Acute and chronic neuropathies

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Abstract

Peripheral nerve disorders are common and often treatable. The 'default' presentation of a polyneuropathy is a chronic, length-dependent, sensorimotor axonopathy. Recognizing deviations from this default, informed by the clinical features and investigations, can help identify the cause of a neuropathy in most cases. For inflammatory causes, such as Guillain–Barré syndrome and chronic inflammatory demyelinating polyradiculoneuropathy, there are effective immunomodulatory treatments. For other neuropathies, management consists of supportive care and treatment of the underlying cause, to prevent or limit progression.

Keywords Carpal tunnel syndrome; Charcot–Marie–Tooth disease; chronic inflammatory demyelinating polyradiculoneuropathy; diabetes mellitus; Guillain–Barré syndrome; mononeuropathy; multifocal motor neuropathy; nerve biopsy; polyneuropathy; vasculitis

Key points

- Mononeuropathies are usually a consequence of nerve entrapment in an enclosed anatomical space

- Polyneuropathies have several distinct modes of presentation, recognition of which can aid elucidation of their cause

- Diabetes mellitus is the most common cause of peripheral neuropathy worldwide

- With the availability of an increasing range of non-invasive investigations, nerve biopsy is now rarely required, but still has a role in the diagnosis of vasculitis

- Inflammatory neuropathies, such as Guillain–Barré syndrome and chronic inflammatory demyelinating *polyradiculoneuropathy*, are amenable to specific immunotherapies

Introduction

Peripheral nerves can be affected individually or collectively by disease — mononeuropathy and polyneuropathy, respectively. Mononeuropathies are usually the result of entrapment[1] (Table 1); there are many causes of polyneuropathy (Table 2). The 'default' presentation of a polyneuropathy is chronic, symmetrical damage to sensory and motor peripheral nerve axons, manifesting with predominantly distal symptoms and signs. This length-dependent 'glove-and-stocking' pattern occurs because the longest axons are statistically most vulnerable to injury, regardless of cause — inflammatory, metabolic, toxic, genetic, etc.

Because the list of causes of polyneuropathy is so long, it helps to subdivide it by looking for deviations from the 'default' presentation — is the neuropathy acute rather than chronic? Is it asymmetrical? Is it purely sensory or purely motor rather than mixed sensorimotor? Other groupings include neuropathies where the disease target is the myelin sheath not the axon (demyelinating versus axonal neuropathies), or is the cell body of sensory neurones in the dorsal root ganglion (ganglionopathy, sensory neuronopathy). The disease process shows a predilection for larger calibre fibres in some neuropathies and small fibres in others. A careful history and examination, focused on the distinctive features of these different clinical presentations, and appropriate investigations, yield a cause in approximately three-

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quarters of patients presenting with peripheral neuropathy. This is important as it can lead to specific treatments.

Clinical features

As the longest neurones are affected first, neuropathic sensory symptoms typically begin in the feet and toes, then ascend proximally. In a truly length-dependent process, this ascent will have reached the knees before the fingertips are involved. Sensory symptoms can be *negative* (loss of sensation, e.g. thermoanaesthesia) or *positive* (tingling, pins and needles, itching, pain). Neuropathic pain, often described as like an 'ice-burn' but sometimes of different character, commonly accompanies small fibre neuropathy, where there is also loss of pain and temperature sensation. This apparent paradox is caused by generation of ectopic impulses in partially damaged nociceptive neurones. Because autonomic fibres are also small calibre, they can be affected by conditions targeting small sensory fibres, causing a coexistent autonomic neuropathy, with postural hypotension, gastrointestinal dysmotility, erectile dysfunction and sweating disorders. Large fibre sensory neuropathies or neuronopathies, however, are usually painless and characterized by sensory ataxia, with balance and coordination difficulties, mimicking a cerebellar syndrome, consequent on proprioceptive impairments. Very severe sensory neuropathies are associated with mutilating features, particularly in the feet (e.g. Charcot joint deformities, neuropathic ulceration).

