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Article type : Original Article

No association between migraine frequency and white matter lesions and silent brain infarctions: a study in a series of chronic migraine women

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Running title: White matter lesions in chronic migraine

Key words: brain MRI, migraine, migraine aura, silent brain infarctions, vascular risk factors, white matter lesions

Total Word Count: 5381

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ENE.14284

ABSTRACT

Background and purpose: It has been suggested that silent infarctions (SI) and hyperintense white matter lesions (WML) are related to migraine frequency. We studied their prevalence and anatomical distribution in chronic migraine (CM) patients.

Methods: 96 CM (mean age 43; range 16-65 years) and 29 episodic migraine (EM) women (36, 16-58 years) underwent a 1.5 T MRI following CAMERA protocol. Number, size and location of SI and deep WML (dWML) were recorded and a modified Fazekas scale was applied to assess periventricular WML (pWML).

Results: WML were found in 59 (61.5%) CM and 17 (58.6%) EM women (OR= 1.13; 95% CI 0.48-2.62, p= 0.784). The majority (63% CM and 71% EM) were small dWML. Exclusive pWML were exceptional. Of the 739 WML seen in CM patients, 734 (99.3%) were hemispheric and mostly frontal (81%). Posterior fossa WML were seen in only 5 (0.7%) CM (always in the pons) and 2 (2.1%) EM women. Age >45 was the only vascular risk factor (VRF) associated with a higher WML number (medians of 0 < 45 and of 3 >45 years, p= 0.004). We found 7 SI in 6 CM women (6.5%).

Conclusions: As compared with the expected prevalence at this age, this study confirms that the prevalence of WML, in most cases small, deep and frontal, is increased in CM and EM. However, our results do not support an association of WML or SI with a higher frequency of attacks, but with the presence VRF and mainly age > 45 years.

Introduction

Although migraine is associated with a relevant burden, traditionally it has been contemplated as a condition without long-term consequences. Migraine, however, is considered an independent vascular risk factor (VRF), especially in young women with migraine with aura [1,2].

MRI series have found that migraineurs are at increased risk for brain abnormalities of unknown pathophysiology and clinical significance, such white matter lesions (WML), silent infarct-like lesions (SI). It has been suggested that of SI and WML prevalence has a direct relationship with attack frequency [3-7]. The CAMERA study showed that migraineurs had a 7-fold increased risk for posterior fossa SI compared and that this risk increased with attack frequency (OR= 15.8 with >1 attack/month) [5-7]. We did not reproduce these findings in chronic migraine (CM) [8]. Kruit et al also found that, among migraine women, the risk of deep WML (dWML) load was significantly increased and that increased with attack frequency (OR= 2.6 with > 1 attack/month) [4].

These findings raise concerns about the consequences of migraine, specifically in women with a high frequency of attacks. In this work our aim was to address this point by analyzing the presence and distribution of WML in a series of CM women.

Patients and Methods

Patients

We included consecutive women between 16-65 years diagnosed as CM [9]. We recruited a group of women with episodic migraine (EM).

We excluded pregnant or breast-feeding women, excessive use of alcohol and serious active psychiatric or somatic disorders. We specifically excluded those patients with a stroke history, but patients with the psychiatric comorbidities commonly seen in migraine (anxiety and depression) or fibromyalgia were not excluded.

Detailed charts and calendars were available for every participant. VRF, including age >45 years, arterial hypertension, hypercholesterolemia, smoking, history of aura and analgesic overuse [9] were elicited. All subjects underwent a general and neurological examination. The study was approved by the institutional board and participants gave their written consent.

MRI protocol

MRI studies were acquired on a 1.5-T unit (Signa LX 9.1; GES, Wisconsin, USA) using a standard quadrature head coil and following the CAMERA-I protocol [4]. Brain images were acquired with 40 contiguous, 3-mm axial slices (field of view, 22 cm; matrix, 192x256). Sequences included FLAIR (TR/TE/TI/NEX, 8000/120/2000/1) and DP/T2 /TR/TE/NEX/echo-train length, 2100/12.5-76/2/6). In addition, 20 5-mm, sagittal brain images fast T1 FLAIR (TR/TE/TI/NEX, 1800/7.7/750/2) were acquired as part of the routine protocol, but not included in the analysis.

