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Phantom pain: a therapeutic challenge

Abstract

Following the amputation of a limb or a part of it, the patient may experience sensations, illusions that the limb is still there. Such symptoms are referred to as phantom experiences. Directly after an amputation these symptoms are present in the majority of patients (in up to 97% of cases). With time, the sensory experiences and pain disappear and most patients develop a sensation that the amputated limb is shrinking and, as with a telescope, getting closer to the stump. Two years after the amputation and when the wound has completely healed, chronic and generally refractory pain affects only 2–4% of these patients. This pain is referred to as phantom pain. Both phantom experiences and phantom pain may also develop after the surgical amputation of other parts of the body, for instance after amputation of a breast. In some patients phantom pain may resolve after many years but quite often recurs. Its severity varies from the barely perceptible to the very troublesome, limiting a patient's activity. The management of phantom pain is a considerable challenge, not only for doctors but also for the entire team providing comprehensive therapy (such as physical therapists and psychologists). Knowledge of the pathomechanisms of phantom pain and an understanding of the principles of and the need for a multidirectional approach determine the optimal treatment for a patient suffering from this kind of pain.

Key words: phantom pain, phantom experiences, stump pain

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Introduction

Phantom pain is a specific form of pain that develops after the complete or partial loss of a limb, breast, tooth, tongue or eye and, less frequently, after the loss of genitals (penis, testes) or visceral organs (bladder, rectum) [1–5].

This pain is projected onto the parts of the body that are no longer present. The bibliographical data on the incidence of phantom pain vary considerably and range from 2% to 97%. This huge discrepancy results from the fact that very often phantom experiences are not differentiated from the actual phantom pain. Phantom experiences are illusions that the amputated part of the body is still there; they develop directly after an amputation and are experienced by the majority of patients. Phantom pain, on the other hand, is the type of pain that persists beyond two years after amputation and the complete healing of the wound. The incidence of phantom pain is much lower and does not exceed 2–4% [6]. Another type of pain that may develop after amputation is so-called stump pain. It is localized in the stump and may develop at various time points after the amputation, whether the stump has healed or not, and is most commonly a result of a neuroma, painful scar, painful bedsore, stump inflammation or osteitis. Phantom pain is most common fol-

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lowing limb amputation. Phantom pain following mastectomy occurs in 15–30% of the patients and is more common in women with preoperative pain. Phantom pain following rectum resection occurs in 15% of the patients [1, 3, 7].

Factors increasing the risk of phantom pain include old age and severe (e.g. ischaemic) preoperative pain. The coexistence of stump pain, vascular disorders and extensive tissue damage (e.g. burns) also plays an important role [2]. The experience of pain within the amputated limb going back years (e.g. Achilles tendonitis, sciatica) may recur as a tiresome phantom pain. This so-called "pain memory" is encoded in the cerebral cortex and the spinal cord [1, 3].

The severity of phantom pain varies greatly. Some patients may find it barely perceptible, while others report tormenting and troublesome pain that interferes with any activity, sleep and rest. The nature of the pain also varies and patients describe it using words such as burning, crushing, shrinking or shooting. The pain may be constant with peaks or paroxysmal. The pain may also be considerably worsened by certain factors, such as fatigue, lack of sleep, anxiety, nervousness, or irritation of the stump by mechanical and thermal stimuli [6].

The phenomena accompanying amputation

The phenomena accompanying amputation can be divided into the following:

— phantom experiences: painless sensations; illusions that the amputated part of the body is still present;
— stump pain: pain within the amputation wound or scar;
— phantom pain: painful sensations which persist beyond two years after the amputation and are located in the non-existent (amputated) part of the body [3, 6].

Phantom experiences

Phantom experiences most commonly affect the entire lost limb, a fragment of the limb or another amputated part of the body. They may take the form of phantom sensations and phantom movements.

Phantom sensations

Phantom sensations are characterized by painless experiences or perceptions in the phantom limb or organ. These symptoms, of varying severity, are present in all amputees for some time.