Motor neuropathies also have distal emphasis. Chronic wasting and weakness of the intrinsic muscles of the foot, dating back to childhood, as seen in many hereditary neuropathies (collectively termed Charcot–Marie–Tooth (CMT) disease) can produce a characteristic foot deformity — pes cavus (Figure 1). Such deformities are absent in later-onset, acquired neuropathies, but lower limb wasting and weakness is still distal in distribution, ultimately leading to bilateral foot drop. Muscle wasting, which takes weeks to become apparent after nerve injury, is more prominent in chronic axonal neuropathies, where

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Common entrapment neuropathies

	Nerve and site of compression	Clinical features	Associations
Carpal tunnel syndrome	Median nerve at wrist	Pain and tingling in hands, especially at night. Wasting and weakness of thenar muscles. Cutaneous sensory loss in median distribution. Tinel's sign, Phalen's test	Diabetes mellitus, pregnancy, rheumatoid and osteoarthritis, hypothyroidism, acromegaly, chronic kidney disease, amyloidosis, mucopolysaccharidosis, local injury.
Ulnar neuropathy	Ulnar nerve at elbow (occasionally wrist)	Pain and tingling from elbow radiating to ulnar border of hand. Weak finger ab/adduction, claw hand, cutaneous sensory loss in ulnar distribution	Diabetes mellitus, local injury/pressure e.g. excessive leaning on elbows
Radial nerve palsy	Radial nerve at humerus	Wrist drop (weak wrist and finger extension), sensory loss in/near 'anatomical snuff box'	Alcohol intoxication and awkward posture ('Saturday night palsy')
Meralgia paraesthetica	Lateral cutaneous nerve of thigh under inguinal ligament	Pain, tingling and sensory loss over lateral aspect of thigh	Weight gain or loss, cardiac surgery?
Common peroneal nerve palsy	Common peroneal nerve at fibular neck	Foot drop — weak ankle dorsiflexion and eversion, weak extensor hallucis longus, variable sensory loss in distribution of common peroneal nerve	Diabetes mellitus, operations, immobility, local injury/pressure e.g. excessive leg-crossing

Table 1

the trophic influence of the nerve on the muscle is lost. Demyelinating neuropathies, in which there is relative preservation of the structural integrity of the motor unit, are often characterized by weakness disproportionate to the degree of wasting. Upper limb motor involvement is also predominantly distal, beginning with wasting and weakness of the intrinsic hand muscles; this affects manual dexterity, eventually resulting in a 'claw hand' deformity. The presence of both proximal and distal weakness, in the upper and/or lower limbs, is likely to signify involvement of roots as well as peripheral nerves — a polyradiculoneuropathy.

Tendon reflexes are diminished or absent in length-dependent neuropathies, particularly affecting ankle reflexes, but there is often a more generalized areflexia. Tendon reflexes are more likely to be preserved in non-length-dependent neuropathies. The archetypal non-length-dependent process — multifocal neuropathy, sometimes termed 'mononeuritis multiplex' — is characterized by asymmetrical neural damage, often in an anatomical distribution of motor and sensory deficits allowing identification of individual affected nerves. Cranial nerves are occasionally involved in multifocal and other neuropathies, which is not surprising as most cranial nerves are part of the peripheral nervous system (PNS). Some neuropathies are associated with nerve hypertrophy, detectable radiologically but sometimes clinically if the nerve is located superficially and close to a firm surface, so it is palpable (Table 2).

If a peripheral neuropathy is suspected clinically, its cause may be elucidated by information from the history. Thus, a past history of diabetes, a family history of similar symptoms, or a history of smoking, alcohol or drug exposure may clinch the pathological diagnosis. Likewise, the general (non-neurological) examination can provide clues to a neuropathy's cause, such as characteristic skin lesions (e.g. purpuric rash in vasculitis, angiokeratomas in Fabry disease) or skeletal deformities (e.g. in hereditary neuropathies).

Investigation and diagnosis

Because diabetes is the most common cause of neuropathy worldwide, it is essential to make or exclude this diagnosis even if another cause seems likely. If other measurements are ambiguous or the clinical index of suspicion remains high, investigation should include an oral glucose tolerance test. Table 3 outlines other general 'screening' tests for the cause of a neuropathy. More specialized blood and urine tests can be triggered by specific departures from the 'default' presentation (Table 2), or, for DNA analysis, by pointers towards a hereditary neuropathy (family history, personal history dating back to childhood, etc.)

Nerve conduction studies are important in confirming a neuropathy and distinguishing various patterns — sensory versus motor, demyelinating versus axonal, neuronopathy versus neuropathy, asymmetry suggesting a multifocal neuropathy versus symmetry, etc. Small fibre neuropathies may not produce any abnormalities on standard nerve conduction studies, which depend on large fibre function, but other forms of psychophysical quantitative sensory testing, such as thermal thresholds, can be informative here.

