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White matter hyperintensities and carotid intima media thikness In migraine without aura patients

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Abstract

Background: Migraine is associated with atherosclerosis and white matter hyperintensities. This study aims to evaluate the relationship between white matter hyperintensities and carotid intima-media thickness in patients who have migraines without auras. *Methods***:** The study enrolled 105 patients; of these, 43 patients had migraine without white matter hyperintensity (WMH) and 32 had migraine with WMH. There were also 30 healthy control subjects. The patients were divided into two groups according to whether or not they had WMHs on their brain magnetic resonance imaging (MRI). All subjects, including the control group, underwent brain MRI and carotid ultrasonographic examination to evaluate WMH and carotid intima-media thickness (CIMT), respectively. *Results:* The groups did not differ with regard to demographics and clinical findings. The CIMT was significantly greater in patients who had migraine without WMH than in the control group ($p < 0.001$) and in those who had migraine with WMH than in those who had migraine without WMH ($p = 0.004$)
Conclusion: CIMT values were higher in migraine patients with WMH than in migraine patients without WMH. Migraine patients with WMH may be at a greater risk of developing future vascular events.

Keywords: carotid intima-media thickness, white matter hyperintensity, migraine

INTRODUCTION

Migraine is a common neurovascular disease in the general population, especially in women, and affects daily life activities.[1] Migraine pathophysiology has not been clearly elucidated; however, certain theories exist. The risk of stroke in patients with migraines is higher than in the normal population.[1,2] This risk is even higher in patients who have migraines with aura. The causes are unclear, but the suspected mechanisms include cortical spreading depression, endothelial dysfunction, vasoconstriction, shared genetic defects, cervical artery dissection, and patent foreman ovale.[1,2] There is also a positive relationship between migraine, ischemic heart disease, and myocardial infarction.[3]

Increased carotid intima-media thicken (CIMT) is indicative of subclinical atherosclerosis and is associated with recurrent ischemic stroke.[4] A consistent and robust relationship was found between increased CIMT and MR abnormalities, such as ventricular expansion, sulcal expansion, and increased white matter signal intensity.[5] Migraine is associated with atherosclerosis, and studies show that CIMT increased in patients with migraine.[6,7]

White matter hyperintensities (WMHs) are multiple small lesions that are especially visible in T2 and fluid-attenuated inversion recovery (FLAIR) sequences on MRI. WMHs do not cause mass effects and appear in a healthy population. It seems to be a manifestation of small vessel disease.[8,9] The clinical significance of WMH lesions is not fully understood. One population-based study showed that the presence of silent WMH increases stroke risk independent of other risk factors such as with the increase in CIMT.[10] WMH lesions in migraines, both with and without auras, are increased.[11,12] Although the pathophysiology of WMH in migraine is unclear, focal cerebral hypoperfusion, induced by a migraine attack may affect vulnerable, small, deep-penetrating arteries and cause WMH.[13] Both CIMT and WMH lesions correlate with cognitive complaints, vascular dementia, and stroke.[14]

In our study, we compared the healthy control group and patients who had migraines with and without WMH to determine the differences in CIMT thickness among the three groups.

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METHODS

This prospective, cross-sectional study was conducted from June 2018 to June 2019 at the Neurology Department of Harran University Hospital after obtaining the approval of the local ethics committee. We enrolled 129 subjects (Figure 1); of these, 24 did not meet inclusion criteria or declined to participate in the study and were excluded. We analyzed 105 subjects; 43 had migraine without WMH and 32 who had migraine with WMH as well as 30 healthy control patients. Only patients with migraine without aura were included to form a homogeneous group. The patients were divided into two groups depending on whether they have WMHs on brain MRI. Exclusion criteria were patients <18 and >50 years, with body mass index (BMI) >35, hyperlipidemia, known heart disease, hypertension, diabetes mellitus, oral contraceptive usage, history of the previous stroke, multiple sclerosis, and inflammatory disease. In our study, subjects in the control group (non-migraineurs) had normal brain imaging with no WMHs. Patients provided written informed consent before they participated in the study. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure 90 mm Hg, and/or taking antihypertensive medication, and/or a history of diagnosed hypertension. Diabetes mellitus was defined as fasting serum glucose ≥126 mg/dL (7 mmol/L), non-fasting glucose ≥ 200 mg/dL (11.1 mmol/L), diabetic medications, or a previously established diagnosis. Hyperlipidemia was defined as low-density lipoprotein >160 mg/dL and/or taking a lipid-lowering agent.

