Structural brain changes in migraine and cluster headache

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Microstructural white matter changes preceding white matter hyperintensities in migraine

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Abstract

Objective:

We used magnetization transfer imaging (MTI) to assess white matter tissue integrity in migraine, to explore whether white matter microstructure was more diffusely affected beyond *visibile* WMHs, and to explore whether focal *invisible* microstructural changes precede *visible* focal WMHs in migraineurs.

Methods:

We included 137 migraineurs (79 with aura, 58 without aura) and 74 controls from the CAMERA study, a longitudinal population-based study on structural brain lesions in migraine patients, who were scanned at baseline and at a 9-year follow-up. To assess microstructural brain tissue integrity, baseline magnetization transfer ratio (MTR)-values were calculated for whole brain white matter. Baseline MTR-values were determined for areas of normal appearing white matter that had progressed into MRI-detectable WMHs at follow-up and compared to MTR-values of contralateral NAWM.

Results:

MTR-values for whole brain white matter did not differ between migraineurs and controls. In migraineurs, but not in controls, normal appearing white matter that later progressed to WMHs at follow-up had lower mean MTR (mean [SD]: 0.354 [0.009] versus 0.356 [0.008], p=0.047) at baseline as compared to contralateral white matter.

Conclusions:

We did not find evidence for widespread microstructural white matter changes in migraineurs compared to controls. However, our findings suggest that a gradual or stepwise process might be responsible for evolution of focal invisible microstructural changes into focal migraine-related visible WMHs.

Introduction

We previously identified migraine as a risk factor for subclinical focal deep white matter hyperintensities (WMHs).[1;2] The etiology of these lesions remains to be clarified.

In migraineurs, diffuse invisible white matter changes may be present that extend beyond the visible focal WMHs on conventional MRI. Magnetization transfer imaging (MTI) is an MRI technique that provides quantitative information on microstructural tissue integrity. MTI detects structural changes both in areas with abnormal signal intensity on conventional MRI and in normal-appearing brain tissue.[3;4] Magnetization transfer ratio (MTR) values reflect the proportion of exchange between free water protons and water protons bound to macromolecules (f.i. myelin, proteins, and cell membrane molecules). Reduced MTR-values suggest lower macromolecular content or microscopic edema, indicating microstructural changes.[5] Brain parenchyma in migraineurs has scarcely been studied with MTI[6-8] and indeed suggested migraine-related focal microstructural damage in some studies.[6;7] However, another study found no difference in MTR for whole brain and normal-appearing white matter (NAWM) in migraineurs compared to controls.[8] These findings may have been biased by investigating more severe migraine phenotypes. Hence, we examined whole-brain white matter integrity in migraineurs from the general population.

The 9-year follow-up data of the CAMERA study revealed that the WMHs in female migraineurs were progressive also in those who no longer had migraine activity during follow-up.[2] Whether WMHs in migraineurs develop acutely or in progressive way needs further assessment. Therefore, we investigated whether baseline MTR might reveal invisible brain changes in NAWM at sites that had changed to visible WMHs at follow-up.

Methods

Study population

Participants were included from the Maastricht subpopulation of the Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA) 1 and 2 studies, a longitudinal population-based MRI study on structural brain lesions in migraine patients. Characteristics of the study population and the assessment of migraine have been described in detail elsewhere.[1;2;9] The original participants of the CAMERA-1 study included 295 well-characterized migraineurs and 140 controls, divided into two subpopulations from the Dutch cities of Doetinchem and Maastricht. The Maastricht subpopulation of this study consisted of 213 participants (n=80 migraine with aura, n=58 migraine without aura, n=75 controls). For 211 of these 213 participants, the MR imaging protocol included MTI at baseline. The participants included in current analyses were more likely to smoke than those participants who were excluded because of missing MTI data (Table 6.1). Further demographics and clinical characteristics were comparable between groups. A total of 128 participants of the original Maastricht subpopulation (n=55 migraine with aura, n=35 migraine without aura, n=38 controls) participated in CAMERA-2, a 9-year follow-up study.[2] Reasons for participants not to participate in CAMERA-2 included inability to recontact the participant due to relocation, loss to civil registry information, no interest, inability to visit the research center, claustrophobia, non-neurological illness and death. The MR imaging protocol did not include MTI at follow-up.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the Leiden University Medical Center ethics committee. All participants gave written informed consent.

