THE BARE ESSENTIALS

Peripheral nerve diseases

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EPIDEMIOLOGY

Peripheral nerve diseases are surprisingly common. Population-based studies indicate a prevalence of symmetrical polyneuropathy of about 2.4%, more in the elderly. Carpal tunnel syndrome is present in 5% of women and 0.5% of men. While many patients with symmetrical polyneuropathy are not severely disabled, pain is common and some forms of neuropathy are progressive, disabling and ultimately fatal. Fortunately the peripheral nervous system has remarkable regenerative capacity so that peripheral nerve diseases are usually treatable and may be curable.

CLASSIFICATION

There are several patterns of peripheral nerve disease:

- mononeuropathy
- multiple mononeuropathy (better than the old-fashioned mononeuritis multiplex)
- symmetrical polyneuropathy
- plexopathy
- radiculopathy
- polyradiculoneuropathy.

The time course may be:

- acute, reaching its nadir in <4 weeks, as in Guillain-Barré syndrome (GBS)
- subacute, reaching its nadir in 4–8 weeks
- chronic, taking >8 weeks to develop.

The deficit may be:

- purely or predominantly sensory, as in diabetic distal symmetrical polyneuropathy
- purely motor, as in acute motor axonal neuropathy, a less common form of GBS in the UK
- motor and sensory, as in most cases of Charcot-Marie-Tooth (CMT) disease
- autonomic; although autonomic involvement is common in some neuropathies, pure autonomic neuropathy is rare.

The underlying pathology may be identified by nerve conduction tests as:

- axonal
- demyelinating or
- mixed.

Large and small diameter nerve fibres are usually affected together but only large fibre involvement can be detected by conventional nerve conduction tests. Some patients have pain and distal impairment of pinprick and temperature sensation due to:

- small fibre neuropathy.

DIFFERENTIAL DIAGNOSIS

The possibility of peripheral nerve disease comes into the differential diagnosis of sensory, motor or autonomic symptoms, and of loss of the tendon reflexes. If there are cognitive or visual symptoms, peripheral nerve disease cannot be the only diagnosis, although it may be present as well.

- Distal numbness and paraesthesiae are commonly caused by peripheral neuropathy but may also be caused by spinal cord disease, eg in multiple sclerosis, and have to be distinguished from symptoms of hyperventilation.
- Foot pain in small fibre neuropathy has to be distinguished from arthritis and ischaemic pain.
- Bilateral weakness of toes and feet is usually due to peripheral neuropathy but can be caused by bilateral L5 root lesions or distal myopathy.
- The proximal weakness of polyradiculoneuropathy has to be distinguished from muscle disease and from myelopathy.
- Involvement of the sphincters brings to mind spinal cord disease but can occur with peripheral neuropathy; for example, inability to pass urine and ileus are features of severe GBS.
- Loss of tendon reflexes is usually due to peripheral neuropathy but also occurs in root lesions, Holmes-Adie syndrome, tabes dorsalis and spinal shock.

CLINICAL FEATURES

History taking

- Let patients tell their own story, record descriptions verbatim: "burning pain", "like when you have slept on your arm", "toes catching on the pavement", "feet feeling tight".
- Watch out for symptoms which indicate a central cause, such as Lhermitte's symptom.
- Sort out whether the symptoms are continuous, or intermittent as in carpal tunnel syndrome.
- Find out when symptoms started and whether there was any antecedent illness or possible toxin exposure.
- Establish the course of the illness: acute, subacute, chronic progressive or relapsing, and especially whether it is still getting worse.

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It may be necessary to wait until the examination to determine whether the symptoms are due to a peripheral neuropathy or a central cause, but usually the symptoms alone are enough. Then, further questions can pursue the cause of the peripheral neuropathy at this stage rather than after the examination:

- Any history of delayed milestones, difficulty walking as a child, foot or ankle surgery, or inability to play sport at school to suggest an early onset and probably genetic neuropathy?
- Any family history? Ask about peripheral neuropathy, high arched feet or foot deformity, and difficulty walking. If the suspicion is strong, this should extend to second degree relatives. Because de novo mutations are common, there may be no family history.
- In acquired neuropathies, ask about diabetes mellitus, alcohol and drugs, which are the commonest causes.
- A full system review to detect systemic disease, such as vasculitis, endocrine disease or cancer, as possible causes of peripheral neuropathy.

Examination

The conventional neurological examination needs to be complete and requires slight expansion to elicit all the helpful physical signs in peripheral nerve disease:

- Start by watching the patient stand and walk, do Romberg's test, rise onto their heels and toes (much better than testing ankle dorsiflexion and plantar flexion on the couch) and walk heel to toe. Then invite the patient to undress by stages so that you can inspect the full length of their limbs.
- Look for trophic skin changes and ulcers in distal sensory neuropathy.
- Inspect the feet for pes cavus and claw toes.
- Look for wasting of the intrinsic hand and foot muscles and extensor digitorum brevis.
- Look for postural tremor, which may occur in both acquired and hereditary demyelinating neuropathy, and for pseudoathetosis (wavering movements of the fingers and even the whole upper limb when the patient holds their arms outstretched with their eyes closed), due to severe loss of position sensation.
- Palpate nerves for thickening in some cases of CMT1, chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and leprosy.
- Note the pattern of weakness, which is usually symmetrical and distal in length-dependent neuropathy, and may be distal and proximal, or only proximal in polyradiculoneuropathy.
- Testing should include extensor hallucis longus to detect distal lower limb weakness.
- Tendon reflexes are usually absent in demyelinating neuropathy but may be preserved in axonal neuropathy unless weakness is present, and are usually preserved in multiple mononeuropathy, leprosy and small fibre neuropathy.
- Sensory testing should include light touch, vibration, position and pinprick sensation at the fingertips and toes.
- If the patient reports any sensory impairment, then map out and record its extent by moving your stimulus from the area of reduced sensation to the area of normality. If the abnormality is of hyperalgesia, you need to map from the normal to the abnormal area.

