REVIEW ARTICLE

Trigeminal neuralgia, pathophysiology. Considerations in its etiology

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ABSTRACT

Introduction: trigeminal neuralgia has been referred since ancient times as one of the most intense facial pains; its etiology is controversial and its prevalence rises along with life expectancy.
Objective: to integrate criteria on the etiology of trigeminal neuralgia.
Methods: documentary review through an automated search in the databases PubMed/Medline, Cochrane Library, Scielo, Medigraphic and Science Direct, using the Google Scholar search engine, during the period from March 2021 to the same month of 2022. Thirty-one articles related to the proposed objective were selected; 23 (74.2%) are updated.
Results: the causal factors of trigeminal neuralgia (trauma, infectious diseases and compression by neighboring anatomical structures or tumors) promote an inflammatory process in the connective tissue that composes the nerve, the release of leukocyte products causes its destruction and the nervous tissue is exposed; action potentials are triggered that cause the painful symptoms typical of the disease.
Conclusions: the development of an inflammatory process in the connective tissue constituent of the trigeminal nerve causes a decrease in the excitability threshold of the affected fibers and provokes pain in response to different stimuli.
Key words: pain; neuralgia; trigeminal; V cranial nerve

RESUMEN

Introducción: la neuralgia del trigémino ha sido referida desde la antigüedad como uno de los dolores faciales más intensos; su etiología es controversial y su prevalencia asciende junto con la expectativa de vida.
Objetivo: integrar criterios sobre la etiología de la neuralgia trigeminal.
Métodos: revisión documental a través de una búsqueda automatizada en las bases de datos PubMed/Medline, Cochrane Library, Scielo, Medigraphic y Science Direct, mediante el motor de búsqueda Google Académico, durante el período de marzo de 2021 hasta igual mes de 2022. Se seleccionaron 31 artículos relacionados con el objetivo propuesto; 23 (74,2%) están actualizados.
Resultados: los factores causales de la neuralgia trigeminal (traumatismos, enfermedades infecciosas y compresión por estructuras anatómicas vecinas o tumores) promueven un proceso inflamatorio en el tejido conectivo que compone al nervio, la liberación de productos leucocitarios provoca su destrucción y el tejido

nervioso queda expuesto; se desencadenan potenciales de acción que ocasionan los síntomas dolorosos propios de la enfermedad.
Conclusiones: el desarrollo de un proceso inflamatorio en el tejido conectivo constituyente del nervio trigémino ocasiona una disminución en el umbral de excitabilidad de las fibras afectadas y provoca dolor ante diversos estímulos.
Palabras clave: dolor; neuralgia; trigémino; V par craneal

INTRODUCTION

An essential concept in medical practice is pain, which represents one of the major health problems and is, consequently, the most frequent reason for consultation and the one that incapacitates a large number of people in the world.
The International Association for the Study of Pain (IASP), founded in 1973 by Dr. John J. Bonica, was the first to bring together professionals with the common goal of understanding the diagnosis and treatment of pain, and defines this symptom as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[1] Although acknowledged to be correct, it contemplates only its symptomatological aspects: in some circumstances pain can be experienced in the absence of ongoing tissue injury, a consequence of this statement is the reasoning that pain is subjective; hence a patient's description of pain should always be believed if there is no evidence to the contrary.[1,2,3,4,5]
Pain perception is complex and is affected by a multitude of factors including not only nociceptor activation, but also emotions (e.g., fear, anxiety), memory and cognition, sociocultural context, and expectations.[2,3]
Different criteria have been used to classify pain according to anatomical source, etiology and duration. By etiology it can be classified as neuropathic, nociceptive or mixed.
The first has been defined as resulting from diseases or lesions of the peripheral or central somatosensory nervous system; it includes neuralgia, a term used to describe the sensation of pain that extends over one or more of the cranial or spinal nerves.[2,3]
The most common facial neuralgia is trigeminal neuralgia (TN), defined by the IASP as: "paroxysmal, unilateral, severe, penetrating, short-lasting, recurrent pain in the distribution of one or more branches of the fifth cranial nerve (V pair)".[1,6,7]
The International Classification of Headache, revised in its third version (ICHD-3), suggests three variants: 1- Idiopathic TN, its cause is unknown, even after surgical treatment or magnetic resonance imaging, in approximately 10% of patients, 2- Classic or primary TN, often caused by neurovascular compression at the nerve entry zone in the brainstem, 3- Symptomatic or secondary TN, caused by other neurological diseases such as cerebellopontine angle tumors and multiple sclerosis, among others,[6,7,8,9,10,11] such as the SARS-Co-2 coronavirus.[12,13]
The prevalence of TN is 0.015% in the general population, is three times more frequent in women than in men, and is usually diagnosed between the fourth and seventh decades of life.[3] In addition to advanced age, the presence of arterial hypertension and atherosclerosis seem to be associated with a higher

