Trigeminal neuralgia: peripheral and central mechanisms

Neuralgia trigeminal: mecanismos periféricos e centrais

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ABSTRACT

BACKGROUND AND OBJECTIVES: Trigeminal neuralgia is one of the most common neuropathic pains that compromise head and neck. It manifests as shock or burning pain normally evoked by non-noxious facial stimulations. Its etiopathology is not totally understood, but it is known that different mechanisms contribute to the establishment and maintenance of pain. This study aimed to address current contexts of epidemiology, diagnosis, management and pathophysiological mechanisms underlying trigeminal neuralgia in peripheral and central nervous systems.

CONTENTS: Inflammation and release of inflammatory mediators, neuropeptides and neurotrophic factors, as well as degenerative changes of nervous fibers caused by direct nervous injury are relevant peripheral mechanisms which lead to altered sensitivity of nociceptive neurons, development of spontaneous and exacerbated activity, allodynia and hyperalgesia. Among central mechanisms, exacerbated activation of central nociceptive neurons, neuroplasticity, changes in electrophysiological properties and neuronal hyperexcitability, in addition to changes in modulatory pain controls, lead to pain establishment and maintenance.

CONCLUSION: Several mechanisms are involved in neuropathic pains, both in peripheral and central levels, although specific trigeminal neuralgia events are not totally described. Studies concerning its specific neurobiology are needed to understand functional and behavioral changes, which can contribute to trigeminal neuralgia clinical management and treatment.

Keywords: Central sensitization, Etiopathology, Neuropathic pain, Peripheral sensitization, Trigeminal nerve, Trigeminal neuralgia.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A neuralgia do trigêmeo é uma das dores neuropáticas mais comumente encontradas na região de cabeça e pescoço e manifesta-se como crises de choque ou queimação geralmente desencadeadas por estímulos não dolorosos na região da face. A sua etiopatogenia não é totalmente conhecida, mas sabe-se que diversos mecanismos contribuem para seu estabelecimento. O objetivo deste estudo foi abordar os contextos atuais de epidemiologia, diagnóstico, tratamento e mecanismos fisiopatológicos subjacentes à neuralgia do trigêmeo nos sistemas nervoso periférico e central.

CONTEÚDO: A inflamação e a liberação de mediadores inflamatórios, neuropeptídeos e fatores neurotróficos, assim como alterações degenerativas das fibras nervosas decorrentes da lesão nervosa direta são mecanismos periféricos relevantes que, em conjunto ou isoladamente, levam à sensibilidade alterada dos neurônios nociceptivos, com desenvolvimento de atividade espontânea e exacerbada e, consequentemente, dor espontânea e hiperalgesia. Dentre os mecanismos centrais, a ativação exacerbada de neurônios nociceptivos centrais, a neuroplasticidade, as alterações nas propriedades eletrofisiológicas e a hiperexcitabilidade neuronal, além das modificações nos controles modulatórios da dor, são eventos que levam à instalação e à manutenção da dor.

CONCLUSÃO: Diversos mecanismos estão envolvidos nas dores neuropáticas, tanto a nível periférico quanto central, apesar dos eventos específicos da neuralgia do trigêmeo não estarem totalmente elucidados. Estudos que abordem a sua neurobiologia específica são necessários para a compreensão das alterações funcionais e comportamentais presentes, com claras repercussões no tratamento e manuseio clínico da neuralgia do trigêmeo.

Descritores: Dor neuropática, Etiopatologia, Nervo trigêmeo, Neuralgia do trigêmeo, Sensibilização central, Sensibilização periférica

INTRODUCTION

According to the International Association for the Study of Pain (IASP), pain is defined as an "unpleasant sensory and emotional experience associated to real or potential injuries or described in terms of such injuries"[1]. Neuropathic pain is caused by central or peripheral somatosensory nervous system injury or dysfunction and affects approximately 8% of the population[1,2]. Its etiopathology is complex and involves several biological mechanisms still not totally explained[3].