Migraine was diagnosed according to the International Classification of Headache Disorders, 3rd edition, diagnostic criteria of migraine without aura.[15] Patients with migraine were evaluated by a single neurologist (M.K.), who determined migraine type, localization of headache, previous use of oral contraceptive pills, pain frequency, duration of pain, duration of migraine, family history, episodic and prophylactic treatments, and pain score of 1–10 according to the visual analogue scale (VAS). The patients' demographic characteristics, such as age, gender, height, weight, and smoking habits, were recorded. Neurological examination findings and laboratory findings were reviewed.

Patients' levels of total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, and hemograms were noted. The BMI was calculated by dividing the patient's weight (kg) with height × height (m^2).

Carotid-intima media thickness measurements

The same neurologist (Ö.K., who had five years of ultrasonography experience and was blinded to migraine diagnosis and clinical data) conducted bilateral ultrasonography examination on the carotid arteries within one month after MRI.

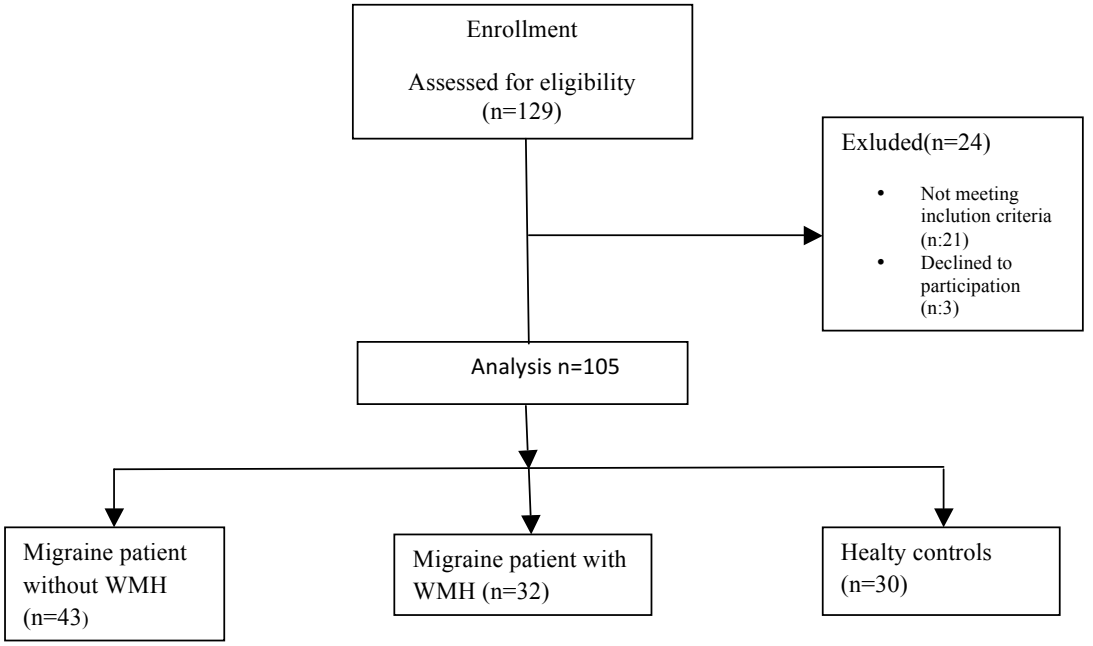

Figure 1. CONSORT flow diagram of three groups (WMH: White matter hyperintensity)

The examinations were performed using the LOGIQ V5 (GE Medical Systems, Wuxi, China) with the same linear-array transducers. In the supine position, bilateral common and internal carotid arteries were examined for the presence of atherosclerotic plaques using grayscale and color Doppler modes. CIMT was defined as the thickness of the hypoechoic layer between the vessel lumen and hyperechoic adventitia. CIMT was measured in the posterior walls of both left and right common carotid artery at 1 cm below the carotid bifurcation outside the regions of plaque, and the average of two values (right wall and left wall) was recorded as the CIMT mean. All measurements were made in inter-ictal periods.

