PERIFERAL NERVOUS SYSTEM DISORDERS

The peripheral nervous system refers to the cranial nerves and spinal nerves from their origin to their end. The afferent (sensory) system begins in the periphery and ends in the CNS; the efferent (motor) system begins in the CNS and ends at the target muscle.

Anatomy and Physiology

Thirty of the 31 pairs of spinal nerves consist of an anterior (ventral) motor root and a posterior (dorsal) sensory root; C1 has no sensory root. Efferent motor fibers emerge from anterior horn cells located in the gray matter of the spinal cord. A motor unit consists of an anterior horn cell, its motor axon, the muscle fibers it innervates, and the connection between them (neuromuscular junction). The cell bodies of the afferent sensory fibers lie in dorsal root ganglia, located outside the spinal cord. The ventral and dorsal roots combine to form a spinal nerve, which exits via an intervertebral foramen. Because the spinal cord is shorter than the vertebral column, the more caudal the spinal nerve, the further the foramen is from the corresponding cord segment. Thus, in the lumbosacral region, nerve roots from lower cord segments descend within the spinal column in a near-vertical sheaf, forming the cauda equina.

The cervical and lumbosacral spinal nerves anastomose peripherally into plexuses, then branch into nerve trunks that terminate up to 1 m away in peripheral structures. The intercostal nerves are segmental.

The term peripheral nerve refers to the part of a spinal nerve distal to the root and plexus. Peripheral nerves are bundles of nerve fibers ranging in diameter from 0.3 to 22 μm. Schwann cells form a thin cytoplasmic tube around each fiber and further wrap larger fibers in a multilayered insulating membrane (myelin sheath), which enhances impulse conduction. The largest and most heavily myelinated fibers conduct quickly; they convey motor, touch, and proprioceptive impulses. The less myelinated and unmyelinated fibers conduct more slowly; they convey pain, temperature, and autonomic impulses. Because nerves are metabolically active tissues, they require nutrients, supplied by blood vessels called the vasa nervorum.

CERVICAL SPONDYLOSIS

Cervical spondylosis is degenerative changes in the intervertebral disk and annulus and formation of bony osteophytes, which narrow the cervical canal or neural foramina, causing radiculopathy and sometimes myelopathy.

A congenitally narrow canal increases the risk of cervical spondylosis. If the spinal cord is compressed, progressive myelopathy and a spastic gait typically develop. Pain may predominate with radicular signs in the dermatome most affected, usually between C5 and C6 or C6 and C7. Neural foraminal root compression causes arm weakness and atrophy with segmental reflex loss; spinal cord compression causes hyperreflexia, increased muscle tone, vibratory impairment, and extensor plantar responses in the legs.

Diagnosis and Treatment

If symptoms of cervical root or cord impingement occur, MRI and electrodiagnostic tests (eg, electromyography, somatosensory evoked potentials, motor evoked potentials) are indicated. Spinal x-rays, including oblique views of the neural foramina, may show degenerative changes with osteophytes and narrowing of disk space, but these findings are neither sensitive nor specific. If the sagittal diameter of the cervical canal is < 10 mm, risk of cord compression is higher.

Occasionally, signs lessen or stabilize spontaneously. Conservative treatment includes a soft collar and NSAIDs or other mild analgesics. Decompressive laminectomy is indicated for patients with

myelopathy and cord compression or, if conservative treatment is ineffective, for patients with radiculopathy and electrodiagnostic evidence of neurologic dysfunction.

Guillain-Barré Syndrome (GBS)

Guillain-Barré syndrome is an acute, usually rapidly progressive inflammatory polyneuropathy characterized by muscular weakness and mild distal sensory loss. Cause is thought to be autoimmune. Diagnosis is clinical. Treatment includes plasmapheresis, γ-globulin, and, for severe cases, mechanical ventilation.

Guillain-Barré syndrome is the most common acquired inflammatory neuropathy. Although the cause is not fully understood, it is thought to be autoimmune. There are several variants. In some, demyelination predominates; others affect the axon.

In about ⅔ of patients, the syndrome begins 5 days to 3 wk after a banal infectious disorder, surgery, or vaccination. Infection is the trigger in > 50% of patients; common pathogens include *Campylobacter jejuni*, enteric viruses, herpesviruses (including cytomegalovirus and those causing infectious mononucleosis), and *Mycoplasma* sp. A cluster of cases followed the swine flu vaccination program in 1975.

Symptoms and Signs

Flaccid weakness predominates in most patients; it is always more prominent than sensory abnormalities and may be most prominent proximally. Relatively symmetric weakness with paresthesias usually begins in the legs and progresses to the arms, but it occasionally begins in the arms or head. In 90% of patients, weakness is maximal at 3 wk. Deep tendon reflexes are lost. Sphincters are usually spared. Facial and oropharyngeal muscles are weak in > 50% of patients with severe disease. Respiratory paralysis severe enough to require endotracheal intubation and mechanical ventilation occurs in 5 to 10%.

A few patients (possibly with a variant form) have significant, life-threatening autonomic dysfunction causing BP fluctuations, inappropriate ADH secretion, cardiac arrhythmias, GI stasis, urinary retention, and pupillary changes. An unusual variant (Fisher variant) may cause only ophthalmoparesis, ataxia, and areflexia.