risk of TN. Likewise, this disease appears to show a higher incidence in patients with diagnoses of migraine or multiple sclerosis.[14]
TN is notorious for its complex and difficult treatment, and its cause is not well understood.[11] It is reflected negatively on the quality of life of patients.
It reflects negatively on the quality of life of patients because it significantly impairs the mental health and autonomy of individuals. It generates worry, fear of new episodes, depression, leads to changes in lifestyle in order to avoid any stimulus that can trigger it and, in some cases, to suicide.[6,14,15]
This review article emphasizes the pathophysiological mechanisms of TN, which are still poorly understood, with the aim of integrating criteria on its etiology.

METHODS

A documentary review was carried out about the subject during the period from March 2021 to the same month of 2022. The bibliographic databases PubMed/Medline, Cochrane Library, Scielo, Medigraphic and Science Direct were consulted using the Google Scholar search engine. The key words used in the search strategy were: pain, neuralgia, trigeminal and V cranial nerve. The selection criteria included articles in English and Spanish, of foreign or national origin, subject matter consistent with the keywords used, date of publication in the present century and preferably during the last five years.
Thirty-one papers related to the proposed objective were selected: 23 (74.2%) correspond to the last five years and 29 (93.5%) to the last decade. Of the total, 29 articles were written by foreign authors and two by national authors.

DEVELOPMENT

To establish an adequate strategy in the treatment of pain, it is important to know its nature and pathophysiology, especially when the neuropathic component is not clearly established or is absent,[16] which implies the need to consider the morphofunctional organization of the nervous tissue.

Components of the connective tissue of a peripheral nerve

The greater part of a peripheral nerve is composed of nerve fibers and their supporting cells, the Schwann cells. The individual nerve fibers and their associated Schwann cells are held together by connective tissue organized into three components:

- Endoneuro, is the lax connective tissue around each individual nerve fiber
- Perineurium, is the specialized connective tissue around each nerve bundle. It functions as a metabolically active diffusion barrier that contributes to the formation of the blood-neural barrier. In general, only fibroblasts, a small number of resident macrophages and occasional mast cells are present within the nerve compartment
- Epineurium is the irregular dense connective tissue that surrounds an entire peripheral nerve and fills the spaces between nerve fascicles. The blood vessels that supply the nerves run in the epineurium and their branches penetrate the nerve and run within the perineurium.

Lesions of nerve evaginations (axons and dendrites), both in the peripheral nervous system (PNS) and central nervous system (CNS), induce axon degeneration and neuronal regeneration. These processes involve not only neurons, but also supporting cells, such as Schwann cells and oligodendrocytes, as well as phagocytic cells, such as macrophages and microglia. Injury to axons in the PNS leads to their degeneration, which is accompanied by mitosis and dedifferentiation of Schwann cells and disruption of the blood-neural barrier along the entire length of the injured axon. This allows massive infiltration of monocyte-derived macrophages, which are responsible for the process of myelin elimination.[17]

Various exogenous or endogenous stimuli can cause tissue injury and inflammation, which is a complex defensive reaction of the vascularized connective tissue, involving microvascular injury, extravasation of leukocytes through the vascular walls, and leakage of plasma and proteins into the tissue. Under normal circumstances very well-controlled responses protect against further injury and eliminate damaged tissue.

In disease, however, pathological inflammation can lead to extracellular matrix (ECM) destruction and organ dysfunction. The stimulated local cells, together with the newly arrived inflammatory cells, release toxic reactive nitrogen and oxygen intermediates, as well as an array of proteases, especially matrix metalloproteinases (MMPs), serine-proteases and cysteine-proteases.

