ABSTRACT

BACKGROUND AND OBJECTIVES: Headache is a very prevalent symptom, being considered the second most frequent type of pain by international epidemiological studies. It is also an expensive symptom for patients, relatives, society and general health systems, impairing quality of life of those suffering from this problem. Primary headaches, among them migraine and tension headache are classified as dysfunctional headaches. It is important to understand why these two disorders cannot be seen as somatic, neuropathic or visceral pain. This article shall use the terms migraine and megrim as synonyms. This study aimed at defining dysfunctional pain and at justifying why primary headaches are considered dysfunctional pain.

CONTENTS: a) Migraine pathophysiology, most prevalent primary headache in medical offices, it is explained as a disease made up of crises which may have up to five phases and not simply as a headache. Migraine crisis phases are: premonitory symptoms, aura, headache, autonomic/hypothalamic symptoms and postdrome. b) Classify migraine as dysfunctional pain because it does not meet criteria to be classified as neuropathic or somatic pain. c) Discuss which type of pain secondary headaches are.

CONCLUSION: It is possible to accept the idea that primary headaches are demodulatory pains, but that secondary headaches are nociceptive or visceral.

Keywords: Dysfunctional pain, Headache, Migraine or megrim, Secondary headaches.

INTRODUCTION

Along the last decades, the understanding of mechanisms producing primary headaches has evolved; especially the understanding of migraine pathophysiology. Initially considered primarily a vascular disorder, migraine was then understood as neurovascular disorder. However, the neurovascular model does not supply explanations involving all its aspects, which involve several nervous system levels, because in addition to headache there are also neurovegetative, affective, cognitive and sensory symptoms. Currently, migraine is understood as brain dysfunction, thus primarily a neuronal rather than vascular disorder.

Migraine is a primary, disabling, recurrent or chronic and common headache which may last 24 to 72h. Pain is in general unilateral, pulsing, with moderate to severe intensity, worsened by daily routine activities, associated to nausea and/or vomiting and/or photophobia and phonophobia. It may or may not be followed by totally reversible symptoms lasting minutes, such as visual and sensory changes or other central nervous system (CNS) symptom (aura). Some patients also have a premonitory phase, preceding in hours or days the onset of headache and including: hyperactivity, hypoeffectivity, depression, specific appetite for some foods, repeated yawning and other unspecific symptoms (ICHD 3)².

PATHOPHYSIOLOGY REVIEW

Headache is a very prevalent symptom, being considered the second most frequent type of pain by international epidemiological studies. It is also an expensive symptom for patients, relatives, society and general health systems, impairing quality of life of those suffering from this problem. Primary headaches, among them migraine and tension headache are classified as dysfunctional headaches. It is important to understand why these two disorders cannot be seen as somatic, neuropathic or visceral pain. This article shall use the terms migraine and megrim as synonyms. This study aimed at defining dysfunctional pain and at justifying why primary headaches are considered dysfunctional pain.

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Migraine, neuropathic pain (NeuP) and nociceptive pain (NocP) are classified differently. Migraine is not neuropathic pain. It seems to be a progressive disorder, according to neuroimaging studies in pain networks of migraine patients, with abnormal connectivity between MPM and limbic system which seems to be progressive, according to neurophysiologic studies. Chronic migraine patients have hypersensitive to sensory stimuli and abnormally process sensory information, which is characterized by increased amplitude and decreased habituation of event-related evoked potentials. In chronic migraine patients, increased cortical visual excitability follows BS activation and mesencephalic periaqueductal matter (MPM) inhibition, in addition to somatosensory inhibition, which suggests descending inhibitory pathways dysfunction.

Many evidences support the view that migraine is characterized by central dysfunctional pain control. In addition to sensitization of peripheral nociceptors and sensitization of trigeminal caudal nucleus (TCN)20, there is central modulation of nociceptive signals which may facilitate or inhibit TCN responses. For example, corticofugal fibers of the insular cortex which project contralaterally may facilitate TCN laminae I-II neurons responses, while primary somatosensory cortical areas generate inhibitory stimuli to laminae III-IV21.

Several studies document limbic and prosencephalic pathways which influence BS pain modulator circuits, and functional connectivity studies suggest that the anterior cingulated cortex (ACC)-SPA rostromedial spinal cord complex is a migraine pain modulation network11. Altered connectivity of limbic system to BS in migraine patients has been documented, which supports the view of migraine as pain neurolimbic networks disorder.

Neurophysiologic studies show that even in the interictal period, migraine and other diseases having in common the lack of overt tissue injury which fit the nociceptive or neuropathic pain groups24. As example, fibromyalgia syndrome, the counterpart in spinal cord dorsal horn. This would be the second similarity of migraine and NeuP.

In migraine, Léo’s CSD probably results from changes in membrane pae-
tency and ion channels dysfunction, allowing intra and extraneuronal ion changes of ions Na+, K+, Ca2+ and Mg2+. As already mentioned, which would put it closer to NeuP, in addition to peripheral and central sensitization changes.

So, one could consider that migraine, NeuP and NocP would share a common structural and functional organization consisting of: 1- peripheral sensitization (in DRG or Gasser Ganglion); 2-central sensitization; 3-modulation at spinal cord, brainstem and thalamus level, before final pain perception in pain cortical matrix (consisting of primary and second-
ary sensory cortex, prefrontal cortex, anterior cingulum region, insula and amygdala).

