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Characteristics and clinical correlates of white matter changes in brain magnetic resonance of migraine females

Iwona Rościszewska-Żukowska [a,*], *Monika Zając-Mnich* [b], *Piotr Janik* [c]

[a] *Department of Neurology, The Holy Family Specialist Hospital, Rudna Mala, Rzeszow, Poland*
[b] *Clinical Department of Radiology, Provincial Hospital No. 2, named after St. Jadwiga the Queen, Rzeszow, Poland*
[c] *Department of Neurology, Medical University of Warsaw, Poland*

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ABSTRACT

Objective: White matter hyperintensities (WMHs) were often found in migraine patients. The aim of study was to characterize WMHs, assess their prevalence, determine relationship to clinical symptoms and homocysteine levels in migraine females.

Methods: 69 women 38 with migraine without aura (MO), 31 with migraine with aura (MA) who underwent brain MRI with 1.5T scanner were enrolled. The WMHs number, location and size in FLAIR sequence were evaluated. Migraine severity was measured by pain intensity, number of attacks per month and MIDAS scale.

Results: WMHs were found in 39.1% females. There was no WMHs and migraine type correlation. The total WMHs number was higher in MO ($p = 0.027$). Patients with WMHs were older ($p = 0.025$), have higher BMI ($p = 0.042$), suffered longer ($p = 0.001$), more often had positive pregnancy history ($p = 0.010$) and less frequent prodromal symptoms. The age of onset, migraine's severity and homocysteine did not correlate with WMHs. No effect of antimigraine medication and oral contraceptive pills (OCP) was found. Both in MO and MA groups WMHs were located only supratentorially. In MO females WMHs were mainly located in one cerebral hemisphere ($p = 0.024$) whereas in MA were found bilaterally. WMHs were most commonly located in the frontal lobes. In MO lesions were small ≤3 mm and present in almost all MO patients ($p = 0.027$).

Conclusion: WMHs are present in more than one third of migraine females, regardless of aura. WHMs are located supratentorially, subcortically and in the frontal lobes. Older age, longer disease's duration, obesity and positive history of pregnancy are main risk factors for WMHs. Symptomatology and migraine severity, hyperhomocysteinemia, OCP and antimigraine medications do not increase WMHs.

* *Corresponding author at*: Department of Neurology, The Holy Family Specialist Hospital, Rudna Mala 600, 36-060 Glogow Malopolski, Poland.
E-mail address: iwona.rosciszewska@op.pl (I. Rościszewska-Żukowska).
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1. Introduction

Migraine is one of the most common primary headaches [1] that affects approximately 10–15% of the general population. Its incidence has been gradually increasing in recent years; by 15.3% over the past decade [2]. It provokes significant disability and affects negatively the quality of life [3]. In Polish population the incidence is about 10%, three times more often in women than in men [4]. Among patients with migraine various vascular pathologies are found in the brain magnetic resonance imaging: mainly white matter hyperintensities (WMHs) and subclinical infarcts mostly located in posterior circulation territory [5]. Results of previous studies concerning WMHs, relationship with type of migraine, sex and age are not conclusive. It has been reported, that WMHs are two times more frequent in migraine patients than in general population [6,7]. According to Bashir et al. it is even four times more frequent [8], while other authors report that its prevalence is not different from the healthy population [9]. They are found in 9–59% of migraine patients, according to some researchers more frequently in migraine without aura (MO) [10], while others report it more frequently in migraine with aura (MA) [7]. Moreover, new WMHs may appear with disease progression. The wide range of WMHs prevalence is due to age and gender population differences, the variety of slice thickness and magnetic field strength MRI scanners, and definition of WMHs (Table 1). The relationship between the severity of migraine symptoms and the presence of WMHs is not definitively established. While Seneviratne et al. found correlation between WMHs and rate of migraine attacks [11], Kruit et al. reported this relationship only for females [6]. There are also papers where no such correlation was established [7,12]. Although pathology of WMHs is still not well known and may be multifactorial [13], some authors claim that WMHs strongly correlate with cerebrovascular diseases and risk factors related to them [14,15] but other studies have not confirmed that finding [16–19].

