

Research Article / Araştırma Makalesi

The Relationship Between the Circle of Willis Variations and White Matter Hyperintensities in Different Migraine Subtypes

Farklı Migren Alt Tiplerinde Willis Poligonu Varyasyonları ve Beyaz Cevher Lezyonları Arasındaki İlişki

¹Aslı Yaman Kula, ²Serdar Balsak

¹Bezmialem Foundation University Medical Faculty, Department of Neurology, Istanbul, Türkiye

²Bezmialem Foundation University Medical Faculty, Department of Radiology, Istanbul, Türkiye

Abstract: It is known that the Circle of Willis (CoW) variations and white matter hyperintensities (WMHs) are common in migraine. This retrospective study aims to investigate the relationship between the CoW variations and WMHs in migraine without aura (MWOA) (n=38) and migraine with aura (MWA) (n=40) patients. Demographic, clinical and radiological findings (the CoW variations and WMH burden) of the patients were recorded, and the relationship between the variables was evaluated in both groups. The overall incomplete CoW, incomplete anterior or vertebrobasilar portion of the CoW, or the presence of fetal PCA showed no significant difference between the MWOA and MWA groups ($p > 0.05$). An incomplete posterior portion of the CoW was significantly higher in the MWA group than in the MWOA group ($p = 0.034$). In the MWA group, the visual aura was present in 72% of patients with the overall incomplete CoW; all of these were posterior portion variations of the CoW. When the WMH burden was compared, no significant difference was seen between the MWOA and MWA groups ($p > 0.05$). Among patients with the CoW variations in the MWOA group, the rate of patients without WMHs was significantly higher ($p = 0.030$). No significant difference was observed between the variations and WMH burden in the MWA group ($p > 0.05$). According to our study results, variations in the posterior portion of the CoW are common in MWA, and while this variation is associated with visual aura, it was found to be unrelated to WMH burden.

Keywords: Migraine with aura, Migraine without aura, Circle of Willis

Özet: Migrende Willis Poligonu varyasyonlarının ve beyaz cevher lezyonlarının sık gözlemlendiği bilinmektedir. Bu retrospektif çalışma aurasız migren (n=38) ve auralı migren (n=40) hastalarında Willis Poligonu varyasyonları ile beyaz cevher hiperintensiteleri arasındaki ilişkiyi araştırmayı amaçlamıştır. Hastaların demografik, klinik ve radyolojik bulguları (Willis Poligonu varyasyonları ve beyaz cevher hiperintensite yükleri) kaydedildi ve değişkenler arasındaki ilişki her iki grupta değerlendirildi. Herhangi bir Willis Poligon varyasyonu varlığı, Willis Poligonu'nun anterior ya da vertebrobaziler kısmında varyasyon olması veya fetal PCA varlığı aurasız migren ve auralı migren grupları arasında anlamlı fark göstermedi ($p > 0.05$). Willis Poligonu'nun posterior kısmında varyasyon varlığı auralı migren grubunda aurasız migren grubuna göre anlamlı derecede yüksek bulundu ($p=0,034$). Auralı migren grubunda, herhangi bir Willis Poligon varyasyonuna sahip hastaların %72'sinde görsel aura mevcuttu ve bu varyasyonların tümü Willis Poligonu'nun posterior kısım varyasyonlarıydı. Aurasız ve auralı migren gruplarında beyaz cevher lezyon yükü karşılaştırıldığında, gruplar arasında anlamlı farklılık görülmedi ($p > 0,05$). Aurasız migren grubunda, Willis Poligonu varyasyonuna sahip olan hastalar arasında beyaz cevher lezyonu olmayan hastaların oranı anlamlı olarak daha yüksekti ($p = 0,030$). Auralı migren grubunda, Willis Poligon varyasyonları ile beyaz cevher lezyon yükü arasında anlamlı bir fark gözlenmedi ($p > 0,05$). Çalışma sonuçlarımıza göre auralı migrende Willis Poligonu'nun posterior kısım varyasyonları sık görülmüştür ve bu varyasyon görsel aura ile ilişkili, beyaz cevher lezyon yükü ile ilişkisiz bulunmuştur.