Magnetic Resonance Imaging

Fast field echo MTI images (TR 106 ms, TE 5.9 ms, 28 axial 5 mm slices, 256x256 acquisition matrix, field of view 220 mm, flip angle 12º, in-plane resolution 0.86x0.86 mm) were acquired on a 1.5T MRI scanner (Philips Gyroscan Intera ACS-NT, Best, the Netherlands) at baseline. MTI comprised two consecutive sequences, one without (M0) (resulting in proton density

Table 6.1 Baseline characteristics of included & excluded CAMERA-1 study participants for current MTR substudy

	Included (n=211)	Excluded (n=224)
Migraine	137 (65)	158 (71)
With aura	79 (37)	82 (36)
Age, years	48.8 (7.7)	47.9 (7.6)
Female	146 (69)	171 (76)
Low education †	113 (54)	114 (51)
Body mass index, kg/m^2	25.2 (4.4)	24.9 (3.9)
Blood pressure, mmHg		
Systolic	134.0 (18.0)	134.7 (17.4)
Diastolic	90.9 (10.5)	91.5 (9.3)
Hypertension	80 (38)	87 (39)
Diabetes	1 (0.5)	3 (1)
Smoking		
Ever	151 (72)	136 (61)*
Current	82 (39)	63 (28)*
Pack years	13.0 (15.3)	7.5 (10.2)*
Cholesterol, mmol/l	5.25 (0.94)	5.37 (0.99)
HDL cholesterol, mmol/l	1.37 (0.35)	1.44 (0.42)
Medication (migraineurs only) §		
Prophylactics	9 (7)	3 (2)
Abortive treatment		
Triptans	14 (10)	8 (5)
Ergotamines	9 (7)	9 (6)
Migraine disease duration, years	23.6 (11.6)	23.2 (12.0)
Migraine attacks per year #	17.5 (20.5)	15.2 (14.6)
Migraineurs with high attack frequency #	60 (44)	76 (48)

Excluded participants included the Doetinchem subpopulation (n=222) and those participants from the Maastricht subpopulation that did not undergo MTI (n=2)
Mean (SD) for continuous, number (%) for categorical variables. N/A=not applicable
*p<0.05 (one-way ANOVA (or non-parametric test in case of skewed distribution) for continuous, Fisher exact test for categorical variables)
† Low education indicates primary school or lower vocational education
§ Ever use of medications
# Mean number of lifetime migraine attacks; high migraine attack frequency defined as mean ≥1 attack per month

contrast) and one with (Ms) radiofrequent saturation pulse (1100 Hz upfield of H2O resonance). In addition, dual echo T2 (TR 3000 ms, TE 27-120 ms, echo train length 10) and fluid-

attenuated inversion recovery (FLAIR) (TR 8000 ms, TE 100 ms, inversion time 2000 ms, echo train length 19) images were acquired to check images for structural abnormalities and to be able to segment WMHs at baseline and after a 9-year follow-up, using the same MRI scanner and protocols.

Image post processing

MTI data were post-processed using FSL (FMRIB Software Library, FMRIB Center, Oxford, United Kingdom)[10] and ELASTIX.[11] First, M0 images were linearly registered to the Ms images using FLIRT.[12] Non-brain tissue was removed from M0 images using BET;[13] a binary mask created in this processing step was applied to remove non-brain tissue from Ms images. The MTR was then calculated by the equation (M0-Ms)/M0. The MTR images were linearly registered to the MNI152 (Montreal Neurological Institute) stereotactic standard space implemented in FSL using FLIRT again. To optimize image registration in the white matter around the ventricles, these normalized MTR images were registered to MNI152 space once again using standard parameters in ELASTIX. The MNI152 template was segmented into gray matter, white matter and cerebrospinal fluid binary masks using FAST.[14] MTR histogram parameters (mean and normalized peak height) were retrieved for white matter for all participants by overlaying the binary masks on the normalized MTR images. The mean MTR reflects the average MTR in a region-of-interest (i.e., white matter in this case). The peak height of the MTR histogram shows the number of voxels with the most common MTR value and reflects the uniformity of the underlying voxels in terms of MTR-values. As the peak height depends on the total number of voxels, normalized peak height is calculated by dividing the number of voxels with the most common MTR by the total number of voxels in the region-of-interest. To decrease influence of extreme outliers, only MTI measures within 3 standard deviations of the mean were included in the statistical analysis.

