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Review

The Role of Immune System in Migraine Pathophysiology

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Abstract

Migraine is a disease characterized by recurrent episodes of headache mediated by trigeminal activation and release of Calcitonin Gene-Related Peptide (CGRP) peptide. Additionally, there is a complex interaction with the immune system through neurogenic inflammation and neuroinflammation, with an imbalance between the pro-inflammatory response and the regulatory response. The innate immune system acts in migraine mainly through the increase of pro-inflammatory cytokines, notably IL-1β, whose production may occur in the cortex-meningeal complex due to spreading cortical depression or in the trigeminal ganglion sensitized by CGRP. Some evidence also suggests an effect of the adaptive immune system Th1 and mainly Th2, culminating in the activation of meningeal mast cells. On the other hand, regulatory T cells are quantitatively decreased in migraine, and there are fluctuations in the levels of IL-10, the main anti-inflammatory cytokine. There is evidence of the immune system's involvement in migraine; however, its effect is still poorly understood, requiring further investigation.

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Introduction

Migraine is a prevalent and debilitating primary headache disorder that affects over one billion people worldwide, accounting for 14.4% of the global population. Women are more commonly affected, representing two--thirds of the cases (1). The primary symptom of a migraine is usually a pulsating headache of moderate to severe intensity, often felt on one side of the head, and it is often accompanied by some degree of disability. The headache can last from 4 to 72 hours, and during the pain episode, individuals may experience sound sensitivity (phonophobia), light sensitivity (photophobia), nausea, and/or vomiting (2).

Migraine is closely linked to the imbalance of homeostasis in the human body. The attacks can be triggered by hormonal and metabolic changes, disruptions in routines, and stressors, leading to extensive pathophysiological alterations in the central and peripheral nervous systems, accompanied by immune responses that are still not fully understood (3).

The objective of this review article was to describe the interaction of the innate and adaptive immune systems, as well as regulatory components, with the physiopathological mechanisms of migraine.

Methods

This review adopts a comprehensive approach to explore the interaction between migraine and the immune system and was based on an extensive search for relevant references in PubMed, including articles from the period of 1993 to 2023, using the keywords: "migraine," "immune system," "inflammation," and "cytokines." The selected sources were critically examined, prioritizing studies that provide insights into the immunological mechanisms underlying migraine pathophysiology, including the role of cytokines and immune cells.

Pathophysiology of migraine

The migraine attack begins with hypothalamic activation and its strong coupling with the spinal trigeminal nucleus in the brainstem, hours to days before the onset of headache. Consequently, the hypothalamus modifies itsconnectivity with pain-processing and modulatory areas, lowering the threshold for trigeminal nociceptive afferent activation, rendering the brain susceptible to pain (4, 5).

Subsequently, cortical spreading depression occurs, characterized by a slow wave of neuronal and glial depolarization followed by cortical depression or silent electrical activity, accompanied by hyperemia followed by oligemia. This phenomenon leads to the efflux of K+ and H+, glutamate, and adenosine triphosphate (ATP), activating trigeminal nociceptive endings located in the meninges adjacent to the cortex (6).

Pain initiates as a result of the activation of trigeminal afferents located in blood vessels and meninges, carrying nociceptive information to the thalamus and cerebral cortex. Additionally, these afferents release Calcitonin Gene-Related Peptide (CGRP) in an antidromic manner at their nerve endings and trigeminal ganglion, amplifying and perpetuating pain (7-9).

The primary biological functions of CGRP include vasodilation, sensitization of Aδ fibers (lightly myelinated), and activation of satellite glial cells (8, 9). When included in cultures of glial cells derived from the trigeminal ganglion, CGRP is capable of promoting inflammatory activity (10, 11), as well as enhancing its effect by increasing messenger ribonucleic acid (mRNA) expression of its own receptor in satellite glial cells (11).

The interaction between the trigeminal system and the immune system is demonstrated in various clinical and experimental studies. However, there are still several gaps in our understanding of this interaction. It occurs in different phases and anatomical structures related to migraine, such as meninges, blood vessels, ganglion, and trigeminal nucleus, affecting circulating immune cells and plasma inflammatory molecules (12-14). The Figure 1 represents the main pathophysiological mechanisms of migraine and its interaction with the immune system.

