Investigation of the relationship between thrombophilic disorders and brain white matter lesions in migraine with aura*

Investigación de la relación entre los trastornos trombofílicos y las lesiones de la sustancia blanca cerebral en la migraña con aura

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Abstract

Background Migraine is associated with several genetic or acquired comorbidities. Studies conducted in recent years emphasize that the frequency of thrombophilia is high in migraine, especially migraine with aura (MA). Similarly, the presence of white matter lesions (WMLs) on brain magnetic resonance imaging (MRI) scans has been associated with migraine for many years.

Objective Based on the knowledge that both WMLs and thrombophilia variants are frequently observed in MA, we aimed to investigate whether there is a relationship between genetic thrombophilia and the presence of WMLs in these patients.

Methods The levels of proteins S and C, antithrombin III activities, activated protein C (APC) resistance, antiphospholipid immunoglobulin G/immunoglobulin M (IgG/IgM) and anticardiolipin IgG/IgM antibodies were investigated in 66 MA patients between the ages of 18 and 49 years who presented no cardiovascular risk factors. The presence of WMLs and the Fazekas grade was determined from the brain magnetic resonance imaging (MRI) scans' T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequence taken from the patients. The rates of WMLs were compared in patients with and without thrombophilia.

Results Thrombophilia was detected in 34.8% of the patients, and 27.3% were determined to have WMLs in brain MRI scans. The WMLs were detected in 23.3% of the patients without thrombophilia, in 34.8% of those with thrombophilia, and in 50% of the subjects with multiple thrombophilia disorders. Among the thrombophilia disorders, only APC resistance was significantly more common in patients with WMLs.

Conclusion The results of the present study showed that thrombophilia may be a mechanism that should be investigated in the etiology of increased WMLs in MA.

Keywords
- Migraine with Aura
- Thrombophilia
- White Matter

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Resumen

Antecedentes La migraña se asocia con una serie de comorbilidades genéticas o adquiridas. Los estudios realizados en los últimos años destacan que la frecuencia de trombofilia es elevada en la migraña, especialmente en la migraña con aura (MA). De manera similar, la presencia de lesiones de la sustancia blanca (LSB) en las imágenes por resonancia magnética (RM) del cerebro se ha asociado con la migraña hace muchos años.
Objetivo Con base en la información de que se suelen observar tanto LSB como variantes de la trombofilia en MA, nuestro objetivo fue investigar si existe una relación entre la trombofilia genética y la presencia de LSB en estos pacientes.
Métodos Se investigaron los niveles de proteína S y de proteína C, actividades de antitrombina III, resistencia a la proteína C activada (PCA), anticuerpos antifosfolípidos inmunoglobulina G/inmunoglobulina M (IgG/IgM) y anticuerpos anticardiolipina IgG/IgM en 66 pacientes con MA entre 18 y 49 años que no presentaban factores de riesgo cardiovascular. Se determinaron la presencia de LSB y el grado de Fazekas a partir de imágenes por RM del cerebro en la secuencia ponderada en T2 y recuperación de la inversión atenuada de fluido (*fluid-attenuated inversion recovery*, FLAIR, en inglés) obtenidas de los pacientes. Se compararon las tasas de LSB en pacientes con y sin trombofilia.
Resultados Se detectó trombofilia en el 34,8% de los pacientes y LSB en el 27,3%. Las LSB estuvieron presentes en el 23,3% de los pacientes sin trombofilia, en el 34,8% de los que tenían trombofilia, y en el 50% de los que tenían múltiples trastornos trombofílicos. La resistencia a la PCA fue significativamente más común en aquellos pacientes con LSB.
Conclusión Los resultados del presente estudio mostraron que la trombofilia puede ser un mecanismo que debe investigarse en la etiología del aumento de LSB en MA.

