This study examined the relationship between fractional anisotropy (FA) values of magnetic resonance-diffusion tensor imaging (DTI) and motor outcome (1 month after onset) in 15 patients with hemiparesis after ischemic stroke of corona radiata lesions. DTI data were obtained on days 14-18. FA values within the cerebral peduncle were analyzed using a computer-automated method. Motor outcome of hemiparesis was evaluated according to Brunnstrom stage (BRS; 6-point scale: severe to normal) for separate shoulder/elbow/forearm, wrist/hand, and lower extremity functions. The ratio of FA values in the affected hemisphere to those in the unaffected hemisphere (rFA) was assessed in relation to the BRS data (Spearman rank correlation test, \( P < .05 \)). rFA values ranged from .715 to 1.002 (median = .924). BRS ranged from 1 to 6 (median = 4) for shoulder/elbow/forearm, from 1 to 6 (median = 5) for wrist/hand, and from 2 to 6 (median = 4) for the lower extremities. Analysis revealed statistically significant relationships between rFA and upper extremity functions (correlation coefficient = .679 for shoulder/elbow/forearm and .706 for wrist/hand). Although slightly less evident, the relationship between rFA and lower extremity function was also statistically significant (correlation coefficient = .641). FA values within the cerebral peduncle are moderately associated with the outcome of both upper and lower extremity functions, suggesting that DTI may be applicable for outcome prediction in stroke patients with corona radiata infarct. Key Words: Ischemia—paralysis—prognosis—recovery—stroke.

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Introduction

Stroke is a common cause of disability among the elderly adults, and rehabilitation is often scheduled as a treatment to minimize disability. To facilitate the most effective rehabilitative treatment, outcome prediction is critically important.1 Recent advances in neuroimaging techniques have contributed to outcome prediction after stroke.2 In particular, diffusion tensor imaging (DTI) has recently been found to be useful for evaluating neural degeneration because of stroke, subserving outcome prediction in both ischemic3-10 and hemorrhagic11-15 stroke cases. DTI sensitively detects the path of the diffusion gradient of water molecules, consequently revealing the orientation of neural fibers, and enables clinically useful characterization of Wallerian degeneration after stroke.16

The vast majority of DTI studies on stroke outcome have used tractography, which assesses the integrity of neural fibers.5,7,8,11,13,14 One of the advantages of DTI tractography is eyeball fit-comprehensible visualization of neural fibers. Typical analytical procedures of tractography studies
employ categorical classification of neural fiber integrity (eg, intact, partially disrupted, totally disrupted) in relation to motor outcome. However, in reality, axonal damage cannot be assessed by using such a simple classification system.

Another popular means for bringing DTI data into clinical practice is fractional anisotropy (FA).\textsuperscript{16} The FA value is a quantitative measure of the degree of anisotropy, which is characterized by the random motion of water preferentially restricted to monodirectional movement, such as in neural fibers. Because it is an interval scale, stroke outcome can be better characterized by using FA values. In fact, in our previous studies, we successfully applied FA values for probabilistic prediction of the motor outcome of patients with intracerebral hemorrhage.\textsuperscript{15} For ischemic stroke, however, only a limited number of studies that have systemically analyzed the relationships between FA values and motor outcome have been reported in the literature.\textsuperscript{5,9,10} To address this issue, we assessed FA values in relation to motor outcome in cases of ischemic stroke.

**Methods**

**Patients**

The study population (N = 15) comprised 9 male and 6 female stroke patients with corona radiata infarct who were admitted to our hospital between December 2010 and December 2012. Typically, patients were transferred to our hospital soon after stroke onset. They were then examined by diffusion-weighted magnetic resonance imaging (MRI) (diffusion-weighted imaging [DWI], details presented subsequently) and cerebral infarct was diagnosed. Patients subsequently underwent conservative treatments such as medication (eg, anticoagulants or antiplatelet agents). During hospitalization, patients also underwent physical therapy, occupational therapy, and speech therapy for a combined daily total of up to 180 minutes. The therapeutic regimen for rehabilitation was uniformly prescribed by a single physiatrist (T.K.).

Criteria for inclusion in the database were no history of angina pectoris, or other coincidental conditions were excluded. For MRI safety, patients with metal implants (eg, pacemaker) were also excluded. Comparable with previous studies in this field, we limited our sample population to patients with corona radiata lesions to minimize variability arising from portions of stroke lesions.\textsuperscript{5,7} Patients (or relatives when necessary) provided written consent for inclusion in the study.

**DWI Acquisition**

On arrival at our hospital, patients manifesting hemiparesis or related symptoms were suspected of stroke and underwent head MRI with a 3.0 T (Trio; Siemens AG, Erlangen, Germany) or a 1.5 T (Signa; General Electric Medical Systems, Milwaukee, WI) scanner contingent on availability. For the 3.0 T scanner, employing a single-shot echo-planar imaging sequence, the DWI scheme acquired an image with diffusion gradients (b = 1200 s/mm\textsuperscript{2}) and non-DWI (b = 0 s/mm\textsuperscript{2}). We obtained 22 axial slices from each patient. The field of view was 220.0 × 220.0 mm, the acquisition matrix was 128 × 128, and the slice thickness was 5 mm with a 1.5-mm gap. Echo time was 81 milliseconds and the repetition time was 5000 milliseconds. Acquisition parameter settings were the same for the 1.5 T scanner, except for diffusion gradient (b = 1000 s/mm\textsuperscript{2}) and echo time (100 milliseconds).

