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REVIEW ARTICLE

PHANTOM LIMB COMPLEX: PATHOGENESIS, CLINICAL PRESENTATION AND TREATMENT

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ABSTRACT

Objective: To review the literature for evidence based understanding of the clinical presentation, pathogenesis and treatment of the phantom limb syndrome.

Background: Phantom limb pain (PLP) refers to the sensation of pain in the missing part of the amputated limb. It usually manifests as a burning sensation, a gripe and may vary in both intensity and frequency. It is associated with stump pain (SP) and phantom limb sensation (PLS). The incidence of this is very high, among patients who have undergone any amputation. The reason for this phenomenon is not fully understood and various hypothesis have been emerging since its original discovery. It has the potential to worsen the quality of life of the amputees. There are several methods of treatment, but their efficiency varies from patient to patient.

Design: We conducted a systematic review of original research papers investigating the phantom limb syndrome, its cause and treatment and quality of life. Literature was sourced from articles and reviews in PubMed and Google scholar.

Results and Conclusions: The phantom phenomenon is a chronic post-surgical pain with high incidence and profoundly affects the quality of life in amputees. Its treatment poses a huge challenge as the potential of the efficacy of treatment varies from person to person. Larger studies are required to investigate this phenomenon, both in terms of pathogenesis and effective treatment as it has a high morbidity.

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INTRODUCTION

In 1551, Ambroise Pare a French military surgeon was the first to document, in soldiers, phantom limb pain in the amputated region[1]. The term "phantom limb" was originally coined by Mitchell in 1871[2]. The phantom limb complex comprises 3 components-phantom limb pain (PLP), phantom limb sensation (PLS) and stump pain (SP). These often coexist in a single patient. Phantom limb pain (PLP) refers to the sensation of pain in the missing part of the amputated limb. It usually manifests as a burning sensation, a gripe and may vary in both intensity and frequency.[3] PLS is any sensation other than pain like numbness, itching etc., SP is the pain felt in the residual limb or stump. It should be noted that phantom limb pain differs from pain in the stump, or residual limb. It may be due to skin complications, vascular compromise, inappropriate healing, neuromas, excess soft tissue and bone irregularities. [4,5] Initially, it was believed to have a psychological origin. However, more recently it has been found to have a physiological basis. Although there are several therapies, only 10% of patients report long-term relief [5,6,7,8]. Patients often claim that the postoperative syndrome affects their way of life more than the amputation of the limb itself [6–8]. It is associated with significant psychological trauma, having a major impact on their lifestyle [3]. It is also associated with significant disability and impaired function leading to decreased quality of life [5-9]. There is still a need for effective treatment for all aspects of the phantom limb complex.

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Incidence

80% of amputees experience neurological sequelae in the form of phantom sensation, residual limb pain, or PLP [10-12, 2]. Although the incidence of PLP remains significant, many patients did not consult a doctor for fear of being labeled mentally disturbed [2,10]. Over half of these patients reported moderate-to-severe pain

Pathogenesis

PLP was originally classified as a psychiatric illness. It is now known that it is not an isolated perception in the mind but an

actual experience of pain in the body. [13] With resources from modern researches, the paradigm has shifted toward the neural axis. Both peripheral and central neural mechanisms have been proposed. Nevertheless, no single hypothesis can explain the phenomenon of PLP. It is believed that multiple mechanisms play a role.

Peripheral Mechanism

The dominant hypothesis here is irritation in the severed nerve endings (called "neuromas").The process of amputation detaches several peripheral nerves resulting in disruption of the normal pattern of afferent nerve input to the spinal cord and the proximal portion of the severed nerve sprouts to form neuromas [14]. There is an increased stimulation of the spinal cord neurons and increased activity of the sodium channels. Studies reporting the reduction of phantom pain with drugs blocking the sodium channels lend further support to this theory [15, 16]. The nerve endings become inflamed, and transmit unclear signals to the brain. These signals are interpreted by the brain as pain. Some cases have had a second amputation done, further shortening the stump, with the thought of removing the irritated nerve endings. This however provided only temporary relief following which the symptoms worsened. Many were left with the sensations of both the initial phantom limb pain, as well as the new phantom stump pain[17]. The sensory nerves leading to the spinal cord were severed as a treatment option. In severe cases a partial thalamectomy was performed[18] However, none of these interventions have clarified the precise mechanism of PLP.

