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Axonal loss of white matter in migraine without aura: A tract-based spatial statistics study

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Abstract

Aim: Multiple diffusion tensor imaging (DTI) derived indices may help to deduce the pathophysiological type of white matter (WM) changes and provide more specific biomarkers of WM neuropathology in the whole brain of migraine patients without aura (MWoA).

Methods: Twenty MWoA and 20 age-, education- and gender-matched healthy volunteers participated in this study. Tract-based spatial statistics (TBSS) was employed to investigate the WM abnormalities in MWoA by integrating multiple indices, including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD).

Results: Compared with healthy controls, MWoA showed significantly lower FA, MD and AD in multiple brain regions, whereas no difference in RD was observed. Specifically, the overlap among the lower FA, MD, and AD was found in the genu, body, and splenium part of the corpus callosum (CC), the right anterior limb of the internal capsule (ALIC) and the posterior limb of the internal capsule (PLIC) in MWoA compared with healthy controls. Additionally, some of the above WM findings were significantly correlated with duration and headache frequency in MWoA.

Conclusion: Given that decreased AD may suggest axonal loss, our findings may reveal axonal loss in MWoA.

Keywords

Migraine without aura, diffusion tensor imaging, tract-based spatial statistics, axonal loss

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Introduction

As a common type of primary headache syndromes, migraine has a prevalence range from 8.4% to 12.7% in the Asian population (1). Frequent migraine attacks may cause significant individual and social burdens as a result of pain, environmental sensitivities, disability (2), and even increase the risk of subtle lesions in white matter (WM) (3). With the help of diffusion tensor imaging (DTI) techniques, WM abnormalities in migraine patients have been investigated (4–9). Relative to healthy volunteers, migraine patients had abnormal diffusion characteristics shown as a lower mean diffusivity (MD) histogram peak height of the normal appearing WM (9). The reduced fractional anisotropy (FA) of the corpus callosum (CC) was detected in migraine patients without aura (MWoA). Moreover, there were significant negative correlations between abnormal FA values of the CC and clinical characteristics, i.e. the disease course, headache frequency, Hamilton anxiety and Hamilton depression scores (6). In addition, several other WM tracts with reduced FA in migraine patients were also reported, such as the optic radiation (OR), the subjacent WM

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of MT+ and the V3A, the superior colliculus, the lateral geniculate nucleus, the periaqueductal gray, the ventroposterior medial thalamus, and the corona radiata (CR) (4–8). All of these DTI findings strongly supported the assertion that repeated migraine attacks over time may have cumulative effects and result in selective damage to several WM tracts involved in trigeminal somatosensory and modulatory pain systems (4–11).

Using histogram analysis and voxel-based analysis (VBA) (4–9), previous DTI studies revealed abnormal WM properties in migraine patients. However, histogram analysis and VBA analysis of DTI also have several limitations despite their prominent advantages, that is local features or imperfect image registration and smoothing (12). Recently, the tract-based spatial statistics (TBSS) method was employed to investigate the WM abnormality between migraine patients and healthy controls (13), which was more sensitive and robust for detecting WM abnormalities (12). It is noteworthy that patients in the TBSS migraine study consisted of both MWoA and migraine with aura patients. According to previous findings, some WM differences do exist between these two sub-groups (5,14), which may affect previous results in the TBSS migraine study. In our opinion, to specify the WM abnormalities in MWoA, it is necessary to divide the patients into MWoA and migraine with aura. Therefore, only MWoA patients were recruited in the present study.

In order to specify the pathophysiological features of WM abnormalities of MWoA (ischemia, myelination, demyelination, axonal loss, inflammation, or edema), the TBSS method was employed along with the multiple DTI-derived indices analysis (i.e. FA, MD, radial diffusivity (RD), axial diffusivity (AD)) in the present study (15–20). Finally, a correlation analysis was carried out to investigate the relationship between WM changes and clinical symptoms (duration and attack frequency) of MWoA. Given that previous migraine DTI studies reported abnormal structural properties of WM involved in pain processing, we hypothesized that the multiple DTI-derived indices analysis may provide more specific pathophysiological features of WM abnormalities in pain-related brain regions in MWoA and the abnormalities may be correlated with clinical symptoms (duration and attack frequency).