The main purpose of lumbar puncture in investigating neuropathies is to detect a raised cerebrospinal fluid (CSF) protein concentration, which can provide support for a diagnosis of an inflammatory demyelinating neuropathy. Imaging investigations in neuropathy range from chest radiography (e.g. to show bilateral hilar lymphadenopathy in sarcoidosis or an occult neoplasm underlying a paraneoplastic neuropathy) to

Causes of polyneuropathy according to mode of presentation

Mode of presentation	Distinctive clinical features	Examples of causes
Acute	Rapid progression from onset to nadir, typically <4 weeks	GBS, vasculitis, porphyria, toxins, infections (e.g. Lyme disease, diphtheria), critical illness neuropathy
Subacute	Progression from onset to nadir = 4–8 weeks	Vasculitis, SIDP, vitamin B_{12} deficiency
Multifocal	Patchy, asymmetrical, non-length-dependent	Vasculitis, HNPP, MMN, diabetes mellitus, leprosy, sarcoidosis, malignant infiltration, occasionally CIDP
Demyelinating, predominantly motor	Weakness disproportionate to wasting, nerve hypertrophy, postural upper limb tremor	AIDP, SIDP, CIDP, CMT1, CMTX, paraproteinaemic, amiodarone
Large-fibre sensory neuropathy/neuronopathy	Sensory ataxia, pseudo-athetosis, loss of vibration and joint position sensation	Sjögren's syndrome, paraneoplastic, idiopathic, occasionally CIDP, paraproteinaemic, vitamin B_{12} deficiency
Small-fibre	Neuropathic pain, autonomic involvement	Diabetes mellitus, idiopathic, amyloidosis, HIV, HSN, Fabry disease
Hypertrophic	Palpable (and sometimes visible) nerves, e.g. ulnar, superficial radial, common peroneal, greater auricular	Leprosy, CIDP, CMT1, Refsum's disease, amyloidosis, neurofibromatosis
'Default'	Chronic, axonal, length-dependent	Diabetes mellitus, idiopathic, CMT2, HIV, alcohol, thiamine deficiency, chronic kidney disease, many drugs and toxins

GBS, Guillain–Barré syndrome; SIDP, subacute inflammatory demyelinating polyradiculoneuropathy; HNPP, hereditary neuropathy with liability to pressure palsies; MMN, multifocal motor neuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; AIDP, acute inflammatory demyelinating polyradiculoneuropathy; CMT1, autosomal dominant demyelinating Charcot–Marie–Tooth disease; CMTX, X-linked Charcot–Marie–Tooth disease; HSN, hereditary sensory neuropathies; CMT2, autosomal dominant axonal Charcot–Marie–Tooth disease.

Table 2

computed tomography (CT) or even CT-positron emission tomography of the chest, abdomen and pelvis (for similar reasons). Nerve roots and sometimes peripheral nerves can be imaged by magnetic resonance imaging, which can reveal neural hypertrophy and contrast enhancement, indicating breakdown of the blood–nerve barrier, particularly seen in inflammatory neuropathies.

More invasive investigations, used selectively, include skin biopsy to assess intraepithelial nerve fibre density to confirm a small fibre neuropathy, lip biopsy for evidence of Sjögren's syndrome in an unexplained ganglionopathy, for which non-invasive investigations have proven negative, and bone marrow biopsy in suspected myeloma. Nerve biopsy is now used very sparingly as genetic and immunological blood tests can explain many previously 'idiopathic' neuropathies. It still has a role in diagnosing vasculitis,[2] particularly when this disease process is confined to the peripheral nerves (non-systemic vasculitic neuropathy (NSVN)) (Figure 2).

Despite this range of investigations, the cause remains unclear in up to a quarter of patients presenting with polyneuropathy. Typically, these 'idiopathic' neuropathies develop in later life and are chronic, slowly progressive, predominantly sensory, length-dependent, often painful axonopathies. Even in the absence of a family history, many such neuropathies are suspected to be genetic.

General management of neuropathies

The management of peripheral neuropathy can be subdivided into specific treatments and general measures. Specific treatments include vitamin B_{12} replacement therapy for deficiency and immunotherapies for various inflammatory neuropathies (see below). General measures, common to a range of neuropathies, include symptomatic drug treatment for neuropathic pain, for example antidepressants (amitriptyline, nortriptyline, venlafaxine, duloxetine) or anti-epileptic agents (carbamazepine, gabapentin, pregabalin).