MRI acquisition and analysis

MRI was performed using a 1.5-T scanner (Magnetom Avanto; Siemens, Erlangen, Germany) using a dedicated head coil with patients in the supine position. The scanning protocol included a T2-weighted fast spin-echo (FSE) and a T1-weighted FSE sequence in the axial plane with a FLAIR sequence obtained in both the axial and coronal planes. All images were analyzed by a neurologist (M.K.).

WMHs were defined as the presence of hyperintense lesions on both FLAIR and T2-weighted images, without prominent hypointensities on the T1-weighted image.[16]

WMH were counted on FLAIR images, and patients were grouped into four subgroups according to the number of lesions: 0, 1–3, 4–8, and 9. Patients were further divided into juxtacortical, subcortical/deep white matter, and periventricular subgroups.[17] The WMH locations were classified as frontal, temporal, parietal, occipital, and infratentorial. Figure 2 shows an example of an MRI with WMH.

Statistical analysis

The parameters were analyzed by SPSS for Windows version 23.0. The continuous variables are expressed as median (25^{th}–75^{th} percentile); numbers and percentages were used to express categorical variables. The Mann–Whitney *U* test was used to calculate the differences between continuous variables of two groups. The Chi-square test was used to analyze categorical parameters, and $p < 0.05$ was considered statistically significant.

RESULTS

The study data were compared by dividing the subjects into three groups: control, migraine with WMH, and migraine without WMH. During the study period, 81 migraine patients and 30 healthy controls underwent MRI scans and carotid ultrasonography examination. Six patients were excluded due to incomplete evaluations, and 75 patients were included, of whom 33 patients had WMH. Table 1 shows the clinical and demographic features of the patient and control groups. The

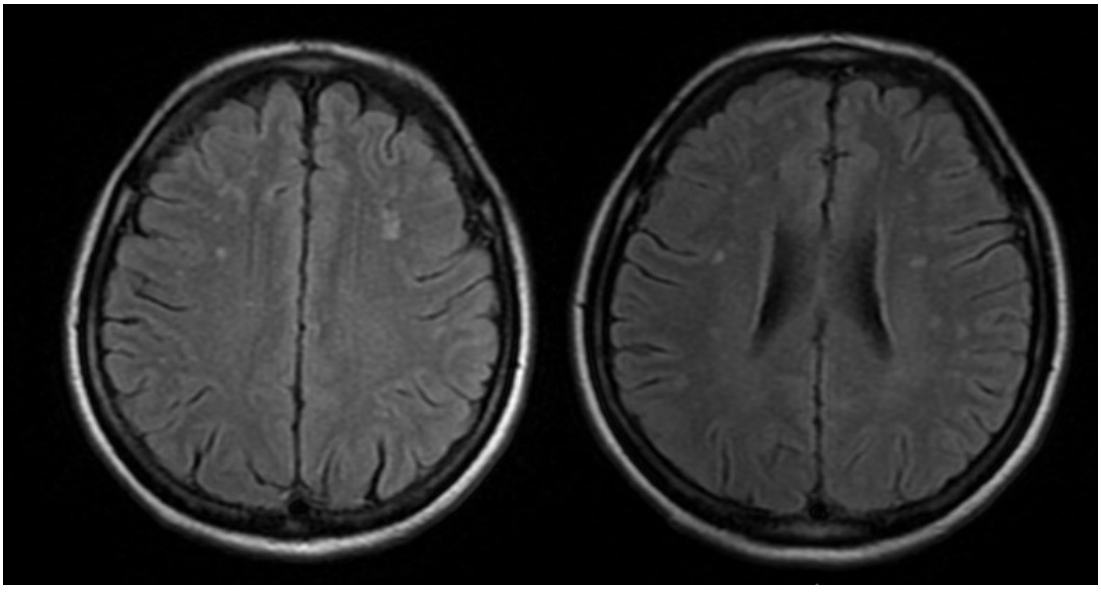

Figure 2. Axial FLAIR MRI images shows small multiple bright focus(white matter hyperintesity) at the bilateral periventricular and centrum semiovale regions.

