Original Article

Relationship between White Matter Lesions and Neutrophil–Lymphocyte Ratio in Migraine Patients

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Abstract

Objectives: In this study, we aimed to compare the neutrophil/lymphocyte ratio (NLR) levels of migraine patients with and without gliotic lesions on brain magnetic resonance imaging (MRI). **Materials and Methods:** The records of the patients who were followed up in the neurology outpatient clinic of Ufuk University, Faculty of Medicine, between 2016 and 2019 with the diagnosis of migraine between the ages of 18 and 50 were reviewed retrospectively. Eighty-six patients without systemic, neurological, and infectious diseases between 18 and 50 years of age were included in the study. Patients were divided into two groups: Group 1 – subclinical ischemic/gliotic lesions on MRI and Group 2 – normal MRI. Subparameters and calculated NLRs in whole blood results were compared between the two groups. **Results:** When the two groups were compared in terms of leukocyte and neutrophil counts, a statistically significant difference was found. The leukocyte and neutrophil counts of the patients in Group 1 were significantly higher than those of Group 2 ($P = 0.038$/$P = 0.004$). NLR was higher in patients with gliotic lesions on MRI than in patients with normal MRI and was statistically significant ($P = 0.016$). **Conclusion:** This study aimed to evaluate the relationship between NLR and white matter lesions in patients with migraine. We have conducted this study to see if we can confirm this with a parameter in migraine patients with white matter lesions. Despite the small number of patients, leukocyte count, neutrophil count, and NLR were significantly higher in migraine patients with white matter lesions which support our hypothesis.

Keywords: *Migraine, neutrophil–lymphocyte ratio, white matter lesions*

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Introduction

Migraine is one of the primary headaches in which genetic and environmental components play a role. Prevalence is 6%–13% in males and 15%–25% in females. It starts before the age of 30 in more than 80% of patients.[1] The pathophysiology has not been fully understood despite numerous studies. The mechanism of migraine is still unclear, but biphasic intracerebral basal vascular constriction and subsequent extracerebral arterial dilatation are known to be involved in the pathophysiology of migraine.

Today, pain in migraine is considered as a consequence of neurogenic inflammation and accompanying meningeal vasodilatation. Enlarged blood vessels stimulate nerve endings, leading to the release of neuropeptides such as calcitonin gene-related peptide, substance P, and neurokinin A. These are vasoactive peptides that cause plasma extravasation and rapid inflammatory response.[2,3]

The relationship between migraine and ischemic vascular events has been studied for many years. Migraine with aura and subclinical ischemic lesions are risk factors for ischemic stroke.[4,5] Investigation of subclinical markers of vascular disease showed that migraine is associated

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with thickening of the arterial intima of small vessels.[6] The cause of the relationship between ischemic vascular disease and migraine is not clear. It has been suggested that cortical spreading depression may cause brain lesions by reducing blood flow and causing a chain of inflammatory events, and it was found that the risk of cerebral lesion increased with the number of attacks in migraine patients with aura.[7]

Immunocompetent white blood cells: Lymphocytes, neutrophils, and monocytes play an important role in the systemic inflammatory response against severe infection, trauma, injury, and shock.[8] Lymphocytopenia: A significant reduction in the number of circulating lymphocytes after severe trauma, major surgery, severe sepsis, and systemic inflammation has been described by many authors.

Menges *et al*. examined the rapid changes in lymphocyte count by flow cytometry in patients with severe trauma and found a significant reduction in T-lymphocytes.[9] When the clinical status and causes of lymphocytopenia are examined, myocardial infarction, ischemia-reperfusion injury, septic syndrome, margination and apoptosis, neuroendocrine stress in major surgery, and proinflammatory cytokines in acute pancreatitis have been shown to cause this condition. The increase in the number of neutrophils seen during systemic inflammation is caused by demargination of neutrophils, delayed neutrophil apoptosis, and stimulation of stem cells by growth factors.[10] Therefore, the ratio of these two subgroups to each other is used as a marker of inflammation. The neutrophil/lymphocyte ratio (NLR), which has been used recently, is an inexpensive and useful marker that can be easily calculated from whole blood count. Increased NLR in patients with normal leukocyte count may reflect inflammation and inflammation-related pathologies.[11-13]

