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Cerebral distribution of white matter lesions in migraine with aura patients

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Abstract

Objective: The objective of the study was to compare the cerebral distribution of white matter lesions (WMLs) between migraine patients with different aura symptoms.

Methods: Migraine with aura (MA) patients were consecutively enrolled as part of the Shunt-Associated Migraine (SAM) study. According to clinical symptoms, aura was classified as motor, aphasic, sensory, visual or vertebrobasilar. Standard and FLAIR (fluid attenuated inversion recovery) T_2-weighted MRI sequences were inspected for WMLs by three independent raters blinded to clinical data. WMLs were assessed in the periventricular areas (PV-WMLs) with the Fazekas scale and in the deep white matter (D-WMLs) with the Schelten's scale. Interobserver agreement was good to excellent ($k = 0.64$ to 0.96, $p < .0001$).

Results: One hundred and eighty-five patients (77% women) were included. Aura symptoms were classified as visual in 172 (99%) patients, sensory in 76 (42%), aphasic in 54 (30%), motor in 39 (21%) and vertebrobasilar in 17 (9%) patients. One hundred and four patients (57%) exhibited more than one type of aura. D-WMLs were mainly detected in the frontal lobes (86%). There was no association between type of aura and the presence of WMLs in any cerebral location.

Conclusion: Aura symptoms do not influence the cerebral distribution of WMLs associated with migraine disease.

Keywords
white matter lesions, migraine, MRI

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Introduction

Migraine patients have an increased prevalence of white matter lesions (WMLs) located in the periventricular (PV-WMLs) and deep white matter (D-WMLs) (1). The pathophysiology and clinical significance of WMLs in these patients are unclear. In particular, it is currently unknown if a relationship exists between aura symptoms and WMLs. This information might improve our understanding of migraine.

In a prospective cohort of migraine with aura (MA) patients (2), we previously found that PV- and D-WMLs load did not increase with the frequency of migraine attacks, in female patients or in the presence of a right-to-left shunt (RLS). WML load was only associated with the age of patients. Based on the same population, in this study we compared the cerebral distribution of PV- and D-WMLs between patients affected by different types of aura (motor, aphasic, sensory, visual and vertebrobasilar). We investigated whether a particular type of aura was associated with an increased WML load and whether an association existed between aura symptoms and the presence of WMLs in a particular brain location.

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Methods

Patients were prospectively enrolled as part of the SAM study. The full clinical and MRI study protocols have been previously published (2,3). Each local Ethic Committee approved the study protocol, and each subject's participation required signed informed consent. The patients were eligible to participate if they had a diagnosis of MA according to the International Headache Society criteria (4), their age was between 15 and 55 years and they were not taking prophylactic treatments for migraine at the time of inclusion. We excluded patients showing intracranial abnormalities potentially mimicking headache and migraine. Five domains of aura symptoms were systematically reviewed using a questionnaire performed by a neurologist with expertise in migraine. Aura symptoms included visual scotomas, unilateral somatic sensory disturbances, aphasia, lateralized motor weakness and vertebrobasilar symptoms such as dizziness, diplopia or faintness.

MRI protocol and WML rating

Brain MRI scans were performed on 1–1.5-tesla scanners. The MRI protocol consisted of spin echo and FLAIR (fluid attenuated inversion recovery) T2-weighted sequences acquired on the axial plane and one T1-weighted sequence on the sagittal plane. For each image series, 20 slices covering the entire brain (matrix 240-256X256-320; field of view [FOV] 22–24 cm; thickness 5 mm; interslice gap 1.5 mm) were obtained. TR/TE/TI/FA values were optimized on each scanner for the best available image contrast. MRI scans were evaluated by three raters blinded to clinical and other instrumental data. We investigated the cerebral distribution of WMLs using the Fazekas scale for PV-WMLs (5) and Schelten's scale for D-WMLs (Figure 1) (6). Cases with a disagreement ≥ 3 points within the raters underwent a consensus reading. The κ-weighted (Cohen's kappa) coefficient ranged between 0.64 and 0.84 for PV-WMLs and from 0.74 to 0.96 for D-WMLs ($p < .0001$). Only patients with a final score ≥ 2 on the Fazekas scale were diagnosed as having PV-WMLs (2). Final WMLs values were averaged between the raters.

Statistical analysis

We used the Mann-Whitney U-test to assess the association between type of aura and global PV-WML and D-WML load, and the Fisher's exact test to assess the association between type of aura and WML load at each brain location. The correlation between the number of aura attacks and WML load was measured with rank correlation tests. WML load was compared among different age groups by mean using the Pearson chi-square test. Significance was set at $p < .05$.

Results

Between January 2005 and December 2006, the SAM study enrolled 460 (77% women) MA patients. As previously discussed (2), 195 patients (42%) completed the MRI protocol. There were no differences in the baseline or in migraine characteristics between the patients who did or did not undergo the study MRI (2). Seven patients were excluded for low quality of MRI due to movement artifacts, and three patients had relevant brain pathologies potentially associated with headache (one arterial aneurysm, one arterial-venous malformation and one Arnold-Chiari type II malformation). This left 185 (77% women) available for the present analysis. The demographics and the clinical characteristics of patients with and without WMLs have been previously published (2). Briefly, in multivariate analysis, only the age of the patients was associated with WMLs.