Table 1: Clinical and demographic features of the patient and control groups

	Patient group			p		
	Control	Migraine without WMH	Migraine with WMH	Control & Migraine with WMH	Control & Migraine without WMH	Migraine without & with WMH
	(n=30)	(n=42)	(n=33)			
	n(%) or median (25th –75th percentile)					
CIMT (mm)	0.39 (0.36-0.41)	0.44 (0.4-0.48)	0.48 (0.44-0.53)	**<0.001**	**<0.001**	**0.004**
Age (years)	31 (27-39)	30.5 (28-36)	36 (30-40)	0.100	1.000	0.057
Female	21 (70%)	35 (83.3%)	25 (75.8%)	0.607	0.180	0.416
BMI (kg/m2)	24.6 (22.27-26.72)	25.55 (23.26-29.3)	24.35 (22.59-28.44)	0.409	0.201	0.725
Smokers	5 (16.7%)	9 (21.4%)	5 (15.2%)	0.869	0.615	0.489
Family History (%)	-	18 (42.9%)	11 (33.3%)	-	-	0.401
Diagnosis time (years)	-	5 (3-10)	5 (2-10)	-	-	0.978
Attack duration (h)	-	24 (12-48)	24 (24-24)	-	-	0.792
Attack frequency (per month)	-	4 (3-10)	5 (3-6)	-	-	0.686
VAS score (number)	-	7 (6-8)	7 (6-8)	-	-	0.080
Attact Treatment	-	35(83.3%)	25(75.8%)	-	-	0.447
Hgb (g/dL)	13.22 (13.22-14.05)	13.22 (12.6-14.1)	13.09 (12.3-13.8)	0.082	0.501	0.285
Cholesterol (mg/dL)	179.55 (164-179.55)	179.55 (164-191)	179.55 (176-183)	0.051	0.243	0.613
LDL (mg/dL)	100.85 (99-107)	100.85 (90-113)	100.85 (100.85-114)	0.394	0.532	0.170
HDL (mg/dL)	48.38 (47-56)	48.38 (43-54)	48.38 (46-54)	0.297	0.210	0.796
Triglyceride (mg/dL)	138.5 (89-141)	140.19 (78-149)	140.19 (91-140.19)	0.792	0.797	0.867

WMH: White matter hyperintensities; CIMT: Carotid intima-media thickness; VAS: Visual analogue scale; BMI: Body mass index; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Table 2: Linear regression analyses to show independent effect of migraine on CIMT increase

	Odds Ratio (95%CI)	p
Migraine	0.070 (0.039-0.101)	<0.001
Age (years)	0.004 (0.003-0.006)	<0.001

median age of migraine patients without WMH was 30.5 (28–36) years, that of those with WMH was 36 (30–40) years, and that of the control group was 31(27–39) years.

A comparison of clinical and demographic findings among the study groups indicated similar findings. There were no significant intergroup differences with regard to age, percentage of smokers, sex, and BMI. Lipid profile, VAS score, hemoglobin values, family, migraine duration, localization of headache, the average number of headaches per month were similar between the two groups ($p > 0.05$) (Table 1). Age was similar between the groups, but the p-value tended to reach statistical significance ($p = 0.057$). Therefore, linear regression analysis was performed to calculate the effect of migraine on CIMT. As a result, age was positively correlated with an increase in CIMT, but migraine was an independent factor affecting CIMT (Table 2).

In the group of patients who had migraine with WMH, 13 (39.4%) had 1–3 lesions, 8 patients (24.2%) had 4–8 lesions, and 12 patients (36.4%) had >9 lesions. Regarding WMH localization, 7 (21.2) patients had juxtacortical, 29 (87%) patients had subcortical, 4 (12.1%) patients had periventricular, 30 (90.9%) had frontal, 1 (3%) patient had temporal, and 8 (24.3%) patients had parietal WMH. Table 3 summarizes the MRI findings of the patient group. On evaluating the relationship between lesion burden (number of lesions on MRI) in MRI and attack frequency, VAS, and attack duration, there was no difference between lesion burden and migraine severity (attack frequency, VAS, and attack duration). (Table 4)

Carotid ultrasound findings showed that CIMT was greater in patients who had migraine without WMH than in the control group ($p < 0.001$), and CIMT was greater in patients who had migraine with WMH than in those who had migraine without WMH ($p = 0.004$) (Table 1) (Figure 3)

DISCUSSION

In this study, we aimed to investigate the relationship between CIMT and WMH in patients with migraine and compared them with the control group. To our knowledge, although some reports have correlated CIMT values with patients who have migraine, no study has investigated CIMT, migraine, and WMH lesions. We found that CIMT

Table 3: MRI findings of the migraine with WMH patients group

	n(%)
Number of lesion	
None	-
1-3 lesions	13 (39.4%)
4-8 lesions	8 (24.2%)
9≥	12 (36.4%)
Localization of Lesions*	
Justacortical	7 (21.2%)
Subcortical deep	29 (87.9%)
Periventricular	4 (12.1%)
Frontal	30 (90.9%)
Temporal	1 (3%)
Parietal	8 (24.2%)
Occipital	-

*: There were more than one localization, percentages were calculated by patient number.

