Complex neuropathic pain states

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Learning objectives

After reading this article, you should be able to:

- diagnose complex neuropathic pain states
- explain pathophysiology
- select treatment options

Abstract

In this article we discuss complex neuropathic pain states: diabetic peripheral neuropathic pain (DPNP), phantom limb pain (PLP), central post-stroke pain (CPSP), and complex regional pain syndrome (CRPS). Pain in these conditions can often be severe, significantly affect quality of life and be resistant to current treatment options. Multidisciplinary assessment and treatment is essential.

Keywords Central post-stroke pain; complex regional pain syndrome; diabetic peripheral neuropathic pain; painful diabetic neuropathy; phantom limb pain

Royal College of Anaesthetists CPD Matrix: 2E03

Diabetic peripheral neuropathic pain (DPNP)[1,2]

Painful diabetic neuropathy is pain arising as a direct consequence of abnormalities in the somatosensory system in diabetic patients. It is the most common cause of peripheral neuropathy, occurs in type 1 and type 2 diabetes, and can affect up to 50% of patients. However, the pain is often under-recognized, and up to 40% of sufferers have never received treatment.

The risk is increased with poor glycaemic control, elevated triglycerides, high body mass index, smoking, hypertension, age and duration of diabetes. Initial treatment therefore includes blood glucose optimization, dietary assistance, smoking cessation, weight loss and regular exercise. Tight glucose control is much more effective at preventing neuropathy in patients with type 1 diabetes than in those with type 2.

Presentation

The most common presentation is sensory-motor distal symmetric polyneuropathy in which there is symmetrical sensory loss in the 'glove and stocking' distribution. A third of these patients will develop painful diabetic neuropathy, and it is more prevalent in type 2 diabetes than in type 1. Eight per cent of patients with type 2 have neuropathy at the time of diagnosis. DPNP usually starts as a distal, symmetrical shooting or stabbing pain (with associated paraesthesia) which gradually ascends. It typically increases at rest or at night. Pain may also occur with focal mono- or multi-neuropathies (e.g. ulnar or lateral cutaneous nerve of thigh) or as the 'burning feet syndrome' of small fibre neuropathy.

Simple assessment scales are valuable to screen for neuropathic pain, e.g. the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and the Douleur Neuropathique Scale (DN4).

Diagnosis

Diagnosis is by history and clinical examination, documenting the area of sensory loss (pain with pin, touch with cotton wool, pressure with monofilament, temperature with hot and cold water tubes), impaired vibration (tuning fork) and altered proprioception and reduced tendon reflexes. The symptoms are not in a dermatomal or single-nerve distribution. Allodynia (pain sensation from a normally non-painful stimulus such as touch or cold) and hyperalgesia (increased response to a stimulus that is normally painful) are common findings.

The most commonly performed diagnostic tests are nerve conduction studies (NCS) and skin biopsy. NSC can confirm damage to large myelinated fibres; the earliest changes noted are slowing of conduction velocity. Skin biopsy measures epidermal nerve fibre density, and is a sensitive measure of both diabetic and non-diabetic small fibre neuropathy. However DPNP remains mainly a clinical diagnosis.

Mechanism

DPNP reflects a complex interaction between hyperglycaemia-induced metabolic and biochemical changes and inadequate perfusion due to microvascular changes. Due to the deficit in axoplasmic transport it predominantly affects the longest axons. As with most neuropathic pain states, central mechanisms are also important; distal abnormalities with spontaneous impulses lead to central sensitization, alterations in sodium and calcium channels, and loss of descending inhibition.

Treatment[3]

Initial pharmacological treatment (NICE 2013)[4] should be a choice of amitriptyline, duloxetine, gabapentin or pregabalin. If the initial treatment is not effective or not tolerated, one of the remaining three drugs should be offered, and with no improvement drugs should be switched again. Tramadol should only be used if acute rescue therapy is needed. Capsaicin cream may be useful if oral treatment cannot be tolerated, although pain on application may be a problem. Capsaicin 8% patch (Quetenza) has recently been approved for use in DPNP. Lidocaine patches can be used for focal pain but are less valuable for diffuse neuropathy because the maximum area of application may be too small.

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Opioids should be administered only if multiple first-line agents have been ineffective — oxycodone, morphine, tramadol, and tapentadol significantly improve pain in DPNP.

Phantom limb pain (PLP)[5–7]

Amputation of a limb frequently results in non-painful phantom sensations, stump pain and phantom limb pain.