Methods

Subjects

The MWoA patients were screened following the International Headache Society criteria (21). The diagnostic criteria of the International Headache Society for MWoA include the occurrence of at least five headache attacks. Simultaneously, the patients must fulfill the following criteria: (1) headache attacks lasting 4–72 hours (untreated or unsuccessfully treated); (2) featuring at least two of the following characteristics: unilateral location, pulsating quality, moderate to severe pain intensity and aggravation by causing avoidance of routine physical activity (e.g. walking or climbing stairs); (3) during headache, at least one of the following: nausea and/or vomiting, photophobia and phonophobia; and (4) headache must not be attributed to another disease. In addition, 29 age- and gender-matched healthy controls who either had no headache days per year or had family members who suffered regularly from a migraine or other headaches were enrolled in the study. Exclusion criteria for both groups were: (1) any physical illness such as a brain tumor, hepatitis, or epilepsy as assessed according to clinical evaluations and medical records; (2) pregnancy or menstrual period in women; (3) alcohol, nicotine, or drug abuse; (4) existence of a neurological disease; and (5) claustrophobia.

At last, 20 MWoA (16 females, aged 22–55 years, mean age 36.1 ± 10.2 years) and 20 age- and gender-matched healthy controls (16 females, aged 21–54 years, mean age 31.5 ± 13.9 years) were recruited in our study. Patients did not have a migraine attack at least 72 hours prior to scanning (7) or a migraine precipitated during or on the day following the scan. Average pain intensity of migraine patients was rated as 5.8 ± 1.7 on a 0–10 scale from attacks in the previous 4 weeks, with 10 being the most intense pain imaginable. Attack frequency in the previous 4 weeks was also rated. All the participants were right-handed as measured by the Edinburgh Handedness Inventory (22). Additionally, prior to scanning, urine drug screening was performed on all subjects to exclude the possibility of substance abuse. The clinical and demographic characteristics of participants are shown in Table 1. This study was approved by the Medical Ethics Committee of the West China Hospital at Sichuan University. After the experimental procedure was fully explained, all participants gave their written informed consent.

Data acquisition

This experiment was carried out in a 3T Siemens scanner (Allegra; Siemens Medical System) at the Huaxi MR Research Center, West China Hospital at Sichuan University, Chengdu, China. Ear plugs were used to reduce scanner noise and the heads of the subjects were positioned carefully with restraining foam pads to minimize head motion. Prior to the DTI run, a high-resolution T1 structural image for each subject was acquired using a spoiled gradient recall sequence

Table 1. Clinical details of migraine patients without aura and healthy controls (mean ± SD).

Clinical details	Migraine patients without aura ($n = 26$)	Healthy controls ($n = 26$)
Age (years)	36.1 ± 10.2	31.5 ± 13.9
Sex (F, female; M, male)	16F, 4 M	16F,4M
Disease duration (years)	11.1 ± 6.4	—
Information on migraine attacks during previous 4 weeks		
Attack frequency (times)	5.3 ± 3.7	—
Average duration of a migraine attack (hours)	15.9 ± 14.0	—
Average pain intensity (0–10)	5.8 ± 1.7	—

with a voxel size of 1 mm^3 (repetition time (TR) = 1900 ms; echo time (TE) = 2.26 ms; data matrix = 256 × 256; slices = 176; field of view (FOV) = 256 × 256 mm^2). The diffusion tensor images were obtained with a single-shot echo-planar imaging sequence and the diffusion sensitizing gradients were applied along 30 non-linear directions (b = 1000 s/mm^2) together with an acquisition without diffusion weighting (b = 0 s/mm^2). The imaging parameters were 45 continuous axial slices with a slice thickness of 3 mm, TR = 6800 ms, TE = 93 ms, data matrix = 128 × 128, FOV = 240 × 240 mm^2. Diffusion tensor images were acquired with two averages. Two expert radiologists examined the T1 images and T2* weighted images of all participants to exclude the possibility of clinically silent lesions.