Mean age was 36 ± 10 years (Table 1). Visual aura was diagnosed in 172 (99%) patients, whereas only 17 (9%) had the vertebrobasilar type. One hundred and four patients (57%) had more than one type of aura. Thirty-five patients (19%) had PV-WMLs. PV-WMLs were slightly more frequent in the anterior (33 patients, 18%) than in the posterior (28 patients, 15%) horns of lateral ventricles. Only six patients showed WMLs in lateral bands. Eighty-six patients (47%) had D-WMLs. These were mostly detected in the frontal lobes (74 patients, 86% of those with D-WMLs). Fifty patients had D-WMLs located within the frontal lobes only. In all patients except six the presence of D-WMLs in the parietal, occipital and temporal lobes was associated with the coexistence of D-WMLs in the frontal lobes.

No association was found between type of aura and total PV-WML and D-WML load or between each type of aura and the presence of WMLs in any cerebral location ($p > .10$). There was a trend for a reduced PV-WML load in the anterior horns in patients with aphasic aura ($p = .056$). However, these patients were significantly younger than other patients (32 ± 9 vs. 37 ± 11 years, $p < .001$). Because almost all patients experienced visual aura, it was not possible to test the association between this type of aura and WML distribution. However, patients with more than one type of aura did not exhibit an increased load of WMLs. Moreover, there was no correlation between number of aura attacks and global WML load (PV-WMLs, $p = .656$; D-WMLs, $p = .132$).

WML load tended to increase with age in all cerebral locations (Figure 2). However, only in the frontal lobes was this increase significant.

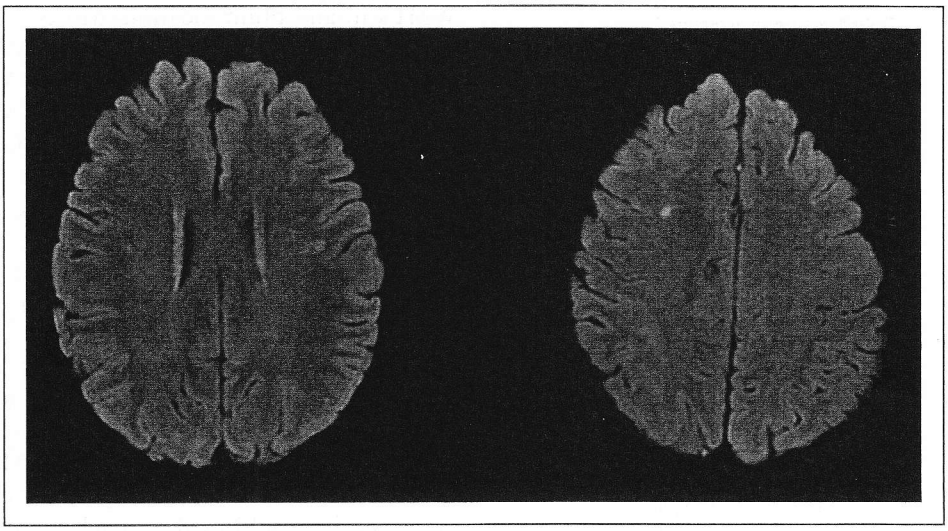

Figure 1. Axial brain slices (FLAIR sequence) showing the presence of deep white matter lesions (D-WMLs) in a 31-year-old migraine with aura (MA) female subject. FLAIR = fluid attenuated inversion recovery.

Table 1. Clinical characteristics of patients ($N = 185$) and WML frequency by distribution

Aura symptoms	PV-WMLs	D-WMLs	PV- and D-WMLs	PV-WMLs[a]	D-WMLs[a]
Motor 39 (21%)	No: 150 (81%)	No: 99 (53%)	No: 164 (89%)	Anterior: 33 (18%)	Frontal: 74 (40%)
Aphasic 54 (30%)		Yes: 86 (47%)	Yes: 21 (11%)	Posterior: 28 (15%)	Parietal: 17 (9%)
Sensory 76 (42%)	Yes: 35 (19%)			Lateral: 6 (3%)	Occipital: 10 (5%)
Visual 172 (99%)					Temporal: 8 (4%)
Vertebrobasilar 17 (9%)					

PV-WMLs = periventricular white matter lesions. D-WMLs = deep white matter lesions. Age, years: 36 ± 10; females: 143 (77%). Values are expressed as mean ± standard deviation (SD) or nr (%). [a]Chi-square test: $p < .001$.

Discussion

This study shows no relationship between aura symptoms and the cerebral distribution of WMLs associated with migraine disease. Rather, in MA patients, we found a stereotypical WML brain pattern independent of aura type. PV-WMLs were more frequent in the anterior than posterior horns of lateral ventricles, whereas they were rarely present in the lateral bands. D-WMLs occurred most often in the frontal lobes and then, in turn, in the parietal, occipital and temporal lobes. With aging, the D-WML load significantly increased only within the frontal lobes.