Anahtar Kelimeler: Auralı migren, Aurasız migren, Willis Poligonu

ORCID ID of the authors: AYK. [0000-0001-8857-9210](https://orcid.org/0000-0001-8857-9210), SB. [0000-0001-8765-4418](https://orcid.org/0000-0001-8765-4418)

Received 05.05.2024

Accepted 30.05.2024

Online published 03.06.2024

Correspondence: Aslı YAMAN KULA– Bezmialem Foundation University Medical Faculty, Department of Neurology, Istanbul, Türkiye
e-mail: dr.asliyaman@gmail.com

1. Introduction

Migraine is a neurological disorder with a very high incidence and is the second common cause of disability worldwide [1]. It progresses with recurrent headache attacks and accompanying symptoms (photophobia, phonophobia, nausea, and/or vomiting) lasting from 4 to 72 hours [2]. According to the International Classification of Headache Disorders, 3rd edition (ICHD-3) classification [3], migraine can be classified as migraine with aura (MWA) and migraine without aura (MWOA) among other categories and the diagnosis is based on the patient's clinical history and neurological findings [4].

Aura occurs as recurrent, transient neurological symptoms and ends within 5-60 minutes. Visual auras are found in more than 90% of migraine patients with aura. Sensory symptoms and speech or language disturbances are less common, and they are often accompanied by visual aura symptoms [3]. It is estimated that MWA is found in 1/5 to 1/3 of migraine patients in the USA [5].

The literature reports a high Circle of Willis (CoW) variation in migraineurs with aura, especially for the posterior circulation [6]. CoW variations may change cerebral blood flow, leading to local ischemia and triggering a cortical spreading depression [7]. Spreading depolarizations are the electrophysiological reflections of aura and affect the visual field of occipital cortex in the posterior vasculature [8]. In addition, recent studies investigating migraine with aura and other types of migraine have revealed that a significant proportion of migraine cases (29%-73%) have white matter hyperintensities (WMHs). Most studies have shown that these lesions are more common in MWA. However, results on the link between WMHs and migraine characteristics and cerebrovascular manifestations are conflicting [9]. On the basis of these data, present study aims to define the morphology of the CoW in different migraine subtypes and to demonstrate the link between the CoW variations and white matter lesions in the brain.

2. Materials and Methods

2.1. Patients

The data of 78 migraine patients who were followed up in the Headache Outpatient Clinic of xxx University Hospital between January 2023 and January 2024 and their brain MRI and MR angiography (Angio-MRI) examinations were retrospectively analyzed. Migraine has been diagnosed according to the currently used ICHD-3 criteria [3]. The study consisted of two groups: a group of 38 migraine patients with aura (MWA group) and a group of 40 migraine patients without aura (MWOA group).

Patients aged < 18 years or > 80 years, patients lacking brain MRI with Angio-MRI, patients with a history of stroke, history of carotid artery occlusion or > 30% stenosis, history of aneurysm and patients with vascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia, current smoking) were excluded as these conditions may alter the CoW configuration and cause white matter lesions. The Declaration of Helsinki was followed in all procedures.

For each patient, age, gender, migraine type (with or without aura), aura type, age of migraine onset, migraine frequency, migraine duration, Migraine Disability Assessment Scale (MIDAS) scores, which was developed and widely used to measure disability in migraine patients [10], and Visual Analog Scale (VAS) scores, which reflect headache severity, were recorded. In patients with more than one aura subtype in the MWA group, the most common aura type was recorded.

