

CHAPTER 16.

Diseases of the Peripheral Nerves and Motor Neurons

PERIPHERAL NEUROPATHIES

The peripheral nervous system (PNS) includes all structures related to the Schwann cells from the pia-arachnoid membrane to the nerve endings. The first (olfactory) and second (optic) cranial nerves are not considered peripheral nerves. These nerves are extensions of the central nervous system (CNS) and contain oligodendroglia instead of Schwann cells. The other cranial nerves, spinal motor and sensory nerves, and peripheral components of autonomic nervous system are included in PNS.

Disorders that affect peripheral nerves can affect one or more components of the nerve fiber. Disorders predominantly affecting myelin are *demyelinating neuropathies*. When disease process affects distal portion of axons with preservation of parent cell bodies in dying-back manner, this is *axonopathy or axonal neuropathy*. Disorders affecting cell bodies in dorsal root ganglia and their axons are *neuronopathies*. Neuropathies may be generalized and symmetrical (polyneuropathy) or focal and affect one (unifocal or mononeuropathy) or multiple (mononeuropathy multiplex) nerves.

SYMPTOMS AND SIGNS

Symptoms and signs can be motor, sensory, or autonomic.

Motor Findings

Weakness or paralysis in neuropathies is usually hypotonic in type and is associated with muscle wasting (atrophy). Weakness can develop *acutely* in external compression of a superficial nerve ("Saturday night" or "crossed leg" paralysis), when penetrating trauma injures a nerve, or when vascular occlusion causes infarction of nerves as in diabetic femoral neuropathy or ophthalmoplegia (third cranial nerve) or in vasculitis such as in polyarteritis nodosa. *Subacute* onset of weakness takes less than 4 weeks as is usually seen in para-infectious polyneuropathies. (see Guillan-Barré Syndrome) Weakness in *chronic* neuropathies progresses slowly over several months to years. Patients show distal wasting of muscles. Chronic neuropathies are usually due to hereditary or toxic-metabolic causes. Pes cavus, hammer toes, kyphoscoliosis and other orthopedic deformities are associated with chronic hereditary neuropathies due to muscle imbalance. Weakness in mononeuropathies is localized to muscles innervated by affected nerve. Weakness in polyneuropathies usually begins distally in feet and hands and progresses in ascending symmetrical fashion to involve legs and arms and sometimes facial, bulbar, and respiratory muscles. Initial proximal weakness in neuropathies suggests a radicular (nerve roots) involvement or more likely primary muscle involvement (myopathy). *Fasciculations* are a rare occurrence in neuropathies and, when present, suggest distal motor axonal involvement or more likely anterior horn cell disease. *Myokymia* or undulating worm-like rhythmic movements of muscle is rarely seen in neuropathies.

Sensory disturbances appear in two different ways. Positive sensory symptoms occur when aberrant sensation occurs in the absence of normal stimulation. Negative symptoms occur when adequate stimuli fail to produce a sensory response. *Positive* sensory symptoms: A sensation of tingling (paresthesia) in the hands or feet over the distribution of one or more nerves is a frequent complaint in sensory neuropathies and can be the first sign of nerve involvement. Some patients experience a peculiar unpleasant sensation of tingling in the feet that occurs mainly during the night and that can be temporarily relieved by movement of the affected limb, the neuropathic pain restless legs syndrome. Ischemic pain of peripheral vascular disease, which has to be

differentiated from this, occurs during activity rather than at rest and improves with rest. Paresthesias are characteristic of acquired neuropathies, whereas numbness is seen in congenital neuropathies. Dysesthesia, or unpleasant feeling triggered by any ordinary stimuli, is usually evident after partial nerve injury or during recovery from some neuropathies. A burning sensation, hyperesthesia, or exaggerated normal feeling, hyperpathia, is felt when stimulus is moving rather than when stationary pressure is applied. Dysesthesias, hyperesthesias, and hyperpathias can occur in diabetic and alcoholic neuropathies and in some neuropathies associated with malignancies (multiple myeloma). Terms frequently used in reference to abnormal sensation in some peripheral neuropathies are neuralgia, which implies stabbing or throbbing pain in distribution of a nerve as is found in tic douloureux, herpetic neuritis, and causalgia, which implies burning, persistent pain that radiates distally along an injured nerve trunk. When causalgic pain is associated with autonomic dysfunction, such as abnormal sweating, trophic skin and nail changes, or edema, it is known as reflex sympathetic dystrophy or complex regional pain syndrome.

Negative sensory symptoms: Sensory loss can be an early sign and occasionally the only sign of peripheral neuropathy; however, it frequently is associated with motor disturbances. Sensory loss can be limited to one nerve trunk as in herpetic neuritis or, more frequently, can be bilateral, symmetrical, and distal in stocking or glove distribution as seen in polyneuropathies. There are several different patterns of sensory loss: (1) Loss of all modalities of sensation in distal distribution with gradual return of sensation is usually produced by conduction blocks caused by demyelination. (2) Loss of touch-pressure, vibratory, and position sense with preservation of pain and temperature, so-called sensory ataxia, is seen in tabes dorsalis, but also is seen in some diabetic neuropathies and Friedreich's ataxia. This type of sensory deficit is due to large fiber loss. (3) Selective loss of pain and temperature with preservation of touch-pressure is seen in leprosy and some hereditary sensory neuropathies. This type of sensory deficit is due to loss of small myelinated sensory fibers. (4) Pure sensory syndrome with positive (dysesthesia) and negative (hypesthesia) phenomena and associated with sensory ataxia is seen in neuronopathies and is due to damage to nerve cell bodies in dorsal root ganglia.

Autonomic Findings

Orthostatic hypotension without change in the pulse rate is probably the most important and earliest abnormality in some autonomic neuropathies. Painless nocturnal diarrhea, heat intolerance, and localized excessive sweating in unaffected areas with anhidrosis in affected areas may be the complaint of some patients. Other symptoms of autonomic dysfunction include bladder (atonic) dysfunction manifested by difficulty voiding, sexual impotence, retrograde ejaculation, decreased tearing, and pupillary abnormalities. Autonomic involvement is seen predominantly in diabetic and amyloid neuropathies, but maybe seen in neuropathies of other etiologies.