Phantom movements

Phantom movements affect about 20–50% of the patients and are actually experienced movements of the phantom body part(s). Sometimes these patients report unpleasant and even bizarre movement patterns, such as apparent hyperextension in a non-existent knee or elbow joint. Phantom movements may be divided into involuntary, spontaneous and reflex movements (often coexisting with movements of the contralateral limb). The effect of the doubling of particular body parts may develop. These symptoms disappear under visual control.

In 30–50% of the patients, in the later phases of the follow-up the so-called telescoping effect is observed, which involves a sensation that the amputated limb is shrinking and approaching the stump in a manner resembling the contraction of a telescope [1, 6].

Stump pain

Stump pain is pain experienced within a stump. It is generally a receptor pain but can also have a neuropathic component if caused by a growing neuroma. Its incidence is estimated to be up to 60% of post-amputation cases. Stump pain may develop as early as immediately after the surgery, although it may occur at any time later. The most common cause of stump pain is vascular disorder (thromboocclusive vascular disease, vasculitis) or inflammation of the stump tissues (a painful and inflamed scar, inflammation around the scar, bedsores or osteitis). An important role is also played by proliferative factors (neuroma, callus formation) and mechanical factors (excessively tight dressings that exert pressure on the stump or inappropriately fitted prosthetic devices). Stump pain may also be caused by arthralgia and pain radiating from other body parts (e.g. from the spine).

The nature of stump pain varies. It can be dull, drilling or pulling and even has the quality of tightness, which gives the impression of a pinpoint stinging. It may also involve a burning sensation. Stump pain is generally constant, although it may be paroxysmal [1, 3, 6].

Stump pain caused by neuroma, irritation by a bone fragment or resulting from painful scars is an indication for surgical intervention. In the case of neuroma, if the pain persists despite the surgical removal of a tumour, then, after a positive diagnos-

tic and prognostic blockade using a local anaesthetic, thermolesion may be used. Two techniques of thermolesion are available: classical thermolesion and pulse wave thermolesion. The more modern pulse wave thermolesion is the preferred technique in this case. In this technique the temperature of the lesion does not exceed 45°C and the extent of the lesion is lower, which reduces the risk of deafferentation pain [2].

Phantom pain

Phantom pain is projected onto the body parts which are no longer present and causes unpleasant sensory and emotional experiences. The pain is usually limited and concentrated in the distal part of the phantom limb.

The nature of phantom pain

The nature of phantom pain may vary and may be:
— constant or paroxysmal;
— burning;
— stinging, crushing;
— shooting;
— electrocuting, resulting in the sensation of an electric current passing through the affected body part;

The highest severity of pain is most commonly observed in the evening or at night.

Accompanying symptoms may be present as a manifestation of vegetative dysfunction, e.g. sweating.

Location may vary and the pain may affect the entire limb or only a part of it, most commonly a distal part (hands, feet).

The pain may be continuous or be worsened or relieved by certain triggering mechanisms (e.g. touching of the stump – mechanical or thermal stimulation, fatigue, lack of sleep, anxiety, nervousness) [1–3].

Pathomechanism

A fundamental role in the development of phantom pain is played by pathological remodelling processes in the peripheral and central nervous systems. It has been suggested that excessive activation of the NMDA receptors plays a key role. The development of phantom pain is largely explained by the existence of brain areas responsible for representing specific fragments of the body (a system composed of such areas makes up a homunculus) (Figure 1).

The absence of peripheral stimulation (e.g. as a result of removing a certain part of the body) grad-

