CLINICAL STUDY

EVALUATION OF INFLAMMATION PARAMETERS IN COMPLETE BLOOD COUNT IN PATIENTS DIAGNOSED WITH VESTIBULAR MIGRAINE

Zehra ÇINAR, MD; Özgür YİĞİT, MD; Çiğdem KALAYCIK ERTUGAY, MD;

İstanbul Eğitim ve Araştırma Hastanesi, Kulak Burun Boğaz ve Baş Boyun Cerrahisi Kliniği, İstanbul, Turkey

SUMMARY

Objectives: To investigate the possible role of total blood count cell ratios and mean platelet volume, which are considered as new inflammation markers, in the pathogenesis of vestibular migraine.

Methods: 30 patients diagnosed with vestibular migraine and 40 healthy individuals were included. The medical records of patients who were evaluated in the otorhinolaryngology-vertigo clinic during a vertigo attack and consulted to the neurology clinic, and were diagnosed with vestibular migraine were evaluated. Routine complete blood count results were used to calculate the neutrophil-, platelet-, eosinophil- and basophil-lymphocyte ratios, lymphocyte-monocyte ratio and mean platelet volume. The vestibular migraine and the control groups were compared statistically in terms of neutrophil-, platelet-, eosinophil-, basophil-lymphocyte ratios, lymphocyte-monocyte ratio and mean platelet volume.

Results: The mean platelet volume was significantly higher in the vestibular migraine group than the control group ($p < 0.05$). Platelet, neutrophil, lymphocyte, eosinophil and monocyte counts and neutrophil-/eosinophil-lymphocyte ratios and lymphocyte-monocyte ratio did not differ significantly ($p > 0.05$) between the groups. The basophil count was significantly higher in the vestibular migraine group ($p < 0.05$). The platelet-lymphocyte ratio was significantly lower ($p < 0.05$), the basophil-lymphocyte ratio was significantly higher in the vestibular migraine group ($p < 0.05$).

Conclusions: Mean platelet volume, basophil-lymphocyte ratio, and basophil count were significantly higher, and platelet-lymphocyte ratio was significantly lower in the vestibular migraine group. Our results showed that systemic inflammation may contribute to the pathogenesis of vestibular migraine.

Keywords: Vestibular Migraine, Inflammation, Complete Blood Count Cell Ratios, Mean Platelet Volume, Basophil Lymphocyte Ratio, Basophil

VESTİBÜLER MİGREN TANILI HASTALARDA TAM KAN SAYIMINDA İNFLAMASYON PARAMETRELERİNİN DEĞERLENDİRİLMESİ

ÖZET

Amaç: Vestibüler migren patogenezinde yeni inflamasyon belirteçleri olarak kabul edilen total kan sayımı hücre oranlarının ve ortalama platelet hacminin olası rolünü araştırmak.

Gereç ve Yöntemler: Çalışmaya vestibüler migren tanısı alan 30 hasta ve 40 sağlıklı birey dahil edildi. Kulak Burun Boğaz-vertigo kliniğinde vertigo atağı sırasında değerlendirilen ve nöroloji kliniğine konsülte edilen vestibüler migren tanısı almış hastaların tıbbi kayıtları değerlendirildi. Nötrofil-, platelet-, eozinofil- ve bazofil-lenfosit oranlarını, lenfosit-monosit oranını ve ortalama platelet hacmini hesaplamak için rutin tam kan sayımı verileri kullanıldı. Vestibüler migren ve kontrol grubu nötrofil-, platelet-, eozinofil-, bazofil-lenfosit oranları, lenfosit-monosit oranı ve ortalama platelet hacmi açısından istatistiksel olarak karşılaştırıldı.