2.2. Assessment of MRI and Angio-MRI

All MRI sequences were obtained using a 1.5 Tesla (T) scanner (Avanto; Siemens Medical Solution, Erlangen, Germany) and a 24-channel head coil. All WMH measurements were made using axial T1-weighted (slice thickness: 5 mm; field of view (FOV): 250 x 250 mm²; repetition time (TR): 500 milliseconds; echo time (TE): 87 milliseconds; matrix size: 320 x 224) axial and sagittal T2-weighted (slice thickness: 5

mm; FOV: 250 x 250 mm²; TR: 4050 milliseconds; TE: 90 milliseconds; matrix size: 320 x 224), axial T2-weighted FLAIR (slice thickness: 5 mm; FOV: 250 x 250 mm²; TR: 8000 milliseconds; TE: 118 milliseconds, matrix size: 320 x 224) images. Circle of Willis variations were determined using 3D intracranial TOF (Time of Flight) Angio-MRI (slice thickness: 5 mm; FOV: 230 x 230 x 74 mm³; TR: 27 milliseconds; TE: 7 milliseconds; flip angle: 20 degrees; matrix size: 800 x 406) and a 1 mm isotropic voxel resolution were employed. Angio-MRI examinations were reformatted using MIP (maximum intensity projection) reconstruction and multiplanar reformat reconstruction.

2.3. Definitions of the CoW Variations and WMH

Radiologist SB blindly evaluated the Brain MRI and Angio-MRI of all patients. The CoW variations observed on Angio-MRI were divided into the following four main groups. In arteries outside the vertebrobasilar system, segments narrower than 0.8 mm were categorized as hypoplastic. The vertebral artery was categorized as hypoplastic if its diameter was less than 2 mm.

a. Incomplete anterior portion of the CoW: Variation of the anterior cerebral artery (ACA) in which one of the A1 segment(s) and/or anterior communicating artery (Acom) is hypoplastic, dysplastic or displaced.

b. Incomplete posterior portion of the CoW: Variation of the posterior cerebral artery in which one of the P1 segment(s) and/or posterior communicating artery (Pcom) is hypoplastic, dysplastic or displaced.

c. Incomplete Vertebrobasilar System: Hypoplasia or dysplasia of one of the vertebral and/or basilar artery.

d. Fetal Posterior Cerebral Artery (PCA): Partial or complete fetal configuration (The PCA originates from the ipsilateral ICA, instead of the basilar artery) of PCA without basilar hypoplasia

Subcortical or periventricular WMHs were grouped according to their numbers calculated on MRI. '0' meant no lesion was seen.

Group 1: 1-5 WMHs

Group 2: 6-10 WMHs

Group 3: > 10 WMHs

2.4. Statistics

All statistics were performed with the SPSS package program version 26 (IBM, Armonk, NY, USA). Frequencies and percentages represented categorical variables. Mean±standard deviation, median, and interquartile range (IQR) represented continuous variables according to their distribution. Distribution patterns of numerical variables were examined with the Shapiro-Wilk test. Fisher's Exact Test and Chi-square test were used to compare the qualitative variables between groups. In comparisons between the two groups, an independent samples t-test or Mann Whitney U test was used according to their distribution pattern. For three or more groups, a one-way analysis of variance test (One-way ANOVA) was applied if the data were parametric, and the Kruskal-Wallis test was used if the data were non-parametric. During multiple comparisons, Bonferroni correction was used to p values to avoid type I errors. The statistical significance level was 0.05.

3. Results

Of the 78 patients diagnosed with migraine, 38 (48.7%) were in the MWOA group, and 40 (51.2%) were in the MWA group. The study population was middle-aged, and it was predominantly female. No significant difference was observed in age and gender between migraineurs with and without aura. There was a significant difference between MWOA and MWA groups in terms of attack frequency (p=0.020), MIDAS scores (p=0.011), presence of photophobia (p=0.007), and phonophobia (p=0.013), and they were significantly higher in the MWOA group (Table 1).