Two neuroradiologists (A.M. and E.S.) blinded to diagnosis (CM or EM) rated SI and WML on hard copies. A third neuroradiologist (A.S.) made the final diagnosis in cases in which the raters disagreed. Infarcts were defined as non-mass parenchymal defects, with a vascular distribution, isointense to cerebrospinal fluid signal on all sequences, and, when supratentorial, surrounded by a hyperintense rim on FLAIR and proton density images (Figure 1). Number, location, and size of infarcts were recorded. Virchow-Robin spaces were excluded as infarcts based on location, shape, size and absence of a hyperintense border [10]. To determine whether there was a preferential damage for any one vascular system, we scored infarct by location and vascular supply. Topographical maps were used to define 4 categories that reflected the 2 major territories of blood supply to the brain (anterior circulation and posterior circulation) and 2 areas with a heterogeneous blood supply (basal ganglia and corona radiata/centrum semiovale) [11]. Posterior circulation SI were classified into supra and infratentorial. The infratentorial SI were further subclassified as either territorial or junctional according to previously reported criteria and following Kruit et al [4]. Territorial lesions occupied the territory of the posterior inferior cerebellar artery, the medial or lateral branches of the posterior inferior cerebellar artery, the territory of the superior cerebellar artery, the medial and lateral branches of the superior cerebellar artery or the territory of the anterior inferior cerebellar artery. Junctional lesions were located at the boundary region (defined as $\leq$5 mm from the indicated border in the template) between two territories.

WML had to be hyperintense on all sequences and were divided into periventricular (pWML) and dWML. Both were evaluated following CAMERA-I methodology. pWML by the Fazekas semiquantitative scale [12], which evaluates pWML globally, but we modified it to be

applied in three regions: adjacent to anterior (frontal) horns, walls of the lateral ventricles (bands) and occipital horns. pWML were assessed in these 3 regions and rated as 0 (no pWML), 1 (pencil-thin lining), 2 (smooth halo or thick lining) or 3 (large confluent lesions). The 3 regional scores were added for the final score (0-9). dWML were rated by lobe location, number and size, as measured with a caliper on the FLAIR image (Figure 2). The WML count was combined to get a measure of load by multiplying each lesion by a size-dependent constant (0.0042 mL for small [≤3 mm] lesions, 0.114 mL for medium [4-10 mm] and 0.9 for large [>10 mm] lesions. All values of the lesioned volume were grouped and divided into quintiles; a volume in the superior quintile was considered as "high load".

Data analysis

Continuous variables were described by mean±standard deviation, minimum and maximum values are provided. They were compared by using standard parametric Student-Welch or non-parametric Mann-Whitney tests, depending the distribution normality. Categorical variables were described by absolute and relative frequencies. Exact proportion test was used from testing the equality among the groups. Crude and adjusted odd ratios were used as effect sizes measures. Relationship between the number of WML and headache frequency was studied through linear regression. P-values below 0.05 were considered significant. Analyses were carried out with software R 3.1 (www.r-project.org). We followed the STROBE statement (https://www.strobe-statement.org/index.php?id=strobe-home) and therefore, no multiple testing corrections have been made.

Results

We included CM 96 (mean age 43 years; range 16-65 years) and 29 EM (36; 16-58, p=0.015) women. This final numbers allow us to declare significant (at standard Type I error of 5%) 80% of the times (Type II error of 0.2) those differences above 30%. By history, the average time in which patients had remained in a CM situation was 8.4 years (range 1-38 years). A history of aura was elicited in 48 (50%) of CM and in 15 (51.7%) of EM patients. Only 5 CM and 2 EM patients

exhibited aura in more than 50% of attacks in the last year. Comorbidities, VRF and treatments appear in table 1.