All the cranial nerves must be examined as they may be affected or provide important clues to the cause:

- anosmia: Refsum's disease
- papilloedema: CIDP or Polyneuropathy, Organomegaly, Endocrinopathy, M protein and Skin changes (POEMS) syndrome
- retinal abnormalities: diabetes, vasculitis
- ptosis: mitochondrial disorders
- facial palsy and vagus nerve involvement: GBS
- tongue involvement: amyloidosis.

As peripheral neuropathy is commonly a component of a systemic disease, whether metabolic, inflammatory, toxic or genetic, a full general medical examination is also necessary.

MONONEUROPATHIES

Any nerve may be affected. However, a mononeuropathy may be the "tip of the iceberg", the most severely affected nerve in a generalised neuropathy.

Facial palsy

The most commonly affected cranial nerve. Causes include:

- Bell's palsy
- tumours in the cerebellopontine angle
- meningeal carcinomatosis
- skull base fractures and tumours
- middle ear infections
- sarcoidosis
- Lyme disease
- inflammatory neuropathy including GBS, Miller Fisher syndrome and CIDP
- herpes zoster
- parotid gland tumours.

Bell's palsy

- Annual incidence about 25 per 100 000.
- May be due to herpes simplex infection.
- Usually reaches its nadir within 24 h and is often associated with pain in the mastoid.
- In severe cases, taste is lost and paralysis of the stapedius muscle causes hyperacousis.
- Partial facial palsy is usually due to conduction block and recovers completely, but about 15% of patients develop axonal degeneration and have incomplete recovery and persistent disfiguring facial asymmetry, contractures and synkinetic movements (grimacing on blinking)

and crocodile tears (tear production on salivation), both due to aberrant reinnervation.
- Oral prednisolone 25 mg twice daily, started within 72 h and continued for 10 days, significantly increases the percentage of patients with complete recovery from 82% to 94%, but oral acyclovir makes no difference.
- Surgical decompression of the nerve and electrical stimulation of the muscle do not work.
- Protection of the cornea in severe persistent palsy may require lubricant drops and sometimes a lateral tarsorrhaphy.
- Cosmetic surgery may be offered to those with disfiguring palsy persisting for more than a year.

Carpal tunnel syndrome

Carpal tunnel syndrome has a lifetime incidence of 10%. It is due to compression of the median nerve under the flexor retinaculum at the wrist. It usually presents with numbness and tingling in the fingers; confusingly, the pain and tingling may radiate above the wrist and the tingling may affect all the digits, although usually worse in a median nerve distribution. Pain and paraesthesiae often wake the patient from sleep and are relieved by shaking the hand; also brought on by activities such as knitting, typing and carrying shopping bags. There may be no abnormal signs, but in advanced cases atrophy of abductor pollicis brevis develops and there is sensory loss in the median nerve distribution. Percussing the carpal tunnel (Tinel's sign) or sustained hyperextension or flexion of the wrist (Phalen's sign) may reproduce symptoms but are inconstant, unreliable signs. Contributory causes are:

- genetic predisposition
- excessive use of the hands
- wrist injury or arthritis
- pregnancy
- obesity
- myxoedema
- acromegaly
- infiltration of the flexor retinaculum in primary and hereditary amyloidosis.

Although most tingling in the fingers is due to carpal tunnel syndrome, there are other causes:

- hyperventilation
- spinal cord lesions (multiple sclerosis)
- root lesions (cervical spondylosis)
- thoracic outlet syndrome (see below)
- median nerve lesions in the forearm.

These alternative causes can usually be ruled out by the history and examination. Nevertheless you should perform nerve conduction studies if the symptoms warrant treatment to:

- confirm the diagnosis before operation
- reveal any otherwise undetected underlying peripheral neuropathy which will require investigation
- provide a benchmark for follow-up in case surgery is ineffective.

Characteristic nerve conduction abnormalities include a reduced, delayed median nerve sensory action potential and slowed median nerve conduction across the flexor retinaculum, recognised as a delayed distal motor latency.

Management

- Symptoms fluctuate and 20% of patients recover spontaneously
- Rest, weight reduction and wrist splints are the first line treatment.
- Those who do not remit may be offered corticosteroid injection which is safe and can be followed by surgery if it does not work (in about 50% of cases).
- Operative decompression by dividing the flexor retinaculum works in about 75%. However, it is more complicated and expensive than corticosteroid injection may cause a painful scar, and makes 7% of patients worse.
- Patients who already have persistent median nerve deficit should undergo carpal tunnel compression to prevent further damage.