Central Mechanisms

At the level of the spinal cord

A windup phenomenon involving upregulation of NMDA receptors mediated by neurotransmitters such as substance P, tachykinins, and neurokinins [19] brings about a change in the firing pattern of the central nociceptive neurons. The target neurons at the spinal level for the descending inhibitory transmission from the supraspinal centers may be lost. There also may be a reduction in the local intersegmental inhibitory mechanisms at the level of the spinal cord, resulting in spinal disinhibition and nociceptive inputs reaching the supra spinal centers. This lack of afferent input and changes at the level of the spinal cord have been proposed to result in the generation of PLP [19 -21].

At the level of the brain

Melzack [22] advanced the neuro matrix theory, which states that the brain possesses a neural network that integrates multiple inputs to produce the output pattern that evokes pain. The synaptic architecture of the neuro matrix is determined by genetic and sensory influences. Tim Pons and team showed that the primary somatosensory cortex undergoes substantial reorganization after the loss of sensory input [23] Vilayanur S. Ramachandran hypothesized that phantom limb sensations could be due to this reorganization in the somatosensory cortex, which is located in the postcentral gyrus, and which receives input from the limbs and body [17]

In recent years the most cited reason for the cause of PLP is cortical reorganization which explains some of the non painful phantom limb phenomena. A strong relationship has been reported between the magnitude of the phantom limb pain and the extent of cortical reorganization, indicating PLP is an outcome of plastic changes in the somatosensory cortex. Using MRI, MacIver *et al* [24] showed that reduction in intensity of constant pain was associated with reduction in cortical reorganization. Pain researchers dispute that phantom limb pain is principally the result of "junk" inputs from the peripheral nervous system[25] According to Preissler *et al* [26], visual adaptation mechanisms may accommodate for lack of sensorimotor response and may, therefore, function as a defense mechanism against development of phantom limb pain Recently it was observed that injecting a local anesthetic into the lower back of subjects, helped reduce or in some cases eliminated PLP in the legs of amputees This result supports the hypothesis that phantom limb pain is generated primarily in the peripheral nervous system.[27]

Psychological Mechanism

Even though stress, anxiety, exhaustion, and depression are believed to intensify PLP, it is not assumed to be of psychogenic origin in current literature [28] . Most research on the relationship between psychological symptoms and PLP has been retrospective and cross sectional rather than longitudinal and thus only limited inferences can be derived from these studies.

Clinical Presentation

Localization

PLP is primarily localized to distal parts of the missing limb. A peculiar phenomenon, “telescoping” may occur rarely when the distal part of the phantom is gradually felt to approach the residual limb and in the end, may even be experienced within the stump.

Onset and duration

In most cases the onset of pain starts within a few days [29, 30, 31, 32 , 33] from amputation. This is susceptible to change as it can surface after several months or years as well. It is claimed that PLP is more commonly reported in women[34, 35]. However, other studies found no such gender-based differences in the occurrence of PLP [11, 36]. Phantom limb pain is usually intermittent. The frequency and intensity of attacks usually declines with time.[37] However, some patients have a constant sensation of pain [38, 39, 40].

Nature

Prevalence of PLP is greater in patients with SP.SP and PLP are interrelated phenomenon [10] Phantom limb pain (PLP) is often described as a shooting, stabbing, boring, squeezing, throbbing, burning and aching [2, 41.] Warmth, cold, itching, squeezing, tightness, and tingling are some of the other induced sensations.[17,] PLP and SP are episodic, and there are variations in their reported intensities. A significant proportion of patients with PLP and SP are bothered by pain. [11, 12, 42, 43]

Stimulating factors

Factors like attention, emotion, touching the stump or pressure, temperature change, autonomous reflexes, pain from other sources, placement of a prosthesis aggravate the pain. Stress and anxiety can worsen pain. SP is induced by peripherally originating impulses, whereas centrally arising nerve impulses induce phantom pain. [44]

