Seminar

Peripheral neuropathy

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Peripheral neuropathy is a common neurological problem. Because the presentation of neuropathy is variable and the causes are disparate, a logical and sequential clinical approach is necessary for evaluation and management. Through a combination of clinical findings, electrodiagnostic tests, and laboratory investigations tailored to individual patients' circumstances, most neuropathies can be categorised by subtype and aetiology. Such classification allows rational assessment of prognosis and treatment options. Treatments for peripheral neuropathy are divided into those that are specific for the subtype of neuropathy and those that are useful for neuropathies in general.

Peripheral neuropathy is a general term that indicates any disorder of the peripheral nervous system. Since this broad definition includes all varieties and causes of peripheral nerve disease, a meaningful and useful diagnosis needs the definition to be refined. Since definition of the type of peripheral neuropathy needs a sequential and logical approach, we outline well-founded principles of clinical diagnosis useful for both general physicians and specialists.

Epidemiology

The overall prevalence of the condition is about 2400 (2·4%) per 100 000 population, but in people older than 55 years, the prevalence rises to about 8000 (8%) per 100 000.[1] Since these figures do not include traumatic peripheral nerve injuries, the total burden of peripheral neuropathy on society is even greater. Although traumatic nerve injuries are important, they are not covered in this review since their diagnosis and management are highly specialised. Comprehensive coverage of peripheral nerve injuries is available elsewhere.[2]

In the developed world, the most common cause of peripheral neuropathy is diabetes mellitus. Since the prevalence of diagnosed diabetes mellitus has increased in the general population in the USA, the prevalence of diabetic peripheral neuropathy is also expected to rise.[3] Although uncommon in the USA and Europe, leprous neuritis is still highly prevalent in Southeast Asia, India, Africa, and Central and South America.[1,4] In global terms, leprosy is a continuing major cause of neuropathy. Other common systemic causes of peripheral neuropathy include a range of metabolic disorders, infectious agents, vasculitis, toxins, and drugs. Dysimmune neuropathies and inherited polyneuropathies constitute a substantial proportion of chronic neuropathies.

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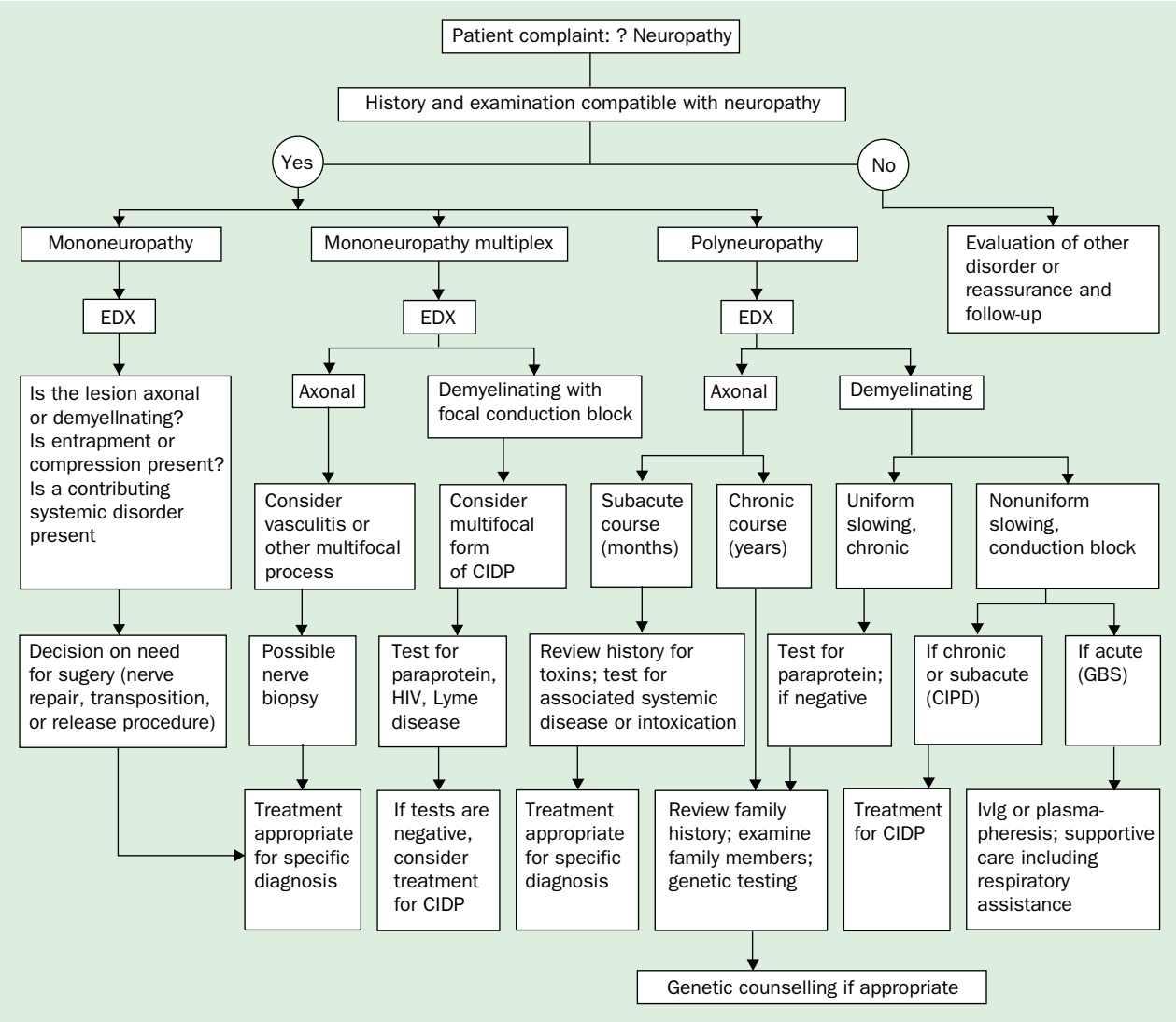
Diagnosis

The clinical manifestations of peripheral neuropathy vary widely. Presenting features encompass varying combinations of altered sensation, pain, muscle weakness, or atrophy, and autonomic symptoms. Accurate diagnosis rests on the skill with which clinical symptoms, signs, and electrodiagnostic study findings can be woven together. In accordance with this diagnostic approach, patients whose history and clinical examination suggest the presence of a peripheral neuropathy should have confirmation by electrodiagnostic studies (figure). Electrodiagnostic studies are sensitive, specific, and validated measures of the presence of peripheral neuropathy.[5-14] Electrodiagnostic studies, which include nerve conduction studies and needle electromyography, are judged to be an extension of the neurological examination.