Trigeminal nerve is the fifth cranial nerve pair, being respon-

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sible for general head and face sensitivity. Trigeminal neuralgia (TN) is one of the most common neuropathic pains found in head and neck and is manifested as shock or burning crises in undefined intervals, in general triggered by non-painful stimulation in the face (allodynia)[4].

In general population, TN has incidence of 12.6 to 27/100,000 inhabitants[5], being uncommon in people below 40 years of age and more common after 60 years of age. The incidence on people above 80 years of age is 25.9/100,000 inhabitants[6]. Recent data show that 55 to 70% of TN patients are females, being that 45% of patients refer maxillary pain[7].

TN diagnosis is essentially clinic, based on patients' history and diagnostic criteria of IASP and of the International Headache Society (IHS)[1,8]. Pain attacks are paroxysmal lasting from fractions of seconds to two minutes in one or more trigeminal nerve innervation territories, being that the frequency may vary between hundreds of attacks per day to years of remission between one crisis and the other. Pain shall mandatorily have the following criteria: 1) severe, acute and superficial pain; 2) pain described as similar to electric shock, cutting or burning; 3) pain with spontaneous start in trigger zone or triggered by innocuous stimulations in the trigger zone[5,9].

According to the International Classification of Headache Disorders (ICHD-III, 2013)[8], there are two major types of TN: classic and painful, which are subdivided as shown in figure 1.

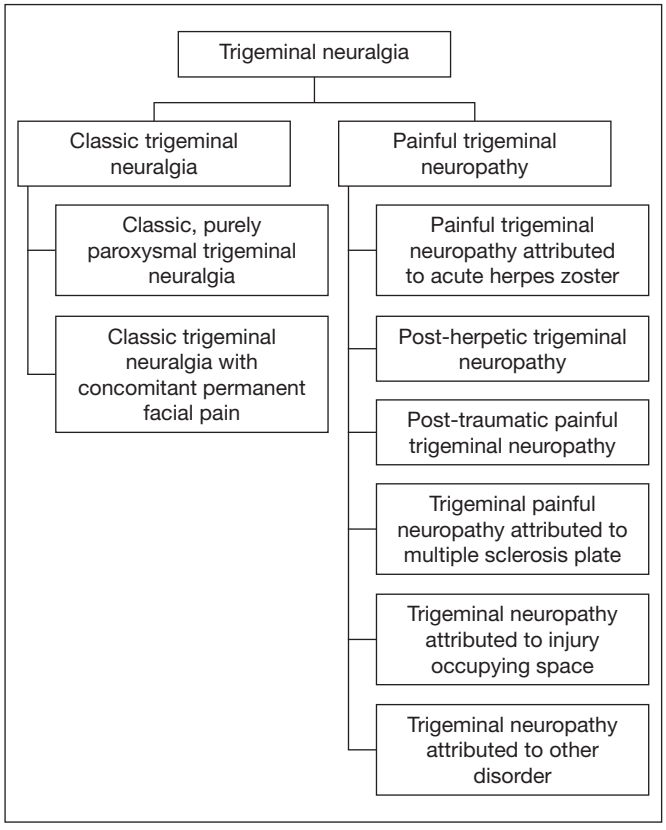

Figure 1. Classification of trigeminal neuralgia, according the International Classification of Headache Disorders (ICHD-III)

Adapted from International Classification of Headache Disorders, 2013[8].

Classic TN includes all cases without known etiology, as well as those amenable to having vascular trigeminal nerve compression. Painful TN, in turn, is diagnosed in cases secondary to herpetic infection, trauma, tumors, multiple sclerosis or structural skull base deformities. Clinical presentation might be similar, by painful TN results from a structural injury different from vascular compression[9-12]. Studies point to a third type of TN, family TN, which is an extremely uncommon condition, with few literature reports and represents less than 1% of all TN cases[13].

Etiopathogenic mechanisms of TN are still not totally known, but the vast majority of classic TNs documented worldwide are related to trigeminal nerve compression at its exit from the pons by an aberrant arterial or venous loop. In cases of painful TN, associated comorbidities seem to have etiopathogenic relationship with the establishment and maintenance of the disease[14].

