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Immature granulocyte and other hematological inflammatory parameters in patients with migraine headache

Migren baş ağrısı olan hastalarda immatür granülosit ve diğer hematolojik inflamatuar parametreler

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ABSTRACT

Background: Today, many hypotheses have been proposed in the pathogenesis of migraine. The inflammatory hypothesis is one of them. The immature granulocyte count (IGC) is also an inflammatory parameter which importance has been understood recently. There are no studies evaluating IGC in migraine. The aim of the study to investigate the levels of IGC and other hematological inflammatory parameters in migraine.

Material and Method: Materials and Methods: Forty-eight patients diagnosed with migraine who applied to Kastamonu Training and Research Hospital Neurology outpatient clinic between 07.01.2020 and 10.01.2021 were included in the study. 42 people with similar age and gender distribution were included for the control group. Data on laboratory tests, age and gender of patients were obtained from the hospital Laboratory Information System (LIS). CBC parameters of the patients at the first admission and before any treatment, calculated with an automated hematological analyzer (XN-1000-Hematology-analyzer-Sysmex Corporation, Japan) were analyzed. Using Complete Blood Count (CBC) data, neutrophil count (NEUT#), neutrophil percentage (NEUT%), lymphocyte percentage (LYMPH%), and IGC were recorded. Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and systemic immune inflammation index (SII) values were calculated with the formula.

Results: In our study, NLR and IGC was significantly higher than the healthy control group (p=0.002, p=0.025). PLR was also found to be high, but it was not statistically significant (p=0.063).

Conclusion: The significantly higher NLR and IGC levels in migraine patients compared to the healthy controls support the role of inflammation in etiopathogenesis.

Keywords: Migraine, hematological parameters, immature granulocyte, inflammatory pathogenesis

ÖZ

Arka Plan: Günümüzde migren patogenezinde birçok hipotez ileri sürülmüştür. İnflamatuar hipotez de bunlardan bir tanesidir. İmmatür granülosit sayısı da son zamanlarda önemi anlaşılan bir inflamatuar parametredir. Migrende immatür granülosit sayısını değerlendiren çalışma bulunmamaktadır. Çalışmanın amacı; migrende immatür granülosit ve diğer hematolojik inflamatauar parametrelerin düzeylerini araştırmaktır.

Gereç ve Yöntem: Çalışmaya Kastamonu Eğitim ve Araştırma Hastanesi Nöroloji polikliniğine 07.01.2020-10.01.2021 tarihleri arasından başvuran migren hastalığı tanısı almış, başka da bir hastalığı olmayan 48 hasta dahil edildi. Kontrol grubu için ise hasta gruba benzer yaş ve cinsiyet dağılımı olan 42 kişi dahil edildi. Laboratuvar testleri ile ilgili veriler, hastaların yaşları ve cinsiyetleri hastane Laboratuvar İnformasyon Sistemi (LİS)'nden elde edildi. Otomatik hematolojik analizör (XN-1000-Hematology-analyzer-Sysmex Corporation, Japan) ile hesaplanan, hastaların ilk başvurusuna ait ve herhangi bir tedavi almadan önceki tam kan sayımı (CBC) parametreleri incelendi. CBC verilerinin kullanılmasıyla nötrofil sayısı (NEUT#), nötrofil yüzdesi (NEUT%), lenfosit yüzdesi (LYMPH%) ve immatür granülosit (IG) sayısı kaydedildi. Nötrofil lenfosit oranı (NLR), platelet lenfosit oranı (PLR) ve sistemik immün enflamasyon indeks (SII) değerleri formül ile hesaplandı.

Bulgular: Çalışmamızda NLR ve IG sayısı sağlıklı kontrol grubuna göre anlamlı olarak yüksekti (p=0.002, p=0.025). PLR da yüksek bulundu fakat istatisitiksel olarak anlamlı değildi (p=0,063).

