An older man with painful peripheral polyneuropathy

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This section focuses on the immediate management and investigation of an acute pain presentation in general practice.

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Anthony is a 59-year-old man who has been an infrequent patient of your practice over the past decade. His known problems include hypertension, for which he takes ramipril 5 mg daily, and obesity (his body mass index is 30 kg/m^2). Two years ago he had a fasting glucose test, the result of which was in the impaired glucose tolerance range, but he has not returned for follow up. Anthony presents today with an eight-month history of bilateral lower leg and foot pain, associated with numbness over the feet. The pain is now keeping him awake at night. His hands are not affected. You are concerned Anthony has a neuropathic pain process, specifically painful peripheral polyneuropathy.

What is neuropathic pain and what criteria are required to diagnose it?

Answer: The International Association for the Study of Pain (IASP) has recently redefined neuropathic pain as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'.[1] It is categorised as being peripheral or central. A further grading system has been proposed to classify the certainty with which neuropathic pain can be diagnosed (see flowchart).

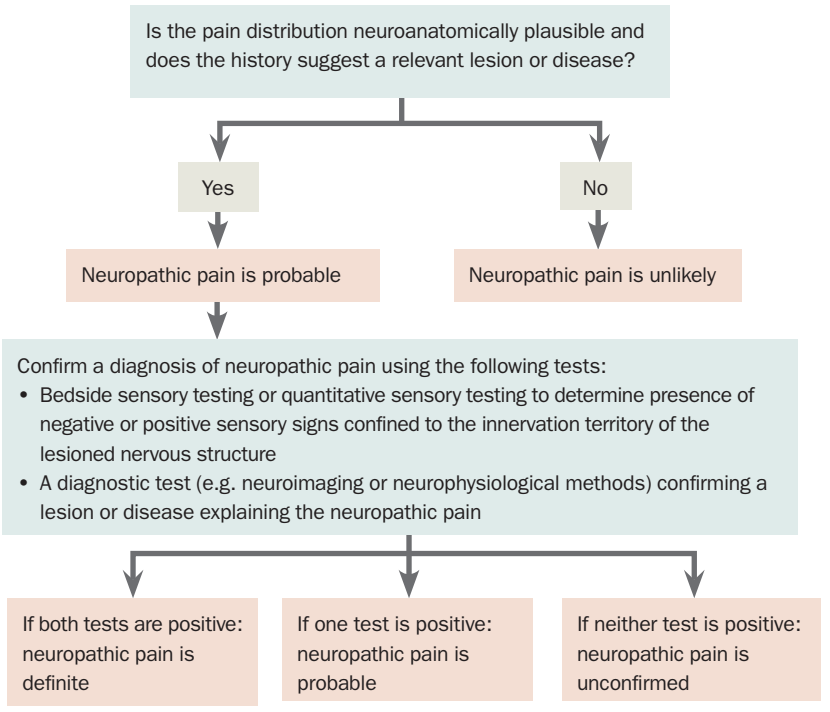
What features in Anthony's history might suggest neuropathic pain versus nociceptive pain? What other questions will you ask to help find a potential cause of polyneuropathy?

Answer: There are no pathognomonic symptoms for neuropathic pain.[2] A careful assessment of the pain, including site, duration, intensity, fluctuations, aggravating features and character, is required. Careful mapping of pain site is important because a diagnosis of neuropathic pain requires the region to be neuroanatomically plausible.[3] Neuropathic pain is generally maximally located in an area of sensory deficit. Pain descriptors such as burning, shooting, lancinating and aching are often used; however, the presence of these features only serves to point to the possibility of a neuropathic process and is not diagnostic. Pain may be spontaneous, provoked or both. Often there are associated positive sensory symptoms, such as allodynia, paraesthesia and dysaesthesia, in addition to somatosensory deficits (see the Box).

The causes of painful peripheral polyneuropathy are diverse.[2,4] For a significant percentage of patients, no causative factor will be identified.[2] Although rare, a family history of disorders that cause polyneuropathies, such as Fabry disease, amyloidosis, autoimmune conditions (e.g. Sjögren's syndrome) and familial neuropathies, should be enquired about. An alcohol consumption history, nutritional history, drug and toxin exposure, and infectious diseases exposure (including HIV and hepatitis C risk factors) will also need to be explored.