To study the baseline MTR of brain tissue that developed into WMHs at follow-up, supratentorial WMHs were segmented semi-automatically as hyperintense lesions on PD, T2 and FLAIR images both at baseline and follow-up using QBrain 1.1.[2] As we had a particular interest in the development of deep WMHs, which were more prevalent and more progressive in (female)

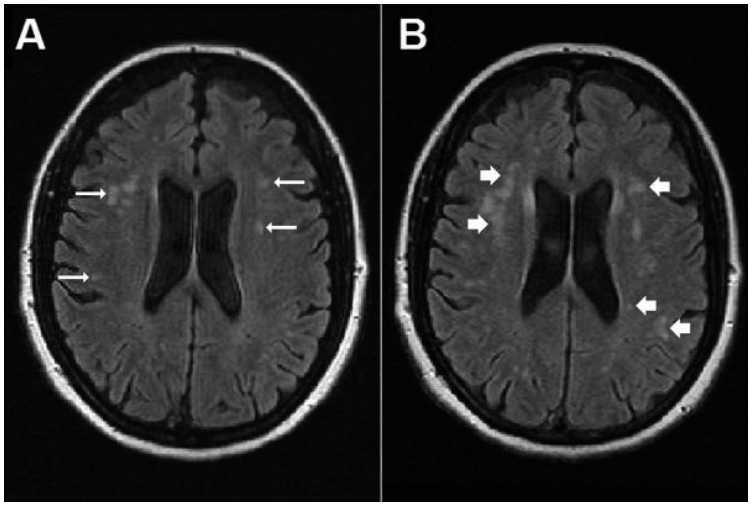

Figure 6.1 Example of deep white matter intensities at a similar level on FLAIR images of one participant showing DWMHs at baseline (A, long thin arrows) and progressive and new DWMHs at follow-up (B, short thick arrows)

migraineurs in CAMERA-2,[2] we differentiated between deep and periventricular WMHs. WMHs attached to the lateral ventricles were classified as periventricular WMHs. For follow-up analyses, we included all study participants with deep WMH progression, defined as increase in size or number of WMHs, or both (Figure 6.1). Segmented deep WMHs at baseline and at follow-up were registered to normalized MTR-images in MNI152 space using FLIRT. Mean MTR was computed for deep WMHs at baseline and for tissue that had progressed to deep WMH at follow-up. As deep WMHs often occur as asymmetric, punctate lesions, we considered that white matter contralateral to the deep WMHs could serve as NAWM for within-participant comparisons. MTR-values of this contralateral white matter were computed by per slice mirroring deep WMH maps about the sagittal axis.

Statistical analyses

Demographic characteristics were compared applying one-way ANOVAs (normal distribution), non-parametric tests (skewed distribution) and Fisher's exact tests (Statistical Package for Social Science 20.0, SPSS Inc., Chicago, IL, USA). The primary analysis of MTR histogram parameters of whole brain white matter and NAWM comprised the comparison between migraineurs, migraine subgroups and controls for the whole population that underwent MTI (n=211) using gen-

eral linear models adjusting for age, sex, hypertension, diabetes, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and body mass index (BMI).[15]

To decrease the effect of possible misregistration between conventional T2 and MTI images, which is theoretically largest for the smallest WMHs, paired sample t-tests comparing mean MTR of deep WMHs and contralateral NAWM were weighted for the deep WMH volume. Mean MTR of deep WMHs was also compared between migraine (subgroups) and controls using general linear models adjusting for age, sex, hypertension, diabetes, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, and BMI. P-values <0.05 were considered statistically significant. An explorative subanalysis was performed for subgroups of migraineurs based on disease activity (>1 year free of attacks [inactive] vs at least 1 attack within the last year [active]).

Results

MTI data at baseline were available for 137 migraineurs (n=79 with aura; n=58 without aura) and 74 controls. Demographics and clinical characteristics were similar between migraineurs and controls, except for a higher BMI in migraineurs (25.7 [4.8]; mean [SD]) versus controls (24.3 [3.3], p=0.02; Table 6.2), particularly in migraineurs with aura (26.2 [5.1], p=0.005).

Whole brain analyses

Mean MTR and normalized MTR peak height in baseline whole brain white matter (including areas with WMHs at baseline and follow-up) and NAWM (excluding areas with WMHs at baseline and follow-up) did not differ between migraineurs (or subgroups of migraine patients) and controls (Table 6.3).