Data analysis

The data processing and analysis in this study were mainly carried out using FMRIB's Diffusion Toolbox (FDT) 2.0 and TBSS 1.2 (12), and parts of FMRIB Software Library (FSL) software 4.1.9 (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library, http://www.fmrib.ox.ac.uk/fsl). Firstly, the Brain Extraction Tool (BET) 2.1 was used for brain extraction. Then, the eddy current distortion and head motion of raw diffusion data were corrected using FDT. Secondly, FA, MD and eigenvalue maps were calculated by fitting a tensor model at each voxel of the diffusion data using FDT. An AD image was the 1st eigenvalue (L1) map. RD images were calculated via the mean of the 2nd and 3rd eigenvalue maps using *fslmaths* command-line utilities. Thirdly, TBSS analyses were performed. All of the subjects' FA images were nonlinearly registered to an FMRIB58-FA standard-space template (FMRIB Centre University of Oxford, Department of Clinical Neurology, John Radcliffe Hospital Headington, Oxford, United Kingdom; http://www.fmrib.ox.ac.uk/fsl/data/FMRIB58_FA.html) and aligned to the Montreal Neurological Institute (MNI) space. The mean image of all aligned FA images was created and thinned (non-maximum-suppression perpendicular to the local tract structure) to create a skeletonized mean FA image, which was thresholded at the FA value of 0.2 (12). Each aligned FA image of all participants was projected onto this skeleton. Next, the MD, AD, and RD images were also aligned into MNI space and projected onto the mean FA skeleton using the protocol of non-FA Images in TBSS. After controlling age and gender as a covariant, the permutation-based non-parametric inferences within the framework of the general linear model were performed to investigate the differences between the healthy controls and migraine patients. The threshold for statistical significance was $p < 0.05$, using threshold-free cluster enhancement (TFCE) with the family-wise error (FWE) correction for multiple comparison corrections (corrected $p < 0.05$, 10,000 permutations) (12). Finally, the regions in which MWoA showed significantly different DTI properties overlapped. The index values of these brain regions were extracted, averaged, and regressed against the duration of the migraine and attack frequency in the previous 4 weeks.

Results

Compared with healthy controls, migraine patients showed significantly lower FA, MD, and AD in several brain regions, whereas no difference was observed in RD. Migraine patients had lower FA in WM tracts of the genu, body, and splenium part of the CC, bilateral anterior limb of the internal capsule (ALIC) and posterior limb of the internal capsule (PLIC), bilateral cerebral peduncle, CR, part of the cingulum bundle, corticospinal tract and thalamus (Figure 1(a)) ($p < 0.05$, FWE corrected). Patients showed lower MD in the genu, body and splenium part of the corpus callosum, the right ALIC, PLIC, and thalamus radiation (Figure 1(b)) ($p < 0.05$, FWE corrected). Simultaneously, lower AD values appeared in the