Although some researchers recommend investigation of common causes of peripheral neuropathy before undertaking electrodiagnostic tests,[15] evidence does not support this conclusion.[5-14] In evaluation of peripheral neuropathy, the most important details to determine are the distribution, the type (mainly demyelinating *vs* mainly axonal features), the duration, and the course of the neuropathy. Electrodiagnostic studies are helpful in establishing whether the distribution conforms to a mononeuropathy, mononeuropathy multiplex, plexopathy, or polyneuropathy; and they are essential in determining whether the primary pathophysiology is

Search strategy and selection criteria

We searched the Cochrane Library (January, 1990 to October, 2003), OVID MEDLINE (January, 1990 to October, 2003), OVID Excerpta Medica (EMBASE: January, 1990 to October, 2003), and OVID Current Contents (January, 2002 to October, 2003). The search included reports of research in human beings only, and all languages. The search terms selected were "peripheral neuropathy", "polyneuropathy", and "guideline". We then limited the search using the terms "epidemiology", "diagnosis", "nerve conduction studies", "laboratory test", "nerve biopsy", "pathology", and "treatment". We translated all non-English language publications that resulted from this search strategy. We largely selected publications in 1996–2003, but did not exclude commonly referenced and highly regarded older articles. We cross-checked the reference lists of all articles identified by this search strategy and selected those we judged relevant. Several review articles and book chapters were included since they provide comprehensive reviews that are beyond the scope of this Seminar. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.



Approach to the evaluation of peripheral neuropathies
CIDP=chronic inflammatory demyelinating polyneuropathy. EDX=electrodiagnostic studies. GBS=Guillain-Barré syndrome. IvIg=intravenous immunoglobulin.

demyelinating or axonal in type. Taken together, the history, clinical examination, and electrodiagnostic studies provide an accurate profile of the type of neuropathy and the possible causes, and thus suggest treatment options (figure). Classification of neuropathy into the subtypes of mononeuropathy, mononeuropathy multiplex, or polyneuropathy is a necessary step in reaching a specific diagnosis.

Mononeuropathy

The term mononeuropathy implies a focal lesion of a single peripheral nerve. The usual causes are trauma, focal compression, and entrapment. The most common mononeuropathy is carpal tunnel syndrome caused by entrapment of the median nerve in the carpal tunnel.[16–19] Ulnar neuropathy due to compression of the nerve at or near the elbow is the second most common mononeuropathy.[20,21] Electrodiagnostic studies are indispensable in the accurate diagnosis of mononeuropathies. They serve to localise the site of injury and determine the severity of the lesion. The evaluation and management of such focal neuropathies are beyond the scope of this seminar, but detailed information is available from several sources.[2,21] Evidence-based summaries of the management of carpal tunnel syndrome are also available in the Cochrane reviews (http://www.cochrane.org). In the assessment of mononeuropathies, a few additional points are worth noting. Focal mononeuropathies, especially carpal tunnel syndrome and ulnar neuropathy at the elbow, can be associated with more generalised metabolic or toxic neuropathies such as diabetic polyneuropathy. Electrodiagnostic studies can show that a mononeuropathy is actually an unsuspected mononeuropathy multiplex, which could be due to vasculitis, or nerve infiltration by tumor, sarcoidosis, or amyloidosis. Multiple compression neuropathies are increasingly recognised as part of the spectrum of hereditary neuropathy with liability to pressure palsies.[22,23]

Mononeuropathy multiplex

Mononeuropathy multiplex describes the involvement of multiple separate noncontiguous peripheral nerves either simultaneously or serially. The pattern of nerve involvement is random, multifocal, and frequently evolves quickly. In some cases, the neuropathy might progress to a point at which individual nerve lesions summate, resulting in confluent and symmetric deficits that can mimic a distal symmetrical polyneuropathy. Attention to

Disease*	Sensory (S), motor (M), or sensori-motor (SM)	Axonal (A) or demyelinating (D)	Comment
Diabetes mellitus (very common)	S, SM, rarely M	A and D	Commonest cause of chronic polyneuropathy
Renal insufficiency	SM	A	Controllable with dialysis; curable with renal transplantation
Nutritional deficiency (mainly B vitamin deficiencies); often exists with chronic alcoholism	SM	A	Deficiency of thiamine, pyridoxine, folic acid, pantothenic acid, and probably others
Vitamin B-12 deficiency	S	A	Neuropathy may be overshadowed by myelopathy (subacute combined degeneration)
Chronic liver disease	S or SM	A and D	Polyneuropathy usually mild
Porphyria (rare)	M or SM	A	Often acute; might be proximal rather than distal, with arms affected more than legs; distinguish from Guillain-Barré syndrome
Malabsorption (inflammatory bowel disease, short bowel syndrome)	S or SM	A	Some have deficiency of vitamins (especially vitamin E or B-12); in others, the basis is unknown
Coeliac disease	S or SM	A	Rarely due to vitamin deficiency; might have an autoimmune basis
Primary systemic amyloidosis (rare)	SM; might have prominent small fibre component	A	Most have serum paraprotein. Some have multiple myeloma, Waldenstrom's macroglobulinaemia, or lymphoreticular malignancy
Acromegaly (rare)	S	A	Carpal tunnel syndrome frequent
Chronic obstructive pulmonary disease (rare)	S or SM	A	Only seen with severe pulmonary insufficiency
Leprosy (tuberculoid, dimorphous, and lepromatous)	S; less often SM	A	Most often involves cutaneous nerves in coolest parts of body
Lyme disease (occasionally)	S>M	A	Focal or multifocal radiculoneuropathy. Facial neuropathy also common
HIV infection	S>M	A	Chronically causes distal mainly sensory polyneuropathy. Other types of neuropathies occur, especially with early infection
Sarcoidosis	S or SM	A	Mononeuropathy multiplex or polyneuropathy. Facial neuropathy common.
Carcinoma (pure sensory) (rare, but distinctive)	Pure S	A	Paraneoplastic ganglionitis mostly with small cell lung or breast cancer; might have positive paraneoplastic antibodies in serum
Carcinoma (sensori-motor)	SM	A	Mainly with lung carcinoma; might have positive paraneoplastic antibodies in serum
Lymphoma (Hodgkin's and non-Hodgkins)	SM	A and D	Usually axonal, but sometimes demyelinating polyneuropathy
Multiple myeloma	S, M, or SM	A	Uncommon and usually axonal
Myeloma (osteosclerotic)	SM	D	Usually demyelinating; might be associated with POEMS syndrome
Monoclonal gammopathy of unknown significance (MGUS)			
IgM	S or SM	D	IgMκ most common; may bind to myelin associated glycoprotein; usually demyelinating predominantly sensory polyneuropathy.
IgG	SM	A	Usually axonal polyneuropathy
IgA	SM	A	Usually axonal polyneuropathy
Cryoglobulinaemia (rare)	SM	A	May be mononeuropathy multiplex; sometimes associated with chronic hepatitis C infection

