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Phantom pain - etiopathogenesis and treatment methods

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ABSTRACT

Introduction and Purpose

Phantom limb pain (PLP) is a complex and multifactorial phenomenon that arises following limb amputation, affecting a significant number of patients. This study aims to explore the underlying mechanisms of PLP, assess current treatment strategies, and evaluate the effectiveness of various therapeutic interventions, including pharmacological and non-pharmacological approaches.

Material and Methods

A comprehensive literature review was conducted using the PubMed database, focusing on articles published up to the end of 2023. The search included the keywords: "amputation", "mirror therapy", "pain", "phantom limb", "amputation-induced pain", "chronic pain" in various combinations. Relevant studies were selected based on criteria such as the etiopathogenesis of phantom pain and its treatment methods.

Results

The findings indicate that PLP is associated with both peripheral and central nervous system changes, influenced by individual risk factors such as genetics and psychological state.

Therapeutic interventions such as mirror therapy, graded motor imagery, and neuromodulation have shown promise in alleviating symptoms, although the evidence for their effectiveness remains variable. The implementation of a multidisciplinary approach significantly improves outcomes in managing PLP.

Conclusions

Effective management of phantom limb pain requires a comprehensive understanding of its etiology and a tailored treatment strategy that incorporates both pharmacological and non- pharmacological methods. Future research should focus on establishing robust clinical protocols and long-term efficacy studies to enhance the quality of life for individuals suffering from PLP.

Keywords: Amputation, mirror therapy, pain, phantom limb, Amputation-induced pain,chronic pain,

INTRODUCTION

Amputations are most commonly caused by trauma, war, armed conflict, vascular disease, and cancer. [1] Phantom limb pain (PLP) is a common complication of amputation, affecting approximately 80% of patients after such procedures. It should be distinguished from other phantom phenomena, which are not painful, and from residual limb pain, which refers to the discomfort felt in the rest of the amputated limb.[2] PLP is characterized by a wide variation in intensity and frequency, which often makes it difficult to provide long-term relief for patients suffering from chronic neuropathic pain. [3] Phantom pain can have a significant impact on the mental health and functioning of amputees, resulting in decreased quality of life, difficulty with activities of daily living, and an increased risk of depression.[4] Psychosocial factors, such as stress or trauma associated with limb loss, may also influence the course and severity of pain.[5] Chronic pain can be profoundly debilitating, limiting the patient's independence, which directly affects their personal and economic independence.

Therefore, the management of phantom pain is critical in the rehabilitation process aimed at restoring function and improving quality of life for amputees. Studies show that phantom pain most commonly occurs between a few days and a month after surgery, and its intensity usually diminishes over time. However, in 5-10% of patients, the pain remains intense for an extended period of time, further interfering with treatment and full rehabilitation[6] Theories on the causes of phantom pain include neuroplastic changes in the primary sensorimotor cortex that occur after peripheral nerves are transected during amputation. Reorganization of the cortex and lack of proprioceptive stimuli can lead to abnormal sensation and pain in the area of the amputated limb. In addition, a mismatch between motor commands and expected but nonexistent sensory stimuli also contributes to PLP. [7] Phantom limb pain is a rare cause of chronic pain in children, but it is associated with pain and disability that is extremelydifficult to manage. Amputations in this age group are most often the result of cancer or trauma treatment and are less common than in adults[8] Understanding the causes and mechanisms of this phenomenon is key to developing effective treatments that include both drug therapy and multidisciplinary approaches. Modern therapeutic approaches focus not only on pain relief, but also on psychological and functional support to help patients adapt to living with pain and improve their overall quality of life.[5]

Etiopathogenesis

Phantom limb pain (PLP) is a very common and difficult to treat condition. The high incidence, the intensity of the pain experienced, and the significant impact on patients' qualityof life have forced physicians and researchers to continually search for new methods to prevent, treat, and reverse this chronic pain condition. The problem is further complicated by the fact that patients often experience phantom pain of varying degrees and severity, which can greatly hinder the implementation of effective therapeutic interventions. [4] To date, few treatments for phantom pain have been proposed based on its mechanisms. The etiology of phantom limb pain (PLP) is complex and multifactorial. Some studies suggest that central changes, especially in brain structures, play a key role, but peripheral and psychological factors also influence its occurrence. The importance of pre-amputation pain and its associated central and peripheral changes has also been highlighted. [2] Modern science often accepts the hypothesis that PLP results from reorganization of the cortex after amputation.