There was an incomplete CoW in 64 (82%) migraine patients. When the patients' migraine

duration, attack frequency, attack duration, MIDAS, and VAS scores were compared according to the CoW variation, there was no difference between the groups with and without the CoW variation ($p > 0.05$). The age of the patients in the group without the CoW variation was significantly higher than in the group with the CoW variation ($p = 0.014$) (Table 2). Since the male gender was found in small numbers, a comparison of genders and the CoW variations could not be applied.

There was an incomplete CoW in 28 (73.7%) patients in the MWOA group and 36 (90%) in the MWA group. Still, no significant difference was observed between the groups in the overall incomplete CoW, incomplete anterior portion, incomplete vertebrobasilar portion variations, or the presence of fetal PCA ($p > 0.05$). Posterior portion variation was significantly higher in the MWA group than in the MWOA group ($p = 0.034$) (Table 3). In the MWA group, 31 (77.5%) patients had visual aura, 7 (17.5%) had sensory aura, and 3 (5%) had motor aura. Visual aura was present in 29 (72.5%) of 36 patients with the

CoW variation (OR=4.1 CI 95% [0.4 to 34.7]), and all the CoW variations seen in patients with visual aura were posterior portion variations.

WMH was observed in 34 (43.5%) migraine patients. When the age, migraine duration, attack frequency, attack duration, MIDAS, and VAS scores of the patients were compared according to the WMH groups, no significant difference was observed between the groups with high hyperintensity burden and those without ($p > 0.05$) (Table 4). Since the male gender was found in small numbers in the WMH groups, a comparison of genders with hyperintensity burden could not be applied. There was no difference in terms of WMH burden in the MWOA and MWA groups ($p > 0.05$) (Table 5).

When the relationship between the CoW variations and the presence of white matter lesions in the MWA and MWOA groups was evaluated, the proportion of patients without WMH among those with the CoW variations in the MWOA group was significantly higher ($p = 0.030$) (Table 6).

Table 1. Clinical characteristics of the MWOA and MWA groups

	MWOA (n = 38)	MWA (n = 40)	p
Age (mean \pm SD)	39.92 \pm 9.91	35.65 \pm 11.84	0.089 ^a
Female, n (%)	33 (86.8%)	31 (77.5%)	0.283 ^b
Migraine duration, years (median, IQR)	6 (31)	8 (35)	0.346 ^c
Attack frequency, per month (median, IQR)	9.50 (29)	5 (29)	0.020 ^c
Attack duration, hours (median, IQR)	24 (68)	24 (70)	0.214 ^c
VAS (median, IQR)	6 (5)	6 (6)	0.346 ^c
MIDAS (median, IQR)	22 (57)	12.50 (58)	0.011 ^c
Nausea and/or vomiting, n (%)	23 (60.5%)	22 (55%)	0.621 ^b
Photophobia, n (%)	25 (65.8%)	14 (35%)	0.007 ^b
Phonophobia, n (%)	22 (57.9%)	12 (30%)	0.013 ^b

^aIndependent-sample t-test, ^bChi-Square test, ^cMann-Whitney U test

Abbreviations: MIDAS, Migraine Disability Assessment Scale; MWA, migraine with aura; MWOA, migraine without aura; VAS, Visual Analogue Scale; IQR, intraquartile range; SD, standard deviation

Table 2. Comparison of demographic and clinical characteristics of migraine patients according to the CoW variations

	Incomplete CoW (n = 64)	Normal CoW (n = 14)	p
Age (mean \pm SD)	36.30 \pm 10.68	44.29 \pm 10.88	0.014 ^a
Migraine duration, years (median, IQR)	7 (35)	12 (28)	0.167 ^b
Attack frequency, per month (median, IQR)	8 (29)	7 (29)	0.768 ^b
Attack duration, hours (median, IQR)	24 (70)	24 (68)	0.603 ^b

VAS (median, IQR)	6 (6)	7 (4)	0.816 ^b
MIDAS (median, IQR)	18 (58)	19 (42)	0.695 ^b