White matter lesions

Seventy-six migraineurs (60.8%) had at least one WML. WML were found in 59 (61.5%) CM and in 17 (58.6%) EM women (p=0.517, crude OR of 1.43 (0.49-4.18)). The OR adjusted by individual VRF ranged between 1.04 (0.44-2.44) and 1.11 (0.47-2.61). Adjusting by number of VRF, age and comorbidities, OR was 0.94 (0.28-3.15). Time of evolution of CM was associated with a higher risk of WML (OR 1.09; 1.02-1.18); however, this effect disappeared when we adjusted by number of VRF, age and additional comorbidities (OR 1.02; 0.94-1.10)). The majority were dWML (63% for CM and 71% for EM). Twenty-two patients (22.9%) with CM and 5 (17.2%) with EM had pWML (p=0.942 crude and adjusted OR of 1.03 (0.28-3.15) and 0.70 (0.27-1.85), respectively). Exclusive pWML were exceptional; they were detected in only 2 CM and in no EM women (p=1.00). The most frequent location for pWML was around anterior horns (90.9% in CM and 100% in EM women), followed by posterior horns (54.5% in CM and 20% in EM) and ventricular bands (40.9% in CM and 0% in EM). None were significant due to the low number of cases. Even though final scores in the Fazekas scale was numerically, in average, higher for CM (0.6) as compared to EM (0.2), differences were not significant (p= 0.432) and exactly 50% in both groups had a 0 score in this scale. When patients were classified in three categories according their scores in the modified Fazekas scale (0= no lesions: 77.1% of CM vs 82.8% EM patients; 1-2= mild load: 12.5% of CM vs 17.2% EM patients; and 3-9= moderate-severe load: 10.4% of CM vs 0% EM cases) no differences were found (p=0.671). Table 2 shows crude and adjusted OR. Age, VRF and other comorbidities (yes/no) were included in the models. To further analyze a potential association between migraine frequency and WML we did a regression analysis considering the average number of headache days in the three months previous to the MRI study in each patient. WML were not affected by medications. Median WML number in those were taking symptomatic or preventive treatment and in those who were not taking these drugs was 1 in both cases (p=0.260 for symptomatic treatment and p=0.762 for preventatives). Differences in median number of WML in those who were using or not NSAIDs, triptans, beta-blockers, topiramate or amitriptyline were below 2 with p-values > 0.2. Regression coefficient for WML/frequency of

headache days was 0.15 (-0.26 to 0.55), with p and r2 values of 0.477 and 0.008, respectively. When adjusted by covariables, regression coefficient was 0.10 (-0.32 to 0.52), with p and r2 values of 0.362 and 0.085, respectively

We saw dWML in 57 women (59.4%) with CM and in 17 (58.6%) with EM (p=0.784, crude and adjusted OR of 1.13 (0.48-2.62) and 0.73 (0.27-1.94), respectively). Regarding dWML, the average number was 7.7 (range 0-177) in CM (total number 739) and 3.2 (0-27) in EM (total number 93) (p= 0.078), most of small size. In both groups, 50% of patients showed 0 or 1 lesions. Of the 832 WML, 734 (99.3%) were hemispheric, frontal being the most common (80.6% in CM and 82.8% in EM), followed by parietal (14.7% in CM and 14.0% in EM), temporal (3.8% in CM and 1.1% in EM) and occipital (0.1% in CM and 0% in EM). At least one frontal lesion was seen in 57 (59.3%) CM and in 15 (51.7%) EM women. The average number of frontal dWML in CM was 10.5 vs 5.1 in EM (p= 0.065). dWML prevalence in terms of size did not significantly differ between CM and EM: large lesions (6.3% vs 3.4%), medium lesions (43.8% vs 31.0%) and small lesions (53.1% vs 51.7%). We could not find significant differences between CM and EM in the proportion of large (3.2% vs 1.1%) or medium size (38.6% vs 29.0%) dWML, but the percentage of small size lesions was significantly higher (69.9% vs 58.2%; p= 0.040) in CM vs EM women. In terms of dWML lesional load, there was no difference between CM and EM in any of the 5 quintiles. The low dWML load group was the most numerous (40.6% for CM and 41.4% for EM), while high dWML load was seen by 20.8% of the CM vs 17.2% of the EM patients. Regardless of migraine type, pWML prevalence was higher in patients also showing dWML vs without dWML (33.8% vs 3.9%; p< 0.001). Also, women with high dWML load had a higher prevalence of pWML as compared to those without high lesion load (52.0% vs 14%; p< 0.001). pWML prevalence was higher in women with than in those without dWML, both in CM (35.1% vs 5.1%; p< 0.001) and EM (29.4% vs 0.0%; p< 0.001). Posterior fossa WML were seen in only 5 (0.7%) CM and 2 (2.1%) EM women.

Relationship between WMLs and VRF

Prevalence of at least one VRF among women with dWML in the CM group was 89.5% and 70.6% in the EM group (p= 0.112). dWML prevalence was numerically different in those patients with at

least 1 VRF vs those without VRF, both in CM (63.0% vs 40.0%; p=0.151) and EM (63.2% vs 50.0%; p=0.694).

