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Original Article

Pattern of Interleukin-17A and Interleukin-1β in Migraine Patients

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Abstract

Background: Migraine is a complex neurological disorder. The precise etiology of migraine is not clear. Many studies have been conducted on the association of the immune system with migraine pathophysiology. Neurogenic inflammation, the main pathomechanism of migraine, is well described. This study evaluated the pattern of changes in interleukin (IL)-1β, IL-17A, total antioxidant capacity (TAC), and malondialdehyde (MDA) in migraine patients.

Methods: In this case-control study, serum samples were taken from 31 migraine patients referred to the neurology clinics of medical centers associated with Arak University of Medical Sciences. The severity of the headache was assessed with standard questionnaires. Serum samples were also obtained from 30 normal individuals. The IL-1β and IL-17A levels were measured by a sensitive ELISA method. TAC was measured by the FRAP technique, and lipid peroxidation levels were evaluated by an MDA assay. Data were analyzed descriptively and analytically using SPSS 21 software.

Results: The results showed that the mean level of IL-1β in the case group was significantly higher than the control group ($P=0.01$). The mean level of IL-17A was not significantly different in the two groups. The mean serum MDA level in the study group was significantly higher than in the controls ($P=0.005$). No statistical difference was observed in the mean serum level of TAC between the two groups.

Conclusion: According to our results, the pathogenesis of migraine can be associated with immune system function, and inhibition of pro-inflammatory cytokine production may be effective in treating migraine patients.

Keywords: Cytokines, Interleukin-1β, Interleukin-17A, Migraine

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Introduction

Migraine is a complex and debilitating neurological disorder with periodic attacks of moderate to severe headaches accompanied by nausea or vomiting or photophobia and phonophobia. Migraine is a genetic disorder, and therefore, most patients have a positive family history. The disease usually begins in childhood, adolescence, or early middle age (80% before age 30) and is more prevalent among women. Symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell (1,2).

The exact etiology of migraine is still unclear. In particular, the biochemical pathways that initiate the "headache phase" of migraine are not well known. However, the etiology seems to be multifactorial, and migraine is defined as a complex disease with different pathogenic mechanisms. Throughout the years, many theories on the pathophysiology of migraine have been suggested. Various factors such as alcohol use, physical exercise, menstrual cycles, nutrition, and stress have been associated with migraines (3-5). One of the latest and most acceptable theories about the pathomechanisms of migraine is "neurogenic inflammation." Changes in immune system homeostasis have been associated with migraine, with evidence of local and systemic inflammation in migraine.

Activation of the trigeminal system with the release of calcitonin gene-related peptide (CGRP) causes neurogenic inflammation and contributes to the pathophysiology of migraine (6-8). There is also evidence that oxidative stress is considered to play a significant role in migraine pathogenesis (9). Cytokines are small proteins essential

in several physiological and pathological settings, such as inflammation and pain. Cytokines are prominent mediators in inflammatory pathways, which considerably influence sensory neurons. The effect of cytokines on nociceptors can be direct; however, more commonly, cytokines act indirectly by releasing substances, mainly prostaglandins. Cytokines and their receptors are widely expressed by all types of neuronal cells (10,11). Besides prostaglandins, other substances that might be associated with headaches, including vasoactive substances, platelet-activating agents, etc., are produced by neutrophils, macrophages, and other cells in response to cytokines (12). Cytokines also play an essential role in the pathophysiological mechanisms involved in migraine headaches. Many studies have been conducted on the association of cytokines with migraine pathophysiology. These studies show the role of cytokines and inflammation in migraine headaches (13-15). Plasma levels of pro- and anti-inflammatory cytokines increase during migraine attacks. Various studies have shown that tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1 can lead to hyperalgesia and are therefore considered mediators of pain in neurogenic inflammation (16-18).

Interleukin 17A (IL-17A) is a pro-inflammatory cytokine produced by T helper 17 cells. IL-17 promotes inflammation by inducing the production of many other cytokines (such as IL-6, G-CSF, GM-CSF, IL-1β, TGF-β, TNF-α), chemokines, and prostaglandins from many cell types (19-21).

The association between IL-17A levels and migraine has not been studied extensively. Therefore, this study aimed to evaluate the levels of IL-1β and IL-17A, malondialdehyde (MDA) as a marker of lipid peroxidation, and total antioxidant capacity (TAC) cytokines in migraine patients.