^aIndependent-sample t-test, ^bMann-Whitney U test

Abbreviations: CoW, Circle of Willis; MIDAS, Migraine Disability Assessment Scale; VAS, Visual Analogue Scale; IQR, intraquartile range; SD, standard deviation

Table 3. Comparison of Circle of Willis variations between MWoA and MWA groups

	MWoA (n = 38)	MWA (n = 40)	p ^a
Incomplete CoW, overall n (%)	28 (73.7%)	36 (90%)	0.061
Incomplete CoW, Anterior portion, n (%)	5 (13.2%)	3 (7.5%)	0.410
Incomplete CoW, Posterior portion, n (%)	27 (71.1%)	36 (90%)	0.034
Incomplete CoW, Vertebrobasilar portion, n (%)	7 (18.4%)	3 (7.5%)	0.149
Fetal PCA, n (%)	5 (13.2%)	1 (2.5%)	0.077

^aChi-Square test

Abbreviations: CoW, Circle of Willis; MWA, migraine with aura; MWoA, migraine without aura; PCA, Posterior Cerebral Artery

	WMH				p
	0 (n = 44)	Group 1 (n = 23)	Group 2 (n = 5)	Group 3 (n = 6)	
Age (mean ± SD)	36.02 ± 10.37	36.96 ± 12.08	48.20 ± 8.92	44.50 ± 8.31	0.046 ^a
Migraine duration, years (median, IQR)	7 (34)	10 (30)	11 (29)	15 (19)	0.620 ^b
Attack frequency, per month (median, IQR)	8 (29)	7 (29)	8 (9)	9.5 (28)	0.786 ^b
Attack duration, hours (median, IQR)	24 (70)	24 (68)	24 (64)	18 (68)	0.922 ^b
VAS (median, IQR)	6 (6)	6 (5)	7 (4)	7 (4)	0.958 ^b
MIDAS (median, IQR)	18 (47)	18 (43)	15 (27)	26 (55)	0.688 ^b

Table 4. Comparison of demographic and clinical characteristics of migraine patients according to WMH groups

^aOne-way analysis of variance test, Post-hoc significance values have been adjusted using the Bonferroni correction; the post-hoc significance p-value was < 0.008, and no significant difference was detected between groups. ^bKruskal-Wallis test

Abbreviations: WMH, white matter hyperintensity; MWA, migraine with aura; MWoA, migraine without aura; MIDAS, Migraine Disability Assessment Scale; VAS, Visual Analogue Scale; IQR, intraquartile range; SD, standard deviation

Table 5. Comparison of WMH burden between MWoA and MWA groups

	MWoA (n = 38)	MWA (n = 40)	p ^a
Participants with 0 WMH, n (%)	23 (60.5%)	21 (52.5%)	0.475
Group 1, n (%)	8 (21.1%)	15 (37.5%)	0.111
Group 2, n (%)	2 (5.3%)	3 (7.5%)	0.687
Group 3, n (%)	5 (13.2%)	1 (2.5%)	0.077

^aChi-Square test

Abbreviations: WMH, white matter hyperintensity; MWA, migraine with aura; MWoA, migraine without aura

Table 6. Comparison of the presence of WMH according to the CoW variations in MWoA and MWA groups

		MWoA Group (n = 38)			MWA Group (n = 40)		
		WMH, n (%)		p ^a	WMH, n (%)		p ^a
		No	Yes		No	Yes	
Incomplete CoW, overall	No	3 (7.9%)	7 (18.4%)	0.030	1 (2.5%)	3 (7.5%)	0.331

