Characteristics of Diffusional Kurtosis in Chronic Ischemia of Adult Moyamoya Disease: Comparing Diffusional Kurtosis and Diffusion Tensor Imaging

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ABSTRACT

BACKGROUND AND PURPOSE: Detecting microstructural changes due to chronic ischemia potentially enables early identification of patients at risk of cognitive impairment. In this study, diffusional kurtosis imaging and diffusion tensor imaging were used to investigate whether the former provides additional information regarding microstructural changes in the gray and white matter of adult patients with Moyamoya disease.

MATERIALS AND METHODS: MR imaging (diffusional kurtosis imaging and DTI) was performed in 23 adult patients with Moyamoya disease and 23 age-matched controls. Three parameters were extracted from diffusional kurtosis imaging (mean kurtosis, axial kurtosis, and radial kurtosis), and 4, from DTI (fractional anisotropy, radial diffusivity, mean diffusivity, and axial diffusivity). Voxelwise analysis for these parameters was performed in the normal-appearing brain parenchyma. The association of these parameters with neuropsychological performance was also evaluated.

RESULTS: Voxelwise analysis revealed the greatest differences in fractional anisotropy, followed, in order, by radial diffusivity, mean diffusivity, and mean kurtosis. In patients, diffusional kurtosis imaging parameters were decreased in the dorsal deep white matter such as the corona radiata and superior longitudinal fasciculus (P < .01), including areas without DTI abnormality. Superior longitudinal fascicular fiber-crossing areas showed weak correlations between diffusional kurtosis imaging and DTI parameters compared with tissues with a single-fiber direction (e.g., the corpus callosum). Diffusional kurtosis imaging parameters were associated with general intelligence and frontal lobe performance.

CONCLUSIONS: Although DTI revealed extensive white matter changes, diffusional kurtosis imaging additionally demonstrated microstructural changes in ischemia-prone deep white matter with abundant fiber crossings. Thus, diffusional kurtosis imaging may be a useful adjunct for detecting subtle chronic ischemic injuries.

ABBREVIATIONS: AD = axial diffusivity; AK = axial kurtosis; CPT = continuous performance task; DKI = diffusional kurtosis imaging; FA = fractional anisotropy; IQ = intelligence quotient; MK = mean kurtosis; MD = mean diffusivity; MMD = Moyamoya disease; RD = radial diffusivity; RK = radial kurtosis; RST = Reading Span Test; SLF = superior longitudinal fasciculus; TMT = Trail-Making Test

Moyamoya disease (MMD) is characterized by compensatory development of enlarged and weak basal perforating arteries (Moyamoya vessels) due to bilateral occlusive changes in the internal carotid system. In addition to cerebral ischemia and intracranial hemorrhage, patients with MMD demonstrate neurocognitive issues, such as executive dysfunction, attention deficits, and working-memory disturbances. Brain atrophy may explain cognitive impairment in the absence of infarction, but detection of these changes has been hampered by the limited sensitivity of conventional neuroimaging methods. Diffusion tensor imaging is useful for determining white matter integrity and providing parameters sensitive to changes in axons, myelin, and organelle structures. Indeed, DTI analysis has revealed a widespread decline in white matter integrity in the normal-appearing brain with MMD. Thus, DTI can detect...
Table 1: Characteristics of the study participants

|                                | Control | Moyamoya Disease | P Value |
|--------------------------------|---------|------------------|---------|
| No. of subjects                | 23      | 23               |         |
| Age (mean) [range] (yr)        | 39.0 ± 8.1 [25–56] | 40.9 ± 9.5 [21–58] | .48     |
| Sex (F/M) [No. of subjects]    | 13/10   | 17/6             | .35     |
| Risk factor (DM, HT, HL) [No. of subjects] | 0 | 5 | .049 |
| Symptoms (No. of subjects)     | –       | 13               |         |
| Asymptomatic                   | –       | 13               |         |
| TIA                            | –       | 10               |         |

Note: DM indicates diabetes mellitus; HT, hypertension; HL, hyperlipidemia.

