Original Article

Do Mean Platelet Volume and Platelet Distribution Width Have An Association with White Matter Hyperintensities in Migraine Patients?

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Abstract

Objective: Increased prevalence of white matter hyperintensities (WMH) is reported in migraine patients; however, the pathophysiology and the progression of these lesions are not definitely clear. Mean platelet volume (MPV) and platelet distribution width (PDW) are easily obtained markers for platelet activity. The aim of this study is to evaluate the relationship between the presence of WMH and MPV and PDW in patients with migraine in order to determine the role of platelet activity in the pathophysiology of WMH. **Methods:** Patients who were admitted to the neurology outpatient clinics of Baskent University Hospital from January 2011 to December 2015 with migraine and between 18 and 55 years of age were evaluated retrospectively. The blood samples were taken and total blood count parameters including MPV and PDW were analyzed. Brain magnetic resonance images were evaluated. **Results:** Totally, 218 patients were evaluated in this study. Forty-eight (22.0%) patients had WMH in the brain magnetic resonance imaging. In patients with WMH, the median of age was higher than the patients without WMH and the difference was statistically significant ($P < 0.05$). There was no statistically significant difference between MPV, PDW values, and the presence of WMH. **Conclusions:** There are multiple theories suggested for the mechanism of WMH, but the major cause and pathophysiology are still undetermined. Our data suggested that increased platelet activity is insufficient by itself to explain the pathophysiology of WMH in migraine patients and to improve the knowledge on this issue further large longitudinal studies should be performed.

Keywords: Mean platelet volume, migraine, platelet distribution width, white matter hyperintensities

Introduction

Migraine is a common neurological disorder that affects 10–15% of the general population.[1] Migraine diagnosis is based on clinical symptoms and neuroimaging is generally used to exclude other secondary headache causes both in children and adult migraine patients.[2,3] With the increased usage of magnetic resonance (MR) imaging and the advances in techniques, studies have shown that both migraine with and without aura patients are at high risk of developing a variety of structural and morphological brain abnormalities such as white matter hyperintensities (WMH), silent infarct-like lesions (SILL), grey and white matter volume changes, and these abnormalities provide additional insights and researches on this issue.[1-4]

Increased WMH prevalence is reported in migraine patients, but the prevalence of WMH in migraine patients varies widely in different studies.[2] However, the pathophysiology, role, and progression of these lesions were not definitely clear and the studies are controversial.[3,5]

Platelets have a major role in atherothrombosis and several methods have been suggested for the evaluation of the platelet activity.[6] Mean platelet volume (MPV) and platelet distribution width (PDW) increase during platelet activation and these are easily obtained markers for the platelet activity.[7,8] Some studies have reported that MPV and PDW are associated with cerebrovascular diseases, cardiovascular diseases, and are associated with worse clinical outcomes in acute myocardial infarction and stroke patients.[6,9,10]

The aim of this study is to evaluate the relationship between WMH observed in brain MR images and MPV and PDW values in patients with migraine in order to determine the role of platelet activity in the pathophysiology of WMH. Also secondly, the relationship between WMH and neutrophil, platelet count, neutrophil lymphocyte ratio (NLR) are aimed to be analyzed statistically.

Materials and Methods

Patients who were evaluated on neurology outpatient clinics of Baskent University Hospital from January 2011 to December

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2015 with a complaint of headache, with a diagnosis of migraine according to The International Classification of Headache Disorders, 3rd edition (beta version) and between the 18 and 55 years of age were evaluated retrospectively. Patients who did not have a brain MR imaging during the evaluation, had systemic diseases such as diabetes mellitus, hypertension, hyperlipidemia, had neurological diseases such as cerebrovascular diseases or demyelinating diseases, had infectious disease within a month of evaluation, had hematological diseases, malignancies, and pregnancy were excluded.

Detailed histories, demographic characteristics, information on the frequency of migraine attacks, attack duration, disease duration, the presence of aura, presence of vomiting/nausea, photophobia/phonophobia, and family history were recorded for each patient.

The blood samples were taken in the interictal period and collected in ethylene-diamine-tetra-acetic acid-containing tubes. Total blood count parameters including MPV and PDW were analyzed by an autoanalyzer.

