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Research Article

ACE I/D and MTHFR C677T Gene Polymorphisms and Matrix Metalloproteinase-9 Gene Expression in Migraine Patients with and without Aura and Correlation with Cranial Magnetic Resonance Imaging Findings: A Case-Control Study

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Summary

Aim: To investigate methylenetetrahydrofolate reductase (MTHFR) C677T and angiotensin converting enzyme (ACE) I/D gene polymorphisms and matrix metalloproteinase 9 (MMP-9) gene expression in migraine patients and correlation with cranial magnetic resonance imaging (MRI) findings.
Methods: Migraine patients with (n=50) and without aura (n=50) and age- and gender-matched healthy individuals (n=100) were included. MTHFR C677T and ACE I/D gene polymorphisms and MMP-9 gene expression were explored in the blood samples. Volumes of hyperintense lesions detected on MRI were calculated.
Results: No significant difference was determined among the migraine patients with and without aura and controls regarding MTHFR C677T and ACE I/D genotype distribution and MMP-9 gene expression. Comparing all migraine patients with controls, the rate of ACE I/D genotype was higher in the patients, whereas DD genotype was higher in the controls. The number and volume of MRI lesions were significantly higher in the migraine patients with aura as compared to the controls. The number of lesions was higher in ACE DD genotype group than in the ID genotype group.
Conclusions: Migraine was a risk factor for silent hyperintense cerebral lesions; however, the role of MTHFR C677T and ACE I/D gene polymorphism and MMP-9 gene expression in migraine pathophysiology remained unresolved.

Key words: Migraine, ACE I/D, MTHFR C677T, MMP-9, cranial MRI

Auralı ve Aurasız Migren Hastalarında ACE (I/D) ve MTHFR C677T Gen Polimorfizmleri, Matrix Metalloproteinaz-9 Gen Ekspresyonu ve Kranial Manyetik Rezonans Görüntüleme Bulguları ile Korelasyonu

Özet

Amaç: Auralı ve aurasız migren tanılı hastalarda metilentetrahidrofolat redüktaz (MTHFR) C677T ve anjiotensin converting enzim (ACE) I/D gen polimorfizmini, matrix metalloproteinaz 9 (MMP-9) gen ekspresyonunu ve kranial manyetik rezonans görüntülemede (MRG) saptanan patolojik bulgularla korelasyonunu araştırmak amaçlandı.

Yöntemler: Erişkin 50 auralı migren ve 50 aurasız migren hastası ile yaş ve cinsiyet olarak eşleştirilmiş 100 normal kişi kontrol olarak çalışmaya alındı. Hastalardan atak arası dönemde olmak üzere tüm katılımcılardan alınan kan örneklerinde MTHFR C677T ve ACE I/D gen polimorfizmi ve MMP9 gen ekspresyonu araştırıldı. MRG'de saptanan tüm hiperintens lezyonlar işaretlendi ve hacimleri hesaplandı.
Bulgular: Auralı, aurasız migren ve kontrol grupları arasında MTHFR C677T ve ACE (I/D) genotip dağılımları ile MMP-9 gen ekspresyonu açısından anlamlı fark saptanmadı. Tüm migrenliler birlikte değerlendirildiğinde migrenli grupta ACE I/D genotipi, kontrol grubunda DD genotipi yüksek oranda bulundu. MRG lezyonlarının sayısı ve hacmi auralı grupta kontrol grubuna kıyasla anlamlı yüksek bulundu. ACE DD genotip grubunda lezyon sayısı ID grubuna kıyasla fazla idi.
Sonuç: Migrenin sessiz serebral hiperintens lezyonlar açısından bir risk faktörü olduğu; MTHFR C677T, ACE I/D gen polimorfizminin ve MMP-9 gen ekspresyonunun migren patofizyolojisindeki yeri hakkında kesin sonuca varılamadığı söylenebilir.