Materials and Methods

Participants

This prospective study was approved by the Research Ethics Committee of Hokkaido University Hospital, and written informed consent was obtained from all participants. Participants in the present study are the same as those of our previous study analyzing the relationship between DTI parameters and neuropsychological test scores. The selection period was 25 months (April 2012 through April 2014). Twenty-three patients (6 men and 17 women; 21–58 years of age; mean age, 40.9 ± 9.5 years) were enrolled. The control group also consisted of 23 subjects (10 men and 13 women; 25–56 years of age; mean age, 39.0 ± 8.1 years). A brief summary of patient characteristics is provided in Table 1.

Neuropsychological Assessment

Neuropsychological examinations consisted of the Wechsler Adult Intelligent Scale-III, Wisconsin Card Sorting Test, Trail-Making Test (TMT; parts A and B), continuous performance task (CPT), Stroop test, and Reading Span Test (RST). The details of neuropsychological examinations and the results are provided in the On-line Appendix.

MR Image Acquisition

MR imaging was performed with a 3T scanner (Achieva TX; Philips Healthcare, Best, the Netherlands). 3D magnetization-prepared rapid acquisition of gradient echo T1-weighted imaging and axial single-shot spin-echo echo-planar DKI were acquired to evaluate subtle gray and white matter alterations, respectively. The scan parameters for DKI were as follows: TR = 5051 ms, TE = 85 ms, flip angle = 90°, FOV = 224 × 224 mm², matrix size = 128 × 128, b-values = 0, 1000, and 2000 s/mm², number of diffusion gradient directions = 32, section thickness = 3 mm, intersection gap = 0 mm, number of sections = 43, and NEX = 1. The 3D-MPRAGE imaging was performed with TR = 6.8 ms, TE = 3.1 ms, flip angle = 8°, and TI = 1100 ms.

Image Processing

Registration between the echo-planar images with no diffusion weighting (b=0 s/mm²) and the corresponding DKI data and correction for eddy current distortion were performed at the MR imaging operator console. The DKI data were processed by using Matlab R2012b (MathWorks, Natick, Massachusetts) and Diffusional Kurtosis Estimator (Version 2.5.1; http://nitrcc.org/projects/dke). Seven DKI and DTI parameters were extracted from the Diffusional Kurtosis Estimator: mean kurtosis (MK), radial kurtosis (RK), axial kurtosis (AK), FA, mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). The DTI parameters (FA, MD, RD, and AD) were calculated from a portion of the DKI data by using a monoexponential model that assumes a Gaussian probability diffusion function by using data from b-values of 0 and 1000 s/mm².

Following calculation of DKI and DTI parameters, the b=0 echo-planar images were warped to the standardized T2 template.

early-stage ischemic injury, which potentially predicts future cognitive outcomes. However, DTI is constrained by technical insufficiencies: It is based on the assumption that water molecules diffuse freely and that diffusion can be characterized by a Gaussian distribution.

Furthermore, because hypoxic-ischemic injury induces neurodegeneration and regression of dendrite arborization in gray matter, the diffusion properties of gray matter may also reveal the early stages of ischemic injury. Nevertheless, analyzing isotropic or near-isotropic tissue such as gray matter by DTI may not be valid because its major parameter, fractional anisotropy (FA), reflects structure only if it is spatially oriented. A more recent method called diffusional kurtosis imaging (DKI) quantifies the deviation of water molecule diffusion from the Gaussian distribution without assuming any specific diffusion model. Its parameters are thought to represent the complexity of tissue microstructure. Previous studies have suggested that DKI is sufficiently sensitive to detect age-related alterations in white matter microstructure. Furthermore, measurements of diffusion anisotropy by DKI can reveal sex-related and pathologic changes in gray matter.