Therapeutic approaches for TN are divided in two modalities: pharmacological and surgical, according to the case[15]. For pharmacological treatment, anticonvulsants, such as carbamazepine, oxcarbazepine, baclofen, lamotrigine and pimozide are the most frequently prescribed drugs[12]. These drugs block the propagation of the nervous impulse through changes in conductance of the nervous fiber by blocking ion channels, allowing the control of neuronal excitability and of the synaptic activity[16]. Carbamazepine is successful in up to 70% of cases and has been the most frequently prescribed drug[17].

Surgical treatment is indicated when patients do not respond to clinical treatments or when there is detection of vascular compression by imaging exams[17,18]. Among surgical techniques, there are vascular microdecompression, consisting in surgical deviation and isolation of a vessel close to the nerve. Alcholization of peripheral branches is also a feasible alternative in refractory cases and consists in alcohol injection in trigeminal nerve peripheral branches. Recently, some other procedures have been widely used, such as percutaneous electrocoagulation and thermocoagulation by radiofrequency. Both cause injury to the trigeminal ganglion, preventing the passage of nociceptive stimuli and generating pain relief, associated to sensory deficits[18].

ETIOPATHOGENY AND NEUROPATHOLOGY

Several factors contribute for the establishment of neuropathic pain without a specific etiology. TN pathophysiology involves different neurophysiologic mechanisms, both in peripheral and central nervous systems, such as activation of receptors, transmission and projection of nociceptive information and convergence of nociceptive afferents to central neurons, in addition to interactions between neurotransmitters and neuromodulators[19,20]

Recent studies have established some theories for TN etiology. One pathophysiological hypothesis is trigeminal convergence/projection. This theory proposes that nociceptive entries recurrent from head and neck converge to the trigeminal spinal nucleus (caudal sub-nucleus), leading to the release of neurotransmitters and vasoactive substances. These mediators decrease second order neurons activation threshold, which also receive impulses from non-nociceptive fibers, generating in-

creased flow of information transmitted to upper centers which interpret pain[5,21-23]. The bioresonance theory states that vibration frequency of structures involving the trigeminal nerve may injury nervous fibers, leading to abnormal transmission of impulses and generating facial pain[24]. Another hypothesis is ignition. This suggests that injuries in trigeminal afferents of the root or of the trigeminal ganglion generate hyperexcitability of the axon and/or cell body, originating pain paroxysms as a function of exacerbated neuronal activity[25].

In addition to such hypotheses, TN may also be induced by progressive dystrophy of trigeminal nerve peripheral branches which, in turn, may be evoked by compression syndrome and/or immunoallergic reactions[26]. Nervous and tissue injury caused by these processes leads to release of mediators which sensitize peripheral nervous terminations (peripheral sensitization), leading to neurochemical and phenotypic changes and increased excitability of trigeminal ganglion afferent neurons and trigeminal nuclei (central sensitization). In addition, there are changes in descending modulating pathways which change pain thresholds and perception[27]. Some studies also suggest that increased levels of IgE and histamine, common in some allergic processes, may be involved with the origin of TN. In these cases, the build-up of IgE in regions close to the trigeminal nerve may promote degranulation of mast cells with release of substances such as histamine and serotonin, which seem to play a relevant role in TN etiology[28-30].

All proposed theories for TN etiology are based on central and peripheral cellular, molecular and electrophysiological mechanisms, described below.

These mechanisms were, in their majority, shown through experimental models of trigeminal nerve neuropathic pain, due to the difficulty in studying such mechanisms in humans.

Peripheral mechanisms

After the injury of a trigeminal nerve branch, as well as of other nerves, inflammatory process leads to the release of pro-inflammatory cytokines, growth factors, hydrolytic enzymes and nitric oxide (NO), with consequent decrease in nociceptors activation threshold and increase in nervous fiber excitability[31,32]. In addition to inflammation and inflammatory mediators release, neuropeptides and neutrophic factors, degenerative nervous fibers changes caused by direct damage, such as axonal injury and demielination, are also relevant peripheral mechanisms.