Anahtar Kelimeler: Migren, anjiotensin converting enzim I/D, metilentetrahidrofolat redüktaz C677T, matrix metalloproteinaz 9, kranial manyetik rezonans görüntüleme

INTRODUCTION

Migraine is a frequent and complex disease of central nervous system with indefinite etiology. The facts that it has various clinical characteristics, there are many triggering factors, and there are various biological and functional abnormalities have led to the generation of numerous theories on the pathophysiology of migraine[13]. Genetic, neurophysiological, radiological, and biochemical analyses are necessary methods to verify the diagnosis, to illuminate pathophysiology, and to develop therapeutic options in migraine patients. Hereditary characteristics of migraine have accelerated genetic investigations in recent years and identification of polymorphism and investigation of genetic biomarkers have been important subjects of researches performed to illuminate the pathophysiology[5,13]. Within this context, studies on the relationship of migraine with methylenetetrahydrofolate reductase (MTHFR) C677T and angiotensin converting enzyme (ACE) I/D gene polymorphisms and matrix metalloproteinase-9 (MMP-9) gene expression have been conducted.

MTHFR is an enzyme with an important role in folate metabolism and with a decrease in its activity, plasma homocystein concentration is increased. Hyperhomocysteinemia is associated with susceptibility to thrombosis, arterial diseases, and stroke and triggers migraine development by sensitizing dura mater and cerebral arteries. For these reasons, MTHFR C677T gene polymorphism has been suggested as a risk factor for migraine[17]. ACE, which is synthesized in the vascular endothelial cells, regulates blood pressure by causing vasoconstriction and dilation and, owing to this property, it is thought that it may have a role in migraine pathophysiology and that ACE I/D polymorphism may be a risk factor for migraine[14]. Neuroinflammatory process occurs during migraine attack due to alteration in the function of blood-brain barrier. It has been observed that proteolytic MMP-9, which has destructive properties on basement membranes of cerebral arteries, has also a role in the 'cortical spreading depression' model[7].

Presence of white matter lesions, which are considered as the risk factor for stroke, has been demonstrated in magnetic resonance imaging (MRI) studies conducted in migraine patients[29]. Migraine history was suggested as a risk factor for stroke in a large epidemiological study[20].

In the present study, it was planned to assess genetic properties that might have

been associated with migraine pathophysiology and to evaluate MRI results. For this purpose, it was investigated MTHFR C677T and ACE I/D gene polymorphisms and MMP-9 gene expression in migraine patients with and without aura and their correlation with pathological findings detected on cranial MRI.

MATERIAL AND METHODS

Patient

The present study was designed as case-control study. The study comprised 50 migraine patients with aura and 50 migraine patients without aura presented to the outpatient clinic of Neurology Department of Ege University Medical Faculty. All of the patients were aged between 16 and 55 years and fulfilled the diagnostic criteria published by International Society of Headache in 2004[8]. Among subjects presented to the same outpatient clinic, age- and gender-matched 100 subjects constituted the control group. Patients with cardiovascular and cerebrovascular diseases, malignancy and inflammatory bowel disease, those were smoking, and those were receiving vitamin B12 and folic acid replacement therapies were excluded. Ethics Committee approval of Ege University Medical Faculty was obtained for the study. Informed consent was obtained from all participants.

Participants were evaluated by two neurologists at different times; their demographic features and medical histories were recorded, neurological examination was performed, and visual analogue score (VAS) was measured in migraine patients.

Laboratory measurements

Fasting blood sample was obtained from antecubital veins of all participants in the morning (during interictal period for migraine patients). MTHFR C677T and ACE I/D gene polymorphisms were analyzed by real-time PCR method in the DNA isolated from blood containing EDTA. RNA was isolated from blood samples to detect MMP-9 gene expression and SYBR Green-based real-time PCR protocol was performed.

Magnetic Resonance Imaging

Cranial MRI of the patients was performed using 1.5 Tesla MRI scanner (Siemens Symphony MAESTRO Class 2005, Enlargen, Germany) in axial FLAIR sequences (TR: 10.000 msec, TE: 117 msec, slice: 40, dismis factor: 0, phase direction: right-left, thickness: 4mm, faw: 230mm, matrix: 224x256). FLAIR images were converted into DICOM-3 using JIM 4.0 program (Xinapse Systems, Colchester, UK). After all hyperintense lesions were marked by ROI (region of interest) technique, volumetric value was automatically calculated in mm^3.