Diagnosis

Diagnosis is clinical. Similar acute weakness can result from myasthenia gravis, botulism, poliomyelitis (primarily outside the US), tick paralysis, West Nile virus infection, and metabolic neuropathies, but these disorders can be distinguished. Myasthenia gravis is intermittent and worsened by exertion. Botulism may cause fixed dilated pupils (in 50%) and prominent cranial nerve dysfunction with normal sensation. Poliomyelitis usually occurs in epidemics. Tick paralysis causes ascending paralysis but spares sensation. West Nile virus causes headache, fever, and asymmetric flaccid paralysis but spares sensation. Metabolic neuropathies occur with a chronic metabolic disorder.

If Guillain-Barré syndrome is suspected, patients should be admitted to a hospital for electromyography (EMG), CSF analysis, and measurement of forced vital capacity every 6 to 8 h. Initial EMG detects slow nerve conduction velocities and evidence of segmental demyelination in ⅔ of patients; however, a normal EMG does not exclude the diagnosis and should not delay treatment. CSF analysis may detect albuminocytologic dissociation (increased protein but normal WBC count), but it may not appear for up to 1 wk and does not develop in 10% of patients.

Prognosis

Most patients improve considerably over a period of months, but about 30% of adults and even more children have some degree of residual weakness at 3 yr. Patients with residual defects may require retraining, orthopedic appliances, or surgery. This syndrome is fatal in < 2%.

After initial improvement, 3 to 10% of patients develop chronic relapsing polyneuropathy. Pathology and laboratory findings are similar to those in the acute syndrome, but weakness may be more asymmetric and progress more slowly. Eventually, nerves may become palpable because of repeated episodes of segmental demyelination and remyelination.

Treatment

Guillain-Barré syndrome is a medical emergency, requiring constant monitoring and support of vital functions, typically in an ICU. Forced vital capacity should be measured frequently so that respiration can be assisted if necessary; if vital capacity is < 15 mL/kg, endotracheal intubation is indicated. Inability to lift the head off the pillow by flexing the neck is another danger sign; it frequently develops simultaneously with phrenic nerve (diaphragm) weakness.

Fluid intake should be sufficient to maintain a urine volume of at least 1 to 1.5 L/day. Extremities should be protected from trauma and from the pressure of bed rest. Heat helps relieve pain, making early physical therapy possible. Immobilization, which may cause ankylosis, should be avoided. Passive full-range joint movement should be started immediately, and active exercises should be initiated when acute symptoms subside. Heparin 5000 units sc bid helps prevent deep vein thrombosis in bedbound patients.

Corticosteroids do not improve the outcome and should not be used. Plasmapheresis helps when done early in the syndrome and is the treatment of choice in acutely ill patients. It is relatively safe, shortens the disease course and hospital stay, and reduces mortality risk and incidence of permanent paralysis. Immune globulin (γ-globulin) 400 mg/kg IV once/day for 5 consecutive days is equally effective when given early, with benefit demonstrated up to 1 mo from disease onset. However, because plasmapheresis removes any previously administered γ-globulin, negating its benefits, γ-globulin is typically used if plasmapheresis is ineffective or unavailable.

In chronic relapsing polyneuropathy, corticosteroids lessen weakness and may be needed for a long time. Immunosuppressants (eg, corticosteroids, azathioprine), γ-globulin, and plasmapheresis benefit some patients

NERVE ROOT DISORDERS

Nerve root disorders result in predictable segmental radicular symptoms (pain or paresthesias in a dermatomal distribution, weakness of muscles innervated by the root). Diagnosis may require neuroimaging, electromyography, and systemic testing for underlying disorders. Treatment depends on cause but includes symptomatic relief with NSAIDs and other analgesics.

Nerve root disorders (radiculopathies) are precipitated by chronic pressure on a root in or adjacent to the spinal column. The most common cause is a herniated intervertebral disk. Bone changes due to RA or osteoarthritis, especially in the cervical and lumbar areas, may also compress isolated nerve roots. Less commonly, carcinomatous meningitis produces patchy multiple root dysfunction. Rarely, mass spinal lesions (eg, epidural abscesses and tumors, spinal meningiomas, neurofibromas) may manifest with radicular symptoms instead of the usual spinal cord dysfunction. Diabetes can cause a painful thoracic or extremity radiculopathy. Infectious disorders, such as fungal (eg, histoplasmosis) and spirochetal diseases (eg, Lyme disease, syphilis), sometimes affect nerve roots. Herpes zoster infection usually causes a painful radiculopathy with dermatomal sensory loss and characteristic rash, but it may cause a motor radiculopathy with myotomic weakness and reflex loss.

Symptoms and Signs

Nerve root disorders tend to cause characteristic radicular syndromes of pain and segmental neurologic deficits based on the affected cord level. Muscles innervated by the affected motor root become weak and atrophy; they also may be flaccid with fasciculations. Sensory root involvement causes sensory impairment in a dermatomal distribution. Corresponding segmental deep tendon reflexes may be diminished or absent.

Pain may be exacerbated by movements that transmit pressure to the nerve root through the subarachnoid space (eg, moving the spine, coughing, sneezing, Valsalva maneuver). Lesions of the cauda equina, which affect multiple lumbar and sacral roots, cause radicular symptoms in both legs and may impair sphincter and sexual function.

Findings indicating spinal cord compression include a sensory level (an abrupt change in sensation below a horizontal line across the spine), flaccid paraparesis or quadriparesis, reflex abnormalities below the site of compression, early-onset hyporeflexia followed later by hyperreflexia, and sphincter dysfunction.

Diagnosis and Treatment

Radicular symptoms require CT or MRI of the affected area. Myelography is sometimes used if multiple levels are affected. The area imaged depends on symptoms and signs; if the level is unclear, electromyography (EMG) should be done to localize the affected root, but EMG cannot identify the cause.