Anthony reports that the pain is deep aching, constant and severe (7 out of 10 on average), with occasional prickling sensations. The pain involves both his feet and lower legs to the mid-shin. He is able to wear socks and shoes without

A grading system for the likelihood of neuropathic pain[1]



Modified from: Haanpää M, Treede RD. Diagnosis and classification of neuropathic pain. Pain; Clinical Updates 2010; XVIII (7): 1-6.[1]

Definitions of common features suggestive of neuropathic pain

Paraesthesia
An abnormal sensation (spontaneous or evoked)

Dysaesthesia
An unpleasant sensation (spontaneous or evoked)

Hypoaesthesia
Decreased sensitivity to stimulation (tactile or thermal; both are frequent)

Hyperaesthesia
Increased sensitivity to stimulation (tactile or thermal; both are rare)

Hypoalgesia
Diminished pain response to a stimulus that is normally painful

Hyperalgesia
An increased response to a stimulus that is normally painful

Allodynia
Pain due to a stimulus that does not normally activate the nociceptive system

discomfort; however, he has a persistent feeling of numbness in his feet. He denies weakness of his limbs, bladder or bowel habit changes, or erectile dysfunction. He becomes light-headed when he stands up too quickly, and admits to dyspnoea climbing a flight of stairs. He denies other symptoms of end-organ damage and reports being otherwise well. He has only ever had one glass of wine per night with dinner and he does not smoke. There is no history of exposure to drugs or toxins associated with polyneuropathies, or a family history of similar problems; however, his mother has type 2 diabetes.

What features on examination will you look for to support the presumptive diagnosis of peripheral polyneuropathy?
Answer: Bedside sensory testing is crucial to provide supporting evidence for the diagnosis of symmetrical sensory polyneuropathy. The function of both small and large sensory fibres can be assessed. Small unmyelinated C-fibres and small myelinated Aδ-fibres convey thermal, nociceptive and autonomic information.[4] Large myelinated Aβ-fibres transmit mechanical and vibration stimuli. Each dermatome is tested and any abnormality mapped with different modalities: light touch and vibration will assess large fibre function whereas pinprick, cold and warmth will assess small fibre function. Warmth sensation is only transmitted by C-fibres. A range of abnormalities may be found, reflecting sensory gain or loss. In the case of polyneuropathy, attempts to ascertain a proximodistal delineation should be made. Tone, motor function, deep tendon reflexes and assessment of autonomic function will provide further evidence for the location of the lesion or the underlying disease process.

Anthony's neurological examination reveals hypoaesthesia to pinprick, warmth and cold from his feet to mid-shin on the right and to the knee on the left. Light touch and vibration senses are intact. There are no areas of allodynia. Tone and power are normal bilaterally. Lower-limb reflexes are intact. Peripheral pulses are present except for dorsalis pedis bilaterally. There is hair loss over the lower third of the legs. Anthony has a resting pulse rate of 95 beats per minute, and a supine blood pressure of 148/97 mmHg, which falls to 122/84 mmHg on standing. These examination findings suggest a predominantly small-fibre neuropathy, involving both somatic and autonomic fibres.

What investigations will you order?
Answer: Despite the myriad of potential causes, there are simple investigations that may provide an aetiology. Anthony's history is highly suggestive of type 2 diabetes, which is the most likely diagnosis. In addition to fasting blood glucose and HbA_{1c}, you order vitamins B1 and B12, electrolytes, renal function test, serum electrophoresis, liver function test, thyroid function test, erythrocyte sedimentation rate and full blood count. There is evidence that hyperlipidaemia may contribute to neuropathy,[4] hence a lipid profile could also be added. HIV and hepatitis C serology may need to be ordered after informed consent is obtained. You ask Anthony to return within a week to have his results reviewed.

Anthony returns to discuss his results. As you suspected, he has diabetes with a fasting blood glucose level of 14.5 mmol/L and an HbA_{1c} of 10.8%. His other blood test results are normal except for mild-moderate renal impairment with an estimated glomerular filtration rate of 80 mL/min. You institute a

comprehensive diabetes management plan for Anthony, including the commencement of oral hypoglycaemic agents, and referrals for specialist management.

Is there a role for referral for further testing of Anthony's neuropathy?

Answer: Specialist referral for diagnosis and management of peripheral polyneuropathy is not routinely required. However, if bedside testing and simple investigations are inconclusive, neurology and/or pain management referral may be necessary for diagnosis of an underlying cause and management of disease and symptoms.[3] Investigation of large fibre function is widely available and includes electromyography and nerve conduction studies, which may be normal in predominantly small-fibre neuropathy. Assessment of small fibre function is possible using a variety of techniques, including quantitative sensory testing and skin biopsy looking for epidermal fibre density.[4] These investigations are not standardised in Australia and are most often used in the research setting.