These products are potent mediators of endothelial and tissue injury and amplify the effects of the initial inflammatory stimulus. Thus, when it evolves in a persistent and uncontrolled manner, the leukocyte infiltrate itself becomes the damaging agent; in fact, tissue injury produced by leukocytes constitutes a basic pathogenic mechanism in many human diseases.[18,19]

Physiological mechanisms of pain

Pain is a consequence of the activation of specialized peripheral receptors (nociceptors) due to a noxious event (stimulus). These stimuli fall into three categories: mechanical (e.g. pressure, tumor growth, incision), thermal (e.g. heat or cold) or chemical (e.g. ischemia or infection). The stimulus is then converted into an electrical nerve signal (transduction) that is transmitted along the axons of lightly myelinated (A-delta) or unmyelinated (C) nerve fibers via specific pathways (transmission). Modulation refers to the attenuation of painful signals by intrinsic inhibitory activity in the central and peripheral nervous system before it is perceived as an unpleasant sensation (perception).[2]

Injury causes alterations in the process of generation of pain signals. A relevant example of pathological pain arising from injury to the nervous system is peripheral sensitization. This form of pain is characterized by the development of spontaneous ectopic activity in damaged nerves and ganglion cells, as well as by an increased sensitivity to mechanical, thermal or chemical stimuli. Recent studies have shown the significant role of cytokines such as tumor necrosis factor a (TNF-a) and interleukins, released by macrophages and other inflammatory cells, in the process of peripheral sensitization.

Prolonged and repeated activation of afferent nociceptive fibers results in central sensitization, a state of increased sensitivity of central neurons that generate pain signals.

Other central neuroplastic changes that may contribute to neuropathic pain states include deafferentation hyperactivity that can occur after spinal cord injury or avulsion, loss of afferent inhibition of long nerve fibers, reorganization of central connections of primary afferent fibers, and descending excitatory modulation mechanisms.
Central and, to a lesser extent, peripheral sensitization are considered the fundamental causes responsible for pain induced by innocuous stimuli (allodynia) and for exaggerated or prolonged pain due to normally noxious stimuli (hyperalgesia or hyperpathia), which are commonly observed in neuropathic pain states.[2]
Neuropathic pain was redefined by the IASP in 2011; it was clarified that nervous system injury or disease is specific to the somatosensory system.[16,20]

Anatomical considerations

The trigeminal nerve (V pair) is the thickest and most extensive of all cranial nerves, is predominantly sensitive and constitutes the facial somatosensory system. It conducts sensory impulses from most of the face and head, from the mucous membranes of the nose, mouth and sinuses, and from the cornea and conjunctiva. It also innervates the dura mater of the anterior and middle cranial fossae.
The cell bodies of the sensory part of the nerve are located in the ganglion of Gasser or semilunate. This, the largest sensory ganglion in humans, is located in the medial portion of the middle cranial fossa at the base of the cranium.[21,22]
The central axons of the ganglion cells constitute the sensory root. These fibers divide into short ascending and long descending branches as they enter the medial portion of the pons. The former is mainly related to the sense of touch and light pressure and synapses with second order neurons in the main sensory nucleus. The proprioceptive afferent fibers terminate in the mesencephalic nucleus. Fibers mediating pain and temperature sensation do not enter these nuclei, but form the long descending branches of the spinal trigeminal fasciculus. This pathway, which contains facilitatory and inhibitory fibers along with its nucleus, runs from the junction of the pons and medulla oblongata to the higher segments (C2 or C3) of the medulla.
The peripheral branches of Gasser's ganglion form the three sensory divisions of the nerve: ophthalmic (V1), maxillary (V2) and mandibular (V3).
The sensory component of the three divisions innervates: mucous membranes (paranasal, nasopharyngeal, palatine, corneal and buccal), lips, gums, teeth, external auditory canal (except the tragus) and the anterior two thirds of the tongue (general sensibility only). The motor portion originates in the trigeminal motor nucleus in the medial part of the bridge; the outgoing fibers pass under Gasser's ganglion and incorporate into the mandibular nerve. The motor component innervates the muscles of mastication (temporalis, masseter, medial and lateral pterygoid muscles).[6,21,22,23]
The spinal nucleus is divided into three subnuclei: oral (non-discriminative tactile sensation of the oral mucosa), interpolar (painful sensation of dental origin) and caudal (painful and thermal sensation). It is the main site of relay of oral-facial nociceptor information. On its neurons there are central patterns of convergence of superficial and deep impulses (from skin and buccal mucosa

in 100%), which supports an explanation for referred pain and trigger points in TN.