2. Material and methods

A total of 69 female patients with migraine, aged 18–60 yrs (mean: 36.2 ± 9.3) were included in the study: 38 women with MO and 31 with MA. Minimal disease duration was of one year with frequency of migraine attacks ranging from 1 to 8 per month. All the participants met the criteria of migraine as defined by ICHD-3 Beta Headache Classification Criteria 2013 [1], that was revised in 2018. All subjects were diagnosed and evaluated in Neurology Outpatient Clinic. The patients were consecutive women with the diagnosis of migraine. We found only few male cases while recruiting patients into the research. There are some evidence that the incidence of WMH in brain may be dependent on gender and because of relatively small group of our patients we decided to not include males to avoid confusion and non-matched gender population. The following inclusion criteria were established: female sex, age ≤60 yrs, and absence of significant risk factors for cardiovascular disease (hypertension, diabetes mellitus, coronary heart disease and thromboembolic disease). According to study protocol vital signs and biometric parameters (weight, BMI) were assessed as well as physical and neurological examinations were performed. All participants completed the questionnaire containing personal data, disease characteristics such as the frequency and intensity of migraine pain in the past 3 months, pain location, type of migraine aura, the presence of prodromal symptoms, the presence of menstrual migraine pain, pregnancy history including spontaneous abortions, family history of migraine, smoking, drinking coffee, current treatment and MIDAS questionnaire assessing migraine-related disability measured by reduced number of days with normal functioning at work, household chores and non-workers activity (social, family and leisure activities) due to migraine in the last 3 months. The MIDAS score was the sum of missed work days, household chores days, non-work activity days, and days at work and days of household chores where productivity was reduced. In addition, serum homocysteine level in blood was measured. Fasting serum was examined with CLIA analyzer ADVIA Centaur XP by Siemens (reference range: 3.70–13.9 μmol/l). Hyperhomocysteinaemia was determined at >15 μmol/l, which is the most commonly used cut-off [26]. All patients underwent brain magnetic resonance imaging (MRI) scans, with OPTIMA MR 360 1.5T scanner. Imaging was performed in FSE T1 sequence (axial plane, without and with contrast), FR-FSE T2 sequence (axial, sagittal and coronal planes), IR-FSE 2D T2 FLAIR sequence (axial, sagittal planes) and SE/EPI DWI sequence (axial plane), 3 mm slices thickness. Initial analysis was performed by a non-blinded radiologist who evaluated the presence of pathology in the whole brain without thorough analysis of the changes in the white matter. Then, two independent researchers: a blinded radiologist and a neurologist experienced in neuroimaging, trained particularly in assessing of WMHs, assessed the presence, number, anatomical location and size of WMHs. In cases of doubts, decision to qualify the change as WMHs was made jointly. To compare the results obtained in other studies, the definition of WMHs foci was derived from the consensus of the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) 2013 [27], which is consistent with the methods used in other studies [6,23]. According to the STRIVE criteria, WMHs are hyperintensive in both T2 and FLAIR images, which could be seen as iso- or hypointensive in T1-dependent images (Table 2). Number, location and size of lesions were assessed in 2D FLAIR axial plane, size of the foci was estimated using caliper similar to the CAMERA study [6]. The changes were grouped according to the location: lobes (frontal, parietal, temporal, occipital), hemisphere (one and both hemispheres), artery circulation territory (anterior cerebral artery, medial cerebral artery, posterior cerebral artery), location in the white matter (juxtacortical, subcortical, periventricular, infratentorial using the Barkhof criteria for multiple sclerosis). Based on the size of the foci, they were grouped into three subgroups: small changes: ≤3 mm, medium: 4–6 mm and large: >6 mm – similarly to other studies [23]. The study protocol was approved by the Bioethics Committee.