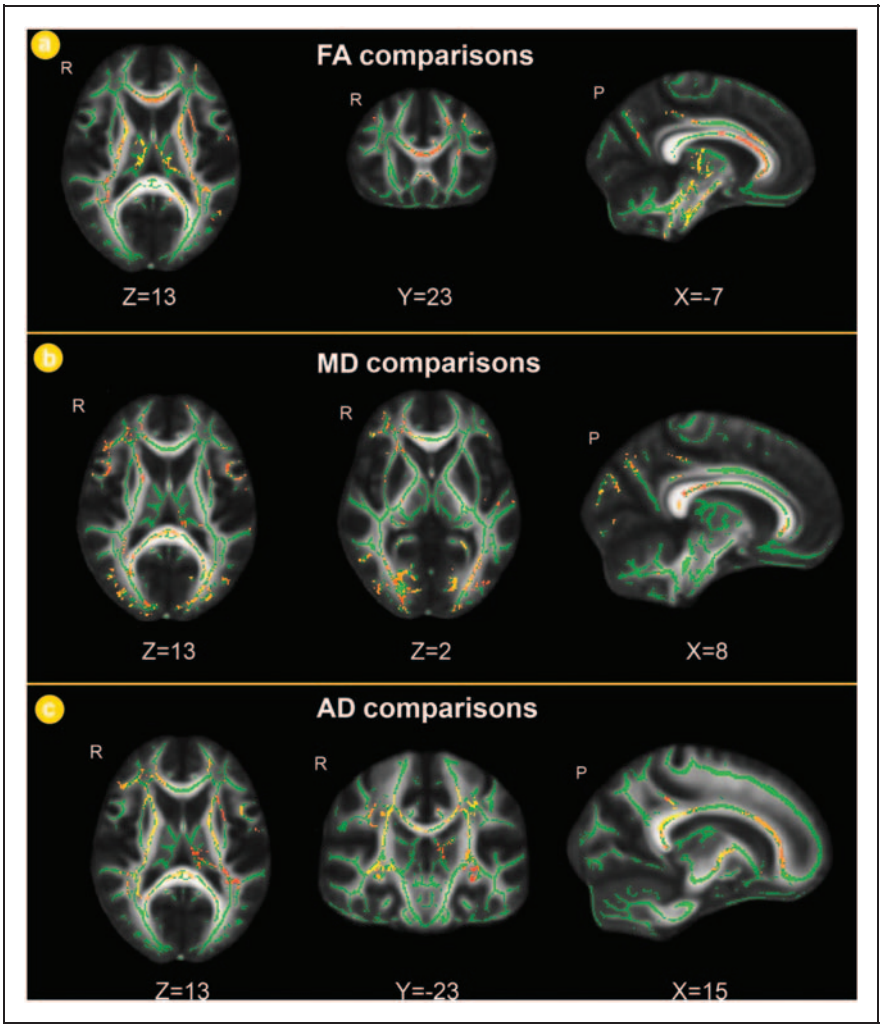

Figure 1. Compared with control subjects, migraine patients showed significantly lower fractional anisotropy (FA) (a), mean diffusivity (MD) (b) and axial diffusivity (AD) (c) in multiple brain regions ($p < 0.05$, FWE corrected), whereas no difference in radial diffusivity (RD) was observed.

genu, body, and splenium part of the CC, bilateral ALIC and PLIC, bilateral superior corona radiata (SCR), bilateral superior longitudinal fasciculi (SLF) and thalamus (Figure 1(c)) ($p < 0.05$, FWE corrected). Migraine patients did not show higher FA, RD, and AD in any brain regions compared to control subjects ($p < 0.05$, FWE corrected).

As shown in Figure 2, the overlap of the lower FA, MD and AD is shown as a warm color including the genu, body, and splenium part of the CC and the right ALIC and PLIC; the overlap of the lower MD and AD without lower FA is shown in green including the genu, body, and splenium part of the CC, the right ALIC and PLIC, the right SCR and the left SLF; and the overlap of the lower FA and AD without lower MD is shown in blue including the genu, body, and splenium part of the CC, bilateral ALIC and PLIC, the right SCR and the left SLF. No overlapping region with lower FA and MD without lower AD was found.

Furthermore, correlation analysis results demonstrated that there were significant negative correlations among the average FA, MD and AD values in the overlapped regions and the duration of migraine (Figure 3). Significant negative correlations were also found between DTI values and the frequency of migraine (Figure 4). There were significant negative correlations between the average FA values and the duration of migraine including the splenium part of the CC ($r = -0.4773$, $p = 0.0333$), the body part of the CC ($r = -0.4845$, $p = 0.0304$), and the right PLIC ($r = -0.5779$, $p = 0.0076$) (Figure 3(a)). There were significant negative correlations between the average MD values and the duration of migraine including the splenium part of the CC ($r = -0.4599$, $p = 0.0413$), and the right ALIC ($r = -0.5002$, $p = 0.0247$) (Figure 3(b)).