The cranial nerve V is surrounded by a myelin sheath up to 7 mm after leaving the brainstem, as opposed to only a few millimeters for other cranial nerves and spinal nerves; this may explain the high frequency of TN in multiple sclerosis, a disorder of the myelin of oligodendrocytes.[21]

At the trigeminal entrance to the bridge there is a transition between myelination by Schwann cells in the peripheral nerve to myelination by oligodendroglia in the CNS. This transition is thought to be an area vulnerable to pressure and may be where nerve injury occurs most readily.[6]

Pathophysiology of TN

There are several theories in this regard, among the most recognized are:

1. Theories related to demyelination problems at the ganglionic level, which originate a state of hypersensitivity of the afferent branches of the trigeminal, secondary to an excessive entry of sodium to the neurons, which causes repetitive discharges that stimulate the reticulobulbar nucleus, which translates into a conscious neuralgic sensation.
2. Theory postulated by Jannetta,[24] in which there is a compression or deformation of the dorsal trigeminal root at the entrance of the pons, caused by malformations or vascular anatomical variants, the most important being the superior cerebellar artery which is most frequently compressed (95% of cases).
3. The theory formulated by Fromm and collaborators,[25] the "epileptogenic theory", which can encompass most of the above theories, in which it is proposed that chronic irritation of the trigeminal nerve endings induces alterations in the segmental inhibitory systems (trigeminal sensitive nuclei) and, therefore, an increase in the activity of these nuclei, secondary to the activation of ectopic action potentials. The increased activity of the primary afferent fibers, together with the deterioration of the inhibitory mechanisms of the sensitive nuclei, is what would lead to the production of paroxysmal discharges of the interneurons of these nuclei in response to tactile stimuli (trigger) and, as a result, to the painful crises. This mechanism may explain the effectiveness of the antiepileptic drugs used in the pharmacological treatment of TN.

Other mechanisms that have been postulated in the etiology of TN is focal demyelination of primary trigeminal afferents near the trigeminal root entry into the pons. These areas of demyelination become hyperexcitable and respond more readily to any type of stimulus causing ectopic generation of impulses with high frequency afterdischarges (occurring after stimulus termination) and crosstalk between fibers, called ephaptic transmission (across membranes rather than synapses), also implicated in TN etiology. Histological evidence indicates that the nerve fibers most involved in demyelination are the Aβ fibers (large, non-nociceptive fibers). Finally, hyperactivity of primary afferents could induce central sensitization of wide dynamic range neurons in the trigeminal spinal nucleus and, even, in other more central areas of the

CNS, with subsequent sensitization to pain and non-nociceptive stimuli to be perceived as paroxysmal pain.

Burning or stabbing type pain or discomfort is likely to be mediated by deterioration of C-fibers (amyelene sensory axons that transmit impulses slowly), as shown in other neuropathic pain conditions. Loss of C-fibers in the trigeminal sensory root may cause abnormal spontaneous activity in second-order neurons in the brainstem.[26]

In secondary TN, pathophysiological changes similar to those in classic TN occur, although the structural lesion depends on the etiology. In multiple sclerosis (MS) demyelinating plaques occur, while occupying lesions (meningiomas, epidermoid cysts, acoustic neuromas and cholesteatomas) produce compression in the cerebellopontine cistern, as do aneurysms and arteriovenous malformations.[27,28] Patients with MS are 20 times more at risk of having TN and the prevalence is two to 5%.[6]

In classic TN, magnetic resonance imaging (MRI) studies show neurovascular contact in up to 89% of cases; however, in 11% of patients no cause is found, so a correct way to classify them would be as idiopathic TN.[6]

Recent advances in magnetic resonance imaging (MRI) studies have been able to visualize neurovascular compression, which is widely accepted as a cause of TN. In addition, MRI of patients with TN have shown other features such as atrophy of the trigeminal nerve and reduction of the pontomesencephalic angle and the pontocerebellar angle on the affected side, which may be factors involved in the pathogenesis of TN.[29] In cases of vascular compression, the MRI of patients with TN has been shown to be associated with a reduction of the pontomesencephalic angle and the pontocerebellar angle on the affected side.

