Testing nerves: an overview of investigations for neuropathy

This article reviews the main investigations available to assess and diagnose patients with neuropathy. It details the most commonly used as well as investigations now becoming routine in neuromuscular centres, and those which are less widely available. Current practice and recent developments are discussed.

Peripheral neuropathy is diagnosed on clinical grounds. A number of investigations (*Table 1*) is available to characterize the location, nature and type of nerve fibre involved, and to suggest the possible underlying cause. Blood tests (*Table 2*) are routinely performed to establish the presence of an eventual underlying cause, acquired or genetic. Of the available tests, neurophysiology has the most important role. Neurophysiology consists of nerve conduction studies and needle electromyography. Small fibre neuropathies are not picked up by routine neurophysiological tests.

Quantitative sensory testing, available in some laboratories, is helpful to diagnose small fibre neuropathy which can also be identified by skin biopsy and determination of the intraepidermal nerve fibre density. A very promising technique is corneal confocal microscopy which may in future represent an easy and non-invasive method of diagnosing small fibre neuropathy. Autonomic neuropathy is tested in specialized laboratories looking at sudomotor, cardiovascular and sometimes pupillary functions.

Nerve biopsy has previously been widely used although in more recent years this has changed with better use of neurophysiology, advent of genetics and availability of more exhaustive immunological tests, as well as improved knowledge of the potential aetiologies. Nerve imaging is developing fast, both magnetic resonance and also ultrasonography. The routine practical utility of these techniques in day-to-day clinical practice remains to be confirmed, although magnetic resonance neurography is now used more widely. This article provides an overview of current investigations for neuropathy, older and newer, proven as well as promising. Routine blood work-up for acquired neuropathy, immunological studies and genetic studies is briefly covered. CSF study, used in several clinical circumstances in the setting of neuropathy, is not discussed.

Table 1. Common investigations for neuropathy

Blood investigations	
Neurophysiology	■ Nerve conduction studies ■ Electromyography
Quantitative sensory testing	
Autonomic testing	
Skin biopsy	
Confocal corneal microscopy	
Nerve imaging	■ Ultrasonography ■ Magnetic resonance neurography
Nerve biopsy	

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Investigation techniques for clinically suspected neuropathy

Neurophysiology

Nerve conduction studies and electromyography are helpful in the overwhelming majority of neuropathic disorders (*Table 3*), including entrapment syndromes (such as carpal tunnel syndrome and ulnar compression at the elbow or wrist), large fibre sensory axonal neuropathies (as in the early stage of diabetic neuropathy), sensory and motor axonal neuropathy (as in later stage diabetic neuropathy), mononeuritis multiplex (as in vasculitic neuropathy), acquired demyelinating neuropathy (as in Guillain–Barré syndrome or chronic inflammatory demyelinating polyneuropathy), genetic demyelinating neuropathy (such as Charcot–Marie–Tooth disease type 1A), and conduction block neuropathy (as in multifocal motor neuropathy). Nerve conduction studies and electromyography may also help distinguish neuropathy from radiculopathies, plexopathies or from anterior horn cell disease.

Table 2. Blood investigations and relevant investigations for neuropathy

Routine first-line investigations	Full blood count Renal and liver function tests and gamma glutamyltransferase Thyroid function tests Serum cholesterol, triglycerides Serum calcium, phosphate Serum fasting glucose Glycated haemoglobin $A1_C$
Additional investigations	
Infective screening	HIV Syphilis Lyme serology If suspect Guillain–Barré syndrome: ■ *Campylobacter jejuni* serology ■ Hepatitis A, B, C and E ■ *Haemophilus influenzae* ■ *Mycoplasma pneumoniae* ■ Epstein–Barr virus, cytomegalovirus
Nutrition	Serum folate level Serum vitamin B_1, B_6 and B_{12} level and metabolites (methylmalonic acid and fasting homocysteine)
Vasculitis screening	Erythrocyte sedimentation rate, C-reactive protein, anti-neutrophil cytoplasmic antibody, extract nuclear antigens, antinuclear antibodies, hepatitis B and C, cryoglobulins
Malignancy screen	Anti-neuronal antibody screen
Other relevant investigations	Serum electrophoresis and immunofixation Serum angiotensin-converting enzyme level Anti-ganglioside antibody
Additional investigations	Chest X-ray Lumbar puncture Computed tomography of thorax, abdomen and pelvis Whole body positron emission tomography scan
Genetic screening	For different Charcot–Marie–Tooth disease subtypes