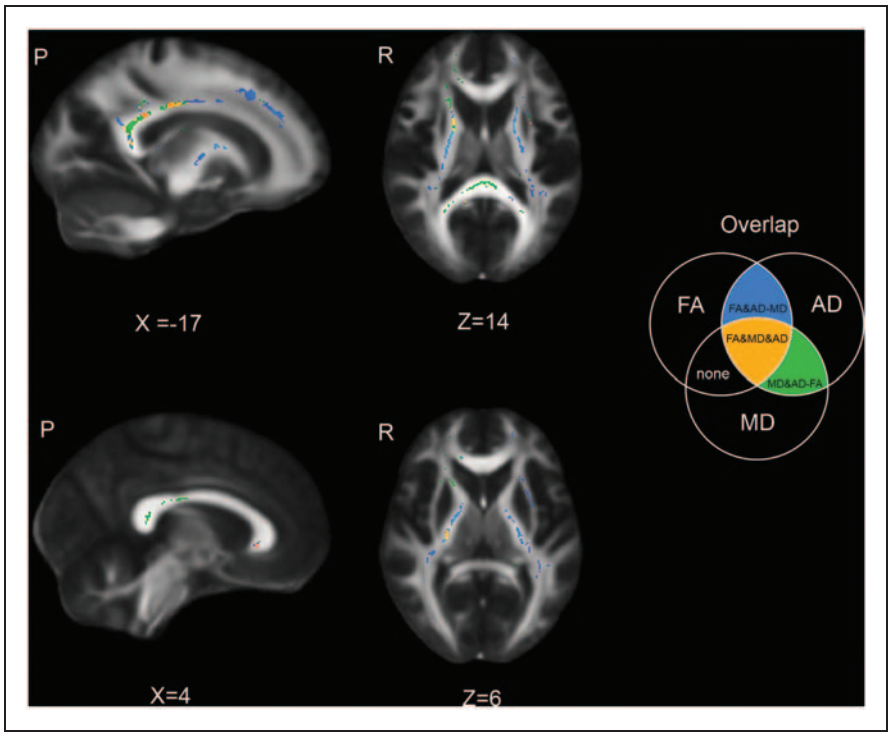

Figure 2. Brain regions with abnormal diffusion tensor imaging (DTI) properties (Figure 1) in migraine patients without aura overlapped. The abnormal brain regions with lower fractional anisotropy (FA), mean diffusivity (MD) and axial diffusivity (AD) (shown as a warm color) may reveal axonal loss in the genu, body, and splenium part of the corpus callosum (CC), right anterior limb of the internal capsule (ALIC) and posterior limb of the internal capsule (PLIC). The other abnormal brain regions with lower MD and AD without changes in other indices (shown in green) and lower FA and AD without changes in other indices (shown in blue) may suggest less severe axonal loss. No overlapping region with lower FA and MD without lower AD was found. On the right is the diagrammatic drawing with regards to the colors and the relationship of the overlap.

