

The Relationship of Migraine Clinical Features with Neutrophil-Lymphocyte Ratio

Fatma Şimsek¹, Nuray Bilge², Mustafa Ceylan³

Atatürk Üniversitesi Tıp Fakültesi,
Nöroloji, Erzurum, Türkiye

Fatma Şimsek, Asst. Prof
Nuray Bilge, Asst. Prof
Mustafa Ceylan, Assoc. Prof

Correspondence:

Asst. Prof. Fatma Şimsek
Atatürk Üniversitesi Tıp Fakültesi, Nöroloji,
Erzurum, Türkiye
Phone: +90 505 834 77 80
E-mail: klamaks@hotmail.com

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ABSTRACT

Purpose: Migraine is associated with serious social and economic burdens. Migraine attacks are associated with trigeminal nerve stimulation and neurogenic inflammation. It has been reported that the frequency of the attacks and disease progression are related to certain inflammatory indicators. Neutrophils are the paramount cells in causing inflammatory response during acute phase reactions. Neutrophil/Lymphocytes ratio (N/L) has been associated with the prognosis and mortality of several diseases.

Methods and Materials: The patients and control group in the age range of 18–45 years were included in the study. The relationship between N/L ratio in patients and control group was investigated.

Results: There was a statistically significant difference between the N/L ratios determined during the migraine attacks and the N/L ratio values obtained in the control group. But the non-attacks were not different compared to those of the control group. No statistically significant relationships of N/L ratio were detected with any of the clinical features of migraine, VAS and MIDAS.

Conclusions: The N/L ratio is associated with a migraine attack. However, with N/L ratio, disease duration, attack duration, pain frequency and pain severity; the disease disability cannot be predicted.

Keywords: Migraine, neutrophil/lymphocyte ratio, inflammatory pathophysiology

MİGREN KLİNİK ÖZELLİKLERİNİN NÖTROPİL-LENFOSİT ORANI İLE İLİŞKİSİ

ÖZET

Giriş: Migrenin ciddi sosyal ve ekonomik etkisi vardır. Migren atakları trigeminal sinir uyarılması ve nörojenik inflamasyonla ilişkilidir. Atak sıklığının bazı enflamatuar belirteçlerle ilişkili olduğu bildirilmiştir. Nötrofiller akut faz reaksiyonlarında enflamatuar cevaba yol açan en önemli hücrelerdir. Nötrofil/Lenfosit oranının (N/L) birçok hastalıkta prognoz ve mortalite ile ilişkili olduğu bildirilmiştir.

Materyal-Metod: Çalışmaya 18–45 yaş arası hastalar ve kontrol grupları dâhil edildi. Hasta ve kontrol grupları ile N/L oranı arasında ilişki araştırıldı.

Bulgular: Migren atak ile kontrol grubu N/L oranı arasında istatistiksel olarak anlamlı fark vardı, ancak non-atak ile kontrol grupları karşılaştırıldığında farklı tespit edilmedi. Migren klinik özellikleri, VAS ve MIDAS ile N/L arasında ilişki tespit edilmedi.

Tartışma: N/L oranı migren atakları ile ilişkilidir. Ancak, N/L oranı ile hastalık süresi, atak süresi ve ağrı sıklığı, ağrı şiddeti ve hastalık disabilitesi tahmin edilemez.

Anahtar sözcükler: Migren, nötrofil/lenfosit oranı, enflamatuar patofizyoloji

Migraine is a common neurological disorder; holding the third rank in the disease burden list and the seventh rank in the list of disease-associated disability (1–3). Therefore, it is associated with a serious social and economic burden (4). Migraine is characterized by severe unilateral headache, nausea, phonophobia, and photophobia; adversely affecting the activities of daily life (5). The vasoactive peptides released in association with the trigeminal nerve stimulation cause increased blood flow, extravasation of the plasma proteins, and neurogenic inflammation during the migraine attack (6). Along with the inflammatory system involvement in the migraine pathophysiology, it has been reported that the frequency of the attacks and disease progression are related to certain inflammatory indicators (7).