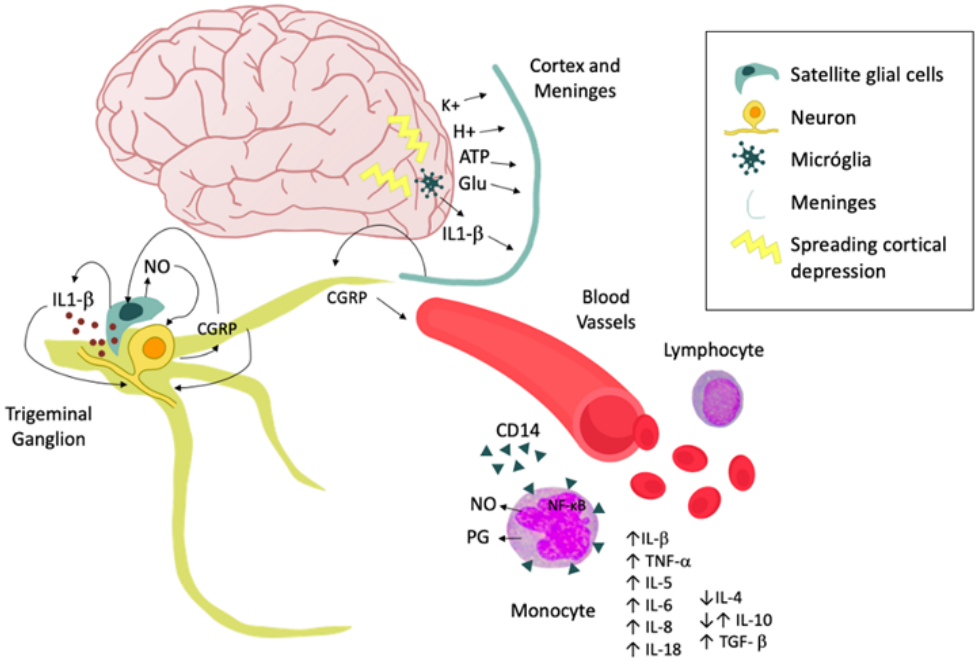

Figure 1. Immunopathogenic mechanisms of migraine in the cortex, meninges, trigeminal ganglion, and blood. Spreading cortical depression releases molecules that activate trigeminal afferents in the meninges, as well as stimulate the production of IL-1 by microglia. From trigeminal activation, ganglion neurons express CGRP, which acts on the neuron itself in a feedback system. CGRP also acts on satellite glial cells that express IL-1 and NO, which further stimulate the neuron and the release of CGRP. Finally, the release of cytokines and inflammatory mediators occurs in the blood, with a predominance of pro-inflammatory mechanisms.
IL, interleukin; NO, nitric oxide; CGRP, calcitonin gene-related peptide; PG, prostaglandin; K+, potassium; H+, hydrogen; ATP, adenosine triphosphate; Glu, glutamate; NF, nuclear factor; TNF, tumor necrosis factor; TGF, transforming growth factor.
Adapted from Vitali-Silva et al. Imunopatogênese da Migrânea. In: Valença MM, ed. Cefaleia. Recife: 2022. p. 53-67.

Immunopathogenesis of migraine

Several studies have demonstrated a relationship between inflammation and the development of migraine, particularly neurogenic inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been widely used to treat migraine attacks, as several cytokines, such as IL-1β, tumor necrosis factor alpha (TNF-α), and IL-6, are associated with the onset of migraine and exhibit altered levels in patients with this condition. Furthermore, there are evidences of increased pro-inflammatory cytokines and reduced subsets of regulatory lymphocytes in the peripheral blood of migraine patients, which seems to corroborate the role of inflammation in the pathophysiology of this disease (15).

Neurogenic inflammation is defined as acute sterile inflammation induced by the peripheral release of neural mediators, particularly neuropeptides, from nociceptive fibers, leading to vasodilation and plasma protein extravasation. Neuroinflammation refers to an inflammatory process that occurs in the central nervous system (CNS), mediated by microglia, and/or the peripheral nervous system, represented by the trigeminal ganglion, mediated by satellite glial cells. Both mechanisms appear to be involved in migraine, a phenomenon referred to as neurogenic neuroinflammation (16).