Palabras Clave
- Migraña con Aura
- Trombofilia
- Sustancia Blanca

INTRODUCTION

Migraine is a disabling disease with a high socioeconomic burden affecting 15 to 18% of the population, with a 2:3 predominance among women.[1,2] The headaches are typically pulsatile, lasting 4 to 72 hours, and ranging from moderate to severe.[3] During an attack, temporary neurological deficits, defined as aura, develop in 1/3 of individuals with migraine. Aura includes visual, sensory, linguistic, or motor symptoms and, sometimes, brainstem symptoms.[4] Visual symptoms are the most common aura feature.[4] Studies on the pathophysiology of migraine provide new information about the conditions that accompany it. About 10 years ago, a study[5] identified a genetic comorbidity of migraine with thrombophilia. New information has shown that there is a significant relationship between antiphospholipid syndrome (APS) and migraine, and that protein S (PS) deficiency is five times more common in migraine patients than in healthy controls.[6] The most common characteristic of genetic or acquired thrombophilia is the increased risk of developing thrombosis.[7,8] The most prominent genetic variants include factor V Leiden (FVL) mutation, antithrombin 3 (AT III) activity, protein C (PC) and PS deficiency, thrombophilia associated with prothrombin, and active protein C (APC) resistance.[9,10] These prothrombotic genetic abnormalities may be common risk factors in ischemic stroke (IS) and migraine with aura (MA), and they may even play a role in increasing the risk of cerebrovascular disease in migraineurs. It is not known exactly by which pathophysiology mechanism the MA and thrombophilia pathways intersect. The most acceptable mechanism that explains the association of MA with thrombophilia is that microthrombi caused by genetic thrombophilia facilitate the formation of visual, sensory, and motor auras through cortical spreading depression (CSD).[11]

Another condition associated with MA is white matter lesions (WMLs), which are viewed as parenchymal hyperintensities on brain magnetic resonance imaging (MRI) scans and found to be higher in patients with MA compared to healthy controls.[12] The diagnostic value of WMLs in the brain MRI scans of patients with migraine is unknown; however, the presence of WMLs in young people is considered to favor migraines.[13] They are significantly more common in patients with MA compared to patients with migraine without aura. The number of lesions increases in parallel with the frequency of attacks, the severity of pain, the presence of nausea, the degree of disability, resistance to treatment, and the advance in age.[14] We hypothesized that thrombophilia, a group of diseases in which blood tends to clot, may play a role in the etiology of WMLs. We investigated the presence of WMLs in the brain MRI scans of MA patients with and without thrombophilia.

METHODS

The present retrospective study was approved by the institutional Ethics Committee (approval date: 05.04.2023/No: 038), and informed consent was not required.

The study was conducted on MA patients diagnosed and treated at the neurology headache outpatient clinic of our hospital between 2016 and 2022. The medical files of 146 MA patients were reviewed. The files of 94 patients diagnosed with MA, who presented with IS mimicking symptoms such as complete visual loss, dysarthria, hemiparesis, and hemihypesthesia, as well as difficulty in finding words, and thus underwent a detailed evaluation, including investigation of thrombophilia disorders and brain MRI scans, were separated. Patients who had MA characterized by bright lights or starry visual phenomena, flickering light spots, or zigzag patterns were not included in the study, as detailed laboratory and brain MRI examinations were not conducted. The sample size was not calculated for the present study. Out of the 94 patients with MA whose files were separated, 66 patients aged between 18 and 49 years, without metabolic and cardiovascular risk factors, were included in the study. Migraine was diagnosed in accordance with the third edition of the International Classification of Headache Disorders (2018).[3] During the diagnostic phase, we evaluated the results of thrombophilia tests and brain MRI scans of MA patients who had disabling auras (auras that cause temporary difficulty or disability in work and social life), that caused symptoms such as complete visual loss, dysarthria, hemiparesis, and hemihypesthesia. Patients with known stroke, neurodegenerative disease, hypertension (arterial blood pressure $\geq$ 140/90 mmHg), diabetes (hemoglobin A1c, HbA1c, $\geq$ 6.1 mmol/L), thrombophilia, connective tissue, blood, heart, and kidney diseases, smokers, as well as patients using oral contraceptives were excluded from the study. Patients with infection, malignancy, history of surgical intervention, immobility, and anticoagulant drug use that may cause acquired thrombophilia were also excluded from the study.

Values for PC, PS, AT III activity and APC resistance below laboratory reference values were considered as thrombophilia disorder (reference values are presented in ►**Table 1**). The test results for anticardiolipin immunoglobulin G/immunoglobulin M (IgG/IgM) and antiphospholipid IgG/IgM antibodies were evaluated as negative and positive; positive results were considered pathological.