Table 3. Common conditions diagnosed with nerve conduction studies and electromyography

Nerve conduction study	Entrapment syndromes	■ Carpal tunnel syndrome ■ Ulnar compression at elbow or wrist
	Sensory axonal neuropathies	Early stage diabetic neuropathy
	Sensory and motor axonal neuropathy	Later stage diabetic neuropathy
	Mononeuritis multiplex	Vasculitis neuropathy
	Acquired demyelinating neuropathy	■ Guillain–Barré syndrome ■ Chronic inflammatory demyelinating polyneuropathy
	Genetic demyelinating neuropathy	Charcot–Marie–Tooth disease 1A
	Conduction block neuropathy	Multifocal motor neuropathy
Nerve conduction study and electromyography	Distinguish neuropathy from radiculopathies, plexopathies and anterior horn cell disease	

Table 4. Common parameters measured during nerve conduction study or electromyography

Type of study		Parameters measured
Nerve conduction study	Motor nerve conduction studies	■ Compound muscle action potential ■ Distal motor latency ■ Motor nerve conduction velocity ■ Temporal dispersion ■ Conduction block
	Sensory nerve conduction studies	■ Sensory nerve action potential ■ Sensory conduction velocity
	F-wave	Minimum latency
Electromyography	Insertional activity	
	Spontaneous activity	Fibrillation potentials, fasciculations, positive sharp waves and complex repetitive discharge
	Motor unit action potential	Recruitment, duration, amplitude and morphology

Nerve conduction studies

In nerve conduction studies, superficial peripheral nerves are electrically stimulated using surface electrodes. The elicited sensory or motor responses are detected with standard percutaneous recording electrodes placed distally over the target muscles (Preston and Shapiro, 2013).

Nerve conduction studies analyse three main types of peripheral nerves responses: motor, sensory and F-waves (*Tables 4* and *5*).

Motor nerve conduction studies

Motor potentials are recorded as compound muscle action potential (*Figure 1*). In neuropathy, reduction in the amplitude of the compound muscle action potential reflects loss of motor nerve fibres as a result of axonal loss. Other quantifiable parameters include distal motor latency (or time taken for the impulse to reach target muscle fibres recorded from stimulation point) and motor nerve conduction velocity (calculated by measuring latencies of response from two stimulation points and the distance separating them).

Table 5. Example of normative values of common nerves studied in nerve conduction study (used in the authors' laboratory)

		Latency (ms)	Amplitude*	Conduction velocity	F-wave latency
Sensory nerve action potential	Median	-	10 µV	50 m/sec	-
	Ulnar	-	10 µV	50 m/sec	-
	Radial	-	15 µV	50 m/sec	-
	Sural	-	5 µV	40 m/sec	-
Compound muscle action potential	Ulnar	3.3 ms	4 mV	48 m/sec	31 ms
	Median	4.0 ms	5 mV	48 m/sec	30 ms
	Peroneal	6.5 ms	1.5 mV	44 m/sec	55 ms
	Tibial	6.1 ms	3 mV	44 m/sec	55 ms

**Amplitude is orthodromic for sensory nerve action potential.*

In a primary demyelinating process, distal motor latency is prolonged and motor nerve conduction velocity is reduced. Proximal compound muscle action potential durations are compared to distal compound muscle action potential durations to assess for temporal dispersion, which occurs as differential conduction slowing affects different fibres. Eventually, conduction will fail in a proportion of the fibres, leading to conduction block, defined by a significant reduction in the amplitude or area of the proximal compound muscle action potential. Both temporal dispersion and conduction block are seen typically in acquired demyelinating neuropathies such as Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy or multifocal motor neuropathy, but are not expected in genetic neuropathies such as Charcot–Marie–Tooth disease type 1A.

Sensory nerve conduction studies

Sensory responses are recorded as a sensory nerve action potential (*Figure 2*). Sensory responses can be recorded from either direction of travel of the electrical impulses: orthodromic (same direction as electrical impulses from distal to proximal) and antidromic (opposite direction). Reduced sensory nerve action potential amplitude indicates axonal loss of sensory nerve fibres. The pattern of sensory abnormalities may be helpful to distinguish axonal from demyelinating disease (Bromberg and Albers, 1993; Rajabally and Narasimhan, 2007). In sensory studies, velocities can be measured by dividing the distance travelled by the onset latency. However, although specific, sensory velocity slowing is a poorly sensitive marker of demyelinating neuropathy (Bragg and Benatar, 2008).