Relieving factors

Resting, distraction, stump movement, wearing prosthesis, lifting the stump, percussion or stump massage significantly relieve pain[45]. Peripheral interventions like local anaesthesia of the neuroma or peripheral nerve can modulate SP. However PLP remains unaffected by these interventions.[44]

Significant attributes

The missing limb often feels shorter and may feel as if it is in a distorted and painful position. Studies have reported people feeling their phantom limb gesturing or trying to pick things up. Some people's representations of their limbs do not actually match what they used to be. For example, a patient claimed her phantom arm was 6 inches shorter. [17]

Associated factors

PLP can be influenced by pre- and postoperative pains [10,14, 36, 39,46,47] Those with a history of ischaemia and gangrene had higher pain levels.[48] Younger patients with depressed moods and two or more co-morbidities also tend to report greater intensity of PLP and SP[12].

Treatment

Pharmacological Approaches

Preemptive Analgesia and Anesthesia

Preemptive use of analgesics and anesthetics during the preoperative period is believed to prevent the noxious stimulus from the amputated site from triggering hyperplastic changes and central neural sensitization which may prevent the amplification of future impulses from the amputation site [49]. The use of analgesia, at 48 hours, both preoperatively and post operatively lead to decrease in PLP at six months [50]. Ketamine or morphine are effective during surgical intervention. Long term benefits may be achieved by the use of morphine. The view on gabapentin is controversial.[51] Recently it was observed that injecting a local anesthetic into the lower back of subjects, helped reduce or in some cases eliminated PLP in the legs of amputees [27].

Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Most commonly used treatment for PLP is acetaminophen and NSAIDs [52]. Acetaminophen's action is not clear and other central nervous system pathways are involved [53]. The nociceptive stimulus peripherally and centrally is decreased by NSAIDs. The latter inhibit enzymes needed for synthesis of prostaglandin[54].

Opioids

Opioids (oxycodone, methadone, morphine, and levorphanol) are used for the treatment of neuropathic pain including PLP. Opioid binds to opioid receptors and provides analgesic effect without the loss of sensation, proprioception, or consciousness. Cortical reorganization may reduce and thereby lessen PLP [55]. However opioids are associated with frequent side effects [56]. Tramadol, a weak opioid and mixed serotonin-noradrenalin reuptake inhibitor may be helpful in providing relief from the pain of PLP [55, 57].

Antidepressants

Tricyclic antidepressants are among the most commonly used medications for PLP. It acts by inhibiting serotonin-norepinephrine uptake, NMDA receptor antagonism, and sodium channel blockade [58]. An average dose of 55 mg of amitriptyline provides stable PLP control [57, 59]. Nortriptyline and desipramine are equally effective and with fewer side effects compared to amitriptyline [60]. The effectiveness of mirtazapine, an alpha 2 receptor antagonist with fewer side effects than tricyclic antidepressants was established in a small case series [61].

Anticonvulsants

Gabapentin has shown mixed results [62- 64]. Carbamazepine reduced the brief stabbing and lancinating pain of PLP. Oxcarbazepine and pregabalin may also play a role in the treatment of PLP [55, 65].

Calcitonin

The mechanism of action of calcitonin in treatment of PLP remains uncertain and has a mixed view on its benefits [66, 67].

NMDA Receptor Antagonist

Benefits of Memantine have been observed in some case studies only [68, 69]. It is more effective immediately after amputation rather than chronic neuropathic pain conditions[70].The mechanism of action of NMDA receptor antagonism in PLP is not clear.

Other Medications

The beta blocker propranolol and the calcium channel blocker nifedipine have been employed but their efficiency is indistinct and demands further research before coming to any substantial conclusion. [65]

Nonpharmacological Treatment

Transcutaneous Electrical Nerve Stimulation (TENS)

Availability of Portable TENS devices have made this treatment easy, having a small number of side effects. Low-

frequency and high-intensity TENS showed the efficient management of PLP [71].