Ulnar nerve palsy

Although much less frequent than carpal tunnel syndrome, ulnar nerve palsy is still common. The most frequent symptoms are tingling, numbness and pain in the little and ring fingers (but transient nocturnal ulnar paraesthesiae are so common as to be within the range of normal). More severely affected patients have weakness of the ulnar innervated muscles in the hand, of which the first dorsal interosseus is the most obvious, and, in extreme cases, of the flexor digitorum profundus branch to the little finger and flexor carpi ulnaris. If the lesion is at the wrist, the last two muscles are not affected (but they may also be spared in mild lesions at the elbow) and sensation may not be involved because the sensory branches separate from the motor nerve just proximal to the wrist. The ulnar nerve is at risk of compression at the level of the medial epicondyle by fracture or joint deformity, and by leaning on the elbow; if none of those is present, the nerve may be compressed as it passes through the cubital tunnel formed by the heads of the flexor carpi ulnaris, which is made more likely by a wide carrying angle or arthritis.

Management

- Neurophysiological tests will confirm the presence of an ulnar nerve lesion and whether it lies at the wrist or the elbow, but may not distinguish between a lesion at or above the cubital tunnel.
- Acute ulnar nerve lesions may recover spontaneously, especially if the patient can be encouraged not lean on the nerve.
- If symptoms persist for more than three months, refer the patient to a surgeon with

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experience of exploring the nerve. It may be sufficient to decompress the cubital tunnel, which is preferable to transposition of the nerve to the front of the medial epicondyle.
- Longstanding complete ulnar nerve lesions with atrophy of the first dorsal interosseus will not recover with surgery and are not worth treating.
- Fortunately, an isolated ulnar nerve lesion is not disabling for most people.

Radial nerve palsy

- The radial nerve may be damaged by wounds or fractures of the upper arm. However, it is more commonly compressed as it winds round the back of the humerus when the comatose, paralysed or drunk patient lies on the nerve—so-called "Saturday night palsy"; this causes wrist and finger drop and impairment of sensation in the anatomical snuff box. Fortunately, spontaneous recovery is the rule and treatment is not necessary. In the interim, a splint holding the wrist in extension helps hand function.
- The posterior interosseus branch of the nerve may be compressed by a constitutionally tight fibrous arcade of Frohse, which binds together the superficial and deep heads of the supinator muscle as they arise from the lateral epicondyle of the humerus and lateral border of the radius. This differs from a higher lesion by sparing extensor carpi radialis and sensation, and causing a finger drop without much wrist drop. Neurophysiological confirmation should be sought and the nerve explored and decompressed if the palsy lasts more than 12 weeks.
- A partial posterior interosseus nerve palsy is a common presentation of multifocal motor neuropathy which must be considered and distinguished by the neurophysiologist.

Meralgia paraesthetica

Compression of the lateral cutaneous nerve of the thigh as it passes under the inguinal ligament causes tingling and numbness of the lateral aspect of the thigh. The distribution of symptoms and signs varies in its extent but is helpfully lateral to the midline of the thigh to differentiate it from an L2 lesion. The knee reflex is preserved.

- It often gets better on its own.
- Claims that steroid injections or exploration and decompression of the nerve are helpful have not been substantiated.

Common peroneal nerve palsy

The common peroneal nerve branch forms from the sciatic nerve in the thigh and descends with the tibial nerve until the two separate at the knee. Apparent peroneal nerve involvement may therefore be due to a lesion in the thigh as well as more distally. The common peroneal nerve winds round the neck of the fibula and divides into superficial and deep branches. The superficial peroneal nerve supplies peroneus longus and brevis, and the skin on the lateral aspect of the lower leg, dorsum of the foot and toes. The deep peroneal branch supplies tibialis anterior, extensor digitorum longus, extensor hallucis longus, peroneus tertius, extensor digitorum brevis and the skin between the first and second toes.

The common peroneal nerve is most commonly affected by compression at the neck of the fibula from crossing the legs, pressure during prolonged sleep, anaesthesia or coma, or from damage produced by a fracture or plaster cast.

Management

- Compressive lesions usually permit spontaneous recovery within 12 weeks.
- A footdrop orthosis may be helpful while recovery is awaited.
- Patients who do not improve should be offered investigation with neurophysiological tests, imaging and eventually exploration of the nerve.

Multiple mononeuropathy

Causes include:

- Underlying diabetic or alcoholic neuropathy on which are superimposed pressure palsies.
- Multiple entrapments, as in hereditary neuropathy with liability to pressure palsies (see below).
- Known or clinically diagnosable systemic vasculitis due to polyarteritis nodosa, Churg-Strauss syndrome, microscopic polyarteritis, rheumatoid arthritis or systemic lupus where the clinical picture and neurological presentation often allow a confident diagnosis.
- Non-systemic vasculitis confined to nerves and muscles. This can only be diagnosed histologically and is one of the few occasions when nerve biopsy is advisable (preferably of a nerve whose territory is already analgesic so there is unlikely to be more extensive deficit or pain). The vasculitis may remain confined to nerves for many years and may or may not cause significant disability.
- Sarcoidosis
- Lyme disease
- Lymphomatous or carcinomatous infiltration
- Amyloid.

The management of multiple mononeuropathy is of the underlying condition. Vasculitic neuropathies usually need treatment with corticosteroids and intravenous or oral cyclophosphamide for 3–6 months followed by corticosteroids and azathioprine or methotrexate to maintain remission.

The causes of upper limb multiple mononeuropathy include neuralgic amyotrophy, thoracic outlet syndrome and multifocal motor neuropathy (see demyelinating neuropathies).