F-waves

F-waves are elicited by stimulation of a motor nerve distally and measured for their minimum latency, representing the conduction time along the motor pathways from

Figure 1. **a.** Median nerve motor study with **(b)** wrist stimulation and abductor pollicis brevis recording.

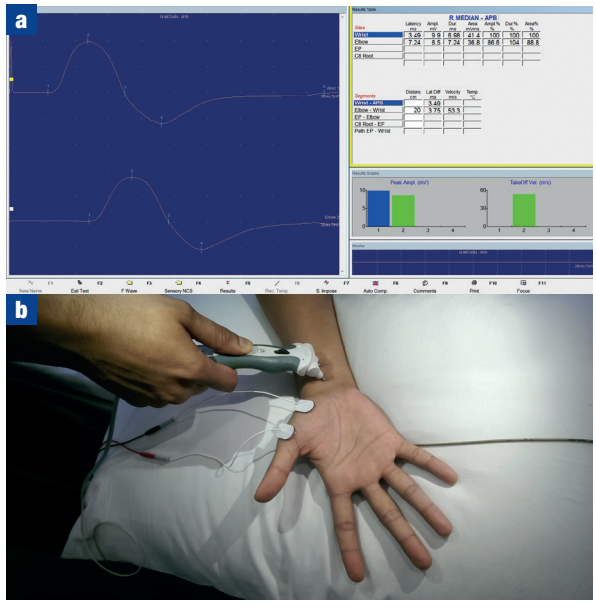
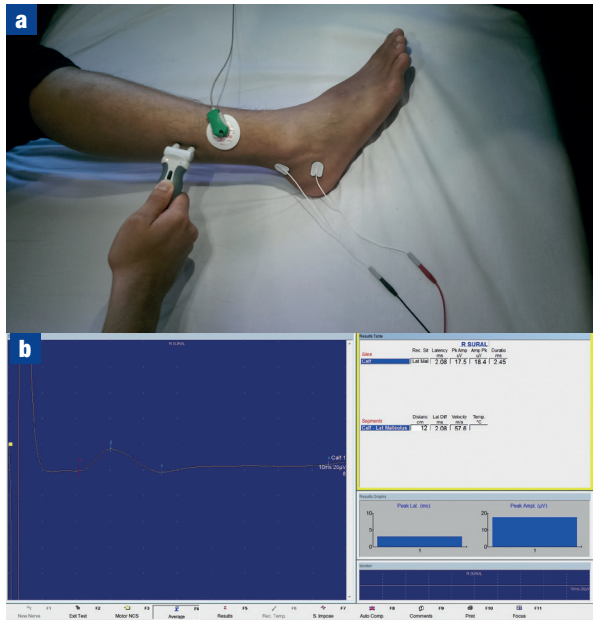


Figure 2. **a.** Antidromic sural sensory conduction study. **b.** Recorded sural sensory nerve action potential



stimulation point up to the spinal cord (anterior horns) where another potential (F response) is generated and travels back down to the target muscle. They are useful in evaluating demyelinating root and nerve disorders, such as in the acute inflammatory demyelinating polyradiculoneuropathy form of Guillain–Barré syndrome (Hadden et al, 1998), or chronic inflammatory demyelinating polyneuropathy (Rajabally and Varanasi, 2013), as demyelination or conduction block may occur initially in the proximal segment of the nerves. However, they are also useful when absent to diagnose axonal Guillain–Barré syndrome (Rajabally et al, 2015). F-waves have also been shown, when minimally prolonged, to be

the earliest sign of diabetic polyneuropathy (Andersen et al, 1997) as well as being helpful in diagnosis of axonal neuropathy of any cause (Rajabally et al, 2009).

Electromyography

Electromyography records electrical signals generated from a motor unit, termed the motor unit action potential. The motor unit comprises all muscle fibres innervated by a single motor nerve fibre. Recording is done by a needle inserted into the relevant muscles and turned into an electromyography signal.