Brain MR imaging examinations were performed with a 1.5 T MR imaging scanner (Siemens, Avanto, Germany) with a 16-channel phased array head coil. The scanning protocol included the following sequences: fluid attenuated inversion recovery (FLAIR) axial (repetition time/echo time [TR/TE]: 8000/84 ms, slice thickness: 5.5 mm, field of view[FOV]: 22 cm, matrix: 256 × 157, bandwidth: 190, flip angle: 150, number of slices: 20); axial T1 weighted images (T1W) (TR/TE: 410/9.2 ms, slice thickness: 5.5 mm, FOV: 22 cm, matrix: 448 × 186, bandwidth: 130, flip angle: 90, number of slices: 20); axial T2-weighted (T2W) images (TR/TE: 3630/103 ms, slice thickness: 5.5 mm, FOV: 22 cm, matrix: 512 × 325, bandwidth: 191, flip angle: 150, number of slices: 20); coronal T2W images (TR/TE: 3630/103 ms, slice thickness: 5.5 mm, FOV: 22 cm, matrix: 512 × 302, bandwidth: 191, flip angle: 150, number of slices: 20); sagittal T2W images (TR/TE: 3630/103 ms, slice thickness: 5.5 mm, FOV: 22 cm, matrix: 512 × 358, bandwidth: 191, flip angle: 150, number of slices: 20).

The brain lesions were categorized as WMH and SILL according to MR features. WMH were evaluated as small, punctate, multiple, and discrete high signal intensity lesions with no mass effect seen on T2W and FLAIR MR images and without prominent hypointensity on T1W scans.[11,12] Silent infarct-like lesions were defined as small nonmass lesions that have same intensity with cerebrospinal fluid, were seen hyperintense on T2W images with vascular territory distribution and cause no symptoms.[2,13] Lesions also had corresponding prominent hypointensities on T1W images.[12]

The location and distribution of the lesions were described according to the methodology reported by Barkhof *et al.*[14] in multiple sclerosis patients. White matter hyperintensities were counted on FLAIR images and patients with WMH were categorized according to juxtacortical, subcortical/deep white matter, callosal/subcallosal, and periventricular subgroups. The locations of WMH were classified as supratentorial, infratentorial, and both supratentorial and infratentorial.

Statistical analyzes were performed using statistical software (IBM-SPSS 21.0 for Windows, Chicago, Illinois, USA). Numerical data with normal distribution were presented as mean ± standard deviation (SD) and data with non-normal distribution were presented as median (25–75th percentile) values. Categorical data were described as percentages. Normality of data distribution was checked using the Shapiro–Wilk test. Numerical variables with non-normal distribution were tested with the Mann–Whitney U test between the two groups. Categorical variables were analyzed using the Chi-square test, Fisher Exact test, or Fisher–Freeman–Halton test. Spearman correlation analysis was used to examine the correlation between numerical variables. For all analyzes, a two-tailed P value < 0.05 was considered statistically significant.

This study was approved by the local ethical committee (Baskent University, Human Ethics Committee, and Study No: KA 15/92 Ankara, Turkey).

Results

Due to the exclusion criteria, a total of 218 patients were evaluated retrospectively in this study. The median age of the patients was 34 (25–75th percentile: 27–43) years, 184 (84.4%) were female. Thirty-four (15.6%) patients had migraine with aura. The characteristics of the patients are shown in Table 1.

Forty-eight (22.0%) patients had WMH in the brain MR imaging. In patients with WMH, 44 patients (20.2% of 218 patients) had supratentorial WMH. Also, SILL were observed

Table 1: Baseline characteristics of the patients

Variables	*n*=218
Age, years, median (25th–75th percentile)	34 (27-43)
Female, *n* (%)	184 (84.4%)
Smoking, *n* (%)	63 (28.9%)
Migraine with aura, *n* (%)	34 (15.6%)
Vomiting, *n* (%)	143 (63.6%)
Photophobia, *n* (%)	144 (66.1%)
Photophobia, *n* (%)	141 (64.7%)
Duration of the disease, *n* (%)	
<1 year	16 (7.3%)
1–5 years	77 (35.3%)
5–10 years	52 (23.9%)
>10 years	73 (33.5%)
Frequency of the attacks, *n* (%)	
<2 per month	89 (40.8%)
2–8 per month	85 (39.0%)
>8 per month	44 (20.2%)
Duration of the attacks, *n* (%)	
<24 hours	165 (75.7%)
24–72 hours	37 (17.0%)
>72 hours	16 (7.3%)

in 8 patient (3.7%). The characteristics of the structural brain lesions are shown in Table 2.

