REVIEW

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Peripheral neuropathy: pattern recognition for the pragmatist

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Long lists of causes of peripheral neuropathy make peripheral nerve disease a dry and uninspiring subject. A simple scheme based on the answers to just six questions should enable the clinician to recognise characteristic patterns, investigate relevant subgroups appropriately, and identify treatable disorders quickly: which systems are involved? What is the distribution of weakness? What is the nature of the sensory involvement? Is there any evidence of upper motor neuron involvement? What is the temporal evolution? Is there any evidence for a hereditary neuropathy? Standard screening investigations suffice for the common length dependent axonal neuropathies while complex presentations need more detailed investigations targeted to their clinical phenotype.

INTRODUCTION

Peripheral neuropathy is incredibly common, and like most neurological disorders can be dull and uninspiring if reduced to its most simplistic. In most general neurology clinics, an elderly person with tingling feet prompts a series of 'standard investigations' (more or which later) which are usually normal, and a lengthy wait for nerve conduction studies, allowing the neurologist to move on to the next recipient of his or her clinical wisdom. Such assessments, while 'appropriate' in many clinical encounters, do nothing to inspire interest in our students or trainees, and their repetitive nature unfortunately often clouds our ability to recognise characteristic presentations and make useful diagnoses. Furthermore, although complexity and variety may well garner our interest as clinicians, the long list of 'causes of peripheral neuropathy' in our minds somehow makes the assessment and management of neuropathy a process of merely ensuring that a checklist has been completed.

Another problem with peripheral neuropathy is that its teaching often gets caught up in pathological or neurophysiological terminology which either frightens (or bores) the general neurologist, who inevitably seeks something more accessible. But there are easily recognisable clinical patterns in neuropathy, just as there are in stroke or epilepsy, and recognising and using them makes the practice of assessing peripheral neuropathy much more rewarding. It leads to a targeted approach to investigation, which makes clinicians feel that they are serving some sort of purpose, and allows him or her to identify those neuropathies that might have a serious underlying cause or respond to treatment.

SIX QUESTIONS TO BE ANSWERED DURING THE DIAGNOSTIC ASSESSMENT

This 'pragmatic pattern recognition' needs a framework, which is easy to remember and inclusive, and is best achieved by considering six key questions[1]:

1. Which systems are involved? Motor, sensory, autonomic, combinations

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2. What is the distribution of weakness? Distal versus proximal and distal; focal/asymmetrical versus symmetrical
3. What is the nature of the sensory involvement? Pain/burning or proprioceptive loss
4. Is there any evidence of upper motor neuron involvement?
5. What is the temporal evolution? Acute, subacute, chronic
6. Is there any evidence for a hereditary neuropathy? Family history, skeletal deformity, lack of sensory symptoms despite sensory signs

Question 1: Which systems are involved?

This is a simple question but is central in narrowing the differential diagnosis of neuropathy. A pure motor disorder should immediately raise suspicion of motor neuron disease and lead to a hunt for the mixed upper and lower motor neuron features which characterise that disorder. Multifocal motor neuropathy characteristically causes focal upper limb weakness and (eventually) wasting (figure 1). Both motor neuron disease and multifocal motor neuropathy patients can have sensory symptoms but not clear sensory signs. Hereditary disorders can be pure motor, and myopathies can initially be misdiagnosed as neuropathic.

Prominent weakness is usually a feature of acute and chronic inflammatory demyelinating polyneuropathies, and also characterises acute porphyric neuropathy, lead intoxication and the various forms of Charcot–Marie–Tooth disease. All of these normally have sensory signs on examination although they are considerably less evident than the motor features.

If autonomic features are prominent, in the chronic situation one should think of diabetes or amyloidosis, and in the acute situation acute inflammatory demyelinating polyneuropathy (AIDP). The differential diagnosis of purely sensory disorders is aided by an assessment of the *nature* of the sensory involvement, which is addressed in question 3.

Question 2: What is the distribution of weakness?

