PHANTOM LIMB SYNDROME: A REVIEW

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Abstract

Phantom limb syndrome is a condition in which patients experience sensations, whether painful or otherwise, in a limb that does not exist. It has been reported to occur in 80-100% of amputees, and typically has a chronic course, often resistant to treatment. Risk factors include the presence of preoperative pain, traumatic amputation, and the type of anesthetic procedure used during amputation. Several pathophysiologic theories have been proposed, including spinal mechanisms, central sensitization, and somatosensory cortical rearrangements, and while recent studies have shed light on some interesting and significant data, a lot remains to be understood. Treatments include pharmacologic, mechanical, and behavioral modalities, but substantial efficacy in well-designed, randomized controlled trials has yet to be demonstrated. Phantom limb syndrome continues to be a difficult condition to both understand and treat.

Introduction

Phantom limb syndrome is a condition in which patients experience sensations in a limb that does not exist. Some patients feel their amputated limb is entirely still present, and these patients can describe the

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posture in which it is held, feel that it moves around, and even does specific tasks. Patients sometimes continue to feel a wedding ring on an amputated finger, or that they are wearing a watch on their amputated arms. Others experience, alone or in combination, pain, tingling, or parasthesias.

The phrase "phantom limb syndrome", and the first clinical description of it, are the work of Silas Mitchell in 1872. Since then extensive research has been done in describing explaining and treating it. Most case reports describe "phantoms" in limbs, but there are reports of phantoms following breast amputation[1,2], parts of the face[3], and internal viscera[4]. There are also descriptions of phantom erections[5], and menstrual cramps after hysterectomy[6]. Phantom limb syndrome has also been reported in congenitally missing limbs[7].

The phrase phantom limb syndrome encompasses both pain and other sensations in the amputated limb; phantom limb pain is approached as a separate clinical entity from phantom limb syndrome. Pain in the stump, called residual pain, or stump pain, is also considered separately in terms of both etiology and treatment, and will not be discussed here.

Course and Clinical Description

Most studies show that 80-100% of amputees experience non-painful phantom sensations. The reported incidence of phantom limb pain is between 60-80% in the early postoperative period. As time passes, the number of patients with pain decreases but remains significant; the duration and intensity of painful episodes does decrease in most. In one series studied in 1984, more than 70% of patients continued to experience phantom limb pain for more than 25 years[8].

In a study by Jensen et al[9], which studied 58 patients undergoing limb amputation, and followed them up for over two years, 84% of patients experienced non-painful sensations in the phantom limb at 8 days postoperatively, 90% experienced such sensations at 6 months, and 71% were still experiencing them at 2 years. 72% of post-amputee patients were experiencing pain 8 days post-op, and 59% at 2 years. The nature of

the phantom pain was reported as knifelike, sticking, burning, squeezing, pricking, or throbbing in the majority of patients. The pain was constant in 50% of subjects and intermittent in the rest. Most patients in this study experienced pre-amputation limb pain. It was reported that the duration of phantom limb syndrome increases in those that had a more prolonged period of pre-amputation pain. Initially, the location of the post-amputation pain was usually very similar to that experienced pre-amputation. Approximately half of all patients experienced pain only in the distal part of their limb, often localized to the digits only, while the other half had pain either in the entire limb or only at its ends[9].

Telescoping

Telescoping refers to the phenomenon in which a phantom arm, which is initially felt as the entire limb, eventually, after years, is felt by the patient to be a phantom hand, ectopically originating at the stump[10]. It occurs in approximately 30% of amputees[11]. It has been suggested that while phantom pain eventually decreases or fades completely in most patients because of the brain's ability to gate or inhibit certain signals, telescoping occurs because "the hand is very much over-represented in the somatosensory cortex... such that its sensations may survive longer"[6].

Risk Factors

The incidence of phantom limb pain increases in those that had preoperative pain as compared to those that had non-painful limbs[9]. As mentioned above, the duration of phantom limb pain seems to be related to the duration of preoperative pain. The incidence of phantom limbs is higher following traumatic amputation as compared with surgical amputation[6]. It has been suggested that this finding may be due to the increased attention paid to the mutilated or painful limb preoperatively[6], others have suggested that the phantom pain in this case represents "the survival of pre-amputation 'pain memories'"[12]. It is less common when amputation occurs in early childhood. In one study, phantom limb

syndrome occurred in only 20% of patients who lost a limb below the age of 2, while 75% experienced it when amputation occurred between ages 6-8, and there was a 100% incidence above the age of 8[8]. Katz suggested that pre-amputation pain, noxious intraoperative stimuli, and acute postoperative pain may contribute to the incidence and duration of phantom limb syndrome[14].