Table 4: Relationship between WMHs numbers on MRI and severity of the migraine

	Number of lesion			p		
	1-3 lesions (n=13)	4-8 lesions (n=8)	9≥ lesions (n=12)	1-3 & 4-8 lesions	1-3 & 9≥ lesions	4-8 & 9≥ lesions
Attack frequency (per month)	4 (2-20)	4 (2-15)	6 (2-15)	0.794	0.134	0.159
Attack duration (h)	24 (4-72)	24 (4-24)	24 (4-72)	0.105	0.930	0.199
VAS score (number)	6 (4-9)	7 (5-9)	7 (5-8)	0.416	0.596	0.691

VAS : Visual analogue scale

was significantly higher in patients with migraines with/without WMH than in healthy controls (p< 0.001, p < 0.001, respectively). Furthermore, we determined that CIMT values were higher in migraine patients with WMH compared with migraine patients without WMH (p = 0.004).

In our study, to obtain more accurate data, we tried to exclude known factors contributing to atherosclerosis that might affect the presence of WMH and CIMT values. There was no statistical difference between the three groups in terms of demographic characteristics (Table 1). Age, on the other hand, tended to have statistical significance between groups (P = 057). In the linear regression analysis, we found that migraine was an independent factor affecting CIMT increase (Table 2).

The increased CIMT, which is an indicator of subclinical atherosclerosis and is easily evaluated using ultrasonography, is an independent, powerful predictor of future vascular events.[18,19] Therefore, detecting the increase may be helpful in terms of monitoring and precautionary measures. Although there are conflicting results in studies on CIMT in migraine, the weight of the evidence is that it is increased in migraine patients.[6,20] A recent meta-analysis indicated increased CIMT in migraine patients.[7] Differences in results may be due to differences in clinical characteristics, age, gender, migraine type, and study group distribution. Our study group consisted of mostly female patients who were aged 18–50 years and had migraine without aura.