If imaging does not detect an anatomic abnormality, CSF analysis is done to check for infectious or inflammatory causes, and fasting blood glucose is measured to check for diabetes.

Specific causes are treated (see elsewhere in the manual). Acute pain requires appropriate analgesics (eg, NSAIDs, sometimes opioids). Use of low-dose tricyclic antidepressants at bedtime may help. Muscle relaxants, sedatives, and topical treatments rarely provide additional benefit. Chronic pain can be difficult to manage; NSAIDs are often only partly effective, and opioids have a high risk of addiction. Tricyclic antidepressants and anticonvulsants may be effective, as may physical therapy and consultation with a mental health practitioner. For a few patients, alternative medical treatments (eg, transdermal electrical nerve stimulation, spinal manipulation, acupuncture, medicinal herbs) may be helpful.

Herniated Nucleus Pulposus

(Herniated, Ruptured, or Prolapsed Intervertebral Disk)

Herniated nucleus pulposus is prolapse of the central area of an intervertebral disk through the surrounding annulus. Symptoms occur when the disk impinges on an adjacent nerve root, causing segmental radiculopathy with paresthesias and weakness in the distribution of the affected root. Diagnosis is by CT, MRI, or CT-myelography. Treatment of mild cases is with NSAIDs and other analgesics if needed. Bed rest is rarely indicated. Patients with progressive neurologic deficits, intractable pain, or sphincter dysfunction may require urgent surgery (eg, diskectomy, laminectomy).

Spinal vertebrae are separated by cartilaginous disks consisting of an outer annulus fibrosus and an inner nucleus pulposus. When degenerative changes (with or without trauma) result in protrusion or rupture of the nucleus through the annulus fibrosus in the lumbosacral or cervical area, the nucleus is displaced posterolaterally or posteriorly into the extradural space. Radiculopathy occurs when the

herniated nucleus compresses or irritates the nerve root. Posterior protrusion may compress the cord or cauda equina, especially in a congenitally narrow spinal canal (spinal stenosis). In the lumbar area, > 80% of disk ruptures affect L5 or S1 nerve roots; in the cervical area, C6 and C7 are most commonly affected. Herniated disk is common, often causing no symptoms.

Symptoms and signs are similar to those of other nerve root disorders, although pain is somewhat more likely to develop suddenly if the disk herniates, and the cord may be compressed. In patients with lumbosacral herniation, straight-leg raises, which stretch the roots, may cause back or leg pain (bilateral if disk herniation is central); with cervical herniation, neck flexion or tilting is painful. Cervical cord compression may cause spastic paresis of the lower limbs. Cauda equina compression often results in urine retention or incontinence due to loss of sphincter function.

Diagnosis and Treatment

CT, MRI, or CT-myelography of the affected area is done. Electromyography may help identify the involved root. Because asymptomatic herniated disk is quite common, the clinician must carefully correlate symptoms with MRI abnormalities before invasive procedures are considered.

Because up to 95% of patients with herniated disk recover without surgery within about 3 mo, treatment should be conservative, unless neurologic deficits are progressive or severe. Heavy or vigorous physical activity is restricted, but ambulation and light activity (eg, lifting objects < 5 to 10 lb) are permitted as tolerated; prolonged bed rest (including traction) is contraindicated. NSAIDs and other analgesics should be used as needed to relieve pain.

If lumbar radiculopathies result in persistent or worsening objective neurologic deficits (weakness, sensory deficits) or in severe, intractable nerve root pain, invasive procedures should be considered. Microscopic diskectomy and laminectomy with surgical removal of herniated material are usually the procedures of choice. Percutaneous approaches to remove bulging disk material are being evaluated. Dissolving herniated disk material with local injections of the enzyme chymopapain is not recommended. Lesions acutely compressing the spinal cord or cauda equina (eg, producing urine retention or incontinence) require immediate surgical evaluation.

If cervical radiculopathies result in signs of spinal cord compromise, surgical decompression is needed immediately; otherwise, it is done electively when nonsurgical treatments are ineffective.

SYMPTOMS OF COMMON RADICULOPATHIES BY CORD LEVEL

Level	Symptoms
C6	Pain in the trapezius ridge and tip of the shoulder, often radiating to the thumb, with paresthesias and sensory impairment in the same areas; weakness of biceps; and decreased biceps brachii and brachioradialis reflexes
C7	Pain in the shoulder blade and axilla, radiating to the middle finger; weakness of triceps; and decreased triceps brachii reflex
T (any)	Bandlike dysesthesias around thorax
L5	Pain in the buttock, posterior lateral thigh, calf, and foot; footdrop with weakness of the anterior tibial, posterior tibial, and peroneal muscles; and sensory loss over the shin and dorsal foot
S1	Pain along posterior aspect of the leg and buttock, weakness of the medial gastrocnemius muscle with impaired ankle plantar flexion, loss of ankle jerk, and sensory loss over the lateral calf and foot

PERIFERAL NEUROPATHY

Peripheral neuropathy is dysfunction of a spinal nerve or nerves distal to a plexus or root. It includes numerous syndromes characterized by varying degrees of sensory disturbances, pain, muscle weakness and atrophy, diminished deep tendon reflexes, and vasomotor symptoms, alone or in any combination. Initial classification is based on history and physical examination and must be confirmed with electromyography and nerve conduction velocity studies. Treatment is aimed mainly at the cause.

Peripheral neuropathy may affect a single nerve (mononeuropathy), ≥ 2 discrete nerves in separate areas (multiple mononeuropathy), or many nerves simultaneously (polyneuropathy).