Distal symmetrical weakness is seen in axonal 'length dependent' neuropathy (the term used for the common distal 'dying back' neuropathy affecting the feet and sometimes the hands over years), and genetic demyelinating neuropathies. It is usually a sign that the neuropathy is not amenable to treatment. There are, however, exceptions to this rule: distal symmetrical weakness can also occur in distal acquired demyelinating symmetrical (DADS) neuropathy—a subtype of chronic inflammatory demyelinating polyneuropathy (CIDP)—and rarely vasculitic neuropathies. The coexistence of sensory ataxia in DADS, and the subacute presentation with pain in vasculitic neuropathy, help distinguish these two entities.

Proximal and distal weakness is the hallmark of AIDP and CIDP, both of which are usually accompanied by areflexia. Although demyelinating neuropathies can be asymmetrical, asymmetrical weakness generally suggests radiculopathy (root), plexopathy (plexus) or mononeuropathy multiplex. Focal weakness affecting the neck or pharyngeal muscles is characteristic of motor neuron disease and myopathic/neuromuscular junction disorders although it can be a feature of demyelinating syndromes.

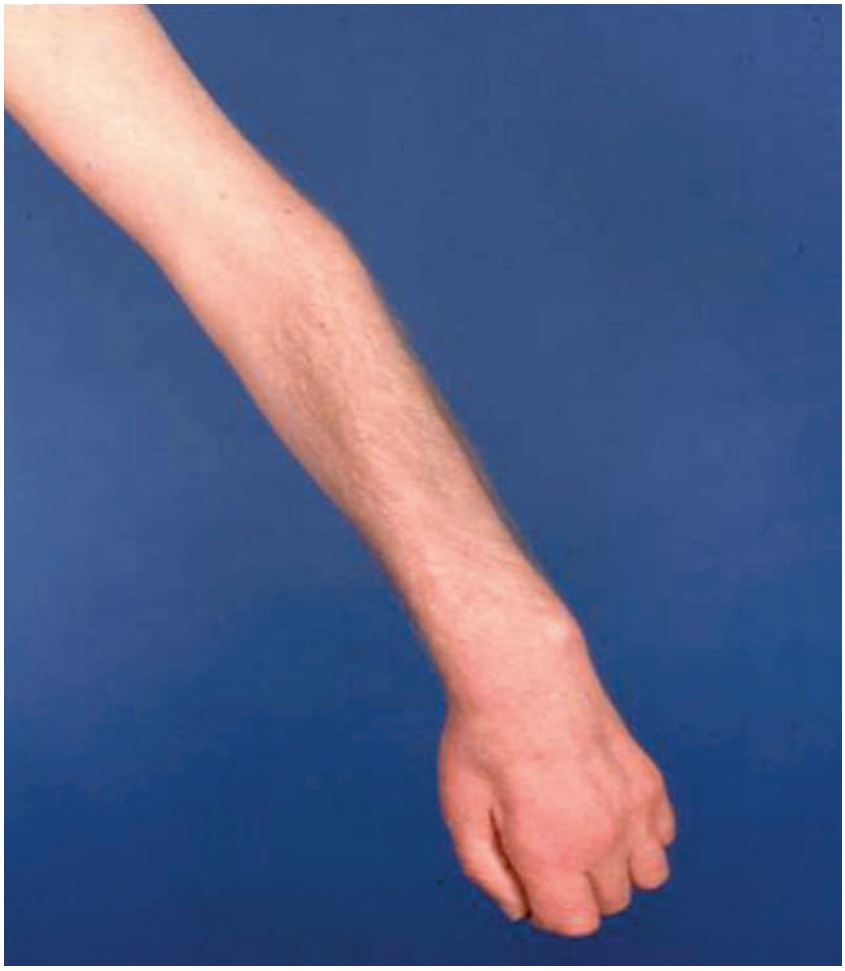

Figure 1
Wasting of the forearm and hand musculature in multifocal motor neuropathy.

The differential diagnosis of mononeuropathy multiplex is aided greatly by the neurophysiological distinction of axonal from demyelinating injury, and the causes to consider in each category are listed in table 1 (this table is necessarily an oversimplification—sometimes it can be hard to demonstrate conduction block, especially when that block is proximal (ie, at root level)).

