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Risk factors for white matter lesions in migraine patients: Insights for prevention and management

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Abstract

Background & Objective: White matter lesions (WML) are commonly observed in cerebral Magnetic Resonance Imaging scans of individuals with migraine. However, the exact causes of these lesions in migraine patients remain unclear. This study aims to identify and assess risk factors associated with WML in migraine patients. *Methods:* Our study included 63 migraine patients with and 64 patients without WML. We compared clinical characteristics and laboratory data between the two groups, including age, gender, age of migraine onset, duration of migraine disease, history of cigarette smoking, presence of hypertension, presence of an aura, attack frequency, photophobia and phonophobia. *Results:* Multivariate analysis revealed that the risk of developing WML increased two times with age (odds ratio [OR] = 2.00; 95% confidence interval [CI] for OR = 1.24–3.19) and was nearly five times higher in women (OR = 4.92; 95% CI = 1.14–21.11). Compared to patients experiencing a single attack a month, those with 2-5 attacks per month had a seven-fold higher risk, while those with more than five attacks per month had a nine-fold higher risk of developing WML (OR = 7.82; 95% Cl = 1.40–43.64, 9.17; 95% CI = 1.59–52.54). Additionally, a 100-unit increase in TG levels doubled the chances of developing WML (OR = 2.22; 95% CI = 1.23-4.00).
Conclusion: This study identifies age, female gender, attack frequency, and elevated TG levels as significant risk factors for the development of WML in migraine patients. These findings provide insights for the prevention and management of WML in individuals with migraine.

Keywords: Migraine, white matter lesions, magnetic resonance imaging, attack frequency

INTRODUCTION

Migraine is a reversible headache syndrome characterized by moderate to severe attacks lasting 4–72 hours, unilateral or bilateral pain, and accompanying systemic and neurological symptoms.[1,2] The diagnosis of migraine is based on criteria established by the International Headache Society (beta version, revised in 2013).[3] While cerebral imaging is not necessary for diagnosing migraine, it may be required to rule out secondary causes. Magnetic resonance imaging (MRI) of the brain in migraine patients often reveals white matter lesions (WMLs). Even young patients without any risk factors can exhibit these lesions.[4-6] These lesions, which are typically punctate and diffusely distributed, do not exert mass effects on T2-weighted and fluid-attenuated inversion recovery MRI images. They are mostly found in the deep white matter or periventricular regions, and rarely, in the brainstem.[7-9]

The association between migraines and the clinical significance of WML, which is four times more prevalent in the MRIs of patients with migraines compared to the general population, remains unknown.[10,11] According to a study by Debette and Markus, the presence of WML doubles the risk of dementia and cognitive decline and triples the risk of stroke.[10,12] While the risk of hemorrhagic stroke is not as high as ischemic stroke, it has been suggested to increase by 1.5 times.[13]

Despite various investigations on the pathogenesis and risk factors of WMLs, the relationship between these lesions and migraine remains poorly understood. In this study, we aimed to compare patients with and without lesions to examine the clinical features and laboratory findings that may be risk factors for WML development.

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METHODS

This study included patients who presented to the Neurology Department of Mersin University Medical Faculty in February 2018 with the complaint of headache. Patients with migraine diagnosed according to ICHD-3 Beta criteria were included.[3] Subjects were divided into two groups according to their cerebral MRI findings: 63 patients with WML and 64 patients without WML. Patients younger than 18 or older than 80 years, those with cerebrovascular disease, metabolic disease, or a diagnosis of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy), were excluded.

The study evaluated 63 migraine patients with supratentorial WMLs in cerebral MR T2 and FLAIR (Fluid Attenuated Inversion Recovery) sequences, along with a control group comprising 64 migraine patients without WMLs. Demographic and clinical data, including age, gender, smoking, age of disease onset, duration of migraine disease, migraine attack frequency, attack duration, presence of aura, and hypertension, were collected. Patients were categorized based on monthly attack frequency (less than 2 attacks, 2-5 attacks, and more than 5 attacks), and the relationship between lesions and attack frequency was assessed. Biochemistry tests were conducted, and values for urea, creatinine, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), LDL (low-density lipoprotein) cholesterol, total cholesterol, triglycerides, fasting and postprandial blood sugar, as well as thyroid function were recorded. These laboratory parameters were considered potential initiators of inflammatory processes and ischemic events. The parameters were compared between the two patient groups (with and without WMLs) to determine the risk factors for WML.

Imaging protocol

Cerebral MRI scans were performed on all patients using a 1.5 Tesla MR Imager at the Radiology Department of Mersin University Hospital. T2 and FLAIR MR sequences were obtained for each patient, and the density of supratentorial and cortical lesions was evaluated.

