The causes and treatments of phantom limb pain

Phantom limb pain (PLP) is a form of neuropathic pain. It was first documented in 1551 and later formally named PLP in 1871 by Silas Weir Mitchell who described the condition as ‘ghostly replicas of lost limbs, some of which are painful’ (Watt, 2001).

Phantom sensation
Almost all patients who undergo amputation suffer ‘phantom sensations’, a sensory perception of the missing limb, possibly caused by a neural imprint or memory of the limb within the brain. The patient may experience abnormal kinaesthetic sensation (perception of one’s own body parts, weight and movement) such as feeling that the limb is in an abnormal position. Perceived changes in length, size or temperature of the limb are also common.

One-third of patients report a telescoping phenomenon (Montoya et al, 1997) – a sensation of the limb gradually shrinking towards the stump until it feels as though the digits of the phantom hand/foot are directly attached to the stump.

The phenomenon is inversely related to PLP, therefore telescoping is reduced or absent when PLP is present (Wesolowski and Lema, 1993).

Stump pain
This type of pain is localised to the stump itself. It is due to a variety of factors including neuroma formation, bony spurs, infection, ischaemia, necrosis, adhesions, muscle spasm, a poorly fashioned stump or an ill-fitting prosthesis (Wilson, 2001).

There is a significant positive relationship between the occurrence and intensity of stump pain and PLP (Montoya et al, 1997).

Phantom pain
Phantom pain is a neuropathic-type pain that is perceived in the territory of the amputated limb. It can occur after removal of a wide variety of body parts, but is most common in patients after limb amputation or mastectomy (McCaffery and Pasero, 1999).

There is documented evidence that, for a quarter of patients with PLP, the onset of pain occurs within seven days of amputation (Macrae, 2001). For other patients, PLP may not occur for weeks, months or even years after surgery has been performed (O’Hara, 1996). Some amputees have periodic painful episodes either daily or weekly; others (approximately 10 per cent of amputees) have pain that is constant and unremitting (Wilson, 2001). For many, the sensation of the phantom limb will fade with time, but for some it will remain a painful, distressing part of daily life.

The intensity and frequency of phantom pain varies enormously. It is usually described in terms of typical neuropathic-type pain symptoms, with intermittent sharp shooting pains superimposed on a constant burning, cramping, throbbing or crushing sensation (Waldman, 2002). Patients are sometimes reluctant to report pain because they feel that they will be disbelieved. There is no doubt that the feeling of PLP is a reality to the amputee and not a ‘vague illusion’, which the term ‘phantom’ infers (Watt, 2001). However, because of the unusual nature of PLP, a behavioural component to the pain is invariably present (Waldman, 2002).

Phantom limb pain may be caused by: trauma; systemic disease (peripheral arterial occlusive disease (PAOD) or infection secondary to diabetic foot ulceration); malignancy and congenital malformation.

Incidence and pathophysiology
The incidence of phantom limb pain is so great among amputees – most recent reports suggest between 65 and 85 per cent (Montoya et al, 1997) – that it poses a considerable clinical problem. The rate of ‘all-cause’-acquired amputation has been reported as being between 1.2 and 4.4 per 10,000 (Ephraim et al, 2003).

The risk of amputation is greatest among people with diabetes mellitus, although upper limb amputation is much less common in these people because PAOD and diabetic ulceration both affect mainly the lower limbs (Gibson, 2001).

Some researchers have reported that poorly controlled preamputation pain significantly increases the incidence of PLP (Macrae, 2001), but other investigators have failed to prove this correlation (Waldman, 2002). The genesis is not fully understood: early literature suggested that congenitally absent limbs did not appear to be subject to the same phenomenon (Waldman, 2002). This view has been challenged recently, and studies have shown that some patients with congenitally missing limbs do suffer PLP, although the incidence is smaller in this group of patients than in those who have undergone surgical amputation (Wilkins et al, 1998).

Physiological mechanisms
The precise pathophysiology of PLP is not entirely known, but there are a growing number of clinical and scientific studies that are helping to inform practice. What is known is that an amputation sections nerves, and that nerve injury is followed by a series of changes that occur first in the periphery and then cascade into structural and chemical changes within the central nervous system (CNS); psychological mechanisms may also be implicated (Doln et al, 1997).