Question 3: What is the nature of the sensory involvement?

The key features to look for here are ataxia and pain. Pain is the result of small nerve fibre involvement. Selective small fibre neuropathy is most commonly idiopathic but can be caused by impaired glucose tolerance or diabetes, amyloid (familial and primary), Fabry's disease and hereditary syndromes (hereditary sensory and autonomic neuropathies). Prominent pain is a feature of vasculitic neuropathy (usually in the context of mononeuropathy multiplex), AIDP (in the context of acute weakness), toxic neuropathies (eg, arsenic) and HIV related distal polyneuropathy.

Severe proprioceptive loss (especially if asymmetrical) is the clinical feature of sensory neuronopathy (also called sensory ganglionopathy), the best recognised cause of which is a paraneoplastic syndrome associated with anti-Hu antibodies, often due to small cell lung cancer. Sjögren's syndrome, cisplatin toxic neuropathy and pyridoxine toxicity can produce a similar clinical picture, although many cases remain 'idiopathic' despite extensive workup and careful follow-up. Generally these patients are very disabled, and if the cause is paraneoplastic usually remain so.

AIDP and IgM paraproteinaemic demyelinating neuropathies (specifically those associated with anti-GD1b antibodies) can produce the clinical picture of sensory ataxia secondary to large fibre sensory neuropathy. Hereditary (eg, Friedreich's ataxia) and mitochondrial syndromes (eg, POLG mutations causing sensory ataxic neuropathy, dysarthria and ophthalmoparesis) can lead to sensory ataxia as a result of dorsal root ganglionopathy or sensory neuropathy.

Question 4: Is there any evidence of upper motor neuron involvement?

In a pure motor disorder this would be supportive of motor neuron disease but in the setting of symmetrical sensory symptoms or signs it would suggest vitamin B12 deficiency, or the much rarer copper deficiency myeloneuropathy. Vitamin E deficiency, HIV, Friedreich's ataxia and adrenomyeloneuropathy can also produce this 'combined' system degeneration. A more common cause in general clinical practice is the coexistence of a neuropathy and an unrelated upper motor neuron problem, such

Table 1 Differential diagnosis of mononeuropathy multiplex

Axonal injury	Vasculitis (systemic or non-systemic) Diabetes mellitus Sarcoidosis Lyme disease Leprosy HIV Hepatitis C
Focal demyelination/conduction block	Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) Multifocal motor neuropathy Multiple compression neuropathies* Hereditary neuropathy with a predisposition to pressure palsy Lymphoma

*Multiple compression neuropathies are often superimposed on a background of axonal neuropathy secondary to a common cause such as alcohol or diabetes. Bilateral carpal tunnel syndrome is a common presenting feature of amyloidosis.

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as previous stroke or compressive cervical myelopathy.

Question 5: What is the temporal evolution?

Perhaps the most important and simplest observation. AIDP, vasculitis, paraneoplastic sensory neuronopathy and diabetic lumbosacral radiculoplexus neuropathy (what used to be known as diabetic amyotrophy) are acute or subacute disorders. B12 deficiency myeloneuropathy can present subacutely. CIDP (sometimes), porphyria and vasculitis (sometimes) are relapsing disorders. Everything else is chronic.

Question 6: Is there any evidence for a hereditary neuropathy?

A family history, chronic very slowly progressive distal weakness over many years associated with prominent wasting, very little in the way of sensory symptoms but sensory signs on examination and skeletal or foot deformities should all alert the clinician to this possibility. In addition, recurrent compressive mononeuropathies should raise the question of hereditary neuropathy with a predisposition to pressure palsy.

The history and examination in the assessment of neuropathy should be directed to answering these six key questions but clearly there are other features that might be detected during a thorough clinical assessment which will have major diagnostic implications. Chief among these is an assessment of exposure to toxins (specifically alcohol and neurotoxic drugs). The answers to the six questions will usually lead to a fairly narrow differential diagnosis, and a directed set of investigations.