Research shows that "the transmission of noxious afferent input from the periphery to the spinal cord induces a prolonged state of central neural sensitization, which amplifies subsequent input"[15,16]. Limb amputation used to be performed under general anesthesia in order to eliminate awareness and memory of the procedure. However, it was found that the incidence of phantom limb syndrome is higher when using this type of anesthesia rather than regional anesthesia. One proposed explanation is that the spinal cord still "experiences" the insult of the amputation procedure because central sensitization is not influenced by the general anesthesia. Today, nerve block or epidural anesthesia are included in the anesthetic management during most amputations, in an attempt to decrease the risk of phantom limb pain[14,17].

Etiology

Phantom limb syndrome was classically attributed to ectopic, irritative impulses entering the spinal cord from nervous scar tissue or neuromas in the stump of an amputated limb[17]. This theory was later challenged because of the finding that injecting local anesthetic into the area of the stump or surgical removal of neuromas does not abolish the phantom limb pain[18].

Others attempted to explain the phenomenon on a purely psychological basis, as if "phantom limbs are mainly a form of Freudian 'denial', with the pain being part of the 'mourning' process'"[6]. Psychopathological factors have been shown to contribute to the course of the pain, but not the etiology[19,20].

Spinal mechanisms may play a role in the pathogenesis of phantom-

limb pain; increased input from peripheral nociceptors have been shown to increase dorsal-horn neuron excitability, reduce inhibitory processes, and cause structural changes in primary sensory neurons, interneurons, and projection neurons. This is known as central sensitization and is mediated by NMDA receptors and glutamate[21,22].

A possible contribution of the sympathetic nervous system to phantom limb pain has been proposed based on findings that blockade or interruption of the sympathetic supply to the stump results in a temporary alleviation of phantom pain[11].

Melzack proposed that there is a neuromatix, "a network of neurons in several brain areas including the thalamus and somatosensory cortex, the reticular formation, the limbic system, and the posterior parietal cortex-that are the anatomical substrate of the self"[23]. The output from this neuromatrix, which is thought to be genetically determined but modified by experience, forms a "neurosignature", which is unique to each individual and provides each person with information about his/her body and its sensations. The abnormal input into the neuromatrix resulting from amputation stems from both the lack of normal sensory activity and an over-activity in damaged nerves and results in an altered "neurosignature", resulting in phantom limb syndrome[23].

As early as in the 19th century, it was noted that phantom limb sensations could be elicited by stimulating certain areas of the body[24]. Recently, this was explained with the use of magnetoencephalogram (MEG) studies on humans. Ramachandran et al showed that in patients with amputated hands, the areas surrounding that of hand representation in the cortex, namely the face and upper arm areas, expand into the adjacent hand area within a short period of time, as early as 4 weeks post-amputation[6]. This study also demonstrated that stimulation of specific areas on the face causes sensation in specific points in the phantom limb. Theses findings were later reproduced in several studies. Reorganization has also been shown to occur in the thalamus of amputees[25].

Ramarchandran theorized that "tactile and proprioceptive input from the face and tissues proximal to the stump "takes over" the brain hand

area... consequently, spontaneous discharges from these tissues would get misinterpreted as arising from the missing limb and might therefore be felt as a 'phantom'[6].

These results can not explain all aspects of phantom limb syndrome, including the occurrence of phantom limb syndrome in patients with congenitally absent limbs, nor the sensations of voluntary and involuntary phantom limb movements. Ramachandran et al proposed a multifactorial model of phantom limbs syndrome. They suggested that the phenomenon results from the integration of experiences from five different sources: scar tissue or neuromas in the stump, central neuronal plasticity causing the remapping of referred sensations, "the monitoring of corollary discharge from motor commands to the limbs", a genetically determined, internal 'image' of the body, and the presence of somatic memories of the original limb, whether positional, painful, or otherwise.

Treatment

Pre-emptive Analgesia

While in the past, the general approach to postoperative pain management was to treat pain when it occurs, it is now recognized that trauma to nervous tissue and bone intraoperatively may "induce long-lasting changes in central neural function that amplify postoperative pain intensity and increase the need for analgesics"[14], what has been termed central sensitization. This is plausible in the case of phantom limb pain, and can be extrapolated to explain the increased incidence of phantom limb pain when general, rather than spinal or regional, anesthesia is used. Furthermore, this idea justifies pre-emptive analgesia, or analgesia before surgical incision, in the form of regional or epidural anesthesia, prior to amputation[14]. However, obviously this does not completely eliminate the development of phantom limb pain; other potential effectors of central sensitization, that are not eliminated by the short-term effect of regional anesthesia, such as pre-existing pain memories and neural impulses generated at abnormal sites, including transected nerves or neuromas may be implicated. Several studies suggest that epidural anesthesia, started

prior to surgery and continuing for several days postoperatively, decreases the incidence of phantom limb syndrome[26, 27], whereas intraoperative and postoperative analgesia do not affect the occurrence of phantom limb pain, possibly because central sensitization had already occured[14].