In cases of vascular compression, the encephalic subsidence due to aging and the increased thickness of the vessel wall and its flexuosity may explain the prevalence of trigeminal neuralgia in later life.[6]

Evidence shows that the most frequent chronic irritation that triggers the pathophysiological processes described for primary TN is vascular compression of the nerve at its exit from the brainstem that induces morphological changes in the adjacent root;[27] however, vascular compression of the nerve is not observed in all cases, so it currently remains a controversial issue. Regarding secondary TN, in which there is an initial complaint that is the origin of the structural or functional lesion of the trigeminal nerve, the most frequent causes are multiple sclerosis, which causes demyelination of the fibers that form the nerve, or some brain tumors, which can compress the nerve and cause symptomatic TN.[29]

Advanced imaging methods are now available for the diagnosis of TN: CT scan of the internal auditory canal or projections showing the foramen ovale (mandibular branch outlet), foramen teres (maxillary branch) or orbital fissure (ophthalmic branch); neurophysiological examinations, such as the corneal-orbicular reflex (blink reflex), and trigeminal evoked potentials, although adequate stimulation for the performance of these techniques may be poorly tolerated, and computerized axial tomography, which includes skull base bone window slices and is important to rule out some of the structural causes such as meningiomas, neurinomas and other tumors or skull base bone disease, although for the detection of posterior fossa processes and vascular or

demyelinating lesions in the trunk, magnetic resonance imaging (MRI) is the magnetic resonance imaging (MRI) of choice.[30,31]

The diagnosis of TN is fundamentally clinical and is based, above all, on the anamnesis, in which the exact localization of pain, free intervals, buccofacial sensitive points, triggers during chewing and speaking, etc., are indicative.

In the physical examination, the anatomical distribution of the three branches of the V pair (ophthalmic, maxillary and mandibular) and the facial sensory evaluation and the corneal reflex with examination of the masticatory muscles, which are of particular relevance, should be taken into account. The complementary examination par excellence, when in doubt, is magnetic resonance imaging because the image is more useful to determine the presence of lesions such as cysts or tumors, vascular malformations and plaques of multiple sclerosis, as well as vascular compression of the trigeminal nerve.[1,18,19,21,28]

Diagnostic criteria include characteristic signs: facial paroxysmal character, unilateral seizure and tendency to involve the second and third trigeminal branches, intensity causing facial twitching or twitching, presence of a trigger point, lack of demonstrable sensory or motor deficit, and response in more than half of the cases to carbamazepine, phenylhydantoin and similar drugs. Each seizure is stereotyped and there are usually no other neurological deficits.[7,22,29]

Classic TN usually presents with episodes of several weeks or months duration followed by pain-free periods, although some patients may have continuous residual pain, whereas in secondary TN there are no such pain-free periods and there is usually constant baseline pain, accompanied by paroxysms.[29]

CONCLUSIONS

The current view is that TN is a neuropathic pain caused by proximal cranial nerve V root compression, leading to secondary demyelination, probably mediated by ischemic changes at the microvascular level. The excitability threshold decreases and promotes cross-communication between adjacent fibers. Thus, tactile signals from fast myelinated fibers (A-beta) can directly activate slow nociceptive fibers (A-delta) and sometimes C-fibers, resulting in high-frequency discharges to various stimuli that generate paroxysmal TN pain.

BIBLIOGRAPHIC REFERENCES

1. HIS Classification ICHD-3 [Internet]. London: International Headache Society; 2021 [cited 12/23/2021]. Pain attributed to a lesion or disease of the trigeminal nerve; [about 2 screens]. Available at: https://www.ichd-3.org/13-painful-cranialneuropathies-and-other-facial-pains/13-1-trigeminal-neuralgia/
2. Cohen SP, Raja SN. El dolor. In: Cecil y Goldman Tratado de Medicina Interna. 24 ed. Spain: Elsevier; 2013. p. 135-136.
3. Leach JP, Davenport RJ. Neurology. Davidson's Principles and Practice of Medicine. 23 ed. Spain: Elsevier; 2018.
4. Nugraha B, Gutenbrunner C, Barke A, Karst M, Schiller J, Schäfer P, et al. The IASP classification of chronic pain for ICD-11: functioning properties of chronic pain. Pain [Internet]. 2019 [cited 06/15/2022];160(1):88-94. Available at:

https://pubmed.ncbi.nlm.nih.gov/30586076/. https://doi.org/10.1097/j.pain.0000000000001433
5. Treede RD. The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. Pain Rep [Internet]. 2018 [cited 06/15/2022];3(2):e643. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5902252/. https://doi.org/10.1097/PR9.0000000000000643
6. Marín Medina DS, Gámez Cárdenas M. Neuralgia del trigémino: aspectos clínicos y terapéuticos. Acta Neurol Colomb [Internet]. 2019 [cited 06/15/2022];35(4):193-203. Available at: http://www.scielo.org.co/pdf/anco/v35n4/0120-8748-anco-35-04-193.pdf. https://doi.org/10.22379/24224022267
7. Headache classification committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia [Internet]. 2018 [cited 06/15/2022];38(1):1-211. Available at: https://journals.sagepub.com/doi/10.1177/0333102417738202. https://doi.org/10.1177/0333102417738202
8. Alcántara Montero A, González Curado A. Neuralgia del trigémino: nueva clasificación y tipificación diagnóstica para la práctica clínica y la investigación. Rev Soc Esp Dolor [Internet]. 2017 [cited 03/17/2022];24(2):105-107. Available at: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1134-80462017000200105. https://dx.doi.org/10.20986/resed.2016.3483/2016
9. Migueláñez Medrán BC, Goicoechea García C, López Sánchez A, Martínez García MA. Dolor orofacial en la clínica odontológica. Rev Soc Esp Dolor [Internet]. 2019 [cited 03/17/2022];26(4):233-242. Available at: https://scielo.isciii.es/pdf/dolor/v26n4/1134-8046-dolor-26-04-00233.pdf
10. Jones MR, Urits I, Ehrhardt KP, Cefalu JN, Kendrick JB, Park DJ, et al. A comprehensive review of trigeminal neuralgia. Curr Pain Headache Rep [Internet]. 2019 [cited 03/17/2022];23(10):74. Available at: https://link.springer.com/article/10.1007/s11916-019-0810-0. https://doi.org/10.1007/s11916-019-0810-0
11. Gambeta E, Chichorro JG, Zamponi GW. Trigeminal neuralgia: An overview from pathophysiology to pharmacological treatments. Mol Pain [Internet]. 2020 [cited 03/17/2022];16:1744806920901890. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6985973/. https://doi.org/10.1177/1744806920901890
12. Molina Gil J, López López B, Zunzunegui Arroyo P, Criado Antón Á, González Fernández L, García-Cabo Fernández C. Neuralgia del trigémino como única manifestación neurológica de la COVID-19. Open Respir Arch [Internet]. 2021 [cited 03/17/2022];3(SC1):459-464. Available at: https://www.elsevier.es/en-revista-open-respiratory-archives-11-pdf-X2659663621007830
13. Öztürk Ş. COVID-19 and Neurology. Turk J of Neurol [Internet]. 2020 [cited 03/17/2022];26(2):109-111. Available at: https://tjn.org.tr/jvi.aspx?pdir=tjn&plng=eng&un=TJN-73384. https://dx.doi.org/10.4274/tnd.2020.73384
14. Llerena Freire LF, Acurio Chingo DJ, Zambrano Saldarriaga LC, Izurieta Mera LM, Gordon Escalante VC, Zurita Villacres AX, et al. Alternativas emergentes en la farmacoterapia de la neuralgia del trigémino. Arch Venez Farmacol Ter [Internet]. 2019 [cited 03/17/2022];38(2):34-42. Available at: https://www.redalyc.org/journal/559/55964524006/55964524006.pdf
15. Zakrzewska JM, Wu J, Mon-Williams M, Phillips N, Pavitt SH. Evaluating the impact of trigeminal neuralgia. Pain [Internet]. 2017 [cited 03/17/2022];158(6):1166-1174. Available at: https://pubmed.ncbi.nlm.nih.gov/28114183/. https://doi.org/10.1097/j.pain.0000000000000853