CLINICALLY RECOGNISABLE PATTERNS

Individual patients can be 'summarised' by charting their neuropathy pattern in a simple summary box (see box). Important patterns to recognise are highlighted by each of the examples shown (A–F) although it is impossible to cover all possible clinical scenarios or the subtleties of diagnosis in each individual.

STANDARD INVESTIGATION

The key role of the neurologist assessing a patient with peripheral neuropathy is to identify (using the answers to the six questions above) those patients with clinical features that are outwith those of the common length dependent sensory or mixed motor and sensory axonal neuropathies (table 2).

If the clinical phenotype corresponds with that of length dependent sensory or mixed axonal neuropathy, 'standard screening tests' should be employed. The 'standard screen for neuropathy' is something we all hold dear, perhaps because it enables us not to think about what we are doing. Everybody's standard screen is somewhat different but what evidence there is suggests that the diagnostic yield from many of these screening tests is low and that their specificity is poor.[2] The key investigations are full blood count, renal, liver and thyroid function, B12 (with metabolites, see below), glucose (and if negative, a glucose tolerance test) and serum protein (preferably immunofixation) electrophoresis. One could argue about the advisability of a chest x ray (many of my mentors regarded this as part of a general examination, and since we never examine peoples' chests. . .) and an erythrocyte sedimentation rate as part of a standard screen but the routine testing of autoantibodies usually just leads to 'false' positive results that you do not know what to do with. And nerve conduction studies in a patient with a clinical picture of length dependant axonal neuropathy are likely to merely confirm what you already know.

B12 testing

B12 deficiency is a very well recognised cause of neuropathy but some specific clinical features (namely sudden onset, concomitant involvement of the upper and lower limbs or onset in the upper limbs and painless sensory dominant symptoms) suggest B12 deficiency neuropathy,[3] and these are at least partly explained by the fact that B12 deficiency causes both myelopathy and neuropathy.

Most general practitioners, and all neurologists, request B12 levels in all patients with peripheral neuropathy, treat it (normally parenterally) if it is 'low' (as defined by their local laboratory) and otherwise feel justified in taking the assessment no further. However, international consensus guidelines now recommend testing vitamin B12 *and* its metabolites (methylmalonic acid with or without homocysteine) in patients with distal symmetrical neuropathy.[2] This is rarely done

Box Some common peripheral neuropathy patterns. The clinical features of patterns A to F are highlighted in orange

Pattern A

1. Motor	Sensory	Autonomic	Combined
2. Distal	Proximal	Asymmetrical	Symmetrical
3. Pain		Sensory ataxia	
4. Upper motor neuron involvement		No upper motor neuron involvement	
5. Acute/subacute		Chronic	
6. Hereditary evidence		No hereditary evidence	

Symmetrical proximal and distal weakness with sensory loss is suggestive of either acute inflammatory demyelinating polyneuropathy or chronic inflammatory demyelinating polyneuropathy

Pattern B

1. Motor	Sensory	Autonomic	Combined
2. Distal	Proximal	Asymmetrical	Symmetrical
3. Pain		Sensory ataxia	
4. Upper motor neuron involvement		No upper motor neuron involvement	
5. Acute/subacute		Chronic	
6. Hereditary evidence		No hereditary evidence	

Asymmetrical distal weakness with sensory loss. Consider the causes of mononeuropathy multiplex summarised in table 1. Vasculitic neuropathy is usually painful and subacute, while hereditary neuropathy with a predisposition to pressure palsy and MADSAM (multifocal acquired demyelinating sensory and motor neuropathy) are painless and chronic

Pattern C

1. Motor	Sensory	Autonomic	Combined
2. Distal	Proximal	Asymmetrical	Symmetrical
3. Pain		Sensory ataxia	
4. Upper motor neuron involvement		No upper motor neuron involvement	
5. Acute/subacute		Chronic	
6. Hereditary evidence		No hereditary evidence	

Asymmetrical proximal and distal weakness with sensory loss suggests root or plexus pathology. Lumbosacral radiculoplexus neuropathy (often diabetic, but sometimes idiopathic) is dominated by pain, and infiltrative causes are also usually painful