Non-pharmacological pain management and instigation of other general measures involves input from the multidisciplinary team. They should include physiotherapists, occupational therapists and, where appropriate, speech and language therapists and psychotherapists (depression being a common accompaniment of these potentially disabling and painful long-term conditions). Orthotics may be required for foot drop or upper limb palsies. More severe limb deformities, particularly those of the feet potentially dating back to childhood in hereditary neuropathies, can warrant orthopaedic input. Severe acute neuropathies, such as Guillain–Barré syndrome (GBS), may necessitate intensive care in the early phase, with ventilator support, cardiovascular monitoring and attention to care of an immobilized patient – venous thromboembolism prophylaxis, respiratory physiotherapy, nasogastric feeding, skin care, passive limb movement
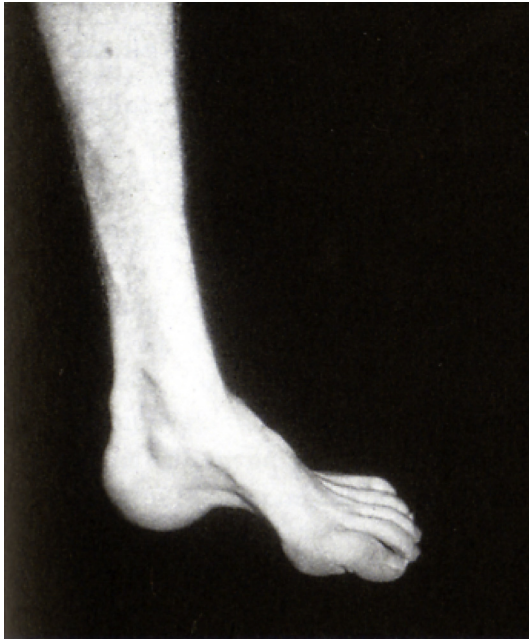
Figure 1 Pes cavus. Reproduced from Ginsberg L, Lecture Notes: Neurology, 9th Edition, Wiley Books 2010 with permission from John Wiley and Sons.

to prevent contractures, bladder and bowel management, and mouth and eye care.

Specific causes

Hereditary neuropathies[3]

CMT is one of the most common neurogenetic groupings, with an overall prevalence of approximately 1:2500. To date, >100 genes have been identified as potential molecular causes. Electro-diagnostic findings can be in the demyelinating, axonal or in-termediate ranges. Autosomal dominant, autosomal recessive and X-linked patterns of inheritance are all represented. By far the most common form of CMT in the UK and many other countries is CMT1A, usually caused by a duplication in chro-mosome 17 involving the myelin protein gene *PMP22*. CMT1A is an autosomal dominant condition, typically with childhood onset and slow progression. Patients have foot deformities in the form of pes cavus (Figure 1), distal lower limb wasting and weakness, some loss of tendon reflexes, milder motor features in the upper limbs and generally more motor than sensory findings. Nerve conduction studies show a demyelinating pattern. While many other CMT variants clinically resemble CMT1A, some genes are associated with distinctive clinical features, and others have a 'purer' phenotype of motor or sensory involvement — hereditary motor and hereditary sensory neuropathies, respectively.

For all these disorders, the mainstays of management are genetic counselling and symptomatic treatment of complications, particularly foot deformities. Specific therapies are available for some genetic neuropathies that are part of a multisystem disorder arising from an established inborn error of metabolism, such as enzyme replacement therapy for Fabry disease, which is associ-ated with a painful small fibre neuropathy.

Blood and urine investigations in peripheral neuropathy

Initial 'screening' blood investigations
- Full blood count and erythrocyte sedimentation rate
- Renal, liver, bone and thyroid profiles
- Fasting blood glucose and glycated haemoglobin
- Vitamin B_{12} and folate
- Serum protein electrophoresis, immunoglobulins and immunofixation
- Antinuclear antibodies, double-stranded DNA antibodies, extractable nuclear antigens