The loss of sensory input to the area of the brain responsible for the amputated limb allows neighboring regions to take over the area, leading to abnormal processing of sensory stimuli and experiences. These adaptive neuronal changes have been shown to underlie the PLP phenomenon, which in turn has inspired the development of new therapeutic approaches, such as mirror therapy (MT) and sensory discrimination techniques, which aim to reduce symptoms by restoring somatosensory structure in the brain. [9] Studies show that brain activity associated with phantom hand movements correlates with PLP, suggesting that the preserved functional representation of the limb may influence the occurrence of pain. This suggests the need for further investigation of brain mechanisms beyond S1 reorganization, as well as contextual factors that influence brain changes, to better understand and alleviate PLP.[10] The original theories of PLP focused on the involvement of neurofibromas, or abnormal growths of nerve tissue, but cases of pain occurring immediately after amputation were also noted, suggesting the influence of other factors. More recent studies have focused on the limitations of repairing severed nerves, the influence of the dorsal root ganglion (DRG), and preamputation pain. For example, patients who experience pain prior to surgery have an increased susceptibility to PLP, although the discomfort may subside over time.

Conflicts in the neuromatrix-the cortical representation of the body that adapts to life experiences-may also play a role. The lack of feedback from the amputated limb may amplifypain because the cortical areas responsible for the missing limb continue to function. These effects may explain experiments such as the "rubber hand illusion," in which the synchronization of touch makes participants feel the rubber limb as their own. Animal studies have found that after amputation, the somatosensory cortex reorganizes as neighboring areas take over the functions of the amputated limb. Human studies suggest a similar reorganization, in which activity in the facial area can evoke a sensation of pain at the site of the missing arm. The partial role of proprioception - awareness of the body's position - may result in memories of the limb's position being stored in a "proprioceptive memory", leading to the sensation of phantom pain despite the amputation.[11] Autonomic dysfunction iscommonly observed in patients with chronic pain and plays a significant role in the severity or relief of pain. Studies suggest that the nervous system contributes to the pathophysiology of amputation pain. For example, the administration of epinephrine often exacerbates pain, while sympathetic blockade relieves it. These mechanisms include increased reactivity of damaged sensory nerves to catecholamines and increased expression of alpha-1-adrenergic receptors on primary afferent nociceptors, which can lead to hyperalgesia. This phenomenon is also associated with central sensitization, which renders A-beta mechanoreceptors sensitive to pain, and increased secretion and proliferation of sympathetic nerve endings in the dorsal root ganglia.[12] Patients with chronic phantom pain (PLP) and complex regional pain syndrome and chronic neuropathic pain show increased levels of pro-inflammatory mediators and decreased levels of anti-inflammatory mediators. This suggests that PLP is closely associated with chronic inflammation. Studies in animal models have shown that after peripheral nerve injury, microglial proliferation occurs in both the dorsal root ganglia (DRG) and the dorsal horns of the spinal cord, leading to sensitization of neurons in these areas.