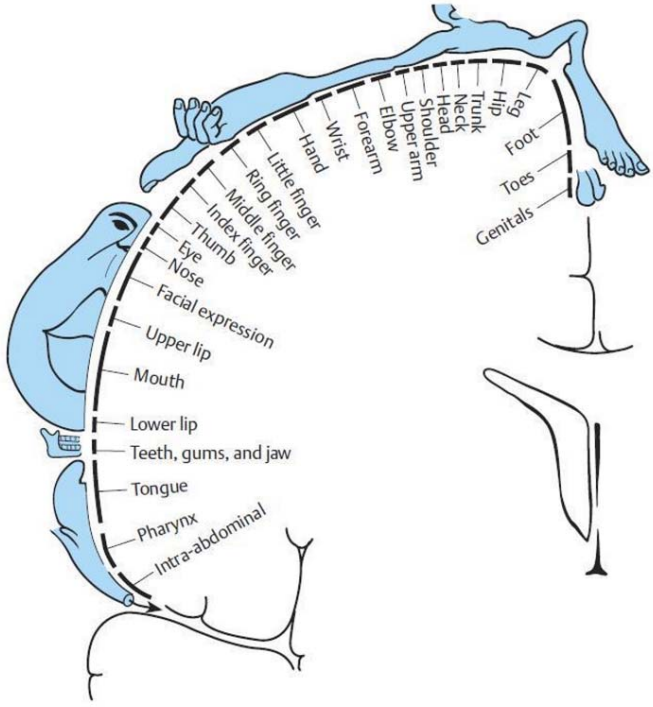

Figure 1. The somatosensory homunculus [8]

ually leads to the extinguishing of cortical "memory". The parts of the body with the strongest and earliest representations are the hands and feet, which is why they remain in the cortical memory for the longest time. This would explain why phantom experiences and phantom pain are rare in children and why, if they do occur, tend to disappear rapidly. This is associated with the limited distribution of the cortical body pattern characteristic of children. Cases of patients experiencing sensations from amputated limbs when other body parts are stimulated suggest the existence of cortical reorganization [9]. This particular phantom pain affects cortical reorganization leading to reduced cortical representation, which most likely results from a disturbed thalamocortical transmission of impulses. Thanks to magnetoencephalography, it has been shown, for instance, that the area of the cerebral cortex responsible for the distal part of an amputated limb becomes responsible for the analysis of stimuli from the facial area and the proximal parts of the limbs [9]. This reflects the tendency for the enlargement and migration of the neighbouring areas. It has also been shown that there is an association between the severity of phantom pain and the degree of cortical reorganization. The higher the degree of reorganization, the more severe and more painful the phantom experiences [11]. Central reorganization after losing a body part may be reversible in some patients even after a considerable time has elapsed, and the reversal of nervous system plasticity processes offers a chance for developing effective treatments for phantom pain [1, 3]. It has also been demonstrated that combination treatment consisting of behavioural therapy, relaxation and electric stimulation (within the stump for two hours daily) improves blood flow within the stump and reduces muscle tone, which makes it possible to reduce the burning component of phantom pain as well as the cramping. Several months later, normal function in the altered areas of the cerebral cortex can be restored [2, 6].

Management of phantom pain

Numerous treatments for phantom pain exist, including pharmacological, surgical and psychological interventions. None of these is, however, fully effective and reproducible in a larger number of patients. However, there is evidence, although unconfirmed and still rather controversial, that continuous extradural anaesthesia administered several days before limb amputation and continued in the postoperative period reduces the incidence and severity of phantom pain [2, 3, 6]. The management of phantom pain is a serious challenge, particularly in patients who have been suffering from this health problem for many years. In such patients the treatment depends on the time that has elapsed since the surgery and on the nature and severity of the pain. Obviously, following a limb amputation a patient's lifestyle will change. These changes are mainly caused by disability, in which phantom pain that considerably reduces the quality of life is an important contributing factor.

The management of phantom pain includes pharmacological and non-pharmacological interventions. The predominant opinion is that the optimal course of management involves appropriate analgesia which should be started before surgery takes place and continued, depending on the nature and severity of pain, afterwards. This can be effected using the technique of continuous extradural anaesthesia mentioned above, which should be started preoperatively and continued intra- and postoperatively until postoperative pain subsides [2, 3].