POEMS=polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. *Other diseases that rarely cause polyneuropathy include hypoglycaemia, primary biliary cirrhosis, hypothyroidism, and polycythaemia vera.

Table 1: **Systemic diseases associated with polyneuropathy**

the pattern of early symptoms is important in correct diagnosis of mononeuropathy multiplex. For example, a history of sequential digital nerve involvement in hands or feet should alert the examiner to a multifocal process. Assessment of patients with mononeuropathy multiplex is an urgent matter since many of them have a vasculitis. The vasculitis is usually systemic and associated with diseases such as polyarteritis nodosa, Churg-Strauss disease, or one of the connective tissue diseases (rheumatoid arthritis, Sjogren syndrome), but it can be a vasculitis confined to peripheral nerves.[24] Diabetic amyotrophy, which presents acutely with pain and weakness in the proximal lower extremity, is probably due to microvasculitis in the lumbosacral plexus nerves.[24,25]

Other systemic diseases such as sarcoidosis, lymphoma, carcinoma, amyloidosis, leprosy, Lyme disease, HIV infection, and cryoglobulinaemia can also present as a mononeuropathy multiplex. Except in cases where the diagnosis is obvious (eg, diabetic amyotrophy), or the disease is well documented by other means, patients with mononeuropathy multiplex should be considered for biopsy of a sural or superficial peroneal sensory nerve.[27–34] Ideally, the nerve from which the biopsy is to be taken should be selected on the basis of abnormal results of nerve conduction study. If vasculitis is confirmed, patients usually need treatment with immunosuppressive agents. Corticosteroids remain the mainstay of treatment, but cyclophosphamide or other potent immunosuppressants are also frequently necessary depending upon the particular condition.

Up to a third of patients with the picture of mononeuropathy multiplex have electrodiagnostic findings of multifocal demyelination usually secondary to chronic inflammatory polyradiculoneuropathy (CIDP) or a variant such as multifocal motor neuropathy.[35–42] Additionally, a form of multifocal neuropathy is seen with hereditary neuropathy with liability to pressure palsies, an inherited disorder that is most commonly associated with a deletion of the *PMP22* gene.[22,23]

Polyneuropathy

The most common variety of polyneuropathy is distal symmetrical polyneuropathy.[15,43] In this setting, nerve fibres are believed to be affected in a length–dependent way; length in this context meaning distance from the parent nerve cell body (either the dorsal root ganglion sensory neuron or the anterior horn motor neuron). Thus, toes and soles of the feet are affected first. This pattern of neuropathy is associated with several acquired systemic diseases, metabolic disorders, and exogenous toxins (tables 1 and 2). The prototype is chronic sensory and motor polyneuropathy associated with diabetes mellitus,