Table 1 Descriptive results, thrombophilic disorder rate, and rate of lesions found on MRI

	Minimum	Maximum	Mean	Standard deviation
Age (years)	18.00	49.00	32.26	±8.914
			n	%
Gender		Female	51	77.3
		Male	15	22.7
Presence of WMLs in the FLAIR MRI		No	48	72.7
		Yes	18	27.3
		Fazekas 1	11	16.7
		Fazekas 2	4	6.1
		Fazekas 3	3	4.5
Antithrombin 3 activity (75–125)*		Normal	64	97.0
		Deficient	2	3.0
Protein S (60–130)*		Normal	47	71.2
		Deficient	19	28.8
Protein C (70–130)*		Normal	64	97.0
		Deficient	2	3.0
Active protein C resistance (0.65–1.54)*		Normal	58	87.9
		Deficient	8	12.1
Anticardiolipin antibody		Negative	64	97.0
		Positive	2	3.0
Antiphospholipid antibody		Negative	66	100.0
		Positive	0	0
Presence of thrombophilia		No	43	65.2
		Yes	23	34.8
Single/Multiple thrombophilia		None	43	65.2
		Single	17	25.8
		Multiple	6	9.1

Abbreviations: FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; WML, white matter lesion.
Note: *Reference range.

The WMLs on the brain MRI scans were examined in the T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequence and in the axial section. The Aera 1.5T MRI scanner (Siemens Healthineers, Erlagen, Germany) was used. The MRI findings were interpreted and classified by an experienced neurologist who had been dealing with headaches for twelve years. The presence and number of WMLs were taken into consideration in the MRI examination. The severity of the vascular lesions was determined based on the Fazekas grading system (Fazekas 0: no lesion or a single punctate lesion; Fazekas 1: multiple punctate lesions; Fazekas 2: lesions that tend to merge; and Fazekas 3: large, combined lesions). Demographic characteristics and the presence of WMLs in the MRI T2 FLAIR sequence in patients with and without thrombophilia were compared.

Statistical analysis

The data were transferred to IBM SPSS Statistics (IBM Corp., Armonk, NY, United States) software, version 26.0, and prepared for analysis. After the analysis, descriptive statistics were presented with numbers, percentages, and minimum and maximum, mean and standard deviation, and median, and interquartile range values. The Shapiro-Wilk test was used to assess if the data met the assumption of normal distribution. In both comparison groups, when the *p*-value obtained from the Shapiro-Wilk test was greater than 0.05, a *t*-test was used (only for protein S). When the *p*-value was lower than 0.05 in either both groups or one of the two groups, the Mann-Whitney U test was used. Differences between the two independent groups were evaluated using the *t*-Test and Mann-Whitney U test. The Chi-squared test was applied to determine the relationships regarding the categorical variables. Statistical significance was set at $p < 0.05$.

RESULTS

Among the 66 patients included in the study, 51 were female (77.3%), 15 were male (22.7%), and the mean age was of 32.3 ± 8.9 (range: 18–49) years. According to the results of the test investigating the presence of thrombophilia, 23 patients (34.8%) were found to have thrombophilia disorders; among them, 6 (9.1%) presented multiple thrombophilia disorders. The AT III activity was below the reference value in 2 patients (3%), PC deficiency, in 2 patients (3%), PS deficiency, in 19 patients (28.8%), and APC resistance, in 8 (12.1%) patients: these patients were considered as having thrombophilia disorders. Anticardiolipin antibodies were positive in 2 patients (3%), and antiphospholipid antibodies were negative in all patients. No significant relationship was found between the presence of thrombophilia and gender ($p = 0.654$), nor between the presence of thrombophilia and age ($p = 0.540$).

According to the brain MRI T2 FLAIR sequence from the axial section, 18 patients (27.3%) presented WMLs. Of these lesions, 11 (16.7%) were Fazekas 1, 4 (6.1%), Fazekas 2, and 3 (4.5%), Fazekas 3. No significant relationship was found between the presence of WMLs and gender ($p = 0.206$); however, the rate of WMLs was significantly higher in the elderly ($p = 0.039$). According to the results of the comparative analysis between thrombophilia and the presence of WMLs, 34.8% of the patients with thrombophilia and 23.3% of those without thrombophilia presented WMLs. No significant correlation was found between WMLs and thrombophilia ($p = 0.477$); WMLs were present in 29% of patients with a single thrombophilia disorder and in 50% of those with multiple thrombophilia disorders, but with no significant relationship ($p = 0.427$). In the comparative analysis between the thrombophilia variants and the presence of WMLs, among the 8 (12.1%) patients with low APC resistance, 5 had WMLs (62.5%), and the relationship was significant ($p = 0.030$). Neither was there a meaningful relationship between the presence of thrombophilia and the Fazekas grade ($p = 0.654$).

