



Correlation of Hematological Parameters, Imaging Results, and Clinical Findings in Primary Headache Disorders

Primer Baş Ağrılarında Hematolojik Parametreler ve Görüntüleme Bulgularının Klinik ile Korelasyonu

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Abstract

Objective: Headache is the most common and challenging neurologic problem in society. There is a relationship between hematologic parameters and headache disorders. White matter lesions are known to be common in migraine. In this study, we aimed to evaluate the hematologic parameters in migraine and tension-type headache, and assessed the correlation of these parameters with headache characteristics and neuroimaging findings.

Materials and Methods: The medical records of patients from the neurology outpatient clinic in Adnan Menderes University Faculty of Medicine between December 1st, 2015, and December 1st, 2016, were retrospectively reviewed. Six hundred thirty-nine patients aged 18-65 years were included. Two hundred seventy-two were diagnosed as having migraine and 323 had tension-type headache according to the IHS 2013 Beta version. The initial hematologic parameters were studied. Patients who had brain magnetic resonance imaging (MRI) were examined separately.

Results: Patients were classified according to their headache types. Age, sex, pain frequency, headache severity, and hematologic parameters were recorded. There was no significant difference between the two groups in terms of hematologic parameters ($p>0.05$) and there was a negative correlation between pain frequency and headache severity ($p<0.05$). White matter lesions were more common in migraine cases, compatible with the literature. In patients with migraine with white matter lesions, hemoglobin, hematocrit, and mean corpuscular volume were positively correlated with the frequency of attacks ($p<0.05$).

Conclusion: We observed no relationship between migraine and GTA and hematologic parameters. This may be due to the role of inflammatory processes in both groups. The absence of significant differences in MRI findings may be related to the inadequate number of patients. Studies involving control groups with larger cohorts may be more elucidative.

Keywords: Migraine, tension-type headache, hematologic parameters, white matter lesions

Öz

Amaç: Baş ağrısı toplumdaki en yaygın ve en zorlu nörolojik sorundur. Hematolojik parametreler ile baş ağrısı bozuklukları arasında bir ilişki olduğu açıktır. Beyaz madde lezyonlarının migrende yaygın olduğu bilinmektedir. Bu çalışmada migren ve gerilim tipi baş ağrısında hematolojik parametreleri değerlendirmeyi amaçladık ve bu parametrelerin baş ağrısı özellikleri ile nörogörüntüleme bulguları arasındaki ilişkiyi değerlendirdik.

Gereç ve Yöntem: Adnan Menderes Üniversitesi Tıp Fakültesi'nde 1 Aralık 2015-1 Aralık 2016 tarihleri arasında nöroloji polikliniğinden gelen hastaların kayıtları retrospektif olarak incelendi. 18-65 yaşları arasında 639 hasta çalışmaya dahil edildi. IHS 2013 Beta sürümüne göre 272'sine migren tanısı konuldu ve 323'ünde gerilim tipi baş ağrısı vardı. İlk hematolojik parametreler incelendi. Beyin manyetik rezonans görüntülemesi (MRG) olan hastalar ayrı ayrı incelendi.

Bulgular: Hastalar baş ağrısı tiplerine göre sınıflandırıldı. Yaş, cinsiyet, ağrı sıklığı, baş ağrısı şiddeti ve hematolojik parametreler kaydedildi. İki grup arasında hematolojik parametreler açısından anlamlı fark yoktu ($p>0,05$) ve ağrı sıklığı ile baş ağrısı şiddeti arasında negatif korelasyon vardı ($p<0,05$). Beyaz cevher lezyonları literatürle uyumlu olarak migren olgularında daha sıkı. Beyaz cevher lezyonlu migren hastalarında, hemoglobin, hematokrit ve ortalama hücre hacmi atak sıklığı ile pozitif korelasyon gösterdi ($p<0,05$).

Sonuç: Migren ve GTA ile hematolojik parametreler arasında herhangi bir ilişki gözlenmedi. Bu, her iki gruptaki enflamatuvar süreçlerin rolüne bağlı olabilir. MRG bulgularında önemli farklılıkların olmaması, yetersiz hasta sayısı ile ilişkili olabilir. Daha geniş kohortlu kontrol grubunu içeren çalışmalar daha aydınlatıcı olabilir.