Bulgular: Ortalama platelet hacmi vestibüler migren grubunda kontrol grubuna göre anlamlı olarak daha yüksekti ($p< 0.05$). Platelet, nötrofil, lenfosit, eozinofil ve monosit sayıları ile nötrofil- / eozinofil-lenfosit oranları ve lenfosit-monosit oranı gruplar arasında anlamlı ($p> 0.05$) farklılık göstermemiştir. Bazofil sayısı vestibüler migren grubunda anlamlı olarak daha yüksekti ($p < 0.05$). Vestibüler migren grubunda platelet- lenfosit oranı anlamlı olarak daha düşük ($p < 0,05$), bazofil lenfosit oranı anlamlı olarak daha yüksek bulundu ($p < 0,05$).

Sonuç: Vestibüler migren grubunda ortalama platelet hacmi, bazofil-lenfosit oranı ve bazofil sayısı anlamlı olarak yüksek ve platelet-lenfosit oranı anlamlı olarak düşüktü. Sonuçlarımız, sistemik inflamasyonun vestibüler migren patogenezine katkıda bulunabileceğini göstermiştir.

Anahtar Sözcükler: Vestibüler Migren, Enflamasyon, Tam Kan Sayımı Hücre Oranları, Ortalama Platelet Hacmi, Bazofil Lenfosit Oranı, Bazofil

INTRODUCTION

Although the co-occurrence of migraine and vertigo is known to be 1.1% in the population, it is thought that the relationship between recurrent vestibular symptoms and migraine is higher in clinical practice [1,2]. In 2002, Neuhauser et al. defined vestibular symptoms as a part of migraine disorder and developed diagnostic criteria for VM [3]. After a while, the Barany Society and the International Headache Society identified VM as a separate disease, and the internationally recommended

Corresponding Author: Zehra ÇINAR MD İstanbul Eğitim ve Araştırma Hastanesi, Kulak Burun Boğaz ve Baş Boyun Cerrahisi Kliniği, İstanbul, Turkey, E-mail: drzehradonmez@hotmail.com

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diagnostic criteria were recently included in the 3rd issue of the International Classification of Headache Disorders (ICHD-3) [4,5]. Vertigo can occur between headache episodes, or before, during, or after a headache episode [6-9].

In particular, vascular and neurogenic inflammation that occur as peripheral and central triggers of migraine and all central neural mechanisms are found in the central vestibular pathways and inner ear. A sterile inflammatory response occurs in the meningeal vessels due to the peptide secretion from trigeminal ganglion cells' axon terminations [9]. Particularly, some reports revealed that various pro-inflammatory factors and cytokine levels have increased in VM patients' peripheral blood [10,11,12].

Neutrophils, lymphocytes, and platelets are blood cells that play a role in the control of inflammation [13]. In recent years, mean platelet volume (MPV), neutrophil-lymphocyte ratio (NLR), and platelet-lymphocyte ratio (PLR) have been investigated as new inflammatory markers in many inflammatory, cardiovascular, and malignant diseases [14-16].

It was demonstrated that low lymphocyte monocyte ratio (LMR) might indicate systemic inflammatory activity [17]. The basophil lymphocyte ratio (BLR) and eosinophil lymphocyte ratio (ELR) have been stated to reflect the inflammation activity in systemic autoimmune inflammatory diseases [18].

Although inflammation has been demonstrated in vestibular migraine's pathophysiology, it has not been previously investigated whether there is a change in MPV, NLR, PLR, ELR, BLR, and LMR values, which are accepted as new systemic inflammation markers. This study aims to reveal that whichever changes occur in MPV, NLR, PLR, ELR, BLR and LMR values due to inflammation that has a place in the pathophysiology of vestibular migraine.

MATERIAL and METHODS

Study Design

The study was approved by the Local Ethics Committee of a Tertiarry Hospital (Date: 07.02.2020, Decision No: 2179). This study was a retrospective comparative study conducted using the medical records of patients diagnosed with vestibular migraine who were followed up and treated in the Otolaryngology-Head and Neck Surgery Clinic and Neurology Clinic of the Tertiarry Hospital between 2017-2019.