Pattern D

1. Motor	Sensory	Autonomic	Combined
2. Distal	Proximal	Asymmetrical	Symmetrical
3. Pain		Sensory ataxia	
4. Upper motor neuron involvement		No upper motor neuron involvement	
5. Acute/subacute		Chronic	
6. Hereditary evidence		No hereditary evidence	

Chronic asymmetrical distal weakness (without sensory loss) should raise concerns about motor neuron disease, but is also seen in multifocal motor neuropathy

Pattern E

1. Motor	Sensory	Autonomic	Combined
2. Distal	Proximal	Asymmetrical	Symmetrical
3. Pain		Sensory ataxia	
4. Upper motor neuron involvement		No upper motor neuron involvement	
5. Acute/subacute		Chronic	
6. Hereditary evidence		No Hereditary evidence	

Symmetrical sensory ataxia with upper motor neuron signs is the clinical picture seen in B12 deficiency and its mimics (eg, copper deficiency). It can also be seen in hereditary disorders such as Friedreich's ataxia

Continued

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Box 1 Continued

Pattern F

1. Motor	Sensory	Autonomic	Combined
2. Distal	Proximal	Asymmetrical	Symmetrical
3. Pain		Sensory ataxia	
4. Upper motor neuron involvement		No upper motor neuron involvement	
5. Acute/subacute		Chronic	
6. Hereditary evidence		No hereditary evidence	

(Asymmetrical) proprioceptive sensory loss without weakness is caused by sensory neuronopathy (ganglionopathy) which may be paraneoplastic, or may occur in Sjogren's syndrome, and generally presents in an acute or subacute fashion. More symmetrical forms may be related to vitamin B6 toxicity or chemotherapeutic agents, or may remain 'idiopathic'

in standard UK practice but there are data to suggest that serum B12 levels (with or without assessment of mean cell volume) are not sufficiently sensitive to diagnose deficiency and that metabolite testing improves diagnostic accuracy, revealing B12 deficiency in 5–10% of those with a B12 level in the 'low normal' range of 200–500 pg/dl.[4 5] In a study examining patients with B12 deficiency neuropathy, 44% (12 of 27) of patients had B12 deficiency based on the finding of raised metabolites alone. In this group of 12 patients, six (50%) had pernicious anaemia (defined by positive intrinsic factor antibodies), which is 25 times higher than the expected frequency in an age matched control population.[3]

At this stage it seems reasonable to check B12 metabolites in neuropathy patients with low normal B12 levels or a raised mean cell volume, and in all neuropathy patients with clinical features that specifically suggest that B12 deficiency may be the problem. It should be noted that genetic conditions, renal failure, hypothyroidism and hypovolaemia can all raise homocysteine and methylmalonic acid levels, and that pyridoxine (B6) and folate deficiency can raise homocysteine levels.

Glucose

It is important to recognise that diabetes is not an 'all or nothing' disorder; it is preceded by impaired glucose tolerance. The literature suggests that impaired glucose tolerance is associated with axonal length dependant neuropathy, and is likely to be found in around 25% of patients with idiopathic neuropathy (frank diabetes explaining a further 25%).[6–8] Pain is a very common feature of both 'prediabetic' and diabetic neuropathy.

Table 2 Features of cryptogenic (or idiopathic) length dependent sensory or mixed motor and sensory neuropathy

Symptoms	Begins after the age of 50 years Starts in toes or feet Symmetrical Slowly progressive
Physical findings	Symmetrical Length dependent No significant sensory ataxia May include weakness, but this is mild and distal
Nerve conduction studies/EMG (if done)	May be normal Abnormalities are mainly axonal Abnormalities are symmetrical

While evidence that dietary intervention (to improve glucose tolerance) affects the natural history of neuropathy is proving slow to emerge, there is good evidence that lifestyle modification in patients with impaired glucose tolerance can prevent progression to diabetes.[9] Therefore, I recommend not just a fasting blood glucose but also glucose tolerance testing (and subsequent lifestyle modification if impaired glucose tolerance is detected) in all patients with idiopathic axonal length dependent neuropathy.