Muscle Stretch Reflexes

Stretch reflexes are decreased (hyporeflexic) or abolished early in demyelinating neuropathies. Preservation of stretch reflexes can be seen in axonal neuropathies. The presence of Babinski signs should alert the physician to a central disease process or more diffuse process involving peripheral nerves and corticospinal tracts as noted in subacute combined degeneration or Friedreich's ataxia. Positive Babinski sign should never be seen in peripheral neuropathy alone.

Nerve Enlargement: Observation and Palpation

Inspection and palpation of nerves is essential part of examination when diagnosis of peripheral neuropathy is being considered. Enlarged nerves are easier to detect in slender patients. When superficial nerves are enlarged they can be seen through skin. Physician should observe and palpate for nerve enlargement along course of

great auricular nerve in posterolateral surface of neck and superficial peroneal nerve over anterior aspect of ankle or dorsal aspect of the feet. Palpation of enlarged nerves needs to be done in supraclavicular area for supraclavicular nerves, above elbow for ulnar nerve, and at lateral aspect of neck of fibula for common peroneal nerve.

LABORATORY TESTS

The diagnosis of peripheral neuropathy can be confirmed by electrophysiologic studies. Nerve conduction studies define distribution and extent of neuropathy and differentiate between axonal and demyelinating process. Based upon nerve conduction velocities, it is possible to suggest the etiology of the neuropathy in some cases. The presence of multifocal conduction blocks indicates acquired demyelinating neuropathy, whereas hereditary neuropathies show uniform slowing of conduction velocities. Nerve conduction studies can localize level of lesion in compressive (entrapment) neuropathies. Laboratory investigation should include a complete blood cell count, erythrocyte sedimentation rate, fasting blood glucose, serum protein and plasma immunoelectrophoresis, liver function tests, chest roentgenograms, thyroid function tests, and serum vitamin B₁₂ and folate levels. Cryoglobulins, urinary porphyrins, and heavy metals should be ordered in selected cases. Ganglioside-monosialic (GMI) acid antibodies are detected in some patients with multifocal neuropathies and lower motor neuron disease. Myelin-associated glycoprotein (MAG) and sulfate-3-glucuronyl paragloboside are detected in some patients with inflammatory neuropathies. Commercially available motor and sensory neuropathy diagnostic panels are already available. Deoxyribonucleic acid analyses for the CMT1A duplication and for peripheral neuropathy with liability to pressure palsies are also commercially available. Cerebrospinal fluid (CSF) protein is elevated in some neuropathies, most frequently in Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. Finally nerve biopsy can be helpful in diagnosis of neuropathies caused by vasculitis (polyarteritis nodosa), autoimmunity, infections, and amyloid.

APPROACH TO THE PATIENT WITH A SUSPECTED NEUROPATHY

Many different disease processes can affect peripheral nerves; however, clinical features are uniform and stereotyped. When confronted with peripheral nerve diseases the following questions should be answered:

Evolution

Is it an acute (few hours or days), subacute (less than 4 weeks), or chronic (more than a month) process? Is it a recurrent or chronic relapsing disease?

Distribution

Is it isolated lesion of one nerve (mononeuropathy), or are multiple isolated scattered individual nerves affected (multiple mononeuropathy)? Is it symmetrical bilateral involvement of nerves (polyneuropathy)? If so, are spinal roots also involved (polyradiculoneuropathy)? What nerve is affected? Is it peripheral or cranial nerve? Is entire plexus or part of plexus involved (plexopathy)? Are distal or proximal parts of nerve involved?

Modality

Is nerve involved motor in type? Is it a sensory nerve? Are autonomic nerves involved? Is there combination of different types of nerves involved?

Electrophysiology and Pathology

Is neuropathy caused by damage of myelin (demyelination)? Is it segmental? Or diffuse? Is it due to axonal damage (axonal neuropathy)? Is it both axonal and demyelinating? Is it due to nerve cell damage of dorsal root

ganglion (neuronopathy)? Is it the neuropathy due to nerve fiber ischemia? (vasculitis)? Is it due to chronic autoimmune inflammatory phenomena (chronic inflammatory demyelinating polyneuropathy)? Has focal portion of nerve been injured, causing compressive or entrapment neuropathy? By the time you have answered the questions listed above, you should have idea of type of neuropathy and cause of nerve lesion.

Etiology

Is there evidence of systemic disease that can provide clue as to disease cause (e.g., diabetes, uremia, connective tissue disorder, cancer, alcoholism)? Has patient been exposed to neurotoxic agents? Is there family history of same disease? If so, who is or has been affected? (Obtaining pedigree of family will determine possible inheritance pattern.)

CLINICAL SYNDROMES

Of disease processes affecting peripheral nerves, only most common problems and those that typify group of similar disorders are discussed here.

Neuropathies Caused by Compression and Entrapment

Neuropathies can be produced by local injury of superficial nerves (compression) or during passage of nerve through narrow anatomical site (entrapment). Compression can be external (outside the skin) or internal such as that caused by hematoma, inflammation, or scarring. Predisposing factors in both compression and entrapment include pregnancy, hypothyroidism, acromegaly, and rheumatoid arthritis. Increased susceptibility to compression of nerves occurs in malnutrition, diabetes, alcoholism, renal failure, and genetic defects. In certain compressive neuropathies, onset can be abrupt; patient wakes up after deep sleep induced by heavy alcohol ingestion or heavy sedation induced by drugs and can not use one hand due to wrist weakness; this is Saturday night palsy, which is produced by compression of radial nerve against humerus. If wrist can not be extended, hand is not functional and is useless as it can not be placed in functional position. If peroneal nerve is compressed at knee, patient suddenly develops foot drop. Sudden onset in these compressive neuropathies is due to conduction block. In other compressive neuropathies such as median nerve compression in the carpal tunnel or ulnar nerve compression at the elbow, onset is more insidious and is produced by repeated minor trauma. The main symptoms are variable degrees of weakness in innervated muscles and paresthesias confined to cutaneous distribution of the nerve. Pain is poorly localized and can be felt in areas away from compression site. Sensory examination is important followed by palpation of nerve to look for nerve thickening and percussion of nerve to look for local pain or paresthesias. Electrophysiologic studies are very important to confirm diagnosis, to localize the site of compression, and for prognostic implications.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is produced by compression of median nerve as it passes beneath transverse carpal ligament at wrist. It is most common entrapment neuropathy and usually causes nocturnal pain and paresthesias in the wrist and hand; pain can radiate proximally into forearm, elbow, and at times into the shoulder. Distally discomfort radiates into palmar aspect of thumb, index finger, and middle finger. Patients may complain of sensory impairment involving entire hand; however, detailed sensory testing usually shows decreased sensation on palmar surface of hand involving first three fingers and radial side of ring finger with normal sensation on ulnar surface of ring finger. Weakness of opponens pollicis and abductor pollicis brevis may be seen later. Thenar atrophy may occur with severe compression. Signs and symptoms are aggravated by kneading, typing, or any activity involving flexion and extension of wrist. This condition is very common in typists, carpenters, and plumbers; these occupations involve repetitive pressure on median nerve at wrist. Percussion of median