Although WMH lesions are not migraine-

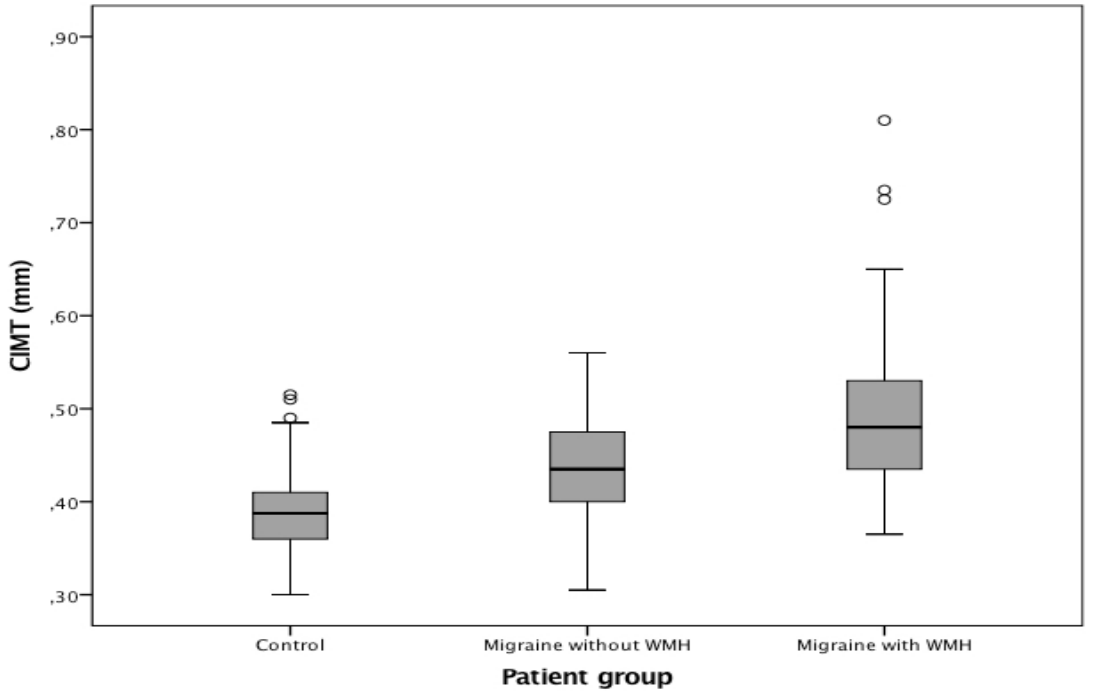

Figure 3. Error Bar diagram for mean CIMT measurements according to study group. CIMT=Carotid intima-media thickness WMH= white matter hyperintensity.

specific, the incidence of WMH lesions in migraine with and without aura is higher than in the normal population.[13,21] The clinical significance of these lesions in migraine is unknown. However, these lesions increase the risk of stroke in the normal population.[22] Although its pathophysiology in migraine is unclear, microvascular ischemic disturbance, migraine attack-related oligemia, and focal hypoperfusion may affect vulnerable, small, penetrating arteries and cause these lesions.[13] In another study, the hypoperfusion theory did not fully explain WMH pathophysiology, and a multifactorial etiology was suggested for these lesions.[23] Vasoconstrictor agents used to treat migraine attacks may cause also these lesions.[24] Our patients did not receive prophylactic medication for six months prior to the study. However, in our patient group, we could not report the attack treatment in detail.

A previous study evaluated the relationship between WMH and CIMT in the elderly population and reported that increased CIMT was related to cerebral WMH lesions, independent of demographics and traditional vascular risk factors. Therefore, it was evident that atherosclerosis could contribute to WMH lesions.[14] Unlike this study, our study group consisted of patients with migraine who were younger.

Although the relationship between migraine and atherosclerosis is controversial, many studies support this relationship.[25] The reason for this relationship has not been fully elucidated, but inflammation is involved in the pathophysiology of both atherosclerosis and migraine.[25-27] Inflammation-induced thrombosis may cause microvascular damage, which seems to result in WMH.[28] Another population-based study indicated that WMH pathophysiology might result from endothelial dysfunction caused by chronic subclinical inflammation.[29] The relationship between migraine, increased CIMT, and WMH may be explained by inflammation.

A study evaluating the clinical features of migraine in terms of WMH presence showed that family history, episode frequency, and increased age were related to WMH lesions.[30] In contrast, another study found that the frequency and duration of episodes are associated with the presence of lesions.[31] The authors of this study linked this to oligemia and hypoperfusion theory. We evaluated our patients in terms of clinical features, but we did not find a significant difference between the two groups (Table 1). Similar to our results, there are reports in which clinical features do not affect the presence of WMH.[23] This may be due to the difference in the distribution of the study group. Our study group was similar to studies that did not find clinical differences with the presence of WMH lesions in terms of age and other demographic characteristics.[23] When patients who had migraine with WMH were examined in terms of lesion distribution and location, MRI lesions were consistently reported in the literature[30,32] (Table 3). When we evaluated the relationship between lesion burden in MRI, attack frequency, VAS, and attack duration, there was no difference between lesion load and existing migraine characteristics (Table 4).

This study has several limitations. First, our study is cross-sectional, and there is no follow-up in terms of CIMT increase or WMH lesion progression. Second, we evaluated lesion distribution and lesion burden in our study but did not investigate their effects on CIMT. Finally, the number of patients included in our study was limited. We could not report the patients' attack treatment in detail (triptan vs. non-steroidal anti-inflammatory drug).

In conclusion, WMH may be the manifestation of small vessel disease and ischemic microvascular disturbance. The fact that CIMT was significantly increased in the migraine without WMH group compared to the control group suggests a correlation between migraine and the atherosclerotic process. On the other hand, the increased CIMT in the group with WMH compared to without WMH suggests a more active atherosclerotic process in the group positive for lesions. This finding may help us understand the pathophysiology of these lesions in migraine. Our study results suggest that patients who have migraine with WMH may have a more potent atherosclerotic process and are at greater risk of future vascular events. Our treatment choice and approach to patients who have migraine with WMH may be differentiated in the light of future large studies when compared to migraine patients without WMH.

DISCLOSURE

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