Statistical analysis

Statistical analysis was performed using Jamovi (Version 2.3) [Computer Software. Sydney, Australia]. The Shapiro–Wilk test was used to assess normality of the data. Continuous variables were presented as medians and 25th-75th percentiles (Q_1-Q_3) if they did not follow a normal distribution. Categorical variables were presented as frequency and percentages. The Mann–Whitney U test, a nonparametric test, was used to compare medians of the groups with and without lesions. The relationships between categorical variables were evaluated using chi-square analysis.

Variables with $p < 0.25$ in the univariate analysis were considered potential candidate risk factors for lesion development. The effects of these candidate variables on lesion development were assessed using both univariate and multivariate logistic regression analyses.

Odds ratios (ORs), 95% confidence intervals (CIs), regression coefficients (β), and standard errors for β were calculated. ORs with CIs excluding "1" were considered statistically significant. To analyze the increase in risk associated with a change of 10 years in age and 100 mg/dl in triglycerides (instead of a change of 1 unit in variables with large measurement units), the relevant regression coefficients were multiplied by 10 and 100.

The backward Wald method was used for variable selection in the multivariate logistic regression analysis. The model selection was based on the model Chi-square test statistic. The classification performance of the model was assessed using accuracy values. Statistical significance level (p) was accepted as ≤ 0.05 for all comparisons.

Ethics

This study was initiated with the approval of the local ethics committee of Mersin University Faculty of Medicine on 21.12.2017, under Board Decision No. 2017-356.

RESULTS

Based on brain MRI scans, patients with migraines were divided into two groups: those with WML (63 patients), and those without WML '(64 patients). There were 111 women and 16 men. Overall, 49 (77%) patients in the WML group and 58 (90.6%) in the non-WML group were below the age of 50.

Epidemiological factors and laboratory findings were first evaluated in the WML and non-WML groups. In Table 1, in addition to epidemiological factors such as age, female gender and smoking, our study identified age at migraine onset as a significant factor contributing to the incidence of WML. The median age of patients with WML was significantly higher compared to the median age of those without WML ($p \leq 0.001$). When

patients over the age of 50 were excluded from analysis, the median age of patients with WML in the 18–50-year age group remained significantly higher ($p < 0.001$) than the median age of patients without WML. In this age group, an increase in age by 10 years raised the risk of WML by 3.034 times (OR = 3.034; 95% CI for OR = 1.68–5.46).

WML were found to be statistically significantly more frequent in females than in males ($p = 0.035$). A comparison between the WML and non-WML patient groups revealed a significantly higher median age of migraine onset in the WML group ($p = 0.004$).

In our analysis of duration of migraine disease, attack frequency, attack duration, pain region, and the presence of aura, only the frequency of attacks showed a significant association with WML. (Table 1).

In our evaluation of comorbid symptoms of migraines such as nausea, vomiting, photophobia,

Table 1: Comparison of parameters of WML (+) and WML(-) patients

	WML+ (n=63)	WML- (n=64)	p
Age (Median (Q_1-Q_3))	43 (36-48)	35 (27.25-42)	**<0.001***
Female, n (%)	59 (87.4)	52 (81.3)	**0.035**
Male, n (%)	4 (6.3)	12 (18.8)	
Smoker, n (%)	14 (22.2)	18 (28.1)	0.444
Migraine onset age, (Median (Q_1-Q_3))	30 (20-38)	21.5 (18-31.5)	**0.004***
Duration of disease, (Median (Q1-Q3))	10 (2-23)	8 (3-15)	0.379
Aura, n (%)	37 (58.7)	36 (56.3)	0.777
Attack frequency, n (%)			
1/month	2 (3.2)	10 (15,6)	0.05
>5/month	34 (54)	31 (48.4)	
2-5 month	27(42.99	23 (35.9)	
Headache side			
Unilateral, n (%)	40 (63.5)	48 (75.0)	0.160
Bilateral, n (%)	23 (36.5)	16 (25.0)	
Attack duration (hour) (Median (Q_1-Q_3))	20 (4-48)	24 (4.25-45)	0.825*
Nausea			
Positive n(%)	49 (77.8)	51 (79.7)	0.793
Negative n (%)	14 (22.2)	13 (20.3)	
Vomiting			
Positive n (%)	21 (33.3)	20 (31.3)	0.802
Negative n (%)	42 (66.7)	44 (68.8)	
Photophobia			
Positive n (%)	46 (74.2)	57 (89.1)	**0.031**
Negative n (%)	16 (25.8)	7 (10.9)	
Phonophobia			
Positive n (%)	52 (83.9)	53 (82.8)	0.873
Negative n (%)	10 (16.1)	11 (17.2)	
Hypertension, n (%)	12 (19)	3 (4.7)	**0.012**
Systolic (mmHg) (Median (Q_1-Q_3))	120 (110-132.5)	117 (109.5-120)	0.092
Diastolic, (mmHg) (Median (Q_1-Q_3))	80 (70-85.5)	74 (70-80)	**0.024***

*p value for the Mann-Whitney U test and others for the Chi-square test.

and phonophobia, we found that photophobia was negatively associated with WML (p = 0.031).