Table 1 – Population-based studies and clinical-based studies of white matter hyperintensities in migraine.

Ref.	MRI	Slice thickness	Population	Number of patients with migraine	Age (yrs) mean (SD)	MA:MO	Women (%)	WMHs N	OR (95 CI)	Number of healthy controls
Population-based studies										
CAMERA-1 Kruit et al. 2004 [6]	1.0–1.5T	3 mm	Dutch	295	48.2 (0.6) MA 48.8 (0.7) MO	161:134	72 MA 75 MO	65 (22%) 34 (21%) MA 31 (23%) MO	MA 2.0 (1.0–4.3) MO 2.1 (1.0-4.7)	140
EVA MRI Kurth et al. 2011 [7]	1.0T	1.4 mm	French	116	68.9 (2.8)	17:99	85.3	48 (41%) 10 (59%) MA 38 (38%) MO	MA 12.4 (1.6–99.4) MO 1.6 (0.9–2.7)	617
CAMERA-2 Palm-Meinders et al. 2012 [20] Progression of WMH in followed up after 9 years	1.0–1.5T	Not given	Dutch	203	57 (7.3)	114:89	71	58 (29%) 33 (29%) MA 25 (28%) MO	Progression of WMHs over time 2.1 (1.0–4.1)	83
ARIC MRI Hamedani et al. 2013 [10] Progression of WMH in followed up after 11 years	1.5T	Not given	American	1425	59 (5.4) MA 58 (5.5) MO	422:1003	82 MA 76 MO	Only severe WMHs included ≥3 scores (range: 0–9) (used CHS – Cardiovascular Health Study scale)	MA 0.55 (0.17–1.83) MO 1.87 (1.04–3.37) Progression of WMHs over time MA 2.09 (−0.99 to 5.16) MO 1.86 (−0.39 to 4.11)	10082
HUNT MRI Honningsvåg et al. 2015 [21]	1.5T	Not given	Norwegian	91	57.7 (4.3)	Not given	73.6	9 (9.9%) Only severe WMHs included ≥2 Fazekas scores; (range: 1–3)	Not given	552
Clinical-based studies										
Rossato et al. 2009 [22]	1–1.5T	5 mm	MA	185	36.0 (10)	185 MA	77	87 (47%)	NA	Not given
Trauninger et al. 2010 [17]	3.0T	3 mm	MA + MO	186	35.4 (8.9)	45:141	83.9	58 (31.2%) 16 (35.6%) MA 42 (30.5%) MO	NA	Not given
Seneviratne et al. 2012 [11]	1.5T	5 mm	MA + MO	44	44.7	18:26	84	19 (43%) 12 (63.4%)MA 7 (36.8%)MO	NA	Not given
Toghae et al. 2015 [12]	1.5T	Not given	MA + MO	90	36.1 (13.1)	20:70	76.7	29 (32.2%)	NA	Not given
Avci et al. 2015 [23]	1.5T	5 mm	MA + MO	216	32.6 (3.9) MA 30.9 (7.6) MO	73:143	82.2 MA 73.4MO	69 (32%) 25 (34.2%) MA 44 (30.8%) MO	4.35	216

Table 1 (Continued)

Ref.	MRI	Slice thickness	Population	Number of patients with migraine	Age (yrs) mean (SD)	MA:MO	Women (%)	WMHs N	OR (95 CI)	Number of healthy controls
Vijiaratnam et al. 2016 [24]	1.5T	Not given	MA + MO	505	41 (13.6) MA 39 (14) MO	257:248	84 MA 87 MO	202 (40%) 100 (39%) MA 102 (41%) MO	NA	Not given
Zhang et al. 2016 [25]	3T	3 mm	MA + MO	116	33.6 (6.9) MA 33.8 (6.8) MO	56:60	86 MA 75 MO	75 (32%) 34 (29%) MA 41 (35%) MO	Not given	54