So, it could be understood that migraine is not NeuP or NocP. Dysfunc-
tional pain might be the definition of choice, completing the old definition and excluding neuropathic pain – “NS dysfunction”.

Migraine: dysfunctional pain

The concept of dysfunctional pain is relatively new and has gained evidence when the NeuP study group of the International Association for the Study of Headache (IASP) suggested a new neuropathic pain definition in 200818 to replace the definition used since 199421. By that time, neuropathic pain was defined as pain triggered or caused by primary injury or dysfunction of central or peripheral nervous system.

Bowsher21 has published in 1991 one article on neuropathic pain, defining it as pain due to peripheral (PNS) or central (CNS) nervous system dysfunction and lack of nociceptors stimulation by trauma or disease. It had been established the need for the pain process to go through peripheral nocicep-
tors when it was nociceptive, otherwise it would be neurogenic pain.

Neuropathic and neurogenic pain are different from each other by the acceptance of CNS transient perturbation in neurogenic pain, but differences between these two types of pain were forgotten and were not routinely used in pain clinics or publications. Both terms were used as synonyms.

A new concept of neuropathic pain was proposed by a group of neurologists and neurophysiologists16,18. They have proposed: “pain directly caused by somatosensory system injury or disease”. First, this restricts the triggering event to “injury” or “disease”, which could be more objectively documented and moves away from the vague term “dysfunction”. Secondly, it restricts the injury to the somatosensory system rather than to “nervous system” as in the previous version. This proposal is closer to what we see in the clinical practice and brings advances in the sense of separating NeuP from other syndromes, having major impact on studies on the subject.

Recently, IASP has accepted this neuropathic pain definition proposal with minor changes in the text: “Pain induced by somatosensory system injury or disease”.

Considering this new definition, a large group of painful syndromes would not fit the nociceptive or neuropathic pain groups16. As example, fibromyalgia syndrome, mouth-burning syndrome, irritable bowel syndrome, migraine and other primary headaches, complex regional pain syndrome of other diseases having in common the lack of overt tissue injury which would explain the presence of pain17. These are considered demodalatory or dysfunctional pains. Dysfunctional painful syndromes encompass a large number of diseases having in common the lack of overt tissue injury to explain the painful syndrome. The term “dysfunctional” remits exactly to the fact that these syndromes are caused by altered nervous system functioning, be it central or peripheral. With the advance of knowledge, our understanding about many diseases classified as dysfunctional syndromes may increase21,22.

Under the umbrella of dysfunctional pain, many diseases are sheltered, which are very different from each other in terms of symptoms, patho-

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physiology and treatment, which indicates the need for advances in current knowledge, which could give to these so different disorders a common neurological/neurochemical basis. It is believed that neurophysiologic bases of demodulatory pains are located in specific brain regions as it has been shown by sophisticated neuroimaging studies\textsuperscript{74}.

Types of pain of primary headaches

There are more than a hundred causes of headache mentioned in the International Classification of Headache Disorders, 3rd ed. (beta version). Specific pains of the cephalic segment have not yet been classified according to type of pain. Secondary headaches are possibly nociceptive. In meningitis and related diseases, pain would be generated by stimulation of peripheral nociceptors of large vessels of the base and of meninges by the inflammatory process generating nociceptive pain. The same may be said of expansion injury headaches, in which structures compression, traction or dilatation could stimulate local nociceptors and also generate NocP. The same is true for arthritis and vasculitis in general, when vascular nociceptors would be stimulated\textsuperscript{\textsuperscript{27}}.

Type of pain of primary headaches could not be classified as NocP or NeuP. Migraine headache is triggered by stimulation of peripheral nociceptors of trigeminal terminations of meninges innervated by the first trigeminal branch at this level. Would it then be a nociceptive pain? The major difference between this headache and classic nociceptive headache is that in the latter nociceptors stimulation is by their direct aggression by tissue injury and release of local neurotransmitters. In migraine, nociceptors stimulation is by neurogenic inflammation caused by central dysfunction – cortex or specific brainstem nuclei. Neurogenic inflammation is caused by endovascular factors released by local vasodilation, with nociceptors activation. Meningeal dilatation is primarily caused by CGRP, neurokinins and substance P retrogradely released by trigeminal terminations. Major difference between classic nociceptive pains and migraine pain is that in the latter peripheral nociceptors stimulation is made by processes started in the NS rather than in the periphery\textsuperscript{\textsuperscript{27}}. So, migraine pain has been considered de-modulatory pain because processes giving origin to neurogenic meningeal inflammation start in the CNS. They could also not be classified as neuropathic pain due to the absence of specific central or peripheral nervous system injury or disease.

Other primary headaches may be similarly interpreted and are other examples of demodulatory pain.

Central demodulation process in primary headaches is not static, being influenced by several endogenous factors (hormonal, sleep, emotions, phases of life) and exogenous factors (climate, season of the year, food intake, alcoholic drinks, odors, etc.) leading patients to spend days/months/years asymptomatic, with periods of symptoms exacerbation\textsuperscript{\textsuperscript{27}}.

In conclusion, one may accept that the primary headaches are de-modulatory pains, but that secondary headaches are nociceptive or visceral.

REFERENCES