Thoracic outlet syndrome is caused by compression of the roots of the lower trunk of the brachial plexus by a cervical rib, or fibrous band from the seventh cervical vertebra to the first rib. This causes pain, paraesthesiae and numbness along the medial

forearm into the ulnar nerve territory and in extreme cases wasting of the intrinsic hand muscles, especially abductor pollicis brevis. Symptoms are worse on carrying. Neurophysiological tests and ultrasound imaging of the subclavian artery with the arm abducted are useful. Surgical decompression may be helpful. A rib or band may also compress the subclavian artery causing unilateral Raynaud's phenomenon or emboli, for which operation is necessary and urgent.

Neuralgic amyotrophy: severe shoulder pain heralds the onset of multifocal weakness and then wasting of the shoulder girdle muscles. Sensory impairment is common but less prominent than weakness. The middle and upper trunks of the brachial plexus and long thoracic or suprascapular nerves are most affected. However, the involvement is patchy and any nerve trunk or component of the brachial plexus can be affected. The pain subsides in about four weeks and spontaneous improvement of the weakness occurs gradually, but complete recovery is unusual. Recurrent attacks occur in about a quarter of patients and are more common in the rare autosomal dominant form, which has a worse prognosis. An immune pathogenesis has been proposed but there is no treatment which definitely improves prognosis.

Diabetic lumbosacral radiculoplexus neuropathy, also called proximal diabetic neuropathy and formerly known as diabetic amyotrophy, is uncommon but occurs in Type 2 diabetes, often quite well controlled, and is associated with weight loss. It presents with acute or subacute severe unilateral or bilateral thigh pain (which may be severe enough to require opiates) and causes unilateral or bilateral asymmetrical weakness of the anterior thigh muscles and hip flexors, and sometimes also the anterolateral muscles of the lower leg. There is generally little or no associated sensory loss. This is caused by ischaemic lesions in the lumbosacral plexus and femoral nerve associated with microvasculitis. Reports of improvement with intravenous methylprednisolone or immunoglobulin are difficult to judge because spontaneous improvement is the rule, albeit slow and usually incomplete.

Idiopathic lumbosacral plexus neuropathy is rare but does occur in non-diabetic patients and produces a similar clinical picture.

GENERALISED PERIPHERAL NEUROPATHIES

The differential diagnosis of more or less symmetrical generalised neuropathy is much more extensive and complicated than that of mononeuropathies, although most cases are accounted for by relatively few diagnoses—principally diabetes mellitus and alcohol overuse. The approach to the diagnosis can be simplified by considering chronic and acute situations. The history and then the examination are critical in identifying the cause and reducing the need for a long and expensive list of investigations. At the initial consultation the investigations in table 1 are a reasonable compromise.

Nerve conduction tests are particularly important because they should identify the neuropathy as axonal or demyelinating, with profound implications for further investigation and treatment:

- Motor nerve conduction velocities below 40 m/s in the upper limb and 30 m/s in the lower limb generally mean demyelination.
- Lesser degrees of slowing of nerve conduction velocity indicate peripheral nerve damage which could be due to axonal loss as in axonal neuropathy or neuronopathy.
- There are many caveats, especially that very small compound muscle action potentials in severe axonal neuropathy due to loss of fast conducting axons may cause slower nerve conduction velocities, which might be misinterpreted as due to demyelination.
- The most controversial part of the testing is the detection of partial conduction block, which, to be definite, requires the proximally evoked compound muscle action potential to be less than half that obtained from distal stimulation. Conduction block usually means that focal demyelination is present. It is common for axons to be lost in demyelinating neuropathy which adds to the complexity. However, axonal neuropathy does not cause neurophysiologically detectable demyelination.
- The mysteries of clinical neurophysiology will be revealed in a subsequent article in this series.

Most neuropathies are chronic and axonal. If the initial consultation and investigations in table 1 have not revealed a diagnosis, it is time to review the clinical history and make sure none of the diagnostic categories in box 1 is relevant.

Things to check:

- Serum gamma glutamyl transferase concentration increased to suggest alcohol overuse?
- Is the patient on any medication? Check the summary of product characteristics for each drug to make sure it does not cause a neuropathy. Table 2 contains only a partial list.
- What about possible toxins from the health food store, internet or abroad?
- Any exposure to industrial toxins, especially insecticides, solvents and heavy metals (box 2)?
- If the diagnosis remains unclear, consider which investigations in table 4 are appropriate in the context.

At the end of the day, about 25% of patients remain without a satisfactory explanation for their chronic axonal neuropathy although with the

Table 1 Initial investigation of symmetrical polyneuropathy

Urine	Glucose, protein
Haematology	Full blood count, ESR, B12, folate
Biochemistry	Random glucose, HbA1c, renal, liver and thyroid profiles, serum protein electrophoresis
Immunology	Antinuclear factor
Radiology	Chest *x* ray
Neurophysiology	Nerve conduction tests

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Box 1 Commonest causes of chronic axonal neuropathy

- Diabetes mellitus
- Alcohol
- Uraemia
- Cirrhosis
- Amyloidosis due to plasma cell dyscrasia, and in amyloidosis with myeloma (light chain amyloidosis)
- Myxoedema
- Acromegaly
- Toxins (box 2)
- Drugs (table 2)
- Deficiency diseases (table 3)
- Paraneoplastic
- Hereditary
- Infection: leprosy, HIV
- Idiopathic

passage of time a cause may occasionally emerge, most often alcohol or drug abuse, or genetic neuropathy. Some, especially those with a slowly progressive predominantly sensory, often painful, neuropathy, constitute a rather stereotyped entity which has earned the title "chronic idiopathic axonal neuropathy". Many such patients have elements of the metabolic syndrome, including impaired glucose tolerance, short of frank diabetes, and hyperlipidaemia, especially hypertriglyceridaemia.