Following examinations and laboratory tests were performed for the patients with multiple hyperintense lesions: carotid-vertebral artery Doppler ultrasound, cardiologic examination, ECG, transthoracic ECHO, and laboratory analyses including total cholesterol, HDL, LDL, triglyceride, fasting blood glucose, HbA1c, fibrinogen, D-dimer, protein C, protein S, anti-thrombin 3, erythrocyte sedimentation rate, CRP, vasculitis markers (ANA, C-ANCA, P-ANCA, F-ANCA, anti-DS DNA, RF, anti-RO, anti-LA, anticardiolipin IgG and IgM, anti-SCL70, anti B2 glycoprotein IgG, IgM, IgA), and factor V Leiden mutation. The results of these examinations and tests were found to be normal. Thus, probability of occurrence of multiple hyperintense lesions due to vascular risk factors was minimized.

Statistical analysis

The Predictive Analytics Software (SPSS Inc., Chicago, IL, USA) version 18.0 for Windows was used for statistical analysis. Analyses were performed using chi-square test (Fisher's Exact Test), Mann-Whitney U Test, Kolmogorov-Smirnov Test, Shapiro-Wilk Test, and Spearman's rho

correlation test. No adjustments were performed for multiple comparisons for the analyses of patient- and disease-related secondary study parameters. For pairwise comparisons within each parameter, however, the appropriate post-hoc methods were used.

RESULTS

There was no significant difference among the study groups (migraine with aura, migraine without aura, and control groups) in terms of age and gender. The rate of patients with family history of migraine was higher in the migraine groups with and without aura as compared to the control group. While no difference was observed between the migraine groups in terms of age at onset of disease and duration of disease, annual number of attacks was higher in the migraine group without aura and VAS was higher in the migraine group with aura (Table 1).

No significant difference was determined among the groups in terms of MTHFR C677T and ACE (I/D) genotype distribution and MMP-9 gene expression (Table 2). Comparing overall migraine patients (with and without aura) with the control group, no significant difference was also determined in terms of MMP-9 gene expression and MTHFR C677T polymorphism (p=0.712 and p=0.349, respectively). With regard to ACE I/D polymorphisms, ID genotype was significantly higher in overall migraine patients, whereas DD genotype was significantly higher in the control group (p=0.037).

With regard to MTHFR C677T gene allele, no significant difference was determined among three groups in terms of number of C and T alleles (p=0.382); there was also no significant difference between the overall migraine patients and the control group (p=0.168). Evaluating the ACE gene allele, no significant difference was determined among three groups in terms of number of I and D alleles (p=0.634); there was also no significant difference between the overall migraine patients and control group (p=0.634). All polymorphisms except for MTHFR C677T polymorphism in the migraine with aura group satisfied the Hardy-Weinberg equilibrium.

Characteristics of MRI lesions are summarized in Table 3 and MRI samples in migraine cases are demonstrated in Figures 1 and 2. Number and volume of MRI lesions were different among the study groups; paired comparisons revealed that number and volume of the lesions were higher in the migraine with aura group as compared to the control group (p>0.001 for each). It was attracted attention that the number of lesions with multiple locations was higher in the migraine with aura group. In terms of vascular localization, number of multiple artery areas was higher in the migraine with aura group.

Correlation analysis revealed no significant correlation between MMP-9 gene expression and number and volumetric value of lesions detected on MRI in each study group (Table 4).

No difference was determined among the MTHFR genotype groups in all migraine patients in terms of number and volume of lesions. However, there was a significant difference among the ACE genotype groups regarding number and volume of lesions. Number of lesions was higher but volume of lesions was lower in DD genotype group as compared to ID genotype group (Table 5).