nerve at wrist can produce painful discomfort radiating to hand (Tinel's sign) and forced flexion of wrist causes paresthesias in median distribution (Phalen sign). Treatment consists of wrist immobilization in neutral position in early cases, local injection with corticosteroids and anesthetics in mild cases, or surgical decompression after failure of conservative treatment.

Ulnar Entrapment

Ulnar nerve can be compressed at elbow, axilla, or wrist. Condylar groove or cubital tunnel at elbow is most frequent site for ulnar entrapment. Predisposing factors for compression include elbow deformities from previous fractures, arthritis, and soft tissue tumors. Numbness and tingling of fourth and fifth fingers and medial border of palm are frequent complaints. Weakness of interossei muscles (guttering between fingers on back of the hand) can be absent, or else insidious progressive wasting of hand muscles can develop without sensory symptoms. Treatment consists of padding elbow, nonsteroidal anti-inflammatory agents, or surgical transposition of ulnar nerve.

Radial Nerve Injury

The radial nerve can be compressed or entrapped in the axilla. This injury commonly results from incorrect or prolonged use of crutches or compression of axilla during intoxicated sleep. Radial nerve injury at this level can cause weakness of triceps, wrist extensors, brachioradialis, and finger extensors. The most frequent compressive site is at humerus as nerve courses around bone. Compression at this level can occur during sleep or during general anesthesia. This compression causes weakness of forearm extension and "wristdrop" with inability to extend wrist but with preservation of triceps muscle. Because hand cannot be placed in position of function, there appears to be marked hand weakness. This apparent weakness is eliminated by placing wrist in splint with hand in neutral position. The sensory loss of radial nerve injury is limited a small area adjacent to dorsum of thumb. Most patients recover with time and with avoidance of further compression. Treatment includes placing wrist in splint to allow use of the hand. Surgical exploration is indicated when there is continuous symptom worsening.

Common Peroneal Nerve Palsy

Common peroneal nerve palsy is produced by compression of nerve as it passes around head and neck of fibula. Pressure is usually produced during sleep or anesthesia, by casts or obstetrical stirrups, tight high boots, squatting, or habitual leg crossing while seated. Symptoms consist of foot-drop as result of inability to dorsiflex foot and toes and numbness on lateral aspect of leg and dorsum of foot. Treatment consists of physical therapy and foot braces (ankle-foot orthosis) and removal of compressive agent.

Lateral Femoral Cutaneous Nerve Compression (Meralgia paresthetica)

The lateral femoral nerve innervates anterolateral thigh from pelvic crest to knee. The nerve passes underneath inguinal ligament. Compression of this nerve can result from abdominal or pelvic surgery or can be caused by wearing tight garments around hip region. This nerve is commonly damaged in patients who are obese or who have diabetes mellitus. Because this is superficial purely sensory nerve, symptoms include numbness, paresthesia, or dysesthesia over lateral thigh with no motor weakness.

Femoral Nerve Injury

Femoral nerve is derived from second through fourth lumbar roots. It can be injured in abdomen (e.g., caused by neoplasm, hemorrhage, or abscess) or as it exits from pelvic region. Motor symptoms include weakness of psoas and quadriceps muscles such that there is weakness of hip flexion and impaired leg extension. Anterior thigh can appear wasted as result of quadriceps atrophy. Knee jerk is diminished. Sensory impairment involves

anteromedial thigh. For patients with femoral neuropathy computed tomography (CT) scanning of abdomen and pelvis should be performed to exclude mass compressing femoral nerve in these regions. If these tests are negative, diabetes mellitus must be excluded as the potential etiology

Sciatic Nerve Injury

The sciatic nerve is derived from fourth and fifth lumbar and first and second sacral roots. Sciatic nerve involvement affects both peroneal and posterior tibial nerve branches. This nerve supplies hamstring muscle and all muscles below the knee (including dorsiflexion and plantar flexion, of foot eversion and inversion of the foot). Sensory distribution involves posterior thigh, posterior and lateral leg, and entire foot. In complete sciatic nerve injuries, knee cannot be flexed and entire foot is paralyzed. This is flail or useless foot in which no motor function is possible and ankle needs to be fused to avoid further ankle injury. If there is gluteal muscle weakness and sensory impairment in saddle (buttock) region, this indicates involvement of sciatic nerve at lumbosacral plexus in pelvis. Sciatic nerve can be injured by abdominal and pelvic fractures, poorly administered (intramuscular) injections into buttock region, or tumors. It is important to differentiate lumbosacral plexopathy or herniated disk with radiculopathy from sciatic nerve injury and this can be accomplished by clinical exam.

Posterior Tibial Nerve Injury

The posterior tibial nerve is a branch of sciatic nerve. It passes from popliteal fossa down leg and through tarsal tunnel (located along medial calcaneus at ankle). Motor branch of this nerve supplies plantar flexion and inversion of foot as well as intrinsic foot muscles except extensor digitorum brevis. Sensory supply is plantar (sole) foot surface. Posterior tibial nerve can be compressed at tarsal tunnel to cause pain and dysesthesias over sole of foot. It is important to consider tarsal tunnel syndrome with posterior tibial nerve entrapment in differential diagnostic consideration of foot pain.