Small fibre painful axonal neuropathy

There is a small subset of patients where the small fibres alone are affected and in whom pain and temperature sensation but not large fibre modalities are impaired. Conventional clinical neurophysiological tests are normal because they do not access small nerve fibres. Quantitative sensory testing detects abnormal temperature thresholds but is not objective and nor particularly helpful. Some centres now use skin biopsies to confirm the diagnosis by showing drop-out of the unmyelinated axons crossing the junction between the dermis and epidermis. Most patients have diabetes mellitus or at least impaired glucose tolerance but a few have Sjögren's syndrome. The condition is persistent and initially slowly progressive although it may plateau. The pain usually responds to some extent to antiepileptics or tricyclic antidepressants.

Box 2 Industrial and environmental toxins which cause peripheral neuropathy

- Acrylamide
- Arsenic
- Lead
- Mercury
- Thallium
- Organophosphates
- Carbon disulphide
- Organic solvents: *n*-hexane and methyl-*n*-butyl ketone

Box 3 Causes of chronic demyelinating neuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy:
- Typical symmetrical
- Multifocal acquired demyelinating sensory and motor neuropathy
- symmetrical motor
- symmetrical sensory

Multifocal motor neuropathy
Paraprotein associated demyelinating neuropathy
Charcot-Marie-Tooth disease type 1 and type X

CHRONIC DEMYELINATING NEUROPATHY

The differential diagnosis is much simpler than that of chronic axonal neuropathy (box 3).

Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the commonest acquired cause of chronic demyelinating neuropathy with a prevalence of about 3 per 100 000. It is a chronic progressive or relapsing disorder with symmetrical weakness and sensory changes in the limbs developing over more than 8 weeks. Atypical variants include pure motor, clinically pure sensory and multifocal forms, the last called the Lewis-Sumner syndrome or multifocal acquired demyelinating sensory and motor neuropathy. It is important to distinguish CIDP from chronic axonal neuropathy because it responds well to treatment with immunotherapy. Clues are:

- a relapsing course
- proximal as well as distal weakness
- increased CSF protein and normal cell count (in at least 80% of patients).

The diagnosis critically depends on neurophysiological tests showing slowing of nerve conduction into the demyelinating range or partial conduction block. There are no diagnostically useful antibody assays. In particular antibodies to gangliosides are not helpful, only being found in 10% of patients. MRI may reveal abnormal signal and thickening of spinal nerve roots, brachial or lumbar plexuses and sometimes enhancement following injection of contrast, but its usefulness in the diagnosis of CIDP has not been adequately investigated. Nerve biopsy is not usually performed because the diagnosis can be made from the clinical and neurophysiological picture. The results of sural nerve biopsies are often disappointing. Although most patients have demyelinated nerve fibres, ongoing inflammation is only found in about

Table 2 Drugs which cause peripheral neuropathy

Adriamycin	Nitrofurantoin
Amiodarone	Nitrous oxide (with a myelopathy)
Bortezomib	Nucleoside analogue reverse transcriptase inhibitors: zalcitabine, didanosine and stavudine
Chloroquine (with myopathy)	
Dapsone	Phenytoin
Disulfiram	Platinum: cisplatin and carboplatin
Ethambutol	Podophyllin
Gold	Pyridoxine
Isoniazid	Suramin
Metronidazole	Taxanes: paclitaxel and docetaxel
Misonidazole	Thalidomide
	Vincristine

10% and in about a quarter the only change is non-specific loss of axons.

When CIDP is suspected, a careful search for one of the conditions with which it may be associated is important, especially diabetes mellitus or a paraprotein (box 4). In these conditions the pathology of the neuropathy may be the same as that in CIDP or different. In particular, CIDP in diabetes mellitus often resembles and responds to treatment in the same way as CIDP without diabetes. Confusingly, diabetes can cause a neuropathy with some slowing of nerve conduction due to the diabetic process itself which can be difficult to distinguish.

Management

- Corticosteroids, intravenous immunoglobulin (IVIg) and plasma exchange are all beneficial but prolonged treatment is necessary, which is hazardous with corticosteroids, expensive with intravenous immunoglobulin and inconvenient with plasma exchange. Faced with this dilemma, initial treatment with prednisolone 60 mg daily is usually the most appropriate. If the response is inadequate or adverse effects intolerable, then a trial of IVIg 2.0 g/kg, which can be given over two days, is the next step.
- In pure motor CIDP, which may be worsened by corticosteroids, IVIg should be the first treatment.
- If neither corticosteroids nor IVIg work, then plasma exchange is worth trying.
- If a patient responds to corticosteroids or IVIg, continue treatment until a maximum response has been reached.
- For corticosteroids, monitor blood pressure, blood glucose and symptoms of dyspepsia and provide bone protection. Reduce the dose as soon as a maximum response has been achieved. *The doctor who puts a patient on corticosteroids has the responsibility for taking the patient off them.*
- For IVIg, repeat infusions with half the initial dose about every 4 weeks until maximum response achieved. Try to anticipate the worsening which begins after intervals that range from 2–6 weeks in different patients.
- For patients who are established on IVIg, try withdrawing it by reducing the dose every 6 months so as to avoid continuing this very expensive treatment unnecessarily. In the UK, national guidelines must be followed (see further reading).
- If the response to these three agents is inadequate, it is usual to try cytotoxic drugs based on anecdotal experience. Trials of methotrexate and of beta interferon 1a have not shown significant benefit. More powerful immunosuppressive regimes are being considered but until they become available azathioprine is the easiest and most familiar drug.
- If the disease is resistant to treatment, the diagnosis should be reviewed, a renewed search made for an associated plasma cell dyscrasia, and the possibility of a genetic neuropathy reconsidered.