Peripheral immune cells in peripheral blood such as leukocytes, neutrophils, and lymphocytes play a role in the atherosclerotic process besides inflammatory response.[14,15] The rate of circulating leukocytes provides a measure of inflammatory status and can be used as a predictive predictor of potential cardiovascular risk. Neutrophils are proinflammatory cells, and besides being detected in atherosclerotic plaque, they also synthesize and secrete chemokines. Lymphocytes provide regulation of the immune response. Furthermore, it promotes atherosclerosis and active inflammation by providing the release of proinflammatory cytokines.[16,17]

In this study, we aimed to compare the NLR levels of migraine patients with and without gliotic lesions on brain magnetic resonance imaging (MRI). Based on the knowledge that neutrophils and lymphocytes play a role in both the inflammatory and atherosclerotic processes, we tried to determine whether brain lesions in migraine patients are associated with NLR.

Materials and Methods

Patient selection procedure

The records of the patients who were followed up in the neurology outpatient clinic of Ufuk University between 2016 and 2019 with the diagnosis of migraine between the ages of 18 and 50 were reviewed retrospectively. Migraine was diagnosed by neurologists according to The International Classification of Headache Disorders, 2nd edition criteria. Eighty-six patients without systemic, neurological, and infectious diseases between 18 and 50 years of age were included in the study. Age, gender, frequency of migraine attacks, duration of migraine, presence, and absence of aura were recorded. Patients were divided into two groups: Group 1 – subclinical ischemic/gliotic lesions on MRI and Group 2 – normal MRI. The study was approved by the local ethical committee (09/01/2019-3) and was accordant with the Declaration of Helsinki ethical standards.

Complete blood count evaluation

Complete blood count parameters were analyzed using a hematology analyzer (Cell-Dyn Ruby Hematology System; Abbott Diagnostics, Lake Forest, Illinois, USA). Parameters of complete blood count results were compared, and NLR and platelet/lymphocyte ratio were calculated.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows, version 23.0 (IBM Corporation, Armonk, NY, USA). Visual (histograms) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) were used to determine whether the variables were normally distributed. Descriptive analyses were presented using medians and minimum–maximum range for the nonnormally distributed data. The Mann–Whitney U-test was used for nonparametric data, the Chi-squared test was used for ratios, and the Pearson correlation test was used to evaluate correlation. $P < 0.05$ was considered statistically significant.

Results

Of the 86 patients included in our study, gliotic lesions were observed on MRI in 42 patients (Group 1) and MRI was normal in 44 patients (Group 2). Thirty-four of the patients in Group 1 were female and 8 were male ($n = 42$), and the mean age of the patients was 36.5 (18–50), whereas 34 of the patients in Group 2

were female and 10 were male (n = 44), and the mean age of the patients was 31 (20–50). There was no statistically significant difference between the two groups in terms of age and gender (P = 0.202/P = 0.675) [the age, number of attacks, blood parameters, and P values of the patients in Group 1 and Group 2 are evaluated and given in Table 1]. The comparison of gender and aura between groups and P values given in Table 2. The comparison of neutrophil/lymphocyte ratio values between groups - patients with aura and without aura given in Table 3.

When the two groups were compared in terms of leukocyte and neutrophil counts, a statistically significant difference was found. The leukocyte and neutrophil counts of the patients in Group 1 were significantly higher than those of Group 2 (P = 0.038/P = 0.004). Although the number of basophils was not significantly different between the two groups, the percentage of basophils was significantly higher in Group 2 compared to Group 1 (P = 0.001). NLR was higher in Group 1 than Group 2 and was statistically significant (P = 0.016). When the correlation analysis between the number of attacks and NLR in Group 1 and Group 2 was performed, there was a positive correlation between the number of attacks and NLR in the whole group and Group 2, and no significant correlation was found in Group 1 [Table 4 shows the correlation analysis between the number of attacks and NLR]. The positive correlation between the number of attacks and NLR in the whole group supports the role of inflammation in the pathophysiology of migraine. However, it is not possible to affirm the reason of the correlation between Group 2 and NLR clearly.

