European Journal of Neurodegenerative Diseases
ISSN 2279-5855/ 2020 vol. 9, ISSUE N. 1, January-June

INFLAMMATION AND PAIN IN TRIGEMINAL NEURALGIA: ROLE OF SOME PRO-INFLAMMATORY CYTOKINES

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ABSTRACT

The trigeminal ganglion transmits all the sensory information of the skull and face to the brain through afferent pathways. Afferent fibres are divided into nociceptive and non-nociceptive fibres. Primary afferent pathways express receptors for cold, heat, mechanical damage, and more. Inflammation in the head and neck can cause pain that can become neuropathic with nerve damage. An alteration of cytokine production, which may be activated by numerous potentially damaging stimuli, is involved in hyperalgesic states of several neurological diseases. In nerve injury, inflammation initiates pain, a process that is mediated by certain cytokines such as IL-1, TNF and IL-6, which cause neuropathic pain. TNF is mostly produced by mast cells and macrophages and is involved in arthritis, graft versus host disease, and other disorders, mediating inflammatory diseases and playing a key role in the neuropathic pain processes. TNF can activate other cytokines (such as IL-1) and after neurological injury it is expressed by macrophages, fibroblasts, neutrophils, and Schwann cells. In trigeminal neuralgia, TNF is linked to hyperalgesia and neuropathic pain. This shows that the inflammatory mechanisms are overlapping with the those of pain. In pain and inflammatory conditions, IL-1 is produced by many cell types, mediates hyperalgesia and neuropathy, and is involved in trigeminal neuralgia, and this effect is down-regulated by IL-1 inhibitors. IL-6 has also been reported to play a major role in the induction of neuropathic pain. In fact, in neuropathies, such as damaged nerves, IL-6 levels are increased, demonstrating that major pro-inflammatory cytokines participate in pain and inflammation. However, the pathophysiological mechanisms involved in pain and inflammation of the trigeminal nerve still need to be elucidated, as there is insufficient research on this topic. Here, in this article, we report the relationship between trigeminal neuralgia, inflammation, and pain that is mediated by pro-inflammatory cytokines.

KEYWORDS: *trigeminal neuralgia, inflammation, pain, cytokine, IL-1, IL-6, TNF, neuropathic pain*

INTRODUCTION

Trigeminal neuralgia (TN) (tic douloureux) is a specific orofacial neuropathic pain manifested by a sudden paroxysmal event on one side of the face affected by the trigeminal nerve and hyperesthesia, and most frequently affects the second and third divisions of the trigeminal nerve (1). TN is a neurovascular disease affecting the root of the trigeminal nerve, is the most common pain pathology due to compression of the cranial nerves, and is characterized by severe episodic, paroxysmal pain which is similar to an electric shock. The intensity of the pain that comes from a trigger area can be of different degrees or even absent. Often, the pain is very strong, excruciating and constant, and can last for long periods.

Received: 26 May, 2020
Accepted: 08 June, 2020

2279-5855 (2020)

The cause of trigeminal neuralgia, which is usually idiopathic or from vascular compression, is due to damage to the nerve and pressure against it which causes some ischemic and mechanical damage including structural changes of neurons. In fact, in TN, there may be a defect in the axons and their myelin sheaths and therefore, the myelin may also be absent or deficient. It can be idiopathic or associated with compression of the trigeminal nerve (3).

Various stimuli, including tactical, sometimes harmless ones, can trigger a pain attack in the trigeminal nerve that usually affects only one side of the face. The sudden pain, which affects females more often than males, worsens rapidly and lasts for seconds to a few minutes and may involve the facial muscles (4). The right facial side seems to be the most affected and the course of the disease can be spontaneous and occurs after several months. Diagnosis with brain magnetic resonance imaging (MRI) can help identify demyelinated areas, and vascular compression at the root of the trigeminal nerve (ganglion of Gasser) which represents the entry area (5). In TN, sodium channel dysfunction along trigeminal nociceptive axons, myelin impairment, and structural changes in the trigeminal nerve with idiopathic pain may occur (6). In these altered areas, the neurons can excite the nearby axons, which when demyelinated, can generate anomalous electrical impulses, increasing the pain effect. Therefore, in trigeminal neuralgia there is a repetitive, high frequency hyperexcitability of sensory neurons with sharp pain (7).