Microglia activated by nerve injury release pro-inflammatory cytokines such as IL-1 and TNF, resulting in the development of inflammation and increased levels of neuropathic pain.[13]

Therapeutic Methods

Phantom limb pain (PLP) is difficult to treat, and many studies of pharmacotherapy have yielded unsatisfactory results. [7] Pharmacologic treatment of PLP focuses on relieving symptoms rather than eliminating the causes of pain. Several groups of drugs are used: NSAIDs, tricyclic antidepressants, antiepileptics, and opioids. Antidepressants, such as amitriptyline, work in several ways - they inhibit serotonin and norepinephrine reuptake, block sodium channels, and block NMDA receptors. Although they have applications in the treatment of neuropathic pain, their efficacy in PLP is limited. Opioids, such as morphine and oxycodone, provide analgesia without loss of sensation and affect reorganization of the sensorimotor cortex, but their use is associated with a higher risk of side effects than antidepressants or gabapentin. Overall, pharmacotherapy provides minimal to moderate relief of PLP.[13] A study of amputees at high risk for acute stump and phantom pain found that continuous infusion of 0.5% ropivacaine effectively controlled pain in 97% of patients.

However, 30-40% of patients developed residual phantom sensation, which may be the result of "premature" termination of the infusion. Continued infusions for a median of 30 days almost completely eliminated significant phantom pain[14]. In another study of 71 lower extremity amputees, a continuous infusion of ropivacaine was used to control phantom and residual limb pain. This infusion significantly reduced pain - the percentage of patients withsevere pain dropped from 73% after surgery to 3% at 12 months. Although phantom sensation remained in 39% of patients, all did well with the infusion at home. The results suggest that prolonged infusion of ropivacaine is effective in relieving pain and phantom sensation after amputation[15] In cases where PLP is associated with painful neuromas, surgical excision is recommended. Although 30-50% of patients experience a reduction in pain, 42% of cases experience a recurrence within a year, often in an aggravated form.

Alternatively, non-pharmacological methods such as mirror therapy and neuromodulation techniques are used to alter the processing of pain signals in the central nervous system. Mirror therapy involves graded motor imagery that allows an amputee to "imagine" the missing limb in motion, which reduces the perception of pain by altering the signals generated by the brain. The TENS technique, which involves transcutaneous electrical nerve stimulation, helps reduce phantom pain and promotes the restoration of afferent function in the cerebral cortex. TENS affects C-fibers or reorganizes the body map in the CNS, but its effectiveness for long-term pain relief is limited. Direct stimulation of neurons in the dorsal root ganglia (DRG) has been shown to be more effective. Mirror therapy and transcutaneous electrical nerve stimulation (TENS) have been shown to be effective for short-term pain relief. In the field of neuromodulation, repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and pulsed radiofrequency ablation (PRFA) have been used. rTMS produces short-term but effective pain relief by stimulating the M1 motor cortex and inhibiting activity in the intact hemisphere. PRFA, a variation of conventional radiofrequency ablation (CRF), provides up to 80% pain relief for at least six months while avoiding the risk of tissue destruction, a common side effect of CRF.[13] Studies suggest that neuromodulation using repetitive transcranial magnetic stimulation (rTMS) may lead to significant improvement in chronic phantom limb pain (PLP). However, the paucity of studies, the heterogeneity of patient characteristics, and the lack of long-term results point to the need for more comprehensive and large-scale clinical trials (RCTs).[16] Both mirror therapy and TENS (transcutaneous electrical nerve stimulation) have shown effectiveness in relieving phantom limb pain in the short term. The study showed no significant differences in the effectiveness of the two methods.[17] Neuromodulatory therapies using deep brain stimulation to treat phantom limb pain are used only in the most severe cases. Stimulation targets include the thalamic nuclei and motor cortex, while new targets such as the anterior cingulate cortex are still experimental due to the risk of serious side effects such as seizures. A multidisciplinary approach that integrates the biopsychosocial aspects of pain management is critical for successful rehabilitation[18] In a study of 24 unilateral lower limb amputees, participants were randomized into two equal groups: control and experimental. The control group received mirror therapy and conventional physical therapy, while the experimental group also received phantom exercises. The standard physical therapy included conventional movement exercises, while the phantom exercises involved imagining the movement of a non-existent limb and attempting to perform those movements. The results showed that patients who also performed phantom exercises achieved significant improvements in pain reduction compared to those who were treated with mirror therapy and standard physiotherapy alone[18] Another study presented the case of a man in his fifties, a truck driver, who experienced phantom and stump pain after amputation of his left ring finger. Despite the use of postoperative medications, rest pain was high. Ulnar and median nerve blocks were performed, which provided significant relief and reduced the pain. Peripheral nerve blocks have been shown to be an effective method of treating phantom and stump pain [19]. One study presented two cases of patients with phantom pain. The first was a 41-year-old woman who experienced piercing hand pain and numbness in her fingers three years after endoscopic carpal tunnel release. The second case is a 42-year-old woman who had unsuccessful calf nerve surgery six years after treatment for a fractured ankle and experienced debilitating pain and numbness. Examination revealed a lack of sensation in the area of the nerve, and nerve blocks failed to provide relief. Both developed chronic phantom pain requiring non-surgical treatments such as pharmacologic pain relief and psychotherapy"[20].