Drug*	Sensory (S), motor (M), or sensori-motor (SM)	Axonal (A) or demyelinating (D)	Comments
Amiodarone (antiarrhythmic)	SM	D and A	Prominent demyelination; also tremor, optic neuropathy; dose related
Chloramphenicol (antibiotic)	SM	A	Rare; usually reversible
Chloroquine (antimalarial)	SM	A and D	Mild demyelination; principal toxicity is myopathy
Colchicine (anti-gout)	S or SM	A	Neuropathy overshadowed by myopathy
Dapsone (dermatological agent; also for leprosy, pneumocystis pneumonia)	M	A	Nearly pure motor with predominant arm, hand weakness
Disulfiram (anti-alcohol)	SM	A	Usually occurs after months to years of treatment
Ethambutol (anti-tuberculous)	S	A	Mild and reversible
Hydralazine (anti-hypertensive)	S>M	A	Pyridoxine antagonist; avoid by co-administration of pyridoxine
Isoniazid (anti-tuberculous)	SM	A	Pyridoxine antagonist; slow acetylators more susceptible; avoid by co-administration of pyridoxine
Metronidazole (antibiotic)	S or SM	A	Mainly large fibre; dose related
Misonidazole (radiosensitiser)	S or SM	A	Congener of metronidazole; neurotoxicity is the dose-limiting factor
Nitrofurantoin (antibiotic)	SM	A	Rapidly progressive; renal failure increases toxicity
Nitrous oxide (inhalational anaesthetic)	S	A	Usually inhalational abuse; often presents with ataxia and is associated with myelopathy and megaloblastic anaemia; interferes with vitamin B-12 metabolism
Nucleosides (ddC, ddI, d4T) (anti-retroviral)	S>M	A	Painful; dose-limiting; "coasting"† can occur; must distinguish from HIV-induced neuropathy
Phenytoin (anti-epileptic)	S>M	A	Rare and only after decades of use
Platinum (cisplatin) (anti-neoplastic)	S	A	Severe large-fibre sensory neuropathy; dose related; coasting can occur; also ototoxicity and nephrotoxicity
Pyridoxine (vitamin B-6)	S	A	Sensory neuronopathy; occurs with high doses (>200 mg per day)
Suramin (anti-parasitic, anti-neoplastic)	M>S	D and A	Prominent demyelination; resembles Guillain-Barré syndrome; related to maximal plasma levels >350 μg/mL
Taxol (anti-neoplastic)	S>M	A	Occurs with doses >200 mg/m^2; often begins suddenly
Thalidomide (sedative-hypnotic; anti-inflammatory, immunomodulatory)	S>M	A	Initial symptoms always sensory often with profound insensitivity to pain and touch; sensory nerve conduction studies useful for detecting subclinical neuropathy
Vincristine (anti-neoplastic)	S>M	A	Onset with sensory symptoms in hands more so than in feet; if weakness occurs, medication should be stopped; autonomic neuropathy (gastroparesis, constipation, urinary retention) frequent
Toxin*			
Acrylamide monomer (grouting and flocculation agent). Acrylamide polymer is non-toxic	S>M	A	Large fibre neuropathy with diffuse areflexia; gait ataxia; high doses can cause CNS dysfuntion (encephalopathy); sensory nerve conduction studies useful for detecting subclinical neuropathy
Arsenic (insecticide, herbicide; also from smelting and wood preservative industries); might be given with suicidal or homicidal intent	SM	A; acutely may have D	Onset with painful sensory symptoms followed by weakness; prominent systemic effects (gastrointestinal symptoms, anaemia) and skin/nail changes (Mees lines); acute intoxication may cause a Guillain-Barré-syndrome-like polyneuropathy with proximal nerve demyelination; however, most acute and chronic intoxications cause a distal symmetrical axonal polyneuropathy
Carbon disulphide (solvent used in manufacture of rayon fibre and cellophane film)	S>M	A	Sensory symptoms followed by motor deficits; primary central distal axonopathy; neurofilamentous swelling of axons causes retraction of paranodal myelin and slowing of nerve conduction
Diphtheria toxin (protein exotoxin from *Corynebacterium diphtheriae*)	SM	D	Rare; begins 8–12 weeks after infection; may be confused with Guillain-Barré syndrome; toxin inhibits myelin synthesis causing demyelination
Ethylene oxide (gas sterilisation)	SM	A	Usually inhalational exposure; inprovement follows termination of exposure
Hexacarbons (n-hexane and methyl n-butyl ketone) (solvents)	SM	A and D	Exposure via inhalation such as inhalational abuse of gasoline or glue; neuropathy might be severe; coasting could last 2 to 4 months; neurofilamentous swelling of axons causes retraction of paranodal myelin and slowing of nerve conduction
Lead (inorganic) (industrial uses in batteries, smelting)	Pure M or M>S	A	Primarily motor neuropathy; arms (wrist drop) affected more than legs; occurs with systemic effects (gastrointestinal symptoms, anaemia)
Mercury (metallic and vapour)	M>S	A	Predominantly motor neuropathy; can mimic Guillain-Barré syndrome; might occur with CNS effects (lethargy, emotional lability, and tremor)
Organophosphates (insecticides, petroleum additives)	M>S	A	Neuropathy is delayed by 10–20 days after exposure; also myelopathy with lower limb spasticity and loss of proprioception
Thallium (rodenticides)	S>M	A	Painful sensory symptoms prominent; occurs with systemic effects (gastrointestinal symptoms, anaemia); alopecia is hallmark but does not occur until 2–3 weeks after exposure

*Other drugs and toxins that rarely cause polyneuropathy include gold (aurothioglucose), perhexilene, allyl chloride, and buckthorn berries. †coasting=continued worsening for several weeks after cessation of toxic exposure.

Table 2: **Drugs and toxins associated with polyneuropathy**

which is the commonest polyneuropathy in the developed world.[1,4] The earliest symptoms of polyneuropathy are usually sensory abnormalities such as numbness, burning, paraesthesias, or dysaesthesias in the toes or feet. The symptoms are distally predominant and symmetrical. In some cases, muscle weakness in the feet and distal legs is an early manifestation, and the patient experiences weakness of toe extension (especially the big toe) and foot dorsiflexion.

As the polyneuropathy progresses, symptoms and signs evolve in a centripetal manner. Sensory loss and dysaesthesias spread up the legs, ankle jerks are depressed or unelicitable, and weakness of toe and foot dorsiflexion can occur. As weakness of foot dorsiflexion progresses, patients have difficulty walking on their heels. In most cases of polyneuropathy, foot plantarflexion remains reasonably strong, allowing patients to walk on their toes. By the time sensory symptoms have ascended to the upper shin, numbness or dysaesthesias are usually noticed in the fingertips. At this point patients can have considerable unsteadiness of gait because of proprioceptive sensory loss and weakness of extensor muscles in the legs. When

sensory loss reaches the mid-thighs and upper forearms, it can also be found on the lower abdomen. A triangle-shaped area of hypoaesthesia with its apex in the midline is the expected finding. It can rise as high as the umbilicus or even the manubrium. The finding is not to be confused with a spinal cord level, which is present both front and back, and not just on the abdomen. At this stage of severe polyneuropathy, patients are usually hyporeflexic or areflexic and cannot stand or walk unsupported. The picture of advanced polyneuropathy with stocking-glove sensory loss (diffuse sensory loss in distal lower extremities and hands), distal muscle wasting and weakness, and absent tendon reflexes is an easily recognisable clinical condition. Such cases exemplify the concept of a "fibre length-dependent" polyneuropathy since nerve fibres seem to be affected according to length irrespective of root or nerve trunk distribution.