NEUROPATHIES ASSOCIATED WITH SYSTEMIC DISEASES

Diabetic Neuropathy

Clinical signs and symptoms of neuropathy are seen in approximately 20% of diabetic patients, but electrophysiologic studies done in asymptomatic diabetics demonstrate higher percentage of subclinical involvement. Rarely, the neuropathy can be initial sign of diabetes. The longer duration and more poorly controlled the diabetic, the increased risk of neuropathy. Rarely neuropathy symptoms are initial presenting sign of diabetes and with treatment, symptoms recede. In addition, distal painful extremity paresthesias may occur 4 weeks after initiation of insulin therapy and achievement of normoglycemic state axonal nerve injury occurs as glucose is not available for nerve metabolism; however, with normalization of blood glucose with insulin, symptoms resolve. Diabetes is major risk factor for all entrapment neuropathies. There are different patterns of diabetic neuropathy; symmetric polyneuropathies, focal and multifocal neuropathies.

Symmetric polyneuropathies: Distal, symmetrical, sensory polyneuropathy of insidious onset is most common form. Symptoms usually start with paresthesias of feet and legs in typical length related pattern. The hands are rarely affected and if affected, first consider alternate diagnosis e.g. cervical radiculopathy, carpal tunnel syndrome, syringomyelia. The anterior midline of the abdomen (truncal neuropathy) may be affected. Burning paresthesias of feet that are worse during night can be seen. Leg weakness is rare. Areflexia of Achilles tendon is constant feature. There is loss of pain and touch in stocking-glove distribution. Acute painful neuropathy can occur and is preceded by rapid and profound weight loss. It is most frequently seen in males and can be associated with impotence. Symptoms subside with adequate control of diabetes and weight gain. In some

patients there is predominant loss of vibratory, position, and deep pain sensation with neuropathic arthropathy and nonreactive pupils resembling tabes dorsalis (diabetic pseudotabes). Transient painful paresthesias can be described by some diabetic patients following treatment with insulin (treatment induced neuropathy). The symptoms improve with tight glycemic control. Proximal symmetric lower limb motor neuropathy, also known as diabetic amyotrophy, can occur. It is insidious in onset and is associated with poorly defined pain and prominent weakness and wasting in proximal distribution.

Autonomic neuropathy: Autonomic involvement increases risk of death in diabetic patients. Due to loss of sensation in diabetic patients, painless myocardial ischemia may occur. Autonomic dysfunction includes pupillary abnormalities that are frequent and consist of miosis, diminished light reflex, and absence of pupillary dilation in dark as result of sympathetic denervation. Tachycardia and postural hypotension can also occur. Painless nocturnal diarrhea or diarrhea after meals is most frequent gastrointestinal autonomic dysfunction. Impotence correlates with presence of neuropathy. Bladder atony with overflow incontinence and large residual of volume after micturition indicate parasympathetic denervation.

Focal and multifocal neuropathies: Acute, painful mononeuropathies caused by nerve ischemia occur in diabetes and include mainly femoral mononeuropathy and diabetic ophthalmoplegia. In femoral mononeuropathy, patient develops severe pain in distribution of femoral nerve (thigh) accompanied by weakness and atrophy of quadriceps muscle with patellar areflexia. In diabetic ophthalmoplegia, third nerve is most commonly affected but with no pupillary involvement. Pupillary sparing seen in diabetic third nerve involvement differentiates it from compression of the third nerve by intracranial carotid artery aneurysms or neoplasms. Sixth cranial nerve is less frequently affected by ischemic diabetic cranial neuropathy. Other presentations of diabetic nerve disease include multiple, painful, asymmetric, usually motor neuropathy (multiple mononeuropathy). Treatment of diabetic neuropathies consists of strict control of diabetes and maintenance of ideal body weight. Vitamin supplementation and aldolase reductase inhibitors have produced no improvement of sensory symptoms. Tricyclic antidepressants e.g., Amitriptyline (Elavil) or nortriptyline (Pamelor), 75 to 100 mg at bedtime, frequently relieves pain in patients with sensory neuropathies, but anti-epileptic drugs (which block sodium channels) either individually or in combination, can also be used for neuropathic pain.

Uremic Polyneuropathy

Uremic polyneuropathy occurs more frequently in males and has insidious onset, usually correlating with renal failure. Clinical manifestations are those of dysesthesias, cramps, and restless legs syndrome. The neuropathy is distal symmetric mixed sensory motor neuropathy that predominantly affects legs. Some improvement of neuropathy can occur after dialysis, but only renal transplantation results in sustained improvement.

Alcoholic Neuropathy

Alcoholic neuropathy is most likely result of dietary deficiency rather than direct neurotoxic effect of alcohol. Alcoholic neuropathy is slowly progressive and manifests predominantly with distal sensory dysesthesias of feet. Patients describe pain as burning or stabbing. Hands involvement is late and less severe. Variable weakness and muscle atrophy also occur. Loss of stretch reflexes and autonomic skin changes are frequent. Autonomic involvement with hypothermia and postural hypotension is also frequent. Treatment consists of dietary improvement, abstinence from alcohol, and vitamin supplements (especially thiamine and other B vitamins).

Amyloid Neuropathy

Peripheral nerves can be involved in primary systemic amyloidosis and rarely in secondary (chronic infection) amyloidosis. The most frequent form of amyloid neuropathy occurs in familial form known as foot disease or

Andrade's disease. It usually starts in young adulthood and progresses slowly for 10 to 15 years. Neuropathy is usually sensory. Autonomic involvement is very frequent with predominant gastrointestinal problems (diarrhea). Cardiac arrhythmias, vitreous opacity, and renal involvement along with positive family history are characteristic of this disorder. Amyloid deposits can be demonstrated in nerve or rectal biopsies.