According to JCHD-3 beta diagnostic criteria, 30 patients who were evaluated by neurologists and headache specialists from the clinic of Otorhinolaryngology and Head and Neck Surgery at a tertiary hospital and diagnosed with VM (21 female,9 male; Mean age ± standard deviation: 43.3 ± 10.2) and 40 healthy individuals with no previous history of chronic headache, vertigo, hearing loss and chronic systemic diasease (12 female, 12 male, Mean age ± standard deviation: 35.0 ± 12), as a control group, were included in the study. We evaluated the VM patients only if the patient was examined and blood was collected at the time of vertigo attack. The patients diagnosed with vestibular migraine had at least 2 episodes a month since last 6 months and treated with calcium canal blockers for prophylaxis. The control group was composed of the patients who admitted to otolaryngology outpatient clinic with symptoms other than headache, vertigo, hearing loss and any chronic systemic disease.

In terms of differential diagnosis of Meniere's disease, benign paroxysmal positional vertigo, and other possible etiologies and related conditions, the patients were evaluated together with the necessary examinations and tests by both the otolaryngologist in the vertigo outpatient clinic and by the neurology specialist in the headache clinic.

The exclusion criteria were an ongoing infection, major depression, pregnancy, severe heart disease, history of malignancy, smoking, anti-inflammatory medicine usage within the last one month or any autoimmune disorder that could affect inflammatory markers' blood levels.

All patients were examined in terms of clinical characteristics such as disease duration, headache characteristics, pain localization, attack frequency, use of analgesics, and treatment options by a neurologist from the headache clinic. Pain severity was evaluated with the visual analog scale (VAS).

Besides, the migraine disability assessment (MIDAS) scale and the Beck depression scale (BDS) were filled out by the patients, and allodynia was evaluated using the validated 12-item allodynia symptom checklist (ASC-12) [19].

Determining Cell Ratios

The medical records of patients who were evaluated in the otorhinolaryngology-vertigo clinic during a vertigo attack and consulted to the neurology clinic, and who were diagnosed with VM to investigate the vertigo etiology were evaluated. We routinely make full otorhinolaryngological examination and perform audio-vestibular tests such as pure tone audiometry, videonystagmography, video-hit-impulse test, vestibular-evoked-myogenic potentials in order to exclude all causes of vertigo in the otorhinolaryngology-vertigo clinic during a vertigo attack. Additionally, we usually recommend routine blood tests to vertiginous patients to identify metabolic problems such as anemia e.g.

Routine complete blood count results of these patients were used to calculate the neutrophil-lymphocyte ratio, PLR, ELR, BLR, LMR, and MPV. The vestibular migraine group and the control group were compared statistically in terms of NLR, PLR, ELR, BLR, LMR, and MPV values. Sysmex hematology analyzer (XT-2100) was used to examine blood samples.

STATISTICAL ANALYSIS

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in the data's descriptive statistics. The distribution of variables was measured with the Kolmogorov Smirnov test. Independent sample t-test and Mann-Whitney U test were used in the analysis of independent quantitative data. A Chi-square test was used to analyze independent qualitative data, and the impact level was investigated by univariate and multivariate logistic regression. SPSS 26.0 program was used in the analysis. Sysmex hematology analyzer (XT-2100) was used to examine blood samples.

RESULTS

Ages of the patients were significantly higher in the vestibular migraine group than the control group ($p < 0.05$). No significant difference was observed in terms of gender distribution between vestibular migraine and control groups ($p > 0.05$). (Table 1) The MPV value was significantly higher in the vestibular migraine group than the control group ($p < 0.05$). Platelet value, neutrophil value, lymphocyte value, eosinophil value, monocyte value, NLR, ELR, and LMR did not differ significantly ($p> 0.05$) between vestibular migraine and control groups. The basophil value was significantly higher in the vestibular migraine group ($p < 0.05$). The PLR was significantly lower ($p < 0.05$), and the BLR rate was significantly higher in the vestibular migraine group than the control group ($p < 0.05$). (Table 1)

A significant ($p<0.05$) impact of age, MPV, basophil, PLR, and BLR values was observed to predict patients with vestibular migraine in the univariate model. In the multivariate reduced model, significant-independent ($p<0.05$) impact of age, MPV, and basophil values was observed to predict patients with vestibular migraine. (Table 2)