Zahorec was the first, reporting the relationship between neutrophils and lymphocytes during the inflammatory response. Neutrophils, lymphocytes, and other white blood cells are essential proinflammatory and anti-inflammatory cells (8). Neutrophils are the paramount cells in causing inflammatory response during acute phase reactions. Lymphocytes constitute the main components of both the humoral and cellular responses (9, 10). Stress response of circulating lymphocytes results in a rise in the neutrophil count and reduction in the lymphocyte count. Therefore, the ratio of these two subgroups of white blood cells (N/L ratio) is used as an inflammatory marker (11). N/L ratio has been associated with the prognosis and mortality of several diseases (12, 13).

Although the N/L ratio is inexpensive and can be obtained easily by performing a complete blood count; the number of studies investigating the relationship of this parameter with migraine or with its disease characteristics is limited. Our study examined the relationship of N/L ratio with the disease duration of migraine, with the disability scale scores, and with the frequency, duration, and severity of attacks.

Methods and Materials

The patients in the age range of 18–45 years, who were diagnosed with migraine according to the ICHD-2 criteria, between the dates January 2016 and January 2018 were included in the study. The control group consisted of patients aged between 18 and 45 years, who had a health status report and had no disease. This study is a retrospective analysis. In this study; a total of 143 patients with migraine were evaluated with their demographic features, disease characteristics, and N/L ratio values during the attacks and

in the intervals between the attacks. The study also included 50 healthy individuals and evaluated their N/L ratio values as controls. Demographic characteristics, duration of disease, duration of attack, attack frequency, migraine disability assessment scale (MIDAS), visual analogue scale (VAS) scores, attack, non-attack and control group N/L ratios were examined. The patients were excluded from the study when they were diagnosed with chronic migraine or headaches attributed to medication overuse; when their hemogram test results, MIDAS and VAS scores obtained in the outpatient clinic were not performed on the same day; when their hemogram test results and VAS scores obtained in the emergency department were not performed on the same day; when the interval between the date of outpatient clinic data and the data obtained in the emergency department was sooner than two weeks; or when missing data were found in the laboratory test results or disease characteristics (MIDAS, VAS scores, hemogram test results obtained in the outpatient clinic or the emergency department). Pregnant patients, patients with congestive heart failure, patients with acute or chronic renal diseases, endocrine disorders, or diseases of the hematopoietic or respiratory systems; patients with hepatobiliary or rheumatic diseases; patients with inflammatory bowel disease; patients receiving oncologic treatments; patients using the pre-specified medications (multi-vitamins, antioxidants, steroids, antipsychotics, and hormone replacement treatments); or patients who underwent surgeries in the past six months were also excluded (Figure).

The relationships between N/L ratio, migraine clinical features, VAS and MIDAS and N/L ratio between the patients and control group were investigated.

The study was approved by the Ethics Committee of our institution (2/18/15.02.2018).

Results

In this study; a total of 143 patients with migraine were evaluated with their demographic features, disease characteristics, and N/L ratio values during the attacks and in the intervals between the attacks. The study also included 50 healthy individuals and evaluated their N/L ratio values as controls. The mean age in the migraine group was 31.2 (± 8.0) years and it was 30.9 (± 8.3) years in the control group. There was not a statistically significant difference in the mean age between the groups. Females constituted 80.4% of the individuals in the migraine group and 78% of the control group. No statistically significant differences were detected in gender preponderance between the two study