When VRF were analyzed separately, analgesic overuse was significantly more frequent in CM than in EM (35.1% vs 0.0%; p=0.004). Age > 45, hypertension, hypercholesterolemia and smoking were more frequent in CM vs EM cases, but not significant (table 1). While overuse did not influence the presence of dWML, in both diagnostic groups dWML prevalence was higher > 45 years as compared to < 45 years, though -due to the sample size- this difference was significant only in CM (76.1% vs 44.0%; p=0.002). dWML were numerically more frequent in CM in those with vs those without hypertension (81.8% vs 56.5%) and in those with vs without a smoking habit (81.8% vs 56.5%), but hypercholesterolemia (58.8% vs 59.5%) or aura (56.3% vs 62.5%) did not influence the number of dWML. Although the numbers for the EM group were lower, numerical data were superimposable.

Analyzing the subjects with high dWML load, dWML prevalence was significantly higher only > 45 years. These results were seen both for CM, where high load was found 37.0% of those > 45 years vs 6.0% in younger women (p< 0.001), and for EM, where high load was found in 50.0% of women > 45 years vs 4.8% in younger women (p= 0.013). While a higher numerical prevalence of high lesion load was seen (for CM and EM) in women with vs without hypertension, hypercholesterolemia, smoking, overuse or aura were not associated with a higher numerical prevalence of high dWML load.

Silent Infarcts

We found 7 SI in 6 CM women (6.5%). Four were in the basilar territory: 2 in the pons, 1 in the cerebellum and 1 in the medial temporal lobe. The remaining 3 were seen 2 in the basal ganglia and 1 in the lateral temporal lobe. The infratentorial lesions were territorial. At least 2 VRF were seen in 5 of these 6 CM patients. No SI images were detected in the EM group. Five (83.3%) of the 6 patients with SI also had WML; all 5 had dWML (4 with high lesion load) and 2 also pWML.

Discussion

Our data confirm that WML prevalence (60.8%) is increased in migraineurs when compared to that expected in the population [13,14], which should fall below 20% at the age of our series [4]. WML prevalence, however, was similar in CM (61.5%) and EM (58.6%) and statistics did not show an association between migraine type or headache frequency and WML. Taking into account the headache frequency of our CM women and their long history, these data do not support a relationship between the presence of these lesions and migraine frequency, as suggested mainly by the CAMERA-I study, which considered "high" attack frequency having ≥1 attack/month [4].

The SI prevalence in the CAMERA-I was 8.1% for migraineurs (most in the posterior circulation) and 5.0% for controls. We found just 7 SI in 6 CM patients (6.5%); 3 of them supratentorial. These results concur with those already reported by our group in CM patients showing that frequency of migraine attacks itself is not a factor increasing posterior fossa SI lesion risk [8].

One of our aims was to analyze the anatomical distribution of these WML and to study its possible relationship with migraine frequency. Two population studies have investigated this point [4,15]. The majority of our patients with WML (62.8%) had exclusively dWML. Less than one-quarter of EM or CM patients had pWML and exclusive pWML were exceptional; they were detected in only 2 CM and in no EM women. Anatomical distribution of pWML (anterior horns>>posterior horns>ventricular bands) and the presence of a maximum 3 lesions, as happened in 9 out of 10 CM cases, are of help in the differential diagnosis between migraine and new onset multiple sclerosis [16]. The most frequent location for pWML was around the anterior horns (90.9% in CM and 100% in EM women), followed by posterior horns and ventricular bands. pWML prevalence in the CAMERA-I was 80.6% [4], much higher than our 22.9% and of that of the EVA-MRI study [15]. As the methodology of this work is superimposable to that of the CAMERA-I study, this relevant difference could be explained by the different origin of our series and, probably, by the higher proportion of VRF and particularly age > 45 years in the CAMERA series. In any case, these findings again do not support a relationship between pWML and migraine frequency.

Our prevalence of dWML (59.4%) was apparently higher than that found in the CAMERA (37%) and EVA-MRI (41%) studies. However, if, in line with the previous studies, we consider only dWML >4 mm, our prevalence of dWML decreases to 40.8% and concurs with previous reports.