Abbreviations: CAMERA, Cerebral Abnormalities in Migrainean Epidemiological Risk Analysis; EVA, epidemiology of vascular ageing; ARIC, atherosclerosis risk in communities; HUNT, the Nord-Trondelag Health Study; MRI, magnetic resonance imaging; *N*, number of patients; SD, standard deviation; MA, migraine with aura; MO, migraine without aura; WMHs, white matter hyperintensities; OR, odds ratio; NA, not applicable, there was no control group and OR was not able to calculate.

2.1. *Statistical analysis*

Since the analyzed laboratory parameters were characterized by quite significant asymmetry of distribution, the tables indicate the median value, which reflects better the average level of these parameters. Statistical significance of tested dependencies was assessed with appropriate statistical tests: the differences in the distribution of clinical parameters were tested with the Mann–Whitney test, the comparison of percentage distribution (or the incidence of certain health events, including the presence, location of WMHs in MR) was tested with chi-square independence test to evaluate the significance of differences between groups. Due to small number of patients distributed in each group, Fisher's test was used to assess statistical significance of antimigraine drugs. Probability value (p) was considered significant at the level of <0.05.

3. Results

WMHs were found in 27 (39.1%) females with migraine, with no correlation with migraine type: MA 10 (32.3%) vs. MO 17 (44.7%). The overall number of lesions was greater in MO (4.65 $\pm$ 3.97) than in MA (3.80 $\pm$ 8.16); $p = 0.027$. It was found, that older age, longer disease duration (Table 3) and BMI $\geq$ 25 (Table 4) were significant risk factors for the incidence of WMHs. There was no relationship between migraine severity and WMHs prevalence (Table 3).

The type of aura, location of migraine pain had no influence on WMHs. Prodromal symptoms were found less frequently in WMH+ group (Table 4). Positive family history, regardless of the proximity of kinship was not a risk factor for WMHs in migraine females, whereas positive pregnancy history was strongly correlated with the presence of WMHs (Table 4). Precise analysis of WMHs+ who had been pregnant indicated that the onset of migraine before pregnancy was the strongest predilection factor for developing of WMHs, irrespective of the frequency of migraine attacks during the pregnancy time (data not shown). All participants were analyzed with regard to the presence of menstrual migraine pain, and this did not correlate with the presence of WMHs (WMHs+ 19; 70.4% vs. WMHs− 23; 54.8%; $p = 0.131$).

Use of stimulants like smoking (WMHs+ $n = 3$; 11.1% vs. WMHs− $n = 7$; 16.7%; $p = 0.561$) or drinking coffee (WMHs+ $n = 22$; 81.5% vs. WMHs− $n = 29$; 69.0%; $p = 0.149$) even with respect to amount of cups of coffee (range: 1–4) consumed during the day did not affect the presence of WMHs.

There was no correlation between the use of oral contraceptive pills and the risk of WMHs regardless of whether the drugs were used in past or currently. Analysis of drugs used to relieve the migraine pain: triptans, non-steroidal anti-inflammatory drugs and used to prevent migraine attacks did not correlate with the presence of WMHs but some of them were used only in small number of patients (Table 5).

Radiological analysis of WMHs location in cerebral artery circulation territory showed that WMHs in all females with migraine were located in the anterior cerebral artery supplies, less frequently in the middle cerebral artery supplies and only in few cases in posterior cerebral artery supplies (Table 6). Also,

Table 2 – WMHs according to STRIVE consensus.