Mononeuropathies

Single and multiple mononeuropathies are characterized by sensory disturbances and weakness in the distribution of the affected nerve or nerves. Diagnosis is clinical but should be confirmed with electrodiagnostic tests. Treatment is directed at the cause, sometimes with splinting, NSAIDs, corticosteroid injections, and, for severe cases of nerve entrapment, surgery.

Trauma is the most common cause of acute mononeuropathy. Violent muscular activity or forcible overextension of a joint may cause focal neuropathy, as may repeated small traumas (eg, tight gripping of small tools, excessive vibration from air hammers). Prolonged, uninterrupted pressure at bony prominences can cause pressure neuropathy, usually affecting superficial nerves (ulnar, radial, peroneal), particularly in thin people; such pressure may occur during sound sleep, intoxication, bicycle riding, or anesthesia. Compression of nerves in narrow canals causes entrapment neuropathy (eg, in carpal tunnel syndrome). Nerve compression by a tumor, bony hyperostosis, a cast, crutches, or prolonged cramped postures (eg, during gardening) may cause compression paralysis. Hemorrhage into a nerve, exposure to cold or radiation, or direct tumor invasion may cause neuropathy.

Multiple mononeuropathy (mononeuritis multiplex) is usually secondary to connective tissue disorders (eg, polyarteritis nodosa, SLE, Sjögren's syndrome, RA), sarcoidosis, metabolic disorders (eg, diabetes, amyloidosis), or infectious disorders (eg, Lyme disease, HIV infection, leprosy). Diabetes usually causes sensorimotor distal polyneuropathy.

Symptoms and Signs

Single and multiple mononeuropathies are characterized by pain, weakness, and paresthesias in the distribution of the affected nerve or nerves. Pure motor nerve involvement begins with painless weakness; pure sensory nerve involvement begins with sensory disturbances without weakness. Multiple mononeuropathy is often asymmetric at its onset; nerves may be involved all at once or progressively. Extensive involvement of many nerves may simulate polyneuropathy.

Ulnar nerve palsy of the elbow is often caused by trauma to the nerve in the ulnar groove of the elbow by repeated leaning on the elbow or by asymmetric bone growth after a childhood fracture (tardy ulnar palsy). The ulnar nerve can also be compressed at the cubital tunnel. Compression at the level of the elbow can cause paresthesias and a sensory deficit in the 5th digit and medial half of the 4th digit; the thumb adductor, 5th digit abductor, and interosseous muscles are weak and may be atrophied. Severe chronic ulnar palsy causes a clawhand deformity.

Carpal tunnel syndrome may be unilateral or bilateral. It results from compression of the median nerve in the volar aspect of the wrist between the transverse superficial carpal ligament and the flexor tendons of the forearm muscles. The compression causes paresthesias in the radial-palmar aspect of the hand and pain in the wrist and palm. Pain may also occur in the forearm and shoulder. Pain may be more severe at night. A sensory deficit in the palmar aspect of the 1st 3 fingers may follow, and the muscles that control thumb abduction and opposition may become weak and atrophied. Sensory symptoms due to this syndrome should be distinguished from C6 root dysfunction due to cervical radiculopathy, by electromyography (EMG) if needed.

Peroneal nerve palsy is usually caused by compression of the nerve against the lateral aspect of the fibular neck. It is most common among emaciated bedbound patients and thin people who habitually cross their legs. It causes footdrop (weakened dorsiflexion and eversion of the foot) and, occasionally, a sensory deficit in the anterolateral aspect of the lower leg and the dorsum of the foot or in the web space between the 1st and 2nd metatarsals.

Radial nerve palsy (Saturday night palsy) is caused by compression of the nerve against the humerus, as when the arm is draped over the back of a chair for a long time (eg, during intoxication or deep sleep). Typical symptoms include wristdrop (weakness of the wrist and finger extensors) and sensory loss in the dorsal aspect of the 1st dorsal interosseous muscle.

Diagnosis and Treatment

Electrodiagnostic tests are generally obtained, either to clarify diagnosis or to assess severity and prognosis.

Underlying disorders are treated. Treatment of compression neuropathy depends on cause. Often, fixed compression (eg, by tumor) must be relieved surgically. Symptoms of transient compression usually resolve with rest, heat, NSAIDs, and avoidance or modification of causative activity. Patients with carpal tunnel syndrome sometimes benefit from corticosteroid injections. For all types, braces or splints are often used pending resolution. Surgery should be considered when progression occurs despite conservative treatment.

Polyneuropathy

A polyneuropathy is a diffuse peripheral nerve disorder not confined to the distribution of a single nerve or a single limb. Electrodiagnostic tests should always be performed to classify the nerve structures involved, distribution, and severity of the disorder in order to focus the search for the underlying cause. Treatment is directed toward attenuating or removing the underlying cause.

Some polyneuropathies (eg, due to lead toxicity, dapsone use, tick bite, porphyria, or Guillain-Barré syndrome) affect primarily motor fibers; others (eg, due to dorsal root ganglionitis of cancer, leprosy, AIDS, diabetes mellitus, or chronic pyridoxine intoxication) affect primarily sensory fibers. Some disorders (eg, Guillain-Barré syndrome, Lyme disease, diabetes, diphtheria) can also affect cranial nerves. Certain drugs and toxins can affect sensory or motor fibers or both.

Symptoms and Signs

Because pathophysiology and symptoms are related, polyneuropathies are often classified by area of dysfunction: myelin, vasa nervorum, or axon. Hereditary neuropathies are discussed below.