Table 3 Deficiencies which cause peripheral neuropathy

Thiamine	In malnourished, alcohol abuse and after gastric surgery
Pyridoxine	Overdose also causes neuropathy
Vitamin E	May be associated with cerebellar syndrome
Vitamin B_{12}	Predominantly sensory, with spinal cord involvement
Strachan's syndrome	Painful sensory neuropathy, optic neuropathy and deafness, in association with orogenital dermatitis: reported from tropical countries
Coeliac disease	Controversial whether coeliac disease causes neuropathy in the absence of vitamin deficiency

Box 4 Concomitant diseases associated with CIDP

- Diabetes mellitus
- Monoclonal gammopathy of undetermined significance
- HIV infection
- Lyme disease
- Chronic active hepatitis
- Systemic lupus erythematosus or other connective tissue disease
- Sarcoidosis
- Thyroid disease

Multifocal motor neuropathy

This is a rare pure motor syndrome causing weakness and wasting predominantly in the upper limbs, sometimes confused with a pure motor form of CIDP; or with motor neuron disease because wasting and fasciculation may be features. The diagnosis depends on finding multifocal motor but not sensory conduction block at sites not subject to compression. IgM antibodies to ganglioside GM1 are present in about 50% of patients and may contribute to the pathogenesis.

It is very slowly progressive and does not necessarily become severely disabling. About 80% of patients respond to IVIg, which has to be repeated approximately every month. Confusingly, some patients with a similar clinical picture but without demonstrable conduction block also respond to IVIg. Corticosteroids make it worse. Immunosuppressive drugs, especially cyclophosphamide, are often tried in severe cases.

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Table 4 Further investigations to be considered (not done automatically) in symmetrical axonal polyneuropathy

Biochemistry	Glucose tolerance test
	Serum angiotensin converting enzyme
	Serum vitamin E concentration
Urine	Bence-Jones protein
	Porphobilinogen
Immunology	Antineutrophil cytoplasmic antigen antibodies
	Antineuronal antibodies (Hu, Yo)
	Antiganglioside antibodies
	Anti-Myelin Associated Glycoprotein (MAG) antibodies
Cerebrospinal fluid	Cells, protein, immunoglobulin
Tests for Sjögren's syndrome	Salivary flow rate
	Schirmer's test, Rose Bengal test
	Anti-extractable nuclear antigen (ENA) antibodies (anti-Ro, anti-La)
Tests for coeliac disease	Antigliadin, anti-endomysial and tissue transglutaminase antibodies
	Jejunal biopsy
Search for carcinoma or lymphoma	Pelvic ultrasound, abdominal CT scan, chest CT scan or PET scan
Genetic tests (see below)	For CMT2
Only as a last resort and preferably in a specialist peripheral nerve centre	Nerve biopsy

Paraprotein associated neuropathy

Paraproteins may be associated with axonal neuropathy, AL amyloid neuropathy and several forms of demyelinating neuropathy. If a paraprotein is found, help from a haematologist in investigating the underlying cause will be necessary. Investigation is likely to need to include a skeletal survey, which is said to be better than a radioisotope bone scan at detecting myeloma, and bone marrow examination.

Possible causes of the association with demyelinating neuropathy are:

- Coincidental with a monoclonal gammopathy of undetermined significance (MGUS).
- Solitary myeloma or plasmacytoma. Recovery occurs following treatment of the plasma cell dyscrasia.
- IgM MGUS and antibodies to Myelin-Associated Glycoprotein (MAG) and other myelin proteins and glycolipids sharing the same epitope. Testing for anti-MAG antibodies is widely available. The clinical picture is usually a very slowly progressive sensory or sensory and motor demyelinating neuropathy, often with a postural tremor. Distal motor latencies are usually disproportionately prolonged because demyelination is more pronounced in distal than proximal nerve segments. Cytotoxic drugs such as chlorambucil and fludarabine are often used but patients may be better left untreated because the neuropathy only worsens slowly. Trials of rituximab are in progress.
- POEMS syndrome is a serious progressive multisystem disorder associated with very high plasma concentrations of vascular endothelial growth factor. Papilloedema, peripheral oedema, skin pigmentation and endocrinopathy are diagnostic clues. Autologous blood stem cell transplantation is beneficial.
- CANOMAD syndrome (chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies) is rare; it resembles a chronic form of Miller Fisher syndrome and can be very disabling.

HEREDITARY NEUROPATHY

The commonest cause is Charcot-Marie-Tooth disease (CMT) with a prevalence of 40 per 100 000. Other causes include:

- Hereditary sensory and autonomic neuropathy
- Distal hereditary motor neuropathy
- Familial amyloid polyneuropathy
- Neuropathy associated with multisystem hereditary disorders such as metachromatic leukodystrophy, mitochondrial disorders and Refsum's disease.

CMT may be due to a demyelinating neuropathy called CMT1 where the median nerve conduction velocity is less than 38 m/s or to an axonal neuropathy called CMT2 where it is more than 38 m/s. Both forms of CMT are usually autosomal dominant but may be X-linked or recessive.