Further blood investigations guided by mode of presentation
- Suspected vasculitis — ANCA, hepatitis B and C serology, HIV, cryoglobulins, complement
- Suspected infections — HIV (low threshold for testing), Lyme serology (if likely exposure)
- Suspected hereditary neuropathy — chromosome 17 studies (duplication for CMT1A, deletion for HNPP). Mutations in specific genes: *PMP22* and *MPZ* (CMT1), *GJB1* (CMTX), *MFN2* (20% of CMT2 patients). Gene panels and next-generation sequencing for rarer causes of Charcot−Marie−Tooth phenotype. White cell enzymes for inborn errors of metabolism. Gene analysis for familial amyloid polyneuropathy.
- Specific auto-antibodies — antineuronal (paraneoplastic neuropathies), anti-GM1 ganglioside (MMN), anti-GQ1b ganglioside (MFS), anti-MAG (IgM paraproteinaemic neuropathy), paranodal (CIDP variants)
- Other — angiotensin-converting enzyme (sarcoidosis), homocysteine and methylmalonic acid (functional vitamin B_{12} deficiency), lipids and lipoproteins

Urine investigations in specific situations
- Microscopy (for evidence of vasculitis)
- Bence Jones proteinuria (for myeloma)
- Porphyrins (hepatic porphyrias in the differential diagnosis of acute neuropathies)

ANCA, antineutrophil cytoplasmic antibodies; CMT1, autosomal dominant demyelinating Charcot−Marie−Tooth disease; HNPP, hereditary neuropathy with liability to pressure palsies; CMTX, X-linked Charcot−Marie−Tooth dis-ease; CMT2, autosomal dominant axonal Charcot−Marie−Tooth disease; MMN, multifocal motor neuropathy; MFS, Miller Fisher syndrome; MAG, myelin-associated glycoprotein, CIDP, chronic inflammatory demyelinating pol-yradiculoneuropathy.

Table 3

Inflammatory neuropathies

Guillain−Barré syndrome:[4] the annual incidence of GBS is 1−2/100,000 population, making it the most common cause of ac-quired acute generalized weakness (Table 4). In a typical severely affected patient, initial neurological symptoms of back pain and tingling in the feet are rapidly overtaken by muscle weakness. This usually starts in the lower limbs and ascends within days to the upper limbs and facial, bulbar and respiratory musculature. Autonomic neuropathic features include labile blood pressure, cardiac arrhythmias and bladder and bowel dysfunction. By definition, GBS reaches its nadir within 4 weeks, often much more rapidly.

Most patients experience an antecedent infection (Table 5), such as a diarrhoeal illness, 1 or 2 weeks before neurological

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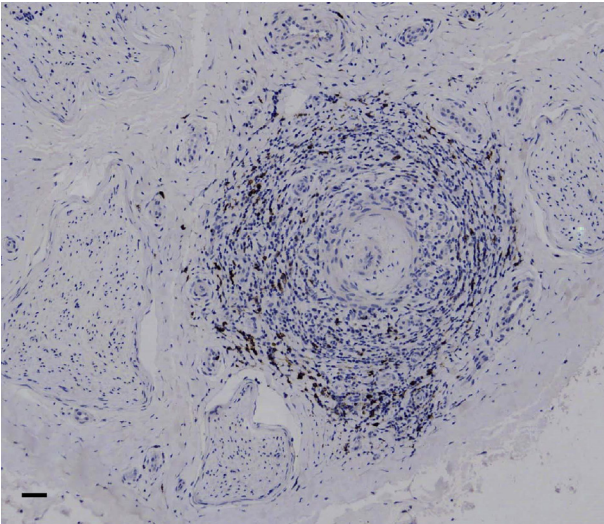
Figure 2 Vasculitic neuropathy Sural nerve biopsy immunostained to show lymphocytes (brown) infiltrating the wall of an epineurial blood vessel. In vasculitic neuropathy, this transmural inflammation is accompanied by histological evidence of damage to blood vessels and to the neural structures supplied by them. Scale bar = 10 micrometres. Image courtesy of Dr Rosalind King, Royal Free Hospital, London.

symptoms. The sequence of pathogenetic events in GBS involves an immune response to the preceding infection, with resulting antibodies 'cross-reacting' with epitopes (generally complex glycolipids — gangliosides) on the myelin sheath or axolemma of peripheral nerves and roots, triggering post-infectious inflammation by molecular mimicry. GBS is often a severe predominantly motor neuropathy, the brunt of damage being on the myelin sheath in acute inflammatory demyelinating poly-radiculoneuropathy, (AIDP), the most common form in the UK, and on the axon in acute motor axonal neuropathy or acute motor sensory axonal neuropathy. Progression can stop before a requirement for ventilator support, or only involve certain body

