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The Evaluation of Inflammation in Chronic Migraine Patients Using the Neutrophil-lymphocyte Ratio

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Abstract

Objective: Migraine is a common primary headache disease. Studies have supported the presence of neurogenic inflammation in the pathophysiology of migraine. The neutrophil/lymphocyte ratio (NLR) has been used as a marker of inflammation in recent years. Although it has been shown that NLR increases during migraine attacks, there are limited data on chronic migraine (CM) patients. We aimed to evaluate the inflammatory status in CM patients using NLR as a biomarker for inflammation.

Methods: Twenty three migraine patients without aura and 18 age-matched control participants were included. The migraine patients who had more than 15 headache days/month were grouped as having CM. The episodic migraine group included migraine patients who had less than 15 headache days/month. Another grouping was performed according to the total duration of migraine-type headaches. Patients having headaches over 10 years were grouped as long-term (LM) migraine patients, and those having headaches under 10 years were grouped as short-term (SM) migraine patients. The patients were in an interictal state during the evaluations. Demographic information, laboratory results, and definite diagnosis of the headache type of the participants were retrospectively collected from the files. NLR was calculated using the total counts of neutrophils and lymphocytes.

Results: The NLR was similar between the control, episodic, and CM groups. No correlation was found between NLR and the frequency of headaches. The NLR was similar between the SM and LM migraine patients.

Conclusion: There is no evidence of ongoing inflammation, which was evaluated by NLR, in the interictal state of patients with both episodic and CM.

Keywords: Migraine without aura, inflammation, neutrophil, lymphocyte, chronic headache

INTRODUCTION

Migraine is a common primary headache disease that affects approximately 15% of the population (1). Studies have supported the role of neurogenic inflammation in migraine pathophysiology. Neurogenic neuroinflammation is defined as inflammatory reactions in the trigeminovascular system in response to neuronal activity (2). The levels of some cytokines are altered in migraine patients. These cytokines include interleukin (IL) 1β, tumor necrosis factor (TNF), and IL-6. It has also been shown that the levels of proinflammatory cytokines and the prevalence of T helper 1 (Th1) lymphocytes increase, whereas there is a depletion in regulatory lymphocyte subsets, which also supports the role of inflammation (3-5).

During a migraine attack, an increase in blood flow and protein leakage from the vessels are observed. In addition, because of neurogenic inflammation, there is a composition of vasoactive peptides. A migraine attack is characterized by sterile inflammation at the end of this process (6-8). The neutrophil/lymphocyte ratio (NLR) has been used as an inflammatory marker in recent years. As a response to a stress factor, there is an increase in neutrophils and a decrease in lymphocyte counts (9,10). NLR can be detected by a total blood count test, which

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makes it a cheap and easy-to-access method. Several studies have compared the inflammatory biomarkers, including NLR, between migraine patients and the normal population, between episodic migraine (EM) patients and chronic pain, and between the interictal and attack periods of migraine-type headaches in the same patient (6,11,12). The results showed that NLR increases during a migraine attack, which supports the neuroinflammatory pathogenesis (11,12).

The International Classification of Headache Disorders-3rd edition (ICHD-3) divides migraine into two categories. EM is defined as having less than 15 headache days per month, whereas chronic migraine (CM) is characterized by having 15 or more headache days per month for at least three months and with at least eight days of characteristic migraine features (13,14). Both chronic and EM patients had higher serum levels of TNF-α than healthy individuals. On the other hand, neither TNF-α, nor C-reactive protein (CRP) did not show any difference between episodic and CM patients (15). However, the literature has limited data on the inflammatory status of CM patients using NLR as a biomarker.

This study aimed to detect a possible ongoing inflammatory status in CM patients using NLR as the biomarker for inflammation because NLR is found to be increased in acute attacks of migraine and can be detected with complete blood count, which is a simple test that can be performed at any medical center.