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Peripheral mechanisms involved in PLP
Peripheral sensitisation
Whenever cell damage occurs, chemicals and enzymes are released:

- Histamine contributes to the inflammatory swelling process; it also stimulates nociceptors (nerve endings that are stimulated by tissue injury and endogenous chemical substances), which initiate pain impulses; Bradykinin stimulates A delta and C fibres (pain-carrying nerve fibres) to increase the rate of nerve action potential. It also stimulates the release of prostaglandins from other nearby tissues. It is one of the most active pain-producing agents known;
- Phospholipases are activated by cell damage, and release an unsaturated fatty acid – arachidonic acid – that is converted by another enzyme, cyclo-oxygenase (COX), into the chemical mediator prostaglandin, which sensitises nociceptors.

Following prolonged exposure, nociceptors respond to lower concentrations of chemical mediators. Therefore, a previously mild stimulus that produced only a few action potentials in the sensory nerves, now produces a rapid increase in the number of action potentials. The CNS interprets the increase in nerve impulses as an increase in the severity of the pain (Bridges et al, 2001).

Increased impulses also produce changes in the cell bodies of nociceptive neurones, causing the release of neurotransmitters, including substance P, from the nerve endings near the site of damage. Substance P activates neighbouring nociceptive nerve endings not involved in the original tissue damage.

The firing threshold of normal afferent neurones is reached only with the input of a stimulus. In PLP the chemical mediators sensitise the nociceptors, and this results in a large increase in spontaneous firing of afferent neurones. These spontaneous impulses are known as ectopic discharges. Repetitive activity in primary afferent neurones induces autonomous firing in groups of neighbouring neurones.

Sodium channels are crucial to the physiology of excitable membranes. In PLP, reorganisation and alterations in sodium channel membrane potential take place, which in turn greatly increase ectopic discharges from afferent neurones (Nikolaensen and Jansen, 2001). Ectopic discharges are a result of up-regulation of sodium channels, therefore increased sodium conduction increases pain. This may play a role in the development of hyperalgesia (extreme sensitivity to pain) and allodynia (a painful response to a normally innocuous stimulus). Calcium channels also influence the generation of hyperalgesia and allodynia.

Central mechanisms involved in PLP
Spontaneous sprouting of afferent neurones
The central terminals of primary afferent neurones are ordered within the dorsal horn. In normal physiology, A delta and C fibres terminate in the superficial laminae I and II and A beta fibres terminate in laminae III and IV of the dorsal horn (Fig 1).

Central sensitisation (‘Wind-up’ phenomenon)
Increased neuronal activity or impulse traffic in the dorsal horn nociceptive neurones following repetitive C fibre stimulation can cause hyperexcitability and central sensitisation. This decrease in threshold and increase in intensity of response to noxious stimuli produces a ‘wind-up’ effect, which persistently maintains PLP.

Following peripheral axotomy of nerve fibres (surgical transection of axons), spontaneous sprouting of the central terminals of large myelinated sensory axons (for example, A beta fibres) occurs outside their normal dorso-ventral termination zone. This sprouting allows the sensory axons to terminate in lamina II instead of laminae III or IV. This means that the ‘wrong connections’ are made and sensory neurones responsible for touch might connect with the inter-neurones that normally receive input from nociceptors, leading to the agonising sensitivity that some people feel to just a light touch (Stalker, 1999).

The trigger for this type of sprouting may be nerve growth factor, a member of the family of peptides known as neurotrophins (McLachlan and Hu, 1998).

Ramer and Bisby (1997) noted that sprouting was detectable at one week post-nerve transection. In this particular study the changes persisted for six months, but at nine months the fibres were no longer identifiable, suggesting that terminal reorganisation is not a permanent feature of axotomy.

REFERENCES


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Glutamate and NMDA receptor complex

Glutamate is the main excitatory amino acid released at central terminals after noxious stimuli. However, N-methyl-D-aspartate (NMDA) receptors must be activated for glutamate to exert its effect. NMDA receptor activation contributes to increased levels of glutamate, causing a positive feedback loop, maintaining sensitisation.

Gamma aminobutyric acid (GABA) is an inhibitory neurotransmitter. Disinhibition, or the loss of such inhibitory mechanisms that usually modulate neural transmission in the dorsal horn, may result in hyper-excitability and spontaneous neural activity, with exaggerated response to stimuli.