The recommended principles of phantom pain management are presented below

Primary prevention of phantom pain involves:

I. Aggressive perioperative pain control (pharmacotherapy):
— continuous extradural anaesthesia started 72 hours before surgery and continued for at least 48 hours afterwards with a combination of a local anaesthetic (e.g. lidocaine or bupivacaine/ropivacaine) and an opioid; combination treatment makes it possible to use lower doses of the two individual agents and to take advantage of their synergistic actions [12];
— continuous brachial or lumbar plexus anaesthesia;
— balanced anaesthesia (extradural and general);
— the use of NMDA antagonists, e.g. ketamine, which may reduce the incidence of severe and acute phantom pain (ketamine administered intravenously for 72 hours at low doses) [13];
— in the case of a mastectomy, intervertebral blocks in the perioperative period are recommended as well as a continuous paravertebral or extradural block.

II. Psychological preparation of the patient for surgery (the feeling of sadness and grief associated with limb amputation):

— individual psychotherapy;
— relaxation;
— cognitive-behavioural therapy.

III. Appropriate amputation technique (an osteomyoplastic technique preventing complications within the stump).
IV. Early provision of a prosthetic device and mobilization of the patient [1–3].

In the postoperative period (the first few months after surgery) the patient requires combination treatment, i.e. pharmacotherapy, psychotherapy and physical therapy (electrostimulation). Management in the postoperative period includes:

— anti-epileptic drugs (e.g. gabapentin, carbamazepine) [14];
— antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors);
— intravenous infusions of lidocaine (2–3 mg/kg);
— antiarrhythmics (mexiletine);
— tramadol (up to 400 mg/day);
— calcitonin (intravenously or intranasally at the dose of 200 μg/day);
— electrostimulation of the stump (two hours a day) improving blood flow within the stump;
— sympathetic blocks (lumbar neurolysis for phantom pain of the lower limb, stellate ganglion neurolysis for phantom pain of the upper limb, Walter ganglion neurolysis for phantom pain following resection of the rectum) [15–17].

Surgical methods

In the past the main method involved the disruption or destruction (ablation) of the nerve containing the neuroma which had developed following amputation or trauma. The benefits of this procedure were, however, short-lived because a new neuroma would form at the site of the excision. In order to improve the outcomes of neuroma removal, thermolesion of the stump can be performed after the procedure.

Currently the most modern methods of treatment used in the management of refractory neuropathic pain include neurostimulation techniques at the level of the spinal cord and the central nervous system. Spinal stimulation is performed with electrodes implanted into the extradural space (stimulation of the myelin fibres of the posterior funiculi of the spinal cord above the level of the pain source). CNS stimulation involves implantation of electrodes into certain areas of the thalamus by image-guided surgery. These areas include VPL-VPM (ventroposterolateral and ventroposteromedial thalamic nuclei) and PAG-PVG (periaqueductal and periventricular grey). PAG-PVG stimulation most likely activates the endorphin system. It has been observed that stimulation of this area leads to increased endogenous opioid concentrations in the cerebrospinal fluid. Naloxone reverses the analgesic effect of PAG-PVG stimulation. VPL-VPM stimulation is most likely mediated by a depolarization block in the spinothalamic tract neurons; it does not activate the endorphin system. Inhibition of active conduction in the spinothalamic tract occurs. The concentration of endogenous opioids in the cerebrospinal fluid does not increase with this technique and naloxone does not reverse the analgesic effects of VPL-VPM stimulation. Classic indications include lower back pain, failed back surgery syndrome (FBSS) and cancer pain of the spine and pelvis. Multipolar electrodes are used for the stimulation. The analgesic effect is achieved by stimulation performed 3–4 times daily for 15–25 minutes. Positive effects are observed in 77% of the patients in the early follow-up and in 57% of the patients long term. VPL-VPM stimulation is used for the treatment of neuropathic pain. Indications for this stimulation technique chiefly include phantom pain but also trigeminal neuralgia, spinal cord injury, brachial plexus injury, and colliculus pain. Unipolar electrodes are most commonly used in this type of stimulation and continuous stimulation is performed. The rate of favourable outcomes with this type of stimulation is 66% in the short term and 42% in the long term. The efficacy in the treatment of phantom pain in particular ranges from 20% to 95%.