Materials and Methods

Patients

In this case-control study, 31 migraine patients (25 females and 10 males) with an age range of 25 to 40 years referred to the neurology clinic of Arak University of Medical Sciences based on the ICHD III criteria (The International Classification of Headache Disorders, Third Edition) were enrolled in the study and informed consent was obtained. Patients who received antimigraine medication had a history of another disorder that might interfere with cytokine levels (infectious, inflammatory/autoimmune diseases, or metabolic/systemic disorders) or had abnormal neurologic tests or abnormal brain CT or MRI results were excluded from the study. 30 healthy controls were selected from the same mean age, sex ratio, and geographic area.

The MIDAS (Migraine Disability Assessment) questionnaire was used to determine the degree of disability caused by migraine. The grading system of the MIDAS categorizes the MIDAS total score into Grades I to IV, from minimal or infrequent disability with a score of 0–5 (Grade I) to severe disability with a score of 21 or higher (Grade IV).

Serum MDA, TAC, and cytokine level assays

Serum samples of patients and control groups were collected and stored in a -80 °C freezer until analysis. Serum MDA concentrations were determined by the 2-thiobarbituric acid spectrophotometric method (22). Serum total antioxidants were measured using the FRAP method described by Benzie and Strain (23). Then, IL-1β and IL-17 cytokine levels were measured by sandwich ELISA kits following the manufacturer's instructions (eBioscience, San Diego, CA, USA).

Statistical analysis

Statistical analysis was performed using SPSS software (IBM Corp., USA) version 21.0. P values < 0.05 were considered statistically significant.

Results

The cytokine concentrations in the case group (migraine patients) and the healthy control group are shown in Table 1. The results show that the mean IL-1β in the case group (migraine patients) was significantly higher than the control group. There is no significant difference in IL-17A levels in the case and control groups. The mean serum MDA level in the study group was significantly higher than in the controls ($P = 0.005$). Serum TAC levels in migraine patients were lower than in the control group. No statistical difference was observed in the mean serum TAC level between the two groups (Table 1). The results of the MIDAS questionnaire showed that the grade of disability due to headache was Grade I in 15% of the patients, Grade II in 32.5% of the patients, Grade III in 30%, and Grade IV in 22.5%. Comparisons of the patient groups based on MIDAS scores revealed no significant relationship between the MIDAS score and the serum levels of IL-1β, IL-17A, MDA, and TAC in the patient group.

Discussion

Migraine is one of the most common neurological

Table 1. Cytokine, MDA, and TAC levels in patients and healthy controls

Cytokine	Migraine patients (n = 31)	Healthy controls (n = 30)	*P* value
IL-1β (pg/mL)	2.2 ± 1.95	1.4 ± 1.1	0.01
IL-17A (pg/mL)	52.1 ± 3.4	55.1 ± 8.4	0.2
MDA (nmol/mL)	3.04 ± 1.74	2.06 ± 0.59	0.005
TAC (mmol/L)	1.34 ± 0.34	1.37 ± 0.33	0.75

Abbreviations: IL, interleukin; TAC, total antioxidant capacity; MDA, malondialdehyde
Values are given as mean ± standard deviation.

disorders worldwide. Although the exact cause of migraine is uncertain, evidence suggests the role of "neurogenic inflammation" in migraine pain. Studies also show the role of immunological mechanisms and *oxidative stress* in the pathogenesis of migraine (24,25).

In our study, MDA values were significantly higher in the patient group than in the control group. However, the mean serum level of TAC was not significantly different between the two groups. Researchers have reported conflicting results regarding the status of oxidative stress in migraine patients. In Geyik et al.'s study, the plasma levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG) were significantly higher in migraine patients than in the control group. However, no significant difference was observed in the total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) values between patients and controls (25). In another study, no difference was found between the patients and controls in TAS, TOS, and OSI (26). Togha et al. investigated oxidative stress biomarkers in episodic and chronic migraineurs (EM and CM patients) and controls. They reported that serum levels of MDA were significantly elevated among subjects with chronic migraine compared to those with episodic migraine and controls (27). Khosravi et al. showed higher levels of oxidative stress and lower levels of antioxidant status in the migraine group compared to controls (28).

The researchers showed that immunotherapy was associated with a reduction in the incidence, frequency, and disability of migraine headaches in younger people (24). Changes in serum levels of immunoglobulins, complement, histamine, immune cells, and cytokines in migraine patients have been studied (29-33).