Monoclonal Gammopathies

A gammopathy is disorder in which there is abnormal proliferation of lymphoid cells producing immunoglobulins. In monoclonal gammopathies, single clone of plasma cells in bone marrow produces immunoglobulin consisting of two heavy polypeptide chains of the same class and subclass and two light polypeptide chains of same type. The monoclonal proteins are classified according to their type of heavy chain. IgG, IgA, and IgM monoclonal gammopathies are sometimes associated with neuropathies. Neuropathies in monoclonal gammopathies are most likely associated with sclerotic myeloma, multiple myeloma, amyloidosis, macroglobulinemia, or lymphoma. Neuropathies associated with monoclonal gammopathy are rare and, when present, are more frequent in males older than 50. They are usually mixed sensory-motor and are seen predominantly in distal legs. They respond to treatment of the underlying process. If these diseases have been excluded, patient is classified as having a monoclonal gammopathy of undetermined significance (MGUS) with associated neuropathy. Antibodies that are active in MGUS associated with peripheral neuropathy are usually of IgM class. These antibodies are frequently directed against myelin associated glycoprotein (MAG), and neuropathy is frequently demyelinating and predominantly sensory.

INFECTIOUS AND POSTINFECTIOUS NEUROPATHIES

Herpes Zoster (Shingles)

Herpes zoster the most frequent infectious neuritis in adults and is due to reactivation of varicella-zoster virus in ganglia and associated sensory axons. It is associated with dermal pain, frequently in thoracic area, with or without vesicular rash along course of affected nerve.

Human Immunodeficiency Virus Infection (Acquired Immune Deficiency Syndrome)

Peripheral neuropathy is most frequent neurologic disorder in infection with human immunodeficiency virus (HIV). Type of neuropathy correlates with stage of infection. In early asymptomatic stages, inflammatory demyelinating neuropathy and Guillain-Barré-like syndrome can occur; however, this may begin with bilateral facial weakness and weakness may descend rather than ascend as is characteristic of Guillain-Barré neuropathy. CSF pleocytosis and laboratory evidence of HIV infection differentiate these neuropathies from idiopathic ones. In early symptomatic phase of infection; vasculitic syndrome that is probably due to immune complex deposits in blood vessel can produce some mononeuropathies or multiple mononeuropathy. During late immunocompromised stage, most frequent form is distal symmetric polyneuropathy. This is typically painful sensory polyneuropathy involving feet and distal leg. At this stage, cytomegalovirus infection (CMV) is frequently found and produces radiculopolyneuropathy or myelopathy. Drugs used for treatment of HIV disease are common causes of neuropathy.

Leprous Neuropathy

Leprous neuropathy is disease endemic in tropical areas and is due to direct invasion of nerve by *Mycobacterium leprae*. Neuropathy is frequently associated with skin lesions and is mixed sensori-motor neuropathy with features of multiple mononeuropathy predominantly affecting cool areas of skin. Painless injury as result of sensory loss is main manifestation. Nerve enlargement is prominent finding. The organisms

can be demonstrated in skin or nerve biopsies. Antibiotic treatment (dapsone, clofazimine, and rifampin) arrests progression and disease may reverse neuropathy.

Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barré Syndrome)

Acute idiopathic polyneuritis is immunologically mediated demyelinating polyneuropathy that affects all ages and both sexes equally. The disease is usually preceded by acute infectious illness, including *Campylobacter jejuni*, viral or *Mycoplasma* infection, surgery, or immunization (rabies, swine influenza) or can occur in patients with malignant disease (lymphomas) or lupus erythematosus. The disease is characterized by rapidly progressive motor weakness, frequently symmetrical, with or without mild ataxia at onset and frequently of ascending nature beginning distally in the legs, progressing to upper extremities, and ending with severe respiratory paralysis. There can be involvement of cranial nerves causing facial paralysis, and external ophthalmoplegia with sixth nerve palsy, which is most frequent extraocular finding. Progression of weakness varies from 3 days to 4 weeks. Areflexia is usually generalized and occurs early; this is constant feature. Although paresthesias are frequently early complaint, sensory signs are mild. Autonomic dysfunction can cause cardiac arrhythmias and postural hypotension, but bladder or bowel dysfunction at onset or persisting during disease is rare. Functional recovery usually begins 2 to 4 weeks after stabilization of symptoms and is complete in most patients. Areflexia can be permanent residual finding. A variant of the disease includes acute onset of ophthalmoplegia, ataxia, and areflexia with or without weakness of the extremities (Fisher syndrome). Rapid onset of symmetrical cranial nerve dysfunction (polyneuritis cranialis) can also be a variant. Pure pandysautonomia of rapid onset with full recovery is considered another variant, and in some cases predominant autonomic symptoms can precede typical course of Guillain-Barré syndrome. Autonomic symptoms can cause sudden death. The increase in CSF protein with less than 10 cells/ml (albuminocytologic dissociation) strongly supports the diagnosis when found after first week of symptoms or when progressive rise of protein content is demonstrated from serial lumbar punctures. Nerve conduction studies confirm demyelinating process by showing reduction in conduction velocity, conduction block or abnormal temporal dispersion in motor nerves, prolonged distal latencies. Treatment consists of maintaining adequate respiratory function and instituting respiratory assistance when vital capacity falls below 12 to 15 ml/kg or when there is decreased blood oxygen saturation. Cardiovascular status should be monitored to control autonomic dysfunction. Passive bedside physiotherapy should be started immediately and followed throughout recovery. There is convincing evidence that plasmapheresis early in disease course reduces duration of acute hospital care, shortens duration of ventilator dependency, and hastens motor recovery. One session every other day with exchange of 40 to 50 ml/kg should be done to achieve cumulative exchange of 200 to 250 ml/kg. Intravenous immune globulin in dosage 0.4 gm per kilogram per day for 5 days is as effective as or superior to plasma exchange. Treatment with high-dose immune globulin as described, combined with 0.5 gm of methylprednisolone/day, is more effective than treatment with immune globulin alone.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic recurrent inflammatory demyelinating polyneuropathy is rare form of both motor and sensory polyneuropathy or polyradiculoneuropathy that affects distal and proximal limbs. Onset of symptoms is usually insidious, and course is slowly progressive, either stepwise or relapsing. Motor weakness predominates, but sensory loss is found in most patients. Muscle atrophy is of lesser degree than would be expected from amount of weakness. CSF protein is elevated without increased cell count. Respiratory involvement is less frequent than in Guillain-Barré syndrome, and there is greater fluctuation of functional impairment. Treatment includes intermittent intravenous immune globulin treatment with or without methylprednisolone, intermittent

plasmapheresis, chronic steroid therapy, or immunosuppression with cyclophosphamide (Cytoxan) or azathioprine (Imuran).