The subclassification of polyneuropathies is complex, but most physicians need to understand only the most common and typical. Historical features are indispensable for accurate diagnosis. The first is the presence of preceding or concomitant circumstances that could be associated with polyneuropathy. Investigation of the presence of other medical conditions, symptoms of systemic disease, recent viral or other infectious diseases, recent vaccinations, institution of new medications (including dietary supplements and vitamins), or exposure to toxins such as alcohol, heavy metals, and organic solvents is important. An often overlooked, but important, aspect of the history is the inquiry into the presence of neuropathy in other family members since this might uncover a genetically determined polyneuropathy, or on occasion, a toxin exposure. Other important features are duration and clinical course of the neuropathy. Acute neuropathies that evolve over several days or a few weeks have different causes than chronic neuropathies that develop over several months or years. Most polyneuropathies evolve slowly and show distally graded sensory and motor symptoms that progress symmetrically and evenly in a centripetal manner. Neuropathies whose development does not fit the typical pattern should be assessed quickly since they might represent serious disease. For instance, rapidly evolving neuropathies can arise with Guillain-Barré syndrome, vasculitis, or toxin exposure. A presentation with asymmetrical or multifocal sensory or motor symptoms suggests the possibility of a mononeuropathy multiplex.

The comparison of large fibre and small fibre neuropathies is useful in classification of polyneuropathies.[33] Most polyneuropathies involve both large and small fibres, although in some instances one fibre group is predominantly affected. Since all motor axons except for the gamma efferents to muscle spindles are large fibres, the presence of weakness or atrophy indicates large fibre involvement. Vibration, proprioception, and the afferent arc of myotatic reflexes are carried via large sensory fibres; therefore deficits of these sensory modalities such as loss of reflexes or sensory ataxia reflect large fibre sensory involvement. On the other hand, pain and temperature sensibility as well as peripheral autonomic functions are mediated by small sensory fibres—therefore, deficits of these modalities represent small fibre involvement. Small fibre sensory polyneuropathies present with loss of pinprick and temperature sensibility often accompanied by positive sensory symptoms such as pain and burning dysaesthesias in the feet. If the polyneuropathy is exclusively small fibre, muscle strength and myotatic reflexes are preserved. Possible causes of small fibre polyneuropathy include diabetes, amyloidosis, HIV infection, and several other diseases. After exclusion of diabetes, probably the most common cause is an idiopathic small fibre painful sensory polyneuropathy that is usually seen in mid-life or older adults.[9,43–47]

Signs of autonomic nervous system involvement usually occur in the context of a generalised polyneuropathy such as diabetic polyneuropathy or Guillain-Barré syndrome. Rarely, an acquired syndrome of pure pandysautonomia, presumably on a dysimmune basis, occurs. Clinical manifestations of autonomic dysfunction include postural hypotension with "dizziness" or syncope, anhidrosis, bladder atony, constipation, dry eyes and dry mouth, erectile dysfunction, and pupillary abnormalities. Other features seen occasionally are paroxysmal hypertension, tachycardia or bradycardia, hyperhidrosis, and diarrhoea. In distal symmetrical polyneuropathy with autonomic involvement, the most common findings are abnormalities of sweating and circulatory instability in the feet. Quantitative autonomic testing performed in selected centres can be useful in documenting the presence of autonomic dysfunction.

Subclassification of polyneuropathies

Separating polyneuropathies into acute and chronic forms is very helpful for refining the diagnosis and treatment.

Acute polyneuropathy

Acute symmetrical polyneuropathy presenting as rapidly progressive paralysis with areflexia and variable sensory involvement is usually one of the variants of Guillain-Barré syndrome. The recognition of this entity is important since the disease can progress rapidly to respiratory insufficiency. Guillain-Barre syndrome is one of the few neuropathies that need urgent diagnosis and treatment. Early symptoms such as distal paraesthesias and extremity weakness are often mild, sometimes resulting in an inappropriate diagnosis of hysteria and dismissal of the patient. Weakness in Guillain-Barré syndrome can progress rapidly and involve cranial muscles (especially face and bulbar muscles) as well as respiratory muscles. A quarter to a third of all patients with Guillain-Barré syndrome need ventilatory support. In view of this potential deterioration, most patients need admission to hospital and monitoring of respiratory function. About half of patients with this syndrome have a history of respiratory or gastrointestinal infection in the 2–3 weeks before onset of the neuropathy.

Guillain-Barré syndrome represents a range of autoimmune inflammatory polyradiculoneuropathies. Most cases are demyelinating, but some forms involve predominant damage to motor axons with little evidence of primary demyelination. Treatment with either intravenous immunoglobulin or plasma exchange is indicated for all subtypes of Guillain-Barré syndrome since either treatment minimises worsening, hastens recovery, and reduces long-term disability.[48–54] Either plasma exchange or intravenous immunoglobulin is recommended for patients who are nonambulatory or need aid to walk within 4 weeks of the onset of neuropathic symptoms.[54] Intravenous immunoglobulin is usually preferred because it is more convenient and has fewer side effects than plasma exchange.[49,51,53,54] The earlier treatment is begun, the better the outcome.[53,54]

Other less common causes of acute symmetrical or asymmetrical neuropathic weakness include porphyria, diphtheria, buckthorn intoxication, tick paralysis, vasculitis, certain medications, paraneoplastic neuropathy, critical-illness polyneuropathy, and poliomyelitis. Most of these diseases are easily

distinguished from Guillain-Barré syndrome. West Nile virus infection can cause a poliomyelitis–like illness with areflexic paralysis, but unlike Guillain-Barré syndrome, West Nile viral infection causes meningitis or encephalitis. Further distinguishing characteristics of West Nile virus poliomyelitis are pleocytosis of the cerebrospinal fluid and electrodiagnostic features that are consistent with anterior horn cell damage.[55-63] Confirmation of infection is possible by testing for antibodies to West Nile virus in the blood and cerebrospinal fluid.[55-63]

Chronic polyneuropathy

Chronic symmetrical polyneuropathy is the most common type of polyneuropathy and usually evolves over months or years. The clinical presentation is variable, but most cases conform to the general description of polyneuropathy. Most chronic polyneuropathies can be narrowed down to just a few specific diagnostic possibilities on the basis of a thorough history, neurological examination, and electrodiagnostic studies. Features to be determined are the rate of development and pattern of the disease (gradually progressive or relapsing), the relative involvement of motor and sensory fibres (predominantly motor, predominantly sensory, or both), the relative involvement of large and small sensory fibres (predominantly large fibre, predominantly small fibre, or both), and the electrophysiological findings (mainly demyelinating, mainly axonal, or both). Such a characterisation simplifies the diagnosis and limits the possible causes to a manageable degree. For example, a chronic, steadily progressive distal symmetrical sensori–motor polyneuropathy with predominantly axonal features is most probably secondary to systemic or endocrine diseases, metabolic disorders, medications or toxins. A longstanding chronic, predominantly motor distal symmetrical polyneuropathy with uniformly demyelinating features is most likely an inherited polyneuropathy (eg, Charcot-Marie-Tooth disease type 1). Acquired demyelinating polyneuropathies (eg, CIDP) or paraproteinaemic, which might mimic inherited demyelinating polyneuropathy, can be excluded by electrodiagnostic studies and serum and urine protein electrophoresis with immunofixation.