For evaluation of peripheral neuropathy, electromyography may follow nerve conduction studies to detect and characterize axonal motor neuropathies. Electromyography records insertional and spontaneous muscle activities, i.e. occurring at rest, as well as changes in characteristic of motor unit action potentials, i.e. recruitment, duration, amplitude and morphology during voluntary contraction. In neurogenic conditions, abnormal spontaneous activities may be seen in the form of fibrillation potentials, fasciculations, positive sharp waves and complex repetitive discharge. These may usually only be expected in distal muscles in a length-dependent neuropathy. Electromyography also involves evaluation of motor unit action potentials. The patient is asked to gradually contract the sampled muscle with increasing force to increase both the frequency and number of motor unit action potentials, and characteristics (size, duration and phases) and firing patterns (recruitment) are determined. In chronic neuropathy, motor unit action potentials are larger and longer than normal and demonstrate polyphasia.

Quantitative sensory testing

Small fibre neuropathy is a disorder caused by structural injury to the thinly myelinated Aδ-fibres and unmyelinated C-fibres, resulting in neuropathic pain and autonomic symptoms. Both groups of fibres are free nerve endings in the epidermis (Hoeijmakers et al, 2012).

Aδ-fibres are responsible for cold and nociceptive input while C-fibres are responsible for detecting warm sense. Aδ-fibres are also involved in preganglionic sympathetic and parasympathetic function, whereas C-fibres are involved in postganglionic autonomic functions. Diagnosis of small fibre neuropathy can be challenging as it is not evaluated by conventional nerve conduction studies which primarily assess only large myelinated fibres. In small fibre neuropathy, pain and positive sensory symptoms are present, objective sensory findings may be detectable or not and routine nerve conduction studies are normal as nerve conduction studies cannot detect changes in electrical potentials of small fibres.

Small fibre function is not evaluated by conventional nerve conduction studies. In small fibre neuropathy, pain and positive sensory symptoms are present, objective sensory findings may be detectable or not, and routine nerve conduction studies are normal. Assessment of small fibre neuropathy therefore requires other diagnostic techniques. Quantitative sensory testing has been designed for this purpose and works by allowing delivery of quantifiable and reproducible sensory stimuli. The method allows the clinician to rate the result by defining sensory thresholds and establishing normal values. Although also able to evaluate large fibre neuropathy, in particular with vibration thresholds, quantitative sensory testing is mainly useful for diagnosis of small fibre neuropathy. In small fibre neuropathy, vibratory thresholds are normal although abnormalities are observed on cooling, warm or heat–pain detection (Jamal et al, 1987). The sensitivity of quantitative sensory testing to diagnose small fibre neuropathy has been reported as varying between 72% and 100%. However, more recent studies have suggested that quantitative sensory testing has a low diagnostic efficiency compared to skin biopsy or even clinical assessment alone (Devigli et al, 2008).

Autonomic testing

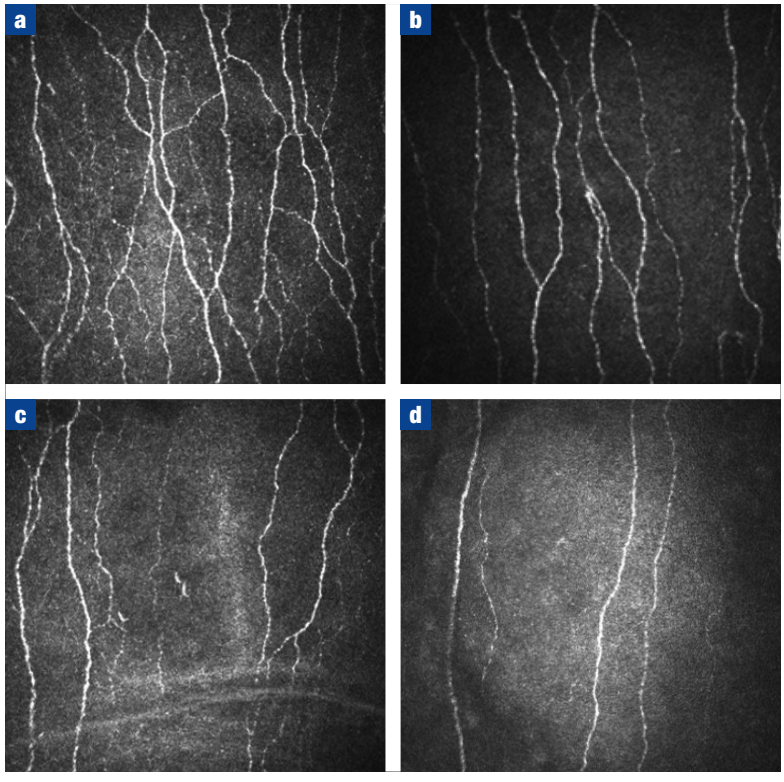
A standardized battery of tests is used in practice to assess sympathetic and parasympathetic functions. Cardiac parasympathetic function is determined through cardiac response to breathing, cardiac sympathetic and parasympathetic functions by the Valsava manoeuvre. Tilt-table testing, or blood pressure response to standing, are used to study vasomotor response (Chémali and Chelimski, 2014). The quantitative reflex axon sweating test, requiring special equipment and a time-consuming procedure, assesses post-ganglionic sympathetic cholinergic sudomotor function. The sympathetic skin response, which can be easily performed during routine nerve conduction studies, can be considered a test of sudomotor function of peripheral sympathetic nerves. In combination, abnormalities of the various tests may allow a diagnosis of autonomic dysfunction, and autonomic neuropathy in particular.