- The commonest form, CMT1a, is caused by duplication of the gene on chromosome 17 for peripheral nerve myelin protein 22, PMP22. This accounts for 70% of all cases of CMT and molecular genetic diagnosis is readily available, albeit expensive. The clinical picture varies from no impairment through slight pes cavus with mild predominantly distal motor lower limb neuropathy to severe and even fatal childhood onset sensory and motor neuropathy.
- The converse of the CMT1a PMP22 gene duplication is hetrozygous deletion of the same gene, which causes most cases of autosomal dominant hereditary neuropathy with liability to pressure palsies. This is worth considering in families where more than two affected members have carpal tunnel syndrome or other compressive nerve syndromes.
- The second commonest form of CMT is CMTX, caused by a mutation of the GJB1 gene for connexin 32 on the X chromosome causing a variable neuropathy, more severe in males in whom it is usually demyelinating than in females in whom it is usually axonal, although intermediate conduction velocities may be found.
- A mutation of the gene for mitofusin accounts for 20% of cases of CMT2 and in these cases the neuropathy may be rapidly progressive and associated with optic atrophy
- Severe childhood onset cases of CMT may be due to dominant mutations in the genes for P0, PMP22 or other genes, or to recessive mutations.
- If a molecular diagnosis of one of the common diseases mentioned cannot be made, referral to a specialist unit is appropriate.

ACUTE NEUROPATHY, GUILLAIN-BARRÉ SYNDROME

Acute neuromuscular paralysis has a wide differential diagnosis (box 5) but GBS is the commonest cause. In most western countries, it is usually due to an acute inflammatory demyelinating polyradiculoneuropathy (about 10% of patients have acute motor axonal neuropathy or acute motor and sensory axonal neuropathy). GBS occurs at any age but is more common in the elderly, in whom the prognosis is worse, and, like most neuropathies, in males than females. About two thirds of patients have had an infection during the preceding six weeks, which is most commonly respiratory; if it is gastrointestinal (often due to *Campylobacter jejuni*), the prognosis is worse.

The presenting weakness may be proximal, distal or both; and descending or ascending. The face and bulbar muscles are commonly affected, the ocular motor nerves sometimes. Numbness and tingling in the extremities are common and sensory loss is sometimes marked. Pain in the limbs or back is often present, especially in children, and can be severe.

Immediate management is first directed towards life-threatening complications:

- measure the vital capacity
- assess bulbar function
- monitor the ECG for arrhythmias
- prophylaxis against venous thromboembolism: graduated compression stockings and low dose subcutaneous low molecular weight heparin.

Investigation is targeted first to make sure that the diagnosis is indeed a neuropathy and not one of the other conditions in box 5, and second to identify its cause. A good history is more important than any blood tests but most of the investigations in table 1 are usually appropriate.

- There is no diagnostic blood test but IgG antibodies to ganglioside GM1 are present in 25% of patients, more often in those with acute motor axonal neuropathy.
- The CSF should be examined and typically shows an increased protein content, but this may be normal during the first week. The white cell count is normal; more than 10 cells per microlitre should raise suspicion of another diagnosis or associated HIV infection.
- Nerve conduction may be normal during the first few days but then becomes abnormal, showing slowing of motor nerve conduction and partial conduction block in acute inflammatory demyelinating polyradiculoneuropathy, or diminution of compound muscle action potentials with preserved conduction velocity in the axonal forms of the disease.

Acute inflammatory demyelinating polyradiculoneuropathy is an autoimmune disease directed against unknown antigens triggered by the preceding infection. The antigens responsible for the less common forms of idiopathic acute neuropathy have been better defined:

Box 5 Differential diagnosis of acute neuromuscular paralysis

- Brain stem lesions: stroke, encephalitis
- Acute anterior poliomyelitis: poliovirus, Coxsackie, ECHO, Japanese encephalitis virus, West Nile virus
- Acute cord lesions: haematoma, abscess, compression, transverse myelitis, infarction
- Acute cauda equina syndrome: haematoma, compression, abscess
- Peripheral neuropathy
  - Guillain-Barré syndrome
  - Post-rabies vaccine neuropathy
  - Paralytic rabies
  - Diphtheritic neuropathy
  - Heavy metals and industrial toxins
  - Drug-induced
  - Acute intermittent porphyria
  - Vasculitic neuropathy
  - Critical illness neuropathy
  - Thiamine deficiency
  - Lymphomatous neuropathy
- Axonal sodium channel blockade
  - Neurotoxic marine poisoning
- Disorders of neuromuscular transmission
  - Tick bite paralysis
  - Myasthenia gravis
  - Lambert-Eaton myasthenic syndrome
  - Biological or industrial toxins
- Disorders of muscle
  - Hypokalaemia
  - Hypophosphataemia
  - Inflammatory myopathy
  - Acute rhabdomyolysis
  - Trichinosis
  - Periodic paralyses

- Acute motor axonal neuropathy: gangliosides GD1a and GM1
- Miller Fisher syndrome (ophthalmoplegia, ataxia and areflexia): ganglioside GQ1b
- Pharyngo-cervical-brachial variant: ganglioside GT1a
- Acute sensory neuronopathy: ganglioside GD1b
- Acute pandysautonomia: ganglionic nicotinic acetylcholine receptor.