Another important piece of information in the subclassification of neuropathy is determination of whether the neuropathy is primarily demyelinating or primarily axonal. The only practical way of making this distinction is by electrodiagnostic investigation. This distinction provides a defining branch point in the evaluation of polyneuropathy since each subtype (demyelinating *vs* axonal) has generally different causes, treatments, and prognosis (figure 1). The electrodiagnostic studies also provide information about the different types of demyelination (uniform *vs* multifocal) and the pattern of nerve involvement. Since these two major subtypes of polyneuropathy (demyelinating *vs* axonal) are largely distinct, they are discussed separately.

Panel 1: **Types of chronic demyelinating polyneuropathy**

Genetic
- Charcot-Marie-Tooth disease type 1, type 4, and type X1
- Hereditary liability to pressure palsies
- Metachromatic leucodystrophy
- Globoid cell leucodystrophy
- Refsum disease

Acquired
- Chronic inflammatory demyelinating polyradiculoneuropathy
- Multifocal motor neuropathy
- Paraproteinaemic demyelinating polyneuropathy
  - Associated with antibodies to myelin associated glycoprotein (MAG)
  - Associated with monoclonal gammopathy of unknown significance (MGUS)
  - Associated with osteosclerotic myeloma

Chronic demyelinating polyneuropathy

This is the easiest category to define since the causes are limited (panel 1). Demyelinating polyneuropathies are either genetically determined or acquired. Electrodiagnostic features are helpful in making this distinction because uniform symmetrical slowing of nerve conduction usually indicates a genetically determined neuropathy, whereas multifocal slowing and conduction block are indicative of acquired demyelinating neuropathies.

Most genetically determined demyelinating polyneuropathies are variants of Charcot-Marie-Tooth disease, and about 70–80% of these patients have a duplication of *PMP22* gene.[64,65] The clinical phenotype of Charcot-Marie-Tooth disease is extremely variable, ranging from the classic picture with pes cavus and "stork legs" to minimal neurological deficits.[64,65] Since different genetic mutations can cause a similar phenotype, the only way to classify this group of neuropathies accurately is by genetic testing, which is now widely available. Different phenotypes can also result from one genotype.

The acquired demyelinating neuropathies represent a heterogeneous group of mostly immunologically mediated neuropathies. Electrodiagnostic tests can further refine the classification by determining the pattern of demyelination and the spectrum of fibre involvement. CIDP is the most common type of acquired demyelinating polyneuropathy. It is estimated to affect approximately two per 100 000 people.[39] The course of CIDP is either relapsing or gradually progressive. The neuropathy is usually primarily motor, affecting both proximal and distal muscles, but can on occasion present with predominantly sensory symptoms.[38,39,66–70] In CIDP, cerebrospinal fluid examination can be helpful in confirming the diagnosis since the protein in the cerebrospinal fluid is almost always raised. A related disease called multifocal motor neuropathy is characterised by partial conduction block restricted to motor axons. Multifocal motor neuropathy usually presents with weakness and atrophy of muscles in the forearms and hands, and clinically, can be mistaken for early motor neuron disease.[40–42] Both CIDP and multifocal motor neuropathy respond to immunotherapy, although treatment is different for the two disorders. Specifically, both can respond to treatment with intravenous immunoglobulin, and immunosuppressive agents such as cyclophosphamide, but only CIDP responds to steroid treatment and plasma exchange.[35–39,42,68,71] In fact, some patients with multifocal motor neuropathy have worsened after steroid administration, and its use is not recommended for these patients.

About 10% of patients with acquired demyelinating polyneuropathy have a serum paraprotein, usually an IgM. Roughly half have antibodies directed against myelin associated glycoprotein, and show an electrodiagnostic pattern of slowing in distal nerve segments with disproportionate prolongation of distal latencies.[72]

Most patients with a paraproteinaemic associated polyneuropathy present clinically with slowly evolving distal symmetrical sensory abnormalities in the feet. Although most patients with a serum paraprotein have a monoclonal gammopathy of unknown significance, all of them need evaluation and serial follow-up to look for plasmacytoma, amyloidosis, or lymphoreticular malignancy.

Chronic axonal polyneuropathy

This is the most common variety of polyneuropathy and has many possible causes. The commonest cause is diabetes mellitus, which should be foremost in the differential diagnosis. However, a range of systemic diseases and metabolic disorders such as nutritional deficiencies, chronic renal failure, and malignant diseases as well as exogenous intoxications from medications, alcohol abuse, or chemical agents can result in this pattern of neuropathy (tables 1 and 2).

Several varieties of hereditary neuropathy, especially the axonal forms of Charcot-Marie-Tooth disease (CMT2), can present with this pattern of neuropathy.[64,65] A typical phenotype with pes cavus and claw toes combined with a positive family history are extremely helpful in arriving at a correct diagnosis of an inherited polyneuropathy. Unfortunately, these features are not always evident. Since a substantial proportion of these patients have de novo genetic mutations, and might not come to medical attention until later in life, a high index of suspicion is required for the diagnosis of an inherited neuropathy.