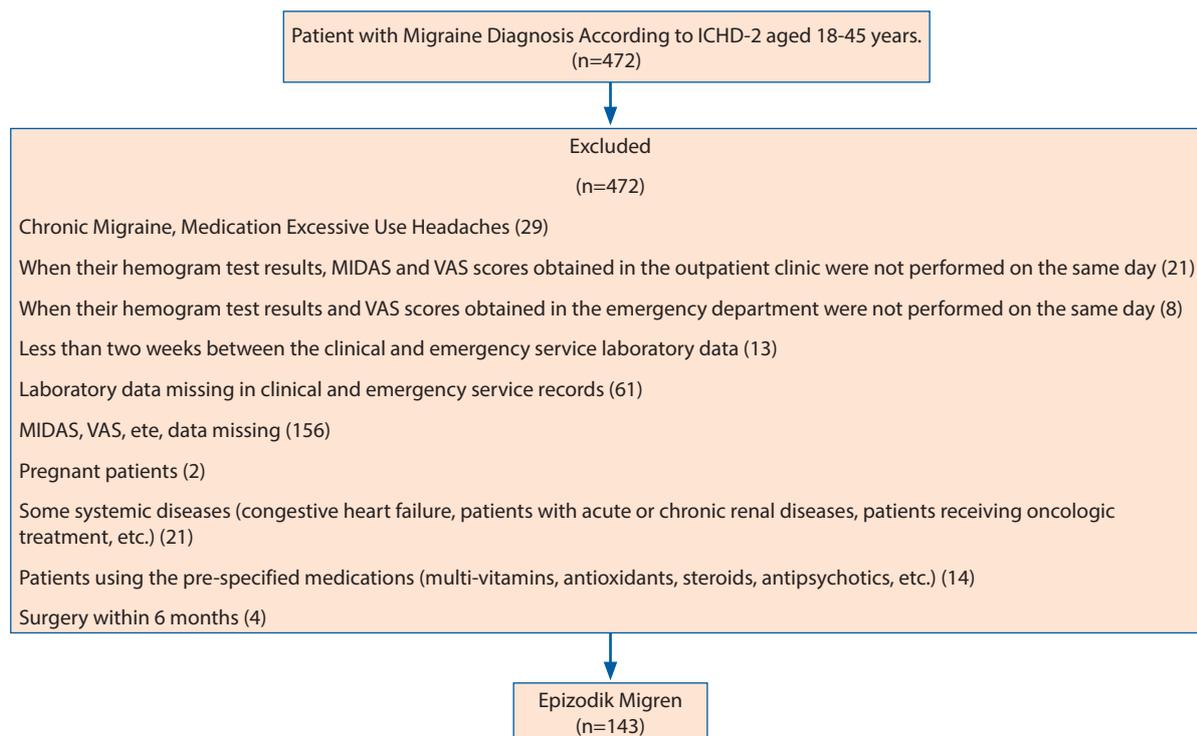


Figure 1.

groups (Table 1). A significant difference was observed between the N/L ratios determined during the migraine attacks and the intervals between the attacks ($p < 0.001$). There was a statistically significant difference between the N/L ratios determined during the migraine attacks and the N/L ratio values obtained in the control group; however, the N/L ratio values obtained in the attack-free interval were not different compared to those of the control group (Table 1). A regression analysis was performed between the N/L ratio obtained during the attacks and the following parameters including age, duration of attacks, disease duration, the frequency of headaches, VAS scores, and MIDAS scores. No statistically significant relationships of N/L ratio were detected with any of these parameters (Table 2).

Statistical method

d'Agostino-Pearson test was used for determining whether the data conformed to a normal distribution. The nominal data were compared using the chi-square test. The intergroup comparisons of the normally distributed data were performed with the independent t-test. The relationship between the disease characteristics and N/L ratio values was analyzed with a regression model. The results were accepted as significant when the two-way p-values were found below 0.05. All statistical analyses were performed using Medcalc (Medcalc, ver. 12, Ostend, Belgium) program.