Anthony reports he has been taking paracetamol regularly with little effect on his pain. He is very keen to commence another medication.

What are your pharmacological choices to manage the pain of diabetic peripheral polyneuropathy?

Answer: The pharmacological approach to neuropathic pain differs significantly from that of nociceptive pain, and simple analgesics including paracetamol and NSAIDs are not effective. Treatment of the underlying condition may or may not improve the pain of neuropathy; however, it is an important first step. In Anthony's case, this would involve good glycaemic control.

The major pharmacological options for pain management include an anticonvulsant or antidepressant medication. The choice will be tailored to the patient, with consideration given to comorbid conditions, medication interactions and side effect profiles. The American Academy of Neurology[5] recommends the use of pregabalin as the first-line agent for painful diabetic neuropathy (level A evidence). Agents with level B evidence supporting their use include the anticonvulsants gabapentin and sodium valproate, serotonin and noradrenaline reuptake inhibitors duloxetine and desvenlafaxine, and tricyclic antidepressants amitriptyline and nortriptyline (of these medications, only pregabalin, gabapentin and duloxetine are indicated for diabetic peripheral neuropathy). With the exception of sodium valproate, these medications are also recommended by the Neuropathic Pain Special Interest Group (NeuPSIG) of the IASP as first-line therapy for neuropathic pain.[6]

Pregabalin is frequently commenced at a small dose of 25 mg twice a day and titrated slowly upwards to assess efficacy and side effects. The maximum dose is 300 mg twice a day, but this may not be required. In people with renal impairment the maximum dose is lower depending on creatinine clearance. Major side effects associated with pregabalin include dizziness, somnolence, confusion, blurred vision, nausea, peripheral oedema and weight gain (which may be a problem for Anthony). Pregabalin is now listed on the PBS for neuropathic pain.

Combination therapy with anticonvulsants and antidepressants (e.g. pregabalin and duloxetine) is possible for the treatment of neuropathic pain if a single agent is only partially effective or causing side effects at higher doses. Topical agents such as capsaicin cream may also be effective. Specialist referral of patients is recommended for failure to respond to a trial of these first- and second-line agents.

Evidence exists for the efficacy of opioids in the treatment of peripheral neuropathy; however, there are several issues surrounding long-term opioid therapy for chronic noncancer pain and they are not recommended as first-line medications. An opioid trial should be instigated in accordance with published guidelines.[7,8]

Mindful of Anthony's renal impairment, and after explaining the major side effects, you commence him on pregabalin 25 mg twice daily, with plans to increase the dose by 25 mg/day every five days, if tolerated and effective. Anthony returns after a week and reports an improvement in his overall pain scores but says he still feels 'very down about it all'.

What is your approach to this?

Answer: Neuropathic pain conditions are associated with an increased burden of psychosocial dysfunction and significantly reduced quality of life.[2] Sleep quality is often extremely poor. A detailed psychosocial history is required to identify functional limitation, pain-associated disability and major mood disturbance. He may require treatment for depression or anxiety, and/or referral to mental health services. Referral to a specialised pain management clinic may also be appropriate for further assessment and/or pain management programs. In addition, the Agency for Clinical Innovation website provides information on education about pain and self-management strategies (see www.aci.health.nsw.gov.au/chronic-pain). Exploring nonpharmacological ways of coping with pain is an important part of overall management. Meticulous foot care is also crucial given the combination of diabetes and neuropathy, and education and referral to a podiatrist are indicated early. PMT

References

1. Haanpää M, Treede RD. Diagnosis and classification of neuropathic pain. Pain; Clinical Updates 2010; XVIII (7): 1-6.
2. Scadding JW, Koltzenburg M. Painful peripheral neuropathies. In: Wall and Melzack Textbook of Pain. 6th Ed. Philadelphia: Saunders. 2013; 926-951.
3. Haanpää ML, Backonja MM, Bennett MI, et al. Assessment of neuropathic pain in primary care. Am J Med 2009; 122: S13-S21.
4. Hovaguimian A, Gibbons S. Diagnosis and treatment of pain in small fiber neuropathy. Curr Pain Headache Rep 2011; 15: 193-200.
5. Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy. Neurology 2011; 76: 1758-1765.
6. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010; 85(3 Suppl): S3-S14.
7. Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists. Principles regarding the use of opioid analgesics in patients with chronic non-cancer pain; 2010.
8. The Royal Australasian College of Physicians. Prescription opioid policy: Improving management of chronic non-malignant pain and prevention of problems associated with prescription opioid use. Sydney: RACP; 2009.

COMPETING INTERESTS: None.