Acute and chronic neuropathies

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Abstract

A detailed history, examination, nerve conduction tests and appropriate laboratory investigations will be diagnostic in most peripheral neuropathies. It is important to identify treatable causes. Guillain–Barré syndrome, vasculitic neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy and multifocal motor neuropathy can have good outcomes with immunomodulation. In addition, hereditary transthyretin amyloidosis neuropathy is now a treatable disorder.

Keywords Amyloidosis; brachial neuritis; chronic inflammatory demyelinating polyradiculoneuropathy; Guillain–Barré syndrome; multifocal motor neuropathy; vasculitis

Key points

- Nerve biopsies are performed to identify vasculitis, amyloid and lymphomatous infiltration
- If a genetic neuropathy is considered and nerve conduction testing demonstrates demyelination, test first for *PMP22* deletion/duplication
- Intravenous immunoglobulins or corticosteroids are first-line therapy for chronic inflammatory demyelinating polyneuropathy
- Multifocal motor neuropathy is an important treatable differential for motor neurone disease
- Hereditary transthyretin amyloidosis neuropathy is now treatable

Introduction

A detailed clinical history and neurological examination is key to diagnosis (Figure 1). General medical assessment is necessary to elucidate underlying conditions (e.g. diabetes, HIV, malignancy) or autonomic involvement.

History

Positive sensory symptoms (spontaneous or evoked pins and needles (paraesthesias)) suggest an acquired neuropathy. A genetic neuropathy is suggested by negative sensory symptoms (numbness) or a lack of sensory symptoms but clear sensory signs and abnormal nerve conduction testing (NCT). Burning, shooting pain or painful sensations from a non-painful stimulus (light stroking) (allodynia) imply small fibre neuropathy or spino-thalamic involvement.

Manual dexterity difficulties (opening jars, fastening buttons) or tripping (foot drop) suggests distal weakness. Proximal weakness (difficulty combing hair or climbing stairs) can indicate radiculopathy, radiculo-neuropathy (e.g. chronic inflammatory demyelinating polyneuropathy (CIDP), vasculitis, infiltration) or myopathy. Childhood athletic difficulties (last in races) or need for special shoes can suggest a genetic aetiology.

Unsteadiness with walking and rombergism (loss of balance with the eyes closed, e.g. showering) suggest large fibre or posterior column dysfunction. Autonomic dysfunction causes orthostatic light-headedness, pain in a 'coat hanger' distribution, impotence, bladder and bowel dysfunction, and sweating disturbance.

All medications including vitamins (B_6 toxicity) should be listed. A history of diet (vitamin B_{12} deficiency in vegetarians and vegans), travel, sexual health, alcohol, smoking, recreational drug use (N_2O, cocaine), occupation (suspected toxins) and country of origin (leprosy) should be ascertained. A detailed multigenerational family history, including consanguinity, is mandatory.

Examination

Long-standing foot deformities (pes cavus, pes planus, hammer toes), wasting of the distal limb muscles and kyphoscoliosis suggest a hereditary neuropathy (Figure 2). Nerve thickening (superficial radial (wrist), ulnar (elbow), common peroneal (fibular head)) can indicate CIDP, Charcot–Marie–Tooth (CMT) disease, Refsum disease, amyloidosis or leprosy. Pseudoathetosis (involuntary movements of the outstretched fingers when the eyes are closed) characterizes large fibre neuropathies (e.g. CIDP, sensory ganglionopathy). Postural hand tremor, weakness disproportionate to the degree of wasting and areflexia characterize demyelinating neuropathies with conduction block in the early stages (e.g. CIDP, multifocal motor neuropathy).

Impaired pain and temperature sensation with retained reflexes suggests pure distal small fibre neuropathy or leprosy. Length-dependent neuropathies (e.g. diabetes, toxic, drug induced) and most genetic neuropathies start distally in the feet and progress proximally. Autonomic dysfunction is demonstrated by orthostatic hypotension (supine and erect (standing for 3 minutes) blood pressure measurement with a >20 mmHg systolic drop and >10 mmHg diastolic drop), loss of sinus arrhythmia and impaired pupillary light and accommodation responses.

Investigations

Table 1 outlines the investigations for evaluating peripheral neuropathy.

