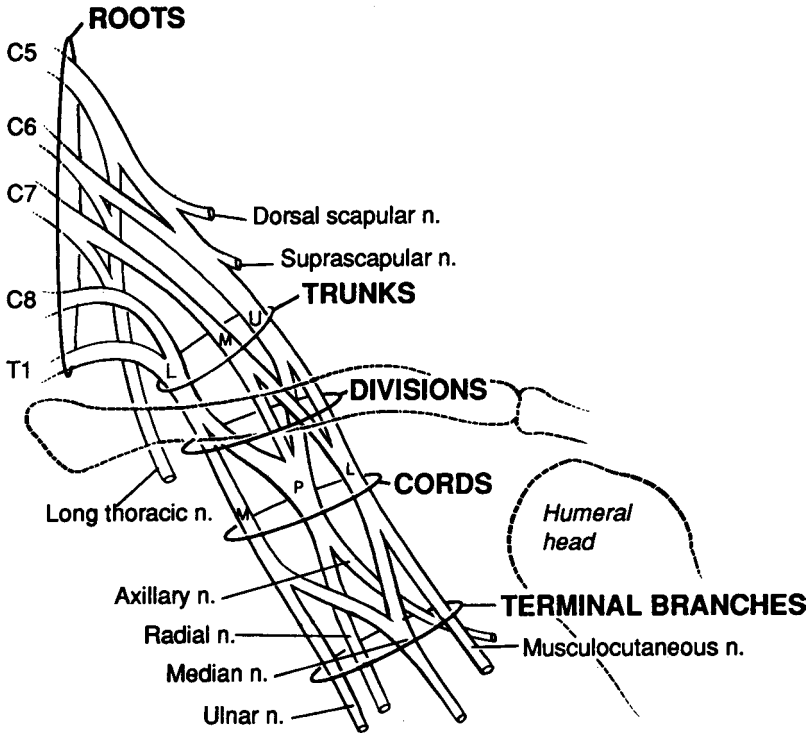


Figure 19-1 . Diagram of the major components of the BP. From Mendell JR, et al.: *Diagnosis and Management of Peripheral Nerve Disorders*. Oxford, New York, 2001, with permission.

arise directly from the middle or lower trunks. The trunks lie in the posterior triangle of the neck. The lower trunk abuts the lung apex and subclavian artery.

The trunks divide into anterior and posterior divisions. All three posterior divisions form the posterior cord. The anterior divisions of the upper and middle trunks form the lateral cord; the anterior division of the lower trunk continues as the medial cord. Off the posterior cord come the following nerves: subscapular to teres major and subscapularis (C5, C6), thoracodorsal to latissimus dorsi (C6-8), and axillary to deltoid and teres minor (C5, C6). Off the lateral cord comes the lateral pectoral nerve to pectoralis major (C5-7). From the medial cord come the following nerves: medial pectoral to pectoralis minor and major (C8, T1), medial brachial cutaneous sensory to the medial arm, and medial antebrachial cutaneous sensory to the medial forearm. The cords lie in the proximal axilla.

The terminal nerves consist of the median nerve, formed from fusion of branches of the

lateral and medial cords, and the musculocutaneous, radial, and ulnar nerves as continuations of the lateral, posterior, and medial cords, respectively. In many textbooks, the axillary nerve is regarded as a terminal nerve.

The clinical and electrodiagnostic features that allow localization of BP lesions are outlined in Table 19-1.

Etiology

The various etiologies of brachial plexopathy are outlined in Table 19-2. Those topics not covered in other chapters are reviewed here.

TRAUMA

Compression, Traction (Stretch), and Penetrating Injuries

The BP is vulnerable to a variety of injuries because of its superficial and exposed location, proximity to bony structures (clavicle, shoulder

Table 19–1 **BP Localization: Clinical and Electrodiagnostic Features**

Plexus Element	Selected Muscles Involved	Sensory Territory / Reflexes Affected	SNAP/CMAP Affected
Upper trunk	Supraspinatus, infraspinatus, deltoid, biceps, teres minor, pronator teres, flexor carpi radialis, brachioradialis, extensor carpi radialis	Over deltoid, lateral arm/ forearm and thumb/biceps and brachioradialis reflexes	SNAP: LAC, median D1 > D2 > D3, SRN CMAP: axillary (deltoid), MC (biceps)
Middle trunk	Pronator teres, flexor carpi radialis, triceps, anconeus, extensor carpi radialis, extensor digitorum communis	Dorsal forearm, hand, radial fingers/triceps reflex	SNAP: median D2/ D3, SRN CMAP: radial (anconeus)
Lower trunk	First dorsal interosseous (FDI), abductor digiti minimi (ADM), adductor pollicis, flexor digitorum profundus, flexor carpi ulnaris, abductor pollicis brevis (APB), flexor pollicis longus, pronator quadratus, extensor indicis proprius (EIP), extensor pollicis brevis, extensor carpi ulnaris	Medial arm, forearm, hand, and D4/D5	SNAP: ulnar D5, DUC, MAC CMAP: ulnar (ADM, FDI), median (APB), radial (EIP)
Lateral cord	Biceps, pronator teres, flexor carpi radialis, pectoralis major	Lateral forearm, lateral 3.5 digits/biceps reflex	SNAP: LAC, median D1/D2 > D3 CMAP: MC (biceps)
Posterior cord	Latissimus dorsi, deltoid, teres minor, triceps, anconeus, extensor carpi radialis, extensor digitorum communis, extensor pollicis brevis, extensor carpi ulnaris, extensor indicis	Over deltoid, posterior arm, forearm, hand and radial fingers/triceps reflex	SNAP: SRN CMAP: axillary (deltoid), radial (EIP, EDC, anconeus)
Medial cord	First dorsal interosseous, abductor digiti minimi, adductor pollicis, flexor digitorum profundus, flexor carpi ulnaris, abductor pollicis brevis, opponens pollicis, flexor pollicis longus	Medial arm, forearm, hand, and D4/D5	SNAP: ulnar D5, DUC, MAC CMAP: ulnar (ADM, FDI), median (APB)

DUC: dorsal ulnar cutaneous; LAC: lateral antebrachial cutaneous; MAC: medial antebrachial cutaneous; MC: musculocutaneous; SRN: superficial radial nerve.

Table 19–2 **Brachial Plexopathy: Etiologies**

Trauma	Compression, stretch and penetrating injuries Burners/stingers Rucksack palsy Obstetric/newborn paralysis Classic postoperative paralysis Postmedian sternotomy Postorthopedic procedures
Thoracic outlet syndrome	True neurogenic thoracic outlet syndrome Disputed neurogenic thoracic outlet syndrome
Neoplastic	Primary: schwannoma, neurofibroma Secondary: direct extension (Pancoast tumor) or metastatic; neurolymphomatosis
Radiation	Radiation-induced fibrosis/ischemia Reversible paresthesias Subclavian artery occlusion

(continued)

Table 19–2 (Continued)

Inflammatory/immune	Immune BP neuropathy (neuralgic amyotrophy) Multifocal motor neuropathy Multifocal acquired demyelinating sensory and motor neuropathy
Hereditary	Hereditary neuralgic amyotrophy Hereditary neuropathy with liability to pressure palsy
Ischemic	Ischemic monomelic neuropathy Vasculitis Medial brachial fascial compartment syndrome Diabetic cervical radiculoplexus neuropathy
Infectious/inflammatory/ granulomatous	Segmental zoster paresis Lyme disease Human granulocytic ehrlichiosis Sarcoidosis Connective tissue diseases Amyloidosis
Toxic	Heroin

joint), and mobility of the neck and shoulder.^{1,4,5} Closed supraclavicular traction injuries are most common, usually following motorcycle or car accidents, falls, and athletic activities. Their severity depends predominantly on the degree of applied force and its rapidity, and lesions may vary from neurapraxia to neurotmesis, including, in the most severe cases, associated root avulsions. As these are preganglionic lesions, root avulsions will spare the relevant sensory nerve action potentials (SNAPs; unless there is concomitant postganglionic plexus injury) despite profound sensory loss, while compound muscle action potentials (CMAPs) are low or absent. In addition, F waves are absent and paraspinal denervation is present on needle electromyography (EMG). Contrast-enhanced magnetic resonance imaging (MRI) or a computed tomography (CT) myelogram may demonstrate pseudomeningoceles, nerve root or stump enhancement, or paraspinal muscle abnormalities.⁶ Other clinical clues to root avulsion include involvement of nerves arising at the root level (long thoracic, dorsal scapular, phrenic), spinal cord injury, and Horner syndrome. Avulsed roots do not regenerate, and surgical repair is problematic; in adults they are often associated with early, severe, burning and paroxysmal shock-like pain that may persist and respond only to lesioning of the dorsal root entry zone.⁷ Shoulder dislocations or fractures may result in infraclavicular plexopathies,