Cytokines tumor necrosis factor alpha (TNF-α), interleukins 1 beta (IL-1β) and 6 (IL-6) have been implied both in central and peripheral sensitization[33]. TNF-α is released by virtually all immune system cells and by glial cells and causes metabolic and hemodynamic changes, in addition to distally activating other cytokines. This cytokine is able to promote neuronal hyperexcitability, to increase excitatory transmission and to promote inflammation in several nervous system levels, becoming an important mediator for chronic neuropathic pain, in addition to an excellent therapeutic target[33].

IL-1β produces systemic inflammation, induces substance P (SP) and NO production, having important function in pain development and maintenance. There are strong evidences that IL-1β reinforces synaptic transmission and neuronal activity in several nervous system sites[33]. IL-6, in turn, promotes neutrophils maturation and activation, maturation of macrophages and differentiation of cytotoxic T and natural killer lymphocytes[34]. IL-6 is predominantly pro-inflammatory in neuropathic pain, promoting inflammation exacerbation through the activation of glial cells in the central nervous system[33].

However, at injury site, it may promote antinociceptive action, as well as peripheral axon regeneration[35]. Due to this different effect, IL-6 is an attractive therapeutic target to treat neuropathic pain, as compared to other cytokines[33]. Notwithstanding described mediators being involved with peripheral sensitization in neuropathic pain, few studies have established their final role specifically for trigeminal neuralgia. While some authors suggest little relevance of IL-6 for trigeminal neuropathic pain[36], others report important correlation of this mediator and of IL-1β for the generation of trigeminal neuropathic pain[37,38].

In addition to inflammatory mediators, neuropeptides have also been associated to neuropathic pain. Nervous injury of some trigeminal nerve branches has caused changes in the expression of neuropeptides such as SP, peptide related to calcitonin gene (CGRP), intestinal vasoactive polypeptide (VIP) and neuropeptide Y (NPY) in trigeminal nerve and trigeminal ganglion. So, it has been suggested that the build-up of neuropeptides at injury site may be related to the development of ectopic neural activity and to the development and modulation of neuropathic pain, although well-defined correlations with the development of pain along time have not yet been totally evidenced. In addition, injured nervous terminations release vasoactive neuropeptides, perpetuating inflammation (neurogenic inflammation) and peripheral sensitization[39].

Different painful conditions, including neuropathic pain, are associated to deregulation of neurotrophic factors expression[37]. Anderson & Rao[37] have observed increased nervous growth factor (NGF) expression in trigeminal nerve and nuclei and have suggested a role for this mediator in the mechanical allodynia observed after nervous injury in a trigeminal neuropathic pain model in rats[40]. Additionally, decreased production of neurotrophic factors, among them glia-derived neurotrophic factor (GDNF), has been associated to the development of peripheral neuropathies. This factor is also involved in neuronal survival and plasticity mechanisms in response to injuries, in nervous injury repair, in addition to having a regulating role in the activity of nociceptive pathways[41-43]. More recent studies suggest that GDNF acts in a paracrine manner in trigeminal hyperalgesia and may be a potential therapeutic target[44].

Another peripheral pathophysiological mechanism described as relevant is the ephaptic transmission or the cross excitation of nervous fibers. This phenomenon involves the transmission of action potentials of injured and hyperexcitable afferent peripheral sensory fibers to adjacent sensory fibers not stimulated or injured, with expansion of the area where pain is perceived[42]. The electromagnetic field generated in a fiber induces depolarization of neighbor fibers, causing cross excitation, and contributes to allodynia and hyperalgesia[45]. Some studies with surgical biopsies of TN patients have observed significant de-

mielination of trigeminal sensory fibers[4].
Focal demielination leads to the apposition of demielinated axons with absence of glial cells processes between them, with possibility of generating ectopic or spontaneous nervous impulses and ephactic transmission between fibers, strengthening the role of cross excitation as relevant pathogenic mechanism[4].
Changes in anisotropy and diffusivity in trigeminal nerve and gray matter were observed in TN patients, suggesting that microstructure abnormalities, not detectable by conventional imaging exams, and demielination without axonal injury are important factors in the pathogenesis of TN[46-48].
All peripheral mechanisms, together or isolated, lead to changed sensitivity of nociceptive neurons, with the development of spontaneous and exacerbated activity and, as a consequence, spontaneous pain and hyperalgesia.