Innate immune system

In migraine, there is a complex interaction between the nervous system and the immune system, with evidence suggesting the involvement of both the innate and adaptive immune systems through the action of T helper (Th)-1 and Th2 responses, as well as a decrease in immunoregulatory response. Anatomically, there is ample evidence that these immune responses primarily occur in the trigeminal ganglion, with a profound interaction with the neuropeptide CGRP(8), and in the cortex-meningeal complex through spreading cortical depression (17). The main clinical evidence of inflammation related to migraine is derived from serum levels of inflammatory markers obtained from the jugular or peripheral vein (18).

The innate immune system performs various essential functions that protect against microorganisms and tissue injury. The cellular response is primarily initiated by macrophages and dendritic cells, which possess receptors that recognize molecular structures of pathogens as well as damaged self-cells. These receptors are known as Toll-like receptors (TLRs) or NOD-like receptors (NLRs). TLRs/NLRs can be present on the cell membrane or in the cytosol, and ligand recognition by TLRs/NLRs results in the activation of various signaling pathways, followed by transcription factors, inducing gene expression and cytokine production (19).

In the CNS, TLR and NLR pattern recognition receptors are primarily expressed in microglia, astrocytes, and macrophages, but they are also expressed in oligodendrocytes, neurons, and endothelial cells. These receptors are capable of recognizing signals of damage, metabolic changes, and tissue stress, initiating an immune response through the formation of a protein complex called the inflammasome, which culminates in the cleavage of pro-IL-1β and pro-IL-18 into active cytokines. The evidence for the role of the inflammasion in migraine is indirect and includes increased production of IL-1β(20) and IL-18 in migraine (13).

In the cerebral cortex, spreading cortical depression (SCD) induces chemical and electrical changes that lead to increased gene expression of TNF-α and IL-1β, as well as IL-1β expression by cortical microglia (21). Pro-inflammatory cytokines such as IL-1β locally increase the sensitivity of meningeal nociceptors and are capable of promoting their activation (22, 23). A classic model for inducing migraine in animal and human models involves the infusion of substances that induce NO production. In an experimental model, intravenous administration of glyceryl trinitrate induced the expression of genes encoding the cytokines IL-1β and IL-6 in the dura mater, accompanied by plasma protein extravasation (24).

Chemical dural stimulation also generates inflammatory changes at distance, in the trigeminal ganglion, inducing the expression of IL-1β by C-fiber type neurons through the formation of the inflammasome PYD-containing protein 3 (NALP3), likely activated by molecular patterns associated with cellular damage after nociceptive stimulation (25). In the trigeminal ganglion, Vause and Durham(10) demonstrated that CGRP induced the production of several cytokines in glial cell culture. In another study, specifically in satellite glial cells, it was shown that CGRP promoted an increase in IL-1β mRNA expression, without altering its levels. When these cells were treated with CGRP along with IL-1β, there was even greater mRNA expression of IL-1β, this time with an increase in its levels, suggesting that this pro-inflammatory interleukin is capable of exacerbating the effect of CGRP on inflammatory activity (11). In human peripheral blood, isolated mononuclear cells enriched with lymphocytes showed that CGRP increased the basal secretion of interleukin-1β, IL-6, and TNF-α (26). Similarly to inducing cytokine production, CGRP also has an effect on increasing the activity of inducible nitric oxide synthase (iNOS), which is responsible for nitric oxide (NO) production (27, 28). During migraine attacks, serum levels of NO are elevated compared to the interictal period (29). As a consequence, there is also an increase in cyclooxygenase expression and prostaglandins (30, 31).The release of CGRP by trigeminal neurons is also directly influenced by inflammatory molecules, being induced by IL-1β(31) and nitroprusside, a NO-releasing agent. Headache can be induced by NO by sensitizing and activating trigeminal branches, with the perpetuation of this mechanism due to NO production stimulated by CGRP, as well as CGRP released in response to the presence of NO(28). Thus, a cycle of stimulation is established between the neuron and the satellite glial cell. The CGRP peptide produced by the neuron acts on the satellite cells, which, in turn, release inflammatory molecules that act on the neuron. As a consequence, neuronal sensitization occurs, reducing its activation threshold and depolarization, resulting in hyperalgesia in migraine. Finally, the release of CGRP can be inhibited by sumatriptan, which acts on neuronal serotonergic receptors, as well as by methylprednisolone, a potent anti-inflammatory agent (18, 28, 32).