		Yes	20 (52.6%)	8 (21.1%)		20 (50%)	16 (40%)	
Incomplete portion	CoW, Anterior	No	18 (47.4%)	15 (39.5%)	0.136	20 (50%)	17 (42.5%)	0.596
		Yes	5 (13.2%)	0 (0%)		1 (2.5%)	2 (5%)	
Incomplete portion	CoW, Posterior	No	4 (10.5%)	7 (18.4%)	0.073	1 (2.5%)	3 (7.5%)	0.331
		Yes	19 (50%)	8 (21.1%)		20 (50%)	16 (40%)	
Incomplete Vertebrobasilar portion	CoW,	No	18 (47.4%)	13 (34.2%)	0.681	20 (50%)	17 (42.5%)	0.596
		Yes	5 (13.2%)	2 (5.3%)		1 (2.5%)	2 (5%)	
Fetal PCA		No	20 (52.6%)	13 (34.2%)	1.000	21 (52.5%)	18 (45%)	0.475
		Yes	3 (7.9%)	2 (5.3%)		0 (0%)	1 (2.5%)	

^aFisher's Exact Test

Abbreviations: CoW, Circle of Willis; WMH, white matter hyperintensity; MWA, migraine with aura; MWoA, migraine without aura

4. Discussion

The CoW is a crucial structure that regulates cerebral blood flow (CBF) distribution. Studies have reported that CoW variations are observed more frequently in migraine patients than in the normal population [6]. CoW variations may cause inadequate response to the increased blood flow demand in the environment of neuronal hyperexcitability that occurs in migraine by changing the distribution of CBF [11]. This may lead to the development of relative ischemia in migraineurs and increased susceptibility to cortical spreading depression, which plays a critical role in the emergence of migraine attacks [12]. According to autopsy and angiography studies, the incidence of the complete CoW in the normal population varies. Alpers et al. (Alpers et al., 1959) showed that 52% of the control series had the complete CoW, while Zaninovich et al. (Zaninovich et al., 2017) found the incidence of the complete CoW to be 37.1%. The definition of the CoW variations has differed between studies. In some studies, vessel diameter was not considered in determining the presence of incomplete CoW, whereas in other studies, variations such as vessel displacement were included in the definitions. These differences in definitions may have led to under- or over-counting of variations in the studies (Henry et al., 2015). In the present study, vessel diameters and displacement of vessels were taken into consideration when defining the CoW variations. This may explain the high CoW variation rates we found in migraine patients. Krabbe-Hartkamp

et al. [13] investigated the CoW variations and vessel diameters in 150 volunteers. They showed that the complete CoW was more frequent in younger individuals (54% in younger versus 36% in older) and women (46% in women versus 37% in men). The average age of migraine patients included in our study was 38, and the patients were predominantly female. The mean age of the patients in the group without the CoW variation was significantly higher than in the group with the CoW variation. Despite all these findings, the CoW variation rate in our study was 82%.

In a study that included 48 MWoA patients and 37 healthy controls, Ezzatian-Ahar et al. [14] observed no difference in the prevalence of incomplete CoW between groups. Post-hoc analysis showed a significant association between age and the CoW variations ($p = 0.003$). In a study by Bugnicourt et al. [8] in 47 migraine patients (23 without aura, 24 with aura) and 77 controls, the relationship between the CoW variations and migraine was evaluated. Posterior CoW was categorized as complete when both Pcom and PCA-P1 segments were present and incomplete when one of these vessels was missing. PCA was categorized as fetal-type PCA when the ipsilateral ICA supplied the PCA via the Pcom. Incomplete posterior CoW was significantly higher in migraineurs than in controls ($P < 0.001$). Multivariate analysis showed the only independent factor associated with migraine was the incomplete posterior

CoW. No difference was found between MWOA and MWA. Inconsistent with this result, in this study, an incomplete posterior portion of the CoW was significantly higher in MWA patients than in MWOA patients. In addition, all CoW variations seen in patients with visual aura were posterior portion variations.