In patients with WMH, the median of age was higher than the patients without WMH and the difference was statistically significant ($P < 0.05$). There were no other significant differences between the groups according to other baseline characteristics [Table 3].

We found no association between the location of the lesions and the type of migraine, duration of the disease, or the frequency of attacks. In addition, no association could be observed between the presence of SILL and the migraine type, duration of the disease, duration of the attacks, or frequency of attacks.

The hematological parameters of the patients were summarized in Table 4. There was no statistically significant difference between the MPV, PDW, and the presence of WMH. Similarly, no statistically significant difference could be found between other hematological parameters and the presence of WMH [Table 4]. Also, no significant difference was shown between the MPV, PDW values, and the presence of SILL. We found no correlation between MPV, PDW, and the number of WMH [Table 5]. Moreover, no correlation was observed between the number of WMH and other hematological parameters [Table 5].

Table 2: Characteristics of the structural brain lesions of the patients

Presence of WMH, *n* (%)	48 (22.0%)
Number of WMH, *n* (%)	
1–5	29 (13.3%)
5–10	12 (5.5%)
10–15	3 (1.4%)
15–20	2 (0.9%)
>20	2 (0.9%)
Localization of WMH, *n* (%)	
Supratentorial	44 (20.2%)
Infratentorial	1 (0.5%)
Supratentorial + Infratentorial	3 (1.4%)
Presence of deep WMH, *n* (%)	45 (20.6%)
Presence of periventricular WMH, *n* (%)	28 (12.8%)
Presence of juxtacortical WMH, *n* (%)	5 (2.3%)
Presence of callosal WMH, *n* (%)	1 (0.5%)
Presence of SILL, *n* (%)	8 (3.7%)
Localization of SILL, *n* (%)	
Supratentorial	5 (2.3%)
Infratentorial	3 (1.4%)

Discussion

Migraine is a complex neurovascular disorder characterized by recurrent headaches and patients with migraine have an increased risk of subclinical brain structural lesions that are detected on neuroimaging.[13] The development of these lesions is important as they can be associated with cognitive impairment, stroke, and disability.[15,16]

Platelets are important for both immune and inflammatory issues.[17] Platelet volume evaluation is correlated with platelet activity and MPV and PDW are commonly used inexpensive markers for the measurement of platelet size.[6,7,18] Platelets secrete multiple mediators for coagulation, inflammation, and atherosclerosis.[6] Large and dense platelets contain more alpha-granules and lead to releasing platelet factor, platelet-derived growth factor, and p-selectin. As a result of more enzymatically active platelets, inflammation and atherogenesis occur.[6,8,9,19]

Table 3: Baseline characteristics of the patients according to the presence of WMH

Variables	WMH (+)	WMH (-)	*P*
Age, years, median (25^{th}–75^{th} percentile)	42.50 (36.00-47.00)	32.00 (26.00–41.25)	*P*<0.05*
Female, *n* (%)	41 (85.4%)	143 (84.1%)	*P*=0.827
Smoking, *n* (%)	13 (36.0%)	50 (29.5%)	*P*=0.434
Migraine with aura, *n* (%)	9 (18.8%)	25 (14.7%)	*P*=0.495
Vomiting, *n* (%)	29 (61.7%)	114 (69.9%)	*P*=0.286
Photophobia, *n* (%)	29 (61.7%)	115 (71.0%)	*P*=0.226
Photophobia, *n* (%)	29 (61.7%)	112 (69.1%)	*P*=0.338
Duration of the disease, *n* (%)			*P*=0.169
<1 year	1 (2.1%)	15 (8.8%)	
1–5 years	20 (41.7%)	57 (33.5%)	
5–10 years	8 (16.7%)	44 (25.9%)	
>10 years	19 (39.6%)	54 (31.8%)	
Frequency of the attacks, *n* (%)			*P*=0.141
<2 per month	25 (52.1%)	64 (37.6%)	
2–8 per month	17 (35.4%)	68 (40.0%)	
>8 per month	6 (12.5%)	38 (22.4%)	
Duration of the attacks, *n* (%)			*P*=0.704
<24 hours	35 (72.9%)	130 (76.5%)	
24–72 hours	10 (20.8%)	27 (15.9%)	
>72 hours	3 (6.3%)	13 (7.6%)	

Table 4: Hematological parameters of the patients according to the presence of WMH