Skin biopsy

Skin biopsy is used in the diagnosis of small fibre neuropathy, using immunological marking to enable visualization of nerve fibres in the epidermis. Skin biopsy can reliably demonstrate the loss of intraepidermal nerve fibre density in small fibre neuropathy and the technique has shown progression over the disease course and has predicted progression to large fibre involvement (Lauria, 2005; Gibbons et al, 2006). Furthermore correlations have been demonstrated between intraepidermal nerve fibre density loss and risk of neuropathic pain (Sommer and Lauria, 2007).

Skin samples are taken at the distal leg by 3 or 4 mm punch biopsy after giving local anaesthesia. This is the preferred site for length-dependent small fibre neuropathy, although biopsies may also be performed at thigh level. Multiple site biopsy may increase diagnostic yield. Fibres are counted after samples are immunoassayed and counts compared to available age-corrected normal values.

Figure 3. Confocal corneal microscopy demonstrating nerve fibre density. **a.** Healthy subject. **b.** Diabetic patient without neuropathy. **c.** Diabetic patient with moderate neuropathy. **d.** Diabetic patient with severe neuropathy.



Confocal corneal microscopy

Confocal corneal microscopy is a non-invasive technique allowing scanning of the cornea from its centre in order to evaluate different parameters including the corneal nerve fibre density, corneal nerve fibre length, corneal nerve branch density and corneal fibre tortuosity (Quattrini et al, 2007). These measurements allow assessment of the integrity of small nerve fibres which are significantly affected compared to normal controls in subjects with diabetes (*Figure 3*), impaired glucose tolerance, idiopathic small fibre neuropathy as well as Fabry's disease, chemotherapy-related neuropathy and chronic inflammatory demyelinating polyneuropathy (Quattrini et al, 2007; Tavakoli et al, 2010; Asghar et al, 2014; Schneider et al, 2014; Ferdousi et al, 2015).

Corneal confocal microscopy appears as reliable as skin biopsy in evaluation of small fibre neuropathy in diabetics (Chen et al, 2015) and the same may be true for all forms of small fibre neuropathy, although further studies are needed. Corneal confocal microscopy may also be a better marker of nerve regeneration with treatment than skin biopsy or quantitative sensory testing, as demonstrated after pancreas and kidney transplants (Tavakoli et al, 2013). Corneal confocal microscopy appears an attractive, non-invasive technique to evaluate small fibre neuropathy although this is currently limited by its availability.

Nerve biopsy

Nerve biopsy is used in cases where specific neuropathy subtypes are suspected which may require specific treatment. This situation is uncommon in clinical practice. The distal sural nerve, located on the lateral aspect of the ankle, is most commonly sampled. This requires a superficial incision and leaves the patient with a small area of sensory loss, although rarely patients may develop persistent painful paraesthesiae in the territory of the biopsied nerve. Other less commonly biopsied nerves include the superficial peroneal and radial nerves. Histological evaluation assesses density of large myelinated and unmyelinated fibres. Electron microscopy provides detailed information on the myelin sheath, axon and cells, and teased-fibre preparations evaluate demyelination. Nerve biopsy allows detection of the presence of axonal degeneration, regeneration, and segmental demyelination and remyelination (Miles and Cohen, 2014). The presence of inflammatory cells may be detected perivascularly, as seen in patients with vasculitis. The most common indications are suspected vasculitic neuropathy in the setting of mononeuritis multiplex or suspected amyloid polyneuropathy. The usefulness of nerve biopsy in inflammatory demyelinating polyneuropathy is not established (Molenaar et al, 1998), although it may be helpful in selected cases (Vallat et al, 2003).