Neurostimulation and Behavioral Modifications

Based on the finding of cortical reorganization in amputees, attempts have been made to change cortical reorganization to influence phantom limb pain. Animal studies show that "extensive, behaviorally relevant (but not passive) stimulation of a body part leads to an expansion of its representation zone"; this plasticity of neurons could be used to address the reorganization in the somatosensory cortex demonstrated by Ramarchandran and theorized to cause phantom limb pain.

Myoelectric Prosthesis

Myoelectric prostheses involve the use of electrodes that receive signals from certain muscles and transmit those signals to a motor that operates the prosthesis. They are more complicated than a simple, cosmetic prosthesis, but they also offer the patient more function, such as a better ability to grasp objects. Lotze et al demonstrated with fMRI of the brain that patients who used a myoelectric prosthesis demonstrated less cortical reorganization than those who did not use one. The use of myoelectric prosthesis was shown to reduce both the incidence of phantom limb pain and to decrease cortical reorganization. It has been postulated that "behaviorally relevant tactile stimulation will lead to an expansion of the cortical representation of the stimulated body region", thus preventing the hand area of the somatosensory cortex, and the area around it, from the reorganization that is theorized to cause phantom limb pain[28].

Fabrabloc

Fabrabloc is a linen fabric with thin threads of steel woven in a specific pattern within it. According to the manufacturer, Fabrabloc,

when applied to the stump of an amputated limb, prevents irritation of stump nerves by electric and magnetic fields in the environment. In a company-driven, double-blind, cross-over designed study, Fabrabloc was shown to decrease phantom limb pain[29].

Behavioral Modification

In one study, patients were trained to discriminate electrical stimuli applied at the stump for 2 hours a day for 2 weeks. This process, referred to as behaviorally relevant stimulation, decreased phantom-limb pain and was shown to reverse cortical reorganization[30].

Another behavioral-oriented approach was conducted by Ramachandran as follows. The patient was asked to place his/her intact arm and the residual limb in a box containing a mirror. The patient would see a mirror image of the intact arm, "which is perceived as an intact hand where the phantom used to be". The patient was then asked to make symmetrical movements with both hands, thus suggesting real movement from the lost arm to the brain. This procedure seemed to decrease phantom limb in some patients, though controlled data is lacking[31].

Transcutaneous Eletrical Nerve Stimulation (TENS)

In a placebo-controlled study by Katz, transcutaneous electrical nerve stimulation (TENS), applied to the contralateral leg, was found to be significantly more effective than placebo in decreasing the intensity of phantom sensation[32]. In another study, application of TENS to the auricle was shown to decrease non-painful and sensations while causing minimal side effects[33].

Pharmacologic Therapy

The conventional treatments of neuropathic pain, such as tricyclic anti-depressants and sodium-channel blockers, have not been studied in controlled trials in the treatment of phantom limb pain[11]. The NMDA antagonist ketamine[34], GABA agonists[35], opioids[36], and calcitonin[37], have all been demonstrated to decrease phantom limb pain in some patients.

GABA agonists[38] and the NMDA antagonist memantine[39] have been shown in animal studies to decrease and even reverse cortical reorganization, but in controlled trials memantine was not effective in decreasing phantom limb pain.

In 2002, Halbert et al conducted a systematic review of the treatment of acute and chronic phantom limb pain. The trials included in the review were those that involved a control group and reported phantom pain as an outcome. Only 12 such trials were identified, 3 of which were randomized controlled studies. Eight of the trials reviewed examined treatment of acute phantom pain including epidural treatments, regional nerve block, treatment with calcitonin, and transcutaneous electrical nerve stimulation (TENS). Four of the trials included in the review examined late postoperative interventions including TENS, the use of Fabrabloc, and the infusion of ketamine. The review concludes that not one study provides conclusive data which can guide the treatment of phantom limb pain, and that the results of most studies inconsistently support the use of any one treatment[40].

Conclusion

Phantom limb syndrome is a very old clinical entity that has continued to gain a lot of attention by the medical community and researchers over the past decades. Despite major advances in our understanding of this mysterious phenomenon, a great deal remains to be clarified in terms of both the pathogenesis and treatment of phantom limb syndrome. Patients suffering from phantoms have to cope with more than just the loss of a once functional body part: they have to suffer from pain and sensations from a body part not even there any more. It is hoped that the frustrations felt because of lack of knowledge will translate into more vigorous basic-science research and well-designed clinical trials that will ultimately address the frustrations of patients experiencing phantom limb syndrome.

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