Sensory Neuronopathy

Sensory neuronopathies are pure sensory syndromes without motor deficit produced by damage to nerve cell bodies in spinal dorsal root or trigeminal ganglia. Sensory manifestations include both positive (dysesthesia) and negative phenomena (hypesthesia). Severe sensory ataxia, caused by deafferentation, is main clinical manifestation. Dependence on visual input for maintenance of postural stability is strong and helps to differentiate this type of ataxia from cerebellar type (positive Romberg test in neuropathy but not in cerebellar disorders). Pseudo-athetosis of upper limbs is frequent, and areflexia is constant feature. Clinical presentation can be acute, subacute, or chronic. Acute form is rare, and the few cases described may have been produced by use of synthetic antibiotics. Subacute form has been associated with carcinoma, pyridoxine abuse, or cisplatin therapy. This form often begins asymmetrically and can first appear in upper limbs or trigeminal distribution. Pain and dysesthesias are followed by proprioceptive loss. The chronic forms are sporadic and of unknown cause, and there is a group of hereditary disorders. The prognosis of this group of disorders is poor except for the toxic ones, which can improve if diagnosis is made early and toxic agent is discontinued.

Neuropathies Associated with Connective Tissue Disorders

Neuropathies associated with connective tissue disorders are usually of ischemic vascular origin caused by arteritis. Clinical evidence of neuropathy in *rheumatoid arthritis*, other than carpal tunnel syndrome, is not frequent but when present is due to arteritis and occurs in patients with longstanding disease, destructive joint disease, rheumatoid nodules, and high titers of rheumatoid factor. The disease can appear as progressive, distal (legs first), sensorimotor polyneuropathy or can have features of multiple mononeuropathy. Neuropathy in *polyarteritis nodosa* occurs in 50% of patients with this disease and can be initial manifestation. The neuropathy appears as multiple mononeuropathy with involvement of two or more nerves in an acute fashion, with pain and paresthesias in distribution of affected nerve, followed by weakness. The distribution can also be that of diffuse, distal, and symmetrical sensorimotor polyneuropathy. Treatment consists of corticosteroids and immunosuppression. Neuropathy in *systemic lupus erythematosus* occurs infrequently; it can be initial symptom of disease and indicates diffuse vasculitis and poor prognosis. The disease appears as progressive symmetrical, distal, sensorimotor neuropathy with elevated CSF protein. More rarely the disease can appear as multiple mononeuropathy.

Cranial Neuropathies

Cranial nerves can be affected by several disease processes without involvement of spinal nerves. They can be individually affected or else several nerves can be involved. When cranial mononeuropathies or polyneuropathies are associated with impaired function in corticospinal, spinothalamic, or cerebellar tracts, lesion is within brain stem. Pure mononeuropathies or polyneuropathies localize lesion outside brain stem. The most common cranial neuropathy is discussed below.

Bell's Palsy (Idiopathic Facial Paralysis)

Bell's palsy is an acute disease of facial (seventh cranial) nerve of unknown causes that produces edema and compressive ischemia of nerve within its bony canal within temporal bone. Onset is sudden or can develop in few hours or days. It occurs in either gender and at any age. Many of patients are diabetic. Facial palsy can develop in patients with basilar meningitis (sarcoid, neoplastic, including leukemia). The most significant finding is infranuclear (peripheral) facial palsy, which can be partial or complete and can be associated with or

preceded by retroauricular (mastoid) pain and decreased taste. Some patients can have hyperacusis (uncomfortable sensation in the ear in response to loud noise) and excessive or decreased lacrimation. Recovery tends to be rapid (weeks) and complete in 80% of patients. Prognostic indicators for delayed or partial recovery include age over forty, complete paralysis with decreased tearing, decreased taste, retroauricular pain, and electromyographic evidence of denervation 10 days after onset of symptoms. Treatment consists of protecting the cornea with eye patch during sleep or when going outdoors. Corticosteroids can have beneficial effect when used within 72 hours of onset (60 mg/day for 4 days, then taper to 5 mg/day in 10 days.) and there is evidence that Acyclovir, used for herpes infection, is effective. No evidence exists that surgical decompression improves outcome.

Brachial Neuritis (Neuralgic Amyotrophy)

Brachial neuritis is a disease of undetermined causes that can be associated with use of foreign sera (tetanus antitoxin) or vaccines. However, most commonly it is idiopathic. Males are predominantly affected. The disease is characterized by sudden, severe, and often nocturnal pain in shoulder, arm, forearm, and hand. This pain is usually severe and is followed within a few days or weeks by proximal shoulder weakness. In most patients, weakness is confined to shoulder girdle, mainly axillary and suprascapular nerves (upper brachial plexus). Partial brachial plexus involvement in one or both sides may be noted usually in asymmetrical fashion. Nerves derived from lower plexus are rarely involved alone. EMG shows denervation in distribution of affected nerves but nerve conduction velocity (NCV) is usually normal. All other tests including CSF studies are normal. The diffuse nonsegmental signs, lack of radicular pain, and normal CSF findings argue against cervical radicular involvement. Prognosis is excellent in most cases with complete recovery in 80% of patients by 2 years. Treatment consists of symptomatic relief of pain and physical therapy. Corticosteroids have been used in the acute phase for relief of pain but do not modify outcome.

TOXIC NEUROPATHIES

A great variety of toxic agents produce damage to peripheral nerves usually to distal portion of axon (dying-back neuropathies). Only a few that have unique features are discussed.

Heavy Metals

Lead produces pure motor neuropathy of radial nerve (wristdrop), which can be unilateral or bilateral. Arsenic poisoning is characterized by mixed polyneuropathy with predominant sensory symptoms usually affecting the lower extremities. Thallium produces mixed polyneuropathy with marked synesthesia and is associated with severe hair loss.