Discussion

Recurrent migraine attacks are thought to be associated with inflammatory arteriopathy of the cerebral vessels.[18] Vascular changes and microinfarcts that may occur as a result of increased platelet aggregation during attacks may play a role in the etiology of gliotic foci in the brain of migraine patients. In a study, white matter hyperintensities were found to be present in 16% of 185 migraine patients.[19]

In another study, which examined 129 migraine patients, hyperintense lesions were detected in deep white matter and subcortical white matter in brain MRI of 19.3% of the patients.[20] It is known that there is a significant correlation between these white matter lesions and age, hypertension, diabetes, and heart disease. Therefore, in our study, we ensured that the mean age of the two groups was similar and that the patients did not have any systemic disease. A study conducted in Turkey in 2007 examined 34 patients who had been diagnosed with migraine with white matter lesions in MRI and

Table 1: The age, number of attacks, and blood parameters between groups and *P* values

	Median (minimum-maximum)		*P*
	Group 1	Group 2	
Age (years)	36.5 (18-50)	31 (20-50)	0.202
Number of attack/month	5 (1-30)	4 (1-30)	0.879
Duration (years)	3.5 (0.17-25)	2 (0.08-35)	0.120
Leukocyte	7.10 (4.80-13.80)	6.40 (3.80-12)	0.038
Neutrophil (%)	58.50 (44.00-82.30)	54.00 (34.00-74.00)	0.002
Neutrophil (count)	4.00 (2.50-10.10)	3.50 (1.90-8.80)	0.004
Lymphocyte (%)	31.00 (11.80-45.00)	33.00 (14.90-55.00)	0.068
Lymphocyte (count)	2.10 (1.20-3.60)	2.10 (1.40-4.00)	0.729
NLR	1.90 (0.86-6.97)	1.66 (0.63-5.29)	0.016
Basophil (%)	0.95 (0.01-1.90)	1.20 (0.05-2.90)	0.001
Basophil (count)	0.06 (0-1.40)	0.08 (0-0.16)	0.102
Eosinophil (%)	1.40 (0.10-6.40)	1.75 (0.18-7.80)	0.223
Eosinophil (count)	0.09 (0.01-0.47)	0.11 (0.01-4.50)	0.326
Platelet	268.50 (167-435)	258 (109-435)	0.228
Platelet/lymphocyte	123.44 (70.00-260.00)	122.89 (52.90-200.00)	0.809
PDW	11.00 (4.30-20.00)	11.00 (10.00-21.00)	0.222
MCV	86.00 (75.00-95.00)	85.00 (69.00-95.00)	0.539
MCH	29.00 (23.00-35.00)	28.00 (21.00-32.00)	0.466
MCHC	33.00 (29.00-37.00)	33.00 (29.00-35.00)	0.233
MPV	7.75 (5.60-10.40)	7.50 (5.40-13.00)	0.554
HGB	13.65 (9.00-16.60)	14.00 (9.00-17.00)	0.691

NLR: Neutrophil/lymphocyte ratio, PDW: Platelet distribution width, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MPV: Mean platelet volume, HGB: Hemoglobin

Table 2: The comparison of gender and aura between groups and *P* values

	Group 1	Group 2	*P*
Gender	34 female/8 male	34 female/10 male	0.675
Aura	7 yes/35 no	11 yes/33 no	0.342

Table 3: The comparison of neutrophil/lymphocyte ratio values between groups - patients with aura and without aura

	Patients with aura	Patients without aura	*P*
NLR	1.74 (0.86-2.70)	1.72 (0.63-6.97)	0.549

NLR: Neutrophil/lymphocyte ratio

Table 4: The correlation analysis between the number of attacks, neutrophil/lymphocyte ratio

	Whole group	Group 1	Group 2
Number of attacks and NLR	R: 0.242	R: 0.067	R: 0.483
	P: 0.025	P: 0.671	P: 0.001