The physiological basis for the efficacy of stimulation of the posterior funiculi of the spinal cord is formed by the gating theory, according to which external electric stimulation of afferent fibres in the spinal cord inhibits afferent impulse conduction. The thick myelinated fibres close the "gate" and the thin non-myelinated fibres open it. The thick fibres undergo a more rapid depolarization as a result of external electric stimulation so that the afferent flow of nociceptive stimuli is inhibited. Indications for the stimulation of the posterior funiculi of the spinal cord mainly include FBSS but also phantom pain, ischaemic pain of the limbs, spinal cord injury, peripheral nerve injury, lower limb spasticity and postherpetic neuralgia. Electrodes are placed in the spinal canal depending on the location of pain: at T11–L1 in the case of the foot; T9–T10 in the case of the lower limb; T8–T10 in the case of lower back pain; T1–T2 in the case of the chest; C2–C5 in the case of the upper limbs and at C1–C2 in the case of the

occiput. The best effects of spinal cord stimulation are observed in FBSS with a rate of success ranging from 35% to 89% (mean: 67%). In the remaining types of pain the average success rate for spinal cord stimulation is 50%. Electrodes are implanted using puncture with a special needle (this technique is preferred by anaesthetists worldwide) and by microlaminectomy and electrode fixation (this is the technique preferred by neurosurgeons) [18,19]. In Poland, the technical issues related to the exact procedure are not so great, but the main obstacles in using these treatment options are the high price of the electrodes and problems with the reimbursement of the procedure costs. Thanks to image-guided surgery and stereotactic placement of the electrodes, these procedures have now become safe. However, due to the high price of the stimulators and the difficulty of postoperative care they are only offered by certain neurosurgery centres in Poland, for instance at the Department of Neurosurgery in the Military Teaching Hospital in Bydgoszcz [19, 20].

In the prevention of phantom pain, attention should also be drawn to surgical preventive measures, such as:

— turning the suture inwards, and the prevention of mechanical irritation of the nerve stump by securing it and covering it with muscle;
— covering the stump with muscle;
— close definition of indications for repeat resections for chronic pain (as they are usually unsuccessful);
— early indications for the correct selection and fitting of a prosthetic device, preferably a bioelectric one, after healing of the stump [1].

Other selected management options

Opioids

Opioids are used for severe pain and for the primary (perioperative) prevention of phantom pain. Opioids may be effective in persistent stump pain and denervation pain, especially in patients with a relatively recent history of pain. Methadone holds a special place among opioids because it is both an NMDA antagonist and a serotonin reuptake inhibitor. Therefore, by using this opioid we are taking advantage of its various mechanisms of action for the treatment of phantom pain [2, 3, 21, 22].

Capsaicin

Capsaicin has been used for stump pain, although relevant data are limited. Capsaicin has been shown to be effective in certain types of neuropathic pain, which is why it is considered helpful in the treatment of stump pain, especially when accompanied by allodynia. Patches containing 8% capsaicin will soon be available in Poland [3, 23].

Calcitonin

Calcitonin is the only drug whose efficacy in phantom pain has been proved. This neurotransmitter is believed to be the agent of choice in the early postoperative management of phantom pain (as confirmed by placebo-controlled studies). In patients responding to calcitonin this effect becomes visible very rapidly, from within several minutes to a matter of hours. The duration of the action of calcitonin is, however, unpredictable. Usually after three infusions, 75% of the patients experience lasting partial or complete pain relief [15, 16]. If after two days of calcitonin administration in the form of infusions (at a dose of 200 IU of salmon calcitonin) no effect is observed, the drug should be discontinued. The lack of efficacy of calcitonin in the early period of phantom pain most commonly results from additional peripheral mechanisms that precipitate or worsen pain (such as stump pain, poor wound drainage or perfusion abnormalities). After these issues have been addressed, calcitonin may be resumed and expected to work. Repeat doses are also effective in cases of recurrent pain (with intranasal therapy indicated in these cases), although the possibility of antibody formation should be borne in mind. In chronic phantom pain, calcitonin has been very effective in some cases and it seems that its administration should be attempted. For stump pain and phantom sensations, on the other hand, calcitonin is completely ineffective [1, 15, 16, 22].