Diffusional kurtosis has been investigated to explore tissue reversibility in acute cerebral infarction. However, there is a paucity of information regarding the microstructural properties measured by DKI in chronic ischemia in living humans. To expand on our prior DTI study, we investigated whether adults with MMD and no overt cerebral infarctions have altered diffusional kurtosis in the entire cerebral. An exploratory voxel-based whole-brain analysis was performed to map regional DKI parameters and to compare DKI and DTI parameters. We also explored correlations of diffusion parameters with measures of neurocognitive impairment in an ROI analysis.
The ROIs were FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Fiber directions) by using the JHU white matter atlas available in placed on the genu of the corpus callosum (ie, a structure with a superior longitudinal fasciculus (Fig 1). The decrease in FA was most extensive within the white matter (161,625 voxels), with its decrease amounting to 12,833 voxels (7.9%) (Fig 2). Significant MK, RK, and AK decreases were observed in 6180 voxels (3.8%), 3828 voxels (2.4%), and 3043 voxels (1.9%), respectively. In contrast, 9028 voxels (5.6%) showed a significant increase in MD; 10,062 voxels (6.2%), in RD; and 548 (0.3%), in AD compared with controls. Figure 1 shows DKI/DTI overlap maps, with MK/RK/FA decreases and MD/RD increases. Areas with FA decrease were more extensive than those with MK decrease; however, the posterior segment of the SLF showed a decrease in only MK/RK. The increase in MD/RD was remarkable in the corona radiata; however, the posterior segment of the SLF showed a decrease in MK/RK without an increase in MD/RD. Decreased AK was observed without changes in AD for the bilateral thalamus, corona radiata, and portions of the temporo-occipital white matter. There was no cortical gray matter with altered DKI/DTI parameters in patients.

**RESULTS**

**Spatial Distribution of DTI/DKI Differences on Voxel-Based Analysis**

Areas with decreased MK included the right frontal white matter, bilateral thalamus, portions of the occipital white matter, corona radiata, corpus callosum, and portions of frontal and parietal white matter corresponding to the posterior segment of the superior longitudinal fasciculus (Fig 1). The decrease in FA was most extensive within the white matter (161,625 voxels), with its decrease amounting to 12,833 voxels (7.9%) (Fig 2). Significant MK, RK, and AK decreases were observed in 6180 voxels (3.8%), 3828 voxels (2.4%), and 3043 voxels (1.9%), respectively. In contrast, 9028 voxels (5.6%) showed a significant increase in MD; 10,062 voxels (6.2%), in RD; and 548 (0.3%), in AD compared with controls. Figure 1 shows DKI/DTI overlap maps, with MK/RK/FA decreases and MD/RD increases. Areas with FA decrease were more extensive than those with MK decrease; however, the posterior segment of the SLF showed a decrease in only MK/RK. The increase in MD/RD was remarkable in the corona radiata; however, the posterior segment of the SLF showed a decrease in MK/RK without an increase in MD/RD. Decreased AK was observed without changes in AD for the bilateral thalamus, corona radiata, and portions of the temporo-occipital white matter. There was no cortical gray matter with altered DKI/DTI parameters in patients.

**Association of DKI/DTI Parameters with Neuropsychological Performance Tests**

The DKI parameter (AK) showed significant correlations with motor intelligence quotient (IQ), full-scale IQ, perceptual organization, and processing speed evaluated on the Wechsler Adult Intelligent Scale-III (Fig 3A, r > 0.42, P < .05). Both DKI (MK) and DTI (FA, MD, and RD) parameters showed significant correlations with the TMT part B (Fig 3B, r > 0.44, P < .05). The Stroop test performance showed moderate positive correlations with MK, RK, and FA and negative correlations with MD, RD, and AD (P < .05). RST was associated with MK and AK (P < .05). The correlations between diffusion parameters and neuropsychological scores (Wisconsin Card Sorting Test, Stroop Test, CPT, and RST) are shown in Table 3.
**DISCUSSION**

We explored the added benefit of diffusional kurtosis measurements in the assessment of ischemic burden due to chronic ischemia in adult MMD. This study confirmed our prior finding that chronic ischemia in MMD preferentially affects the microstructure of normal-appearing white matter. Detecting microstructural changes due to chronic ischemia potentially enables early identification of patients at risk of cognitive impairment.  

However, detecting microstructural changes has been hampered by the limited sensitivity of DTI in fiber-crossing areas. In this study, DKI demonstrated microstructural changes, predominantly in the dorsal part of the deep white matter, where conventional MR imaging frequently demonstrates ischemic lesions. The significant changes in DKI parameters were associated with neuropsychological scores reflecting general intelligence, executive function, attention, and working memory. Thus, DKI is considered a useful adjunct to conventional DTI, particularly for its ability to detect nascent microstructural changes in areas with abundant fiber crossings.

