Phantom Menace: The Mystery of Phantom Limb Pain: A Case Report and Review of the Literature

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Abstract
A significant number of patients with amputations experience phantom limb pain. It is a phenomenon that had been reported as early as the sixteenth century. Notably, in up to 70% of patients, phantom pain persists 25 years after the amputation. A significant medical implication of phantom pain is that the phantom limb becomes a considerable impediment to successful rehabilitation. Neuroras within the stump and spinal cord hyperexcitability are previously proposed mechanisms for this phenomenon that have since been disproven. More recent theories are based upon the concepts of a neuromatrix or cortical remapping, the latter of which challenges the generally accepted notion that the neural connections laid down in fetal life are fixed, and therefore has potential implications for the possibility of future treatment of more central deafferentation processes, including stroke. Currently, few treatments for phantom pain have been proven to be effective. Amitriptyline (Elavil™) has been the most studied tricyclic antidepressant for phantom pain and is recommended as the first choice for treatment. Other pharmacologic agents reported to possess varying efficacies for the treatment of phantom limb pain include antiarrhythmics, anticonvulsants, opioids, GABA receptor agonists, N-methyl-D-aspartate (NMDA) receptor antagonists, adrenergic agonists, and calcitonin.

Truly, it is a thing wondrous, strange, and prodigious which will scarce be credited, unless by such have seen with their own eyes and heard with their own ears, the patients who many months after cutting away the leg, grievously complained that they yet felt exceedingly great pain in that leg so cut off.

-Ambrose Paré (1510 - 1590) French military surgeon1

Mr. A.W., a 64 year old patient, was interviewed four months after his left below knee amputation (BKA) secondary to peripheral vascular disease attributed to advanced Type I diabetes mellitus. Seven years previously, he had a right BKA (also due to his diabetes mellitus) for which he has a prosthesis. Comorbidities included: diabetic nephropathy, for which he had been on hemodialysis for the past two years; ischemic heart disease; hypertension; bowed ischemia with subsequent ileostomy; and diabetic retinopathy. He had experienced delayed wound healing with his recent left BKA, with complete healing of approximately three months duration. At the time of the interview, he had minimal stump edema. He reported no stump pain. However, he did describe intermittent "sharp" phantom pain in his toes, primarily in both large toes, that ranged in frequency between once per day to once every few months. The onset of the phantom pain occurred in each toe "shortly after" the respective amputations. Between the episodes of phantom pain, he had solely phantom limb sensation, whereby he could feel the presence of both his feet.

During peacetime, the primary indication for amputation is peripheral vascular disease (PVD). In fact, 60% of amputations are attributed to PVD, and half of these patients also have diabetes mellitus.2 The majority of patients with amputations are elderly, and therefore the associated physiological phenomenon of "phantom limb" pain is most frequently experienced by this population, and many present with several co-morbidities.2 Phantom pain may not only be excruciating for the elderly patient, but may also reduce self-esteem, impair the ability to perform activities of daily living, limit independence, and can lead to depression.2 Thus, investigation into the pathophysiology of phantom limb pain and the development of rational therapies is especially important to this population. Any intervention, particularly in elderly patients with complex medical issues, must be balanced against potential risks, side effects and complications.

Phantom limb pain is a phenomenon reported as early as the sixteenth century.1 At that time, French military surgeon Ambrose Paré recognized the peculiar fact that patients, often months or even years following their amputation, complained of agonizing pain in the region of the removed limb.3 Subsequently, there have been many clinical examples of phantom pain. Often, through an unexplained concept known as "imprinting", the limb may feel as if it is immobilized in the position that it was in at the time of a traumatic amputation. For example, a motorcyclist who had forcefully gripped his hands onto the handlebars at the moment of impact in a motor vehicle accident reported his phantom pain as a clenched hand with the fingers bent over the thumb and digging into the palm.4 Another patient who had lost his hand when a grenade which he was holding detonated reported a lingering and intense phantom pain of explosive quality.4 Phantom pain discomfort can range in intensity from a cramp in the calf, to the toes feeling that they are "being seared by a red hot poker".5 There have also been reports of phantom pain resembling chronic painful sensations, such as a painful ulcer or bunion, in the limb prior to the amputation.5 Melzack notes it is striking that these patients are not simply recalling such feelings, but are, in fact, experiencing them.
with the details of an ongoing sensation; indeed, the experiences are perceived as real.