The presence of a history of hypertension was a risk factor for the development of WML (p = 0.012). Point systolic and diastolic blood pressure values were measured for all patients, and a significant difference was found in the median values of patients with and without WML only with respect to diastolic blood pressure (p = 0.024) (Table 1).

In our research, Triglyceride, ESR, and free T4 median values were significantly higher in the WML (+) group than the WML (-) group (Table 2). However, according to logistic regression analysis, neither sT4 nor sedimentation was identified as a significant risk factor. Therefore, sT4 and sedimentation were not included in the multivariate analysis.

As seen in Table 1 and Table 2, age, migraine onset age, triglyceride levels, attack frequency per month and gender were significantly associated with developing WML. These were accepted as candidate risk factors for logistic regression analyses. We used multivariate logistic regression analyses to select best risk model (Table 3).

In the multivariate logistic regression (MLR) model, controlling for other variables, the Backward Wald method did not find the effect of hypertension to be statistically significant. In addition, as seen in the MLR analysis results in Table 3, the age of onset of migraine did not have a statistically significant effect on the risk.

DISCUSSION

The aim of this study was to investigate the risk factors associated with WMLs in migraine patients using cerebral MRI. The results revealed several significant associations between the presence of WML with demographic and clinical factors as well as with laboratory findings in migraine patients.

Despite numerous studies, the clinical relevance of WML in migraines remains unknown.[5] In the current study, we analyzed the risk factors for WML and found that higher age and increased age at migraine onset were epidemiological parameters that increased the risk of WML development. Our analysis confirmed the findings of numerous other studies that indicate older age as a risk factor for WML in patients with migraines. The risk of WML increased by 2 times for every 10-year increase in age. When we excluded patients over 50 years of age, it was determined that age increased the risk for WML by 3.034 times. This finding suggests that older migraine patients are more prone to develop WML. However, it is important to note that advanced age is a recognized independent risk factor for WML in the general population.[14]

A study focusing on young patients (age < 50 years) with migraines found no significant difference in terms of gender (p = 0.463) and mean age (p = 0.068)[16,17] with respect to WML prevalence. In contrast, our study identified age as a risk factor for WML in patients below the age of 50, after excluding those above 50 years

Table 2: Comparison laboratory data of WML (+) and WML(-) patients

	WML (+)	WML (-)	p
Fasting blood glucose (mg/dl)	95 (90-100)	92.05(88.75-99.25)	0.400
Postprandial glucose (mg/dl)	98 (9-118)	98 (90-116)	0.283
Urea (mg/dl)	25 (20-29)	23.50 (18.25-29)	0.258
Creatinine (mg/dl)	0.63 (0.58-0.70)	0.63 (0.55-0.74)	0.815
Microalbuminuria (mg/day)	7.25 (3.20-17.01)	6.60 (3.15-15.99)	0.777
TSH (uIU/ml)	1.36 (1.00-2.12)	1.71 (1.03-2.30)	0.656
Free T4 (mg/dl)	15.43 (13.87-16.85)	14.53 (11.27-16.33)	**0.046**
TG (mg/dl)	129 (95-177)	104.50 (71.50-144.75)	**0.017**
LDL (mg/dl)	114 (87-136)	115 (92.50-133.20)	0.912
Total cholesterol (mg/dl)	197 (168-217)	193 (170.50-217.75)	0.691
CRP (mg/dl)	1.8 (0.6-3.7)	2.36 (0.70-4.50)	0.493
ESR (mm/hour)	13 (6 -18)	9 (4-15)	**0.025**

TSH (Thyroid stimulating hormone), T4 (Thyroxine), TG (Triglyceride), LDL (low-density lipoprotein), CRP (C-Reactive protein). p values for the Mann-Whitney U test. All values were summarized by Median (Q_1-Q_3)