Mirror Therapy

The mirror therapy is carried out using a mirror box. It reflects an image of the intact hand or limb and enables reposition the phantom limb, and to ease it from painful positions. [71, 72] .The potential of mirror therapy varies from individual to individual and is liable to the ability of the patient to internalize the reflection of the complete limb as their own limb. About 40% of people do not benefit from mirror therapy. A nonpharmacological neuro-rehabilitation technique was put forward in 1996. It enables the amputee to picture the intact limb as the amputated limb and allows free movement of the same. This aids in relieving it from uncomfortable clenching positions[73]. Rizzolatti *et al*. explained the basis of this therapy using "mirror neuron" [74] which were discovered in humans by Rossi.[75] Mirror neurons serve in perception of others action, sense other's behaviors, intentions, and emotions.[75,76] and for learning new skills by replication and reproduction. Therefore the mere mirror image of the intact limb provides sensations for the phantom limb. A decrease in PLP is felt by decreasing the disagreement between motor system, proprioception, and visual system. In a study by MacLachlan *et al*. an increased perception of motor control over the phantom limb was reported.[77] while most therapies were associated with short-term benefits, mirror therapy had a significant response as the patient had the freedom to relieve the painful position of the limb.[78]

Other non invasive methods

Patients are trained, to control physiological process such as muscle tension, blood pressure or heart rate using a technique called Biofeedback therapy. Patient who are helped with the biofeedback technique are taught to manipulate these parameters at will. Substantial evidence is lacking to match types of PLP with specific biofeedback therapies. In spite of this, bio feedback can be listed as a beneficial treatment plan [79]. Relaxation techniques and hypnosis have been used for treatment of PLP. Acupuncture is said to be therapeutic in healing of PLP [80, 81]. The efficacy of cognitive behavioral therapy in neuropathic pain syndromes is published in a number of case studies [82, 83].

Surgical Intervention

It is a last resort treatment method, when other methods have failed to produce beneficial results. One effective method involves, lesioning the dorsal root entry zone (DREZ) on upper limb phantom pain resulting from brachial plexus avulsions[84]. In another treatment method spinal cord stimulation was found to be successful [85]. Deep brain stimulation of the periventricular gray matter and thalamic nuclei have shown improvement of PLP. Simulation of the Motor cortex was also found to be helpful in a case of PLP [86].

Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is done under general anesthesia, in which small electric currents are passed through the brain, intentionally triggering a brief seizure. ECT seems to cause changes in brain chemistry that can quickly reverse symptoms of certain mental illnesses. A case report employing ECT as the method of treatment and has been successful[87].

Quality of life

Phantom phenomenon affects amputees, compromising their lifestyle and has a major impact on their quality of life. Most of them are entirely or to a degree compromised of daily activities, excepting appetite. The ability to perform various tasks, chores and humor were most affected. Amputation imposes difficulties, limitations and restrictions [88]leading to loss of independence, individual and financial limitations worsened by insufficient public policies. Chronic pain affects their psychological state and many of these patients suffer with chronic depression. The mental impact of amputation is greater than its physical counterpart as the event translates into alterations in body image, psychosocial adjustment, with influence on their sense of worth and the possible surfacing of psychopathological symptoms and puts a hold on social functioning.[89] The loss of a limb challenges the normal functioning of the body and affects physical and psychological conditions amputees. It impacts, not only the patient's body and his perception, but also the view of the world around him [90]. They believe they have lost physical integrity. Moreover their professional life has been altered by the surgery.

Limitations

It is seen that there is no level 1 evidence to manage PLP currently[91]. New evidence shows the involvement of the autonomic nervous system in the pathogenesis of PLP. Sympathetic targets require further investigation.

Conclusions

The phantom phenomenon is a chronic post-surgical pain with high incidence and profoundly affects the quality of life in amputees. Its treatment poses a huge challenge as the potential of the efficacy of treatment varies from person to person. Medication has a satisfactory but limited effect. Mirror therapy is a new non invasive and exciting low cost neuromodulation technique, which has showed promise though it still needs research and further study to ascertain its role in the future management of PLP. Larger studies are required to investigate this phenomenon, both in terms of pathogenesis and effective treatment as it has a high morbidity.

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