A significant medical implication of phantom pain is that the phantom limb becomes a considerable impediment to successful rehabilitation.\(^3\) The incidence of severe pain is such that it constitutes a significant clinical problem: up to 70% of patients with phantom pain report its persistence up to 25 years after the amputation.\(^6\) In fact, pain is present in the first week after amputation in 50-75% of patients.\(^3\) The pain is commonly localized distally in the phantom limb; one study of 64 above-knee amputation patients with phantom pain showed that 66% had pain in the foot or toes, 39% had additional pain in the calves, while only 6% had pain also in the quadriceps region.\(^3\) However, there is great discrepancy among the reports of overall incidence of phantom pain (ranging from 2 to 97%), making the true burden of phantom pain difficult to ascertain. Several explanations have been proposed for this wide variation in incidence. Firstly, there is disagreement over what may be included in the definition of phantom limb pain. The International Association for the Study of Pain (1986) defines the condition as "pain referred to a surgically removed limb or portion thereof." However, there have been many reports of phantom pain subsequent to accidental amputation, as well as in patients with paraplegia, brachial plexus avulsion, and even in those with congenital limb deficiencies.\(^5\)\(^,\)\(^7\) Secondly, differences in patient pain threshold and pain tolerance as well as variation in the methods by which phantom pain sensations are portrayed and recorded, make a distinct definition elusive. Thirdly, the method of eliciting a description of phantom pain is not without bias, since direct questioning is likely to conclude a higher incidence of phantom pain than that determined by waiting for unprompted patients to offer their symptoms.\(^7\)

The incidence of phantom pain specific to the elderly also shows disparity.\(^2\) Historically, behavioural science literature indicated that phantom pain was either a manifestation of an emotional problem or of personality structure; many patients with amputations in earlier years reported that their physicians directly stated that the pain was "just in their heads".\(^8\) Consequently, elderly patients may remain unwilling to divulge that they are experiencing phantom pain for fear of their physician thinking that they may be suffering from a mental illness. In an amputee survey by Sherman et al.,\(^4\) the great majority of patients with amputations stated that they feared losing their credibility with their physician by reporting phantom pain. These patients were concerned that any further reporting of stump difficulties would not be taken seriously, especially when a verbal complaint is often the only evidence of a stump problem with the patient. This rationalization could explain the differences in the reported rate of phantom limb pain in the elderly. Indeed, the most recent evidence implies that phantom pain is influenced by psychological factors such as stress and depression, which can aggravate phantom pain.\(^3\) Like other chronic pain syndromes, however, there is no convincing evidence that personality disorders play a role in the etiology of phantom pain.\(^5\) Rather, the most recent efforts to explain phantom pain, particularly those by Katz and Melzack\(^5\)\(^,\)\(^10\) and Ramachandran and Hirstein,\(^6\) suggest that phantom pain has a very real physiological basis.

The oldest explanation for phantom pain proposes that the remaining nerves at the amputated end of the stump continue to grow into neuromas.\(^3\) These neuromas produce a rapid rate of impulses which travel to the spinal cord, ascend to the thalamus, and then relay to the somatosensory area of the cortex.\(^5\)\(^,\)\(^11\) This concept led to the theory of a peripheral origin of phantom pain. However, attempts to permanently abolish phantom pain have been unsuccessful. These attempts have included the elimination ofafferent input from the stump by administration of local anesthetic and by severing of the nerves immediately proximal to the neuroma from the stump,\(^5\) severing pathways within the spinal cord, and removal of the regions of the thalamus and cortex that receive the removed limb's sensory input.\(^5\) Thus, activity within the stump itself cannot explain phantom pain.

Overactive, spontaneous firing of neurons within the spinal cord was the central theme of another hypothesis for phantom pain. Because these neurons had lost their usual sensory input from the amputated limb, it was reasoned that their resulting hyperexcitability was received by the cortex, thereby causing the perception of phantom pain.\(^1\) This theory was later refuted by observations of phantom pain in the legs of paraplegics who had complete injury to either the thoracic, lumbar or sacral region of their spinal cords. The spinal cord theory could not explain how these nerve impulses, apparently generated below the damaged region of cord, were still able to travel up to the brain.\(^5\)

The most recently proposed explanations for the etiology of phantom pain are those of Katz and Melzack\(^5\)\(^,\)\(^10\) and Ramachandran and Hirstein.\(^6\) Both theories agree that the phantom limb experience is so complex that higher levels of the nervous system, specifically the brain, must be involved. However, each theory has a unique perspective on the origins of phantom pain.

Melzack postulates that within the brain lies a "neuromatrix" – a network of neurons that responds to sensory input and constantly produces a specific pattern of impulses, called the "neuromatrix", which registers that the body is intact.\(^5\) According to this theory, the neuromatrix continues to operate even in the absence of input from an amputated limb, thereby "creating the impression of having a limb even when that limb has been removed".\(^5\) Melzack envisions the neuromatrix to be composed of three brain circuits: the classical sensory pathway, the limbic system pathway responsible for emotion and motivation, and cortical pathways in the parietal lobe essential for the recognition of self.\(^5\) Respectively, these three components potentially account for the sensation of pain, the affective descriptions of phantom limbs as "exhausting" or "penetrating", and the sense that the pain of the limb is actually a part of the patient. Furthermore, Melzack deduces that the neuromatrix must be determined genetically, due to observations that congenital limb deficient patients are also capable of experiencing phantom pain.\(^13\) Little research has been performed to test Melzack's idea. In fact, many studies exploring the causes of phantom pain are methodologically flawed, in that they have small, heterogeneous samples, are non-randomized, lack appropriate control groups, and have short patient follow-up periods.\(^9\)\(^,\)\(^14\)