Serum protein electrophoresis

Monoclonal gammopathies are more common in patients with peripheral neuropathy than in the general population. In one study of 279 patents with neuropathy of otherwise unknown aetiology seen at a referral centre, 10% had a monoclonal gammopathy, which is 6–10 times the proportion in the general population.[10]

IgM paraproteins are more strongly associated with peripheral neuropathy than IgG or IgA paraproteins,[11] and while distal axonal neuropathies are the most common type of neuropathy to coexist with paraproteins, this is probably because they are by far the commonest type of neuropathy in the population, rather than because paraproteins commonly cause that type of neuropathy. Demyelinating neuropathies are more likely to be causally related to the paraprotein and are more likely to respond to immunotherapies.[12]

It should also be remembered that IgM paraproteins may be associated with specific autoantibody activity—antimyelin associated glycoprotein antibody is commonly associated with the DADS phenotype (see above) and anti-Gd1b antibody is associated with a sensory ataxic neuropathy—and with cryoglobulinaemia, which in turn causes vasculitic-type neuropathies and painful sensory neuropathies.[13] IgG paraproteins are associated with myeloma, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes) and with amyloidosis.

If a paraprotein is identified, evaluation for associated disorders (haematological malignancies, lymphoma and amyloidosis) is generally best accomplished in conjunction with a haematologist. Serum protein immunofixation electrophoresis is more sensitive than serum protein electrophoresis, especially for detecting small or non-malignant monoclonal gammopathies,[14] and urine should be sent for Bence-Jones protein if a paraprotein is detected.

ADDITIONAL INVESTIGATIONS

Patients with complex presentations suggesting acquired disease should be investigated in more detail, according to their clinical features (table 3):

Table 3 Additional testing for neuropathy, as guided by clinical pattern

Clinical feature	Potential causes	Potentially useful tests
Proximal weakness	CIDP	LP
Acute or subacute onset	CIDP	LP
	Paraneoplastic	Paraneoplastic antibodies, CT, PET
	Vitamin B12 deficiency	Vitamin B12, MMA, Hcy
Asymmetry	Vasculitis	ANA, RF, ESR, ANCA, cryoglobulins, nerve/muscle biopsy
	HNPP	PMP22 deletion
	MADSAM/MMN	LP, anti-GM1 antibody
	Paraneoplastic	Paraneoplastic antibodies, CT, PET
	Diabetic lumbosacral radiculoplexopathy	Glucose studies
Sensory ataxia	Paraneoplastic	Paraneoplastic antibodies, CT, PET
	Sjögren's syndrome	ANA, ESR, anti-Ro, anti-La, lip biopsy
	DADS neuropathy	Electrophoresis, anti-MAG antibodies
	Chronic immune sensory neuropathies	LP, electrophoresis, antiglycolipid antibodies (GD1b)
	Tabes dorsalis	Syphilis serology
Small fibre predominant, autonomic neuropathy, cardiac/renal disease	Diabetes	Glucose studies
	Amyloidosis	Protein electrophoresis, genetic testing, skin/nerve/abdominal fat biopsy
Myelopathy and neuropathy	Vitamin B12 deficiency	Vitamin B12, MMA, Hcy
	Copper deficiency	Copper, zinc

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CIDP, chronic inflammatory demyelinating polyneuropathy; DADS, distal acquired demyelinating symmetric; ESR, erythrocyte sedimentation rate; Hcy, homocysteine; HNPP, hereditary neuropathy with a predisposition to pressure palsy; LP, lumbar puncture; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MAG, myelin associated glycoprotein; MMA, methylmalonic acid; MMN, multifocal motor neuropathy; PET, positron emission tomography; RF, rheumatoid factor.