Sonuç: Migren hastalarında sağlıklı kontrol grubuna göre NLR ve IG sayısının anlamlı düzeyde yüksek bulunması etyopatogenezde inflamasyonun rolünü desteklemektedir.

Anahtar Kelimeler: Migren, hematolojik parametreler, immatür granülosit, inflamatuar patogenez

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INTRODUCTION

Migraine is among the disabling neurological diseases with symptoms including recurrent, moderate to severe headache attacks, nausea, vomiting, photophobia and/or phonophobia (1). It affects approximately 11% of the adult population worldwide and is three times more prevalent in females than males (2). Migraine is listed as the third well-known cause of disability in people under 50 years (3). Patients usually experience loss of appetite/cravings for eating, diarrhea, constipation, and fatigue. Widespread body pain, muscle pain, irritability, and visual, sensory, and motor auras begin just before the pain and continue with the pain (4,5).

The previous research attempted to explore many possible underlying mechanisms and factors, including obesity and vascular, neurogenic, and trigeminovascular system activation, in migraine pathogenesis(6). Recent studies focused on the theory of "neurogenic inflammation," emphasizing the impacts of inflammatory agents particularly in the activation and sensitization of peripheral nociceptors. In the pathophysiology of migraine, it is known that vasoactive neuropeptides, such as substance P released from trigeminal axons protruding into the meninges, calcitonin gene-related peptide, and neurokinin A, are released. Thus, neurogenic inflammation occurs in the meninges, which is thought to play a role in the occurrence and maintenance of pain accompanying migraine attacks (7,8). Many studies previously suggested abnormal inflammatory markers in the systemic circulation in migraine patients, consistent with the neurogenic inflammation hypothesis above (9-12). Yazar et al. also found high neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), and C-reactive protein (CRP)/albumin (CAR) ratio in migraine patients (13). In addition, the relevant literature host several studies on elevated plasma pro-inflammatory markers, including interleukins (IL) and tumor necrosis factor-alpha (TNF-alpha (14,15). It was also suggested that CRP, a positive acute-phase protein, may play a role in migraine pathogenesis (16).

On the other hand, the research interest seems to miss investigating the link between immature granulocyte (IG), which is an early marker of inflammation, and migraine. IGs, consisting of promyelocytes, myelocytes, and metamyelocytes, are generally not detected in peripheral blood in healthy individuals. However, during periods of infection and inflammation, IGs may enter the peripheral blood and show bone marrow activation (17). IG count (IGC) is a parameter indicating the increase in bone marrow activation in peripheral blood. Immature granulocytes percentage (IG%) is a novel marker of inflammation that can be easily obtained in complete blood count (CBC) on automated hematological analyzers. Some studies showed that IG% increases earlier than traditional parameters, such as CRP and leukocyte count, in inflammatory conditions (e.g., infection and sepsis) (17-19).

To date, many studies have presented the levels of various markers in migraine, and inflammatory biomarkers occupy substantial room among these studies (20-22). However, the previous research seems not to have considered exploring the association between migraine and IG. Ultimately, we aimed to investigate the relationship between migraine and NLR, PLR, and IG since their convenience at application, low cost, and easilydetectable using a hemogram tube.

MATERIALS AND METHOD

Research Design

We included 48 patients who applied to the neurology outpatient clinic of the Kastamonu Training and Research Hospital between 07.01.2021 and 10.01.2021, were diagnosed with migraine and did not have any other diseases. In the control group, we recruited age- and sex-matched 42 individuals who applied to the otorhinolaryngology clinic of the same hospital for routine controls between September 2019 and January 2021. Yet, we excluded those with infection in the last one week, individuals under 18 years of age, the pregnant, those with diseases and malignancies that may alter CBC parameters and inflammatory markers, people with trauma, and those without CBC data.