Myelin dysfunction

Myelin dysfunction polyneuropathies most often result from a parainfectious immune response triggered by an encapsulated bacterium (eg, *Campylobacter* sp), virus (eg, enteric or influenza viruses, HIV), or vaccine (eg, influenza vaccine). Presumably, antigens in these agents cross-react with antigens in the peripheral nervous system, causing an immune response (cellular, humoral, or both) that culminates in varying degrees of myelin dysfunction. In acute cases (eg, in Guillain-Barré syndrome), rapidly progressive weakness and respiratory failure may develop.

Myelin dysfunction usually results in large-fiber sensory disturbances (paresthesias), significant muscle weakness greater than expected for degree of atrophy, and significantly diminished reflexes. Trunk musculature and cranial nerves may be involved. Abnormalities typically occur along the entire length of a nerve, producing proximal and distal symptoms. There may be side-to-side asymmetries, and more rostral parts of the body may be affected before distal extremities. Muscle bulk and tone are relatively preserved.

Vasa nervorum compromise

Chronic arteriosclerotic ischemia, vasculitis, and hypercoagulable states can compromise the vascular supply to the nerves.

Usually, small-fiber sensory and motor dysfunction occurs first. Patients typically have painful, often burning sensory disturbances. Abnormalities tend to be asymmetric early in the disorder and rarely affect the proximal ⅓ of the limb or trunk muscles. Cranial nerve involvement is rare, except in diabetes, which commonly affects the 3rd cranial (oculomotor) nerve. Later, symptoms and signs may appear symmetric if nerve lesions coalesce. Dysautonomia and skin changes (eg, atrophic, shiny skin) sometimes occur. Muscle weakness tends to be proportional to atrophy, and reflexes are rarely lost completely.

Axonopathy

Axonopathies tend to be distal; they may be symmetric or asymmetric.

Symmetric axonopathies result most often from toxic-metabolic disorders. Common causes include diabetes mellitus, chronic renal insufficiency, and adverse effects of chemotherapy drugs (eg, vinca alkaloids). Axonopathy may result from nutritional deficiencies (most commonly, of vitamin B) or from excess intake of vitamin B_6 or alcohol. Less common metabolic causes include hypothyroidism, porphyria, sarcoidosis, and amyloidosis. Other causes include certain infections (eg, Lyme disease), drugs (eg, nitrous oxide), and exposure to certain chemicals (eg, to Agent Orange, n-hexane) or heavy metals (eg, lead, arsenic, mercury). In a paraneoplastic syndrome associated with small-cell lung cancer, loss of dorsal root ganglia and their sensory axons results in subacute sensory neuropathy.

Primary axon dysfunction may begin with symptoms of large- or small-fiber dysfunction or both. Usually, the resulting neuropathy has a distal symmetric, stocking-glove distribution; it evenly affects the lower extremities before the upper extremities and progresses symmetrically from distal to proximal areas.

Asymmetric axonopathy can result from parainfectious or vascular disorders.

Diagnosis

Clinical findings, particularly tempo of onset, aid in diagnosis and identification of the cause. Asymmetric neuropathies suggest a disorder affecting the myelin sheath or vasa nervorum. Symmetric, distal neuropathies suggest toxic or metabolic causes. Slowly progressive, chronic neuropathies tend to be inherited or due to long-term toxic exposure or metabolic disorders. Acute neuropathies suggest an autoimmune response, vasculitis, or a postinfectious cause. Rash, skin ulcers, and Raynaud's phenomenon in patients with an asymmetric axonal neuropathy suggest a hypercoagulable state or parainfectious or autoimmune vasculitis. Weight loss, fever, lymphadenopathy, and mass lesions may suggest a tumor or paraneoplastic syndrome.

Electrodiagnostic tests

Regardless of clinical findings, electromyography (EMG) and nerve conduction velocity studies are necessary to classify type of neuropathy. At a minimum, EMG of both lower extremities should be done to assess for asymmetry and full extent of axon loss. Because EMG and nerve conduction studies assess primarily large myelinated fibers in distal limb segments, EMG may be normal in patients with proximal myelin dysfunction (eg, early in Guillain-Barré syndrome) and in patients with primarily small-fiber dysfunction. In such cases, quantitative sensory or autonomic testing or both may be done depending on the presenting symptoms.

Laboratory tests

Baseline laboratory tests for all patients include CBC, electrolytes, renal function tests, rapid plasma reagin test, and measurement of fasting blood sugar, hemoglobin A_{1C}, vitamin B_{12}, folate, and thyroid-stimulating hormone. Some clinicians include serum protein electrophoresis. The need for other tests is determined by polyneuropathy subtype.

The approach to patients with acute myelin dysfunction neuropathies is the same as that to those with Guillain-Barré syndrome; forced vital capacity is measured to check for incipient respiratory failure. In acute or chronic myelin dysfunction, tests for infectious disorders and immune dysfunction, including tests for hepatitis and HIV and serum protein electrophoresis, are done. In addition, anti-myelin-associated glycoprotein (MAG) antibodies are measured if motor dysfunction predominates; anti-sulfatide antibodies are measured if primary sensory dysfunction is present. A lumbar puncture should also be done; myelin dysfunction due to an autoimmune response often causes albuminocytologic dissociation: increased CSF protein (> 45 mg%) but normal WBC count ($\leq 5/\mu L$).