DISCUSSION

The etiology of WMLs, which are considered silent infarcts of the brain parenchyma observed in MA, is not yet fully known. The coexistence of WMLs with prothrombotic conditions and the possible causal relationships have not been sufficiently investigated in the literature. Therefore, the results of the present study, in which we examined the frequency of thrombophilia in MA patients and the relationship between thrombophilia disorders and the presence of WMLs, are important. We examined the radiological imaging and laboratory test results performed at the diagnosis stage of 66 migraine patients with a disabling aura, and we compared the brain MRI scans of those with and without a thrombophilia disorder.

Thrombophilia disorders are not routinely investigated in MA patients at our center. However, it has long been recognized in the clinical practice that some MA attacks can mimic the symptomatology of cerebrovascular events, and migraine auras can act as an acute trigger for IS in rare cases.[11] Therefore, the thrombophilia status and brain MRI findings of MA patients, such as hemiparesis, hemihypesthesia, dysarthria, and visual loss have been investigated.

In the analysis of the demographic characteristics of the 66 patients included in the current study, the mean age was of 32.3 (± 8.9) years. Female dominance was found to be of 77% in the gender analysis. These results were consistent with those of the literature.[15,16] In the examination of the thrombophilia screening, thrombophilia disorder was detected in 34.8% of MA patients. In a similar study[6] evaluating migraines with and without aura, the rate of thrombophilia was found to be of 32.5%. In another study[15] conducted on female patients with MA, the rate of patients with thrombophilia was found to be of 46%; the reason for the high rate in this study may be that FVL and factor II G20210A (FIIL) mutations were also examined. In our laboratory test results, we found rates of PS deficiency of 28.8%, APC resistance of 12.1%, AT III activity of 3%, PC deficiency of 3%, and presence of anticardiolipin antibodies of 3% (►**Table 1**). According to the results of the studies[17–20] determining the prevalence of thrombophilia in populations of healthy individuals, the rates were as follows: PS deficiency – 0.5%;

PC deficiency – 0.2%; AT-III activity – 0.2%; and APC resistance – 4.7%. The prevalence of APS in the general population was estimated as 50 per 100 thousand people.[21] Looking at these results, we can argue that the rate of thrombophilia in patients with MA is higher compared to the prevalence in the general population.

Parenchymal hyperintensities, which are common among MA patients, are clinically silent lesions. Their limited size suggests an isolated occlusion of a small vessel.[22] The ability of microthrombi caused by genetic thrombophilia to trigger IS and aura may also be relevant to the pathophysiology of WMLs.[11] It has been determined that a single penetrating arteriole occlusion due to microembolism triggered CSD around the arteriole in the acute period; and a few weeks later, small ischemic lesions developed in the region of the occluded vessel. These results suggest that cerebral microembolism may trigger MA attacks and could be responsible for some silent brain lesions.[22] Similarly, in an experimental study with rat models,[23] short cerebral hypoxic-ischemic episodes induced by microembolization were found to trigger CSD, and they could also trigger the aura. When this condition is extrapolated to human beings, it can be concluded that migraine auras due to CSD are associated with transient ischemic attacks and silent infarctions.[23] Microthrombi, which may be caused by thrombophilia risk factors, are also likely to be among these triggers.[24]

White matter lesions associated with migraine are commonly observed in T2 FLAIR sequences.[25] Accordingly, we used these MRI sequences in the present study. In MA patients, we found a rate of WMLs of 27.3%. In a similar study by Al-Hashel et al.,[12] the prevalence of WMLs in MA patients was of 38.3%. The reason for the difference could lie in the age range of the patients included in the study:[12] while our patient group was aged between 18 and 49 years, the age of the patients in the study by Al-Hashel et al.[12] ranged from 18 to 55 years. In addition, the use of different MRI features or imaging techniques may have had an effect. While we used a 1.5-T MRI scanner, Al-Hashel et al.[12] used a 3.0-T MRI scanner.