Table 1. General characteristics of the study groups

	Migraine with aura group n=50	**Migraine without aura group n=50**	**Control group n=100**	**p**
Age, year	32.48±11.18	31.96±8.18	32.57±7.28	0.759
Gender				
Male	13 (26.0)	11 (22.0)	28 (28.0)	0.732
Female	37 (74.0)	39 (78.0)	72 (72.0)	
Family history of migraine	22 (44.0)	16 (32.0)	2 (2.0)	**<0.001**
Age at onset of migraine	23.48±9.35	25.18±7.13	-	0.134
Duration of migraine	9.0±9.42	6.78±5.47	-	0.703
Annual number of attacks	38.74±34.29	57.56±29.44	-	**0.001**
Visual analogue scale score	8.26±0.63	7.64±0.78	-	**<0.001**

Data are presented as mean ±standard deviation or number (%), where appropriate.

Table 2. Genetic results of the study groups

	Migraine with aura group n=50	**Migraine without aura group n=50**	**Control group n=100**	**p**
MMP-9 gene expression	5.73±22.20	2.86±7.26	1.99±4.77	0.764
MTHFR C677T genotype				
CC genotype	22 (44.0)	17 (34.0)	49 (49.0)	
CT genotype	19 (38.0)	30 (60.0)	42 (42.0)	0.067
TT genotype	9 (18.0)	3 (6.0)	9 (9.0)	
ACE I/D genotype				
II genotype	6 (12.0)	4 (8.0)	16 (16.0)	0.129
ID genotype	30 (60.0)	29 (58.0)	41 (41.0)	

DD genotype	14 (28.0)	17 (34.0)	43 (43.0)	

Data are presented as mean ±standard deviation or number (%), where appropriate.
MMP-9, Matrix metalloproteinase 9; MTHFR, Methylenetetrahydrofolate reductase; ACE, Angiotensin converting enzyme

Table 3. Characteristics of the lesions detected on magnetic resonance imaging

	Migraine with aura group n=50	**Migraine without aura group n=50**	**Control group n=100**	**p**
Number of lesions	2.98±6.63[c]	0.78±3.22	0.17±0.67[a]	**<0.001**
Lesion volume (mm^3)	106.46±249.12[c]	32.78±113.15	5.40±19.29[a]	**<0.001**
Location of lesion				
No lesion	33 (66.0)	42 (84.0)	91 (91.0)	
Frontal	0 (0.0)	0 (0.0)	1 (1.0)	
Parietal	6 (12.0)	4 (8.0)	7 (7.0)	
Temporal	0 (0.0)	0 (0.0)	1 (1.0)	-
Occipital	0 (0.0)	0 (0.0)	0 (0.0)	
Multiple locations	11 (22.0)	4 (8.0)	0 (0.0)	
Vascular location				
No lesion	33 (66.0)	42 (84.0)	91 (91.0)	
Anterior cerebral artery	0 (0.0)	0 (0.0)	0 (0.0)	
Median cerebral artery	7 (14.0)	2 (4.0)	6 (6.0)	
Posterior cerebral artery	0 (0.0)	0 (0.0)	1 (1.0)	-
Multiple Arterial areas	8 (16.0)	3 (6.0)	0 (0.0)	
Border Zone	2 (4.0)	3 (6.0)	2 (2.0)	

Data are presented as mean ±standard deviation or number (%), where appropriate.
[a] Different from migraine with aura group
[c] Different from the control group

Table 4. Correlation analysis between MMP-9 gene expression and number and volume of lesions

	p	r
Migraine patients with aura		
Lesion number	0.099	-0.236
Lesion volume	0.103	-0.234
Migraine patients without aura		
Lesion number	0.964	0.006
Lesion volume	0.904	0.018
Control group		
Lesion number	0.298	-0.105
Lesion volume	0.311	-0.102