Panel 2: **Laboratory investigation of peripheral neuropathy***

Basic tests

Haematology
Complete blood count, erythrocyte sedimentation rate or C-reactive protein, vitamin B-12, folate. Methylmalonic acid and homocysteine for vitamin B-12 levels at the low end of normal

Biochemical and endocrine
Comprehensive metabolic panel (fasting blood glucose, renal function, liver function), thyroid function tests. Serum protein electrophoresis with immunofixation. Glycosylated haemoglobin or glucose tolerance test if indicated to look for glucose intolerance.

Urine
Urinalysis, urine protein electrophoresis with immunofixation

Radiology
Chest radiography or spiral CT of chest

Specialised tests for specific diseases

Connective tissue diseases and vasculitis
(Sjögren's disease, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, polyarteritis nodosa, Churg–Strauss disease, Wegener's granulomatosis, ANCA syndrome)
Antinuclear antigen profile, rheumatoid factor, anti-Ro, anti-La, antineutrophil cytoplasmic antibody (ANCA) profile, cryoglobulins

Infectious agents
Campylobacter jejuni, cytomegalovirus (CMV), hepatitis panel (B and C), HIV tests, Lyme disease tests, herpes viruses tests, West Nile virus tests, cerebrospinal fluid analysis

Diseases of gut
Antibodies for coeliac disease (gliadin, transglutaminase, endomysial), vitamin E level, B vitamin levels; most need endoscopic confirmation with biopsy

Sarcoidosis
Serum angiotensin-converting enzyme (ACE), cerebrospinal fluid analysis including ACE

Heavy metal toxicity
Blood, urine, hair, and nail analysis for heavy metals

Porphyria
Blood, urine, and stool for porphyrins

Dysimmune
Antiganglioside antibody profile (GM1, GD1a, GD1b, GD3, GQ1b, GT1b), anti-myelin associated glycoprotein (MAG) antibodies, paraneoplastic antibody profile (anti-Hu, anti-CV2), cerebrospinal fluid analysis including immunoglobulin oligoclonal bands

Genetics
Molecular genetic tests tailored to the clinical profile and available for an increasing number of hereditary neuropathies such as Charcot-Marie-Tooth disease, hereditary neuropathy with liability to pressure palsies, and hereditary amyloidosis

Malignant diseases (carcinoma, myeloma, lymphoma)
Skeletal radiographic survey; mammography; computed tomography or magnetic resonance imaging of chest, abdomen, and pelvis; ultrasound of abdomen and pelvis; positron emission tomography, cerebrospinal fluid analysis including cytology, serum paraneoplastic antibody profile (anti-Hu, anti-CV2)

Nerve biopsy
Should be done by clinicians/pathologists with expertise in nerve pathology

Skin biopsy
Can confirm the presence of small fibre neuropathy but should be done by clinicians/pathologists with expertise in the technique

This list is not intended to include all possible tests or methods that might be useful in the assessment of polyneuropathy, neither is it intended to exclude any reasonable alternative tests or methodologies.

Molecular genetic tests are available for only a few of the multiple mutations that can cause this type of chronic peripheral neuropathy.

Even after thorough evaluation of chronic polyneuropathy, no cause is found in 20–25% of patients.[44–47] Most chronic idiopathic polyneuropathies are mild predominantly sensory distal symmetrical polyneuropathies that affect older patients. A subset of these patients have a predominantly small fibre polyneuropathy with pain and numbness in the feet ("burning feet syndrome") accompanied by few signs and normal nerve conduction studies. Proof of the diagnosis can be obtained by showing decreased density of unmyelinated fibres in skin biopsies, but the technique is not yet widely available.[73–76] Some of these patients have unsuspected glucose intolerance (prediabetes) that can be shown with oral glucose tolerance testing (GTT).[77–80] Fortunately, most idiopathic distal symmetrical polyneuropathies progress slowly and are unlikely to result in serious physical disabilty.[44–47] For many of these patients, treatment of their distressing sensory symptoms, especially pain and dysaesthesias, is the paramount issue.[81]

Laboratory investigations of peripheral neuropathy

The cause of most peripheral neuropathies is evident when the information obtained from the medical history, neurological examination, and electrodiagnostic studies is combined with simple screening laboratory tests (panel 2). All patients with a peripheral neuropathy should have a complete blood count, erythrocyte sedimentation rate or C-reactive protein, comprehensive metabolic panel (fasting blood glucose, renal function, liver function), thyroid function tests, urinalysis, serum B-12 and folate, and a serum protein electrophoresis with immunofixation. Since diabetes mellitus is the commonest cause of distal symmetrical polyneuropathy and up to a third of patients with idiopathic sensory polyneuropathy show impaired glucose tolerance, obtaining a glycosylated haemoglobin or a glucose tolerance test or both may be considered in this group of patients.[77–80] Serum methylmalonic acid and homocysteine, which are metabolites of cobalamin, are elevated in 5–10% of patients whose serum B-12 levels are in the lower end of the normal range of 200–500 pg/dL.[82,83] In a large series of patients with idiopathic polyneuropathy, 2·2% of patients had evidence of B-12 deficiency as indicated by elevations of these metabolites.[45] Thus, serum B-12 assays with metabolites (methylmalonic acid with or without homocysteine) are useful in documenting true B-12 deficiency. At the least, these metabolites should be measured when the serum B-12 level is in the low end of the normal range. Although blood and urine for heavy metal analysis is often routinely obtained as a screening test in patients with neuropathies, it is hardly ever useful unless the neuropathy fits the pattern of an acute or subacute polyneuropathy, and there is strong suspicion of heavy metal exposure. In idiopathic chronic polyneuropathies, a 24-hour urine collection for heavy metals is almost always unproductive. A particular caution applies to the finding of elevated total levels of arsenic in urine collections since this can occur after eating certain seafoods. Arsenic found in seafood is in the form of arsenobetaine, which has low toxicity and is not associated with neuropathy.[84] If, in a particular chronic axonal polyneuropathy, heavy metal intoxication is suspected, analysis of hair or nail samples is indicated.