Drugs

Streptomycin affects cochlear part of eighth nerve. Isoniazid produces polyneuropathy by creating pyridoxine deficiency. Ethambutol and amphotericin can also produce polyneuropathy. With longstanding use, anticonvulsants e.g. phenytoin, frequently produce subclinical symptoms. Antineoplastic agents including vincristine and nitrogen mustard can produce neuropathies. Cisplatin commonly causes sensory neuropathy. Industrial agents, mainly solvents including n-hexane and related compounds, acrylamide, or organophosphates can produce an axonal neuropathy.

INHERITED PRIMARY PERIPHERAL NEUROPATHIES

Hereditary Motor and Sensory Neuropathies or the Charcot-Marie-Tooth Polyneuropathy Syndrome

These are genetically and clinically heterogeneous group of disorders of peripheral nerves characterized by insidious onset and slowly progressive weakness of distal muscles and mild sensory impairment. Symptoms appear in first decade or early in second decade. Children with disease often walk on their toes, and adults complain of abnormalities of gait, foot deformities, or loss of balance. Pes cavus develops as disease progresses. Atrophy of distal legs can be prominent feature ("stork leg" or inverted champagne bottle appearance). Tripping over objects on floor and ankle sprains are frequent as result of weakness of dorsiflexion of foot produced by weakness of peroneal and anterior tibialis muscles. Weakness of the intrinsic hand muscles usually occurs late. The most frequent complaints concerning hand involvement are difficulty using zippers, difficulty buttoning and unbuttoning, and difficulty manipulating small objects when using fine finger movements. In severe cases, wasting of hand muscles gives appearance of claw hands. Muscle stretch reflexes disappear early at ankle and later on at patella. Plantar reflex is flexor or absent. Sensory involvement to any significant degree is rare, but decreased pain to pinprick in stocking distribution is seen in some patients. *Electrophysiological* studies distinguish two major forms of Charcot-Marie-Tooth (CMT) that have same clinical phenotype and some variable clinical features. *CMT type 1 (CMT1)* is a demyelinating neuropathy with moderate to severely decreased motor NCV, absent reflexes, and, in some slender patients, enlarged (hypertrophic), visible, or palpable nerves. Patients with *CMT type 2 (CMT2)*, neuronal axonal form, have normal NCVs, normal muscle stretch reflexes, and normal size nerves.

Genetics of CMT

CMT1 can be inherited as autosomal-dominant (AD), autosomal-recessive (AR), or X-linked disorder. AD CMT1 is most frequently observed pattern, whereas AR CMT1 is rare. In 70% of AD CMT1 patients, disease locus shows DNA duplication in a segment of chromosome 17 (17p11.2p12) that encodes membrane-associated myelin protein with apparent molecular weight of 22 kd (PMP22). CMT 1 B is linked to markers on chromosome 1 (1q21.2q23) that encode for protein zero (Po) myelin. The dominant X-linked form, CMTX (sq1213), has missense mutation in segment of X chromosome that encodes connexin-32 protein (Tables 16-1 and 16-2). All these proteins are found in peripheral nerve myelin and to play a role in keeping compaction of myelin layers.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)

This disorder, which is also called familial recurrent polyneuropathy or tomaculous neuropathy, was originally described in a family in which three generations had recurrent peroneal neuropathy after digging potatoes in a kneeling position. Hereditary neuropathy with liability to pressure palsies (HNPP) can cause periodic episodes of numbness, muscular weakness, atrophy, and in some cases palsies that follow relatively minor compression or trauma of peripheral nerves. Carpal tunnel syndrome and other entrapment neuropathies are frequent manifestations of HNPP. Electrophysiologic studies sometimes show mildly slow nerve conduction velocity in clinically affected individuals as well as in asymptomatic carriers. Conduction blocks can also be seen. Peripheral nerves show segmental demyelination and remyelination with tomaculous or sausage-like focal thickening of myelin sheath. HNPP is associated with a 1.5-Mb deletion in 17p11.2p12. All DNA markers known to be duplicated in patients with CMT1A duplication are deleted in patients with HNPP.

Refsum's Disease (Heredopathia Atactica Polyneuritiformis)

Refsum's disease is hereditary metabolic disorder transmitted as autosomal recessive trait as result of deficiency of phytanic acid α -hydroxylase and accumulation of phytanic acid in tissues and blood. The disease starts in childhood and is manifested by chronic polyneuropathy associated with cerebellar ataxia, retinitis pigmentosa, deafness, and pupillary abnormalities. The disease responds to diet low in phytanic acid.

Hereditary Sensory Neuropathies

Hereditary sensory neuropathies are rare hereditary disorders characterized by sensory loss of dissociated type resembling syringomyelia. These neuropathies can appear early or late in life and are frequently associated with painless traumatic deformities, ulcers of the extremities, and autonomic dysfunction.

DISEASES OF MOTOR NERVES

Amyotrophic Lateral Sclerosis (Motor Neuron Disease, Lou Gehrig's Disease)

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease and often referred to as Lou Gehrig's disease, is a devastating paralytic and fatal disorder of adult patients caused by degeneration of large motor neurons of brain and their corticospinal tract, motor neurons of brain stem, and anterior horn cells of spinal cord. As contrasted with peripheral neuropathy, in ALS there is involvement of both lower and upper motor neuron system. There is no sensory disturbances as disorder is entirely motor. Symptoms usually begin insidiously and there is frequently 12 to 24 month delay in diagnosis and hopefully with enhanced awareness of this disorder, the delay in diagnosis will decrease. The disease usually affects middle-aged patients (males more than females possibly related to involvement of androgen receptor) and risk factors may include exercise, smoking, Gulf War experience, genetics (role of superoxide dismutase), and glutamate excitotoxicity. The disease is characterized by progressive weakness and early wasting (amyotrophy) of muscles with fasciculations and presence of upper motor neuron signs. There is striking sparing of bladder and bowel control, sparing of sensation, and preservation of sexual function, intellect, and eye movements. Clinical presentation varies according to group of neurons or tracts affected. It usually consists of progressive, usually symmetrical, distal weakness of legs or hands. Leg muscle cramps are frequent early complaint. Weight loss and progressive wasting of muscles associated with fasciculations in upper and lower limbs, hypotonia, diminished reflexes indicate anterior horn cell involvement. Spasticity of legs with hyperreflexia and bilateral Babinski signs indicate corticospinal tract involvement. Weakness progresses proximally and affects neck muscles and bulbar musculature to cause difficulty swallowing and speech impairment. Respiratory muscle paralysis is the terminal effect. Emotional lability with uncontrollable bouts of laughing or crying, dysarthria, difficulty swallowing, spastic tongue without fasciculations, and hyperactive jaw jerk can occur (pseudobulbar palsy). Course is relentless, progressing to death within 3 to 7 years or more. Diagnosis is established by EMG-NCV which shows normal nerve conduction velocities and electromyographic evidence of widespread denervation with reinnervation. Muscle biopsy shows severe denervation (fascicular) atrophy. The differential diagnosis includes cervical spondylitic myelopathy and other cervical cord lesions including tumors, disk herniations, syringomyelia, or foramen magnum lesions that can be diagnosed by myelography or CT/MRI scanning. Lead and mercury intoxications, thyroid and parathyroid disease, and familial or tropical spastic paraparesis should be excluded. There is a reluctance to make diagnosis of ALS due to poor prognosis and diagnostic certainty needs to be high before this diagnosis is explained to the patient.