Focal WMHs analyses

At 9-year follow-up, 49 migraineurs (29 MA, 20 MO) and 19 controls had increased deep WMH volume due to new or progressive lesions (Table 6.3). In migraineurs, areas that had undergone transition to deep WMHs at follow-up had lower baseline mean MTR (0.354 [0.009] vs 0.356 [0.008], p=0.047), compared to their own contralateral white matter. This contralateral difference was not seen in controls. Baseline MTR in areas that had progressed to WMHs at

Table 6.2 Baseline (CAMERA-1) characteristics of CAMERA MTR study participants

	Control (n=74)	Migraineurs		
		All (n=137)	With aura (n=79)	Without aura (n=58)
Age, years	48.4 (8.0)	49.0 (8.0)	49.9 (8.0)	47.7 (8.0)
Female	49 (67)	97 (70)	54 (67)	43 (74)
Low education †	37 (50)	61 (37)	33 (42)	28 (48)
Body mass index, kg/m^2	24.3 (3.3)	25.7 (4.8)*	26.2 (5.1)*	24.9 (4.4)
Blood pressure, mmHg				
Systolic	135.7 (17.7)	133.1 (18.1)	134.3 (18.0)	131.4 (18.4)
Diastolic	91.0 (9.6)	90.9 (10.9)	91.3 (10.9)	90.3 (11.1)
Hypertension ‡	25 (34)	55 (40)	32 (41)	23 (40)
Diabetes	0 (0)	1 (1)	0 (0)	1 (2)
Smoking				
Ever	56 (76)	95 (69)	54 (68)	41 (71)
Current	34 (46)	48 (35)	24 (30)	24 (41)
Pack years	14.9 (17.1)	12.0 (14.2)	11.9 (15.5)	12.3 (12.2)
Cholesterol, mmol/l	5.22 (0.94)	5.26 (0.94)	5.22 (0.96)	5.32 (0.92)
HDL cholesterol, mmol/l	1.40 (0.36)	1.35 (0.35)	1.36 (0.34)	1.34 (0.37)
Medication §				
Prophylactics	N/A	9 (7)	7 (9)	2 (3)
Abortive treatment				
Triptans	N/A	14 (10)	10 (13)	4 (7)
Ergotamines	N/A	9 (7)	5 (6)	4 (7)
Migraine disease duration, years	N/A	23.6 (11.6)	24.7 (11.6)	22.0 (11.7)
Migraine attacks per year #	N/A	17.5 (20.5)	17.1 (22.4)	18.2 (17.9)
Migraineurs with high attack frequency #	N/A	60 (44)	33 (42)	27 (47)

Mean (SD) for continuous, number (%) for categorical variables. N/A=not applicable

*p<0.05 (one-way ANOVA (or non-parametric test in case of skewed distribution) for continuous, Fisher exact test for categorical variables)

† Low education indicates primary school or lower vocational education

‡ Hypertension was defined as a systolic blood pressure of ≥160 mm Hg or a diastolic blood pressure of ≥95 mm Hg or use of antihypertensive drugs during CAMERA-1

§ Ever use of medications

Mean number of lifetime migraine attacks; high migraine attack frequency defined as mean ≥1 attack per month

follow-up was not lower than in contralateral white matter in subgroups of active (0.354 [0.008] vs 0.356 [0.009], p=0.12) and inactive (0.353 [0.011] vs 0.356 [0.006], p=0.21) migraineurs. At the sites of deep WMHs present at baseline, mean MTR was lower in migraineurs compared to controls (0.355 [0.008] vs 0.358 [0.012], p=0.048). Baseline mean MTR of areas that progressed to WMHs at follow-up in migraineurs (0.354 [0.009]) was not significantly lower than in similar areas in controls (0.357 [0.010]; p=0.08).

Discussion

In this study using MTI in migraineurs from the general population we found no significant differences in baseline whole brain white matter MTR-values between migraine patients and controls.

Thus, in contrast to four studies using diffusion-weighted MRI[16;17] and MTI,[6;7] but in line with another MTI study,[8] compared to controls, we did not find evidence for more diffuse microstructural changes in the white matter of migraineurs from the general population. A possible explanation might be that compared to the clinic-based patients in previous studies, our participants likely had less severe migraine. They also were less exposed to the potentially confounding effects of prophylactic and abortive medications and concomitant anxiety and depressive disorders, factors that might influence brain architecture as well.[18;19]

In migraineurs we found that mean MTR at baseline was significantly lower in normal appearing areas on conventional T2-weighted images on baseline that progressed to deep WMHs at 9-year follow-up. This suggests the presence of focal occult microstructural alterations or damage in brain tissue integrity prior to the appearance of visible deep WMHs on conventional T2-weighted MRI. This difference was not obviously explained by differences between migraineurs that had active migraine and those with inactive disease (with most being attack-free for >5 years), which is in line with our previous findings of WMHs being progressive in female migraineurs regardless of disease activity.[2] Although the nature of these microstructural changes remains elusive, our findings do suggest that deep WMHs in migraine develop gradually or

Table 6.3 *Volumes and MTR histogram parameters for whole brain white matter, deep white matter hyperintensities and contralateral deep white matter*