Cortical reorganisation

Most nerve fibres, especially C fibres, synapse in the thalamus, where a three-dimensional image of the body is produced, known as the neuromatrix. This network includes neural loops linking it to the cortex (responsible for processing and then transmitting pain information to other parts of the brain) and the limbic system. The latter is a ring of complex structures surrounding the thalamus which coordinates the emotional component of the pain response.

The neuromatrix is a genetically determined ‘hard wired’ system, which represents the anatomical substrate of the physical self. Normally when inputs into the system from the periphery or CNS are processed, the location of a stimulus can be achieved with a considerable degree of accuracy, but with PLP there appears to be a problem with localisation of pain. Thus the brain appears to perceive impulses arising from the stump as originating from the absent limb. The neuromatrix attempts to move the amputated body part and therefore conducts stimuli towards the limb. Excessive activity in the neuromatrix follows because of a lack of signals from the limb (Watt, 2001). It would seem that, although the body has lost a physical part, the brain still has the old geography wired in (Nikolajsen and Jensen, 2001).

Deafferentation is a non-specific term that refers to injury of either the nerve root or peripheral nerve. When this has resulted from limb amputation, there appears to be a shift of cortical representation of adjacent body parts in the direction of the deafferentated areas (Hor et al, 2001).

Changes in CNS function before amputation may also have a significant influence on subsequent pain experience. For example, reshaping of the neuromatrix can occur when a patient’s experience of somatosensory pain preamputation is integrated into the neuromatrix, which therefore leads to the same kind of pain post-operatively. Prolongedafferent input to the brain results in plastic changes within the cells, resulting in the development of a ‘pain memory’ (Dolin et al, 1997). This plasticity appears not to be permanent.

A study by Huse et al (2001) has demonstrated that there is a positive effect on significantly reducing both cortical reorganisation and PLP using active pain management techniques.

Treatment

Management is urgent to prevent more permanent plastic changes from occurring within the nervous system; however, treatment is difficult to establish when the underlying pathophysiology is not fully understood. The current treatment modalities for PLP are as varied and controversial as the aetiology of PLP itself (McCaffery and Pasero, 1999).

Acute postamputation pain management

Poorly controlled acute pain can predispose patients to debilitating chronic pain syndromes. PLP can be prevented or minimised with aggressive postoperative pain management, for example epidural infusion, patient-controlled intravenous analgesia, intrathecal opioids or nerve blocks, along with appropriate adjuvant therapies such as non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol. These patients can also benefit from early physical rehabilitation (McCaffery and Pasero, 1999).

Pharmacological treatment

Non steroidal anti-inflammatory drugs

NSAIDs have an anti-inflammatory and an analgesic role in managing PLP. They are particularly useful in treating stump pain. The mode of action of these drugs includes the inhibition of activity of the enzyme cyclo-oxygenase (COX), which is responsible for the production of prostaglandins from the phospholipids of cell membranes (Jordan and White, 2001).

Anticonvulsants

There is a notable similarity between the pathophysiology and biochemical mechanisms observed in epilepsy and neuropathic pain. ‘Wind-up’ in neuropathic pain can be likened to the ‘kindling’ of hippocampal neurones that occurs in epilepsy.

Both ‘wind-up’ and ‘kindling’ seem to result from activation of NMDA receptors along with other mechanisms. It is not surprising, therefore, that anticonvulsants can relieve PLP.

Phenytoin was the first anticonvulsant drug used to treat neuropathic pain. Its mode of action includes blocking sodium channels and inhibiting presynaptic glutamate release. It also suppresses spontaneous neuronal ectopic discharges.

Carbamazepine is chemically related to tricyclic antidepressants. Its mode of action is to suppress spontaneously active A delta and C fibres responsible for pain conduction without affecting normal nerve conduction.

Gabapentin is a new generation of antiepileptic drug structurally related to the neurotransmitter GABA (but it has no action at GABA receptors). It exerts its effect in a number of ways. Peripherally it acts on calcium and sodium channels because it is also a cell membrane stabiliser capable of suppressing ectopic discharge activity generated from afferent nerve sites. Centrally it acts as a glutamate inhibitor and increases synaptic release of GABA. It also modulates neuronal transmission...
at NMDA receptors and inhibits the release of monoamine neurotransmitters, which modulate descending inhibitory influences in the dorsal horn.