Parameters	WMH (+)	WMH (-)	*P*
Hemoglobin (g/dl), median (25^{th}—75^{th} percentile)	13.50 (12.93–14.53)	13.60 (12.80–14.32)	*P*=0.895
Leucocyte (10^3/μL), median (25^{th}—75^{th} percentile)	6.56 (5.66–7.68)	6.69 (5.74–8.26)	*P*=0.378
Platelet (10^3/μL), median (25^{th}—75^{th} percentile)	252.50 (215.50–286.50)	257.00 (224.75–295.75)	*P*=0.295
Neutrophil median (10^3/μL), (25^{th}—75^{th} percentile)	3.71 (3.16–4.50)	3.77 (3.00–5.01)	*P*=0.932
Lymphocyte (10^3/μL), median (25^{th}—75^{th} percentile)	2.08 (1.62–2.43)	2.20 (1.76–2.67)	*P*=0.110
MPV median (25^{th}—75^{th} percentile)	8.71 (7.73–9.59)	8.60 (7.46–9.51)	*P*=0.305
PDW median (25^{th}—75^{th} percentile)	19.20 (17.93–20.08)	18.50 (17.38–19.80)	*P*=0.088
NLR median (25^{th}—75^{th} percentile)	1.90 (1.35–2.40)	1.67 (1.37–2.26)	*P*=0.178

Table 5: The correlation between the number of WMH and hematological parameters

	Number of WMH	
	Correlation coefficient*	Sig.(2-tailed)
MPV	-0.48	0.746
PDW	-0.144	0.327
Leucocyte	0.030	0.839
Neutrophil	-0.083	0.576
Lymphocyte	0.202	0.168
NLR	-0.179	0.225

*Spearman correlation analysis was used to examine the relationships between variables with non-normal distribution

Previously, MPV was found to be higher in patients with transient ischemic attack, silent cerebral infarction, and ischemic but not hemorrhagic stroke,[8,18] and was associated with a larger volume of cerebral damage and poor clinical outcomes.[19] In addition, MPV is reported to be increased in patients with acute myocardial infarction (AMI) than in non-AMI patients in a meta-analysis and found to be associated with increased mortality after myocardial infarction.[6] Also, PDW, which represents the variability in platelet volume and gives information about platelet activity, may add more information to MPV.[7,20] It was found associated with atherosclerosis, systemic inflammatory diseases, and coronary artery disease.[10] It was suggested to be a predictor for prognosis and outcome in heart failure and stroke patients after mechanical thrombectomy previously.[10,21] In a study, PDW was found to be correlated with the degree of carotid artery stenosis.[7]

The relationship between migraine and platelets was studied formerly and multiple studies reported abnormalities in platelet functions in migraine patients.[17,22] In some studies, platelet activation was found to be increased only in the attack period, although in others, it was observed to be increased both during the periods of attacks and between the attacks.[22,23] Platelet aggregation and activation were found to be increased in migraine patients in various studies previously.[24] Also, spontaneous platelet aggregation and adhesion were found to be higher in migraine patients compared to healthy controls, during the periods without headache.[24]

In previous studies, MPV values were found to increase in migraine patients than the control group but the difference was not statistically significant.[17,24] However, in a different study, it was observed that MPV values were statistically and significantly greater in migraine patients than the control group.[25] The timing of the blood samples and the methodological differences may cause diversities in the interpretation of the studies. Also, other tests for platelet activation such as β-thromboglobulin and plasma factor 4 were investigated and were found to be increased in migraine.[23] Moreover, increased prevalence of genetic prothrombotic risk factors such as Factor V Leiden, Factor II 20210 A mutations, and protein C-S deficiencies were found in migraine patients in a few studies.[23]

Platelet theories provide links between migraine and stroke.[23] Although the mechanism between the migraine and stroke was not fully identified, some data propose that changes in platelet functions could have a role in patients with migraine, especially in relation to aura and its effect on stroke and vascular events.[26,27] White matter hyperintensities are considered to be asymptomatic in early stages in patients, but with progression, they can have a role in the development of cerebrovascular and neurodegenerative diseases.[28] There are multiple theories suggested for the mechanism of WMH, but the major cause and pathophysiology are still undetermined. Focal cerebral hypoperfusion, oxidative stress, presence of patent foramen ovale, endothelial dysfunction, disruption of the blood–brain barrier due to cortical spreading depression, mitochondrial dysfunction, and platelet aggregation were some of the proposed mechanisms for WMH.[4,5,29–31]