Causes of acute flaccid paralysis

Acute neuropathy
- Guillain—Barré syndrome
- Other acute neuropathies (see Table 2)

Acute myopathy (no sensory loss, reflexes often preserved)
- e.g. hypokalaemic periodic paralysis

Acute neuromuscular junction disorders (tend to cause paralysis descending from the cranial nerves rather than ascending from the lower limbs)
- Myasthenic crisis
- Botulism

Acute myelopathy (an acute, severe cord lesion can be associated with 'spinal shock' — flaccidity and areflexia for days before conventional upper motor neurone signs develop — hence MRI of the cervical spine is sometimes justified in the investigation of early Guillain—Barré syndrome, before cranial nerve features have appeared, to exclude cord pathology)

Table 4

regions rather than being generalized. Some forms of the syndrome are not motor predominant, including Miller Fisher syndrome (ophthalmoplegia, ataxia, areflexia), pure sensory and pure autonomic neuropathies. The clinical features of GBS therefore vary widely, but the general pattern is maintained — antecedent infection, progression to a plateau in <4 weeks, a monophasic course and characteristic CSF findings of a disproportionate rise in protein concentration with a normal or near-normal white cell count (<10 cells/microlitre).

Severely affected patients require intensive care support with assisted ventilation, typically if vital capacity falls below 1 litre, usually with severe dysphagia and risk of aspiration pneumonia. Specific treatments — intravenous immunoglobulin or plasma exchange — are given primarily to speed the rate of recovery in these patients, and are usually restricted to those who have progressed to being non-ambulant, in the first 2 weeks of their illness. Most patients with GBS make a good recovery, often over many months, but 10—15% have significant persistent disability, and the mortality rate remains 5—10%. The prognosis is worse in older patients, and with rapid onset of weakness to the point of requiring ventilation, axonal forms of the disorder, a preceding diarrhoeal illness or the presence of antiganglioside antibodies.

Chronic inflammatory neuropathies: patients whose weakness progresses or relapses beyond the 4 weeks' time limit accepted for GBS, indeed beyond 8 weeks, but with features of inflammatory demyelination (slow nerve conduction velocities, high CSF protein, for which no other cause has been identified) can have *chronic inflammatory demyelinating polyradiculo-neuropathy* (CIDP).[5] While CIDP is in some ways the chronic counterpart of AIDP, and has a similar incidence, there are important differences beyond the time course. Antecedent infection is rare in CIDP, as is pain. Patients typically have symmetrical weakness in the limbs (proximally and distally, particularly the lower limbs), with varying degrees of sensory loss and areflexia, but infrequent cranial nerve involvement. Bulbar and respiratory problems are very unusual. Although CIDP is usually a pure neurological disorder, there can be a concurrent illness in some patients (e.g. with malignancy, diabetes mellitus or systemic lupus erythematosus). Antiganglioside antibodies are uncommon in CIDP, but a subset of severely affected patients has autoantibodies against proteins located adjacent to the myelin sheath's nodes of Ranvier ('paranodal'). Most patients with CIDP respond to one or more of three front-line treatments — intravenous (or subcutaneous) immunoglobulin, corticosteroids or plasma exchange — but long-term treatment is generally needed and a few patients require additional immunosuppression.

Multifocal motor neuropathy is another chronic neuropathy of presumed autoimmune origin, distinct from CIDP in having a predilection for the upper limbs, with asymmetrical weakness and no sensory involvement (hence potentially mimicking motor neurone disease). Electrodiagnostic studies show the characteristic finding of partial motor conduction block. Around 50% of patients have immunoglobulin (Ig)M autoantibodies against particular gangliosides. Treatment is with intravenous immunoglobulin, not corticosteroids or plasma exchange, and is usually long term.

In *vasculitic neuropathies,*[2] the primary target of inflammation is the vascular supply to the peripheral nerves — the *vasa*

nervorum. The resulting nerve ischaemia/infarction typically leads to painful multifocal neuropathy of subacute onset. Peripheral nerve vasculitis can be part of a systemic disorder, such as one of the antineutrophil cytoplasmic antibody-associated vasculitides, but up to one-third of patients have NSVN. Either way, treatment comprises immunosuppression, with standard combinations of cyclophosphamide (or rituximab) and corticosteroids in systemic disorders, and in many patients with NSVN.