In an experimental model of migraine using the infusion of an inflammatory mixture into the dura mater, increased expression of IL-18 and its receptor in microglia and astrocytes was identified. Inhibition of this pathway reduced nociceptive behavior in mice (33). Experimental studies associate increased IL-18 with hyperalgesia (34) and its expression in microglia following induction of neuropathic pain, as well as increased expression of the IL-18 receptor in astrocytes (35). Blocking IL-18 through its endogenous inhibitor (IL-18BP) reduced pain symptoms, allodynia, and increased the analgesic effect of opioids (36, 37).

The involvement of the innate immune system is also evidenced by blood alterations in cellular components and cytokines in individuals with migraine. Sarchielli and colleagues(38, 39) demonstrated in two classical studies the serum variation of cytokines and their temporal relationship with the onset of pain, as well as with CGRP levels in blood from the jugular vein.These results are summarized in Figure 2. During the ictal phase, when the main neuroimmune events of migraine occur, there is a plasma increase in pro-inflammatory cytokines and a concomitant decrease in anti-inflammatory cytokines. Sarchielli and colleagues(38, 39) demonstrated that levels of IL-1β increased between 1 and 4 hours from the onset of pain, while levels of TNF-α and IL-6 transiently increased between 1 and 2 hours. Concurrent with the increase in TNF-α and IL-6, there was also an increase in serum levels of soluble intercellular adhesion molecule

1 (sICAM-1). IL-8 increased between 2 and 6 hours. On the other hand, IL-4 values were decreased between 1 and 4 hours.

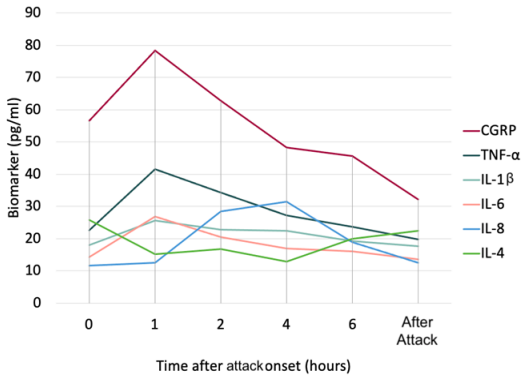

Figure 2. Serum levels of CGRP and cytokines from the jugular vein in individuals with migraine and their temporal evolution after the onset of an attack. The graph represents the average serum levels of CGRP and cytokines based on the results of Sarchielli et al. (38, 39).

Studies on the cytokine profile in migraine have recently been summarized in two meta-analyses. Geng et al. identified higher serum levels of IL-1β, TNF-α, and IL-6 in individuals with migraine compared to healthy controls. There was no difference in IL-10 and IL-2 levels (20). Subsequently, Musubire et al.,(40) in their meta-analysis found increased serum levels of IL-6, TNF-α, and IL-8 in migraine compared to healthy controls. Only IL-1β levels were found to be elevated during the ictal phase compared to the interictal period.

Few studies have assessed changes in plasma levels of IL-18. Vedova et al.,(41) demonstrated an increase in IL-18 levels in men with chronic tension-type headache. Later, Dönder et al.,(42) showed that IL-18 levels were elevated in individuals with migraine compared to healthy controls, but no statistically significant difference was found between the ictal and interictal periods. To date, there are no other studies investigating the role of IL-18 in migraine.

Monocytes are precursor blood cells of macrophages, which are tissue cells and an important component of the innate immune system. They are capable of producing higher levels of nitric oxide (NO) and prostaglandins in individuals with migraine, even in the absence of pain (interictal period), compared to controls (43). Monocytes express surface molecules CD14, which can also be found in their soluble form with opsonization function. In the interictal period, there is an increase in plasma levels of soluble CD14 with a concomitant decrease in TNF-α expression by monocytes compared to controls. It is believed that the paradoxical decrease in TNF-α occurs in response to prolonged stimulation of peripheral monocytes (44). During the pain phase of migraine, monocytes from the jugular vein show increased activity of the transcription factor NF-κB, which can induce increased production of NO through positive regulation of inducible nitric oxide synthase (iNOS), acute-phase proteins, cytokines, and adhesion molecules. In migraine, NO plays an essential role, as demonstrated in animal and human experiments, with increased production during migraine attacks or even between attacks. There is also hypersensitivity to exogenous NO and improvement of migraine with NO synthase inhibitors (39).