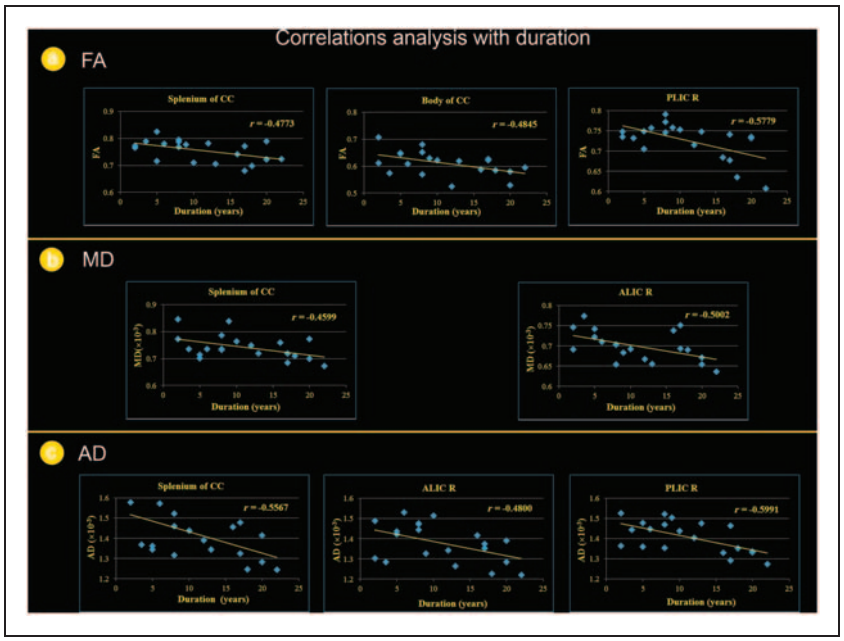

Figure 3. The correlation analysis results demonstrated that there were significant negative correlations between the average fractional anisotropy (FA) (a), mean diffusivity (MD) (b) and axial diffusivity (AD) (c) values in the overlapped regions of the lower FA, MD, and AD and the duration of migraine.

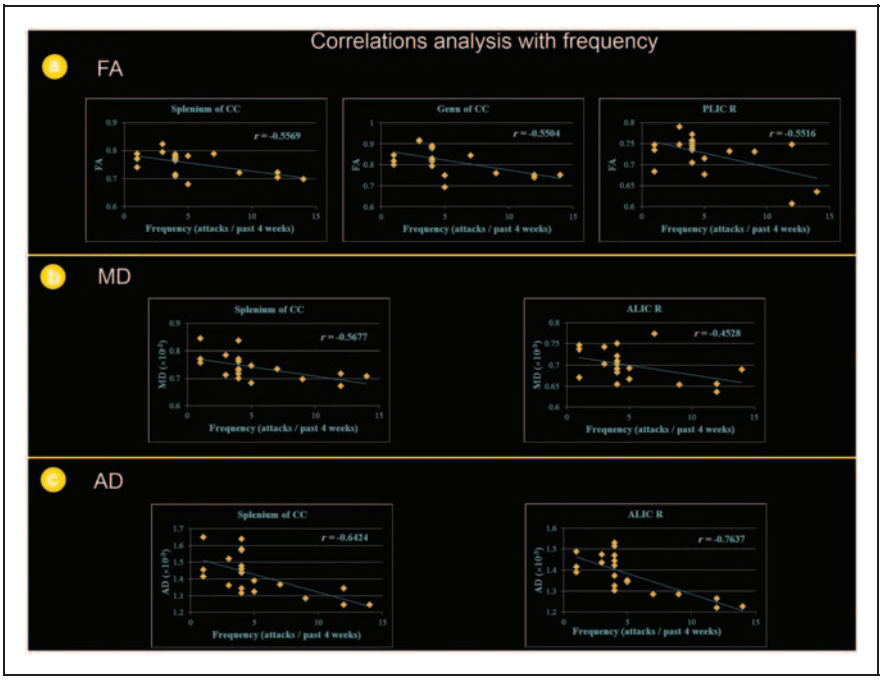

Figure 4. The correlation analysis results demonstrated that there were significant negative correlations between the average fractional anisotropy (FA) (a), mean diffusivity (MD) (b) and axial diffusivity (AD) (c) values in the overlapped regions of the lower FA, MD, and AD and the attack frequency of migraine.

There were significant negative correlations between the average AD values in the splenium part of the CC ($r = -0.5567$, $p = 0.0108$), the right ALIC ($r = -0.4800$, $p = 0.0322$), the right PLIC ($r = -0.5991$, $p = 0.0052$), and the duration of migraine (Figure 3(c)). For the frequency of migraine attacks, there were significant negative correlations between the average FA values and the frequency of migraine attacks including the splenium part of the CC ($r = -0.5569$, $p = 0.0108$), the genu part of the CC ($r = -0.5504$, $p = 0.0119$), and the right PLIC ($r = -0.5516$, $p = 0.0117$) (Figure 4(a)). There were significant negative correlations between the average MD values and the frequency of migraine attacks including the splenium part of the CC ($r = -0.5677$, $p = 0.0090$) and the right ALIC ($r = -0.4528$, $p = 0.0450$) (Figure 4(b)). There were significant negative correlations between the average AD values and the frequency of migraine attacks including the splenium part of the CC ($r = -0.6424$, $p = 0.0023$) and the right ALIC ($r = -0.7637$, $p = 0.0001$) (Figure 4(c)).