Central mechanisms
Central sensitization is the pathological and increased activation of central primary nociceptive neurons, anatomic reorganization (neuroplasticity), changes in electrophysiological properties with development of hyperexcitability and modifications in pain modulation controls.
In the central nervous system, inflammatory mediators also participate in peripheral sensitization, interfere with hippocampus cognitive, memory and mood functions and are able to excessively sensitize nociceptive neurons through excessive release of neurotrasmitters[49], thus showing the role of inflammation in pain generation also at central level.
Molecular and cellular changes lead to the change of broad spectrum neurons phenotype into nociceptive neurons. Additionally, there are neuroplasticity phenomena with the establishment of new synapses between nociceptive and non-nociceptive neurons. These changes lead to allodynia, because changes in non-nociceptive stimuli pathways activate the nociceptive pathway, triggering pain[43]. In addition to mechanical allodynia, central changes lead to modulation controls changes and result in pain amplification, increasing the field where it is perceived and prolonging response to painful impulses[50]. There is facilitation, potentiation and amplification of central responses with decreased inhibitory pathways and permanent activation of excitatory pathways, even in the absence of nociceptive stimuli[51].
Neuronal hyperexcitability is a response to the remodeling of some transmembrane ion channels involved in the beginning of action potentials generation, such as sodium channels. In the neuronal membrane of the injured cell, increased sodium channels density, decreased potassium channels expression and increased expression of the auxiliary subunit of voltage-dependent calcium channels lead to depolarization of the membrane with consequent calcium inflow and action potential generation[3,18]. Changes in channels density increase the period of neuronal depolarization and repetitive discharge[52] and start central sensitization by several mechanisms, among them N-methyl-D-Aspartate receptors (NMDA), c-fos expression and transcription of genes coding dynorphin and encephalin, with consequent functional cell changes[3,41].
Described mechanisms for central sensitization in neuropathic pain in general have not yet been fully tested for trigeminal neuropathic pain, which is highly relevant since pain in brain segments has different mechanisms from pain outside the brain[36].
Studies have observed activation of astrocytes with increased expression of IL-1β in trigeminal nuclei, associated to the development of allodynia and hyperalgesia and pain chronicity[53,54].
Kinase phosphorylation regulated by extracellular signal (ERK) seems to be involved with central sensitization leading to thermal orofacial hypersensitivity, showing the role of cell signaling cascades involving kinase proteins activated by mitogen (MAPK) in trigeminal neurons sensitization[55]. A recent study has shown that astrocytes are involved in NMDA glutamate receptors changes, important for TN central sensitization, through the release of D-serine neuromodulator aminoacid[56].
Specifically with regard to TN, painful stimulations were associated to increased activity of the spinal tract nucleus of trigeminal, thalamus, primary and secondary somatosensory cortex, among other central areas. The activation of trigeminal innervation areas by non-nociceptive stimuli has induced exacerbated activity in many of these central regions, showing the maintenance of a trigeminal nociceptive system sensitization status[57]. Decreased gray matter volume observed in primary and secondary somatosensory cortex, thalamus and other central structures of TN patients was correlated to longer disease duration, suggesting the adaptation of neuroplastic phenomena in response to chronic TN pain[58].

CONCLUSION

Different mechanisms are involved with neuropathic pain installation and maintenance, both at peripheral and central levels. Specific mechanisms underlying TN are not totally explained, in spite of simultaneously and interdependently acting in different types of neuropathic pain. So, future studies addressing specific TN neurobiology in its morphological, electrophysiological and molecular approaches are critically relevant for the understanding of functional and behavioral changes, with clear repercussions on TN treatment and clinical management.

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