Anahtar Kelimeler: Migren, gerilim tipi baş ağrısı, hematolojik parametreler, beyaz cevher lezyonları

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Introduction

Headache is a socioeconomically important health problem because it is a frequent and repeating issue in society, and it also results in losses in labor force and affects quality of life. Headaches are considered to have two types, which are primary and secondary headaches. Primary headaches have no underlying causes and secondary headaches are due to secondary causes. In primary headaches, tension-type headache (TTH) is the most common, with a rate of 31.7%, followed by migraine at 16.4% (1,2).

It is known that there is a relation between hematologic parameters and headaches. In general, this has been associated with anemia, increased blood viscosity, and another similar factor. Few studies have investigated the relationship between hematologic parameters and migraine and TTH. New studies have shown that there is a relation between silent white matter lesion load and migrainous cases. Also, studies have shown that migraine is a risk factor for stroke in young people and migraine has a higher incidence of posterior circulation stroke. There are no studies that investigate migraine and TTH differences in silent white matter lesions. In this study, we compared hematologic parameters [hemoglobin (Hb), hematocrit (Hct), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean cell volume (MCV), red cell distribution width (RDW), platelet, mean platelet volume (MPV), leukocyte, lymphocyte, neutrophil, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR)] of migraine with TTH-diagnosed patients according to the International Classification of Headache Disorders-III-beta version (ICHD-III- beta), and we aimed to examine the correlation of these parameters with headache characteristics. Another aim was to compare the number of white matter lesions in patients with migraine and TTH using cranial magnetic resonance imaging (MRI) and to evaluate the correlation between hematologic parameters and the headache characteristics of these lesions.

Materials and Methods

Neurology patients in Adnan Menderes University Faculty of Medicine Hospital were retrospectively observed between December 1st, 2015, and December 1st, 2016. The study included 639 patients aged 18-65 years, with 272 migraine and 323 TTH diagnoses determined according to the ICHD-III- beta version. Patients with only one type of headache were selected. Patients with no chronic systemic disease, who did not use prophylactic treatment for their headache, no intracranial lesions, cerebrovascular disease, demyelinating disease, and no central nervous system disease such as vasculitis were included. Also, no patients were pregnant during the referral.

The number of painful days, severity, and hemogram of the first visit were recorded within one month. A visual analog scale was used to assess pain severity. Patients with cranial MRI were recorded as imaging findings. MRI lesions were classified as periventricular/subcortical area and anterior/posterior circulation and expressed as a number. The lesion sizes were between 1-10 mm. Ethics Committee Approval was obtained from Adnan Menderes University Faculty of Medicine (protocol no: 2016/1036).

Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences Ver. 18 (SPSS) package program. Data are presented

as median \pm standard deviation. The independent samples t-test, chi-square tests, and Pearson and Spearman correlation analyses were performed. The significance limit was accepted as $p < 0.05$. Chi-square analysis was used to investigate the relationship between sex and groups. Age, pain severity, frequency, and hematologic parameters were compared in the migraine and TTH groups using the independent samples t-test. The relationship between hematologic parameters, patient age, pain severity, and frequency in the groups was determined using Pearson correlation analysis.

Results

Among the 639 patients, 347 (54.3%) patients had TTH and 292 (45.7%) had migraine. Two hundred sixty-eight (77.2%) of the 347 patients with TTH were female and 79 (22.8%) were male ($p < 0.001$). Two hundred fifty-nine (88.7%) of the 292 patients with migraine were female and 33 (11.3%) patients were male ($p < 0.001$). Headache was determined to be more frequent in women in both groups (Figure 1).

There was no significant difference in terms of age distribution between the groups ($p > 0.05$). The severity of pain was higher in the migraine group, but this result was not statistically significant ($p > 0.05$). There was no significant difference between the groups in terms of pain duration ($p > 0.05$) (Table 1). Also, there was no statistically significant difference in hematologic parameters between the groups ($p > 0.05$) (Table 2). Hematologic parameters, patient age, pain severity, and frequency were analyzed to determine if there was any correlation between the groups. Hematologic parameters showed no significant findings, but a negative correlation was observed between pain frequency and severity in both groups. The severity of pain increased as the frequency decreased ($p = 0.002$).