The predisposition to ischemia in migraine patients has been attributed to both ischemic and inflammatory mechanisms, and there is evidence for the release of proinflammatory substances during migraine attacks. Increased metabolic demand as a result of spreading depolarization, a key element in migraine pathophysiology, maybe the mechanism causing cerebral hypoperfusion and neuroinflammation. [15]. Besides that, CBF changes that occur during the hypoperfusion phase following a brief hyperemic phase have been associated with migraine aura [16]. It is suggested that aura symptoms are caused by perfusion changes and neuronal activity rather than cerebral ischemia [17]. Kruit et al. [18] showed that subclinical cerebellar posterior circulation infarcts are common in migraineurs and associated with the frequency of attacks and that this risk is higher in MWA. They observed women with migraine with and without aura are at increased risk for deep white matter lesion burden correlated with attack frequency. In addition to all these data, the CoW configurations are also known to have an effect on white matter lesions. van der Grond et al. [19] have shown that the fetal configuration of the posterior portion of the CoW protects elderly patients against deep white matter lesions.

In a study by Cucchiara et al. [7] consisting of 56 MWA, 61 MWOA patients, and 53 controls, the relationship between the CoW variation and CBF was analyzed. An incomplete CoW was significantly more common in the MWA and MWOA groups than in the control group. When a quantitative score determining the severity of CoW variation was used, a higher variation burden was detected in MWA patients than in controls ($p = 0.02$). Compared to those with the complete CoW, subjects with the incomplete CoW had greater asymmetry in hemispheric CBF ($p = 0.05$). Specific

posterior CoW variants were associated with more pronounced CBF asymmetries in the PCA region. In another study that included 270 migraine patients (204 MWOA, 66 MWA, and 159 controls), Cavestro et al. [20] investigated the relationship between the CoW variations and brain lesions. They observed that there was an anatomical CoW variation in 40% of migraine patients and 21.4% of the control group. There was a significant relationship between the CoW variations and MWOA (OR=2.4 CI 95% [1.5 to 3.9]) and MWA (OR=3.2 CI 95% [1.6 to 4.1]) groups. Unilateral posterior CoW variations accompanied by basilar hypoplasia were statistically significantly higher in MWA patients than controls (OR=9.2 CI 95% [2.3 to 37.2]). They found some type of brain lesion in 33% of MWOA patients and 24% of MWA patients. No statistical relationship was found between the presence of CoW variation and the presence of ischemic lesions seen on MRI. In the present study, there was no significant difference in WMH burden between MWOA and MWA patients. We did not find a linear relationship between the CoW variations and the presence of white matter lesions in migraine patients. On the contrary, the probability of encountering a white matter lesion in patients with CoW variation in the MWOA group was significantly lower. One of the reasons for this result may be that in our study, we evaluated white matter lesions according to their number, not their diameter or volume. However, although Cavestro et al.[20] evaluated WMH according to their diameter, they did not observe a linear relationship between CoW variations and WMH. Again, the possibility that some variations such as fetal PCA may have a protective effect regarding WMH may also have contributed to this result.

This study had some limitations. Firstly, there was no healthy control group. This was due to our inability to access sufficient MRI and Angio-MRI data in healthy individuals due to the study's retrospective design. Another limitation was the relatively small number of patients. Also WMHs were based on the number of lesions, not the white matter lesion volume.

In conclusion, visual aura was associated with the incomplete posterior portion of the CoW, but the WMH burden was unrelated to the presence of aura. The prevalence of WMH is similar across migraine subtypes. There is no

linear relationship between CoW variations and WMH burden in migraine patients, and the contribution of other explanatory mechanisms to WMH formation should be considered.