or axillary and other terminal nerve injuries, in addition to rotator cuff tears and axillary artery injury. Fractures of the clavicle occasionally acutely damage the BP, either directly or by virtue of a hematoma, or chronically by a healed callus. The prognosis for recovery in traumatic brachial plexopathies is better if the lesion is not extensive, involves predominantly the upper plexus, is partial and demonstrates some continuity, is not associated with concomitant root avulsion, and if the underlying pathophysiology is neurapraxia and axonotmesis rather than neurotmesis. Clean lacerating injuries such as stab wounds are explored immediately and sutured end-to-end, and certainly within 1–2 weeks, before nerve retraction occurs (primary repair). Very severe/complete blunt injuries where the nerve endings may be crushed and there is extensive soft tissue damage may be repaired after 2–4 weeks (secondary repair). Most other lesions are managed conservatively for about 2–4 months before a decision is made regarding possible surgical exploration if no improvement is observed.

Burner Syndrome

The *burner* or *stinger* is a common injury in young males engaged in contact sports.⁸ Sudden, forceful trauma to the shoulder results in traction or compression of predominantly the upper plexus and/or C5/6 roots with

transient burning/sharp pain, paresthesias, and sometimes weakness in that distribution, usually lasting for minutes. Some athletes have repeated injuries and symptoms may persist, but this is uncommon. If any electrophysiologic abnormalities are present, they usually consist of some fibrillations in an upper trunk distribution. Management is conservative.

Rucksack Paralysis (Pack Palsy)

A compressive upper brachial plexopathy may result from prolonged use of a heavy backpack.^{1,9} There is usually painless weakness and sensory loss most often in an upper plexus distribution. The pathophysiology in about two-thirds of cases is focal demyelination with conduction block, in which case recovery may occur within 2–3 months; it is slower and less complete when axon loss predominates. Various mononeuropathies are occasionally ascribed to a backpack, including those of the long thoracic nerve. A pack frame and waist belt shifts the weight to the hips and may prevent BP compression.

Obstetric, Postoperative, and Postprocedure Brachial Plexopathies

Obstetric/Newborn Paralysis Upper plexus or both upper and middle plexus stretch injury (Erb palsy) is most common, followed by plexus involvement. Lower plexus (Klumpke palsy) injury is rare. Severe injuries may be associated with root avulsions. Obstetric risk factors include shoulder dystocia, large babies, breech presentation, maternal obesity and multiparity, prolonged labor, and assisted deliveries. While many infants achieve spontaneous recovery, those with substantial deficits at 3–4 months should be considered for surgery.¹

Classic Postoperative Paralysis In this entity, patients awake from general anesthesia for various surgical procedures with painless weakness and paresthesias in an isolated or predominant upper plexus distribution.¹ These are traction injuries from arm malpositioning in the vulnerable anesthetized state. Characteristically, they are associated with predominantly demyelinating conduction block and a good prognosis. Risk factors include the

Trendelenburg position, arm abduction to or beyond 90 degrees and arm board restraint in abduction, and extension and external rotation, with contralateral head rotation and lateral flexion.

Postmedian Sternotomy Splitting and retraction of the sternum for open heart surgery may result in C8 distribution symptoms and signs that may be temporary or persistent and mild to severe.¹⁰ The responsible lesion is thought to be an occult fracture of the very proximal part of the first rib, injuring the C8 anterior primary ramus. In contrast to the pattern in thoracic outlet syndrome, where T1 fibers are predominantly affected, the clinical and electrodiagnostic pattern is consistent with damage to C8. The ulnar SNAP and CMAP are affected, with less or no involvement of the medial antebrachial cutaneous SNAP and median CMAP; needle EMG shows denervation in C8 innervated muscles, most prominent in ulnar muscles. Care must be exercised not to attribute this presentation to postoperative ulnar neuropathy at the elbow or to postoperative disputed thoracic outlet syndrome. Management is conservative; in many cases, although not all, the lesions are partial and associated with demyelinating conduction block, which will improve.

Postorthopedic Procedures Injury to various parts of the BP or individual nerves may follow reduction or surgery for shoulder dislocation, surgery for anterior instability, arthroplasty, arthroscopy, and rotator cuff repair.¹¹ These injuries are usually secondary to traction or contusion and, less commonly, to laceration or inadvertent suturing. The close relationship of the suprascapular, axillary, and musculocutaneous nerves to shoulder structures makes them particularly vulnerable. Care should be taken to distinguish immune-mediated BP neuropathy (neuralgic amyotrophy) that may occasionally follow surgical procedures; the delay in onset and prominent pain are helpful historical points.

Medial Brachial Fascial Compartment (MBFC) Syndrome

The MBFC encloses the neurovascular bundle from axilla to elbow. Terminal nerves of the

infraclavicular plexus can be injured from hematoma or pseudoaneurysm in this compartment following axillary arteriography, axillary regional block, or other trauma.^{12,13} This may involve the median nerve alone or combinations of median, ulnar, radial, and musculocutaneous nerves. Early recognition and urgent surgical intervention, preferably within 4 hours, are critical to avoid severe permanent dysfunction.¹⁴

THORACIC OUTLET SYNDROMES (TOS)

True Neurogenic TOS

The space between the first rib and clavicle, through which the BP and subclavian vessels pass, is referred to as the *thoracic outlet*. The term *thoracic outlet syndrome* is used to refer to four clinical subtypes: *classic or true neurogenic*, *disputed neurogenic*, and *vascular (arterial or venous)*.^{10,15-17} True neurogenic TOS is a very slowly progressive lower trunk brachial plexopathy usually resulting from stretch/compression injury of the T1 > C8 anterior primary rami or the very proximal portion of the lower trunk over a narrow fibrous band extending from the tip of an elongated C7 transverse process or cervical rib to the first thoracic rib. This rare disorder is much more common in women than in men, with a variable age of presentation; the few patients we have seen were young to middle-aged women. Sensory symptoms (aching pain or numbness) and signs are usually in the medial arm, forearm, or hand and may be erroneously ascribed to C8 radiculopathy or ulnar neuropathy, but may be minimal or subclinical. Because the T1 fibers bear the brunt of compression, atrophy and weakness are most pronounced in the thenar muscles, but they involve all C8/T1 muscles in advanced cases. The thenar-predominant findings may be ascribed to carpal tunnel syndrome. Hand cramps may be present. In the absence of significant sensory features, patients with this condition have been referred for possible monomelic amyotrophy, multifocal motor neuropathy, or intraspinal lesions. Electrodiagnostic findings are fairly characteristic, with a normal median SNAP, low-amplitude or absent medial antebrachial cutaneous SNAPs

(most sensitive study) more than ulnar SNAPs, extremely low-amplitude median CMAP, and less affected ulnar CMAP; needle EMG shows mostly chronic denervation in a lower trunk distribution, which is most severe in the thenar muscles.^{10,18} The utility of C8 root stimulation studies in showing focal abnormalities has been suggested in some reports, and we have seen one case demonstrating prominent focal conduction block/temporal dispersion.¹⁹ Imaging will demonstrate the bony anomaly but usually does not visualize the offending fibrous band. Surgical resection of the band by way of the preferred supraclavicular approach usually reduces any discomfort and prevents progression; it may also improve motor function in mild cases but not significantly or reliably in severe cases. Two cases of true neurogenic TOS have been described in competitive swimmers, from a hypertrophied scalenus anticus muscle and fibrous band in one and a fibrous pleural band in the other, without a cervical rib.^{20,21}

Disputed Neurogenic TOS

Disputed neurogenic TOS, a controversial entity, is essentially a nonspecific pain syndrome attributed to traction, compression, or irritation of the BP by various structures without objective clinical, electrodiagnostic, or imaging findings.²² Proponents attribute a variety of symptoms to this entity, not only in a lower plexus distribution. There may occasionally be a history of preceding minor trauma. Many patients are women with droopy shoulders and a long swan neck.²³ In one study of instrumentalists, about 40% received the diagnosis of disputed TOS, which often responded to conservative therapy.²⁴ Various maneuvers purporting to support TOS (Adson test, costoclavicular test, elevated arm stress test, and supraclavicular pressure maneuvers) have a high false-positive rate in normal subjects and an even higher rate in carpal tunnel syndrome patients.^{25,26} Many patients who receive this diagnosis likely have cervical radiculopathy or median or ulnar entrapments. Some of these patients have undergone transaxillary first rib resections and suffered postoperative painful lower trunk plexopathy.²⁷

Arterial and Venous Vascular TOS

Arterial vascular TOS presents with limb ischemia and most often results from compression of the subclavian artery by a cervical rib, with poststenotic dilatation and aneurysm formation that may result in thrombosis and embolism. Venous vascular TOS (Paget-Schroetter syndrome) presents with acute or chronic limb cyanosis, swelling, and pain resulting from thrombosis of the subclavian and axillary veins.