Several previous studies analyzed the presence of WMLs among migraine patients (7–12). None of these studies, however, investigated the relationship between aura symptoms and the cerebral distribution of WMLs. An increased prevalence of D-WMLs within the frontal lobes has been reported by some authors (7,10) but has not been confirmed by others (13). Most of these studies reported the presence of both PV-WMLs and D-WMLs (10,11,14,15), whereas in others only D-WMLs were noted (12). Two authors found no association between the side of D-WMLs and the side of aura symptoms or headache (7,10). Those studies, however, were retrospective in design and performed on low-magnetic-field (≤0.5 tesla) MRI scanners, thus limiting the sensitivity for WML detection. The strengths of the present analysis were therefore the prospective enrollment of patients and the use of higher-magnetic-field scanners. Moreover, we assessed WML load at each cerebral location using standardized rating scales.

It is currently unknown whether WML load and distribution might vary between different migraine subtypes. Fazekas et al. reported a threefold increase of WMLs in MA patients compared to patients without aura (53% vs. 18%) (8). Other studies found no difference in WMLs between MA and migraine patients without aura (1,7,10). These differences might be explained by the different samples of patients and

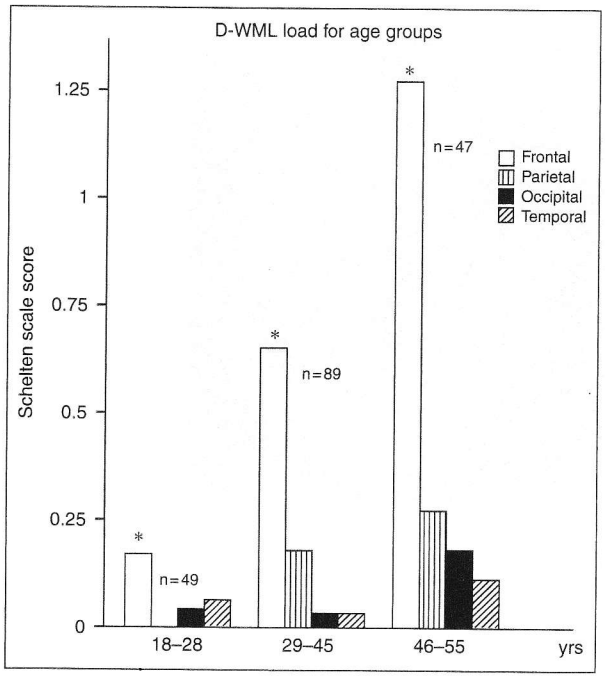

Figure 2. D-WML load by age. The data represent median D-WML load (Schelten's scale) in three age groups. D-WML = deep white matter lesion. *Chi-square test: $p < .001$.

methodology of the above studies. Because the SAM study included only MA patients, we were unable to investigate this matter. The lack of association between aura symptoms and WMLs might support the hypothesis that the presence of aura does not influence the brain pattern or the severity of WMLs that are associated with migraine disease itself. However, because WML load increases with age, longitudinal MRI studies enrolling migraine patients both with and without aura are needed to address this issue.

In a previous study, we demonstrated that WML load associated with MA increased with the age of patients (2). On the other hand, WMLs are also part of normal brain aging. Interestingly, De Leuwe et al. found that D-WML load in the elderly was highest in the frontal lobes, followed by the parietal, occipital, and temporal lobes (16). The similarity of WML distribution in MA and aging might indicate that migraine enhances age-related microvascular changes and thus anticipates the appearance of WMLs.

The coexistence of aura symptoms and the presence of WMLs at brain MRI might be a cause of anxiety for patients and uncertainty for physicians in choosing the most appropriate therapeutic approach. In MA patients, especially in those with patent foramen ovale (PFO), WMLs are often considered to be the results of minor acute ischemic strokes associated with the clinical symptoms of aura. Our data do not support this hypothesis, as we demonstrated no association between frequency and clinical type of aura and the presence of WMLs in any brain location. Moreover, although the majority of patients had visual aura, WMLs were rare in the occipital lobes. Furthermore, MA patients are at increased stroke risk compared with non-migraineurs but this risk is limited to cerebellar infarcts (11), while a similar incidence of both cortical and subcortical ischemic lesions has been found between migraine patients with and without aura and normal subjects (17). The presence and distribution of WMLs in MA patients appear therefore to be related to migraine disease itself (11) rather than aura attacks.

The limitations of the SAM study have been previously discussed (2,3). Regarding the present analysis, our patients were enrolled in hospital clinics, not from the general population. Therefore, SAM patients might not be representative of the general MA population. However, hospital-based headache clinics tend to evaluate migraine patients with more severe aura symptoms. Thus, it is unlikely that a population-based study would yield different results.

Disclosure

The authors report no conflicts of interest.

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