We extracted the data on laboratory tests and demographic information (age and sex) of the patients from the Laboratory Information System (LIS) of the hospital. We went through the CBC parameters of the patients at the first admission (prior to any treatments), calculated with an automated hematological analyzer (XN-1000-Hematology-analyzer-Sysmex Corporation, Japan). Using CBC data, we noted down neutrophil count (NEUT#), neutrophil percentage (NEUT%), lymphocyte percentage (LYMPH%), and immature granulocyte count (IGC). Then, we calculated NLR, PLR, and SII values using relevant formulas. We compared all obtained data between the two groups.

Statistical Analysis

We performed all statistical analyses on "Statistical Package for Social Sciences 18.0 for Windows" (SPSS Inc., Chicago, USA). We presented the categorical data as numbers (n) and percentages (%) while demonstrating median values (25th percentile, 75th percentile) for quantitative data. We performed relevant comparisons between the groups using the Mann-Whitney U test since the data did not show a normal distribution. Finally, we used the chi-square test to reveal whether the groups significantly differ by age and sex. In all statistical analyses, we considered a p-value of <0.05 to be significant.

RESULTS

We carried out the present study with 48 migraine patients (16 males and 32 females) with a median age of 33.5 (25-40 years) and 42 control subjects (15 males and 27 females) with a median age of 28.5 (24-35 years). Yet, we could not find significant differences between the two groups by sex (p<0.05) (**Table 1** and **Table 2**).

Table 1. Distribution of the Patient and Control Groups by Sex

Group	Female	Male	Total	p
Control	27 (64.2%)	15 (35.7%)	42	0.813
Patient	32 (66.6%)	16 (33.3%)	48	

Moreover, the groups did not significantly differ by age (p>0.05)

Table 2. Distribution of the Patient and Control Groups by Age

Group	Median (25th percentile, 75th percentile)	Mean±SD	p
Control (Age)	28.5 (24-35)	30.76±8.54	0.264
Patient (Age)	33.5 (25-40)	32.89±9.05	

As in Table 3, neutrophil count and percentage, immature granulocyte count, neutrophil/lymphocyte ratio, and systemic immune-inflammatory index were significantly higher in the patient group ($p<0.05$). Yet, we found that lymphocyte count was significantly lower in the patient group than in the control group ($p<0.05$). Although the median platelet/lymphocyte ratio was higher in the patient group, it was not statistically significant ($p=0.063$). None of the other hemogram values measured significantly differ between the groups.

Table 3. Comparison of the Groups by Pre-determined Parameters

	Control (n=42)	Patient (n= 48)	p
	Median (IQR)		
NEUT#	3.11 (2.74-3.99)	4.10 (3.39-4.83)	0.005
NEUT%	52.3 (46.9-58.2)	58.7 (54-62.8)	0.003
LYMPH%	36.3 (30.9-43.5)	30.6 (27.4-35.8)	0.003
IGC	0.02 (0.01-0.02)	0.02 (0.012-0.03)	0.025
NLR	1.49 (1.1-1.89)	1.93 (1.50-2.25)	0.002
PLR	106 (87-130)	122 (98-148)	0.063
SII	382 (239-478)	512 (384-591)	0.001

DISCUSSION

Recent research addressing migraine explicitly focused on the theory of "neurogenic inflammation," emphasizing the impacts of inflammatory agents on the activation and sensitization of peripheral nociceptors (7). In the pathophysiology of migraine, it is known that vasoactive neuropeptides, such as substance P released from trigeminal axons protruding into the meninges, calcitonin gene-related peptide, and neurokinin A, are released. Thus, neurogenic inflammation occurs in the meninges, which is thought to play a role in the occurrence and maintenance of pain accompanying migraine attacks (8).

Various studies previously sought for the correlations of inflammatory hematological parameters, such as NLR, PLR, and MLR, with migraine headache (9,10). However, it seems the relevant literature lacks the inquiry about the association between migraine and IG, which has recently become highlighted as an early marker of inflammation. Therefore, in our study, we evaluated NLR, PLR, and IGC in migraine patients and healthy volunteers.