However, Ramachandran and Hirstein\(^6\) have presented the most up-to-date theory of the cause of phantom sensation and pain, and have extensively described their experimental findings. In one experiment, upon touching specific regions in the face of a patient with an amputated left arm, the patient noted a tingling sensation in the fingers of the missing limb. Further investigation showed a systematic one-to-one mapping between specific regions of the face and individual fingers (i.e., cheek to thumb, upper lip to index finger, etc.), and that these relations were stable over 6 months.
These authors postulated that because the map of the hand is adjacent to the face on the sensory homunculus in the cortex, the sensory input from the face may have "invaded" the area of the homunculus normally devoted to the hand. It was proposed that the hand cortical area was overtaken by the facial cortical area because the hand region was no longer receiving sensory input due to the amputation. This theory would also explain why other patients with foot amputations have reported sexual sensations in their missing foot during intercourse: the genital area is located next to the foot area on the homunculus. It is not clear, however, why the sensations are specifically only sexual. This theory may explain why a patient with an amputation can still sense pain in a limb that is physically no longer part of the body; sensory input from adjacent areas on the homunculus may have overtaken the area previously receiving input from the amputated limb. This "theory of cortical remapping," along with several other examples of neural plasticity, challenges the widely-held dogma that neural connections established in fetal life are immutable. If this theory is verified, then the potential to reorganize neural pathways later in life may have implications for treatment of more central deafferentation, such as stroke.

Earlier studies by Sherman et al. suggested that many physicians previously considered phantom pain to be "pure imagination," finding that 50-75% of patients with amputations reported phantom pain to their physicians but that only 20% were offered treatment. Although phantom limb pain is now well recognized to be a physiological phenomenon, the lack of a clearly demonstrated mechanism of causation has hindered the discovery of an effective, long-term treatment for this disorder. Another obstacle to offering effective treatment of phantom limb pain is that although numerous case studies have been reported, there have been few clinical trials investigating definitive treatments for phantom limb pain. The majority of these studies are small, non-randomized, and open-labelled, in addition to having a relatively high placebo response between 30 and 35%. A review of the literature indicates that very few studies have been undertaken to estimate the cost of phantom pain both to the patient and the health care system.

Presently, there are several options for treatment of phantom limb pain. However, none have been demonstrated to be permanently effective. Tricyclic antidepressants such as amitriptyline (ElavilTM), desipramine (NorpraminTM), and maprotiline (LudiomilTM) can be effective in the treatment of both neuropathic pain and phantom pain, although there is a lack of controlled studies looking specifically at their efficacies when used in phantom pain treatment. In individual patients with phantom pain, the tricyclic agent doxepin (SinequanTM) has also been shown to be effective, although amitriptyline has been more thoroughly studied in this regard and is recommended as the first treatment choice. Well designed, non-experimental studies, such as comparative, correlative-descriptive and case studies have demonstrated that antihypertensive agents such as lidocaine (XylocaineTM), meclozine (MexitilTM) and tocainide (TonocardTM) are effective for phantom limb pain. The mechanism suspected in the effectiveness of these drugs is their ability to reduce hyperexcitability in central neurons. Anticonvulsants, through reducing high frequency repetitious discharges, are moderately successful in the treatment of phantom limb pain. No controlled studies have yet been performed which examine the use of opioids for this disorder, although there have been several reports of their benefit and ability to be well tolerated. Other medications noted to diminish phantom limb pain include GABA receptor agonists (e.g., baclofen (LioresalTM)), NMDA receptor antagonists (e.g., ketamine (KetalarPM)), and adrenoceptor agonists. Again, there have been few clinical trials evaluating the clinical utility of these agents in the context of phantom limb pain.

Recently, studies have investigated the use of calcitonin for the treatment of phantom limb pain. A double-blinded study by Jaeger and Maier looked at 21 individuals with phantom pain in various missing limbs. One week after 200 IU per day of intravenous salmon calcitonin treatment, 90% of patients reported pain relief by at least 50%, and 76% were pain-free. At 24 months, 70% of patients remained free of phantom pain. However, calcitonin given in this manner does have a rare risk of a severe hypersensitivity reaction, and is also associated with nausea and vomiting. Surgery affecting the peripheral or central nervous system invariably generates additional deafferentation, and thus, an increased risk of continuing pain. Therefore, it is recommended that surgery be an option of last resort. Non-pharmacological treatments which have demonstrated varying degrees of success include transcutaneous electrical nerve stimulation (TENS), acupuncture, hypnosis, and spinal cord or deep brain stimulation. Nevertheless, approximately half of those with persistent, chronic phantom pain do not respond to any of these interventions.

The phantom limb phenomenon is frequently unrelenting and excruciatingly painful. The pain in the amputated limb often becomes a major obstacle to effective rehabilitation, leading to disruption of daily activities, depression, weight loss, and isolation. In addition to being a challenge for management, the phantom limb phenomenon may cast further doubt about a fundamental assumption in neurology — that neuronal connections established during fetal development are fixed. Effective treatment of phantom pain has thus far eluded neuroscientists, and a solution to this intriguing mystery will require more thorough investigations into its underlying mechanisms.

References