Antidepressants
Tricyclic antidepressants, such as amitriptyline, and selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, are used for PLP pain management. These drugs block the reuptake of the monoaminergic neurotransmitters serotonin and norepinephrine in the CNS. They also peripherally block sodium channels. Because pain transmission relies on the movement of sodium ions between the intracellular and extracellular fluid of nerve cells, blocking sodium ion movement reduces the ability of nerve cells to transmit pain impulses.

NMDA antagonists
Ketamine is an anaesthetic agent that has been reported to reduce wind-up and allodynia. It is an NMDA antagonist, which acts at NMDA receptor sites to reduce hyperexcitability. GABA-ergics, such as baclofen, mimic the effects of GABA at GABA receptors.

Opioids
Opioids have a significant role to play in the initial postoperative period following limb amputation, but have a limited role in the management of PLP, although they can be very effective for stump pain (Waldman, 2002).

Nerve blocks
Sympathetic neural blockade (stellate ganglion block or lumbar sympathetic block) or regional nerve blocks (brachial or lumbar plexus) may be helpful. Trigger point injections, which involve the infiltration of local anaesthetic into a painful area, can also be effective, particularly for those who have defined areas of pain in the limb stump (Waldman, 2002). Local anaesthetic agents are membrane-stabilising agents that block peripheral sodium channels. Thus, by blocking peripheral input, spontaneous ectopic discharges are reduced (Dolin et al, 1997). Steroids can be added to the local anaesthetic to prolong the duration of action.

Surgical intervention
Scar tissue or neuroma excision or even refashioning of the stump may be necessary and can prove effective. Invasive surgical therapies such as cordotomy and neuroablation involve irreversible damage of nerve fibres that carry pain signals. This type of treatment has been shown to have a very low success rate and is usually seen as a last resort because the problems of sprouting can reoccur after the intervention, resulting in a return of the pain, often of greater intensity than before (Nikolajsen and Jensen, 2001).

Pre-emptive analgesia
Pre-emptive analgesia represents a novel approach to pain management. The hypothesis is that prophylactic treatment, by means of epidural infusion of local anaesthetic, interrupts the transmission of noxious inputs to the spinal cord, reducing peripheral input so that any ‘pain memory’ can be abolished. It is also thought to prevent the establishment of central sensitisation. (A noxious stimulus is one that is either potentially or actually damaging to normal tissue.) Trial results to date appear inconclusive.

Non-pharmacological treatment measures
Transcutaneous electrical nerve stimulation
If the spinal cord is bombarded with transmitting impulses from the transcutaneous electrical nerve stimulation (TENS) machine through A beta cutaneous fibres stimulation, it is distracted from transmitting the pathological pain messages, and ‘gating’ occurs in the spinal cord (Dolin et al, 1997). The gate control theory was devised by Patrick Wall and Ronald Melzack in 1965. It states that if activity is greater in large nerve fibres (non-nociceptive) due to non-painful stimulation, the ‘pain gate’ in the dorsal horn is closed and there should be no or little pain. If there is more activity in small nerve fibres (nociceptive) due to painful stimulus, the pain gate will open, allowing messages to be transmitted to the brain, and pain will be experienced. TENS is not a panacea for intractable pain, but it is a useful adjunct. It is simple, safe, and can be used long term with no risk of adverse events (Wartan et al, 1997). It often enables symptoms to be better tolerated and reduces the need for stronger analgesics.

Behavioural therapies
There is a high incidence of depression and anxiety among people with PLP and there is a strong link between anxiety and pain intensity (Wilson, 2001). Strategies to reduce anxiety and stress are therefore essential. Pain management programmes that include a multidisciplinary comprehensive psychological approach to PLP help reduce psychological aspects. They may also have a beneficial physiological effect by reducing plastic changes in the somatosensory cortex (Flor et al, 2001).

Prostheses
There is evidence to suggest that early fitting of a prosthesis postamputation helps to reduce the incidence of PLP significantly (Wilson, 2001). This finding was upheld by Lotze et al (1999), who found that enhanced use of a myoelectric prosthesis in upper limb amputees was associated with reduced PLP and a reduction in cortical reorganisation. This was thought to be due to ongoing stimulation, training of muscles around the stump area and visual feedback from the prosthesis.

Conclusion
PLP is thought to be due to a series of both peripheral and central mechanisms, the consequence of which can be devastating for the patient. Appropriate aggressive pain management is required immediately postamputation in an attempt to avoid chronic PLP, which is notoriously difficult to manage.