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Review

Pathophysiology and treatment of phantom limb pain☆

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ABSTRACT

Introduction: Phantom limb pain may be present in up to 80% of patients subjected to amputation because of trauma or peripheral vascular disease. Several factors have been associated with its occurrence, including pre-amputation pain, the etiology, and the amputation level.
Objective: To review the current status of the pathophysiological mechanisms, treatment options and their efficacy for the management of phantom limb pain.
Method: Non-systematic review of the literature in PubMed and Cochrane, of articles describing the pathophysiology and treatment of phantom limb pain.
Results and conclusions: The proposed pathophysiological mechanisms are still in research and include peripheral, central and psychological factors. Treatment options are still limited, and less than 10% of patients report long-term improvement.

Fisiopatología y tratamiento del dolor de miembro fantasma

Palabras clave:
Miembro fantasma
Dolor

RESUMEN

Introducción: El dolor de miembro fantasma puede ocurrir hasta en el 80% de los sujetos con amputación por trauma o enfermedad vascular periférica. Varios factores se han asociado a su generación, como el dolor preamputación, la etiología y el nivel de la amputación.

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Analgésicos opioides
Estimulación eléctrica
Sistema nervioso autónomo

Objetivo: Revisar el estado actual de los mecanismos fisiopatológicos, las opciones de tratamiento y su eficacia en el dolor de miembro fantasma.
Métodos: Se realizó una revisión de la literatura no sistemática en las bases de datos PubMedy Cochrane sobre artículos que describieran la fisiopatología y el tratamiento del dolor de miembro fantasma.
Resultados y conclusiones: Los mecanismos fisiopatológicos propuestos aún se encuentran en investigación e incluyen factores periféricos, centrales y psicológicos. Las opciones de tratamiento continúan siendo limitadas, y menos del 10% reportan mejoría a largo plazo.

Introduction

Phantom limb pain (PLP) refers to the presence of painful sensations in an absent limb and is classified as pain of neuropathic origin.[1,2] The French surgeon Ambroise Paré was the first to notice in 1552 that patients complained of severe pain after the amputation of a limb, and proposed peripheral and central factors to explain that sensation. Centuries later, Silas Weir Mitchell (1872) coined the term PLP to characterize this entity.[3–6] The incidence varies from 2% to 80%, regardless of the etiology.[2–4] Such differences in the incidence reported by different studies are due to the absence of a unified definition of PLP, or to the fact that many patients do not report their pain for fear of being stigmatized as mentally ill.[1,3,7] The incidence of phantom pain appears to be independent of gender, the level of the amputation, and age in adults. Despite the above, phantom pain continues to be less frequent in children and young adults, and it is practically non-existent in individuals born without a limb.[1,2,8]

Method

A non-systematic review of the literature was conducted in Pubmed and Cochrane, introducing the following key words in English: Pathophysiology, Phantom limb pain, Pain, Neuropathic pain. All the articles were read and referenced articles related to the topic were also reviewed. Overall, 51 references were selected using this methodology.

Results

Pathophysiology of PLP

PLP may be of short duration, with the presence of painful cramps, or it may be constant, associated with intense perception of the lost limb. Characteristically, it is more intense in the distal portions and it is shooting, throbbing, burning or cramp-like pain. It may be of immediate onset or appear many years after the amputation.[2,9] Prospective studies have reported that 50% of subjects may experience pain within the first 24 h after amputation, and 60–70% may do so one year later.[3,7,8] Although it is more common after limb amputation, it may also occur following surgical removal of any part of the body like the eyes, breasts, face, among others.[1,2,10]

The onset and nature of PLP may differ depending on the cause of the amputation, although there are no clear data to reach definitive conclusions. In western countries, the main causes of amputation are diabetes mellitus and chronic vascular disease, with tumors being a less frequent cause. In other parts of the world, civil wars and land mines are causes of traumatic amputations in otherwise healthy individuals.[3,11]

There are some factors associated with the onset of phantom pain (Table 1)[4,8,12]:

Peripheral factors

After nerve sectioning, there is retrograde degeneration and shortening of afferent neurons as a result of the injury, edema and axon regeneration. This phenomenon is known as sprouting and gives rise to neuroma formation, i.e., expanded and disorganized A and C fiber endings with ectopic firing that increases during mechanical and chemical stimulus. Type C fibers are characterized by the expression of an ectopic discharge showing a slow irregular pattern, associated with an up-regulation or “de novo” expression of sodium channels, and down-regulation of the potassium channels; additionally, there is an alteration of the transduction molecules for mechano-sensitivity signals.[2,4,13] An example of the above is the fact that local anesthesia of the stump does not eliminate pain in all cases, while the injection of gallamine, a substance that increases sodium conductance, creates phantom pain.[3,4] The non-functional connection between axons may

Table 1 – Factors associated with PLP generation.

Peripheral factors
Ectopic impulses from the neuroma of the stump and the DRG
Structural alterations of the DRG and the dorsal horn
Formation of non-functional connections
Sympathetic activation
Neurotransmitter up-regulation and down-regulation
Disorders of signaling transduction channels and molecules
Selective loss of type-C fibers
Central factors
Cortical reorganization
Unmasking of nerve connections
Neuroplasticity
Sensory and motor mismatch
Disorders in glial and neuronal activity
Psychological factors
Reorganization of affective pain areas: insula, anterior cingulate gyrus and frontal cortex

Source: Authors’.