Only 20.8% of our CM cases exhibited high lesion load, a percentage lower than the 41.4% seen in the EVA-MIG study [15] and similar to the 22.0% found by Kruit et al [4], which, again, does not support the suggestion that dWML directly correlate with attack frequency. By contrast, and though not significant, both the average number of dWML was higher in CM (7.7) than in EM (3.2) and the average global lesion load was also higher in the CM (0.6 ml) vs EM (0.01 ml). These differences, however, disappeared when VRF, and especially age > 45, were included in our analysis. These findings concur with series which strongly correlate these lesions with VRF and particularly age > 45 [12,17,18]. Interestingly, a history of aura, in general and in both groups, was not associated with a higher dWML prevalence or lesion load. The effect of aura over dWML is controversial. Several studies have found a higher risk of stroke in patients with migraine with aura [14,19-24] and the EVA-MRI was able to find a significant association between dWML in migraine with aura [15]. However, data coming from this series, from the CAMERA study [4] and from a recent study [25] have not found a higher risk of dWML in migraine aura. These differences should be clarified in bigger series and using a homogeneous approach of aura diagnosis.

The distribution of dWML in CM and EM patients was coincidental and suggestive of a microvascular origin: both groups showed dWML of small size, supratentorial predominance and mostly located in the frontal lobes, which fits with the pattern described for WML of vascular origin [26]. It has been proposed that the poor degree of collaterals in the frontal deep white matter could explain its higher vulnerability to develop ischemic lesions of small vessels [26,27]. The nature of pWML is more controversial. Classical studies have suggested that, considering its location and specific morphology (pencil-thin lining, smooth halo or thick lining), these lesions could be the result of dynamic CSF abnormalities [28]. However, recent MRI studies, using white matter segmentation or 3D mapping techniques, have not been able to confirm this hypothesis and suggest that both deep and periventricular lesions would share a common mechanism [29]. Our results, showing a clear association between the two types of lesions and a similar anatomical pattern (frontal for dWML and around anterior horns for pWML) make more probable the hypothesis of a common mechanism.

Several limitations deserve a comment. First, this is a clinic-based series and therefore not necessarily extrapolatable to the population. Second, it can be argued the rather small size of the

EM group. Our objective here was to test whether migraine frequency correlates with a higher number of WML and that was the reason to recruit a bigger CM sample. From several published studies there are already enough data available from general population and for EM patients to be compared with our CM results for all variables analyzed. In fact, one of the reasons to include the EM group was to keep our neuroradiologists blind to their diagnosis. Finally, most of our patients used both acute and preventive treatment for their migraines and it is fair to recognize that their effect on WML is unknown. While fewer than 5% of migraineurs in the CAMERA study took prophylactic therapy, most of our patients used preventatives. It remains uncertain whether preventatives reduce the risk of infarct-like lesions and this could be a hypothetical explanation for our basically negative findings. There are, however, no solid arguments supporting this hypothesis, which seems unlikely considering the long duration of CM and the fact that women included in this study were still meeting CM criteria when MRI was obtained according to their headache diary. On the other hand, most of our patients were using either NSAIDs and or triptans as symptomatic medications. The relationship between NSAIDs/triptans and stroke risk is controversial. Even though some NSAIDs could theoretically be protective due to their potential antiplatelet actions [30], high and frequent doses of these drugs -as happens in CM- have been shown to increase the stroke risk [31,32]. In spite of the vasoconstrictor potential of triptans, there is no evidence that they increase the risk of infarct-like lesions [33] and our results, coming from patients with a high frequency of use of these medications, provide additional reassurance.

Our results indicate that it is premature to conclude that attack frequency itself further increases the presence of WML, already known to be more prevalent in the migraine brain. As the clinical significance of WML (or posterior fossa SI) in terms of negative functional consequences for the migraine brain remains obscure and controversial [34], routine MRI scans are not indicated in CM evaluation but to rule out secondary forms of migraine and priority should be given to address modifiable VRF [35,36].

Acknowledgments

This work was supported by PI14/00020 FISSS grant (Plan Nacional I+D+I, Fondos Feder, ISCIII, Ministry of Economy, Spain

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure of conflict of interest

The authors declare no financial or other conflicts of interest.

References

1. Kurth T, Schurks M, Logroscino G, Gaziano JM, Buring JE. Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. *BMJ* 2008; 337: a636. doi:10.1136/bmj.a636.

2. Schurks M, Rist PM, Bigal ME, Buring JE, Lipton RB, Kurth T. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009; 339: b3914. doi: 10.1136/bmj.b3914.

3. Swartz RH and Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. *Arch Neurol* 2004; 28: 791-798.

4. Kruit MC, van Buchem MA, Hofman PA, *et al*. Migraine as a risk factor for subclinical brain lesions. *JAMA* 2004; 292: 427-434.

5. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Infarcts in the posterior circulation territory in migraine: the population-based MRI CAMERA study. *Brain* 2005; 129: 2068-2077.

6. Kruit MC, van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: The population-based MRI CAMERA-study. *Cephalalgia* 2010; 30: 129-136.

7. Scher AI, Gudmundsson LS, Sirgurdsson S, *et al*. Migraine headache in middle age and late-life brain infarct. *JAMA* 2009; 301: 2563-2570.

8. Santamarta E, Meilán A, Saiz A, *et al*. Chronic migraine does not increase posterior circulation territory (PCT) infarct-like lesions. *J Neurol Sci* 2018; 336: 180-183.

9. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia* 2013; 33: 629-808.

10. Tatu L, Moulin T, Bogousslavsky J, Duvernoy H. Arterial territories of human brain: brainstem and cerebellum. *Neurology* 1996; 47: 1125-1135.

11. Bokura H, Kobayshi S, Yamaguchi S. Distinguishing silent lacunar infarction from enlarged Virchow-Robin spaces: a magnetic resonance imaging and pathological study. *J Neurol* 1998; 245: 116-122.

12. Fazecas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *Am J Roentgenol* 1987; 149: 351-356.

13. Swartz RH, Kern RZ. Migraine is associated with magnetic resonance imaging white matter abnormalities: a meta-analysis. *Arch Neurol* 2004; 61: 1366-1368.

14. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: a systematic review and meta-analysis. Neurology 2013; 81: 1260-1268.

15. Kurth T, Mohamed S, Maillard P, *et al*. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. BMJ 2011; 342:c7357. Doi:10.1136/bmj.c7357.

16. Lapucci C, Saitta L, Bommarito G, *et al*. How much do periventricular lesions assist in distinguishing migraine aura from CIS? *Neurology* 2019; 92: 1739-1744.

17. de Leeuw FE, de Groot JC, Achten E, *et al*. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J Neurol Neurosurg Psychiatry* 2001; 70: 9-14.

18. Konáromy H, He M, Perlaki G, et al. Influence of hemispheric white lesions and migraine characteristics on cortical thickness and volume. J Headache Pain 2019; 20:4. Doi:10.1186/s10194-019-0959-2.

19. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischemic stroke in people with migraine: systematic review and meta-analysis of observational studies. *BMJ* 2005; 330(7482): 63. Doi:10.1136/bmj.38302.504063.8F.

20. Stang, Carson AP, Rose KM, *et al*. Headache, cerebrovascular symptoms, and stroke: The Atherosclerosis Risk in Communities Study. *Neurology* 2005; 64: 1573-1577.

21. Becker C, Brobert GP, Almqvist PM, Johansson S, Jick SS, Meier CR. Migraine and the risk of stroke, TIA, or death in the UK (CME). *Headache* 2007; 47: 13741384.

22. Schurks M, Rist PM, Bigal ME, *et al*. Migraine and cardiovascular disease: systematic review and meta-analysis. *BMJ* 2009; 339:b3914. Doi:10.1136/bmj.b3914. 23. Bigal ME, Kurth T, Santanello N, *et al*. Migraine and cardiovascular disease: a population-based study. *Neurology* 2010; 74: 628-635.

24. Spector JT, Kahn SR, Jones MR, Jayakumar M, Dalai D, Nazarian S. Migraine headache and ischemic stroke risk: an updated meta-analysis. *Am J Med* 2010; 123: 612-624.

25. Uggetti C, Squarza S, Longaretti F, *et al*. Migraine with aura and white matter lesions: and MRI study. *Neurol Sci* 2017; 38: 11-13.

26. Medrano Martorell S, Cuadrado Blázquez M, García Figueredo D, González Ortiz S, Capellades Font J. Hyperintense punctiform images in the white matter: a diagnostic approach. *Radiología* 2012; 54: 321-35.

27. Kruit MC, Launer LJ, Ferrari MD, van Buchem MA. Brain stem and cerebellar hyperintense lesions in migraine. *Stroke* 2006; 37: 1109-1112.

28. Fazekas F, Kleinert R, Offenbacher H, et al. Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology* 1993; 43: 1683-1689.

29. DeCarli C, Fletcher E, Ramey V, Harvey D, Jagust WJ. Anatomical mapping of white matter hyperintensities (WMH): exploring the relationship between periventricular WMH, deep WMH, and total WMH burden. *Stroke* 2005; 36: 50-55.

