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Rational Testing

### **Investigation of peripheral neuropathy**

Richard Hughes, visiting professor of neurology

1National Hospital for Neurology and Neurosurgery, London WC1N 3BG, UK

Correspondence to: rhughes11@btinternet.com

The investigation of the cause of symmetrical polyneuropathy should be guided by careful history taking and examination

### **Learning points**

**Diabetes, alcohol misuse, and HIV infection are the most common causes of distal symmetrical sensory neuropathy**

**Also consider vitamin B-12 deficiency, uraemia, paraproteinaemia, and hypothyroidism**

If the cause and management are obvious, as in diabetes or alcohol misuse, specialist referral may be avoided. Red flags for referral to a neurologist are uncertain cause, severe symptoms, rapid progression, and weakness

Chronic idiopathic axonal polyneuropathy is a diagnosis of exclusion, with uncertain prevalence (10-40% of hospital series of chronic axonal polyneuropathy) and possible association with impaired glucose tolerance or metabolic syndrome

A 65 year old woman presented with gradual onset of burning pain and loss of feeling in her toes spreading up to her ankles over three months. She had no family history of similar illness and no known other disease. She drank only the occasional glass of wine, and had not been exposed to any drugs or known toxins. Examination was normal except that she had a body mass index of 32, absent ankle reflexes; absent flexor plantar responses; and reduced pinprick, light touch, and vibration sensation in her toes.

### **What is the next investigation?**

The clinical picture points to a diagnosis of a distal symmetrical polyneuropathy of large myelinated nerve fibres (causing numbness, impaired light touch and vibration sensation, and loss of ankle reflexes) and small myelinated and unmyelinated nerve fibres (causing pain and impaired pain sensation). Similar symptoms could be caused by a myelopathy, but the absent ankle reflexes and flexor plantar responses rule this out. Cauda equina lesions would probably cause back pain and sphincter problems, which were not present

The investigations should be guided by the clinical picture. Questioning had already made hereditary neuropathy and neuropathy related to alcohol, drugs, and toxins unlikely. Toxins, apart from alcohol, are now rare causes, but arsenic and organic solvents need to be considered. Many drugs can cause peripheral neuropathy (box), so check the side effects of any drug that the patient is taking.

### Drugs that cause peripheral neuropathy

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

Polyneuropathy may arise in the course of many illnesses, particularly diabetes. Table 1 lists other common causes. Thus, in a general practice setting, initial testing would reasonably include the blood tests listed in table 2 ↓.

**Table 1**

Most common causes of symmetrical neuropathy

Disease	Prevalence
Diabetes <sup>1 2</sup>	11-41% (depending on duration, type, and control of diabetes)
Paraproteinaemia <sup>2 3</sup>	9-10%
Alcohol misuse <sup>1</sup>	7%
Renal failure <sup>1</sup>	4%
Vitamin B-12 deficiency <sup>1</sup>	3.6%
HIV infection <sup>1</sup>	16%, but depends on the population studied and is usually much lower
Chronic idiopathic axonal neuropathy <sup>4</sup>	10-40% of different hospital series

Table 2

Initial investigations of symmetrical neuropathy

**Table 2**  
Initial investigations of symmetrical neuropathy

Test	Detects
Fasting blood glucose	Diabetes
Liver function	Occult alcohol misuse; systemic disease
Full blood count	Occult alcohol misuse; systemic disease
Erythrocyte sedimentation rate	Systemic disease
Serum creatinine	Renal failure
Thyroid stimulating hormone concentration	Myxoedema
Serum protein immunofixation electrophoresis	Serum paraprotein
Vitamin B-12	Vitamin B-12 deficiency
HIV serology (in at risk patients)	HIV infection

Unless the cause can be identified and treated, the patient will need immediate specialist referral. Two of the most common and easily treated causes, diabetes and alcohol misuse, can often be identified and managed in primary care. Always refer patients with severe symptoms, rapidly progressive disease, or additional motor symptoms. Further testing should include nerve conduction studies to identify whether the neuropathy is purely sensory or also affects motor nerve fibres, and whether the primary pathology is axonal (causing dying back of axons) or demyelinating (affecting Schwann cells and myelin sheaths). Most neuropathies, especially distal symmetrical sensory neuropathies, are axonal. The causes of demyelinating neuropathy are more limited and more likely to be inflammatory and treatable. Paraneoplastic neuropathy is uncommon but a concern with recent onset neuropathy, and the possibility of an underlying neoplasm—especially a small cell lung carcinoma—should not be forgotten. Many other systemic diseases—such as sarcoidosis, Sjögren’s syndrome, and the vasculitides—can cause a painful symmetrical distal sensory neuropathy, but in these diseases an asymmetrical picture of multiple mononeuropathy is more typical.<sup>5</sup>

Outcome

Fasting blood glucose, full blood count, erythrocyte sedimentation rate, liver and renal function, serum immunofixation electrophoresis, and concentrations of thyroid

stimulating hormone were all normal and her serum vitamin B-12 concentration was low normal. She was referred to a neurologist, and nerve conduction tests showed reduced sensory action potentials, normal motor nerve conduction consistent with a sensory axonal neuropathy, and no evidence of demyelination. A glucose tolerance test showed impaired glucose tolerance but not diabetes, borderline serum cholesterol, and raised triglycerides. Further investigations including tests for antineuronal antibodies, which are present in about half of people with paraneoplastic neuropathy, and chest radiography were negative. Because she had no family history or other features of a hereditary neuropathy, genetic testing was not performed. Serum methylmalonic acid, a vitamin B-12 metabolite, was measured, because her previous B-12 value was in the low normal range, but the result was normal.

In one series, 12 of 27 patients with polyneuropathy and B-12 deficiency had the diagnosis made on the basis of abnormal metabolites.<sup>6</sup> Lumbar puncture was not performed. Examination of cerebrospinal fluid is not helpful in the diagnosis of chronic axonal neuropathies, although cerebrospinal fluid protein concentrations are often high in demyelinating neuropathy.<sup>2</sup> Because the patient had no asymmetry or evidence of inflammation, nerve biopsy was not performed. Insufficient data are available on whether nerve biopsy can help in the diagnosis of chronic symmetrical sensory polyneuropathy.<sup>7</sup> Biopsy carries a slight risk of wound infection with delayed healing and, albeit rarely, persistent neuropathic pain.<sup>8</sup> A diagnosis of chronic idiopathic axonal neuropathy was made by exclusion. The patient was advised about foot care, weight reduction, exercise, and maintaining as active a lifestyle as possible. She was monitored for the development of diabetes and the management of hypertriglyceridaemia.

The cause of chronic idiopathic axonal polyneuropathy is not understood and is probably heterogeneous. In some patients it may be related to the metabolic syndrome because impaired glucose tolerance has been found in 25-36% of patients—about twice as often as in controls.<sup>2</sup> One study found a closer association with hypertriglyceridaemia, a feature of the metabolic syndrome, than with impaired glucose tolerance.<sup>4</sup>

The condition is slowly progressive, with increasing difficulty in walking and often persistent neuropathic pain. Systematic reviews have provided evidence for short term benefit from amitriptyline, pregabalin, duloxetine, and tramadol for pain, but in the long term patients often manage their symptoms without drugs because of adverse side effects.

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