	White matter hyperintensity
Localization	White matter
DWI	→
FLAIR	↑
T2	↑
T1	→/↓
T2*-weighted GRE	↑

Abbreviations: DWI, diffusion-weighted imaging; FLAIR, fluid attenuated inversion recovery; GRE, gradient-recalled echo. ↑ increased signal; ↓ decreased signal; → iso-intense signal.

the location in lobes does not depend on type of migraine. Lesions were situated most frequently in frontal lobes, rarely in parietal and temporal lobes, occasionally in occipital lobes. In both groups, no infratentorial lesions were observed. The type of migraine determined only location of WMHs regarding one or both hemispheres. In MA dominated one-hemisphere changes, in MO changes were present in both hemispheres. Regardless of the nature of WMHs, white matter lesions were located: mostly subcortically, rarely periventricularly and the least frequently juxtacortically. WMHs were assessed in terms of their size: small lesions of ≤3 mm were predominant in MO, whereas medium lesions (4–6 mm) and large (>6 mm) showed similar prevalence in both groups (Table 7).

4. Discussion

WMHs are common findings in general population and can correspond with normal aging process. In asymptomatic healthy individuals WMHs correlate with age: in the forties they are present in about 11% while in the seventies even in 83% [7]. These age related lesions are associated with cardiovascular risk factors: hypertension, hypercholesterolemia, smoking and elevated BMI [28–31]. Therefore, only young and middle-aged women <60 years were included in our study group, without any co-existing vascular disease risk factors. So far, the presence of WMHs has been found to be independent risk factors for ischemic stroke in general population [32,33]. In the Rotterdam scan study, hyperintensive lesions among elderly patients (>70 yrs) were predictive factors of ischemic stroke [33]. According to other researchers, they were also

Table 3 – Clinical characteristics of WMHs in patients with migraine.

	WMHs+ (N = 27)		WMHs− (N = 42)		p-Value
	Mean (SD)	Range (min–max)	Mean (SD)	Range (min–max)	
Age (yrs)	39.0 (8.3)	23.0–60.0	34.5 (9.4)	18.0–57.0	0.025
Age of onset (yrs)	16.0 (7.1)	8.0–38.0	19.5 (8.4)	11.0–43.0	0.126
Duration of migraine (yrs)	21.0 (11.7)	1.0–45.0	11.0 (7.7)	1.0–35.0	0.001
Intensity of migraine pain (range: 0–10)	8.0 (1.73)	4.0–10.0	8.0 (1.58)	1.0–12.0	0.411
Number of migraine attacks per month	3.0 (3.04)	1.0–12.0	3.0 (2.55)	1.0–12.0	0.915
Number of pain days per month	6.0 (3.78)	1.0–15.0	5.0 (3.76)	1.0–15.0	0.188
MIDAS scale	19.0 (23.0)	4.0–72.0	27.5 (20.1)	3.0–105.0	0.118
Serum homocysteine level (μmol/l)	14.8 (5.5)	6.1–35.8	14.2 (4.4)	7.2–24.7	0.306

Abbreviations: N, number of patients; SD, standard deviation; WMHs+, white matter hyperintensities present; WMHs−, white matter hyperintensities absent.

Table 4 – Clinical characteristics of WMHs in migraine population.

	WMHs + (N = 27)		WMHs− (N = 42)		p-Value	Total	
	N	%	N	%		N	%
BMI <25	15	55.5%	33	78.6%	0.042	48	69.5%
BMI ≥25	12	44.4%	9	21.4%	0.042	21	30.4%
Pain location: bilateral	13	50.0%	15	35.7%	0.244	28	41.2%
Hemilateral/unilateral	12	44.4%	18	42.9%	0.896	30	43.5%
Hemilateral/alternating	10	37.0%	16	38.1%	0.929	26	37.7%
Type of migraine aura:							
Visual	10	38.5%	20	47.6%	0.459	30	44.1%
Sensory	0	0.0%	3	7.1%	0.163	3	4.4%
Aphasic	0	0.0%	1	2.4%	0.428	1	1.5%
Prodromal symptoms	5	19.2%	21	50.0%	0.011	26	38.2%
Positive family history	17	65.4%	23	54.8%	0.387	40	58.8%
Positive pregnancy history	23	88.5%	25	59.5%	0.010	48	70.6%

Abbreviations: N, number of patients; WMHs+, present white matter hyperintensities group; WMHs−, absent white matter hyperintensities group; BMI, Body Mass Index.
Probability value (p) was considered significant at the level of <0.05.

