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TRIGEMINAL NEURALGIA DISORDER: IMMUNITY AND INFLAMMATION

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ABSTRACT

Trigeminal neuralgia (TN) is a chronic neuropathic pain condition that results in unpredictable sporadic, episodic painful sensations in the lower face. The pain occurs suddenly, induced by light vibrations or contact with the face, and is severe, being described as sharp, shooting, and shocking. TN causes great psychological and physical distress for patients and results in lowered quality of life. The etiology and pathology of the disorder are complicated and still unclear. Immunoallergic reactions could contribute to the development of TN, as seen in studies showing higher elevations of IgE and histamine levels in patients, which may involve mast cells. Inflammation occurs in response to trigeminal nerve damage, with an innate immune response involving Schwann cells, mast cells, and macrophages, and the release of cytokines such as TNF, IL-1, MCP-1, and IL-17. An overactive immune response can be negative and result in extreme sensitivity to painful stimuli. Here, the inflammatory reaction that occurs is reviewed in regards to its association with pain sensitivity of the peripheral nervous system in TN disorder.

KEYWORDS: *trigeminal neuralgia disorder, inflammation, immunity, pain, sensitization, neuropathic, cytokine*

INTRODUCTION

Trigeminal neuralgia (TN), also referred to as “tic douloureux”, is the most prevalent form of neuropathic pain and affects the somatosensory system. It is chronic, sporadic, and episodic, and attacks of pain can occur for only a few seconds or for up to 2 minutes. The pain is initiated by non-noxious stimuli, such as touching the face, brushing of teeth, or even a breeze blowing against the face and is localized at the branches of the trigeminal nerve, usually affecting one side of the lower face. The pain is described as shooting or shocking and can be disabling to the patient. The condition is not life-threatening but can cause great stress for sufferers and lower quality of life. TN has a prevalence rate between 0.07 to 0.3% of the population (1, 2) and affects women more frequently than men (3). Treatment to decrease pain is achieved with pharmaceuticals and/or surgery.

The pathogenetic mechanisms of TN are complicated, and its etiology is unclear. Different theories exist to explain both, and studies are showing the involvement of inflammation in the development and physiological processes of TN. The disorder could be caused by neurovascular compression of the trigeminal nerve, but could also result from trauma, inflammation, tumour, or another medical condition, including multiple sclerosis. People with multiple sclerosis (MS), a chronic inflammatory disorder that affects the central nervous system (CNS), have a much higher prevalence of TN, with co-occurrence of 3.8% (4).

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Inflammatory mechanisms are involved in TN and increasing evidence has begun to indicate the role of inflammation (5-7). The sensory nervous system is affected by immune processes and inflammation can cause nociceptive pain. However, the etiopathology of neuropathic pain is complex and not fully understood. It can occur as a result of disease or lesion, and it may be induced by excessive inflammation after nerve damage. In this paper, the role of immunity and inflammation in TN will be explored.

Peripheral nerve trauma, neuropathic pain, and inflammation

The most apparent cause of TN is mechanical distortion at the trigeminal nerve root entrance to the brainstem, where compression is seen with demyelination at the area of root entry (8). This is supported by magnetic resonance imaging (MRI) findings that have shown microstructural changes in the root area of the trigeminal nerve in the presence of compression (9-11). However, a neurovascular conflict is not always present in all cases (12), and it can exist asymptomatically without causing TN (13). After peripheral nerve trauma, an inflammatory response is activated to repair nerve damage. But an excessive inflammatory reaction can lead to long-term pain sensitivity and neuronal changes (14).

Schwann cells (SCs) are myelinating cells of the peripheral nervous system. They are activated after trigeminal nerve damage and convert to a repair cell phenotype, secreting neurotrophic factors including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin 3 and 4/5, in addition to producing extracellular matrix proteins (15). SC activation leads to down-regulation of myelin genes and up-regulation of trophic factors, myelin sheath destruction, pain sensitivity, and the innate immune response including the release of cytokines (16,17).

SCs interact with immune cells for nerve regeneration. After peripheral nerve damage, axons activate the extracellular signal-related mitogen-activated protein kinase (MAPK) signaling pathway in SCs, triggering the recruitment of immune cells, such as macrophages and MCs, which produce inflammatory cytokines and chemokines, such as tumor necrosis factor (TNF), interleukin 1 (IL-1), and monocyte chemotactic protein 1 (MCP-1) (17-19).

Half of the damaged myelin sheath of the trigeminal nerve is initially cleared by SCs (20), followed by macrophages which phagocytose remaining myelin debris (21,22). MC activation releases inflammatory mediators including histamine, serotonin, leukotrienes, and NGF. These mediators can cause sensitization of nociceptors as well as neutrophil aggregation to the damaged nerve site (23,24). The activation of neutrophils subsequently stimulates macrophages and T cells. T-helper cells release proinflammatory cytokines including IL-1β, TNF, and interleukin 17 (IL-17) (25) (Fig. 1).