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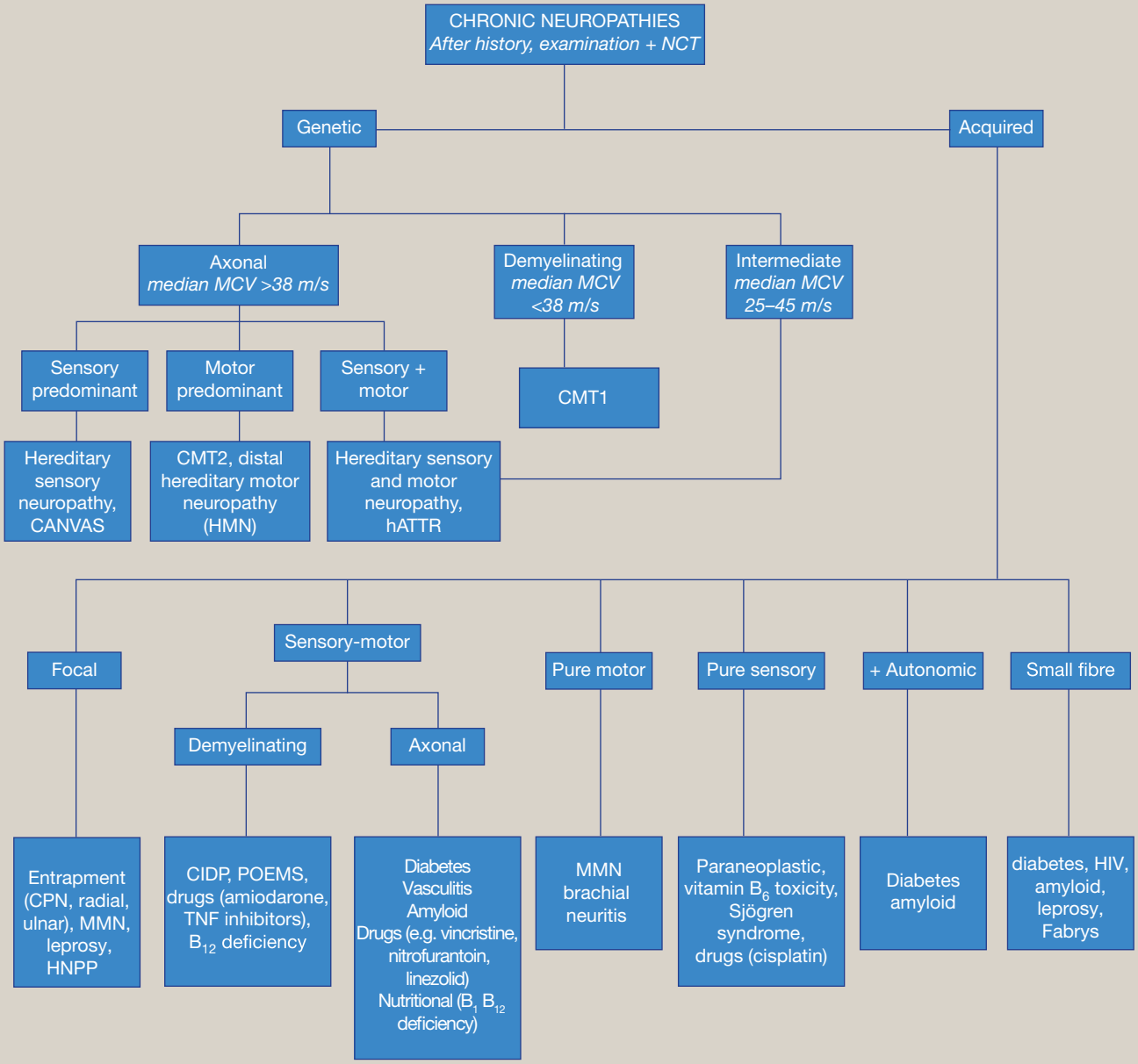
Please cite this article as: Jacinto S, Manji H, Acute and chronic neuropathies, Medicine, https://doi.org/10.1016/j.mpmed.2023.06.013

Algorithm for the diagnosis of chronic neuropathies



CANVAS, Cerebellar Ataxia Neuropathy and Vestibular Areflexia Syndrome; CPN, common peroneal nerve; MCV, motor conduction velocity; MMN, multifocal motor neuropathy; TNF, tumour necrosis factor. For other abbreviations, see text.