While migraine is seen equally in both sexes in childhood, it is 2-3 times more common in females in adulthood. In Europe, the lifetime risk of developing migraine is reported to be 12-28% (23). In our study, similar to the literature findings, 66.6% of our migraine patients were females, and 33.3% were males. Besides, it is known that migraine is mostly diagnosed between the ages of 30-39 years in Western countries and Turkey (24). Similarly, we found the median age was 33.5 years in the patient group.

Serum NLR and PLR levels are widely-resorted biomarkers of peripheral inflammation and oxidative stress in chronic neurological diseases. Neuroinflammation is associated with the pathogenesis of many neurological disorders such as Parkinson's disease, Multiple Sclerosis, and Alzheimer's disease (25-29). Previous studies reported platelet activation to increase in migraine patients. Platelet activation may be part of the inflammatory vascular process underlying migraine. Moreover, platelets secrete a large number of inflammatory mediators without a role in hemostasis, which indicates that they undertake different functions out of hemostasis. They form clusters with leukocytes and bridges between leukocytes and endothelium largely through platelet P-selectin. Platelets are also important coordinators of inflammation because of their interactions with monocytes, neutrophils, lymphocytes, and endothelium (30). In their study, Zeller et al. showed increased platelet levels and platelet-leukocyte interaction in migraine patients. In our study, we found PLR to be higher in the patient group, but it was not statistically significant. This result may be due to the small size of our sample (31).

Recent research showed high NLR value as an important biomarker in cardiovascular diseases and cancer prognosis (32,33). Neutrophils, lymphocytes, and other white blood cells are the primary sources of pro-inflammatory and anti-inflammatory cells (34). The stress response of circulating leukocytes leads to an increase in neutrophil and platelet counts and a decrease in lymphocyte counts. Therefore, the ratio of these values to each other may be used as an indicator of inflammation (35). In our study, migraine patients had lower lymphocyte levels and higher neutrophil, NLR, and PLR levels compared to the control group. In their research, Karabulut et al. found that NLR was higher in patients during migraine attacks (36).

IGs are not found in the peripheral blood of healthy individuals. Polymorphonuclear neutrophil granulocytes induced by a granulocyte-colony stimulating factor (G-CSF) emerge from progenitor cells and develop into mature, segmented neutrophils in the bone marrow at several stages. They then pass into the peripheral blood. Consequently, the incidence of IGs in peripheral blood is indicative of significantly increased bone marrow activation (37). It is now possible to detect IG percentage and counts thanks to recent technological developments in automatic hematological analyzers. Various studies showed that IG can be used as an effective inflammatory marker. In a study by Karakulak et al., IG% was found to be significantly higher in patients with acute pancreatitis in severe cases (38). Another study on patients with acute appendicitis determined that IG is quite specific for diagnosis and an essential parameter in the early diagnosis of complicated cases (17). However, the literature lacks research investigating the association between migraine and immature granulocytes. In our study, IG% was significantly higher in our migraine patients, supporting the inflammatory hypothesis in migraine.

Limitations

Although we believe this is a robust, pioneering study, it has few limitations. Firstly, we did not consider the demographic characteristics of the groups, except for age and sex, and the probable effects of their medication. Secondly, this was a retrospective and cross-sectional study. Ultimately, prospective and more comprehensive studies are needed to evaluate peripheral inflammation and oxidative stress biomarkers, IG levels, and the impacts of agents used during an attack or prophylaxis on inflammatory markers.

CONCLUSION

The inflammatory hypothesis means much for migraine pathogenesis. The significantly higher NLR and IGC levels in migraine patients compared to the healthy controls support the role of inflammation in etiopathogenesis. IG, which is a novel, inexpensive, and easily detectable marker with CBC, may help better understand migraine pathogenesis, which may be revealed with more comprehensive and prospective studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Clinical Research Ethics Committee (Date: 17.11.2021, Decision no: 2020-KAEK-143-127).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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