Table 1: Comparison of groups in terms of age, sex and cell counts and ratios in whole blood count test

		Control Group			Vestibular Migraine Group				
		Mean.±s.d./n-%	Median	Min-Max	Mean.±s.d./n-%	Median	Min-Max	p	
Age		35,0 ± 12,2	37,0	20,0 ± 58,0	43,3 ± 10,2	46,0	21,0 ± 58,0	***0,008***	m
Gender	Female	12 50,0%			21 70,0%			0,134	X^2
	Male	12 50,0%			9 30,0%				
MPV		10,1 ± 0,9	9,8	8,7 ± 12,2	11,1 ± 0,8	11,2	9,1 ± 12,5	***0,000***	m
Platelet		271,2 ± 48,5	276,5	185,0 ± 370,0	249,6 ± 59,4	258,0	2,8 ± 329,0	0,156	t
Neutrophil		4,12 ± 0,89	4,03	2,49 ± 5,67	3,98 ± 1,06	3,96	1,95 ± 5,80	0,120	t
Lymphocyte		2,37 ± 0,59	2,22	1,42 ± 3,56	2,56 ± 0,46	2,60	1,88 ± 3,60	0,151	m
Eosinophil		0,19 ± 0,19	0,11	0,05 ± 0,89	0,23 ± 0,14	0,22	0,02 ± 0,48	0,084	m
Basophil		0,04 ± 0,02	0,04	0,01 ± 0,09	0,06 ± 0,02	0,06	0,02 ± 0,11	***0,003***	m
Monocyte		0,62 ± 0,21	0,63	0,37 ± 1,16	0,63 ± 0,12	0,65	0,36 ± 0,86	0,338	m
PLR		121,5 ± 38,5	110,5	56,6 ± 207,5	98,9 ± 27,4	101,7	1,4 ± 146,6	***0,032***	m
NLR		1,82 ± 0,53	1,80	0,76 ± 2,82	1,60 ± 0,50	1,53	0,62 ± 2,64	0,144	m
ELR		0,08 ± 0,08	0,04	0,02 ± 0,37	0,09 ± 0,05	0,09	0,01 ± 0,21	0,088	m
BLR		0,02 ± 0,01	0,01	0,00 ± 0,05	0,02 ± 0,01	0,02	0,01 ± 0,04	***0,015***	m
LMR		4,11 ± 1,44	3,75	1,88 ± 7,43	4,19 ± 1,00	4,04	2,47 ± 6,56	0,601	m

[t] t test / [m] Mann-Whitney U test / [X^2] Chi-square test/Min-Max: Minimum-Maximum/s.d: Standard Deviation/MPV: Mean Platelet Volume/PLR: Platelet Lymphocyte Ratio/ NLR: Neutrophil Lymphocyte Ratio/ELR: Eosinophil Lymphocyte Ratio/BLR: Basophil Lymphocyte Ratio/ LMR: Lymphocyte Monocyte Ratio

Table 2: Logistic regression analysis in univariate and multivariate models

	Univariate Model			Multivariate Model		
	OR	95% CI	p	OR	95% CI	p
Age	1,067	1,014 - 1,123	***0,013***	1,106	1,030 - 1,188	***0,006***
MPV	3,412	1,654 - 7,038	***0,001***	4,175	1,739 - 10,023	***0,001***
Basophil	>100	>100 - >100	***0,007***	>100	>100 - >100	***0,022***
PLR	,977	,957 - ,997	***0,026***			
BLR	>100	>100 - >100	***0,032***			

Logistic Regression (Forward LR)/OR: Odds Ratio/CI: Confidence Interval/ MPV: Mean Platelet Volume/PLR: Platelet Lymphocyte Ratio/BLR: Basophil Lymphocyte Ratio

DISCUSSION

Although various studies investigated the role of inflammation in migraine's pathophysiology, the importance of inflammation in VM has been studied in a very few reports [1,6,9,20-23]. This research is the first study investigating the role of inflammation and the new inflammation markers, MPV, NLR, PLR, ELR, BLR, and LMR, especially in VM patients. In our study, MPV, BLR, and basophil values were significantly higher, and the PLR value was significantly lower in the VM group than the control group. The age factor was significantly higher in the vestibular migraine group than in the control group. According to the results of this study, age, MPV, and basophil values were found to be significant independent factors in the vestibular migraine group. In this way, it was concluded that vestibular migraine occurs in older individuals and that MPV, which is an inflammation marker, and basophilic cells as a new finding may play a role in its pathogenesis. In general, our results support the role of systemic inflammation in VM pathophysiology.