Treatment

Most cases of GBS should be treated with IVIg 2.0 g/kg over 5 days, or, if contra-indicated (known hypersensitivity or renal failure), with plasma exchange, as early as possible. If they do not improve there is no evidence that a second treatment is effective and there is no theoretical reason for repeating the treatment until at least two weeks have elapsed. Corticosteroids do not help. There is uncertainty about the other conditions but they are usually treated as for GBS. Miller Fisher syndrome

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Patient support organisations

CMT association http://cmt.org.uk
GBS Support Group http://www.gbs.org.uk
GBS/CIDP Foundation International http://gbs-cidp.org/
Neuropathy Trust http://www.neurocentre.com/.php

has a good prognosis and may not need treating, but many patients have weakness suggesting overlap with GBS when treatment may be appropriate.

GENERAL MANAGEMENT

Identification of the cause of the peripheral neuropathy often leads to useful treatment even if it is only the removal of the causative agent (alcohol—easier said than done, drug or toxin) or treatment of the underlying condition (diabetes, B12 deficiency, HIV, Lyme disease, leprosy, etc). The wide range of treatments for the inflammatory neuropathies have been mentioned.

Nerve damage due to inflammation or compression will permit more or less complete recovery due to the ability of Schwann cells to proliferate and remyelinate demyelinated axons. Although severe inflammation and compression may cause axonal degeneration, peripheral nerve axons which have been severed have the capacity to regenerate. The rate of regrowth is slow, about 1 mm per day, and proximal lesions are particularly likely to cause a permanent deficit or aberrant reinnervation.

Generic treatments for the consequences of peripheral neuropathy include:

- Foot care
- Special shoes
- Ankle foot orthoses
- Walking aids: sticks, frame
- Treatment for neuropathic pain especially tricyclic antidepressants, antiepileptic drugs, duloxetine, tramadol, exercise and transcutaneous electrical nerve simulation
- Treatment for erectile dysfunction—sildenafil
- Treatment for postural hypotension; graduated compression stockings, raising head of bed, midodrine.

CONCLUSIONS

- Symmetrical polyneuropathy occurs in 2.4%, and carpal tunnel syndrome in 5% of women and 0.5% of men.
- Treat severe Bell's palsy with oral prednisolone.
- Carpal tunnel syndrome recovers in
  - 20% without treatment
  - 50% with steroid injection
  - 75% with operation.
- Refer ulnar nerve lesions after 3 months for exploration.
- Multiple mononeuropathy may be due to vasculitis.
- Neurophysiological studies are needed to distinguish axonal from demyelinating neuropathies.
- Commonest causes of symmetrical axonal polyneuropathy: diabetes mellitus, alcohol.
- Guillain-Barré syndrome requires excellent intensive care and IVIg.
- In chronic demyelinating neuropathy look for a plasma cell dyscrasia.
- Chronic inflammatory demyelinating polyradiculoneuropathy may be treated with steroids, unless purely motor, but if ineffective with intravenous immunoglobulin.
- Commonest cause of Charcot-Marie-Tooth Disease: duplication of PMP-22 gene.
- Foot care and symptomatic treatments for pain or autonomic failure may be needed.

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Further reading

- Asbury AK, Thomas PK. *Peripheral nerve disorders. A practical approach*. Second edn. London: Butterworths, 1995.
- Birch R, Bonney C, Wynn Parry CB. *Surgical disorders of the peripheral nerves*. Edinburgh: Churchill Livingstone, 1998.
- Department of Health. *Clinical guidelines for immunoglobulin use*. Second edn. DoH, 2008. http://www.ivig.nhs.uk/documents/Clinical%20Guidelines_SECOND%20EDITION%20(2).pdf
- Dyck PJ, Thomas PK. *Peripheral neuropathy*. Fourth edn. Philadelphia: WB Saunders, 2005.
- Halperin JJ *et al*. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review). *Neurology* 2007;**69**:91–102.
- Hughes R *et al*. Peripheral nerve disorders. In: Candelise L, *et al*. eds. *Evidence-based Neurology. Management of Neurological Disorders*. London: BMJ Books 2007:244–57
- Hughes RAC, Cornblath DR. Guillain-Barré syndrome. *Lancet* 2005;**366**:1653–666.
- Hughes RAC *et al*. Supportive Care for Guillain-Barré syndrome. *Arch Neurol* 2005;**62**:1194–8.
- Hughes RAC, Thomas PK. Diseases of the peripheral nerves. Fifth edn. In: Warrell DA, Cox TM, Firth JD, eds. *Oxford textbook of medicine*. Oxford, UK: Oxford University Press, 2009 (in press).
- O'Brien MD. *Aids to the investigation of peripheral nerve injuries*. Fourth edn. Philadelphia, USA: Elsevier Health Sciences, 2004.
- Online Mendelian Inheritance in Man http://www.ncbi.nlm.nih.gov/sites/entrez?db = omim
- Reilly MM. Sorting out the inherited neuropathies. *Pract Neurol* 2007;**7**:93–105.
- Report of a joint task force. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinaemic demyelinating neuropathies. *Journal of the Peripheral Nervous System* 2006;**11**:9–19.
- Report of a joint task force. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. *Journal of the Peripheral Nervous System* 2005;**10**:220–8.
- Report of a joint task force. European Federation of Neurological Societies/Peripheral Nerve Society guideline Guideline on Management of Multifocal Motor Neuropathy: *Journal of the Peripheral Nervous System* 2006;**11**:1–8.
- Stewart JD. *Focal peripheral neuropathies*. Third edn. Philadelphia: Lippincott, Williams and Wilkins, 2000.