Adaptive Immune System

The adaptive immune system also appears to be involved in the pathophysiology of migraine, with the involvement of components of the Th1 and Th2 responses. The Th1 response can be induced by intracellular microorganisms ingested by phagocytes, which produce IL-12p70 that acts on the differentiation of immature T cells into Th1 cells. IL-12p70 is a pro-inflammatory cytokine and has been shown to be increased in the plasma of individuals with migraine during the interictal period, proportional to the frequency of migraine attacks (45, 46). Th1 cells produce IFN-γ, and its gene expression is increased in individuals with migraine with aura compared to healthy controls. The gene expression of IFN-γ was correlated with TNF-α expression, demonstrating an interaction between the innate immune system and the Th1 response (47).

Another immune cell that has been implicated in the pathogenesis of migraine is the mast cell. Mast cells are non-circulating immune cells derived from pluripotent hematopoietic stem cells that migrate and mature near the epithelium, blood vessels, and nerves. Mast cells are present in almost all vascularized tissues and produce, store, and release biologically active products, including cytokines, arachidonic acid compounds, and proteases. Additionally, mast cells participate in both innate and adaptive immune responses (48). Mast cells reside near primary nociceptive neurons, associate with nerves, and are capable of triggering local inflammation. They are involved in the physiology of various tissues and organs, particularly where there is increased angiogenesis. Activated mast cells degranulate pre-formed mediators, including histamine, heparin, proteases (tryptase, chymase), hydrolases, cathepsin, carboxypeptidases, and peroxidase, and also produce pro-inflammatory cytokines/chemokines (49).

Mast cell activation by antigens, in the presence of IL-4, stimulates the differentiation of immature T cells into type 2 helper cells (Th2), which produce IL-4, IL-5, and IL-13. Finally, IL-4 induces mast cell degranulation (19), causing the influx of numerous immune cells into the CNS, important for host defense against infections and tissue repair after trauma. These reactions can also

be accompanied by severe headaches and significant damage (50).

The role of mast cells in migraine is still considered controversial because, although mast cells degranulate in response to CGRP in preclinical models, human mast cells do not express the necessary receptors for CGRP response. Other molecules have been investigated as potential triggers for human mast cell degranulation, such as NO, PACAP (pituitary adenylate cyclase-activating polypeptide), substance P, and vasoactive intestinal peptide, without a definitive conclusion at this time (16).

In the clinical scenario, Hadjikhani and colleagues(51) demonstrated a strong persistent extra-axial inflammatory signal in meninges and calvarial bone overlying the occipital lobe in individuals with migraine with visual aura. With mast cells, along with macrophages, being the main cells possibly implicated in this meningeal inflammation.

IL-4 and IL-5 are cytokines produced by Th2 cells. IL-4, a cytokine capable of inducing mast cell degranulation, has been found to be decreased during the ictal period between 1 to 6 hours after the onset of pain (39). During the interictal period, Munno et al. found higher serum levels of IL-4 and IL-5 in individuals with migraine compared to controls (52). Subsequently, Munno et al. detected elevated levels of IL-4 and IL-5 during the ictal period, 30 minutes after the administration of sumatriptan, an acute treatment for migraine attacks (53).

Interleukin-8

IL-8, or CXC chemokine ligand 8 (CXCL8), is a cytokine with chemotactic activity that is more specific for neutrophils and has little effect on other cells. It is produced by macrophages and other cell types, such as epithelial cells, smooth muscle cells of the airways, and endothelial cells. It has a pro-inflammatory action, attracting and activating neutrophils at the site of inflammation. Elevated levels of IL-8 have been identified between 2 to 6 hours after the onset of migraine pain (38). However, previous studies have shown conflicting results, with some reporting an increase (54) and others reporting a decrease (45) in IL-8 concentrations during the interictal period. A cross-sectional study demonstrated significantly higher levels of IL-8/CXCL8 and MIP-1α/CCL3 among migraine patients, regardless of psychiatric comorbidities, migraine impact, and allodynia (55). A meta-analysis found increased serum levels of IL-8 in individuals with migraine compared to controls, but no difference between the ictal and interictal phases (40).