Table 1. Comparison of demographic features and other study data between the patient and control group

	<i>Migraine (n=143)</i>	<i>Control (n=56)</i>	<i>p value</i>
Age, year (mean \pm SD)	31.2 \pm 8.0	30.9 \pm 8.3	0.852
Gender (%)			
Male	28 (19.6)	14 (21.4)	0.923
Female	115 (80.4)	42 (78.6)	
N/L ratio			
Attack period	2.6 \pm 0.7	1.6 \pm 0.7	<0.001
Attack-free period	1.7 \pm 0.6	1.6 \pm 0.7	0.430

Table 2. Regression analysis results investigating the relationship of disease characteristics with the N/L ratio obtained during migraine attacks

	<i>Co-efficient</i>	<i>Standard deviation</i>	<i>p value</i>
Age	-0.005	0.011	0.636
Disease Duration	0.023	0.018	0.209
Attack Duration	-0.082	0.014	0.459
Pain Frequency	0.073	0.124	0.555
VAS	0.025	0.072	0.726
MIDAS	0.013	0.081	0.872

VAS, visual analogue scale; MIDAS, migraine disability assessment scale.

Discussion

Migraine attacks were found to be related to the N/L ratios; however, a relationship of N/L ratio, with either the disease characteristics or some parameters associated with the attacks, was not detected.

It has been demonstrated that cytokines play a significant role in the pathophysiology of migraine and that the proinflammatory cytokines were related to the pain (14, 15). Animal studies have reported that the neurogenic inflammation around the trigeminal afferent nerve fibers is involved in the development of migraine attacks significantly (16).

Several clinical studies have reported the co-occurrence of inflammation and migraine; associating migraine with the serum levels of fibrinogen, D-dimer, and C-reactive protein, too (6, 7, 17, 18). It has been reported that higher serum procalcitonin levels detected during the migraine attacks compared to the attack-free periods were consistent with the underlying inflammatory mechanism in migraine (19). Similarly, another study found higher levels of pentraxin 3, an inflammatory marker, during migraine attacks and during migraine attacks lasting shorter than 12 hours. The same study has suggested that inflammation could be more prominent initially during the attacks and they could be replaced with other mechanisms later, being effective in the pathophysiology of the disease (20).

Several studies in the literature have reported that the N/L ratio is an indicator of inflammation and is correlated with the prognosis of systemic inflammatory diseases (21-23). A study, investigating the relationship of N/L ratio with the migraine attacks, reported that N/L ratio values were different between the group with migraine attacks and the control group, being higher in the former (24). Consistent with the literature, our study supported the involvement of inflammatory pathophysiology in migraine. When the N/L ratios during the migraine attacks and attack-free periods in the migraine group were compared to those of the control

group, it was observed that N/L ratio was higher in the migraine attack group compared to the latter two groups. No differences were observed between the N/L ratios of the attack-free group and the control group. Furthermore, the relationship of N/L ratio with the characteristics of patients, migraine, and pain was evaluated in our study. However, a statistical relationship of N/L ratio with patient age, duration of attacks, disease duration, pain frequency, VAS scores, and MIDAS scores was not detected. A previous study investigating the relationship of N/L ratio with migraine did not examine the association of N/L ratio with the characteristics of either migraine or pain. A study in the literature, using a different inflammatory biomarker, reported that there was a relationship of the inflammatory marker to the disease duration and the duration of the attack; however, no relationships to Migraine Disability Assessment Scale (MIDAS) scores or frequency of pain were reported (20). Another study reported that there were no relationships of attack duration and disability scale scores to endothelial cell-specific molecule 1 and Claudin-5 (25). Our study results are consistent with these reports in the literature, meaning that N/L ratio is an inflammatory marker not associated with the patient age, attack duration, frequency of attacks, the intensity of the pain, and the scores of functionality scales; and that the characteristics of migraine and pain are not affected by the inflammatory process. This conclusion is consistent with the previous report in the literature suggesting that inflammatory pathophysiology was actively involved early in the migraine pathophysiology but could be replaced later by other pathophysiological mechanisms. However, it is not possible to predict the extent of the impact of the N/L ratio on the disease duration, severity, and frequency of the attacks, and the quality of life.

Conclusion

A biomarker to be used in predicting the prognosis of migraine and in evaluating the efficacy of treatment can be highly practical in managing the disease and its treatment. We have determined that the N/L ratio cannot be used for these purposes.

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