Nerve imaging

Ultrasonography

Peripheral nerve ultrasound is an emerging technique in the diagnosis of peripheral neuropathy. Although initially limited to entrapment syndromes (Cartwright and Walker, 2013), distinctive findings have been reported in a number of diffuse polyneuropathy subtypes, including inflammatory and metabolic (Beekman et al, 2005; Riazi et al, 2012; Kerasnoudis et al, 2013; Zaidman and Pestronk, 2014; Lucchetta et al, 2015). There have been several reports of use of ultrasound in hereditary neuropathy (Beekman and Visser, 2002; Schreiber et al, 2013), although there are discrepancies such as in patients with Charcot–Marie–Tooth disease type 1A, who were found with or without thickened sural nerves in different studies (Pazzaglia et al, 2013; Noto et al, 2015). Ultrasound has the advantage of being non-invasive.

The main feature of pathological significance in nerve ultrasound is enlargement as measured by the cross-sectional area. Ultrasound has been hypothesized as being useful in distinguishing neuropathies. Some studies have postulated differences in the distribution of enlargement areas in patients with different neuropathies, with for instance uniform enlargement in Charcot–Marie–Tooth disease type 1A as opposed to variable enlargement in chronic inflammatory demyelinating polyneuropathy, although that not all forms of Charcot–Marie–Tooth disease are demyelinating makes the usefulness of this doubtful (Gallardo et al, 2015), in particular as clinical differentiation is generally straightforward. Diagnosis of entrapments is also postulated when electrophysiology is insufficient although the practical benefit of this is not established. More recent literature has suggested a role in predicting outcome in acute presentations of inflammatory

neuropathy (Kerasnoudis et al, 2015), but this appears debatable in view of the study methodologies used (Rajabally and Hiew, 2015). The practical usefulness of ultrasound in diagnosis and follow up remains to be demonstrated, and its correlation with neurophysiology and functional disability is emerging (Zaidman and Pestronk, 2014) but its utility in daily clinical practice remains uncertain. The inter-rater reliability of the technique requires further evaluation.

Magnetic resonance neurography

The first reports of magnetic resonance imaging in patients with chronic inflammatory demyelinating polyneuropathy demonstrated enlargement of the cauda equina and nerve roots (Schady et al, 1996; Mizuno et al, 1998). Gadolinium enhancement was described in about 70% of cases (Midroni et al, 1999). Cervical root and brachial plexus abnormalities have also been reported in chronic inflammatory demyelinating polyneuropathy (Duggins et al, 1999), as well as specifically in Lewis–Sumner syndrome, a regional variant of chronic inflammatory demyelinating polyneuropathy (Rajabally et al, 2014) (*Figure 4*). Magnetic resonance neurography using coronal maximum intensity projection reformations of STIR sequences is highly sensitive in detecting abnormalities in chronic inflammatory demyelinating polyneuropathy (Shibuya et al, 2015).

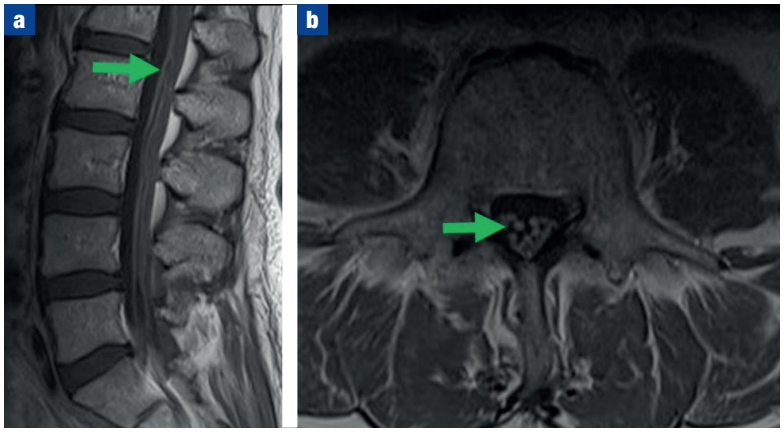
Another magnetic resonance imaging technique that is promising in the assessment of patients with chronic inflammatory demyelinating polyneuropathy is diffusion tensor imaging which measures the restricted diffusion of water in tissue, allowing visualization of nerve tracts. A recent publication by Markvardsen and co-workers (2016) demonstrated that the sciatic and tibial nerves of patients with chronic inflammatory demyelinating polyneuropathy had different diffusion tensor imaging values than the control group. The authors concluded that diffusion tensor imaging of sciatic nerves seems promising in differentiating patients with chronic inflammatory demyelinating polyneuropathy from controls. However, further work is required to determine the added value of diffusion tensor imaging in these patients.