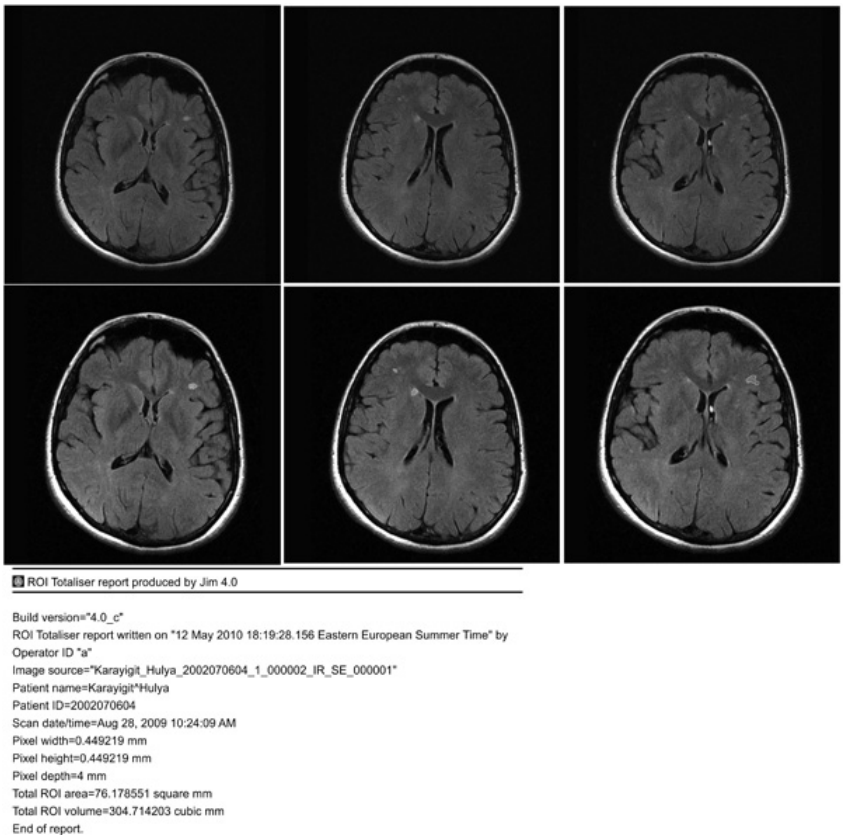

Figure 1: *MRI sample of a case diagnosed with migraine with aura*

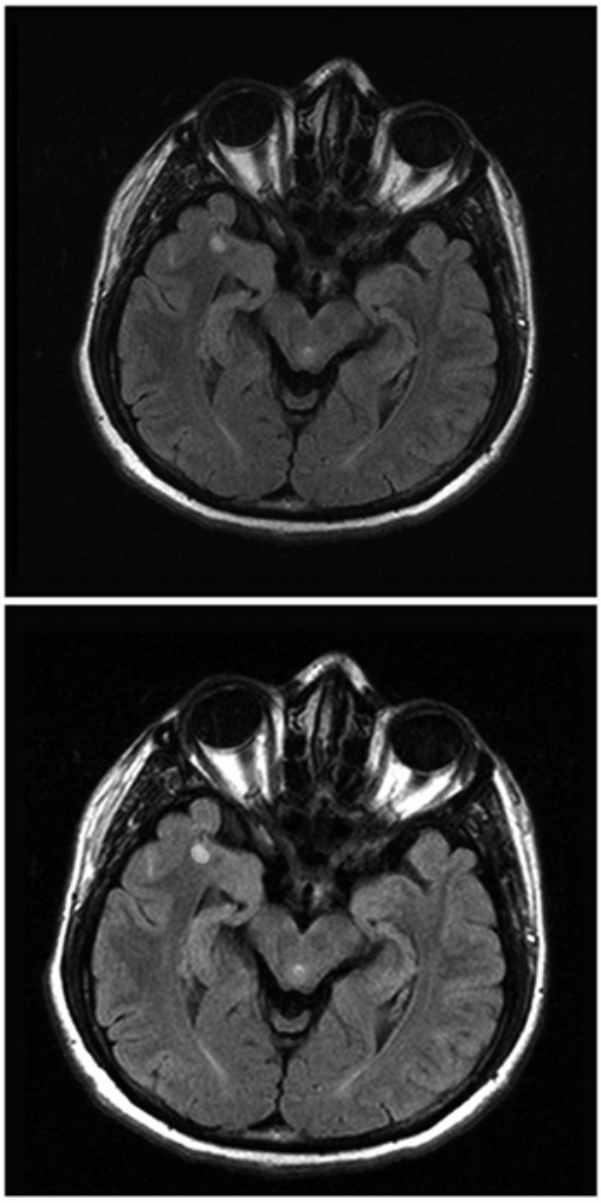

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Figure 2: *MRI sample of a case diagnosed with migraine without aura*