Figure 1

Acute neuropathies

Guillain–Barré syndrome (GBS)

Clinical presentation: the most common cause of acute or subacute flaccid paralysis, this is a monophasic syndrome with symmetrical ascending motor weakness that peaks within 4 weeks. Initially normal, the reflexes gradually become absent. Although paraesthesias are frequent, sensory signs are relatively mild. Progression to weakness of the facial, bulbar and respiratory muscles, requiring ventilation (10–30%), can occur. Rarely, weakness mimics paraplegia, and acute myopathy or spinal cord disease must be excluded. Other variants include Miller Fisher syndrome (ophthalmoplegia, areflexia, ataxia), acute oropharyngeal palsy, a pharyngeal-cervical-brachial variant, a pure sensory form and acute pan-dysautonomia.

Two-thirds of patients have a preceding acute infection such as *Campylobacter jejuni*: the immune response to the infection cross-reacts with shared epitopes on the peripheral nerves (molecular mimicry). An association with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still controversial.

Please cite this article as: Jacinto S, Manji H, Acute and chronic neuropathies, Medicine, https://doi.org/10.1016/j.mpmed.2023.06.013

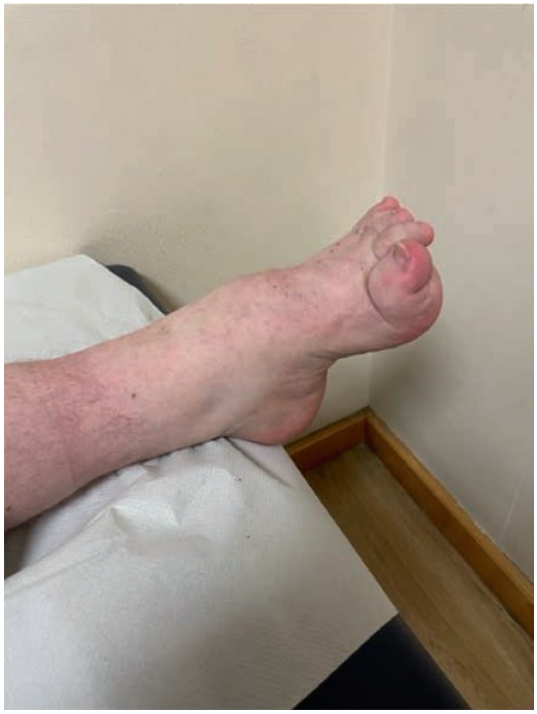


Figure 2 Pes cavus (a high arch that does not flatten with weight-bearing) and hammer toes in a patient with CMT disease type 1a.

Investigation: albuminocytological dissociation in the cerebrospinal fluid (CSF) is usually seen by 3 weeks (but can be absent in the first week). CSF pleocytosis should prompt a search for alternative diagnoses (e.g. HIV, Lyme, sarcoidosis, lymphoma). Early NCT can appear normal, but this can subsequently demonstrate prolonged or absent F-waves, prolonged distal motor latency, conduction block and abnormal temporal dispersion. Sural sparing is suggestive. Magnetic resonance imaging (MRI) may demonstrate enhancement of the nerve roots and cauda equina.

Management: during the acute phase, ensure regular vital capacity assessments and cardiac telemetry with facilities for invasive ventilation and management of autonomic instability (arrhythmias, blood pressure fluctuations). Venous thromboembolism prophylaxis, treatment of infections, optimization of nutrition and management of pain, bladder and bowels are vital.

Intravenous immunoglobulin (IVIg) or plasma exchange hastens recovery in non-ambulatory patients within 4 weeks of onset. IVIg is the treatment of choice (equal effectiveness, fewer adverse effects, easier administration). Treatment also seems reasonable for ambulatory patients within 4 weeks of onset who are not improving and have progressive weakness and bulbar or respiratory compromise. Corticosteroids have no role in treatment.

Investigations for evaluation of peripheral neuropathy

Blood tests:

- FBC, ESR, renal, liver and bone profiles
- HbA_{1c}, fasting glucose
- B_{12}, homocysteine, methylmalonic acid, folate
- HIV
- SPEP, immunofixation, immunoglobulins, light chains, urine Bence Jones protein
- ANA, dsDNA, ENA, ANCA, RhF

Nerve conduction test and electromyography:

Define demyelinating (20%) from axonal (80%); hereditary from acquired; symmetrical length-dependent from asymmetrically patchy, entrapment neuropathy

CSF:

Protein, cell counts, cytology and flow cytometry

Table 1

Vasculitic neuropathies

Clinical presentation: these present acutely or sub-acutely with a progressive mononeuritis multiplex — an asymmetrical onset provides a clue as apparent confluence can develop later. The common peroneal, tibial and ulnar nerves are usually involved. Dysaesthetic pain and localized oedema are features. Vasculitis typically occurs as a primary systemic vasculitis (e.g. polyarteritis nodosa) or secondary to autoimmune disease (e.g. systemic lupus erythematosus), infections (e.g. HIV, hepatitis C) or malignancy. An isolated peripheral nerve presentation is classified as non-systemic vasculitic neuropathy. The underlying mechanism is vessel occlusion by vascular inflammation leading to ischaemic nerve damage.

Investigations: NCT can show a patchy axonal neuropathy. Biopsy of a nerve with clinical and NCT involvement confirms the diagnosis.

Management: corticosteroids and cyclophosphamide (intravenous) are favoured for induction therapy, followed by maintenance with azathioprine, methotrexate or mycophenolate. Management is also guided by any underlying disorder. Corticosteroids may suffice for milder cases, particularly isolated peripheral nerve vasculitis.

Neuralgic amyotrophy (brachial neuritis)[1]

Clinical presentation: this mono- or multifocal inflammatory neuropathy typically affects the upper limbs. There is severe pain followed by patchy weakness (within hours to days) and subsequent wasting. The disorder typically involves the suprascapular, long thoracic, musculocutaneous and axillary nerves but can also involve anterior interosseus (median), posterior interosseus (radial) and phrenic nerves. Triggers include infections (e.g. HIV, hepatitis E, SARS-CoV-2), vaccinations, pregnancy and strenuous activity. Recurrent attacks occur in 25% of patients. The pathophysiology is a combination of immunological, biomechanical stress and genetic factors.

Investigations: early NCT can be normal, and denervation changes may become evident after 2–4 weeks. MRI neurography or ultrasound may show hourglass-like constrictions.

Management: there are no proven treatments from randomized trials, but one open-label retrospective series suggested that a short course of oral prednisone given in the first month could shorten initial pain and hasten recovery; 30% of patients have residual motor deficits. Hourglass-like constrictions, especially

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involving the anterior or posterior interosseous nerves, can be amenable to surgical neurolysis or decompression, improving recovery.

Chronic neuropathies

Diabetic neuropathies

These are the commonest cause of neuropathies worldwide, see Table 2.

Chronic inflammatory demyelinating polyneuropathy[2,3]

Clinical presentation: this typically presents with progressive (>8 weeks) or relapsing, symmetrical, proximal and distal weakness of the upper and or lower limbs with large fibre sensory involvement. Cranial nerve, autonomic or respiratory involvement is rare. In 16% of patients, there is an initial acute GBS-like presentation (A-CIDP) with rapid progression within 4 weeks, which continues after 8 weeks or relapses after initial improvement. Variants include focal, multifocal (Lewis–Sumner syndrome, multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)), predominantly sensory and pure motor CIDP. The latter can deteriorate with corticosteroids.

Investigations: NCT are essential in the diagnosis of CIDP with a demonstration of demyelination, i.e. demonstration of motor and sensory conduction abnormalities. Features include prolonged distal motor latency, slowed motor conduction velocity, prolonged or absent F-waves, motor conduction block, abnormal temporal dispersion, prolonged distal compound muscle action potential duration, reduced sensory nerve action potential amplitude or slowed sensory conduction velocity. CSF examination is not mandatory but is indicated if infection or malignancy is suspected. Brachial and lumbosacral plexus MRI may show nerve root hypertrophy, increased signal intensity and/or contrast enhancement. However, these are non-specific findings (e.g. CMT, neurolymphomatosis, amyloidosis, neurofibromatosis). Nerve biopsy is performed if CIDP is strongly suspected but cannot be otherwise confirmed, or there is a poor treatment response.

These patients should routinely have protein electrophoresis, immunofixation, free light chains and urinary Bence Jones protein tests. Paraproteinaemic neuropathies can be misdiagnosed as CIDP (or GBS). Examples include POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, Skin changes). All patients with immunoglobulin (Ig) M paraprotein and demyelinating neuropathy should be tested for anti-Mag antibodies (see Further reading).

Up to 10% of patients with GBS/CIDP have IgG4 antibodies against nodal and paranodal proteins – neurofascin, contactin. Suggestive features of this autoimmune nodopathy include an aggressive course, tremor, sensory and cerebellar ataxia and a lack of response to IvIg but a response to rituximab.