NEOPLASTIC BRACHIAL PLEXOPATHY

Primary neoplasms of the BP are rare.^{28–30} Most are benign and of neural sheath origin (schwannomas; neurofibromas, with or without neurofibromatosis). A supraclavicular location predominates. Some schwannomas extend through the neural foramen and form dumbbell-shaped lesions. Malignant neural sheath tumors (e.g., malignant schwannomas, neurofibromas, neurogenic sarcomas) and benign nonneural sheath tumors (e.g., ganglion cysts, lipomas, desmoids) are even more rare. Presenting signs and symptoms may include a palpable mass and local or radiating pain, and there may be numbness/paresthesias or weakness. Most of these lesions are well characterized by MRI.³¹ Schwannomas are well encapsulated, lie between fascicles, and are usually straightforward to excise; neurofibromas arise within fascicles, which will be sacrificed with excision.

Secondary neoplasms of the BP are more common.^{32,33} These malignant nonneural sheath tumors invade the plexus either by direct extension from the apical lung (Pancoast or superior sulcus syndrome) or by metastasis, usually to the axillary lymph nodes. Metastatic breast or lung tumors and lymphomas account for about three-quarters of the cases. These neoplasms tend to present as painful lower trunk plexopathies, often with a Horner syndrome, but may soon become diffuse or patchy. Perhaps one-third develop epidural spread. Most patients with metastases to the plexus have a known tumor. Pancoast syndrome, on the other hand, is often the first manifestation of an apical lung tumor, typically a non-small cell carcinoma in a male smoker. Electrodiagnostic studies can localize the

lesion and assess its severity; the medial antebrachial cutaneous SNAP may be a sensitive parameter, as it assesses T1 sensory fibers.³⁴ Magnetic resonance imaging is the imaging modality of choice; positron emission tomography (PET) can also be helpful in detecting an active neoplasm.

While there are no absolute criteria, the following features favor neoplastic over radiation BP: pain as the presenting and predominant symptom, shorter course, lower plexus involvement, Horner syndrome, discrete mass on imaging and gadolinium nerve enhancement, and a positive PET scan.

RADIATION-INDUCED BRACHIAL PLEXOPATHY

Most cases occur in women treated for breast cancer.^{1,2,32,33,35–37} Radiation effects on the BP are dose-dependent. Additional risk factors include large daily fractions, “hot spots” from overlapping fields, and concurrent chemotherapy.¹ The latency to onset is quite variable, ranging from several weeks to decades (usually a few years), and the disorder tends to be progressive, with sensory and motor deficits. Paresthesias in median-innervated fingers are often the presenting symptoms. Pain is often said to be absent or mild, but can be severe and prominent, and is quite common in some series. While some reports suggest an upper plexus predilection, others suggest that lower plexus or pan-plexus involvement is more common. There are no established therapies. One small study suggested partial recovery with anticoagulation.³⁸ In patients with severe pain, dorsal root entry zone lesions can be effective therapy.³⁹

A reversible variant of radiation plexopathy is also described with paresthesias that abate spontaneously over 6–12 months.⁴⁰ Rarely, an acute ischemic BP may result from postradiation subclavian artery occlusion.⁴¹ Malignant nerve sheath tumors can be a rare sequela.

The pathology of radiation injury consists of severe fibrosis, vascular occlusion, and myelin and axon loss. The process may begin with demyelinating conduction block, demonstrable electrophysiologically across the supraclavicular stimulation site, and progress to axon loss.⁴² Myokymic discharges, rarely present in neoplastic plexopathy, are seen in about 63% of cases, or there may be fasciculations.^{35,36}

Myokymia is seen in about one-quarter of muscles sampled, most commonly in the pronator teres and abductor pollicis brevis muscles.

While there are no absolute criteria, the following features favor radiation over neoplastic BP: paresthesias as the presenting symptom, pain absent or mild and later in the course (but can be severe), upper plexus involvement by some reports³² but lower plexus or diffuse involvement by others,³⁵ lymphedema, local tissue necrosis, myokymia or fasciculations, conduction block across the BP, paraspinal muscle fibrillations, and a combination of abnormal median SNAP and normal median or ulnar CMAPs.

IMMUNE BRACHIAL PLEXUS NEUROPATHY (NEURALGIC AMYOTROPHY)

Introduction

There are two phenotypically similar disorders referred to as *brachial plexus neuropathy*. One is a sporadic, likely immune-based disorder, *immune brachial plexus neuropathy* (IBPN); the other is a rare recurrent hereditary condition, *hereditary brachial plexus neuropathy* (HBPN) or *hereditary neuralgic amyotrophy* (HNA). Synonyms for the more common IBPN include, *inter alia*, *neuralgic amyotrophy*, *Parsonage-Turner syndrome*, *brachial neuritis*, *brachial plexitis*, and *acute shoulder-girdle neuritis*.⁴³ IBPN and HBPN are both widely held to reflect inflammatory immune processes; however, the detailed pathogenesis of neither condition is certain. HBPN is discussed further in Chapter 14.

Clinical Features

IBPN can occur at almost any age, with an average age of onset of about 41 years and a male-to-female ratio of about 2–3:1.^{44,45} Many of the patients we have seen were young adult men. One study suggests an incidence of 1.64 per 100,000.⁴⁶ A heralding feature in perhaps half of the cases is an antecedent infectious illness (most commonly upper respiratory or flu-like) or other possibly predisposing factors such as unaccustomed exercise, surgery, pregnancy/puerperium, vaccination, or Hodgkin disease with radiation therapy. Postsurgical IBPN may be erroneously ascribed to surgical

error. A few cases have followed immunomodulating therapy with interleukin-2, interferon, or tumor necrosis factor (TNF)-alpha inhibitors.⁴⁷

There are generally no constitutional disturbances. The initial symptom is abrupt, often nocturnal (~60% of cases) onset of severe shoulder girdle-scapular pain, occasionally extending into the arm or hand. The pain is exacerbated by arm movement. Pain is frequently so severe as to require narcotics and suggests an erroneous diagnosis of spinal root compression. Painless attacks occur in a very small minority of adults (3.7%);⁴⁵ pain is less frequent in children with this disorder. Severe neuropathic pain persists for a few weeks to months (average, about 4 weeks; occasionally, as brief as a few hours) and then usually subsides. A subsequent musculoskeletal-type pain may persist in as many as two-thirds of cases. Weakness appears within days to weeks, often appreciated as pain subsides, and involves shoulder girdle muscles innervated from the upper plexus.⁴⁵ Among the most commonly involved nerves are the long thoracic, suprascapular, musculocutaneous, and axillary nerves, but almost any upper extremity nerves can be affected in any combination or in isolation (Fig. 19–2).⁴⁸ When present in this setting, scapular winging is a telltale sign, as is the patchy nature of the involved nerves and weakness. Distal weakness in a lower plexus distribution is less frequent (more common in women),^{45,49} and, rarely, the entire arm and ipsilateral diaphragm may become paralyzed. Muscle atrophy appears rapidly. Weakness may appear sequentially in the other arm; it is almost always asymmetric, and if it is symmetric, disorders of the spinal cord or roots are more likely. Tendon reflexes are normal or diminished in the involved extremity; a minor degree of sensory loss is discernible on careful testing in many cases, but it is rarely of clinical significance.⁴⁴ Lower cranial nerves (IX–XII) are rarely involved. Some cases of isolated and unexplained unilateral or bilateral diaphragmatic paralysis may be due to this cause, as are some instances of isolated anterior or posterior interosseous neuropathy. Horner syndrome is not a feature. Attacks can also be either pure motor or pure sensory.^{45,50}