Table 5. Number and volume of lesions in MTHFR and ACE genotype groups of migraine patients

	MTHFR genotype			
	CC	**CT**	**TT**	**p**
Lesion number	1.8±4.8	2.1±6.2	1.1±2.6	0.775
Lesion volume (mm^3)	58.5±137.4	82.0±241.3	55.2±158.4	0.768
	ACE Genotype			
	II	**ID**	**DD**	**p**
Lesion number	1.4±3.1	1.8±6.2[b]	2.1±4.1[a]	**0.019**
Lesion volume (mm^3)	44.0±85.8	73.1±230.1[b]	71.3±148.3[a]	**0.028**

MTHFR, Methylenetetrahydrofolate reductase; ACE, Angiotensin converting enzyme
[a] Different from ID group
[b] Different from DD group

DISCUSSION

In the present study, MTHFR C677T and ACE I/D gene polymorphisms and MMP-9 gene expression were investigated in migraine patients. Nevertheless, conflicting results have been reported in the studies investigating the relation between MTHFR C677T polymorphism and migraine. In their population-based study, Scher et al.[24] reported that TT genotype was associated with migraine with aura. Azimova et al.[3] reported that migraine with aura was more prevalent in T allele carriers as compared to those with CC genotype. An et al.[2] demonstrated that frequency of T allele was higher in migraine patients without aura as compared to the controls. Ferro et al.[6] determined no difference among migraine with aura, migraine without aura, and control groups in terms of MTHFR C677T polymorphism. They also observed no increase in T allele frequency in migraine with aura group. Joshi et al.[11] demonstrated no difference among migraine with aura, migraine without aura, and control groups in terms of MTHFR C677T gene polymorphism and allele analysis. In meta-analyses including many studies, it was concluded that there was a relationship between MTHFR C677T and migraine with aura and there were differences among ethnic groups[23,27]. In the present study, no significant difference was determined among migraine with aura, migraine without aura, and control groups in terms of MTHFR C677T gene polymorphism (p=0.067). When overall migraine patients were compared with the control group, no difference was observed in terms of polymorphism (p=0.349). Allele analysis revealed no difference both among three groups and between the overall migraine patients and control group.

Since migraine is associated with cerebral vascular circulation, it is considered to be associated with ACE gene. The fact that ACE inhibitors reduce the frequency of attacks corroborates this consideration[25,26]. It has been determined that serum ACE concentration is the highest in DD genotype, moderate in ID genotype, and the lowest in II genotype[22].

It has been demonstrated that ACE DD genotype enhances the frequency of attacks in migraine patients without aura[21]. Kara et al.[12] reported a relation between ACE I/D polymorphism and migraine and suggested that DD genotype was not associated with susceptibility to migraine but D allele might have been a risk factor for migraine development. Horasanlı et al.[9] reported that DD genotype might have been a risk factor for migraine with aura. Nevertheless, there are studies demonstrating that ACE I/D polymorphism is not associated with migraine[1,30]. There is also a study reporting that ACE DD variant plays a protective role in migraine patients[18]. In the present study, no significant difference was found among the migraine with aura, migraine without aura, and control groups in terms of ACE I/D gene polymorphism (p=0.129). Comparing overall migraine patients with the control group, while ID genotype was found to be significantly higher in the migraine patients, DD genotype was higher in the control group (p=0.037). Thus, it can be said that ID genotype is a risk factor for migraine development, whereas DD genotype is protective against migraine. Analyzing ACE gene allele, no significant difference was observed among three groups in terms of number of I and D alleles (p=0.634); there was also no significant difference between the overall migraine patients and control group (p=0.634).