In the current study, the presence of WMLs on MRI scans was of 23.3% in patients without thrombophilia, of 34.8% in patients with thrombophilia, and of 50% in patients with multiple thrombophilia. The gradual increase suggests that there may be a positive correlation between the presence of WMLs and thrombophilia. Microthrombi, which may be caused by thrombophilia risk factors, may trigger the arterial occlusion-CSD-aura-WML cascade. In the comparison of the relationship of each thrombophilia factor with the presence of WMLs, there was no relationship between PC, PS, AT III, anticardiolipin antibodies, and the presence of WMLs; however, we found a significant relationship between APC resistance and the presence of WMLs ($p = 0.030$) (►**Table 2**). This result supports the hypothesis we established. While no significant relationship was found between the presence of WMLs and gender, the presence of WMLs was significantly higher in the elderly patients. These results are also consistent with those of other studies in the literature.[14] This significant association between the presence of WMLs and age may be due to long-term exposure. A study[26] in which the MA patients were followed up demonstrated that the number of WMLs could progress over time; of the 27 patients with WMLs, 61% were classified as Fazekas 1, 22%, as Fazekas 2, and 16.7%, as Fazekas 3. When considering Fazekas grades as the intensity of white matter hyperintensities, a study[27]

Table 2 Association between thrombophilia and lesions found on MRI

			Lesion on MRI		$X^2 = 0.507$ $p = 0.477$
			None	Yes	
Thrombophilia	None	n: 43	33	10	
		%	76.7	23.3	
	Yes	n: 23	15	8	
		%	65.2	34.8	
Multiple/single thrombophilia	Single	n: 17	12	5	$X^2 = 1.952$ $p = 0.427$
		%	7.6	29.4	
	Multiple	n: 6	3	3	
		%	50.0	50.0	
Antithrombin 3 activity	Normal	n: 64	47	17	$X^2 = 0.537$ $p = 1.000$
		%	73.4	26.6	
	Deficient	n: 2	1	1	
		%	50.0	50.0	
Protein S	Normal	n: 47	35	12	$X^2 = 0.038$ $p = 0.846$
		%	74.5	25.5	
	Deficient	n: 19	13	6	
		%	68.4	31.6	

(*Continued*)

Table 2 (*Continued*)

Protein C	Normal	n: 64	46	18	$X^2 = 0.773$ $p = 0.597$
		%	71.9	28.1	
	Deficient	n: 2	2	0	
		%	100.0	0.0	
Active protein C resistance	Normal	n: 58	45	13	$X^2 = 5.696$ $p = 0.030$
		%	77.6	22.4	
	Deficient	n: 8	3	5	
		%	37.5	62.5	
Anticardiolipin antibody	Negative	n: 64	46	18	$X^2 = 0.773$ $p = 0.597$
		%	71.9	28.1	
	Positive	n: 2	2	0	
		%	100.0	0.0	

Abbreviations: χ^2, Chi squared; MRI, magnetic resonance imaging.

has shown that this risk is more prevalent in women and is positively associated with the frequency of attacks. We did not find any significant relationship between thrombophilia and the Fazekas grade regarding the WMLs. We could not find any study in the literature that examined the relationship between the Fazekas grade and thrombophilia. Furthermore, we did not find another study in the literature investigating the relationship between thrombophilia status and WMLs in MA patients. The present study is the first to address this issue. The literature contains some noteworthy case reports[28–30] that indicate the common pathophysiology coexistence of MA and thrombophilia. These reports mention a decrease in the frequency of attacks during anticoagulant use in patients with migraine and thromboembolic risk factors.[28,29] They particularly report the effectiveness of anticoagulant drugs in auras that cause visual impairment and headache.[30] In APS, which presents significant neurological complications such as stroke, transient ischemic attack, and migraine pain, the elimination of headache and neurological symptoms with the appropriate dose of warfarin is also essential in terms of indicating a cause-effect relationship.[31]

In conclusion, we found that approximately 1/3 of MA patients have one or more thrombophilia risk factors. We suggest that some of the attacks experienced by MA patients may be related to underlying hereditary thrombophilia, and that these disorders may play a role in the etiology of WML in migraine. Prospective studies involving larger numbers of patients are needed to elucidate this situation.

Limitations

The present is a retrospective study, and the patient group examined consisted of subjects with MA. It would be more effective to conduct a prospective study with a larger sample size that includes all types of auras.

Conflict of Interest
The author has no conflict of interest to declare.

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