Table 1. Overview of phantom pain treatment methods

Treatment	**Method Type of Intervention**	**Mechanism of Action**	**Effectiveness**	**Comments**
Mirror Therapy	Visual Therapy	Illusion of amputated limb restoration through reflection in a mirror	High (short term)	Limited evidence long term
Imaginal motor stimulation	Cognitive therapy	Imagining the movement of the amputated limb, which activates the motor centers	Moderate	Requires intensive patient involvement

Virtual feedback (VR)	Virtual therapy	Simulation of limb movement in VR, which	High (short term)	Good effects, requires
		creates a realistic impression of limb function		specialized equipment
TENS (Transcutaneous Electrical Nerve Stimulation)	Electrostimulation	Transcutaneous stimulation of nerve endings that modifies pain perception	High (short-term)	Easily accessible and safe
Peripheral Nerve Stimulation	Neuromodulation	Blocking pain signals by stimulating selected peripheral nerves	Moderate to high	Use in refractory cases
Nerve blocks	Local anesthesia	Temporary blockade of pain transmission by injection of an anesthetic into the nerve	High (short-term)	Effective in a short time
Alcohol neurolysis	Chemical ablation	Destruction of a nerve with alcohol to permanently reduce pain signals	Varied	May cause side effects
Analgesics	Pharmacotherapy	Analgesic effects through effects on the central or peripheral nervous system	Moderate to high	Efficacy varies depending on the drug
Transcranial magnetic stimulation (rTMS)	Neuromodulation	Stimulation of the cerebral cortex with a magnetic field to modulate pain perception	High (in some patients)	Still experimental
Psychotherapy	Psychosocial therapy	Psychological support and pain management techniques through cognitive behavioral therapy	Moderate to high	Supports non-pharmacologica l treatment

Spinal cord stimulation (SCS)	Neuromodulation	Implantation of an electrode in the spinal cord area, which dampens the transmission of pain signals	High (for chronic pain)	Invasive, for resistant cases

Summary

Phantom limb pain is a complex process involving profound functional and structural changes in the peripheral and central nervous systems. These changes interact with individual patient risk factors such as medical, psychosocial, and genetic. The amputee population is highly diverse.[21] To reduce the risk of severe phantom pain, consistent prevention and management of postoperative pain is essential. Early implementation of pharmacologic and non-pharmacologic interventions is critical. In addition, both careful planning and precise surgical technique as well as effective interdisciplinary management are important to achieve or restore normal body function.[5] Mirror therapy, imaginal motor stimulation, and virtual visual feedback show potential in reducing phantom limb pain, but there is limited scientific evidence to support their effectiveness.[22] High-quality trials of non-surgical, percutaneous therapies for residual limb pain (RLP) and/or phantom limb pain (PLP) are still lacking.[23]

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