One hundred twenty-four patients had MRI images. Among those, 56 (45.2%) patients had TTH and 68 (54.8%) had migraine, and 45 had lesions on MRI. Among the patients with lesions, 19 (33.9%) had TTH and 26 (38.2%) had migraine (Figure 2). MRI lesions were divided into periventricular-subcortical and anterior-posterior circulation lesions. In the TTH group, 11 patients had only anterior circulation lesions, and eight had anterior and posterior circulation lesions predominantly consisting of anterior circulation lesions. In the migraine group, seven patients had only posterior circulation lesions and 19 had anterior and

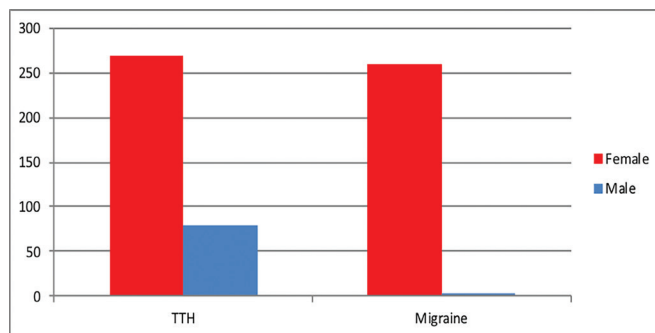


Figure 1. Sex distribution of patients with TTH and migraine
TTH: Tension-type headache

posterior circulation lesions predominantly consisting of posterior circulation lesions. Periventricular lesions were more frequent in migraine headache, but this was not statistically significant (p=0.286). Subcortical lesions were more frequent in migraine headache but they were statistically non-significant (p=0.101).

Regarding the correlation between age, pain frequency, pain severity, and hematologic parameters in patients with lesions, pain frequency increased with raising Hb, Hct, and MCV values in the migraine group (p<0.05); however, this was not observed in the TTH group (p>0.05).

Table 1. Age, VAS, and painful days (days/month) for TTH and migraine

	Groups	Number	Median ± SD	p value
Age	TTH	347	36.38±13.21	5.74
	Migraine	292	35.54±11.37	0.66
VAS	TTH	347	6.66±1.53	0.08
	Migraine	292	7.51±0.99	0.05
Painful days	TTH	347	14.65±9.18	0.49
	Migraine	292	10.66±8.31	0.48

p<0.05, chi-square and independent samples t-tests were used in the evaluation of data values. VAS: Visual analog scale, TTH: Tension-type headache, SD: Standard deviation

Table 2. Comparison of hematologic parameters of TTH and migraine

Parameters	Groups	Number	Median ± SD	Normal value	p value
Hemoglobin	TTH	347	13.56±7.05	11.2-15.7 g/dl	0.38
	Migraine	292	13.43±7.88	-	0.46
Hematocrit	TTH	347	43.65±30.92	37-44%	1.66
	Migraine	292	40.22±4.13	-	0.24
MCV	TTH	347	85.29±7.91	80.4-95.6 fl	0.42
	Migraine	292	89.25±56.01	-	3.27
MCH	TTH	347	29.15±20.03	27.2-33.5 pg	1.07
	Migraine	292	27.44±2.99	-	0.17
MCHC	TTH	347	33.21±16.51	32.5-35.2 g/dl	0.88
	Migraine	292	32.91±11.60	-	0.68
RDW	TTH	347	13.64±1.58	11.7-14.6	0.08
	Migraine	292	13.84±1.67	-	0.09
Platelet	TTH	347	285.45±71.98	150-350 10 ³ µl	3.86
	Migraine	292	287.28±71.64	-	4.19
MPV	TTH	347	10.35±1.06	6.5-11.6 fl	0.06
	Migraine	292	10.33±1.22	-	0.07
Leukocyte	TTH	347	8.41±8.07	3.8-10 10 ³ µl	0.43
	Migraine	292	7.67±1.94	-	0.11
Neutrophil	TTH	347	4.85±1.84	1.8-6.4 10 ³ µl	0.09
	Migraine	292	4.57±1.57	-	0.09
Lymphocyte	TTH	347	2.41±1.21	1.2-3.6 10 ³ µl	0.06
	Migraine	292	2.35±0.67	-	0.05
NLR	TTH	347	2.21±1.18	-	0.06
	Migraine	292	2.11±1.12	-	0.06
PLR	TTH	347	130.38±50.46	-	2.70
	Migraine	292	130.93±49.87	-	2.91

p<0.05, independent samples t-test and Pearson correlation analyses were used in the evaluation of values. TTH: Tension-type headache, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil/leukocyte ratio, PLR: Platelet/leukocyte ratio, SD: Standard deviation