Non-painful sensations include a specific shape, position or movement of the limb, and sensations of warmth or cold, itching, tingling, or paraesthesia are common. The phenomenon of 'telescoping' occurs when the distal part of the missing limb is felt to recede towards the stump, and probably occurs due to alterations within the somatosensory cortex.

Stump pain occurring immediately after amputation is acute nociceptive pain and usually resolves after a few weeks, but a more long-lasting stump pain can persist and may be linked to the development of PLP. It is therefore essential that it is well-managed.

Presentation

PLP occurs in up to 80% of amputees and may be exacerbated by many physical (e.g. temperature changes) and psychological (e.g. stress) factors. It is usually described as stabbing, throbbing, burning, or cramping, and commonly starts in the first week, although it can also develop years later. Risk factors are: pre-amputation pain, presence of persistent stump pain, bilateral limb amputations, and lower limb amputations. It is less common in children and those with a congenitally absent limb.

The pain may be constant but of varying intensity in some amputees; others experience intermittent unpredictable incidences of high-intensity pain. Its duration is similarly unpredictable, resolving in months or persisting for decades. Pain for longer than 6 months has a poor prognosis for spontaneous improvement.

Mechanism

Peripheral mechanisms alter the afferent nerve supply to the central nervous system and include an inflammatory reaction and a process where free endings of Aδ and C fibres sprout, forming a neuroma with resultant altered sodium channel function, reduced activation thresholds, and spontaneous discharge, leading to sensitization.

Further anatomical reorganization within the spinal cord occurring after peripheral nerve injury includes degeneration of unmyelinated C fibres that normally synapse in lamina 1 and 2 in the dorsal horn, and sprouting of connections between larger myelinated Aβ-fibres that are normally involved in touch, pressure and proprioception (normally in lamina 3 and 4) into lamina 1 and 2, thus resulting in non-painful stimuli being experienced as painful (allodynia). Central sensitization of dorsal horn cells occurs in response to the increased barrage of painful stimuli from the amputation site, and is responsible for the resultant hyperalgesia. During this process, there is also an increase in activity at *N*-methyl-D-aspartate (NMDA) receptors mediated by neurotransmitters such as substance P, tachykinins, and neurokinins, and aspects of the central sensitization can be reduced by NMDA receptor antagonists.

Centrally, cortical reorganization has been demonstrated (e.g. the somatosensory cortex corresponding to the missing limb appears to receive sensory information from other areas of the body that synapse at adjacent areas on the somatosensory cortex). The degree of cortical reorganization appears to be directly related to the degree of phantom pain, and imaging studies have correlated greater extent of somatosensory cortex changes with more intense phantom limb experience.

Treatment

Pre-amputation pain intensity is a significant predictor of PLP but pre-emptive analgesia (e.g. epidural/specific nerve blockade with local anaesthetic or use of ketamine) has not reliably been shown to reduce PLP. However, multimodal balanced analgesic regimes are vital for post-operative pain and stress reduction, and since the onset of phantom pain is often in the first 7 days consideration could also be given to the use of additional anti-neuropathic medication at this time. There is recent experience that using continuous perineural blockade for a minimum of 80 hours may reduce the likelihood of PLP.

Revision of the stump is only indicated if there is specific localized pathology.

Anti-neuropathic medication is appropriate and tricyclics and gabapentinoids should be the first line. There is some evidence for the use of opioids.

Heat and cold, ultrasound, acupuncture, transcutaneous electrical nerve stimulation, massage, and alteration of the prosthesis have been used successfully. Mirror-box therapy has been used to good effect for symptoms involving pain due to involuntary movements and spasm of the phantom. The mirror is placed vertically so that it is possible to visualize the unclenching of the affected limb when the unaffected limb is moved appropriately.

Psychological techniques involving explanation and reassurance as well as CBT have been reported as beneficial.

Central post-stroke pain (CPSP)[8,9]

CPSP (originally called thalamic pain syndrome) results from a primary lesion or dysfunction of the central nervous system following a stroke. It has a prevalence of 8–35% and can occur as early as the first month following stroke or some years later. The most common is 3–6 months. Risk factors include a young age, previous depression, smoking, and increased stroke severity. It is more common after ischaemic strokes and often interferes with rehabilitation and quality of life. It is usually on the contralateral side to the stroke, which can be anywhere within the spinothalamic pathway, although lateral medullary (25% incidence) and ventroposterior thalamic (incidence 11–59%) infarctions appear to have the highest incidence. The incidence in non-lateral medullary, non-thalamic stroke is 2–8%. Strokes affecting the right side are more commonly associated with pain. Following lateral medullary infarction pain can involve one side of the face and contralateral body and limbs, whilst in thalamic lesions pain is more commonly hemibody.

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