NLR: Neutrophil/lymphocyte ratio

29 patients with normal MRI findings. Complete blood count, biochemistry, and homocysteine levels of these patients were evaluated. While no significant difference was observed between complete blood and biochemistry test values, homocysteine levels were found to be significantly higher in migraine patients with white matter lesions.[21] In our study, leukocyte and neutrophil counts and NLR were significantly higher in migraine patients with white matter lesions than those with normal MRI. This finding may be attributed to the role of immune cells in peripheral blood such as leukocytes, neutrophils, and lymphocytes in both the peripheral inflammatory response and atherosclerotic process. There are also studies in which the rate of circulating leukocytes provides a measure of inflammatory status and can be used as a predictor of potential cardiovascular risk.[11,13]

In the population-based CAMERA conducted on 435 patients, white matter lesions were significantly higher in migraine patients regardless of migraine type and relapse characteristics.[22] In another analysis examining seven prospective studies, it was reported that the risk of the presence of white matter lesions in migraine patients was higher than the healthy population.[23] Based on these findings, migraine seems to be a risk factor for cerebrovascular diseases.

In Turkey, a study conducted in 2016 evaluated 92 migraine patients in the emergency department during their migraine attacks. Leukocyte, neutrophil, lymphocyte, and platelet results were found to be statistically higher than the healthy control group.[24] In our study, patients were retrospectively analyzed, and NLR, leukocyte, neutrophil, and lymphocyte values were compared between patients with and without white matter lesions, regardless of whether they had attacks or not. Neutrophil count, leukocyte count, and NLR were statistically significantly higher in patients with white matter lesions than those without white matter lesions.

Histamine is a biogenic amine, the majority of which is secreted by basophils. It plays a role in vasodilatation, energy metabolism, wound healing and immunomodulation, and especially allergy and anaphylaxis. Histamine also has an interesting role in migraine. Histaminergic fibers are found in neural structures associated with migraine. Histamine modulates neurogenic inflammation and nociceptive sensitivity.[25] As it is known, the prevalence of migraine is higher in patients with allergic rhinitis.[26] In fact, whether the increase of histamine in migraine patients is a cause or a result remains controversial. In our study, the high basophil percentage in Group 2 may be caused by the incidence of allergic individuals in that group. Perhaps, the basophil may also protect our brain against gliotic lesions in a way that has not yet been identified. We could not find any studies on this subject in the literature. However, we think it is an issue to be investigated.

Recently, a new helper T-cell, called Th17, has been discovered which produces IL-17, different from Th1 and Th2 in helper T-cell differentiation. Th17 cells appear rapidly in the area of inflammation and invoke other Th cells in the area. Therefore, Th17 cells are the main triggers of tissue inflammation. Interleukin (IL)-23 regulates the maturation of autoreactive IL-17 producing T-cells. IL-17 is the key cytokine for recruitment, activation, and migration of neutrophils. Th17 cells and related cytokines have been reported to be important for some autoimmune diseases such as psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, and asthma. In our study, NLR was found to be high in patients with white matter lesions. In this case, it can be thought that the increase in neutrophil count may be due to the neurogenic inflammation and thus increase in IL-17 levels. This raises the question of whether these white matter lesions are the result of this increased inflammation or not. Studies have shown that IL-17 and IL-23 levels are also high in patients with multiple sclerosis.[27] White matter lesions seen in migraine may have been caused by a similar mechanism. Perhaps, migraine form associated with white matter lesions may be a different form of migraine that has not yet been defined.

There are some limitations to our study. The first is the small sample size. Studies involving a higher number of

patients may be more guiding. The second is that our study only compared the complete blood results of the patients. Based on the fact that white matter lesions may be the result of an inflammatory process, NLR could be compared with a biomarker which is another indicator of inflammation, and the correlation between them could also be evaluated.

Conclusion

This study aimed to evaluate the relationship between NLR and white matter lesions in patients with migraine. White matter lesions are also associated with inflammatory and atherosclerotic pathologies. We have conducted this study to see if we can confirm this with a parameter in migraine patients with white matter lesions. Despite the small number of patients, leukocyte count, neutrophil count, and NLR were significantly higher in migraine patients with white matter lesions which support our hypothesis. We believe that more comprehensive research is needed to reach more informative knowledge.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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