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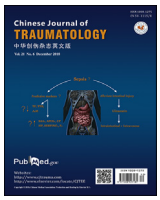

Review Article

Phantom limb pain: A literature review

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ABSTRACT

Since the phantom limb sensation was first described by the French military surgeon Ambroise Pare in the 16th century, the number of studies surrounding phantom limb pain has increased every year. Especially in recent decades, scientists have achieved a better understanding of the mechanism and treatment of phantom limb pain. Although many hypotheses have been agreed and many treatments have been proven effective, scientists still do not have a very systematic understanding of the phantom limbs. The purpose of this review article is to summarize recent researches focusing on phantom limb in order to discuss its definition, mechanisms, and treatments.

Introduction

Limb salvage is a major component of podiatry with the goal to preserve the function and length of the lower extremity while treating possible co-morbidities and infection. Lower extremity anatomy amputation may be involved in the course of treatment as determined by the physician and patient. Lower limb amputation etiologies include vascular disease, trauma, infection, and cancer. Indeed vascular pathology is a recurring cause for lower extremity amputations with increased incident rates in adults of 65 years old or more.[1] In the United States, 1.7 million people live with limb loss each year, and there are 185,000 new lower extremity amputations, which accounted to about 86% of the total amputations.[2,3] Pain can occur due to a variety of stimuli including infection, trauma, stump pain, and in the postoperative setting. Painful post-amputation sensation was first recorded in the 16th century on French military soldier patients; in the 19th century such symptoms were identified as phantom limb pain. More recently, approximately 60%–80% of amputees experience phantom limb sensations.

The incidence of phantom limb pain has varied from 2% in earlier records to higher rates today. Initially, patients were less likely to mention pain symptoms than today which is a potential explanation for the discrepancy in incidence rates. However, Sherman et al.[4] discuss that only 17% phantom limb complaints were initiated treated by physicians. Consequently, it is important to determine what constitutes phantom pain in order to provide efficacious care. Phantom pain is pain sensation to a limb, organ or other tissue after amputation and/or nerve injury.[5] In podiatry, the predominant cause of phantom limb pain is after limb amputation due to diseased state presenting with an unsalvageable limb. Postoperative pain sensations from stump neuroma pain, prosthesis, fibrosis, and residual local tissue inflammation can be similar to phantom limb pain (PLP). Patients with PLP complain of various sensations including burning, stinging, aching, and piercing pain with changing warmth and cold sensation to the amputated area which waxes and wanes.[6] Onset of symptoms may be elicited by environmental, emotional, or physical changes.

Neurology behind phantom limb pain

The human body encompasses various neurologic mechanisms allowing reception, transport, recognition, and response to numerous stimuli. Pain, temperature, crude touch, and pressure sensory information are carried to the central nervous system via the anterolateral system, with pain & temperature information transfer via lateral spinothalamic tracts to the parietal lobe. In detail, pain sensation from the lower extremity is transported from a peripheral receptor to a first degree pseudounipolar neurons in the dorsal root ganglion and decussate and ascend to the third-

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degree neurons within the thalamus.[7] This sensory information will finally arrive at the primary sensory cortex in the postcentral gyrus of the parietal lobe which houses the sensory homunculus.[8] It is unsurprising that with an amputation that such an intricate highway of information transport to and from the periphery may have the potential for problematic neurologic developments.

How does pain sensation, a protection mechanism for the human body, become chronic and unrelenting after limb loss? This is a question researchers still ask today with no concise conclusion. Phantom limb pain occurs more frequently in patients who also experience longer periods of stump pain and is more likely to subside as the stump pain subsides.[9] Researchers have also found dorsal root ganglion cells change after a nerve is completely cut. The dorsal root ganglion cells become more active and sensitive to chemical and mechanical changes with potential for plasticity development at the dorsal horn and other areas.[10] At the molecular level, increasing glutamate and NMDA (N-methyl D-aspartate) concentrations correlate to increased sensitivity which contributes to allodynia and hyperalgesia.[11] Flor et al.[12] further described the significance of maladaptive plasticity and the development of memory for pain and phantom limb pain. They correlated it to the loss of GABAergic inhibition and the development of glutamate induced long-term potentiation changes and structural changes like myelination and axonal sprouting.

Besides the aforementioned neurotransmitters, norepinephrine, another major ligand, may shed light to the influence of the sympathetic nervous system in regulating pain sensitivity. With increased norepinephrine, postganglionic sympathetic nerve fibers in animals become excited and thus more sensitive and this increase in sensitivity can lead to increased pain awareness.[13] Besides the molecular level, patients may also develop signs of localized changes. Locally, upregulation of the sodium channels is correlated to more frequent bouts of pain.[14] At the local amputation site, a neuroma may form where a nerve is severed.[15] Neuroma activity may be triggered with local chemical, manual, and mechanical stimulation, resulting in pain sensation.