Increased MMP-9 activity has been demonstrated in migraine patients whether they have aura or not[16]. Imamura et al.[10] determined that blood level of MMP-9 was significantly higher in the migraine group compared to the control group. However, no significant difference was obtained between migraine with aura and migraine without aura groups. They also reported that MMP-9 level showed no correlation with age, disease duration, frequency and duration of attacks, and treatment for pain. In the present study, no significant difference was determined among three groups, as well as between the overall migraine patients and control group in terms of MMP-9 gene expression.

In a meta-analysis evaluating the results of population-based and clinical studies, it was concluded that structural alterations in the brain, such as white matter abnormality and infarction-like lesions, and volumetric changes in grey and white matters were more prevalent in migraine patients as compared to the control groups[4]. The population-based CAMERA study[15], in which brain lesions were evaluated by MRI in migraine patients, demonstrated the relation of migraine with the presence of subclinical posterior circulatory infarction and white matter lesions. In the same study, it was observed that 65% of subclinical brain infarctions were in the posterior circulatory area with the majority (85%) located in the cerebellum. It was observed that most of the infratentorial infarction-like lesions (88%) were located in the cerebellar vascular border zone. The prevalence of border zone lesions was found different in the groups; 0.7% in the control group, 2.2% in the migraine without aura group, and 7.5% in the migraine with aura group. In the present study, the fact that all lesions showed localization in the anterior circulatory areas, particularly multiple areas in the migraine with aura group, might be explained in the ways that hypoxia/ischemia could occur in multiple areas while cortical spreading depression spreads over entire cerebrum beginning from posterior towards to the anterior hemispheres or that hypoxia/ischemia might appear in different localizations of cerebrum during recurrent attacks. Probable ischemic-originated hyperintense lesions were detected in the cortical and subcortical white matter on MRI in 17 (34%) patients in the migraine with aura group, in 8 (16%) patients in the migraine without aura group, and in 9 (9%) subjects in the control group. As it was expected because of above-mentioned pathophysiological mechanisms, these

lesions were significantly in favor of migraine patients with aura in terms of number and volumetric load. Presence of these lesions in the group without aura could be explained by the hypothesis that silent cortical spreading depression model, which clinically do not cause aura, might have a role in the pathophysiology of migraine without aura. Since other basic vascular risk factors were excluded by means of additional examination and laboratory tests, it could be said that migraine, primarily migraine with aura, might be an independent risk factor for subclinical cerebral hyperintense lesions and probable stroke likely to appear in the future.

With regard to the relationship between number and volumetric values of MRI lesions and ACE I/D gene polymorphism, a difference was observed between ACE genotype groups in the overall migraine patients in terms of number and volume of the lesions. In DD genotype group, number of lesions was higher and volume of lesions was lower as compared to the ID group. It could be said that DD genotype causes subclinical hyperintense MRI lesions and may pose a risk for probable ischemic stroke. DD genotype's being a risk factor for stroke has been corroborated by other studies[19,28]. In the present study, no significant correlation was determined between number and volumetric values of MRI lesions and MMP-9 gene expression. No difference was determined between MTHFR genotype groups in overall migraine patients in terms of number and volume of the lesions.

The limitation of the present study was the limited number of patients with regard to the frequencies of MTHFR C677T and ACE I/D gene polymorphisms in the general population. Another limitation was the lack of adjustments for multiple comparisons for the analyses of patient- and disease-related secondary study parameters.

In conclusion, migraine was a risk factor for silent hyperintense cerebral lesions. No definite conclusion could have been made on the role of MTHFR C677T, ACE I/D gene polymorphisms and MMP-9 gene expression in the pathophysiology of migraine. Further studies that will be conducted in larger population are needed to illuminate pathophysiology and to develop potential medical and genetic therapies.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Article Highlights

• No significant difference was determined among the patients with aura and without aura and control group in terms of MTHFR C677T and ACE (I/D) genotype distribution and MMP-9 gene expression.

• With regard to ACE I/D polymorphisms, ID genotype was significantly higher in overall migraine patients, whereas DD genotype was significantly higher in the control group.

• Number and volume of MRI lesions were higher in the migraine with aura group as compared to the control group.

• Number of MRI lesions was higher in ACE DD genotype group as compared to ID genotype group.

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