Over half of patients receive an erroneous initial diagnosis, usually either cervical radiculopathy or shoulder joint pathology.⁴⁵ Patients

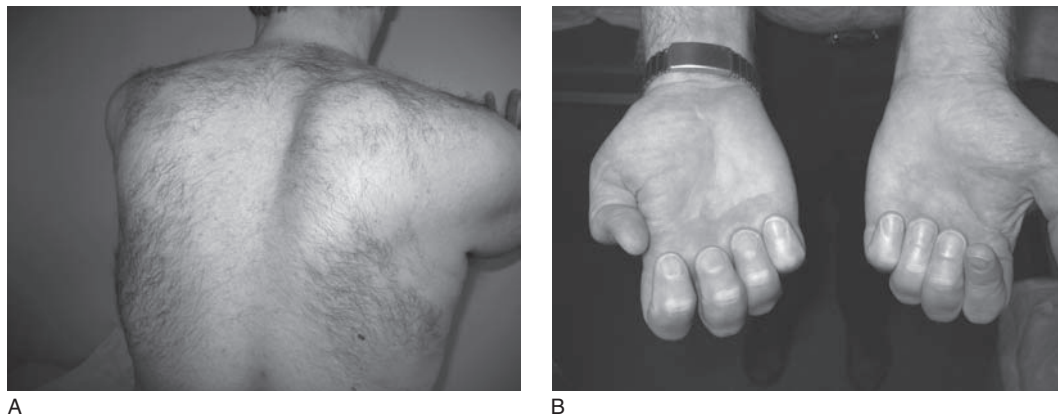


Figure 19-2. Patient with postsurgical immune BP neuropathy demonstrating right scapular winging (A) indicating long thoracic neuropathy (the left was also mildly involved). There is also weakness of the left flexor digitorum profundus of the index finger (B) with lesser involvement of the flexor pollicis longus, indicating anterior interosseous neuropathy.

may initially seek a surgical opinion. In our experience, some surgeons unfamiliar with the disorder embark on a needless evaluation for a radicular or entrapment syndrome, occasionally resulting in unnecessary surgery.

Laboratory and Imaging Studies

Cerebrospinal fluid examination is usually normal or demonstrates a modest elevation of protein and, rarely, a slight pleocytosis. Cervical MRI may be helpful in excluding mimicking conditions such as cervical radiculopathy, but frequently it is likely to show incidental abnormalities. Brachial plexus MRI will not be necessary in every typical case but occasionally it may support the diagnosis, especially when it shows increased T2 signal in the plexus or signal alteration consistent with skeletal muscle denervation.^{51,52} Magnetic resonance neurography may be more sensitive. Many practitioners observing a progressive clinical picture or failure of recovery will obtain a plexus MRI to exclude other lesions. Chest X-ray may show an elevated hemidiaphragm secondary to phrenic nerve involvement. Elevated liver function tests (LFTs) occur in a few cases, particularly those with a more severe phenotype, and likely reflect an antecedent infectious agent causing a transient hepatitis.⁴⁵ Antiganglioside antibodies may be found in up to one-quarter of patients.⁴⁵

Electrodiagnostic studies demonstrate low CMAPs from affected muscles; occasionally, low-amplitude SNAPs are present, particularly in the lateral antebrachial cutaneous nerve. Needle EMG usually demonstrates denervation in clinically affected and some nonaffected muscles; occasionally, it is demonstrable in “normal” muscles of the other extremity as well.⁵³ Paraspinal denervation can be seen in this entity. The electrophysiologic picture is most commonly one of an upper extremity axon-loss-type mononeuropathy, multiple mononeuropathy, or predominantly upper plexopathy, but some reports describe demyelinating conduction block on root stimulation studies early in the course.⁵⁴ Since sensory responses are often normal, the electrophysiology may suggest radicular or polyradicular dysfunction.

Pathology and Pathogenesis

Nerve biopsies of the plexus and distal peripheral nerves demonstrate focal perivascular endoneurial and epineurial lymphocytic infiltrates (mainly T lymphocytes) without evidence of fibrinoid necrosis of vessel walls. These changes are similar to those demonstrated in nondiabetic and diabetic lumbosacral radiculoplexopathies.^{55,56} Fusiform thickening of nerve trunks is a feature of recurrent cases of IBPN, and fiber loss is present in distal nerves.

Taken in concert, the monophasic illness, biopsy findings of inflammation, MRI demonstration of multifocal hyperintensity, and appearance of IBPN following infectious diseases or immunizations strongly suggest an immune-inflammatory pathogenesis for this disorder. Complement-fixing antibodies to peripheral nerve myelin have been demonstrated in the acute phase of IBPN.⁵⁷

Treatment, Course, and Prognosis

No specific immune-modulatory treatment has been established. Pain may respond to a combination of a nonsteroidal anti-inflammatory drug (NSAID) and an opiate; some practitioners administer a short course of tapering corticosteroids if the patient presents during the painful phase. Uncontrolled reports suggest that corticosteroids may have a favorable effect.⁴⁵ Most patients achieve satisfactory improvement, but it is often many months to years before strength increases. One study demonstrated that 80%–90% of patients recover after 2 to 3 years,⁴⁴ but others suggest

a less optimistic prognosis regarding functional deficits or chronic pain.⁴⁵ Recurrence is reported in about 5%–26% of patients followed for up to 6 years.^{44,45}

LUMBOSACRAL PLEXOPATHY

Anatomy

An extensive review of lumbosacral (L/S) plexopathies is provided by Donaghy.⁵⁸ The lumbosacral plexus derives from the ventral rami of the L1–S4 spinal nerves. The lumbar plexus arises from L1–L4; within the psoas muscle, the dorsal branches of L2–4 form the femoral nerve and the ventral branches form the obturator nerve (Fig. 19–3). The following muscles are innervated directly from the lumbar plexus: psoas major (L2–4) and minor (L1), iliacus (L2, L3), and quadratus lumborum (T12–L4). In addition, the iliohypogastric (T12, L1), ilioinguinal (L1), genitofemoral (L1, L2), and lateral femoral

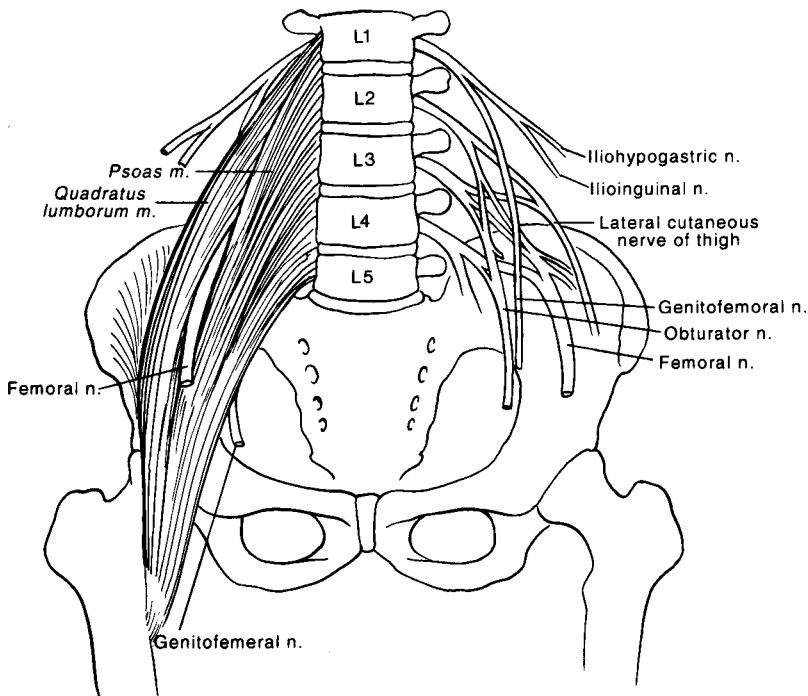


Figure 19–3. Diagram of the major components of the lumbar plexus. From Mendell JR, et al.: *Diagnosis and Management of Peripheral Nerve Disorders*. Oxford, New York, 2001, with permission.

cutaneous (L2, L3) nerves arise from the lumbar plexus; these are discussed in Chapter 18.