METHODS

This was a retrospective case-control study involving 23 migraine patients (15 episodic, 8 chronic) and 18 age-matched headache-free control participants. The confidence level of this study is 95%, and the margin of error is 15%. This study has a power of 80% and an effect size of 0.5. All participants were recruited from the Acıbadem Taksim Hospital Check-up and Neurology Outpatient Clinics. This study included subjects aged between 18 and 60 years. The diagnosis of episodic or CM was performed according to the criteria defined by ICHD-3 (13). To create a homogenous migraine patient group, only patients without an aura were included. All migraine patients were in an interictal state during their evaluation. This study excluded participants having: another type of headache than migraine, a new onset headache (started within the past 6 months), a neurodegenerative disease, a history of allergy, an infectious or inflammatory disease, a history of neoplasia, analgesic overuse, or regular use of anti-inflammatory medications. Participants were also excluded if they had a migraine attack or an infection (detected by either laboratory tests or examination) at the time of evaluation.

Patient files were scanned retrospectively between 2020 and 2022. All demographic information, headache features, laboratory results, and a definite diagnosis of headache type were collected from the files of the participants. The number of days per month with migraine-type headaches and the total time (in terms of year) that the patient had migraine-type headaches were recorded. NLR was calculated for each patient using the total counts of neutrophils and lymphocytes, which were detected by a complete blood test. All blood samples were taken before noon from the antecubital vein while the patient was fasting. All blood samples were analyzed on the same day.

Participants without a complaint of headache were grouped as the control group. According to the number of days with headache per month, EM and CM groups were created. The EM group included participants having headaches <15 days/month and the CM group included participants having headaches ≥15 days/month. Another classification of the participants was also performed as control, long-term (LM), and short-term (SM) migraine patients according to the total time of migraine-type headache to determine the effect of the total disease time on the inflammatory reaction. The LM group involved participants having migraine ≥10 years and the SM group involved participants having migraine <10 years.

The study protocol was approved by the Ethics Committee of Acıbadem University (approval no: 2023-1/22, date: 13.01.2023).

Statistical Analysis

The Shapiro-Wilk test was used to test the normality distribution of the data. The chi-square test was used to compare categorical variables. Numerical variables are given as mean ± standard deviation (SD). An analysis of variance (ANOVA) was used to compare continuous data. Equal variances were checked using Levene's test. Post-hoc analysis of the ANOVA test was performed by the Tukey test in equal variances and by the Tamhane test in unequal variances. Values are given as means and SD and numbers and percentages, according to the type of variables. Pearson correlation analysis was used to estimate the correlations between NLR, headache frequency, and total disease duration. The statistical significance level is considered $p<0.05$. All statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS) version 15 (IBM, Armonk, NW, US).

RESULTS

There was female dominance in the CM group (7 females, 1 male), whereas the gender distribution was similar in the EM (8 females, 7 males) and control groups (9 females, 9 males).

The mean ages of the groups were similar [F (2, 38): 0.625, p=0.541] (Table 1).

The effects of demographic differences in the NLR were checked by grouping the participants according to gender and age. The median age of all participants was 39 years, and the NLR was compared between the participants <39 years old and ≥39 years old. No significant difference was found [t (39): 1.09, p=0.281]. There was also no difference in the NLR between the genders [t (39): 1.59, p=0.119].

The participants of the control, EM, and CM groups showed similar NLR [F (2, 38): 1.245, p=0.299]. The comparison of the NLR between the control, SM, and LM migraine groups also showed no significant difference [F (2, 38): 0.142, p=0.868]. The correlation analysis between NLR and the frequency of migraine-type headaches (headache days per month) did not show any significance [r (23): 0.207, p=0.343]. There was also no significant correlation between NLR and the total duration of migraine-type headaches [r (23): -0.101, p=0.648].

DISCUSSION

It has been shown that inflammatory responses may differ between genders and between old and young populations (16). Healthy femalesunder 50 years of age were found to have higher NLR in recent studies (17-19). One of the suggested factors for this difference is estrogen hormone, which affects the neutrophil count and inflammatory response (20). However, the present study showed similar NLR between males and females and between younger and older participants. The limited number of cases in this study may be the reason for the failure to show the effect of demographic characteristics on the NLR.

In the literature, most studies concern the inflammatory response during a migraine attack. A recent example is a study conducted in 2021 by Panpallı et al. (11), who used NLR to compare the inflammatory response between migraine attacks with aura and interictal state. However, the studydid not include CM patients. It was found that the NLR was higher during a migraine attack than in the interictal state and control patients (11). The present study did not include patients during a migraine attack because the main purpose was to investigate a possible baseline inflammatory reaction in the interictal state.