16. Fármacos en dolor neuropático: puesta al día. INFAC [Internet]. 2018 [cited 03/17/2022];26(8):67-75. Available at: http://www.osakidetza.euskadi.eus/contenidos/informacion/cevime_infac_2018/es_def/INFAC_Vol_26_8_dolor%20neuropatico.pdf
17. Pawlina W, Ross MH. Ross. Tejido nervioso. Histología: Texto y Atlas: Correlación con biología celular y molecular. 7ma ed. Spain: Wolters Kluwer; 2015.
18. Firestein GS. Mecanismos de la inflamación y la reparación tisular. In: Goldman-Cecil. Tratado de Medicina Interna. 24 ed. Spain: Elsevier; 2013.
19. Kumar V, Abbas AK, Aster JC. Inflamación y reparación. Robbins and Cotran. Pathologic Basis of Disease. 9na ed. Spain: Elsevier; 2015.
20. Rincón Carvajal AM, Olaya Osorio CA, Martínez Rojas S, Bernal I. Recomendaciones basadas en la evidencia para el manejo del dolor neuropático (revisión de la literatura). Rev Soc Esp Dolor [Internet]. 2018 [cited 03/17/2022];25(6):349-358. Available at: https://scielo.isciii.es/pdf/dolor/v25n6/1134-8046-dolor-25-06-00349.pdf. https://dx.doi.org/10.20986/resed.2018.3673/2018
21. Flint Beal M, Hauser SL. Neuralgia del trigémino, parálisis de Bell y otros trastornos de pares craneales. In: Harrison's Principles of Internal Medicine. 19 ed. New York: McGraw-Hill Education; 2015. p. 2645-2646.
22. Ropper AH, Samuels MA, Klein JP, Prasad S. Principios de Neurología. 11 ed. Nueva York: McGraw-Hill Education; 2019.
23. Yaya Huaman R, Campos E, Rubio E. V par craneal. Nervio trigémino y Tratamiento quirúrgico de la neuralgia del trigémino. In: Codina Puiggros A. Tratado de Neurología. Barcelona; 2016. p. 754-759.
24. Jannetta PJ. Arterial compression of the trigeminal nerve at the pons in patients with trigeminal neuralgia. J Neurosurg [Internet]. 1967 [cited 03/17/2022];26(1part2):159-162. Available at: https://thejns.org/view/journals/j-neurosurg/26/1part2/article-p159.xml. https://doi.org/10.3171/jns.1967.26.1part2.0159
25. Fromm GH, Terrence CF, Maroon JC. Trigeminal Neuralgia. Current concepts regarding etiology and pathogenesis. Arch Neurol [Internet]. 1984 [cited 03/17/2022];41(11):1204-1207. Available at: https://pubmed.ncbi.nlm.nih.gov/6487105/. https://doi.org/10.1001/archneur.1984.04050220102026
26. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia - diagnosis and treatment. Cephalalgia [Internet]. 2017 [cited 03/17/2022];37(7):648-657. Available at: https://journals.sagepub.com/doi/10.1177/0333102416687280. https://doi.org/10.1177/0333102416687280
27. Cruccu G, Di Stefano G, Truini A. Trigeminal Neuralgia. N Engl J Med [Internet]. 2020 [cited 03/17/2022];383(8):754-762. Available at: https://pubmed.ncbi.nlm.nih.gov/32813951/. https://doi.org/10.1056/nejmra1914484
28. Obata Y, Kawano Y, Tanaka Y, Maehara T. Prognostic Impact and Post-operative Evaluation of Volumetric measurement of the Cerebellopontine Cistern in Trigeminal Neuralgia Using 3 Tesla Magnetic Resonance Imaging. Neurol Med Chir (Tokyo) [Internet]. 2018 [cited 03/17/2022];58(2):71-78. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5830526/. https://doi.org/10.2176/nmc.oa.2017-0157
29. Digree Kathleen B. Cefaleas y otros tipos de dolor cefálico. In: Cecil y Goldman Tratado de Medicina. 24 ed. Madrid: Elsevier; 2013. p. 2255-2256.
30. Roig Fabré E. Neuralgia del Trigémino. Goyenechea Gutiérrez FF, Pereira Riverón R. Neurocirugía. Lesiones del sistema nervioso. Tomo 2. La Habana: Editorial Ciencias Médicas; 2014 [cited 03/17/2022]. Available at:

http://bvs.sld.cu/libros/neurocirugia_lesiones_sistemanervioso2/neurocirugia_completo_tomo2.pdf
31. Santos Velázquez T. Neuralgia del trigémino idiopática. Rev Electrón Dr. Zoilo E. Marinello Vidaurreta [Internet]. 2019 [cited 03/17/2022];44(1):[about 4 p.]. Available at: http://www.revzoilomarinello.sld.cu/index.php/zmv/article/view/1668/pdf_548

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in relation to this article..