Infections

Relatively few microorganisms directly infect peripheral nerves. The archetypal bacterium to do so is *Mycobacterium leprae*. Leprosy was once one of the more common causes of neuropathy worldwide but is rarer now that the disease is confined to just a few tropical enclaves. Regardless of the type of clinical presentation, which varies according to host immune response, the neurological features are of a multifocal hypertrophic neuropathy.

Among viral infections, HIV has a particular predilection for peripheral nerves and a range of patterns of neuropathy have been described, most commonly a painful distal symmetrical polyneuropathy, which can be complicated by neurotoxic effects of some antiretroviral drugs. A GBS-like neuropathy at the time of HIV seroconversion is also recognized, differing from typical GBS by the presence of a CSF pleocytosis as well as the expected rise in CSF protein content. Other infections, such as Lyme disease, herpes zoster and cytomegalovirus, can affect the PNS, but tend to target roots rather than distal structures.

Neoplasia

Although direct nerve infiltration by lymphoma, leukaemia or even carcinoma cells can occur rarely, the effects of neoplastic disorders on the PNS are more often indirect. Thus, sensory neuronopathy is associated with some solid tumours, particularly small cell lung cancer. Antineuronal antibodies (anti-Hu) are a serological marker for this paraneoplastic condition.

Plasma cell dyscrasias can also affect the PNS remotely, through their production of paraproteins. The conjunction of paraproteinaemia and neuropathy in a middle-aged or older patient can be coincidental, but certain patterns stand out. These include the painful sensory and autonomic neuropathy of primary systemic (AL) amyloidosis, where immunoglobulin light chain fragments are deposited in peripheral nerve and other tissues. A late-onset, slowly progressive, sensory ataxic neuropathy, with upper limb tremor and distal slowing on electrodiagnostic studies, is associated with an IgM κ paraprotein that can bind to myelin-associated glycoprotein (anti-MAG neuropathy). The presence of an IgG or IgA λ paraprotein in a patient with a severe painful demyelinating sensorimotor neuropathy of subacute onset suggests POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal band, Skin changes), prompting a search for an underlying osteosclerotic myeloma.

Metabolic and nutritional states

Diabetic neuropathy is typically distal, predominantly sensory, symmetrical, usually initially painful, but sometimes progressive to foot ulceration and Charcot arthropathy. Other manifestations include autonomic neuropathy, cranial nerve palsies and a predisposition to entrapment neuropathies. An acute or subacute lumbosacral radiculoplexopathy presents with painful, asymmetrical wasting and weakness of the thighs, typically in older men. Rarer forms of diabetic neuropathy include a painful neuropathy on starting insulin therapy.

Vitamin B_{12} deficiency causes a subacute axonal polyneuropathy in association with spinal cord damage (to the corticospinal tracts and posterior columns, hence 'subacute combined degeneration of the cord'). The hands can be affected before the feet. Although these neurological features can be associated with pernicious anaemia, or with gastrointestinal disorders affecting vitamin B_{12} absorption, the most common cause is probably nitrous oxide misuse, resulting in 'functional' vitamin B_{12} deficiency.

Other acquired metabolic neuropathies include a painful, length-dependent axonopathy associated with severe chronic kidney disease, and a rare, painful multifocal neuropathy associated with insulinoma, probably resulting from episodes of prolonged hypoglycaemia.

Drugs and toxins

Alcoholic neuropathy can relate as much to nutritional deficiencies, notably of thiamine, as to any direct neurotoxic effect of alcohol. A painful sensory neuropathy, starting in the feet, can later evolve with motor and autonomic features, potentially coexisting with other neurological complications of alcoholism (dementia, cerebellar ataxia, Wernicke–Korsakoff syndrome).

Numerous metals and metalloids are very rare causes of neuropathy. These include thallium, arsenic, gold, mercury and lead – the latter associated with a predominantly motor neuropathy with upper limb predilection, particularly of the radially innervated musculature. Other chemical peripheral neurotoxins include some organic solvents.

Many drugs also cause peripheral neuropathy. The most notable are isoniazid (preventable with co-administration of

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pyridoxine), vincristine, cisplatin, metronidazole, nitrofurantoin, phenytoin, allopurinol, tacrolimus and amiodarone. ◆

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