For asymmetric axonal polyneuropathies, tests for hypercoagulable states and parainfectious or autoimmune vasculitis, particularly if suggested by clinical findings, should be done; the minimum is ESR, serum protein electrophoresis, and measurement of rheumatoid factor, antinuclear antibodies, and serum CPK. CPK may be elevated when rapid onset of disease results in muscle infarction. Coagulation studies (eg, protein C, protein S, antithrombin III, anticardiolipin antibody, homocysteine levels) should be done only if suggested by personal or family history. Tests for sarcoidosis, hepatitis C, or Wegener's granulomatosis should be done only if suggested by symptoms and signs. If no cause is identified, nerve and muscle biopsy should be done. An affected sural nerve is usually biopsied. A muscle adjacent to the biopsied sural nerve or a quadriceps, biceps brachii, or deltoid muscle may be biopsied. The muscle should be one with moderate weakness that has not been tested by needle EMG. Yield is higher if the contralateral muscle has EMG abnormalities. Nerve biopsies tend to be more useful in asymmetric axonopathies than in other polyneuropathy subtypes.

If initial tests do not identify the cause of distal symmetric axonopathies, a 24-h urine collection is tested for heavy metals, and urine protein electrophoresis is done. If chronic heavy metal poisoning is suspected, testing of hairs from the pubis or axillary region may help. History and physical examination should determine whether tests for other causes are needed.

Treatment

Treatment focuses on correcting the causes when possible (see elsewhere in the manual); a causative drug or toxin can be eliminated, or a dietary deficiency corrected. Although these actions may halt progression and lessen symptoms, recovery is slow and may be incomplete. If the cause cannot be corrected, treatment focuses on minimizing disability and pain. Physical and occupational therapists can recommend useful assistive devices. Amitriptyline, gabapentin, mexiletine, and topical lidocaine may relieve neuropathic pain (eg, diabetic burning feet).

For myelin dysfunction polyneuropathies, immune system–modifying treatments are usually used: plasmapheresis or IV immune globulin for acute myelin dysfunction and corticosteroids or antimetabolite drugs for chronic myelin dysfunction.

Appendix

Toxic Causes of Neuropathies

Type	Causes
Axonal motor	Gangliosides; with prolonged exposure, lead, mercury, misoprostol, tetanus, tick paralysis
Axonal sensorimotor	Acrylamide, alcohol (ethanol), allyl chloride, arsenic, cadmium, carbon disulfide, chlorphenoxy compounds, ciguatoxin, dapsone, colchicine, cyanide, DMAPN, disulfiram, ethylene oxide, lithium, methyl bromide, nitrofurantoin, organophosphates, podophyllin, polychlorinated biphenyls (PCBs), saxitoxin, Spanish toxic oil, taxol, tetrodotoxin, thallium, trichloroethylene, TOCP, vacor (PNU), vinca alkaloids

Axonal sensory	Almitrine, bortezomib, chloramphenicol, dioxin, doxorubicin, ethambutol, ethionamide, etoposide, gemcitabine, glutethimide, hydralazine, ifosfamide, interferon-α, isoniazid, lead, metronidazole, misonidazole, nitrous oxide, nucleosides (didanosine [ddI], stavudine [d4T], zalcitabine [ddC]), phenytoin, platinum analogs, propafenone, pyridoxine, statins, thalidomide
Demyelinating	Buckthorn, chloroquine, diphtheria, hexachlorophene, muzolimine, perhexiline, procainamide, tacrolimus tellurium, zimeldine
Mixed	Amiodarone, ethylene glycol, gold, hexacarbons, n-hexane, Na cyanate, suramin

DMAPN = dimethylaminopropionitrile; TOCP = triorthocresyl phosphate; PNU = N-3 pyridilmethyl-N′-nitrophenyl urea.

Cervical Spondylosis and Spondylotic Cervical Myelopathy

Cervical spondylosis is osteoarthritis of the cervical spine causing stenosis of the canal and sometimes cervical myelopathy due to encroachment of bony osteoarthritic growths (osteophytes) on the lower cervical spinal cord, sometimes with involvement of lower cervical nerve roots (radiculomyelopathy).
Cervical spondylosis due to osteoarthritis is common. Occasionally, particularly when the spinal canal is congenitally narrow (< 10 mm), osteoarthritis leads to stenosis of the canal and bony impingement on the cord, causing compression and myelopathy (functional disturbance of the spinal cord). Hypertrophy of the ligamentum flavum can aggravate this effect. Osteophytes in the neural foramina, most commonly between C5 and C6 or C6 and C7, can cause radiculopathy. Manifestations vary according to the neural structures involved but commonly include pain.

Cord compression commonly causes gradual spastic paresis, paresthesias, or both in the hands and feet and may cause hyperreflexia. Neurologic deficits may be asymmetric, nonsegmental, and aggravated by cough or Valsalva maneuvers. After trauma, people with cervical spondylosis may develop central cord syndrome. Eventually, muscle atrophy and flaccid paresis may develop in the upper extremities at the level of the lesion, with spasticity below the level of the lesion.

Nerve root compression commonly causes early radicular pain; later there may be weakness, hyporeflexia, and muscle atrophy.

Degenerative Changes of the Cervical Spine

Cervical spondylosis is suspected when characteristic neurologic deficits occur in patients who are elderly, have osteoarthritis, or have radicular pain at the C5 or C6 levels. Diagnosis is by MRI or CT.

For patients with cord involvement, cervical laminectomy is usually needed; a posterior approach can relieve the compression but leaves anterior compressive osteophytes and may result in spinal instability and kyphosis. Thus, an anterior approach with spinal fusion is generally preferred. Patients with only radiculopathy may try nonsurgical treatment with NSAIDs and a soft cervical collar; if this approach is ineffective, surgical decompression may be required.