In previous studies, the role of platelets in the development of WMH was shown and platelet-derived thrombogenic microvesicles were found to be increased in patients with WMH.[28] Mean platelet volume and PDW were investigated in cerebrovascular or cardiovascular diseases in order to determine the role of platelet activation but until today, the information about the relationship between MPV and WMH is inadequate. Therefore, we evaluated the relationship between the presence of WMH, MPV, and PDW values in order to determine the role of platelet activity on the development of these lesions through the formation of microthrombosis, but our data suggested that increased platelet activity is insufficient by itself to explain the pathophysiology of WMH lesions in migraine patients. Only recently, in one study, the relationship between WMH in non-stroke patients and MPV was examined

and it was found that high MPV level was associated with the prevalence of WMH.[28] Also, the authors observed that the subjects with higher MPV tertile had a higher Fazekas score compared to the subjects with lower MPV level and the differences was found to be statistically significant.[28]

Silent infarct-like lesions are other lesions that can be associated with migraine.[1] The interpretation of the lesions and the association between SILL and stroke is not clearly determined.[1] Formerly, it was shown that migraine patients had an increased risk for SILL in the posterior circulation territory and the risk was higher in migraine patients with aura and with frequent attacks.[32] In a meta-analysis, it was reported that the association of SILL was greater for migraineurs with aura than without.[1] Although we found no association between the presence of SILL and the migraine type, duration of the disease, duration of the attacks, or the frequency of attacks. Moreover, similar to WMH, we could not show a significant difference between the presence of SILL, MPV, and PDW values.

The first study about the prevalence of WMH in migraine patients was reported in 1988 and since then several studies were published about WMH and migraine.[2] The prevalence of WMH in migraine patients was reported higher than controls[15] and the prevalence of WMH in migraine patients varies widely between 4% and 59% in previous studies.[1] We found WMH in 22% of the migraine patients in this study. We think the variability between the reported prevalence of WMH in migraine patients differs in studies due to the number of patients, fewer longitudinal studies, evaluation of risk factors, different inclusion criteria, and the features of the MR imaging that is used.

The data about the association between WMH and the characteristics and severity of migraine are controversial.[16] Previously, several studies did not reveal any association between the WMH and the clinical features of migraine, while other studies reported a relationship between the WMH occurrence and types of migraine, frequency of attacks, or duration of migraine.[16] In our study, we found positive correlation between age and prevalence of WMH. However, we found no difference in the prevalence of WMH in patients due to gender, frequency of the attacks, duration of the attack, or duration of the disease. Similarly, Trauninger *et al.*[31] found no difference between WMH prevalence and gender previously but the presence of WMH was found higher in migraine patients with higher disease duration and attack frequency. Also, Seneviratne *et al.*[4] reported an association between WMH and the frequency of headache.

The association between WMH and migraine with aura is also controversial and both patients with migraine with and without aura have an increased risk for developing WMH in the brain.[1,31] We found no significant difference between the presence of WMH and aura. Similarly, in another study, the prevalence of deep WMH in female migraine patients was reported to increase with attack frequency and it was not affected by aura presence.[13]

The majority of the patients have multiple WMH and commonly, these lesions were located supratentorially in the frontal and parietal lobes.[4,16] Lesions are mostly found in deep and periventricular white matter.[16] Similarly, the distribution of WMH was found to be supratentorial in most of the patients in our study. We found no association between the location of the lesions and the type of migraine, duration of the disease, or the frequency of attacks. Previously also, in another study, no relationship was found between the distribution of WMH lesions and migraine with or without aura or patients with episodic or chronic migraine.[16]

There are some limitations of our study. Firstly, it is a retrospective cross-sectional study and it is difficult to make a definite causal relationship. Secondly, the MPV and PDW levels were measured only at one time and the variability in the timing of the blood samples whether during the attack or between the attacks may have an effect on the results. Also, we could not evaluate other risk factors such as Factor V Leiden mutation, protein C, S, and antithrombin III deficiency in our group. As a result, further researches with high patient number and accurate and definitive methodological processes are needed to confirm this causal relationship between platelet activation and WMH.

Conclusion

In conclusion, migraine can be considered as a neurovascular disease and patients with WMH can possibly be associated with transient ischemic attacks and stroke. Therefore, to improve the knowledge on this issue further large longitudinal studies should be performed in order to identify the relationship and pathophysiology of WMH in migraine patients.

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Conflicts of interest

There are no conflicts of interest.

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