Ventral rami of L4-5 combine to form the lumbosacral trunk, which joins the ventral rami of S1-4 to form the sacral plexus, lying on the posterior and posterolateral walls of the pelvis (Fig. 19-4). The dorsal divisions of L4-S2 form the lateral trunk of the sciatic nerve, which becomes the common peroneal nerve; the medial trunk, which becomes the tibial nerve, is formed by the ventral divisions of L4-S3. Nerves arising from the sacral plexus include the superior (L4-S1) and inferior (L5-S2) gluteal, posterior femoral cutaneous (S1-3), and pudendal (S2-4) nerves. The blood supply of the L/S plexus is from branches of the internal iliac artery.

The clinical and electrodiagnostic features that aid localization of L/S plexus lesions are outlined in Table 19-3. Sacral plexopathies may be difficult to localize definitively by electrophysiology alone.⁵⁹

Etiology

The various etiologies of lumbosacral plexopathy are outlined in Table 19-4. Those

topics not covered in other chapters are reviewed here.

TRAUMA AND ISCHEMIA

The L/S plexus is protected from trauma by its deep location and by the bony pelvic ring. However, it may be susceptible to penetrating injuries, pelvic fractures/dislocations, and iatrogenic surgical trauma.

Obstetric postpartum foot drop may be the result of compression of the lumbosacral trunk by the fetal head at the pelvic brim.⁶⁰ Risk factors include prolonged labor, cephalopelvic disproportion, use of mid-pelvic forceps, short stature, and a large newborn. There is weakness of foot dorsiflexion, eversion, and inversion and sensory loss in an L5 distribution. Typically, the peroneal SNAP is low or absent, the peroneal CMAP may be low, and denervation is present in L5-innervated muscles mostly below the knee. Recovery usually occurs within 5 months. Other differential diagnostic considerations for foot drop in this setting include compressive peroneal neuropathy at the fibular head (from stirrups; or from prolonged squatting for natural childbirth in some countries), as well as L5 radiculopathy from lumbar disc herniation and, rarely, from

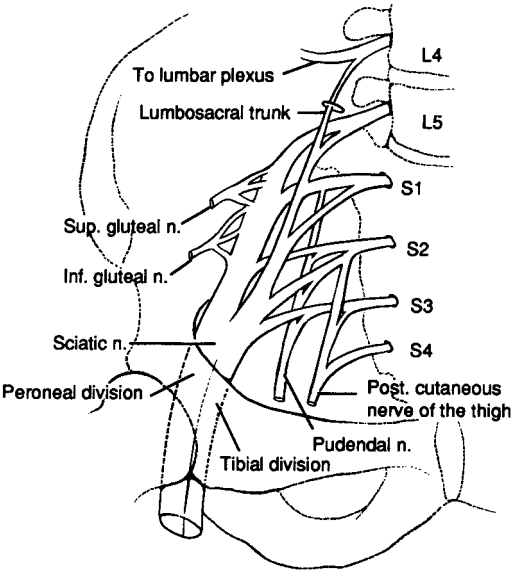


Figure 19-4 . Diagram of the major components of the sacral plexus. From Mendell JR, et al.: *Diagnosis and Management of Peripheral Nerve Disorders*. Oxford, New York, 2001, with permission.

Table 19–3 L/S Plexus Localization: Clinical and Electrodiagnostic Features

Plexus Element	Selected Muscles Involved	Sensory Territory / Reflexes Affected	SNAP/CMAP Affected
Lumbar (L1-4)	Iliopsoas; quadriceps (femoral) and adductor (obturator) groups	Anterior and medial thigh, medial calf */patellar, adductor, and cremaster reflexes	SNAP: saphenous, lateral femoral cutaneous CMAP: femoral
Lumbosacral trunk (L4, L5)	Glutei, tensor fascia lata, hamstring group, tibialis anterior (TA) and posterior (TP), extensor hallucis longus, peronei, flexor digitorum and hallucis longus	Lateral calf, dorsal foot	SNAP: superficial peroneal CMAP: peroneal (extensor digitorum brevis, tibialis anterior)
Sacral (S1-4)	Most of above (L4, L5) except TA/TP; gastrocnemius, soleus, intrinsic foot muscles	Perineum, posterior thigh and calf, sole/ankle reflex	SNAP: sural, plantar CMAP: tibial

* Also may involve pain and small sensory territories of iliohypogastric, ilioinguinal, or genitofemoral nerves.

Table 19–4 L/S Plexopathy: Etiologies

Trauma	Penetrating injuries, pelvic fracture and dislocations Iatrogenic trauma during pelvic surgery Obstetric injuries—lumbosacral trunk plexopathy
Hemorrhage	Retroperitoneal hemorrhage
Neoplastic	Primary: schwannoma, neurofibroma Secondary: malignant, direct extension or metastatic
Radiation	Radiation lumbosacral plexopathy Postirradiation lower motor neuron syndrome Radiation-induced nerve sheath tumors
Inflammatory/immune	Multifocal motor neuropathy Multifocal acquired demyelinating sensory and motor neuropathy
Hereditary	Hereditary neuropathy with liability to pressure palsy
Ischemic	Ischemic monomelic neuropathy Vasculitis Intra-arterial injections Aortic or iliac aneurysms Diabetic L/S radiculoplexus neuropathy Nondiabetic L/S radiculoplexus neuropathy
Infectious/inflammatory/ granulomatous	Retroperitoneal abscess—bacterial, tuberculous Herpes simplex Herpes zoster/segmental zoster paresis Lyme disease Sarcoidosis Connective tissue diseases
Toxic	Amyloidosis Heroin

root damage by an epidural anesthetic catheter.

Ischemic L/S plexopathy may follow inadvertent buttock injections of vasotoxic drugs into the gluteal arteries.⁶¹ This is thought to result in a toxic endarteritis with retrograde

spasm and thrombosis of the iliac arteries; it is also associated with swelling and bluish discoloration of the buttocks (*embolia cutis medicamentosa*) and ipsilateral leg ischemia. In addition, L/S plexopathy has followed intra-arterial infusion of chemotherapeutic agents.⁶²

RETROPERITONEAL HEMORRHAGE

Retroperitoneal hemorrhage occurs secondary to anticoagulation, various coagulation disorders, aneurysmal rupture, or trauma.⁶³ A hematoma within the iliopsoas muscle results in an isolated femoral neuropathy, with severe pain in the lower abdomen and groin radiating to the anteromedial thigh and medial leg, pain on hip extension, and sometimes a visible, palpable mass in the groin. Hemorrhage within the psoas muscle results in a lumbar plexopathy with weakness and sensory disturbance in the femoral and obturator nerve territories; there is less pain on hip extension and usually no visible or palpable mass. The hematoma is readily visualized by CT or MRI. While some patients treated with emergent surgical decompression have fared well, the optimal management of these lesions remains uncertain in the absence of controlled trials.^{58,64,65}

NEOPLASTIC LUMBOSACRAL PLEXOPATHY

Primary neural sheath tumors of the L/S plexus (schwannoma, neurofibroma) are uncommon. Secondary tumors may be locally invasive (colorectal, prostate, gynecologic, bladder, renal) or metastatic from a variety of neoplasms. Perineurial spread is a potential mechanism, as described in two cases with prostate cancer.⁶⁶ The most common neoplasms implicated overall are colorectal, sarcoma, breast, lymphoma, and uterine/cervix.^{33,67,68} They may involve the upper, lower, or pan-plexus. Insidious, severe, unrelenting pelvic or radicular pain, often worse at night, is the cardinal presenting feature, followed later by motor and sensory dysfunction. Leg edema and mechanical signs may be present. Focal dysautonomia in the form of a "hot, dry foot" has been suggested as an early manifestation in some cases.⁶⁹ A rectal mass or hydronephrosis may be additional features. Associated epidural disease is common (~45%). Bilateral involvement occurs in 10%–25% of cases; sacral plexus dysfunction can result in incontinence and impotence. An MRI or CT scan will demonstrate the neoplasm in most cases, with MRI being more sensitive; PET scanning can also be helpful in identifying an active neoplasm. The overall prognosis for these patients, even with radiotherapy and chemotherapy, is poor, with short

survival (86% die within 3.5 years).⁷⁰ Pain palliation is critical.