Current recommendations for chronic inflammatory demyelinating polyneuropathy now include magnetic resonance neurography as an additional supportive criterion for diagnosis (Van den Bergh et al, 2010). Magnetic resonance neurography could be a useful diagnostic addition in cases where neurophysiology is uncertain or equivocal, such as in chronic inflammatory demyelinating polyneuropathy not fulfilling electrodiagnostic criteria or multifocal motor neuropathy not demonstrating conduction block on extensive nerve conduction studies.

Conclusions

Although the diagnosis of neuropathy remains a clinical one, assessment is now considerably improved and enhanced with several investigation techniques available.

Figure 4. **a.** Sagittal and **(b)** axial contrast-enhanced T1-weighted magnetic resonance imaging examination of the lumbar spine demonstrates diffuse thickening and enhancement of the lumbosacral nerve roots and cauda equina (arrows) in a patient with chronic inflammatory demyelinating polyneuropathy.



Neurophysiology undoubtedly remains the most helpful in day-to-day practice, potentially bringing rapid and very useful confirmatory and/or clinically unsuspected information on the location, extent and severity of neuropathic involvement, using widely available basic equipment. It also provides answers as to the fibre type involved and the suggested mechanism, indicating, when correctly interpreted, the predominance of axonal damage or of peripheral nerve demyelination. This is of considerable direct benefit in terms of suggesting potential underlying causes and helps further management and consideration of therapies as in chronic inflammatory neuropathies.

Limitations of neurophysiology in assessing peripheral neuropathy are often poorly understood or disregarded; an example is its relatively low sensitivity in confirming large fibre sensory axonal neuropathy as well its inability to study small fibre neuropathy. For small fibre neuropathy, skin biopsy and quantitative sensory testing are useful to try and reach a confirmatory diagnosis instead of making this purely on clinical grounds which is insufficient and unsatisfactory. Corneal confocal microscopy is a very interesting option for the future, particularly as it is non-invasive. The usefulness of nerve biopsy has greatly diminished in recent years although the procedure is still useful in specific circumstances. It is more likely to be meaningful and helpful when performed and interpreted in sub-specialist units with high levels of experience and expertise. Autonomic testing can be very useful although unfortunately this is often not widely available. Determining the presence of autonomic neuropathy may be diagnostically very helpful in reaching the ultimate diagnosis. Imaging peripheral nerves is a significant advance in diagnostic methods, although definite benefits are uncertain in the practical clinical setting, particularly for ultrasound.

The evaluation of patients with neuropathy is now considerably helped by the above-mentioned techniques. However, these all require expertise and clinical correlation

KEY POINTS

- Neuropathy is diagnosed by clinical examination but a number of investigations are needed to determine subtype and possible cause.
- The most commonly available useful test for neuropathy is neurophysiology.
- Targeted blood investigations may reveal the underlying cause in a proportion of cases.
- Less commonly available tests such as quantitative sensory testing, autonomic testing, skin biopsy and nerve biopsy, may occasionally be very helpful in the diagnostic process.
- Nerve imaging by ultrasonography, magnetic resonance neurography and, more recently, confocal corneal microscopy, represent promising non-invasive investigation techniques.

in their performing and interpretation to avoid irrelevant over-diagnosis as well as under-diagnosis resulting from non-committal reports. Both may lead to inappropriate, unnecessary, sometimes unpleasant and expensive additional tests or, worse still, to patients receiving the wrong treatment or being denied adequate therapy. **BJHM**

Figure 3 *is reproduced courtesy of Professor Rayaz Malik.*
Conflict of interest: none.

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