Neural plasticity is a concept which states that the adult brain is capable of dynamic modulation and is an inherent part of the adaptive structure of the nervous system throughout an individual's lifespan. It has been theorized that such retraining, both short-term and long-term, consists of modulations to neural structures with gray matter and white matter involvement.[16] In detail, it is hypothesized that gray matter changes may involve glycogenesis, vascularization, and synaptogenesis while white matter undergoes axonal sprouting and myelination.[17] The correlation between neural plasticity within the cortex has also been described in study of primates after the development of extremity lesions or sensory pathologic changes.[18] Jiang et al.[19] studied the development of brain gray matter and white matter plasticity after a lower limb amputation in 17 right lower limb amputation patients (13 male and 14 female) alongside 18 healthy control patients using tract-based spatial statistics and tractography analysis. Using T1 MRI they noted any changes in white matter cortical thickness and fractional anisotropy. In amputated patients, the saw evidence for the fractional anisotropy decreasing in white matter areas of the right superior corona radiata in right temporal lobe, left PMC, and right inferior fronto-occipital fasciculus. In addition, the left premotor cortex thinned on average with smaller clusters in visual-to-motor regions. In contrast, they did not notice any significant changes to the aforementioned areas in healthy control patients, thus giving evidence to the changes to cortical areas representing an amputated limb.[19]

Furthermore, an important area of neural plasticity is in the brain of a patient after a stroke. Considerable research has been done on the effects of neural plasticity after stroke. Klein et al. highlighted injured neurons with new and healthy neurons while development of new pathways for axons and in the cortex compensation of function by areas not damaged by stroke for areas damaged and experiencing function loss.[20] Similarly, these dynamic changes would mean that with an upper limb amputation or complete nerve cut, the face somatosensory cortex would invade the arm somatosensory cortex as expressed on the Penfield map.[21] Interestingly, Sivan et al. showed a correlation in phantom limb pain and visceral movement sensation. 200 Patients with lower limb amputations were studied from two rehabilitation centers with thirteen patients experiencing changes in micturition and defecation. With an amputation to the fever, phantom pain symptoms were triggered if the bladder became full in one patient and decreased after micturition.[22]

Phantom limb pain is a type of chronic pain and the genetics of chronic pain is still being established. Nearly 15%–50% of the population experiences pain which may require clinical care. In addition, around 30%–70% of chronic pain is related to heritability.[23] It is unknown the total amount of genes involved with pain symptoms let alone the influence of environmental factors. In Great Britain, research detailed nearly two thirds of genetic variants involved with chronic pain identified through Genome wide analysis technology.[9] Single nucleotide polymorphisms in genes GCH1 and KCNS1 were discovered to increase bouts of chronic pain in mice. The GCH1 gene encodes for serotonin, nitric oxide, and a catecholamine co-factor.[24] When blocked, analgesia was experienced, suggesting that increased GCH1 expression manifests as greater pain sensitivity. Furthermore, the KCNS1 gene encodes for potassium channel subunits and genetic mutations to this gene impact neuron excitability which has been seen in patients post-limb amputation.[9]

Treatment options

Phantom limb pain in some patients may gradually disappear over the course of a few months to one year if not treated, but some patients suffer from phantom limb pain for decades. Treatments include pharmacotherapy, adjuvant therapy, and surgical intervention. There are a variety of medications to choose from, which includes tricyclic antidepressants, opioids, and NSAIDs, etc. Among these medications, Tricyclic antidepressant is one of the most common treatments. Studies have shown that Amitriptyline (a tricyclic antidepressant) has a good effect on relieving neuropathic pain.[25]

Adjuvant therapy includes transcutaneous nerve stimulation (TENS), mirror therapy, biofeedback, electroconvulsive therapy, acupuncture, and massage, etc. Transcutaneous nerve stimulation has been proved to be helpful for reducing the phantom limb pain.[26] In addition, a significant reduction of phantom limb pain during transcutaneous nerve stimulation was found compared with the controlled group.[27]

Mirror therapy refers to the use of flat mirror imaging principle to copy the picture of the healthy side to the affected side and let the patient imagine movement of the affected side. Through the use of optical illusions, visual feedback, and virtual reality, mirror therapy has been found to be an effective treatment for phantom limb pain. With this therapy, patient's limbs are placed within a frontless and topless box with a central-vertical placed mirror. Then the patient places the unaffected limb on a side with the mirror image acting as the missing limb. This mirage tricks the brain to believing the amputated limb has returned. Some of the studies found that mirror therapy is based on mirror neurons. The neurons activated by their own behavior also activate when they observe other people's activities. The behavior of projecting the observed external behavior into their own behavior makes the neurons in the

F5 area be named as mirror neurons.[28] One of the studies showed all 22 patients went through mirror therapy reported a decrease in pain after 4 weeks of treatment. In contrast, only 17% and 33% of the patients in the two controlled groups reported decrease in pain.[29] The most common surgical interventions for treating phantom limb pain includes neurectomy, nerve block, and stump revision, etc.

One of the latest adjunct therapy being presented is virtual reality (VR). Ortiz-Catalan et al. used a myoelectric sensor to detect the muscle potential on the stump, and then predicted what kind of movement the patient wanted to perform on the amputated limb. Immediately afterwards, the virtual limb on the screen will do these movements. Hence, when the patient looks at the screen, he/she patient still has amputated limbs and can do whatever he/she likes. The system makes the patients feel more realistic compare with conventional mirror therapy. Overall, VR therapy is particularly effective for patients with chronic phantom limb pain. In the 14 patients who participated in this research, their pain level decreased by an average of 50% after the VR treatment.[30]

Surgical treatments are not often used unless all other treatments have failed. Besides the surgical interventions mentioned above, some CNS stimulation such as deep brain stimulation and spinal cord stimulation are both found helpful in relieving phantom limb pain in varying degrees.[31]

Conclusion

Phantom limb pain is very common in amputees. As a worldwide issue, it has been studied by a lot of researchers. Although phantom limb sensation has already been described and proposed by French military surgeon Ambroise Pare 500 years ago, there is still no detailed explanation of its mechanisms. Therefore, more research will be needed on the different types of mechanisms of phantom limb pain. Once researchers and physicians are able to identify the mechanism of phantom limb pain, mechanism-based treatment will be rapidly developed. As a result, more patients will be benefit from it in the long run.

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