Treatment (Figure 3): IVIg, corticosteroids and plasma exchange are equally efficacious. The preference between them will be dictated by availability, co-morbidities, convenience and rate of progression. Plasma exchange is usually reserved for patients not responding to corticosteroids or IVIg. Azathioprine, methotrexate and mycophenolate are frequently used as steroid- or IVIg-sparing treatments although adequate supportive data are lacking.

When the response to first-line treatments is limited alternative diagnoses should be considered (e.g. POEMS, AL or hereditary amyloid, autoimmune nodopathies, CMT type X).

Multifocal motor neuropathy with conduction block (MMNCB)[4]

Clinical presentation: this rare, immune-mediated neuropathy typically presents with painless, asymmetrical, upper limb pure

Diabetic neuropathies

Neuropathy	Features
Diabetic polyneuropathy	Most common form of diabetic polyneuropathy; chronic distal symmetrical sensory>motor neuropathy (large and small fibres affected); autonomic abnormalities correlate with severity
Painful small fibre (SF) neuropathy	Distal sensorimotor polyneuropathy (small myelinated fibres affected alone or out of proportion to large fibres)
Diabetic cachectic neuropathy (acute painful neuropathy of DM)	Elderly male with DM2 with poor diabetic control and profound weight loss after starting DM mediation; severe, symmetrical or asymmetrical SF neuropathy symptoms in feet (also trunk)
Insulin neuritis	Onset with insulin treatment; acute painful neuropathy
Diabetic lumbosacral radiculo-plexus-neuropathy (Bruns–Garland syndrome)	Males > 50 years old with DM2; abrupt severe pain in back, hips, anterior thighs followed by progressive proximal weakness and wasting, but may involve distal muscles; usually unilateral but can be bilateral; weight loss
Diabetic truncal radiculoneuropathy	Abrupt burning radicular pain over thoracic spine, ribs, chest or abdomen; weakness of abdominal or respiratory muscles
Cranial neuropathies	Third nerve palsy with pupillary sparing; 50% associated with pain. Sixth nerve palsy
Mononeuropathies	Increased susceptibility to compression injuries: carpal tunnel syndrome, ulnar and common peroneal nerves

Table 2

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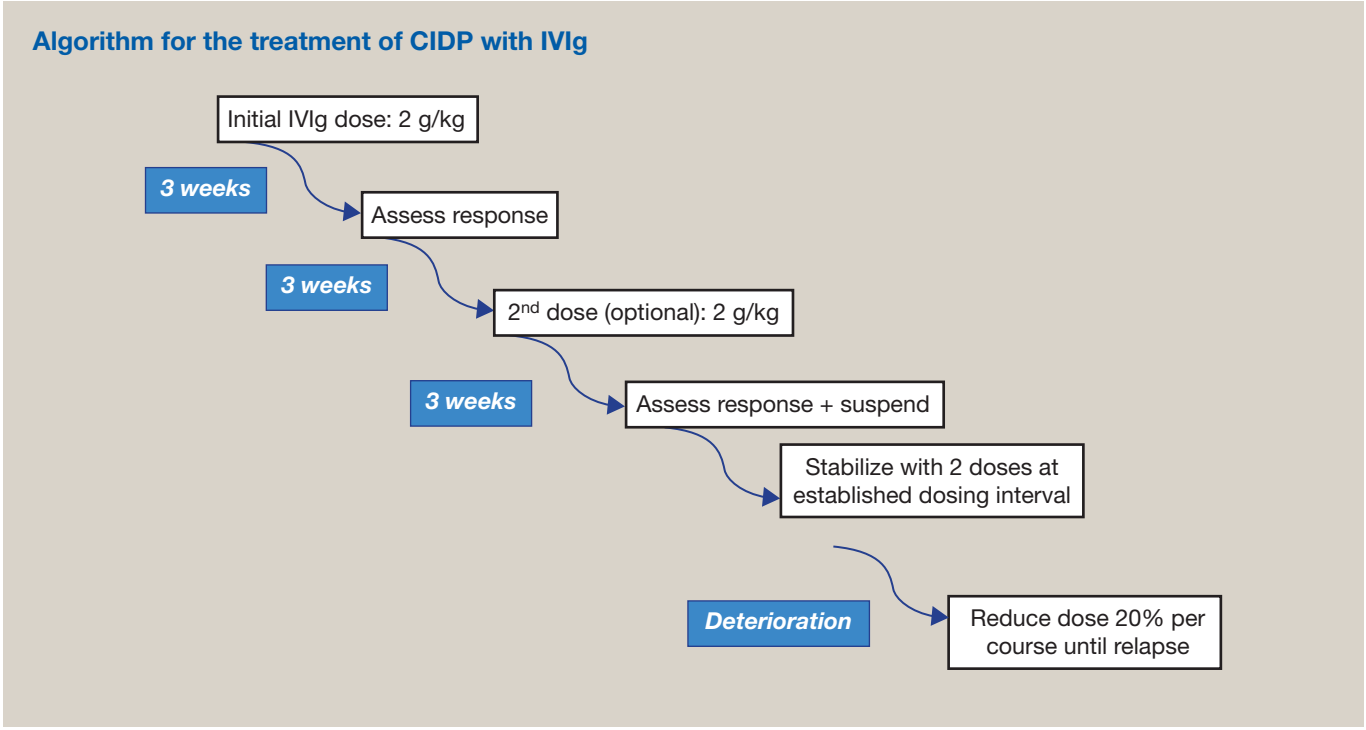