REFERENCES

- Ashina M, Terwindt GM, Al-Karagholi MA-M, de Boer I, Lee MJ, Hay DL, et al. Migraine: disease characterisation, biomarkers, and precision medicine. *Lancet* 2021;397:1496–504.
- Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. *Headache* 2005;45 Suppl 1:S3–13.
- Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38:1–211.
- Kincses ZT, Veréb D, Faragó P, Tóth E, Kocsis K, Kincses B, et al. Are Migraine With and Without Aura Really Different Entities? *Front Neurol* 2019;10.
- Vgontzas A, Burch R. Episodic Migraine With and Without Aura: Key Differences and Implications for Pathophysiology, Management, and Assessing Risks. *Curr Pain Headache Rep* 2018;22:78.
- Hamming AM, van Walderveen MAA, Mulder IA, van der Schaaf IC, Kappelle LJ, Velthuis BK, et al. Circle of Willis variations in migraine patients with ischemic stroke. *Brain Behav* 2019;9:e01223.
- Cucchiara B, Wolf RL, Nagae L, Zhang Q, Kasner S, Datta R, et al. Migraine with aura is associated with an incomplete circle of willis: results of a prospective observational study. *PLoS One* 2013;8:e71007.
- Bugnicourt J-M, Garcia P-Y, Peltier J, Bonnaire B, Picard C, Godefroy O. Incomplete posterior circle of willis: a risk factor for migraine? *Headache* 2009;49:879–86.
- Dobrynina LA, Suslina AD, Gubanov MV, Belopasova AV, Sergeeva AN, Evers S, et al. White matter hyperintensity in different migraine subtypes. *Sci Rep* 2021;11:10881.
- Ertaş M, Siva A, Dalkara T, Uzuner N, Dora B, Inan L, et al. Validity and reliability of the Turkish Migraine Disability Assessment (MIDAS) questionnaire. *Headache* 2004;44:786–93.
- Aurora SK, Wilkinson F. The brain is hyperexcitable in migraine. *Cephalalgia* 2007;27:1442–53.
- Olesen J, Friberg L, Olsen TS, Andersen AR, Lassen NA, Hansen PE, et al. Ischaemia-induced (symptomatic) migraine attacks may be more frequent than migraine-induced ischaemic insults. *Brain* 1993;116 (Pt 1):187–202.
- Krabbe-Hartkamp MJ, van der Grond J, de Leeuw FE, de Groot JC, Algra A, Hillen B, et al. Circle of Willis: morphologic variation on three-dimensional time-of-flight MR angiograms. *Radiology* 1998;207:103–11.
- Ezzatian-Ahar S, Amin FM, Obaid HG, Arnglim N, Hougaard A, Larsson HBW, et al. Migraine without aura is not associated with incomplete circle of Willis: a case-control study using high-resolution magnetic resonance angiography. *J Headache Pain* 2014;15:27.
- Eikermann-Haerter K, Huang SY. White Matter Lesions in Migraine. *Am J Pathol* 2021;191:1955–62.
- Hadjikhani N, Sanchez Del Rio M, Wu O, Schwartz D, Bakker D, Fischl B, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci U S A* 2001;98:4687–92.
- Cucchiara B, Detre J. Migraine and circle of Willis anomalies. *Med Hypotheses* 2008;70:860–5.
- Kruit MC, van Buchem MA, Hofman PAM, Bakkens JTN, Terwindt GM, Ferrari MD, et al. Migraine as a risk factor for subclinical brain lesions. *JAMA* 2004;291:427–34.
- van der Grond J, van Raamt AF, van der Graaf Y, Mali WPTM, Bisschops RHC. A fetal circle of Willis is associated with a decreased deep white matter lesion load. *Neurology* 2004;63:1452–6.
- Cavestro C, Richetta L, L'episcopo MR, Pedemonte E, Duca S, Di Pietrantonj C. Anatomical variants of the circle of willis and brain lesions in migraineurs. *Can J Neurol Sci* 2011;38:494–9.

Ethics

Ethics Committee Approval: The study was approved by Bezmialem Foundation University local ethics committee Committee (Decision no: 224/153, Date: 17.04.2024).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

Authorship Contributions: Methodology and design: AY, SB. Data Collection: AY, SB. Data Analysis: SB. Literature Search: AY. Writing: AY.

Copyright Transfer Form: Copyright Transfer Form was signed by all authors.

Peer-review: Internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.