Discussion

Numerous DTI studies have reported abnormal WM properties in migraine patients (4–9). Although these findings enhanced our understanding of migraine, the methods in previous studies, that is histogram analysis and VBA, have limitations because of few local features or imperfect image registration and smoothing (12). Recently, TBSS, a more sensitive and robust method for detecting WM abnormalities (12), was employed to investigate the WM abnormality in migraine patients including both MWoA and migraine with aura compared with healthy controls (13). Due to the WM differences existing between MWoA and migraine with aura (5,14), this may affect the results in the TBSS migraine study (13). Therefore, to investigate the WM changes in MWoA, only MWoA patients were enrolled in the present study. We detected lower FA, MD, and AD with conserved RD in several WM pathways of MWoA. Specifically, lower FA values were coupled with lower MD and AD values in the genu, body, and splenium part of the CC, the right ALIC and PLIC in MWoA compared with healthy controls (shown as a warm color in Figure 2).

The multiple DTI-derived indices (FA, MD, AD, and RD) may help to deduce the more specific pathophysiological features of WM changes and provide more specific biomarkers of WM neuropathology collectively (18,19,23). In more detail, FA can reflect the structure of axonal cell membranes and myelin sheaths and lower FA may result from several conditions such as demyelination, axonal loss, gliosis, and inflammation

(18). MD is a measure of the average molecular motion which may be affected by AD or RD (24). In order to maximize specificity, AD may detect longitudinal diffusion along axons related to axonal degeneration (23). Reduced AD may suggest axonal loss or loss of bundle coherence (15,18,20). Moreover, RD may be modulated by myelin in white matter and increased RD may suggest disrupted myelination (15,18,20,23). Given that the decrease in AD suggests axonal loss, and the increase in RD suggests demyelination or dysmyelination (15,18–20,23), our findings may reveal axonal loss in the genu, body and splenium part of the CC, the right ALIC and PLIC in MWoA compared with healthy controls (shown as a warm color in Figure 2). The other abnormal brain regions with lower MD and AD without changes in other indices and lower FA and AD without changes in other indices may suggest less severe axonal loss (shown in green and blue in Figure 2). We suggested that abnormalities in local diffusion characteristics may be the biomarker of alterations in functional, clinical, or behavioral measures in MwoA patients (19). To further investigate the association between the WM changes and clinical characteristics in MWoA, a correlation analysis was carried out. The average FA, MD, and AD values of overlapped regions in the CC, the right ALIC and PLIC were negatively correlated with the duration and the attack frequency in MWoA (Figures 3 and 4). Our results suggest that migraine is a progressive disease and that abnormalities in the multiple DTI-derived indices in the CC, right ALIC and PLIC may be more severe with longer duration and higher attack frequency of migraine.

Consistent with previous findings (6), our results validated the WM abnormalities of the CC in MWoA. The CC is the main fiber tract interconnecting the two cerebral hemispheres and has an important role in interhemispheric functional integration and communication of perceptual, cognitive, learned, and volitional information (25). The fibers of the genu part in the CC serve as a bridge between different areas of the prefrontal cortex (PFC), anterior cingulate cortex (ACC), premotor cortex and supplementary motor area (SMA) (25). The fibers projecting into the primary somatosensory cortex located in the postcentral gyrus of the parietal lobe are contained in the body part of the CC (25). The splenium part of the CC communicates somatosensory information between the parietal lobe of the two hemispheres and the visual center in the occipital lobe (25,26). Moreover, abnormal WM properties of the internal capsule (IC) in MWoA were also detected in the present study. The IC consists of axonal fibers that run between the cerebral cortex and the subcortical brain structures such as the basal ganglia, thalamus, and brainstem, which contain both ascending and descending axons (27). The ALIC contains fibers running from the thalamus to the frontal lobe (afferent) and from the frontal lobe to the pons (efferent), which is penetrated by projection fibers (corticospinal tract and thalamic radiations) anatomically; the PLIC contains sensory fibers (afferent), corticospinal fibers (efferent), and a few corticobulbar fibers (28).