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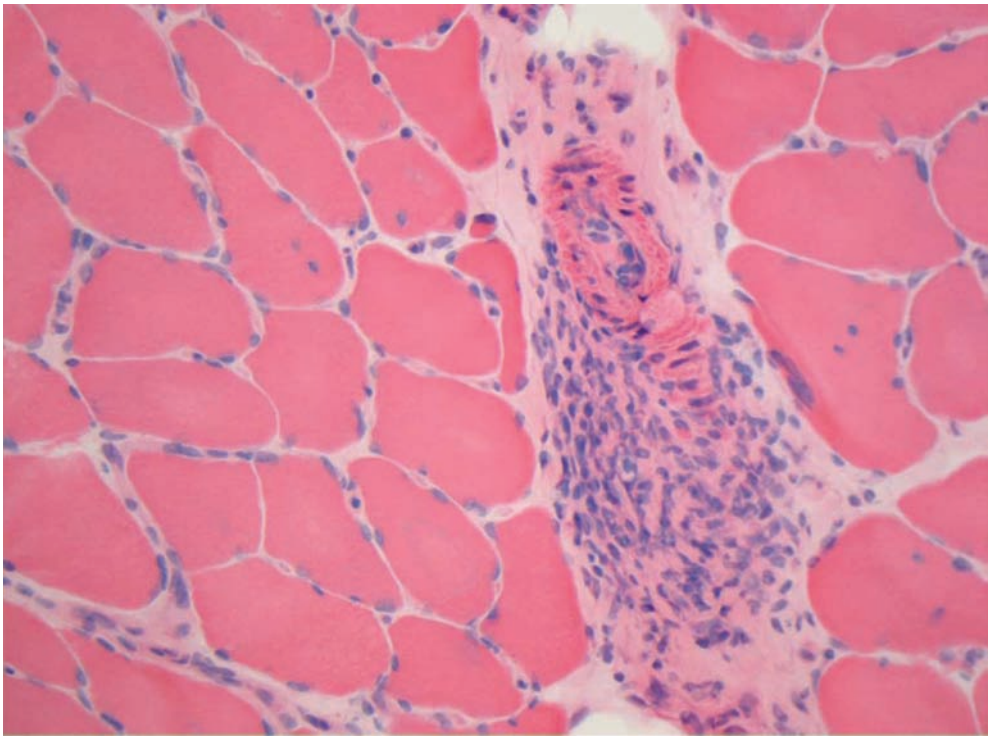

Figure 2
Haematoxylin–eosin stained section of muscle, taken from a combined superficial peroneal nerve and peroneus brevis muscle biopsy. The patient was suspected to have a vasculitic neuropathy and the nerve biopsy specimen revealed axonal changes without evidence of vasculitis. However, in the muscle specimen a vessel is seen surrounded by an inflammatory infiltrate. Small atrophic muscle fibres and target fibres are evident in the muscle fascicle.

- Nerve conduction studies and electromyography should be requested in all of these 'non-standard' patients, chiefly to assess whether the features of the neuropathy are axonal or demyelinating.
- Nerve biopsy is useful in patients suspected to have amyloid related neuropathy or vasculitic neuropathy. The use of nerve biopsy should be restricted to these two specific clinical scenarios outwith specialist centres. Its value depends on the expertise of the neuropathologist interpreting the biopsy, and when used in a less selective way nerve biopsy usually merely confirms the diagnosis of axonal neuropathy rather than revealing its cause.[15] In patients with suspected amyloid related neuropathy, abdominal fat or skin biopsy may yield the diagnosis more readily and with less chance of complications. Combined nerve and muscle biopsy (superficial peroneal nerve and peroneus brevis) increases the chance of identifying vasculitis in patients suspected of having vasculitic neuropathy,[16] as illustrated in figure 2.
- Patients with pure small fibre features can nowadays be referred for skin biopsy to demonstrate dropout of the unmyelinated axons crossing the junction between the dermis and epidermis.
- Patients with small fibre sensory neuropathy and also those with prominent autonomic features can be considered for autonomic tests to confirm autonomic involvement.[15]
- Patients with features to suggest genetic disease should be investigated appropriately, a subject which was covered in detail previously.[17]

The value of my suggested approach lies in the identification of features which suggest a treatable disorder, or a disorder that has a specific *important cause* (because it has implications for the patient or their family even though it may not be treatable). Thus disorders with pure (or marked) motor or autonomic features, asymmetry, proximal weakness, prominent sensory ataxia, upper motor neuron involvement or an acute or subacute course should always prompt further investigation and assessment, both with nerve conduction studies (to characterise the disorder) and further tests to delineate cause. Patients without these features can have the standard screening investigations and symptomatic management, with a plan to investigate further only if 'red flag' features develop.