There are multiple variants of ALS dependent upon whether the upper or lower motor neuron is predominantly involved and whether the disease begins in the extremities or bulbar region. *Progressive bulbar palsy can be the first manifestation of motor neuron disease.* Speech impairment and difficulty swallowing are

early signs associated with tongue atrophy and fasciculations. Symptoms progress to respiratory impairment or aspiration pneumonia. Clinical course usually lasts less than 3 years. Progressive bulbar palsy is final stage of most patients with amyotrophic lateral sclerosis. In *progressive spinal muscular atrophy (PSMA)*, predominant findings are progressive muscle atrophy and fasciculations with lack of corticospinal tract involvement. This can be confused with unusual muscle disease inclusion body myositis, which begins with distal muscle weakness. The progression of this type of motor neuron disease is slower. However, most patients eventually develop upper motor neuron signs and follow regular course of amyotrophic lateral sclerosis. Some patients with primary lateral sclerosis (PLS) have progressive spastic paraparesis (PLS) that later affects upper limbs and that eventually shows signs of lower motor neuron involvement. Rarely, clinical presentation remains as pure upper motor neurons signs.

Care of patients with amyotrophic lateral sclerosis requires multidisciplinary approach. Physical therapy to increase usefulness of preserved muscles is important. Feeding gastrostomy improves general nutrition of patients with dysphagia and prevents aspiration pneumonia. Ventilatory assistance when necessary should be discussed with patient and family early in disease course. There is no effective therapeutic agent but Riluzole which is glutamate antagonist may slow disease progression especially if utilized early. There is some suggestive evidence that anti-oxidants and creatine may be effective therapeutic strategies. Five to 10% of cases are familial, transmitted in autosomal dominant pattern. There is evidence that genetic defect in some families is linked to chromosome 21 (D21S58) segment that encodes for Superoxide Dismutase 1, an important neuronal antioxidant.

A clinically heterogeneous group of hereditary lower motor neuron diseases that predominantly affect infants and young patients is known as *progressive spinal muscular atrophy (SMA)*. Regardless of age of onset, they are linked to chromosome 5. The disease is inherited through autosomal recessive gene. This heterogeneous disease has several clinical presentations with different ages of onset. When present at birth (Werdnig-Hoffman), it is manifested by floppiness, abdominal breathing, fasciculations of tongue, and evidence of denervation on electromyography and muscle biopsy. An form of spinal muscular atrophy appears in infancy. Patients with this form have a longer survival span. Another intermediate type of spinal muscular atrophy with the same type of inheritance but with onset in adolescence is characterized by predominantly proximal muscle involvement and normal life span (*Kugelberg-Welander type*). In this form of SMA, weakness and atrophy are frequently proximal and simulate myopathy; however, in contrast with a myopathy muscle stretch reflexes are usually absent in Kugelberg-Welander syndrome. Electrophysiologic studies and muscle biopsy are necessary for diagnosis. Bracing and physical and occupational therapy to stretch or prevent contractures and to prevent scoliosis improves quality of patient's life.

SUMMARY

Disorders of peripheral nerves (neuropathy) can cause motor, sensory, and autonomic symptoms. Motor features include weakness and wasting in distal distribution (feet, hands). Sensory disturbances include numbness or painful paresthesias in stocking-glove distal distribution. Autonomic features include bladder, sexual, and gastrointestinal dysfunction and skin, hair, and nail changes. Stretch reflexes are decreased early in most neuropathies. The diagnosis of neuropathy is confirmed by nerve conduction velocity slowing. The neuropathy can be generalized (polyneuropathy) or focal as occurs with compressive (entrapment) neuropathies. Patients with motor neuron disease develop distal weakness with signs of corticospinal tract and anterior horn cell involvement. The presence of fasciculations in weak and wasted muscles indicates anterior horn cell disease.

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TABLE 16-1 Genetic Classification of CMT			
Disease	Locus	Mutation	Gene/Protein
AD CMT1A	17p11.2p12	1.5-Mb duplication`	PMP22
AD CMT1A	17p11.2p12	Missense mutation(including Dejerine-Sottas)	PMP22
AD CMT1B	1q21.q23	Missense mutation (including Dejerine-Sottas)	Po
AD CMT1C	—	—	—
ARCMT1A	8q13q2U	—	—
CMTX	Xq1213	Missense mutation	Conexin-32
HNPP	17p11.2p12	Deletion	Deletion of PMP22
AD CMT2	1p35p36	—	—
AR CMT2	—	—	—

TABLE 16-2 Clinical and Genetic Correlations							
	Onset	Weakness		Nerves	MSR	NCV	Wheelchair
		Hands	Legs				
CMT1	1st or 2nd decade	Late	Early	Can be enlarged	Absent	Prolonged	Rare
AD CMT2	2nd decade	Mild	Severe	Normal	Normal*	Normal	Rare
AR CMT2	At birth or infancy	Severe	Severe	Normal	Normal*	Normal	2 nd decade

MSR: muscle stretch reflexes
 NCVs: nerve conduction velocities
 *: may be decreased and are absent in late stages of the disease