RADIATION-INDUCED LUMBOSACRAL PLEXOPATHY

The L/S plexus is less frequently damaged by radiation therapy than the BP.⁷⁰ The most common neoplasms involved are testicular, gynecologic, and lymphoma. Clinical features include variable latency to onset (1 month to 31 years); initial weakness (60%) or numbness/paresthesias rather than pain; eventual pain in about one-half of patients but usually not troublesome, as with neoplasm; a variable rate of progression, from rapid in a few to more commonly gradual, often bilateral, asymmetric involvement; diffuse or distal predominant weakness; and reflex loss. Occasional sphincter dysfunction may be related to proctitis or bladder fibrosis. Skin changes may be apparent in the area of the radiation portals. In addition to signs of a chronic plexopathy or radiculoplexopathy, EMG shows myokymia (and, less frequently, fasciculations) in about 60% of patients, often widely scattered in one or a few muscles and mostly in proximal muscles such as the paraspinals, iliopsoas, glutei, quadriceps, and hamstrings. The CSF protein can be elevated, up to 106 mg/dL in one series.⁷⁰ An MRI and PET scan may help exclude tumor recurrence. A few cases that have come to surgery or autopsy have shown extensive fibrosis of the L/S plexus. This disorder generally progresses to moderate to severe weakness but may plateau in some cases after a number of years; a rare case showed spontaneous improvement.

A rarer postirradiation lower motor neuron syndrome follows radiation exceeding 40 Gy that encompasses the distal spinal cord and cauda equina after a latency of 3–25 years.⁷¹ There is painless leg wasting and fasciculations, although mild sphincter or sensory symptoms may also develop. Gadolinium MRI may show enhancement of the cauda equina. Autopsy in one patient showed a radiation-induced vasculopathy of the proximal spinal roots without involvement of spinal anterior horn cells; *postirradiation lumbosacral radiculoplexopathy* was suggested as a more accurate term.

NONDIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

Although more uncommon, nondiabetic L/S radiculoplexus neuropathy (LRPN) is the lower extremity analogue of IBPN, and its clinical, electrophysiologic and pathologic features are essentially the same as those of diabetic L/S radiculoplexus neuropathy (DLRPN) without the diabetes (see Chapter 10).^{55,72–75} Other authors use the terms *idiopathic lumbosacral plexopathy*, *plexitis*, *neuritis*, or *neuropathy*. Onset is acute or subacute with back, buttock, thigh, or leg pain, followed by evolution of weakness in usually but not invariably proximal > distal segments, with associated sensory and often autonomic involvement as well. The majority of patients develop bilateral asymmetric involvement. About 17% of patients have recurrent episodes. As in DLRPN, weight loss is common. Electrophysiologic studies are consistent with a pattern of axon-loss plexopathy or radiculoplexopathy. A few reported cases have been associated with an elevated erythrocyte sedimentation rate (ESR).⁷⁶ The CSF protein is normal or mildly to moderately elevated (range, 18–283 mg/dL).⁷² All patients improve to some degree over months to years, but morbidity from pain and from persistent weakness can be severe; few recover completely. Pain may persist for many months.⁷⁷ A small minority of patients develop diabetes on follow-up. As in DLRPN, the cause is ischemic injury from microvasculitis.⁷⁸ There seems little doubt that LRPN and DLRPN are immune-mediated disorders. A few uncontrolled reports suggest significant improvement in pain and weakness with intravenous immunoglobulin (IVIG) or intravenous corticosteroid treatment of LRPN.^{79–81} This has been our limited anecdotal experience as well, and pending further guidance from controlled trials, we treat patients with significant pain and weakness, and no contraindications, who are seen within the first few months, when the inflammatory phase of the illness is presumably active. These patients require diligent symptomatic and supportive therapy for what may be a monophasic but prolonged and debilitating illness.

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Disorders of Peripheral Nerve Hyperexcitability

GENERALIZED DISORDERS

Neuromyotonia
Cramps
Fasciculations
Tetany

LOCALIZED DISORDERS

Facial Myokymia
Localized, Focal Myokymia
Hemifacial Spasm
Hemimasticatory Spasm
Hypothenar Dimpling

Disorders associated with excess motor unit activity may arise from the central nervous system (CNS) or the peripheral nervous system (PNS).¹ In the CNS, corticospinal tract lesions result in spasticity. Extrapyramidal lesions cause disorders of muscle posture and tone. Disorders of spinal inhibitory interneurons are associated with stiff-person syndrome, tetanus, and strychnine poisoning. Table 20–1 outlines the disorders associated with hyperexcitability of the peripheral nerve axon. Various ectopic discharges arise along the course of peripheral motor or sensory axons. Their origin in peripheral nerve can be established by the following characteristics: unaffected by general anesthesia, sleep, or nerve block proximal to the lesion site, and abolished by nerve block distal to the lesion site or neuromuscular transmission blockade.

GENERALIZED DISORDERS

Neuromyotonia

The clinical syndrome of neuromyotonia encompasses a number of phenotypic variants and has been called by many terms, including

syndrome of continuous muscle fiber activity, Isaacs syndrome, quantal squander, Armadillo syndrome, neurotonia, undulating myokymia, idiopathic generalized myokymia, and others.^{1–5} The *cramp-fasciculation syndrome* is a milder clinical variant; features are restricted to muscle cramps, aching, exercise intolerance, stiffness, and fasciculations and afterdischarges, without electrophysiologic myokymic or neuromyotonic discharges.⁶ *Morvan syndrome*, with features of neuromyotonia and additional CNS dysfunction (psychiatric disturbances including hallucinations and delusions, mood change, insomnia), is a more severe clinical variant. The syndrome of neuromyotonia may be acquired or hereditary (Table 20–1). Most cases of acquired neuromyotonia have an immune basis, with antibodies to voltage-gated potassium channels (VGKCs) being implicated in many instances; some are related to toxicity from a limited number of pharmaceutical, environmental or industrial agents. Rarely, hereditary neuropathies, spinal muscular atrophy, or VGKC gene mutations (EA-1, episodic ataxia-myokymia, KCNA1 mutation) display features of neuromyotonia. The hereditary peripheral nerve

Table 20–1 Disorders of Peripheral Nerve Hyperexcitability

Generalized Disorders

Neuromyotonia

Acquired

- Immune-mediated (VGKC autoantibodies)
 - Isolated
 - Paraneoplastic
 - Associated with other autoimmune disorders
 - Associated with dysimmune neuropathy (GBS, CIDP)
 - Penicillamine-induced in rheumatoid arthritis
 - Associated with CNS disturbance (Morvan syndrome)
- Toxic
 - Gold, oxaliplatin, timber rattlesnake envenomation, toluene

Hereditary

- Episodic ataxia, type 1 (EA-1; KCNA1 gene mutation)
- Hereditary neuropathies (CMT1, CMT2)
- Spinal muscular atrophy/distal hereditary motor neuropathy
- Schwartz-Jampel syndrome

Cramps

Fasciculations

Tetany

Localized Disorders

Facial myokymia

Localized or focal myokymia

Hemifacial spasm

Hemimasticatory spasm

Hypothenar dimpling

KCNA1: voltage-gated potassium channel, Shaker-related subfamily, member 1; VGKC: voltage-gated potassium channel.

sodium and potassium channelopathies are discussed in more detail in Chapter 14.

CLINICAL FEATURES OF ACQUIRED NEUROMYOTONIA

Acquired neuromyotonia can present at any age, with an average age of onset of about 47, and more commonly in men.² Peripheral nerve hyperexcitability in motor axons results in muscle twitching (myokymia or fasciculations), stiffness, cramps, delayed muscle relaxation (pseudomyotonia), and pseudotetany (carpal or pedal spasms). Muscle twitching is the most common symptom, present in over 90% of patients. The topography is quite variable, with involvement of limb, trunk, or facial/bulbar muscles in any combination, most often affecting the limbs and trunk or limbs only. Symptoms are exacerbated or triggered

by exercise or muscle contraction. Pseudomyotonia is present in about one-third of patients on hand grip, eye closure, or jaw closure, but usually there is no percussion myotonia. Perhaps one-third of patients show some degree of weakness, usually in the most overactive muscles. Involvement of sensory axons causes transient paresthesias or numbness in about one-third of patients, unassociated with the presence of polyneuropathy; positive sensory phenomena predominate.^{2,7} This occurs spontaneously or may be precipitated by minor compression, trauma, or stretching of any nerve; multiple Tinel signs may be present. Hyperhidrosis most likely reflects muscle overactivity; dysautonomia is an alternative explanation. Hyperhidrosis may rarely be the only clinical manifestation of neuromyotonia.⁸ The clinical exam may also reveal muscle hypertrophy or a Chvostek sign; reflexes are usually normal unless stiffness is so pronounced that eliciting a response is difficult.