Finally, activated dural macrophages, microglia, and mast cells in the CNS could act through the release of pro-inflammatory cytokines that are involved in the increased levels of arachidonic acid products, such as leukotrienes and prostaglandins, triggering an inflammatory reaction resulting in migraine and other neurological manifestations, including fatigue, nausea, headaches, and brain fog (49).

Regulatory Immune Response

In response to pro-inflammatory activity, regulatory T cells (Treg) exert an effect on inflammation control by suppressing immune responses and maintaining self-tolerance through the expression of cytokines IL-10 and transforming growth factor-beta (TGF-β) (19). Treg cells are a subset of CD4+ T cells that express CD25 and possess the transcription factor FoxP3. These cells are proportionally reduced in individuals with migraine compared to controls, suggesting a deficiency in the immune regulation process (46, 57). In parallel, an increase in CD4+ T lymphocytes and a decrease in CD8+ T lymphocytes have also been demonstrated in migraine (57).

IL-10 is primarily produced by macrophages and Treg lymphocytes. During the ictal phase, there is an elevation in plasma IL-10 levels compared to the interictal period and healthy controls. After the administration of subcutaneous sumatriptan 6mg, a decrease in IL-10 values was observed (53).The authors suggested that IL-10 might be increased during migraine attacks to neutralize the effects of some inflammatory cytokines and that after treatment with sumatriptan, it would revert to cytokine profiles observed during the interictal period. Decreased levels of serum IL-10 during the interictal period have also been identified (45). Meta-analyses by Geng et al. and Musubire et al. did not find a statistically significant difference in serum IL-10 levels between individuals with migraine and controls (20, 40). On the other hand, TGF-β, another cytokine also produced by Treg cells, was evaluated in the plasma of individuals with migraine during the interictal period in only one study, which identified elevated values compared to healthy controls (58).

Treatment of Migraine and the Immune System

The pharmacological treatment of migraine consists of drugs used in the acute phase and for prevention. Many drugs from different classes have been used over the years, with recent advances and the use of new medications targeting the CGRP peptide pathway (59, 60).

The mechanism of action of preventive drugs is diverse, with effects on different anatomical sites, receptors, or channels. However, they all act on the modulation of pathways involved in the pathophysiology of migraine (60).

Preventive or acute-phase treatments for migraine may

have an effect on the inflammatory mechanisms of migraine. The anti-inflammatory action is still considered a secondary effect in the prophylactic mechanism but is more recognized in acute treatment. In children, a reduction in migraine symptoms was demonstrated concomitant with a reduction in the levels of pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 after 4 months of treatment with propranolol, amitriptyline, flunarizine, or cyproheptadine (61). Botulinum toxin, indicated for chronic migraine, modulates neurotransmitter release, alters the expression of receptors and cytokines, and enhances the transmission of endogenous opioids (62).

In acute therapy, sumatriptan is capable of exerting an inhibitory effect on plasma levels of cytokines such as IL-4, IL-5, and IL-10 (53). Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis, and their effect has also been demonstrated in the trigeminal ganglion (31). Finally, methylprednisolone, a potent glucocorticoid with anti-inflammatory action, can inhibit CGRP secretion, a molecule currently recognized as a key player in the pathophysiology of migraine pain,(32) and dexamethasone is recommended for refractory migraine attacks (63).

Monoclonal antibodies (mAbs) targeting CGRP are medications developed specifically for the treatment of migraine. They target the CGRP peptide or its receptor as a therapeutic target. In contrast to other mAbs that target immune system cells, anti-CGRP mAbs do not have a direct immunomodulatory effect, however its effect can modulate responses immunological disorders related to migraine. The indirect immunological effects of MABs related to migraine are not fully known (64).

The effect of the immune system on the treatment of migraine is still poorly understood, with gaps in knowledge and a need for further investigation. The identification of immunological therapeutic targets would expand the therapeutic arsenal in the face of the clinical and pathophysiological complexity of migraine.

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