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PRACTICE POINTS

- A pattern recognition approach, using six simple questions, can quickly produce an accurate differential diagnosis of peripheral neuropathic disorders, and identify those that are treatable.
- 'Screening tests' are appropriate for axonal length dependent sensory or sensorimotor neuropathies.
- Neuropathies with other features should be investigated more thoroughly, in a manner appropriate to the clinical phenotype.
- Demyelinating and vasculitic disorders are particularly important to identify since they often respond to immunotherapy.
- Paraneoplastic disorders are also important to identify because they are usually the presenting feature of cancer.

REFERENCES

1. **Barohn RJ**. Evaluation of patients with peripheral neuropathy and neuronopathy: a pattern recognition approach. Presented at the Educational Syllabus of the 57th Annual Meeting of the American Academy of Neurology, Miami, Florida, 2005.
2. **England JD**, Gronseth GS, Franklin G, *et al.* Practice parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 2009;**72**:185–92.
3. **Saperstein DS**, Wolfe GI, Gronseth GS, *et al.* Challenges in the identification of cobalamin-deficiency polyneuropathy. *Arch Neurol* 2003;**60**:1296–301.
4. **Lindenbaum J**, Savage DG, Stabler SP, *et al.* Diagnosis of cobalamin deficiency: II. Relative sensitivities of serum cobalamin, methylmalonic acid, and total homocysteine concentrations. *Am J Hematol* 1990;**34**:99–107.
5. **Savage DG**, Lindenbaum J, Stabler SP, *et al.* Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. *Am J Med* 1994;**96**:239–46.
6. **Singleton JR**, Smith AG, Bromberg MB. Painful sensory polyneuropathy associated with impaired glucose tolerance. *Muscle Nerve* 2001;**24**:1225–8.
7. **Novella SP**, Inzucchi SE, Goldstein JM. The frequency of undiagnosed diabetes and impaired glucose tolerance in patients with idiopathic sensory neuropathy. *Muscle Nerve* 2001;**24**:1229–31.
8. **Sumner CJ**, Sheth S, Griffin JW, *et al.* The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology* 2003;**60**:108–11.
9. **Knowler WC**, Barrett-Connor E, Fowler SE, *et al.*; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;**346**:393–403.
10. **Kelly JJ** Jr, Kyle RA, O'Brien PC, *et al.* Prevalence of monoclonal protein in peripheral neuropathy. *Neurology* 1981;**31**:1480–3.
11. **Gosselin S**, Kyle RA, Dyck PJ. Neuropathy associated with monoclonal gammopathies of undetermined significance. *Ann Neurol* 1991;**30**:54–61.
12. **Hadden RD**, Nobile-Orazio E, Sommer C, *et al.*; European Federation of Neurological Societies; Peripheral Nerve Society. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of paraproteinaemic demyelinating neuropathies: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol* 2006;**13**:809–18.
13. **Gemignani F**, Brindani F, Alfieri S, *et al.* Clinical spectrum of cryoglobulinaemic neuropathy. *J Neurol Neurosurg Psychiatry* 2005;**76**:1410–14.
14. **Kahn SN**, Bina M. Sensitivity of immunofixation electrophoresis for detecting IgM paraproteins in serum. *Clin Chem* 1988;**34**:1633–5.
15. **England JD**, Gronseth GS, Franklin G, *et al.* Practice parameter: evaluation of distal symmetric polyneuropathy: role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology* 2009;**72**:177–84.
16. **Said G**, Lacroix-Ciaudo C, Fujimura H, *et al.* The peripheral neuropathy of necrotizing arteritis: a clinicopathological study. *Ann Neurol* 1988;**23**:461–5.
17. **Reilly MM**. Sorting out the inherited neuropathies. *Pract Neurol* 2007;**7**:93–105.

10.1136/jnnp.2011.241612