Table 3: Multivariate logistic regression results

	Multivariate Logistic Regression		
	β (se)	**OR (%95 CI)**	**P**
Age (years)	0.069 (0.024)	2.00 (1.24-3.19)	0.004
Migraine onset age (years)	0.040 (0.023)	1.50(0.95-2.34)	0.087
Triglyceride	0.008 (0.003)	2.22 (1.23-4.00)	0.014
Attack frequency			
>5/month	2.216 (0.891)	9.17 (1.59-52.54)	0.013
2-5 month	2.056 (0.877)	7.82 (1.40-43.64)	0.019
Gender (Men)	1.593 (0.743)	4.92 (1.14- 21.11)	0.032
Hypertension (+)	---	---	---

se: standard error for β coefficients. p: p values for Wald statistics. *Reference categories for logistic regression analysis are men for gender,* one episode per month for attack frequency, and hypertension positive for hypertension group.

old. It is notable that 85% of the participants in our study were below 50 years of age. Jasem Yousef's study found that patients with WML had a longer disease duration (14.54± 7.76versus. 8.58± 6.49 years, p<0.002).[18] However, our study did not find a significant relationship of WML with the duration of migraine disease. Our study identified age at migraine onset as a risk factor for development of WML, with patients who experienced migraine at a later age having a higher risk of developing lesions. A review of the literature indicates that the relationship between WML and mean age at migraine onset has not been previously evaluated.[16-18]

Our study finds that females have a 5 times higher risk of WML compared to males. The CAMERA study conducted by Kruit *et al*., also reported a higher incidence of deep-seated WML in women compared to the control group as in our study.[15] This gender difference in WML prevalence may indicate potential hormonal or genetic influences on the development of these lesions.

The frequency of migraine attacks has a strong positive association with the risk of WML Patients with 2-5 attacks per month had a 7-fold higher risk, while those with more than 5 attacks per month had a 9-fold higher risk compared to patients with a single attack per month. This association indicates that the burden of migraine attacks may contribute to the development or progression of WML. The literature has demonstrated a positive association between migraine with WML and the frequency of attacks.[15,17] However, it has also been observed that WML is unrelated to the frequency of attacks.[18-20] The CAMERA study revealed a positive correlation between increased attack frequency and WML, and also concluded that the presence of aura does not increase the likelihood of developing WML.[15,21]

In another study involving 65 patients aged 18-50 years, WML was found to be more prevalent in patients with aura.[9] However, we found that attack frequency is a risk factor for WML development, but there is no connection between aura and WML. The presence of common migraine-associated symptoms such as nausea, vomiting, photophobia, and phonophobia was compared between our two study groups, but no significant differences were found.

Hypertension, as well as point systolic and diastolic blood pressure levels were positively associated with WML. However, multivariate logistic regression analysis did not find hypertension to be an independent risk factor for WML. It is known that hypertension is associated with the formation of WML in patients without migraine.[17] Some studies on WML in migraine have excluded patients with hypertension.[22] Therefore, management of hypertension may still be effective for reducing the development of WML in migraine patients.

With respect to laboratory findings, triglyceride levels were significantly associated with the presence of WML. For every 100-unit increase in triglyceride levels, the chance of developing WML doubled. This suggests that dyslipidemia and metabolic factors play a role in the pathogenesis of WML in migraine patients. CRP is a sensitive marker for atherosclerosis and inflammation. Patients with migraine (n = 216) have been found to have significantly higher CRP levels (1.94 ± 2.03 mg/L) compared to healthy controls (n = 216) (0.82 ± 0.58 mg/L; P ≤ .0001).[23] In another study, various blood tests were performed in patients with migraine, including assessments of thyroid stimulating hormone, thyroxine, tri-iodothyronine, homocysteine, uric acid, serum cholesterol,

and LDL. It has been found that WML and blood test levels of hyperhomocysteinemia and subclinical thyroid dysfunction (hyperthyroidism/hypothyroidism) were statistically correlated. However, we found no significant correlation between CRP levels, cholesterol levels and WML ($p>0.005$).[24]

Our study had some limitations. The sample size was relatively small, which may have influenced the statistical power and generalizability of the findings. Also no correlation was studied between the extent/grading of WML with the risk factors tested. Additionally, the cross-sectional design of the study limits the ability to establish causal relationships between the identified risk factors and WML. Longitudinal studies with larger sample sizes are needed to validate these findings and provide more insights into the temporal relationship between risk factors and the development of WML in migraine patients.

In conclusion, this study identified age, female gender, high attack frequency, and elevated triglyceride levels as significant risk factors for the presence of WML in patients with migraine. Additionally, migraine onset age and hypertension were found to correlate with the presence of WML. These findings highlight the importance of considering these factors when assessing the risk of WML in migraine patients and provide insights for potential preventive strategies. Further research is needed to confirm these findings and explore the underlying mechanisms.

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