In this study, we demonstrated that DTI showed widespread regions with alterations in FA, MD, and RD. The finding is consistent with previous studies, in which DTI showed more extensive white matter changes compared with DKI parameters. Other studies have demonstrated superior sensitivity of DKI to detect white matter changes compared with DTI.  

DKI showed significant decreases in frontoparietal subcortical structures and deep white matter. A decrease in DKI parameters, a shift of diffusional kurtosis toward free water diffusion, has commonly been interpreted as a reduction in tissue complexity. Considering the location of the DKI alterations, a reduction in complexity is thought to reflect microstructural changes in myelin and/or axonal attenuation. In the corona radiata, DTI (MD/RD) demonstrated more significant changes compared with DKI (MK/RK). Deep white matter tracts are vulnerable to chronic ischemia because they are located in the terminal field of the blood supply. Myelin degeneration or increased periventricular extracellular fluid may increase RD, while tissue complexity in a radial direction may be maintained, in some part, by glial proliferation. In a previous study, a trend toward decreased AD was found via analysis of tract-specific spatial statistics, whereas the voxel-based analysis of the present study did not show definitive AD changes in white matter. AD decreases in axonal fragmentation; however, axonal degeneration or reduced axonal attenuation can increase AD. In contrast with AD, AK showed significant changes in the
Several fiber populations aligned along intersecting axes in In We extracted DKI/DTI values from the These hypoxic-ischemic insults may imply that a reduction in MK in the SLF of controls could be attributed to the crossing/ traveling fibers projecting from the corona radiata and corpus callosum. Several fiber populations aligned along intersecting axes in 1 voxel would diminish anisotropy.

The DKI parameters in patients showed moderate positive correlations with impaired general intelligence and frontal lobe dysfunction. These results are consistent with previous reports showing a relationship between cognitive performance and white matter fiber tracts integrating parietofrontal cortical areas. In MMD, performance IQ is preferentially affected compared with verbal IQ. In the present study, AK was significantly correlated with neuropsychological performance on tests evaluating executive function and working memory (motor IQ, perceptual organization, and processing speed), while no correlation was found with verbal IQ. In an experimental animal model of chronic white matter ischemia, damage to myelin preceded axonal damage, suggesting that the change in myelin is the primary pathologic event. Our observation of a stronger correlation between AK, rather than AD, and general intellectual ability measured by the Wechsler Adult Intelligence Scale-III may imply that a reduction in axonal density and/or axonal degeneration, a more advanced stage of chronic ischemic injury, is better described by AK than AD. Previous investigations by using DTI and probabilistic tractography have shown correlations between neuropsychological examinations and the FA of subcortical white matter. Consistent with previous studies, we observed correlations between DTI parameters and the scores of neuropsychological tests evaluating frontal lobe function in the present study. A significant correlation of FA/MD/RD with scores on the Trail-Making Test suggests that demyelination alone could affect part of the frontal lobe functions.

Transient ischemic attack followed by hyperventilation is a characteristic symptom of childhood MMD, and syncope attacks are occasionally observed in both children and adults with MMD. The spatial characteristics of nascent brain injury are important for understanding frontal-dominant neuropsychological dysfunction in adult MMD. Pyramidal neocortical neurons (layers 3, 5, and 6) in the prefrontal cortex are known to be highly vulnerable to hypoxic-ischemic insults. These hypoxic-ischemic insults can damage the brain and potentially induce neuronal death or regression of dendritic structure. We speculate that microstructural alteration precedes gross volumetric reductions in gray matter. Previous study has revealed gray matter atrophy in the posterior cingulate cortex, suggesting that more widespread gray matter changes might be observed in diffusion parameters, particularly in the frontal lobe. DKI could reveal early microstructural changes less constrained by partial volume effects. Nevertheless, despite discrete white matter damage, no substantial changes in diffusion parameters were found in the cortical gray matter in MMD. Pathologic tissue changes such as glial proliferation may underlie the lack of significant changes in the diffusion parameters of the cortices. A new diffusion MR imaging technique, including neurite orientation dispersion and density imaging, may detect subtle microstructural changes in the cortex and is potentially sensitive to initial ischemic changes before the overt volumetric reductions.