Figure 3 Adapted from Fehmi et al. (2023).[3]

motor neuropathy involving the radial, median and/or ulnar nerves. Foot drop is a presenting symptom in 20% of patients.

Investigations: NCT demonstrates conduction block at non-compressive sites but sensory conduction is unaffected. MRI may show non-specific abnormalities (T2 hyperintensity, enlargement, enhancement) in the cervical roots, brachial plexus and nerves. MMNCB can occur in conjunction with anti-ganglioside GM1 or GD1b antibodies.

Treatment: IVIg is the treatment of choice. Corticosteroids can cause deterioration, and other immunomodulatory drugs are not supported by trial data.

Paraproteinaemic neuropathies[5]

There are several paraproteinaemic neuropathies, with distinct phenotypes. If suspected, seek early consultation with a multidisciplinary team (neurology/haematology) to optimize investigation and allow appropriate management to improve patient outcomes.

Both paraproteins and neuropathy are common and frequently coexist and therefore any causative link is often uncertain. The likelihood of a causal role of a paraprotein is increased when age <55 years old, neuropathy is demyelinating or if the paraprotein is of IgM subtype.

Commonly associated monoclonal gammopathies include monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (MM), lymphoplasmacytic lymphomas and Waldenstrom macroglobulinaemia, and less frequently non-Hodgkin's lymphoma and other lymphoproliferative disorders.

Anti-MAg paraproteinaemic demyelination peripheral neuropathy with presents with an insidious, distal, sensory predominant, sensorimotor neuropathy with unsteadiness and tremor, usually in elderly men. NCT shows prolonged distal motor latencies and conduction slowing, but without other demyelinating features seen in CIDP. Although progression is typically slow, 10% can become severely disabled and wheelchair bound. About 30–50% may respond to treatment with rituximab, especially if used early.

Inherited neuropathies (See Further reading)

These are heterogenous – neuropathy can occur as the sole or predominant feature, or as part of a multisystem syndrome (Friedreich ataxia). Mutations in *PMP22* (duplication), *GJB1*, *MPZ* and *MFN2* account for the most common CMT phenotypes. If *PMP22* testing is negative, whole-genome sequencing (WGS) should be requested.

Hereditary neuropathy with liability to pressure palsies (HNPP), caused by *PMP22* deletions, presents with recurrent pressure palsies or plexopathies after minimal injury. NCT reveals a background polyneuropathy (diffuse sensory nerve conduction velocity slowing, prolonged distal motor latencies, minor slowing of motor nerve conduction velocities) and superimposed conduction block at common compression sites.

Hereditary transthyretin amyloidosis (hATTR) is an autosomal dominant disorder with variable penetrance. AL amyloidosis results from a plasma call dyscrasia (myeloma and other B cell malignancies) with production of monoclonal light chains. Both present with variable combinations of carpal tunnel syndrome, length-dependent sensorimotor neuropathy

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(small and large fibre) and autonomic involvement (70%). TTR stabilizers and gene silencing (anti-sense oligonucleotides, small interfering RNAs) are therapies for hATTR neuropathy. AL amyloid is treated with high-dose melphalan and autologous stem cell transplantation. ◆

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