Table 5 – Correlations of WMHs with medications.

Medication	WMHs+ (N = 27)		WMHs− (N = 42)		p-Value	Total	
	N	%	N	%		N	%
Triptans	12	46.2%	18	42.9%	0.790	30	44.1%
Non-steroidal anti-inflammatory drugs	22	84.6%	35	83.3%	0.889	57	83.8%
Flunarizine	8	30.8%	11	26.2%	0.682	19	27.9%
Topiramate	3	11.5%	1	2.4%	0.118	4	5.9%
Iprazochrom	4	15.4%	10	23.8%	0.403	14	20.6%
Oral contraceptive pills (ever)	6	23.1%	9	21.4%	0.873	15	22.1%

Abbreviations: N, number of patients tested; WMHs+, white matter hyperintensities present; WMHs−, white matter hyperintensities absent.

predictor of recurrent ischemic stroke or stroke after transient ischemic attack (TIA) [34]. Migraine, especially MA correlates with increased risk of cerebrovascular disease [7,35] and this higher risk is present among women, particularly those smoking and using oral contraceptive pills [7,36,37] with pronounced predilection to subclinical infarcts in the posterior circulation territory, especially in the cerebellum [6,32,37–40]. Population Reykjavik Study proved that only middle-aged women with MA are predisposed to appear silent infarct-like lesions in late-life and that these lesions involve only the cerebellum [39]. Similar correlations were found in the studies regarding WMHs. In the CAMERA-1 population study increased risk for deep WMHs in both MA and MO was found only for women irrespective of other risk factors occurrence [6]. Analysis of supratentorially located WMHs progression over time showed that increasing number of these changes were found only in females [20].

Numerous studies have shown that the risk of WMHs in migraine is significantly increased (Table 1). The prevalence of WMHs seems to be higher in studies, in which participants have multiple vascular disease risk factors and are usually older (compare CAMERA-1 and EVA-MRI studies, Table 1). The lowest prevalence was found in the HUNT MRI population study, which only assessed the presence of severe hyperintensive lesions (Fazekas score ≥2 points, range 1–3) [21]. There is heterogeneity when it comes to MRI protocols. The most popular one are 1.5 Tesla scanners [11,12,22–24], while only in two studies 3 Tesla scanners were used [17,25]. The WMHs prevalence in studies that used 3T field scanners (31.2–32%) was not higher than 1.5 Tesla scanners studies (22–40%). WMHs prevalence seems to be not associated with slice thickness in MRI. Studies that used 1.4 mm, 3 mm and 5 mm showed WMHs in 41%, 22–32%, and 32–43% of patients, respectively (Table 1). The prevalence of WMHs in our study (39.1%) was similar to previous findings [11,24]. In both these studies MRI methodology as well as group selection with regard to age, sex and proportion of patients with MA and MO were comparable with our study (Table 1). According to some researchers, the risk of WMHs is significantly higher in MA [6,41]. In our study, as in some previous reports, there was a similar risk of WMHs in both MA and MO subtypes [17,42] and the presence of aura, aura type and pain location were not confirmed as predictive factors for WMHs, as was previously noted [12]. We found that age and overweight (BMI ≥ 25) were independent risk factors for WMHs prevalence in migraine patients which was consistent with other results [11,12,22,23].

So far the origin of WMHs is still unclear. Many possible pathophysiological theories of WMHs have been proposed: repeated, prolonged oligemia, blood-brain barrier dysfunction, mitochondrial dysfunction, oxidative stress, endothelial dysfunction, patent foramen ovale with right to left shunt, vascular wall inflammation [42,43]. It is believed that WMHs

Table 6 – Radiological localization of brain WMHs in migraine patients.