Thoracic Outlet Compression Syndromes

Thoracic outlet compression syndromes are a group of poorly defined disorders characterized by pain and paresthesias in the hand, neck, shoulder, or arms. They appear to involve compression of the lower trunk of the brachial plexus (and perhaps the subclavian vessels) as it traverses the thoracic outlet below the scalene muscles and over the 1st rib before entering the axilla, but this involvement is unclear. Diagnostic techniques have not been established. Treatment includes physical therapy, analgesics, and, in severe cases, surgery.

Pathogenesis is often unknown but sometimes involves compression by a cervical rib, an abnormal 1st thoracic rib, abnormal insertion or position of the scalene muscles, or a malunited clavicle fracture. These syndromes are more common among women and usually develop between age 35 and 55.

Pain and paresthesias usually begin in the neck or shoulder and extend to the medial aspect of the arm and hand and sometimes the adjacent anterior chest wall. Many patients have mild to moderate sensory impairment in the C8 to T1 distribution on the painful side; a few have prominent vascular-autonomic changes in the hand (eg, cyanosis, swelling). In even fewer, the entire affected hand is weak. Rare complications include Raynaud's phenomenon and distal gangrene.

Diagnosis and Treatment

Diagnosis is suggested by distribution of symptoms. Various maneuvers are alleged to demonstrate compression of vascular structures (eg, by extending the brachial plexus), but sensitivity and specificity are not established. Auscultating bruits at the clavicle or apex of the axilla or finding a cervical rib by x-ray can aid in diagnosis. Although angiography may detect kinking or partial obstruction of axillary arteries or veins, neither finding is incontrovertible evidence of disease. Other testing is controversial, but evaluation as for brachial plexopathy may be reasonable.

Most patients without objective neurologic deficits respond to physical therapy, NSAIDs, and low-dose tricyclic antidepressants. If cervical ribs or subclavian artery obstructions are identified, an experienced specialist should decide whether surgery is necessary. With few exceptions, surgery should be reserved for patients who have significant or progressive neurovascular deficits and who do not respond to conservative treatment.

Plexus Disorders

Disorders of the brachial or lumbosacral plexus cause a painful mixed sensorimotor disorder of the corresponding limb.

Because several nerve roots intertwine within the plexus, the symptom pattern does not fit the distribution of individual roots or nerves. Disorders of the rostral brachial plexus affect the shoulders, those of the caudal brachial plexus affect the hands, and those of the lumbosacral plexus affect the legs.

Plexus disorders (plexopathies) are usually due to physical compression or injury. In infants, traction during birth may cause plexopathy. In adults, the cause is usually trauma (typically, for the brachial

plexus, a fall that forces the head away from the shoulder) or invasion by metastatic cancer (typically, breast or lung cancer for the brachial plexus and intestinal or GU tumors for the lumbosacral plexus). In patients receiving anticoagulants, a hematoma may compress the lumbosacral plexus. Neurofibromatosis occasionally involves a plexus. Other causes include postradiation fibrosis (eg, after radiation therapy for breast cancer) and diabetes.

Acute brachial neuritis (neuralgic amyotrophy) occurs primarily in men and typically in young adults, although it can occur at any age. Cause is unknown, but viral or immunologic inflammatory processes are suspected.

Symptoms and Signs

Manifestations include extremity pain and motor or sensory deficits that do not correspond to an isolated nerve root. For acute brachial neuritis, symptoms include severe supraclavicular pain, weakness, and diminished reflexes, with minor sensory abnormalities in the distribution of the brachial plexus. Weakness and decreased reflexes usually occur as pain resolves. Severe weakness develops within 3 to 10 days, then typically regresses over the next few months. The most commonly affected muscles are the serratus anterior, other muscles innervated by the upper trunk, and muscles innervated by the anterior interosseus nerve (in the forearm).

Diagnosis and Treatment

Diagnosis is suggested clinically. Electromyography and somatosensory evoked potentials should be done to clarify the anatomic distribution (including possible nerve root involvement). MRI of the appropriate plexus and adjacent spine is indicated for all nontraumatic plexopathies that are not a typical case of brachial neuritis.

Treatment is directed at the cause. Corticosteroids, although commonly prescribed, have no proven benefit. Surgery may be indicated for injuries, hematomas, and benign or metastatic tumors. Metastases should also be treated with radiation therapy, chemotherapy, or both. Glycemic control can benefit patients with a diabetic plexopathy.

Bell's Palsy

Bell's palsy is sudden, idiopathic, unilateral peripheral 7th cranial nerve palsy. Symptoms are hemifacial paresis involving the upper and lower face. There are no specific tests for diagnosis. Treatment may include corticosteroids, lubrication of the eye, and intermittent use of an eye patch.

Cause is unknown, but the mechanism is presumably swelling of the 7th cranial (facial) nerve due to an immune or viral disorder (possibly herpes simplex virus infection). The nerve is compressed, resulting in ischemia and paresis because the nerve's passageway through the temporal bone is narrow. The orbicularis oculi and frontalis muscles are paretic in peripheral but not in central 7th cranial nerve palsies because these muscles receive input from left and right 7th cranial nerve nuclei.

Symptoms and Signs

Pain behind the ear often precedes facial paresis. Paresis, often with complete paralysis, develops within hours and is usually maximal within 48 to 72 h. Patients may complain of a numb or heavy feeling in the face. The affected side becomes flat and expressionless; ability to wrinkle the forehead, blink, and grimace is limited or absent. In severe cases, the palpebral fissure widens and the eye does not close, often irritating the conjunctiva and drying the cornea. Sensory examination is normal except for the external auditory canal and a small patch behind the ear. If the nerve lesion is proximal, salivation, taste, and lacrimation are impaired, and hyperacusis is present.