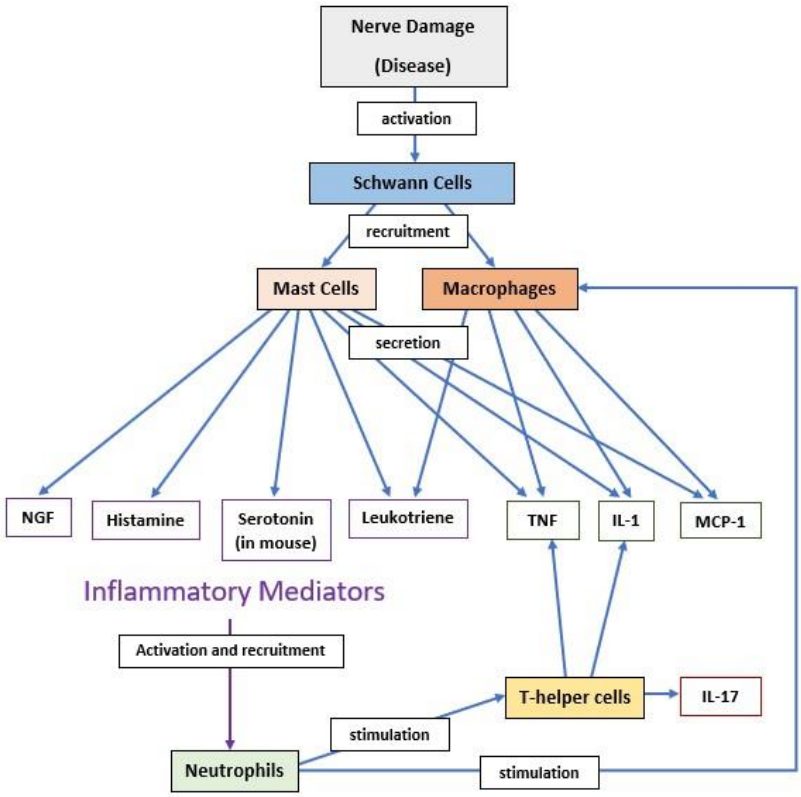

Fig. 1. *Damage to the trigeminal nerve activates Schwann cells, which recruit macrophages and mast cells. These macrophages and mast cells release inflammatory mediators such as TNF, IL-1, MCP-1, histamine, serotonin, leukotrienes, and nerve growth factor, the latter of which cause neutrophil activation and recruitment to the damaged site. The activation of neutrophils subsequently stimulates macrophages and T-helper cells. T-helper cells release proinflammatory cytokines including IL-1, TNF, and IL-17.*

Neutrophil infiltration, and the mediators released afterward by macrophages and T cells, can be linked to the development of hyperalgesia, the extreme sensitivity to painful stimuli (23,26). It was also observed that after nerve damage, hyperalgesia was reduced by macrophage depletion via intravenous injection of liposome-encapsulated clodronate (27), demonstrating the importance of macrophages in this disorder.

In one recent, interesting study it was observed that there were changes in immunological protein levels in cerebrospinal fluid of TN patients before and after treatment of microvascular decompression surgery (28). They found that levels of inflammatory protein markers decreased after surgery to a level that was consistent with a group of healthy controls, and identified two particular proteins of interest, TRAIL, and TNF, that may be involved in inflammation in TN (28).

The peripheral immune response following nerve injury involves the release of mediators that can affect pain sensitivity and could cause changes in the electrophysiological properties of neighboring neurons, leading to long-term neuropathic pain (14,29).

Inflammatory mediators can indirectly affect nociceptors, as cytokine receptors are expressed on sensory neurons. Hyperexcitability of the neural network in neuropathic pain can be caused by changes in ion channel function and nociceptive neuronal activity. Abnormal ion channel functioning leads to spinal and brain sensory signaling changes, which can result in increased neurotransmitter release and excitatory synaptic transmission of nociceptive channels (30). These nociceptor inputs cause central sensitization, producing hypersensitivity to pain, pressure hyperalgesia, and heightened temporal summation, and secondary changes that are produced can be seen by imaging (31).

Inflammation as the origin TN

The etiopathology of TN is unknown, but inflammation may be involved, and different theories exist to support this. Odontogenic inflammatory diseases could be one cause (32,33) and TN development could result from chronic inflammation of maxillary sinuses and inflammatory disorders of the ear, nose, and throat, such as sinusitis, periodontitis, phlegmon, periostitis, and dental cysts (34,35).

Immunoallergic reactions may play a role in the development of TN, as IgE and histamine have been implicated in studies (36-39). Histamine has been proposed to play a key role, as increased serum levels of histamine have been observed in TN patients. Degranulating MCs release mediators, including histamine and serotonin, producing a local hyperergic reaction (40), a process initiated with IgE attachment to MCs in the trigeminal nerve area (41). During the acute period of TN, blood and saliva levels of histamine were found to be raised (42). However, other factors may be responsible for an immune response and the increased IgE and histamine levels observed in TN patients. Therefore, further studies are needed to provide evidence for the allergy hypothesis of TN etiology.

CONCLUSIONS

TN is a chronic neuropathic pain disorder that significantly impacts the quality of life for sufferers, who show higher levels of pain, anxiety, and depression (43). In TN, demyelination occurs at the trigeminal nerve root entry area to the brainstem, and inflammation occurs to repair nerve damage. An exaggerated inflammatory reaction can have effects on central nervous system sensitization, leading to long-term pain sensitivity. An interaction between SCs and immune cells such as macrophages and MCs results in the release of cytokines, chemokines, and other inflammatory mediators, such as histamine. These mediators cause sensitization of nociceptors, contributing to the development of pain hypersensitivity and hyperalgesia.

More research focusing on the role of inflammation in TN should continue, as it could provide therapeutic opportunities. Controlling and containing the extent of inflammation could prevent central nervous system sensitization, therefore limiting pain and improving the outcome for patients.

Conflict of interest

The author declares that they have no conflict of interest.

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