WMHs location	Total		Type of migraine				p-Value
	N	%	MO (N = 17)		MA (N = 10)		
			N	%	N	%	
ACA supplies	27	100.0%	17	100.0%	10	100.0%	1.000
MCA supplies	7	25.9%	5	29.4%	2	20.0%	0.590
PCA supplies	2	7.4%	1	5.9%	1	10.0%	0.693
One hemisphere	14	51.9%	6	35.3%	8	80.0%	0.024
Both hemispheres	13	48.1%	11	64.7%	2	20.0%	0.024
Subcortical	25	92.6%	16	94.1%	9	90.0%	0.693
Periventricular	4	14.8%	2	11.8%	2	20.0%	0.560
Juxtacortical	3	11.1%	3	17.6%	0	0.0%	0.158
Frontal lobe	25	92.6%	16	94.1%	9	90.0%	0.693
Parietal lobe	6	22.2%	4	23.5%	2	20.0%	0.831
Temporal lobe	3	11.1%	2	11.8%	1	10.0%	0.880
Occipital lobe	2	7.4%	1	5.9%	1	10.0%	0.693

Abbreviations: N, number of patients tested; ACA, anterior cerebral artery; MCA, medial cerebral artery; PCA, posterior cerebral artery; WMHs, white matter hyperintensities; MO, migraine without aura; MA, migraine with aura.

Table 7 – WMHs size in migraine patients.

WMHs size	Type of migraine				*p*-Value	Total	
	MO (*N* = 17)		MA (*N* = 10)				
	N	%	*N*	%		*N*	%
Small (≤3 mm)	16	94.1%	6	60.0%	0.027	22	81.5%
Medium (4–6 mm)	11	64.7%	6	60.0%	0.806	17	63.0%
Large (>6 mm)	0	0.0%	1	10.0%	0.184	1	3.7%

Abbreviations: MO, migraine without aura; MA, migraine with aura.

may consist of gliosis caused by local loss of myelin, axons and oligodendroglial cells [44]. The cause is commonly interpreted as ischemic. One of the hypotheses suggests that these neuropathological changes may be the result of hemodynamic ischemia induced by lipohyalinosis of perforating arteries and small vessels. These abnormalities may underlie the pathology of WMHs located in deep white matter of the brain. Damage of ventricular system's endothelium followed by widening of the subendothelial extracellular space results in blood brain barrier injury and periventricular white matter changes [28]. It is known, that during a migraine attack, regional cerebral blood flow is decreased, mainly in the parietal-occipital area spreading to frontal area or exclusively in frontal lobes [45] and does not affect neurovascular boundaries [46]. Nevertheless it may cause local reversible ischemia that, in case of a reduction above the threshold of ischemia, can lead to ischemic stroke [47]. We found, that almost all WMHs were located in frontal lobes, so this could confirm rather the second hypothesis. It is also believed, that recurrent migraine attacks and prolonged oligaemia may cause damage of small perforating arteries resulting in local hypoperfusion and, as a result, occurrence of WMHs, that are often interpreted as an independent markers of local brain hypoperfusion [25].

We assumed, that repeated vascular dysfunction causes local ischemia and may be the cause of WMHs. That is why we investigated the correlation between WMHs, the frequency of migraine attacks and duration of the disease. However, we found that migraine severity measured by the frequency of attacks per month, pain intensity or impairment in MIDAS scale did not influence on WMHs prevalence. These results of our study are in line with other findings [6,7,20,25]. However, others reported that increasing headache frequency was associated with higher WMHs prevalence in MO [11,17,18]. The reason of lack of WMHs correlation with migraine severity in our study may be due to assessment of migraine's parameters only in the last 3 months, not covering the duration of disease. And it is known that migraine is characterized by variability, both exacerbations and remission depend not only on successful therapy but also on numerous other factors. However, we have confirmed, as in other studies [12,17] that longer duration of the disease, irrespective of age of the patients, is a risk factor for the occurrence of WMHs indicating that these changes are developing over time. Surprisingly, we found prodromal symptoms to be protective against WMHs occurring which had not been reported before. We can speculate that pathomechanisms involved in developing of prodromal symptoms and WMHs are different.