As evidenced by experimental and clinical studies, the brain regions connected by the CC and IC, such as the PFC, ACC, SMA, primary somatosensory cortex and basal ganglia, thalamus, and brainstem, are designated as the pain-related regions in the brain (11). Previous voxel-based morphometric (VBM) studies (29–32) and task-related functional magnetic resonance imaging (fMRI) studies (7,33,34) of migraine revealed significant GM reduction and abnormal activation in the ACC, PFC, insula, and SMA in migraine patients. Additionally, a significant decrease in regional homogeneity (ReHo) values during the resting state in the right rostral anterior cingulate cortex (rACC), PFC, OFC, and SMA were reported (35). Furthermore, ReHo values were negatively correlated with duration of disease in the right rACC and PFC (35). As the major WM pathways interconnect several pain-related brain regions, the CC and the IC showed abnormal WM properties, which may be involved in deficits of pain processing in migraine patients.

In addition, WM regions showing significant abnormalities in our study may not coincide with those typically found by previous studies, such as the OR, the subjacent WM of MT+ and the V3A, the lateral geniculate nucleus. In our opinion, the discrepancy with previous findings in the current study may be due to the two reasons. Firstly, different subject enrollment criteria may lead to different results. According to previous findings (4,14,36), some WM differences do exist between MWoA and migraine with aura. The enrolled migraine patients including both sub-groups may affect previous results. To specify the WM abnormalities in different sub-groups of migraine, it is necessary to divide the patients into MWoA and migraine with aura. Therefore, only MWoA patients were recruited in the present study. Secondly, we applied the TBSS method which was different to the VBA method from previous migraine DTI studies (4,14,36). The VBA method of DTI suffers from several limitations despite its prominent advantages, that is local features or imperfect image registration and smoothing (12). Recently, the TBSS method was employed to investigate the WM abnormality, which was more sensitive and robust for detecting WM abnormalities (12). Taken together, we suggest that the discrepancy between our study and previous studies is mainly related to the two reasons mentioned above. Moreover, Szabó et al. suggested increased RD in the

WM region with decreased FA (13). The different findings on RD in our study might be also related to the two reasons mentioned above, but more evidence is needed to prove this.

Conclusion

In the current study, we investigated pathophysiological features of WM changes in MWoA by employing the TBSS method with multiple DTI indices (i.e. FA, MD, RD, and AD). The overlapped WM tracts with abnormal FA, MD, and AD were located in the CC, right ALIC, and PLIC. Moreover, these WM alterations were associated with the duration of disease and attack frequency in MWoA patients. These WM changes suggest axonal loss of the above WM pathways in MWoA and may serve as a sensitive biomarker to reflect the progress and severity of MWoA. However, a more comprehensive experimental design is needed to reveal the accurate roles of these WM changes in the pathology of migraine. We hope that our results could improve understanding of migraine mechanisms and provide treatment strategies and potential diagnostic information in migraine patients.

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Conflict of interest

None declared.

Clinical implications

1. Compared with healthy controls, migraine patients without aura (MWoA) showed significantly lower fractional anisotropy (FA), mean diffusivity (MD), and axial diffusivity (AD) in multiple brain regions.
2. Given that decreased AD could suggest axonal loss, our findings may reveal axonal loss in MWoA.
3. If white matter integrity is measurably plastic and related to migraine without aura, this may serve as a sensitive biomarker to reflect the progression of disease, and have potential use in diagnosing, monitoring, and assessing in a clinical setting.
4. Successful treatment in migraine without aura might be accompanied by a normalization of white matter integrity, our results might help us to monitor the treatment.

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