Additional laboratory investigations of blood and cerebrospinal fluid might be necessary, and should be determined by type of neuropathy and the results of preliminary investigations (panel 2). Although it is not possible to provide guidelines for every conceivable clinical scenario, a few specific situations are worthy of emphasis. If there is suspicion of an infectious, immune-mediated, or neoplastic cause of neuropathy, cerebrospinal fluid should be analysed. Neurotropic infectious agents and malignant diseases that invade the nervous system often cause cerebrospinal fluid pleocytosis. Dysimmune neuropathies such as Guillain-Barré syndrome and CIDP usually show an increased protein level with a normal cell count in the cerebrospinal fluid (ie, albuminocytologic dissociation). Since infection with *Campylobacter jejuni* or cytomegalovirus might precede Guillain-Barre syndrome, antibody testing for these agents is also reasonable in the evaluation of this disorder. Additionally, a neuropathy with characteristics suggestive of an immune-mediated neuropathy might need testing for antibodies to gangliosides, myelin associated glycoprotein, and several other neural antigens. Neuropathies in which there is a suspicion of an underlying connective tissue disease or vasculitis need specialised tests that are outlined in panel 2. Confirmation of the diagnosis of a hereditary neuropathy might need molecular genetic testing. When new disease associations are described, tests that are not usually used for assessment of neuropathy might become useful. A specific example relates to the probable association of polyneuropathy with coeliac disease.[85–91] Although a definite diagnosis of coeliac disease needs small bowel biopsy, screening patients for the presence of elevated antigliadin or transglutaminase antibodies is a reasonable first step.[90,91]

Role of nerve biopsy in evaluation of neuropathies

Nerve biopsy is most useful in documentation of inflammatory disorders such as vasculitis, sarcoidosis, CIDP, infectious diseases such as leprosy, or infiltrative disorders such as amyloidosis or tumour.[24–34] The procedure is best reserved for patients in whom the diagnosis cannot be obtained by other means. Nerve biopsies should always be processed in experienced laboratories with the capability to do teased fibre preparations, semi-thin plastic sections, and electron microscopy. In a practical sense, nerve biopsy is most valuable in mononeuropathy multiplex or suspected vasculitic neuropathy. For the rare cases of storage disease (globoid cell leukodystrophy, metachromatic leucodystrophy, Neimann-Pick disease, sialidosis, Fabry disease, Farber disease, or other unusual hereditary neuropathies (eg, giant axonal neuropathy), nerve biopsy can confirm the diagnosis. Most common hereditary neuropathies, especially the variants of Charcot-Marie-Tooth disease, can be confirmed by a combination of electrodiagnostic tests and molecular genetic testing; however, novel or unusual cases might still need nerve biopsy for diagnosis. Some toxic neuropathies, especially those caused by hexacarbons, have unique findings on nerve biopsy that are indispensable for the diagnosis.[92]

There is little indication for a nerve biopsy in the usual cases of idiopathic chronic distal symmetrical polyneuropathy since the chance of finding a specific or treatable disease is low. However, nerve biopsy as part of an approved research protocol in specialised centres is widely accepted.

The usual site of nerve biopsy is the sural nerve.[27-34] In suspected vasculitis the diagnostic yield is higher if muscle

is also examined, and some recommend combined nerve and muscle biopsy.[30-32] This can be achieved through a single incision for the superficial peroneal sensory nerve and peroneus brevis muscle or for the sural nerve and gastrocnemius muscle. Whichever nerve is biopsied, the yield will be higher if an abnormality of the nerve is documented by previous nerve conduction studies.

Treatment

Treatment of peripheral neuropathy is divided into those that are specific for the subtype of neuropathy, and those that are useful for neuropathies in general. Medical causes such as diabetes mellitus, renal insufficiency, hypothyroidism, vitamin B-12 deficiency, or systemic vasculitis need specific and active treatment. Immune-mediated neuropathies such as Guillain-Barré syndrome or CIDP respond to specific treatments. If treated appropriately, many patients with dysimmune neuropathies have a good prognosis for stabilisation or improvement. The treatment should be specific for each patient, taking into account factors such as efficacy, potential adverse effects, availability, and coexisting medical conditions. Unfortunately, there is no specific treatment for many chronic neuropathies such as chronic idiopathic axonal polyneuropathy or the hereditary neuropathies. Symptomatic management is important for all types of neuropathy, including general preventive and palliative therapy as well as the treatment of specific problems such as neuropathic pain.

Treatment of pain is an important aspect for many patients with chronic polyneuropathies. Neuropathic pain can be difficult to treat. Medications that are most useful include antiepileptic drugs (gabapentin, carbamazepine), antidepressants (especially amitriptyline, nortriptyline, and venlafaxine), and tramadol, which has both mu-opioid agonist as well as antidepressant actions.[81,93–97] Topically applied lidocaine can be useful for treating pain in small discrete cutaneous regions. Some patients need opioid medications for adequate pain relief.[81,95,97]

General aspects of preventive and palliative management include weight reduction, assiduous foot care, good shoes, and ankle-foot orthoses as needed. Patients with substantial leg weakness often need walking aids, and those with hand weakness might need wrist splints. Physical and occupational therapists can be exceptionally helpful in evaluating and designing adaptive equipment for such chronically disabled patients.

As a last point, several organisations provide information and support for patients with peripheral neuropathy (panel 3). Patients with intractable neuropathies often find these and similar organisations of immense benefit in helping them deal with chronic problems. These groups can also provide healthcare professionals with valuable information regarding the diagnosis and treatment of patients with peripheral neuropathy. Evidence-based reviews from the Cochrane group are especially useful for professionals.

Panel 3: **Organisations relevant to peripheral neuropathy**

The Neuropathy Association (http://www.neuropathy.org)
Peripheral Neuropathy Trust (http://www.neuropathy-trust.org)
Guillain-Barré Syndrome Foundation International (http://www.guillain-barre.com)
Guillain-Barré Syndrome Support Group (http://www.gbs.org.uk)
Hereditary Neuropathy Foundation (http://www.hereditaryneuropathy.org)
Charcot-Marie-Tooth Association (http://www.charcot-marie-tooth.org)
CMT United Kingdom (http://www.cmt.org.uk)
Cochrane Neuromuscular Diseases Group (http://www.cochrane.org)

Conflict of interest statement
None declared.

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