Hyperhomocysteinemia is known to be significant risk factor for ischemic stroke caused by small arteries occlusion (lacunar strokes) [48]. According to some authors it is independent predictor of WMHs in the healthy elderly regardless of smoking, hypertension or age [49]. Some researchers found increased homocysteine serum level in migraine patients [50]. However, as in previous studies [19,20], no association of WMHs occurrence with serum homocysteine level in migraine was found in our study.

The fact that, according to some authors, increased risk of WMHs in migraine patients is limited only to women [10,20], imposed the questions about the effect of oral contraceptive pills and pregnancy. It is known that fluctuations in hormone levels occurring in the menstrual cycle affect the risk of migraine. Menstruation is an important risk factor for MA [51] and pregnancy, especially in women with menstrual migraines, improves the course of MO, whereas MA may manifest for the first time in the first and second trimesters [52]. In our study we found link between pregnancy history and WMHs regardless of migraine clinical course during pregnancy. This finding may suggest that changes in the haemostatic system typical for pregnancy with pro-coagulant stimulation and decrease in fibrinolysis may induce an activation of the WMHs pathophysiological process.

We have not found any correlation between WMHs and the use of oral contraceptives which is in line with other studies [6,12,16,53]. Only the CAMERA study showed relationship between WMHs and long-term use of oral contraceptives (>15 years). Smoking is an important atherogenic factor leading to numerous cardiovascular diseases that is why correlation between WMHs and smoking was analyzed. As in previous reports [12], we found no correlation with smoking. The reason of this may be smoking is rather related to atherosclerosis of large vessels and WMHs, if of vascular etiology, result from small vessels pathology.

Our study provides descriptions of the WMHs distribution in the brain. The results confirmed previous outcomes that showed the presence of WMHs in supratentorial region, in anterior cerebral artery circulation territory, mainly in the frontal lobes, and mostly located subcortically [6,11,12,22,23,54]. Based on MRI findings, we were able to classify WMHs in migraine females as subcortical and deep white matter lesions because periventricular white matter changes and juxtacortical lesions were found rare. As in one previous report [11], in our study there were no infratentorial abnormalities. Nevertheless, other studies described this location in individual cases [6,23]. A clear predilection for frontal lobe location is consistent with other studies [11,22,54]. In the majority of females with migraine (81.5%), as in other studies [23], determined lesions were small (≤3 mm). In our study it was also found that WMHs in patients with MA were

predominantly located in one hemisphere, and even though the majority of MA patient had visual aura, the occipital WMHs location was rare. On the other hand WMHs in MO females were found mainly in both hemispheres, being significantly higher in number than in MA. These findings may confirm that aura is not a risk factor for WMHs in migraine females and the presence and distribution of WMHs are related to migraine itself rather than aura.

Our study provides additional data on the white matter hyperintensity risk factors in migraine females, particularly positive history of pregnancy, that could be useful to better understanding of the WMHs pathophysiology in future population studies.

5. Conclusions

1. WMHs are present in more than one third of migraine females regardless of presence of aura.
2. WHMs are exclusively located supratentorially, subcortically, and mainly in frontal lobes.
3. Older age, longer duration of disease, obesity and positive history of pregnancy are main risk factors for WMHs and might provide arguments for vascular etiology of these changes.
4. Symptomatology and migraine severity, hyperhomocysteinemia, use of oral contraceptive pills and anti-migraine medications do not correlate with the developing of WMHs.

Conflicts of interest

None declared.

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