DISCUSSION

In the interesting article by Kashiba H, et al. (8), it was reported that crush injury of small diameter neurons leads to an upregulation of histamine receptor mRNA. Also, other authors confirmed the inflammatory effect of histamine in neuralgia (9), an effect that can be inhibited by blocking the histamine receptors. Histamine exerts its pro-inflammatory effect by acting on endothelial cells, mediating vascular permeability and promoting platelet adhesion, an effect mediated by the adhesion molecule P-selectin. This shows that in addition to the various immune cells that participate in neuroinflammatory process, there are also mast cells (MCs) (10). In fact, MCs are ubiquitous cells that derive from pluripotent stem cells that mature in tissues and can be activated through the FcεRI receptor. The activation of MCs leads to the rapid release of inflammatory mediators residing within their granules, such as histamine, serotonin (in mouse cells), proteoglycans, TNF, and tryptase, a serine proteinase, etc. (11). Furthermore, the activation of these cells can occur without degranulation by producing, through mRNA, pro-inflammatory cytokines, such as IL-1, TNF, IL-33, which play an important role in neuroinflammation (12) (Table I, II).

Table I. *Some compounds that activate mast cells (MCs).*

• Bacteria	• Fungi	• LPS
• Mercury	• SCF	• PTH
• Venoms	• Parasites	• Substance P
• IL-4	• IL-6	• IL-1
• IL-33	• Adenosine	• Oestradiol
• NSAIDs	• CRH	• NGF
• Neurotensin	• Thrombin	• Endorphin
• Endothelin	• Morphine	• Viruses

Table II. *Some compounds released by mast cells (MCs).*

• Histamine	• IL-6	• IL-8
• IL-33	• LCT4	• PAF
• PGD2	• CRH	• NT
• TNF	• Tryptase	• RANKL
• Serotonin	• VIP	• Chymase
• Renin		

TNF, which acts on the two receptors p55 and p75, can also be released from MCs granules immediately (after a few seconds) as this cytokine is the only one that can be stored by MCs. IL-1 induces IL-6 and TNF released and other pro-inflammatory cytokines, increasing the inflammation at the site. In addition, IL-33 is a potent activator of MCs and stimulates the production of cytokines including TNF, IL-1, and IL-13 (13). Chemokines can also be produced by MCs, such as CXCL8 secreted by PMNs and fibroblasts which recruits inflammatory cells and cooperates with the CCL2 / MCP-1 chemokine which mainly attracts monocytes. The activation and release of arachidonic acid compounds by MCs leads to the release of PGD2 and leukotrienes LTC4, D4, E4, which collaborate to increase pain and the inflammatory process (14). Therefore, in neuralgia, damaged nerves are infiltrated not only by MCs, but also by neutrophilic granulocytes that mediate neuropathic pain, especially in the early stages. In addition, macrophages are also found in damaged nerves which produce pro-inflammatory cytokines that contribute to inflammation and neuropathic pain (15).

Therapy

The basic therapy for TN utilizes anticonvulsant drugs such as carbamazepine and oxcarbazepine which are the most common drugs (16). In the case of no pharmacological effect or drug intolerance, microvascular decompression can be used, as vascular compression occurs in TN. The mechanism of action of these drugs is based on the inhibition of voltage-gated sodium channels which have a crucial role with regard to neuronal function, since the control of the sodium exchange between the extracellular and intracellular spaces is essential for the initiation and firing of action potentials (17). These treatments increase the excitability threshold of neurons, reducing both the frequency of attacks and pain. Moreover, when pharmacological treatment is ineffective in idiopathic pain, the "nerve combing" method can be implemented, which consists in splitting the trigeminal root for pain relief (18).

CONCLUSIONS

From the concepts described above, we can conclude that in TN the inflammatory process mediated by cytokines, chemical mediators (produced by MCs), and compounds of the arachidonic acid cascade (PGE2 and leukotrienes) are very important, both for the generation of pain and for the induction of inflammation (19).

Conflict of interest

The author declares that they have no conflict of interest.

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