Studies that compare the inflammatory biomarkers between the interictal state of migraine and healthy participants show various results. Panpallı (11) reported that the NLR was similar between the interictal period of EM patients and the control group. On the other hand, Vanmolkot and de Hoon (6) reported a significantly high level of CRP in the interictal period of EM patients, with and without aura, compared to the control group. Another study Martami et al. (15) used CRP and TNF-as inflammatory biomarkers during an interictal state. It was shown that CRP levels did not differ between the groups of EM, CM, and controls, but TNF- was higher in the episodic and CM patients than in the control group. Both CRP and TNF- did not show any correlation with attack frequency (15). However, there is a controversial result by Uzar et al. (21), who reported similar TNF- levels between migraine patients and the control group. Neuroinflammatory response is a complex process that includes several cytokines (IL-1β, TNF, IL-6, etc.) (3-5). The reason for the controversies in the literature may be the complexity of the inflammatory process. There is a need for studies that will include all the inflammatory biomarkers to make a more precise detection of inflammation in migraine patients and to prevent possible controversies between the studies.

It is also worth mentioning that migraine with aura may have a different pathophysiology than migraine without aura. It has been shown that the CRP level was higher more significantly in migraine patients without aura when compared with the healthy population (6). Although the present study only involved migraine patients without aura, we used NLR instead of CRP as the biomarker and found similar NLR levels between the patient and control groups. CRP could be accepted as another practical

Table 1. Analysis of the groups according to the headache frequency

	Control (n=18)	Episodic migraine (n=15)	Chronic migraine (n=8)	p
Age, years (mean ± SD) [min-max]	40.6±9 [26-59]	37.8±7.1 [26-47]	37.5±8.5 [29-57]	[F (2, 38) = 0.625, p=0.541]
Gender	Female: 9 Male: 9	Female: 8 Male: 7	Female: 7 Male: 1	-
NLR (mean ± SD) [min-max]	1.85±0.5 [0.95-2.8]	1.63±0.6 [0.89-2.95]	1.99±0.5 [1.38-2.79]	[F (2, 38) = 1.245, p=0.299]

SD: Standard deviation, NLR: Neutrophil/lymphocyte ratio

inflammatory biomarker, but it can be affected by other conditions besides inflammation, such as obesity, diabetes, and smoking (22-24). Therefore, we only used NLR for the evaluation of the inflammatory status. As mentioned above, inflammation is a complex process, which may be the reason for not finding a significant change in NLR. It may not be convenient to accept this result as a controversy to the study that used CRP as the biomarker.

Although the literature has limited evidence of a general neuronal inflammatory response in the ictal period of migraine; continuous release of neurotransmitters is thought to be the main pathophysiology in migraine chronification (25,26).

The present study shows that the inflammatory status, which was measured by the biomarker NLR, was similar between the control group and migraine patients, who were in the interictal state, regardless of having chronic or EM. The findings support the literature, which is against an increase in an inflammatory marker in the interictal period of migraine. There was also no correlation between NLR and both the total duration of migraine-type headaches and the frequency of migraine attacks, as supported by previous studies (15). These findings suggest that an interictal period of CM does not show evidence of an ongoing inflammation that could be detected by NLR.

Study Limitations

However, this study has several limitations. First, the sample size of the study was limited. Second, we only used NLR as a biomarker of inflammation. There are several inflammatory biomarkers including cytokines, CRP, serum amyloid A, and TNF. This study did not include all the biomarkers of inflammation because one of the aims of this study was to use a practical and easy-to-access biomarker, and NLR was a good candidate.

On the other hand, the literature has limited papers on the inflammatory response of CM patients, and this paper contributes to the literature by covering the interictal state of CM patients, which makes the strong side of the present study.

CONCLUSION

Although this study showed no evidence of ongoing inflammation in patients with CM, there is a need for future studies involving more inflammatory markers.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Acıbadem University (approval no: 2023-1/22, date: 13.01.2023).

Informed Consent: Informed consent was waived since this is a retrospective study. All personal and medical informations of the subjects are kept confidential.

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