		Controls (n=74)	Migraine		
			All (n=137)	With aura (n=79)	Without aura (n=58)
Whole brain white matter (including WMHs at baseline and follow-up)					
Mean MTR		0.349 (0.006)	0.350 (0.006)	0.351 (0.006)	0.350 (0.006)
MTR NPH		0.184 (0.019)	0.185 (0.019)	0.185 (0.018)	0.184 (0.020)
NAWM (excluding WMHs at baseline and follow-up)					
Mean MTR		0.349 (0.006)	0.349 (0.006)	0.350 (0.006)	0.349 (0.006)
MTR NPH		0.183 (0.018)	0.182 (0.018)	0.182 (0.018)	0.182 (0.019)
DWMH volume, median (range), ml					
Baseline		0.04 (0.00-0.80)	0.07 (0.00-0.77)	0.06 (0.00-0.77)	0.09 (0.00-0.55)
9-y Follow-up		0.24 (0.01-1.56)	0.36 (0.00-4.16)	0.36 (0.01-4.16)	0.36 (0.00-2.55)
Progression/new		0.22 (0.00-1.01)	0.31 (0.00-3.42)	0.26 (0.01-3.42)	0.31 (0.00-2.00)
DWMH and cDWM at baseline					
		n=17 of 74	n=50 of 137	n=30 of 79	n=20 of 58
Mean MTR	*DWMH*	0.358 (0.012)	0.355 (0.008)*	0.356 (0.008)	0.353 (0.008)
	cDWM	0.354 (0.006)	0.354 (0.006)	0.354 (0.006)	0.354 (0.007)
Progressive/new DWMH and cDWM between baseline and follow-up					
		n=19 of 38	n=49 of 90	n=29 of 55	n=20 of 39
Mean MTR	*DWMH*	0.357 (0.010)	0.354 (0.009)†	0.353 (0.011)	0.354 (0.006)
	cDWM	0.356 (0.007)	0.356 (0.008)†	0.356 (0.008)	0.355 (0.008)

MTR=magnetization transfer ratio; NPH=normalized peak height; NAWM=normal appearing white matter, DWMH=deep white matter hyperintensity; cDWM=contralateral deep white matter; averages (SD) per group; *=p<0.05 general linear models comparing migraine (subgroups) vs. controls; †=p<0.05 DMWH vs. cDWM, paired-samples t-test

stepwise, possibly due to complex interplay of electrophysiological and vascular phenomena. We may only speculate about underlying pathophysiology. Cortical hyperexcitability is thought to lower the threshold for cortical spreading depression in migraine. This cortical spreading depression, possibly triggered by ischemic events, leads to a phase of self-expanding oligemia,[20] which may trigger the release of pro-inflammatory and prothrombotic substances. Together with preexistent modulating factors as an increased cardiovascular risk profile, circulating substances associated with vascular impairment, and dysfunctional endothelium,[21] this may ultimately contribute to a state of (chronic) ischemia, leading to axonal loss, demyelination or gliosis, appearing as WMHs on conventional MRI.

Our study was underpowered so we cannot exclude the possibility that WMHs in control participants may develop in a similar gradual or stepwise manner. After all, 50% of controls that participated in the follow-up study had progressive white matter lesions in the same follow-up period as well, compared to 54% in migraineurs. In some controls these white matter lesions may have

been preceded by similar MTR differences as seen in migraineurs. However, it should also be mentioned that the average increase in lesion load was (non-significantly) lower in controls, further decreasing the possibility to find similar MTR changes. Since MTR is not homogeneous throughout the white matter due to local differences in myelination,[3] differences in distribution of deep WMHs between migraine and controls may explain why we found lower mean MTR in deep WMHs at baseline in migraineurs compared to controls. In a previous study based on the whole CAMERA-2 study population indeed showed that WMHs were more diffusely distributed in female migraineurs compared to controls, also affecting subcortical white matter in upper frontal regions.[2] Alternatively, microstructure within WMHs in migraineurs might also just be more severely affected than in controls. Further, we cannot exclude that MTR-values might have decreased even further after our baseline measurement, as MTR changes may show evolution in time.

Nevertheless, the MTR changes in our and older migraine studies[8] are mild compared to those found in, for instance, multiple sclerosis[8] or elderly subjects.[22;23] This might explain why deep WMHs are not associated with clinically relevant cognitive decline in migraine.[2]

Thus, despite being visible, these WMHs only show minor changes in microstructural integrity in migraineurs and may thus well be clinically insignificant. Therefore, when incidentally discovered on conventional MRI, they may be no reason for alarm. Our findings that migraine is not accompanied by occult extensive white matter disease might provide further reassurance for migraineurs and their physicians.

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