30. Antman EM, Bennett JS, Daugherty A, *et al*. Use of nonsteroideal anti-inflammatory drugs: An update for clinicians: A scientific statement from the American Heart Association. *Circulation* 2007; 115: 1634-1642.

31. Capone ML, Tacconelli S, Sciulli MG, *et al*. Human pharmacology of naproxen sodium. *J Pharmacol Exp Ther* 2007; 322: 453-460.

32. Trelle S, Reichenbach S, Wandel S, *et al*. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011; 342: c7086. Doi: 10.1136/bmj.c7C086.

33. Hall GC, Brown MM, Mo J, MacRae KD. Triptans in migraine: the risks of stroke, cardiovascular disease, and death in practice. *Neurology* 2004; 62: 563-568.

34. Kurth T, Mohamed S, Miallard P, *et al*. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. *BMJ* 2011: 342: c7357. doi: 10.1136/bmj.c7357.

35. Kurth T and Tzourio C. Migraine and cerebral infarct-like lesions on MRI: an observation, not a disease. *JAMA* 2009; 301: 2594-2595.

36. Friedman DI and Dodick DW. White matter hyperintensities in migraine: reason for optimism. *JAMA* 2012; 308: 1920-1921.

	CM N=96	EM N=29	p-value
Depression	43 (44.8%)	2 (6.9%)	<0.001
Fibromyalgia	14 (14.6%)	0	0.065
Hypothyroidism	3 (3.1%)	0	0.786
Asthma	6 (6.3%)	0	0.377
Aura	48 (50.0%)	15 (51.7%)	1.000
> 45 years	46 (47.9%)	8 (27.6%)	0.085
Arterial hypertension	11 (11.5%)	1 (3.4%)	0.356
Hypercholesterolemia	18 (18%)	2 (13.3%)	0.216
Diabetes	0	0	-----
Obesity	6 (6.3%)	0	0.377
Smoking	11 (11.5%)	2 (6.9%)	0.722
Vascular risk factors ≥ 1 vascular risk factor ≥ 2 vascular risk factors	 63 (65.6%) 23 (24.0%)	 4 (13.7%) 1 (3.4%)	 <0.001 0.029
Analgesic overuse	34 (35.4%)	0	<0.001
NSAIDs	71 (74.0%)	23 (79.3%)	0.734
Triptans	66 (68.8%)	16 (55.2%)	0.260
Preventive treatment	83 (86.4%)	4 (13.8%)	<0.001

Table 1. Summary of main comorbidities and potential vascular risk factors of chronic migraine (CM) and episodic migraine (EM) women included in this study.

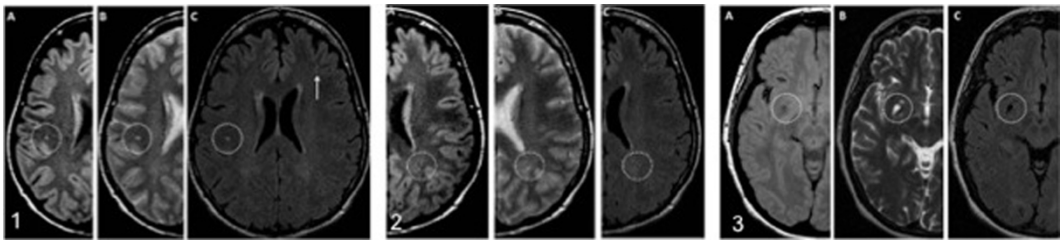
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
WML	1.13 (0.58 – 2.62)	0.784	0.73 (0.27 - 1.94)	0.528
pWML	1.43 (0.49 - 4.18)	0.517	0.94 (0.28 - 3.15)	0.924
dWML	1.03 (0.28 – 3.15)	0.942	0.70 (0.26 – 1.85)	0.469
pfWML	0.74 (0.14 – 4.04)	0.729	0.71 (0.11-4.71)	0.728

Table 2. Crude and adjusted Odd ratios (OR) with 95% confidence intervals (CI) analysis showing that WML are independent of the type of migraine (EM or CM). Adjusted models include: Age, Additional comorbidities (yes/no) and VRF.