Symptoms tend to fluctuate in severity over months.

Differential diagnostic considerations depend on the specific features that predominate but may include benign fasciculations, benign cramps, motor neuron disease, stiff person syndrome, tetanus, myotonic disorders, rippling muscle disease (caveolinopathies), tetany, polyneuropathy, or the syndrome of painful legs and moving toes. The differential diagnosis of Morvan syndrome includes herpes simplex encephalitis, Korsakoff syndrome, Creutzfeldt-Jakob disease, anti-NMDA (N-methyl-D-aspartate) receptor encephalitis and paraneoplastic limbic encephalitis. The presence of hyponatremia is a useful clue in cases of VGKC antibody-associated encephalopathy/limbic encephalitis; these cases may or more often do not have peripheral clinical or electrophysiologic features of neuromyotonia.^{9,10}

Complex repetitive discharges (CRDs) do not arise from nerve but rather from groups of muscle fibers linked by ephapsis and driven by a pacemaker fiber, but they are mentioned here because they can be confused with other discharges and, when abundant, may produce muscle hypertrophy. They are seen in various chronic denervating conditions and certain myopathies. They are regularly recurring, polyphasic, complex waveforms with abrupt onset, a constant firing rate, occasionally abrupt change in firing rate or shape, and abrupt termination; their sound is likened to that of a machine gun. They discharge at rates usually ranging from 5 to 100 Hz. Constant CRDs in abundance are apparently responsible for some cases of neurogenic muscle hypertrophy and pain in the gastrocnemius muscle in S1 radiculopathy, in myotomal muscles of a C6 radiculopathy, and in occasional mononeuropathies, as well as bilateral hypertrophy in spinal muscular atrophy.^{11–14} Botulinum toxin may be helpful.

LABORATORY STUDIES

The creatine kinase (CK) level is raised in about one-half of patients. The cerebrospinal fluid (CSF) may be normal, and occasionally shows oligoclonal bands or a mild-moderate increase in protein. Nerve conduction studies demonstrate an idiopathic, axonal, subclinical polyneuropathy in up to 14% of cases.

Compound muscle action potentials (CMAPs), late responses, or repetitive stimulation studies at 1–5 Hz may show repetitive afterdischarges (Fig. 20–1). Needle electromyography (EMG) shows myokymic discharges, neuromyotonic discharges, or fasciculation potentials in any combination. Doublet discharges are the most common abnormality.² Fibrillations are occasionally observed in cases with abnormal nerve conduction. Neuromyotonic discharges consist of very-high-frequency, irregular bursts of motor unit potentials (150-to 300-Hz intraburst frequency, widely variable interburst frequency), with a waning amplitude resulting in a high-pitched sound (ping). Myokymic discharges are rhythmic or semirhythmic bursts of grouped motor unit potentials as doublets, triplets, or multiplets at varied rates (usually slower intraburst frequency than neuromyotonic discharges) and intervals with the sound of marching soldiers; the resultant twitching has a vermicular (worm-like) or undulating appearance. While the generator site for these spontaneous discharges may lie anywhere along the course of the motor axon, it appears to arise most commonly from the terminal arborizations.¹⁵

PATHOPHYSIOLOGY

There is a strong association with a variety of autoimmune disorders and autoantibodies (~50%), most commonly myasthenia gravis (~20%) or diabetes mellitus, occasionally Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Paraneoplastic cases are usually associated with lung cancer or thymoma and rarely with Hodgkin lymphoma, plasmacytoma with immunoglobulin M (IgM)-lambda paraproteinemia, or amyloidosis. We have seen a recent case associated with ovarian cancer. Tumors may present up to 4 years after the onset of peripheral nerve hyperexcitability, so vigilance is mandatory. Serum antibodies to VGKCs can be detected in about 40% of neuromyotonia cases overall and in about 80% when thymoma is present.² These findings, along with passive transfer of peripheral nerve hyperexcitability to experimental animals by patients' plasma or immunoglobulins, effects of their serum on in vitro VGKC currents, and their response to plasmapheresis, establish that

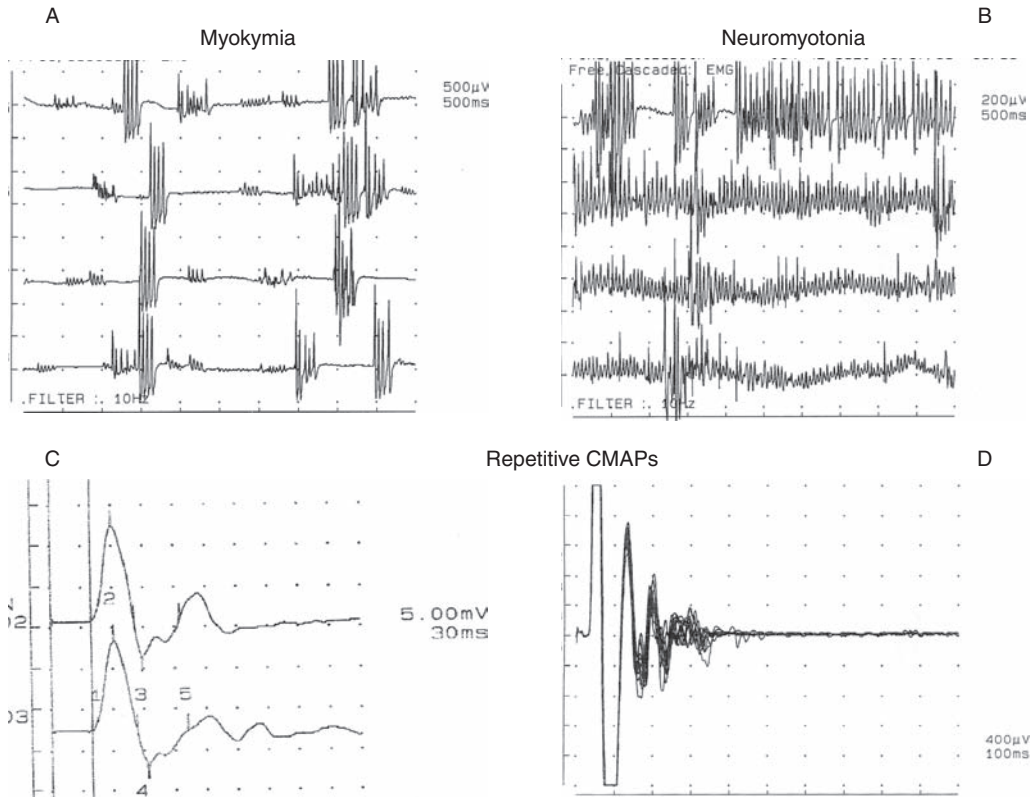


Figure 20-1. Needle EMG and motor nerve conduction study recordings demonstrating myokymia (A), neuromyotonia (B), and repetitive CMAP afterdischarges (C, D) in a patient with VGKC antibody-positive acquired neuromyotonia.

acquired neuromyotonia is, in many cases, an autoimmune channelopathy mediated by antibodies to VGKCs.⁵

TREATMENT, COURSE, AND PROGNOSIS

All patients presenting with peripheral nerve hyperexcitability should be screened for an underlying malignancy, particularly chest tumors (thymoma, lung cancer, lymphoma), and for serum autoantibodies, including VGKC and acetylcholine receptor antibodies, diabetes, and thyroidopathy.² Most patients can probably be managed symptomatically with carbamazepine, phenytoin, gabapentin, sodium valproate, lamotrigine, or acetazolamide.^{7,15} There are no controlled trials to guide the use of immunosuppression. Severe cases may respond to plasmapheresis.^{16,17} Single reports suggest the utility of intravenous immunoglobulin (IVIG), but in general, the impression seems to be that

IVIG is disappointing and that treatment of an underlying malignancy, if present, has little effect.^{4,18} VGKC antibody-associated encephalopathy/limbic encephalitis responds somewhat to variable regimens of immunosuppression.^{9,10}

Cramps

Cramp discharges represent repetitive firing of motor unit potentials at rates as high as 200–300 Hz, involving a large part of the muscle synchronously, with gradual onset and cessation, and are usually associated with painful muscle contraction.¹⁹ Fasciculations occur at the beginning and end of cramps. The weight of evidence suggests that cramps have a peripheral nerve origin, and many may arise in the nerve terminals.