Local anaesthetic agents

Local anaesthetic agents injected into a healthy limb at the level of the most severe phantom pain in the contralateral limb have proved effective in several reported cases. Intravenous lidocaine infusions are, however, more important therapeutically [6, 24, 25].

Physical therapies

Multiple physical methods have been used in the management of phantom and stump pain with transcutaneous electric nerve stimulation (TENS) being the most popular. Some studies have shown improved pain control in about 50% of the patients [26] and improvement was particularly evident in the first months of treatment with this method. A

modification of the typical method is the use of TENS on the contralateral, healthy limb in the same area where the pain is experienced in the phantom limb [27]. In patients using TENS directly after surgery stump healing was improved and the risk of reamputation was reduced [28]. A method sometimes reported as being effective in the treatment of phantom pain is acupuncture [1, 3, 29].

Early resumption of the function of the affected limb is also important through the active use of prosthetic devices, thanks to early and specialist fitting (bioelectrical rather than cosmetic prostheses, whose action involves the processing of myoelectric impulses arising around the contracting muscle and their use for steering the movements of the prosthetic hand. The source of energy in these devices is a small 12V battery). This course of management may enhance the process of cortical reorganization reversal, relieve phantom pain and even prevent its development [30]. This also has a positive effect on the patient's psyche, helps in cardiovascular training, reduces oedema and prepares the stump for later loading. A method is also used in which the patient imagines exercises or movements performed with the lost limb [1, 3].

The remaining physical methods include thermotherapy, ultrasound, movement baths and other methods facilitating deconditioning, such as tactile exercises with sand [1].

Psychotherapy

A psychotherapist employing the correct psychological therapies can help a patient considerably in experiencing the feeling of loss caused by a lost body part. Most commonly patients do not only suffer somatically and this fact cannot be ignored. Depression, anxiety and negative emotions (the effect of the limbic system) may modify the perceived stimuli, usually enhancing them. In addition, the patient's attitude is very important. For example, regarding the loss as catastrophic or waiting for a miracle to happen may increase the pain.

Methods of limiting phantom pain with hypnosis and biofeedback have been reported in the literature [3, 31].

Combining behavioural therapy, relaxation and electric stimulation has led in some patients to an improvement of blood flow in the stump, muscle tension reduction and improvement in the burning component of the pain [2, 6].

The nature of the pain plays a significant role in the selection of the correct method of treatment. If a patient reports a burning pain which worsens at low ambient temperatures, temperature biofeedback and relaxation techniques (including warming-up exercises) are recommended. The peripheral use of vasodilators (e.g. nitroglycerin paste applied topically) or sympathetic blocks may also be tried. In the case of cramping pain or numbness or when phantom pain is accompanied by painful muscle cramps, muscle tone biofeedback or muscle relaxants are recommended [31].

In summary, the drugs and methods whose efficacy in the treatment of phantom pain have been proved in controlled studies include:

— opioids;
— calcitonin;
— gabapentin;
— tricyclic antidepressants;
— NMDA antagonists (ketamine);
— psychological therapies;
— TENS [5].

Conclusions

Phantom pain and stump pain are common phenomena that accompany amputations of various body parts, mainly the limbs. Amputation carries the risk of pain in the early postoperative phase or pain developing at later stages. Stump pain is usually receptor pain and uncomplicated wound healing and appropriate surgical techniques positively affect its course. On the other hand, it is much harder to predict if and when phantom (neuropathic) pain will develop, how severe it will be and whether its treatment proves successful. The management of phantom pain involves a number of pharmacological agents, invasive techniques of nervous system stimulation, TENS, blocks, neurolysis, thermolesions, physiotherapeutic techniques and psychological techniques. None of these methods, however, is 100% effective, but knowledge of them helps to develop an optimal management strategy for the individual patient.

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