In the study performed by Şahin Mİ et al. on patients with vestibular neuritis, MPV, NLR, and PLR values were significantly higher than control group. It has been stated that there may be a relationship between these findings and high MPV levels and vascular thrombosis in vestibular neuritis pathology [24]. In the study of Cayir S et al. higher C-reactive protein to albumin ratio and NLR were associated with poor prognosis in patients with Bell's palsy. They stated that although there might be several etolologic factors in Bell's palsy, the elevation of NLR value may indicate inflammatory event in the present pathology of Bell's palsy [25]. In another clinical study conducted in patients with sudden hearing loss, it was postulated that NLR and PLR values may be the indicators of the prognosis in sudden hearing loss. They pointed out that higher NLR values may indicate local inflammation and higher PLR values may indicate pathological damage in endothelial cells[26]. Hizli et al. evaluated the inflammatory markers in patients with obstructive sleep apnea to find out the indicators of disease severity. The fibrinogen to albumin ratio and CRP to albumin ratio were defined as markers of the severity of OSA [27]. In the case-control study of Karabulut KU et al. in patients with a migraine attack, it was found that NLR was significantly higher in the migraine group compared to the control group [28]. In another study, it was stated that serum NLR and PLR levels might be biomarkers of migraine subtypes with different clinical features, such as migraine attacks, migraine with aura, or patients with a family history of migraine. In the mentioned study, increased NLR and PLR levels were accepted as inflammatory markers indicating the disease's severity [29]. Unlike the study above, according to our study's findings in which we examined patients with VM, it was concluded that the decreased PLR value might be a biomarker in these patients. However, we did not perform visual analog scale or dizziness handicap inventory in these patients. Therefore we could not mention about the relationship between severity of disease and PLR value. This value may change according to the period or severity of disease. This hypothesis may be a new topic for another study.

In the clinical study of Saricam G. et al. in patients with a diagnosis of migraine, it was found that the PLR value was significantly higher in the migraine without aura group compared to the control group. In the same study, an increase in MPV and platelet count was observed in migraine with and without aura groups compared to the control group, despite the statistical insignificance. It has been stated that these results were related to systemic inflammation in patients with migraine and support the existence of an ongoing inflammatory process even in periods without attacks [30]. In our study, an increase in MPV value was observed similarly in patients with VM, but a decrease was observed in PLR value. According to these findings, our study shows that there may be a relationship between high MPV value and potential vascular thrombosis in VM pathology. Furthermore, decrease in PLR value may indicate an inflammatory process including a lymphocyte dominance. In brief, systemic inflammation may play a role in VM

pathophysiology, but the change in markers is different from pure migraine. This situation supports the claim of the Author HU et al. that the PLR level may be a biomarker indicating migraine subtypes with different clinical features [29].

In the clinical study conducted by Turan E and Kilic SS in the pediatric patient population diagnosed with primary Raynaud's phenomenon (PRF), a significant relationship was found between antinuclear antibody positivity and migraine in female children, and it was found that the most common disease accompanying PRF was the migraine. Also, mean platelet volume (MPV) measurements were found to be significantly higher in patients with migraine (Primary Raynaud's Case) than those without migraine [31].

In another clinical study conducted in pediatric patients diagnosed with migraine disease based on the existence of a potential relationship between migraine pathogenesis and platelet biology, although no significant difference was found in MPV values between the migraine group and the healthy control group, MPV values were found to be significantly higher in female children with migraine compared to male children. It was stated that increased MPV and decreased serum iron levels might be associated with migraines [32].