The present study revealed microstructural change in the thalamus, a finding that has never been emphasized with regard to cognitive function in MMD. The mediodorsal thalamus connects to the prefrontal cortex. This is potentially important because innervation of the thalamoprefrontal circuit could modulate prefrontal neural circuits, which are associated with cognitive as well as affective performance. There are several limitations to this study. The statistical power to detect group differences in DKI parameters is significantly influenced by the number of subjects in a study. Therefore, the spatial characteristics of the DKI/DTI alterations found in this study may not represent the topography of ischemic burden in adult MMD. We extracted DKI/DTI values from the contrast T maps generated from group comparisons between controls and patients to explore the relationship between abnormal diffusion parameters in patients and neuropsychological test performance. Although we found an association with neuropsychological test scores, voxel-based correlation analysis would per-
FIG 3. Scatterplots indicating a significant correlation between neuropsychological test performance and diffusion parameters. Pearson moment-production correlation coefficient \( r \) and \( P \) values are demonstrated in each scatterplot. ROIs (green) for each parameter (AK, MK, FA, MD, and RD) are demonstrated with FA template images generated from 23 controls and 23 patients. A, Performance scores evaluated on the Wechsler Adult Intelligent Scale-III are significantly associated with axial kurtosis. Axial kurtosis is positively correlated with full-scale IQ (\( r = 0.42, P = 0.04 \)) and subscores such as motor IQ (\( r = 0.49, P = 0.02 \)), perceptual organization (\( r = 0.47, P = 0.03 \)), and processing speed (\( r = 0.47, P = 0.03 \)). B, Trail-Making Test, part B is inversely correlated with DKI/DTI parameters (MK; \( r = -0.44, P = 0.04 \); and FA; \( r = -0.49, P = 0.02 \)) and positively correlated with DTI parameters (MD; \( r = 0.56, P = 0.007 \); and RD; \( r = 0.56, P = 0.007 \)).
Table 3: Correlations of diffusion parameters with neuropsychological examinations

|        | WCST | Stroop | CPT | RST |
|--------|------|--------|-----|-----|
| MK     | –    | –      | 0.04b  |
| RK     | –    | –      | 0.007b |
| AK     | –    | –      | 0.045c  |
| FA     | –    | –      | 0.024b  |
| MD     | –    | –      | 0.012b  |
| RD     | –    | –      | 0.014b  |
| AD     | –    | –      | 0.031c  |

Note: WCST indicates Wisconsin Card Sorting Test; Stroop; Stroop test.

Data are P values. Correlations of diffusional kurtosis imaging and diffusion tensor imaging parameters with neuropsychological examinations were evaluated in patients with MMD. Three diffusional kurtosis parameters (MK, RK, and AK) and 4 diffusion tensor parameters (FA, MD, RD, and AD) were analyzed. Diffusion parameters and locations that demonstrated significant relationships with clinical variables follow.

CONCLUSIONS

The results of the present study suggest an additional value of DKI as an adjunct to DTI. DKI parameters can become useful neuroimaging markers to track ischemic burden in adult MMD.

Disclosures: Ken Kazumata—RELATED: Grant: This study was supported by a grant from the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan.* Khin K. Tha—RELATED: Grant: This work was supported (in part) by the Creation of Innovation Centers for Advanced Interdisciplinary Research Areas Program, Ministry of Education, Culture, Sports, Science, and Technology, Japan.* Masaki Ito—RELATED: Grant: Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan.* UNRELATED: Grants/Grants Pending: Masaki Ito was funded by a fellowship (grant) Y1,000,000,000 (approximately US $18,000) for 1 year from SENTOSHI Medical Research Foundation donated by the Mitsubishi Corporation, Japan. Funding began April 1, 2015. Takeo Abumiyu—RELATED: Grant: from the Research Committee on Moyamoya Disease, sponsored by the Ministry of Health, Labor, and Welfare of Japan.* Money paid to the institution.

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