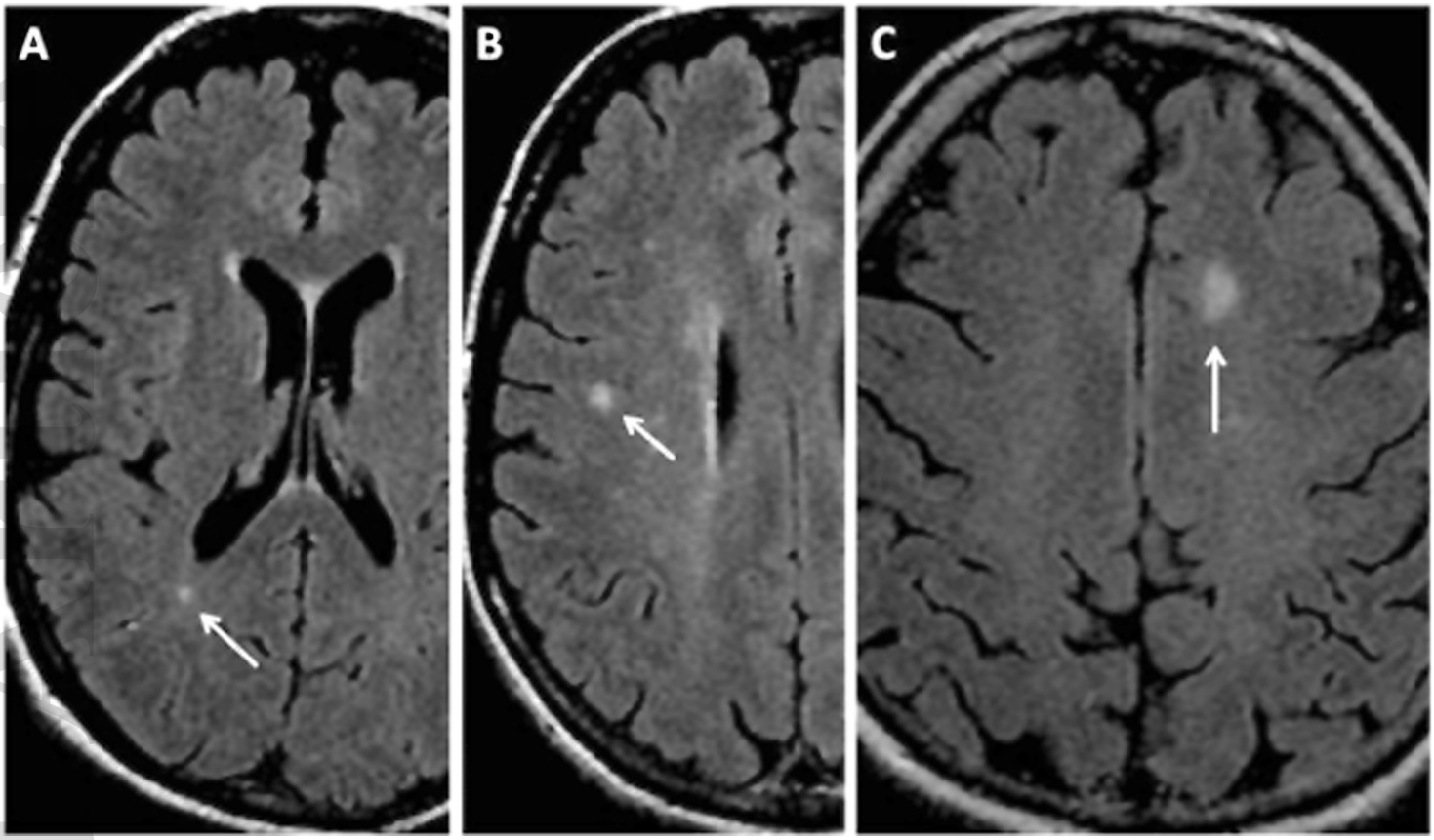
FIGURES

Figure 1. Examples of MRI images in protonic density (A), T2 (B) and FLAIR (C) for WML (1), SI (2) and dilated perivascular Virchow-Robin spaces (3). Contrary to WML, which are seen as hyperintense in the three sequences, SI and dilated spaces follow cerebrospinal fluid behaviour, being hyperintense only in T2. Location (typically inferior third of the putamen) and morphology allow distinguishing between dilated perivascular spaces and SI.

Figure 2. Assessment of dWML size in FLAIR sequences: small (≤3 mm) (A), medium (3-10 mm) and big (>10 mm).



ene_14284_f1.jpg



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