Similar to the migraine patients in the mentioned studies, MPV value was significantly higher in the vestibular migraine group than in the control group in our study. Besides, the PLR value was significantly lower in the vestibular migraine group than in the control group. No significant difference was observed in terms of NLR between vestibular migraine and control groups.

ELR and BLR, which are cheap and easily calculated markers, are other values that determine the inflammatory state. Eosinophils and basophils are associated with allergic conditions and parasitic infections [33]. Basophils and eosinophils are important for cytokine production and usually increases in infammatory disorders, but a reduction in the number of lymphocytes is possible during infammation [25,34].

In the clinical study of Yang Z et al. conducted on 1139 patients diagnosed with systemic autoimmune rheumatic diseases, high NLR and low basophil lymphocyte ratio (BLR) were encountered in many systemic autoimmune rheumatic disease subgroups [18]. In a clinical study investigating the possible relationship between patient satisfaction and blood inflammatory parameters after septoplasty, Kökoğlu K and Şahin MI found that as ELR and BLR increased, patient satisfaction level decreased after septoplasty [33]. In our study, BLR and basophil values were found to be significantly higher in the vestibular migraine group than in the control group. While high ELR was encountered in autoimmune rheumatic diseases other than systemic lupus erythematosus (SLE), low ELR was found in SLE. These biomarkers were accepted to be indicators of the severity of inflammation in systemic autoimmune rheumatic diseases [18].

Brescia K et al. found that NLR, ELR, and BLR values were significantly increased in patients with a recurrent polyp and chronic rhinosinusitis, although the discriminant power of disease recurrence was not acceptable compared to patients without recurrence [35].

The lymphocyte-monocyte ratio has been presented as an indicator of prognosis in many malignant diseases and changed in different directions in different malignancy types. It has been stated that a high lymphocyte monocyte ratio can be used as a prognosis indicator in colorectal cancers. In contrast, it has been stated that patients with advanced clinicopathological characteristics and poor prognosis are encountered with low LMR in esophageal squamous cell cancers [36,37]. However, in the study conducted by Gong S et al. in patients with coronary artery disease, it was stated that LMR could be a useful predictor of future cardiovascular events. This study found that the LMR values were significantly lower in the group with severe atherosclerosis [38]. In our study, no significant difference was observed in ELR, LMR between vestibular migraine and control groups. Basophil value and BLR were significantly higher in the vestibular migraine group than in the control group. Basophil value

and BLR were defined as objective markers in this study.

Although there were statistically significant differences ($p < 0.5$) in basophil, MPV, BLR and PLR values between the two groups, the effect sizes were small. The reason of that might be the small number of patients in the present study. With a much larger number of patients, the effect sizes may increase with future studies.

Our study is critical since it is the first study evaluating the new inflammation markers, MPV, NLR, PLR, ELR, BLR, and LMR, to investigate the role of inflammation in VM pathophysiology. Therefore, according to our literature review, low PLR, basophil value and high BLR in patients with VM have been reported for the first time. These results and MPV elevation can indicate that systemic inflammation may have a possible role in the pathogenesis of VM, but future studies with more patients are needed in order to evaluate also disease severity.

However, the fact that our study was retrospective and that it was not compared with other subgroups of migraines are the major limitations of our study. The relationship between these biomarkers and the severity of vestibular complaints in patients with vestibular migraine and their effect on the quality of life was not investigated, and this situation was another limitation. There is a need for further studies with high patient groups examining inflammation parameters in migraines" all subgroups.

CONCLUSION

In light of the findings of this study, MPV, PLR, and BLR values out of MPV, PLR, NLR, ELR, BLR, and LMR values, which have been put forward in the pathogenesis of inflammation, were shown to vary in the evaluation of complete blood count of patients with vestibular migraine compared to the control group. In our study, MPV, BLR, and basophil values were significantly higher, and PLR value was significantly lower in the vestibular migraine group than in the control group. Our results showed that systemic inflammation may contribute to the pathogenesis of vestibular migraine. Future studies with larger groups may confirm our results.

Declarations:

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