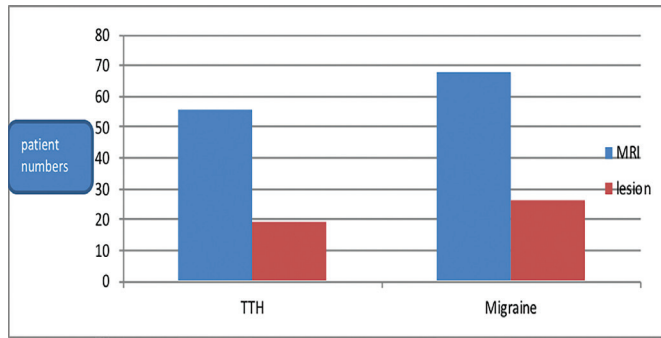


Figure 2. Patients had MRI images and lesions on MRI

MRI: Magnetic resonance imaging, TTH: Tension-type headache

Discussion

Headaches may vary in each individual in terms of pain frequency and severity. Various studies have been performed to determine the cause of this variability. In some studies, blood viscosity and anemia have been evaluated and their effect on pain was investigated. Additionally, platelet counts and diameters also have been evaluated due to its role in serotonin secretion. The variability of the leukocyte counts has been emphasized considering the release of mediators causing neurogenic inflammation (3). In the present study, our purpose was to analyze hematologic parameters such as Hb, Hct, MCV, MCH, MCHC, RDW, platelet, MPV, leukocyte, neutrophil and lymphocyte, and to compare the distribution of hematologic parameters in migraine and TTH, and to examine the effects on imaging findings.

As it is known, silent ischemic lesions are more common in the imaging of patients with migraine. No studies have compared MRI lesions between patients with migraine and TTH. In our study, we compared the ischemic lesions in MRI between patients with migraine and TTH and investigated the correlation of these ischemic lesions with hematologic parameters.

It is suggested that there is a relationship between hematologic disorders and headache (3). However, there are a small number of studies on this subject. Migraine headache is frequently associated with hematologic, neurologic, vascular, and cardiac diseases (4). In particular, there are studies on iron deficiency anemia and headache, both of which are common in society (5,6,7,8,9,10). Patients with migraine headache and healthy controls are compared in most studies, few studies have compared tension-type and migraine headaches.

Iron is distributed in various matters in the body such as Hb, myoglobin, cytochromes, and especially in the structure of enzymes responsible for energy production. Iron deficiency affects the body, and iron accumulation causes harmful effects in the body such as neuronal degeneration and cell death (3). There are studies showing that iron accumulation reduces the threshold of triggering headaches by altering the threshold of excitation of neurons (6). It is suggested that high Hb and Hct levels may cause headache by increasing blood viscosity. Hyperviscosity is thought to cause pain by destroying microcirculation leading to cerebral hypoxia, reactive vasodilatation, and neurogenic inflammation (10,11). Studies have shown that there is a decrease in cerebral

blood flow at the height of Hct in migraineurs. Furthermore, it has been shown that there is a 50% increase in cerebral blood flow after Hct reduction with phlebotomy (12,13). Also, an increase in platelet adhesion contributes to increased viscosity. Demirel et al. (5) reported that the pain frequency increased in a migraine group as the iron-binding capacity decreased and ferritin level increased, and the pain frequency increased as the Hb, Hct, and ferritin levels decreased in the tension headache group. It is thought that hypoxia occurs in brain tissue and reactive vasodilatation in the intracranial arteries due to low Hb values, which may be accompanied by an increase in myofascial input and increased pain frequency (5). Aamodt et al. (14) demonstrated that headache frequency was decreased in patients with Hb levels below 11.5 g/dl. They also reported no relationship between ferritin levels and headache prevalence (14). In the study of Yildırım et al. (15), MCHC and RDW were found to be higher than in healthy controls in the migraine group. In our study, there was no significant difference in Hb, Hct, MCV, MCH, MCHC, and RDW values between the migraine and TTH groups. Another finding was that the pain intensity increased as the pain frequency decreased in both groups. This may be related to the development of desensitization in those who have been in pain for a long time, and thus may be related to a milder assessment of their pain.

In the past years, also, nitric oxide synthase, which is believed to play an important role in central sensitization, is present in platelets, suggesting that migraine is a primary platelet dysfunction. However, this hypothesis has not been supported by further studies (16,17,18). Another relationship between platelet biology and migraine may be explained by inflammation. Following the formation of platelet-leukocyte aggregates, many pro-inflammatory cytokines, primarily interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor- α , may increase and these mediators may contribute to sterile inflammation and pain facilitation in the brain (19,20,21). A number of studies have been conducted to investigate the potential association between platelet biology and migraine, by the presence of frequent headache attacks mimicking migraine in patients who had essential thrombocytosis and significant contribution of cerebral blood flow abnormalities to the pathogenesis of migraine (18,22,23,24,25,26). MPV is regarded as a sign of platelet function and activation. Large platelets have higher thrombosis potential. Several studies have supported the predisposition to platelet aggregation in patients with migraine (27,28,29,30). Different results have been obtained in studies investigating platelet count and MPV in patients with migraine (31,32,33). In our study, there was no statistically significant difference between the platelet counts and MPV values of patients with migraine and TTH. This may be due to the active role of serotonin in the pathophysiology of both headaches.