Muscle cramps are ubiquitous; few persons have never experienced a cramp. Lower motor neuron lesions at all levels (motor neuron disease, post-polio, radiculopathy, peripheral nerve injury, polyneuropathy) may be associated with cramps, most commonly in amyotrophic lateral sclerosis (ALS), where they can be an early feature. Nocturnal leg cramps, particularly in the elderly, and those occurring during exercise or during rest after exercise, are common, benign, and of uncertain pathogenesis. Acute extracellular volume depletion results in cramps during dialysis, as well as from excessive exercise/sweating in a hot environment (heat cramps), diarrhea, vomiting, and the use of diuretics. Some medications, such as statins, may be associated with cramps by other mechanisms. Implicated metabolic/endocrine conditions include hypothyroidism, hypoadrenalism, uremia, liver disease, and pregnancy. In addition to myokymia and neuromyotonia, some patients with Isaacs syndrome also have cramps. The cramp-fasciculation syndrome is discussed above. Some cases of generalized muscle cramps appear to be familial. Satoyoshi syndrome is a rare, progressive, possibly autoimmune, childhood-onset disorder characterized by painful muscle spasms/cramps beginning in the limbs and later involving neck, trunk, and masticatory muscles, alopecia, diarrhea, endocrinopathy with amenorrhea, and skeletal abnormalities.

Stretching before exercise and good hydration/nutrition may help prevent cramps and are advisable in all cases. Quinine sulfate is effective but has potentially serious adverse effects such as torsades-de-pointes, thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, and cinchonism. Alternatives include cabamazepine, phenytoin, gabapentin, and vitamin E. Supplemental magnesium may be helpful in easing the cramps associated with pregnancy.¹⁹

Fasciculations

Fasciculations represent the spontaneous irregular discharge of a group of muscle fibers belonging to a single motor unit and appear as random pops or twitches under the skin unless they arise in the depth of the muscle. They are observed in various neurogenic disorders (anterior horn cell, root, plexus, focal neuropathy, polyneuropathy) and in healthy individuals, but are major

clinical issues only in lower motor neuron disorders or as benign fasciculations. They may be of neuronal (anterior horn cell) or axonal origin.^{20,21} Benign fasciculations tend to have a higher firing rate than the malignant fasciculations of ALS, but this is not a specific enough feature to be of practical use. Benign fasciculations have normal morphologic parameters and are less persistent, while those in ALS may be complex and unstable, worsening with progressive disease, arising proximally in early disease and in distal axonal sprouts in later stages, and usually associated with fibrillation potentials.²² While occasional exceptions are reported, in general, patients presenting with only fasciculations, a normal neurologic examination, and an otherwise normal electrodiagnostic study can be reassured that they have benign fasciculations.^{23,24} In some cases, a follow-up exam within a few months to a year or so, if symptoms persist, will lay the issue to rest. A disproportionate number of patients with benign fasciculations are young men in the health care field with anxiety or obsessive-compulsive traits, and some patients report acute onset after a viral infection. Acral paresthesias may be present. Fasciculations may also be associated with anticholinergics, organophosphate poisoning, stimulants such as caffeine, pseudoephedrine and amphetamines, and asthma bronchodilators. In spinal muscular atrophy in childhood, fasciculations of the eyelids may be an additional clue to the clinical diagnosis.²⁵

Tetany

In tetany, hypocalcemia, hypomagnesemia, or alkalosis (hyperventilation) provokes acral and circumoral paresthesias and spasmodic adduction and flexion of the fingers at the metacarpophalangeal (MCP) joints, flexion at the wrist, and plantar ankle/toe flexion and inversion (carpopedal spasm).²⁶ Severe cases may be associated with laryngospasm or seizures. Percussion of the facial nerve elicits a facial muscle spasm (Chvostek sign), and inflating a blood pressure cuff above systolic for up to 3 minutes elicits finger posturing (Trousseau sign). Needle EMG reveals grouped discharges as doublets or multiplets.

LOCALIZED DISORDERS

Facial Myokymia

Myokymia represents rhythmic or semi-rhythmic bursts of grouped motor unit potentials at varied rates and intervals, with the sound of marching soldiers; the resultant twitching has a vermicular (worm-like) or undulating appearance. A variety of pathologic disorders appear capable of changing the axonal biochemical microenvironment, altering membrane excitability, and resulting in ectopic myokymic discharges.²⁷ Facial myokymia may arise in the intramedullary portion of the facial nerve or along its peripheral course.²⁸ Intra-axially, it occurs with multiple sclerosis, pontine glioma or other tumors, syringobulbia, brainstem infections (tuberculoma, neurocysticercosis), and multiple system atrophy. Extra-axially, it is seen with basilar invagination, subarachnoid hemorrhage, cerebellopontine angle masses, GBS, timber rattlesnake envenomation, and following Bell's palsy or irradiation.

In multiple sclerosis, magnetic resonance imaging (MRI) reveals a pontine tegmental lesion involving the postnuclear, postgenu portion of the facial nerve in about 90% of cases; the myokymia usually resolves within a few months.²⁹ Bilateral facial or limb myokymia may occur in 17% of cases of GBS, early in the course, lasting for 5–40 days and occurring more commonly in women.³⁰ Following Bell's palsy, myokymia was seen clinically in about 9% and electrophysiologically in about 26% in one series of 88 patients.³¹ Very focal myokymia may follow injury to a distal facial nerve branch, as occurred to one of our patients from a dental lidocaine injection of the branch to the depressor septi nasi muscle.³² Timber rattlesnake envenomation results in bilateral facial and limb myokymia and disappears within hours of receiving antivenin therapy.³³

Chronic isolated eyelid twitching (referred to by different authors as either eyelid *fasciculations* or eyelid *myokymia*) is quite common in the general population, tends not to progress, appears to be a benign condition, and may respond to botulinum toxin if treatment is necessary;³⁴ some exceptions to this benign prognosis are reported.³⁵

Localized, Focal Myokymia

Localized appendicular myokymia is rarely seen distal to a nerve entrapment (e.g., abductor pollicis brevis muscle in carpal tunnel syndrome), segmentally in a chronic structural radicular lesion, or with another peripheral nerve injury. About 63% of patients with radiation plexopathy will have myokymia, most commonly in the pronator teres and abductor pollicis brevis muscles.³⁶ Radiation-induced myokymia may also be seen in the cranial motor nerves, including the oculomotor, trigeminal, facial, and hypoglossal nerves.

Hemifacial Spasm

Hemifacial spasm results from ectopic/ephaptic excitation due to compression and demyelination of the intracranial segment of the facial nerve.^{37–39} It is characterized clinically by intermittent, irregular, repetitive tonic and clonic contractions of the facial muscles and is usually associated with compression of the extra-axial facial nerve at the pons by a vascular loop or another mass lesion. The main culprit at surgery is the anterior inferior cerebellar artery, followed by the posterior inferior cerebellar artery, the vertebral artery, or a large vein.⁴⁰ It may also be a late sequela of Bell's palsy and is described in multiple sclerosis with pontine lesions. The lower lid is the most common site of initial involvement. Differential diagnostic considerations may include myokymia, blepharospasm, focal seizures, tics, oromandibular dystonia, and myoclonus. Motor units fire at rates as high as 250 Hz during spasms. The blink reflex and direct facial motor studies are normal, but synkinesis and ephaptic transmission (lateral spread) can be demonstrated electrophysiologically. This disorder can be treated effectively with either botulinum toxin or microvascular decompression; medical treatment with a variety of neuropathic drugs tends to provide only modest benefit.

Hemimasticatory Spasm

In this rare disorder, paroxysmal unilateral spasms of the masticatory muscles are

produced by ectopic activity arising in a focally demyelinated segment of the trigeminal motor nerve fibers.^{41,42} The irregular bursts of motor unit potentials in the masseter muscle on needle EMG are similar to those seen with hemifacial spasm. The masseter reflex and silent period are absent. Some cases have associated facial hemiatrophy. Patients have been successfully treated with botulinum toxin or carbamazepine.

Hypothenar Dimpling

In this rare and benign oddity, there is dimpling of the skin over the hypothenar eminence due to intermittent, irregular, high-frequency bursts of motor units in the palmaris brevis muscle, which is innervated by the superficial branch of the ulnar nerve.⁴³ This condition has also been called the *palmaris brevis spasm syndrome* and is postulated to result from stretch injury of the ulnar nerve superficial branch.⁴⁴

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