Recently, the involvement of immunologic and inflammatory mechanisms, especially macrophages and B and T cells, has been reported in the pathogenesis of migraine. Among these cells, one of the most critical cells in the pathogenesis of migraines is T helper cells (Th).

$CD4^+$T cells are divided into two main subgroups, Th1 and Th2, based on their cytokines production pattern:

- Th1 cells produce IL-2, interferon- γ, and TNF-beta.
- Th2 cells produce IL-4, IL-5, IL-10, and IL-13.

Th17 is the third subset of effector cells that produce IL-17. The role of IL-17-producing T cells in inflammatory and autoimmune reactions has been shown in some studies (34).

Cytokines not only mediate the communication between the cells of the immune system but also

play a role in the communication between the brain and the immune system (29).

In a study by Perini et al, the plasma levels of IL-6, IL-10, TNF α, IL-4, IL -1β, and IL-2 were measured in 35 migraine patients during and after the attacks. The serum levels of IL-10, TNF-α, and IL-1β were significantly higher during attacks. The researchers concluded that TNF-α, IL-1β, and IL-10 may be involved in the pathogenesis of migraine attacks (13). By activating neuronal and glial cells in the trigeminal ganglion, IL-1β causes the release of cyclooxygenase-2. Therefore, IL-1β may be essential in migraine's inflammation-induced "headache phase" (35). Our results are parallel to those of previous studies.

It is evident that some immunological changes take place during migraine attacks, and cytokines are considered to be the possible pain mediators in neurogenic inflammation, which seems to be the best explanation for the headache phase of migraine. Most pro-inflammatory cytokines, such as IFN-γ, IL-1β, and TNF-α, are potent inducers of nitric oxide (NO) released by monocytes. NO plays a vital role in activating the cyclooxygenase type 2 enzyme responsible for synthesizing prostaglandins (36).

One study (15) showed levels of IL-1α, sTNFR1, and TNF-α cytokines to increase in children with migraine. On the other hand, they reported that these cytokines, especially IL-1α, were higher in migraine with aura. Therefore, they suggested that TNF-α, sTNFR1, and IL-1α may be involved in the pathogenesis of migraine attacks.

On the other hand, researchers stated that given that the half-life of cytokines in serum is short and they are rapidly degraded, the level of cytokines in serum may not correctly reflect the changes in cytokine levels in the CNS. Therefore, they recommended sampling from the jugular vein because it can reflect changes in CNS cytokines (36).

In our study, there was no significant difference in the levels of IL-17A between the migraine and control groups. A survey of increased levels of IL-17 during bacterial infection concluded that IL-17 causes vasculitis in the brain**,** which can lead to the sensation of a headache (37).

Possible factors that may have contributed to the contradictions between the results of other studies and also to the differences between the results of other studies and our results may include differences in geography, race, sampling methods (jugular vein or peripheral venous blood), migraine phases cytokines were measured in, and other underlying factors accompanying the migraines.

The last decade has seen an increase in discussions on the role of immune system modification in migraine (37). Cytokines are essential mediators of immune and inflammatory pathways. Therefore, pro-inflammatory cytokines, particularly IL-1, could be a potential target for migraine treatment.

High cytokine levels could stimulate trigeminal nerve activation, release vasoactive peptides, and cause inflammation. Notably, the role of IL-1β in the release of CGRP through PGE2 has been demonstrated (35). The role of CGRP in the increase of pro-inflammatory cytokines secretion has also been highlighted (37); therefore, the effect of CGRP and pro-inflammatory cytokines seems to be reciprocal. This makes pro-inflammatory cytokines potential targets for migraine treatment in the future.

The development of monoclonal antibodies against CGRP has changed the landscape of migraine treatment.

Considering that a monoclonal antibody against IL-1β has already been developed and is being used for some rheumatologic conditions (e.g., ILARIS®, canakinumab) (37), it might also be effective in patients with migraine, particularly in patients who have not responded to anti-CGRP treatment.

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Competing Interests
None declared.

Ethical Approval
The present study was approved by the Ethics Committee of Arak University of Medical Science, Arak, Iran (IR.ARAKMU.REC.1394.264). Informed consent was obtained from all participants. All procedures were performed following the associated guidelines and regulations.

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