Diagnosis

There are no specific diagnostic tests. Bell's palsy can be distinguished from a central 7th cranial nerve lesion (eg, due to stroke or tumor), which causes weakness only of the lower face (grimace). Many disorders cause peripheral 7th cranial nerve palsies; examples are geniculate herpes (Ramsay Hunt syndrome, due to herpes zoster), middle ear or mastoid infections, sarcoidosis (particularly in black patients), Lyme disease (particularly where it is endemic), petrous bone fractures, carcinomatous or leukemic nerve invasion, chronic meningitis, and cerebellopontine angle or glomus jugulare tumors. These disorders typically develop more slowly than Bell's palsy and may have other distinguishing symptoms or signs. If the diagnosis is in doubt, MRI with contrast agent may enhance the 7th cranial nerve in Bell's palsy; CT, usually negative in Bell's palsy, is done if a fracture is suspected or if there is the possibility of stroke. Acute and convalescent serologic tests for Lyme disease are done if patients have been in a geographic area where ticks are endemic. A chest x-ray and serum ACE are checked for sarcoidosis. Viral titers are not helpful.

Seventh Cranial Nerve Palsy, Peripheral

Prognosis and Treatment

The extent of nerve damage determines outcome. If some function remains, full recovery usually occurs within several months. Nerve conduction studies and electromyography predict likelihood of complete recovery after total paralysis in 90% if nerve branches in the face retain normal excitability to supramaximal electrical stimulation and in only about 20% if electrical excitability is absent.

Regrowth of nerve fibers may be misdirected, innervating lower facial muscles with periocular fibers and vice versa. The result is contraction of unexpected muscles during voluntary facial movements (synkinesia) or crocodile tears during salivation. Chronic disuse of the facial muscles may lead to contractures.

No treatment has proved effective for idiopathic Bell's palsy. Corticosteroids, if begun within 48 h after onset, may slightly reduce duration and degree of residual paralysis. Prednisone 60 to 80 mg po once/day is given for 1 wk, then decreased gradually over the 2nd wk. Antiviral drugs effective against herpes simplex virus (eg, valacyclovir 1 g tid for 7 to 10 days, famciclovir 500 mg po tid for 5 to 10 days, acyclovir 400 mg po 5 times/day for 10 days) are also usually given.

Corneal drying must be prevented by frequent use of natural tears, isotonic saline, or methylcellulose drops and by intermittent use of tape or a patch to help close the eye, particularly during sleep. Tarsorrhaphy is occasionally required.

Trigeminal Neuralgia

Trigeminal neuralgia is severe paroxysmal, lancinating facial pain due to a disorder of the 5th cranial nerve. Diagnosis is clinical. Treatment is usually with carbamazepine or gabapentin; sometimes surgery is required.

Trigeminal neuralgia is thought to be caused by abnormal pulsations of intracranial arterial or, less often, venous loops that compress the 5th cranial (trigeminal) nerve root where it enters the brain stem.

The disorder is occasionally due to multiple sclerosis. Trigeminal neuralgia affects mainly adults, especially the elderly.

Symptoms, Signs, and Diagnosis

Pain occurs along the distribution of one or more sensory divisions of the trigeminal nerve, most often the maxillary, and lasts seconds up to 2 min. It is lancinating, excruciating, and sometimes incapacitating. Pain is often precipitated by touching a facial trigger point or by moving (eg, chewing, brushing the teeth).

Symptoms are almost pathognomonic. Postherpetic pain is differentiated by its persistence, typical antecedent rash, scarring, and predilection for the ophthalmic division; migraine, which may produce atypical facial pain, is differentiated by pain that is more prolonged and often throbbing. Neurologic examination is normal. Thus, neurologic deficits suggest an alternate cause for pain (eg, tumor, multiple sclerosis plaque, vascular malformation, other lesions that compress the nerve or its brain stem pathways, or stroke). A pontine lesion disrupts trigeminal nerve sensation, corneal reflex, and motor function. Loss of pain and temperature sensation and loss of the corneal reflex with preservation of motor function suggest a medullary lesion. Trigeminal nerve deficits may occur in Sjögren's syndrome or RA but with a sensory deficit that is often perioral and nasal.

Treatment

Carbamazepine 200 mg po tid or qid is usually effective for long periods; hepatic and hematopoietic function should be checked after 2 wk, then every 3 to 6 mo. If carbamazepine is ineffective or has adverse effects, gabapentin 300 to 900 mg po tid, phenytoin 100 to 200 mg po bid or tid, baclofen 10 to 30 mg po tid, or amitriptyline 25 to 200 mg po taken at bedtime may be tried. Peripheral nerve block provides temporary relief.

If pain is severe despite these measures, neuroablative treatments are considered; however, efficacy may be temporary, and improvement may be followed by persistent pain that is even more severe than the preceding episodes. In a posterior fossa craniectomy, a small pad can be placed to separate the pulsating vascular loop from the trigeminal root. In radiosurgery, a gamma knife can be used to cut the proximal trigeminal nerve. Electrolytic or chemical lesions or balloon compression of the trigeminal (gasserian) ganglion can be made via a percutaneous stereotaxically positioned needle. Occasionally, as a last resort to relieve intractable pain, the trigeminal nerve fibers between the gasserian ganglion and brain stem are cut.