Migraine attacks are thought to be the result of neurovascular inflammation of the cerebral and extra-cerebral vessels (34). The responses, which are given by leucocytes in circulation, causes an increase in the number of neutrophils and a decrease in the number of lymphocytes. For this reason, the NLR is used as an indicator of inflammation (35). As a subclinical inflammatory marker, NLR has been associated with the prognosis and mortality of many patients. PLR is a sign of severe inflammation and promotes the proliferation of megakaryocytes. NLR has been found as high in migraine studies but no significant difference has been found in PLR (36,37,38). In our study, leukocyte, lymphocyte, neutrophil,

NLR and PLR were compared between the TTH and migraine groups in the inter-ictal phase. There was no difference between the parameters in the TTH group, but it was found in the migraine group that as the age increased, the PLR value decreased and the PLR value increased with pain frequency. Also, there was no difference between the groups in NLR values. This may be due to the facts that, depending on the retrospective study design, the attacks of patients cannot be assessed and that there are signs of inflammation in both headache groups. Studies involving a healthy control group are needed.

A few studies have shown that asymptomatic white matter lesions in migraineurs are more common than in the normal population. Several pathophysiologic mechanisms have been proposed including migraine-associated oligemia and focal hypoperfusion (37), glutamatergic excitotoxicity (38), immune-based white matter demyelination (39), and mitochondrial dysfunction (40). It has been suggested that migraine recurrent attacks lead to endothelial damage due to inflammatory arteriopathies in the cranial veins, resulting in thrombosis (41,42). In a study by Silvestrini et al. (43), cerebral vasomotor reactivity responses were evaluated in frontal and posterior circulation in patients with migraine during the non-exacerbation period, and when compared with the control group, vasomotor responses to posterior circulation were low and there was no significant difference in the anterior circulation. These data suggest that adaptive cerebral hemodynamic mechanisms are impaired in the posterior circulation (43). In another study, cerebral vascular reactivity induced by L-arginine in PCA was significantly lower in patients with migraine with and without aura than that of the normal population, and this suggests that posterior circulation infarcts may be more frequent in migraineurs (44). In our study, anterior circulation lesions were more frequent in the TTH group, and posterior circulation lesions were observed more frequently in the migraine group; the findings were consistent with the literature (43,44).

Swartz and Kern (45) reviewed seven retrospective studies conducted between 1991 and 2001 in patients with migraine for the evaluation of white matter lesions and found that the white matter lesion risk in patients with migraine was four-fold higher than in the normal population. There are very few studies on white matter lesions and other types of headache. One study showed that white matter lesions did not develop in new daily persistent headache (46). White matter lesions of medication overuse headache and with patients migraine have been compared and no lesions developed in those who did not have a vascular risk factor in the medication overuse headache (47). In our study, white matter lesions in subcortical and periventricular areas in patients with TTH and migraine were compared concerning the number of lesions and pain characteristics. The number of lesions in both regions of the migraine group was higher but not statistically significant. There was no statistically significant difference between white matter lesions and age, pain frequency, pain severity, and hematologic parameters. The pain frequency increased as Hb, Hct, and MCV values increased in the patients with migraine with lesions. This was not been observed in the TTH group. We assume that the increase in pain frequency may trigger the pro-inflammatory mechanisms and lead to the development or increase the number of white matter lesions in migraine.

Conclusion

As a result, we observed no relationship between migraine and TTH and hematologic parameters. This may be due to the role of inflammatory processes in both groups. The absence of significant differences in MRI findings may be related to the inadequate number of patients. Studies involving control groups with larger cohorts may be more elucidative.

Ethics

Ethics Committee Approval: Ethics Committee Approval was obtained from Adnan Menderes University Faculty of Medicine (protocol no: 2016/1036).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Z.A., A.A., Concept: A.A., Design: Z.A., S.Y.A., A.A., Data Collection or Processing: Z.A., Analysis or Interpretation: A.A., S.Y.A., Literature Search: Z.A., A.A., Writing: Z.A., S.Y.A.

Conflict of Interest: The authors have not declared any conflict of interest related to this article.

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