**DTI Acquisition**

DTI was performed on days 14-18 after admission using the 3.0 T magnetic resonance scanner with a 32-channel head coil. The DTI scheme acquired 12 images with noncollinear diffusion gradients (b = 1000 s/mm\textsuperscript{2}) and 1 non–diffusion-weighted image (b = 0 s/mm\textsuperscript{2}) by employing a single-shot echo-planar imaging sequence. We obtained 64 axial slices from each patient. The field of view was 230.4 × 230.4 mm, the acquisition matrix was 128 × 128, and the slice thickness was 3 mm with no gap, which resulted in voxel dimensions of 1.8 × 1.8 × 3.0 mm. Echo time was 83 milliseconds and the repetition time was 7000 milliseconds. Besides DTI scans, we obtained T1- and T2-weighted magnetic resonance images for other diagnostic usage. Including these scans, the total time for MRI acquisition was approximately 20 minutes per patient. Patients who were unable to keep still long enough to enable complete MRI acquisition were excluded from our database.

**Image Processing**

Image processing was conducted with the brain image analysis package, FSL,\textsuperscript{17} which comprises various tools, including the Brain Extraction Tool (BET), FMRIB’s Diffusion Toolbox (FDT), FMRIB’s Nonlinear Image Registration Tool (FNIRT), FSLUTILS, and FSLVIEW. Using the FDT to align all images in volumetric relation to the first image (b = 0 s/mm\textsuperscript{2}), DTI data were corrected for motion and eddy current distortion. Next, extracerebral matter was excluded from the images using BET tool. To evaluate tensor diffusion and calculate brain FA values, DTI data were analyzed using the FDT (FA brain map). These FA values were mapped to a standard stereotaxic space by using FNIRT (International Consortium of Brain Mapping DTI-81 Atlas; ICBM DTI-81 Atlas).\textsuperscript{18} As recommended in the manual, we employed the “standard tasks” setting for FNIRT to keep the transformation procedure simple. Spatial transformations of the FA brain maps were confirmed
by visually comparing images with those generated by FSLVIEW.15

In accordance with previous studies in the same field,3,4,9 we then specified regions of interest (ROIs) in the left and right cerebral peduncles defined in the standard brain (Fig 1). To do this, we used FSLUTILS to discriminate the left and right cerebral peduncles and abstract them from the JHU-WhiteMatter Labels implemented within FSL. FA values within the separate left and right ROIs were assessed, and mean values for single voxels were subsequently estimated. In further analysis, the ratio between FA values in the affected and unaffected sites (rFA) for cerebral peduncles was calculated. These image processing procedures were the same as those used in our previous study.15

Outcome Measurements

Outcome measurements were obtained 1 month after admission. Brunnstrom stage (BRS), commonly used by Japanese rehabilitation therapists, was used to assess poststroke motor function impairment of the upper and lower extremities on the hemiparetic side. In this assessment, the recovery process of the affected extremities was evaluated in terms of associated reactions and flexion and extension synergy patterns of the extremities (6-point scale: severe to normal).19,20 Conventionally, BRS is used for separately evaluating proximal (shoulder/elbow/forearm) and distal (wrist/hand) portions of the upper and entire lower extremities. Assessments were made by an occupational or physical therapist blinded to the purpose of the present study. As well as motor function assessment by BRS, patient ADL were also assessed using a 5-grade modified Rankin Scale (mRS: level 1, no significant disability; level 5, severe disability).21

Statistical Analysis

Spearman rank correlation tests were used to determine the relationship between rFA values and outcome assessed by BRS (shoulder/elbow/forearm, wrist/hand and lower extremities) and mRS. All statistical analysis was performed using the JMP software package (SAS Institute, Cary, NC). P less than .05 was considered statistically significant.

Results

Patient age ranged from 45 to 78 years (median = 67 years); 6 patients had right hemisphere lesions and 9 had left hemisphere lesions (Table 1, Fig 2). rFA values ranged from .715 to 1.002 (median = .924). BRS ranged from 1 to 6 (median = 4) for shoulder/elbow/forearm, from 1 to 6 (median = 5) for wrist/hand, and from 2 to 6 (median = 4) for lower extremities and mRS scores ranged from 2 to 5 (median = 3).

Figure 3 shows the relationship between rFA and motor outcome assessed by BRS. Analyses revealed statistically significant relationships between rFA and extremity functions. rFA values showed moderate correlations between shoulder/elbow/forearm (correlation coefficient = .679, P = .005) and wrist/hand (correlation coefficient = .706, P = .003) functions. The relationship between rFA and lower extremity function was similar to that for upper extremity functions but less evident (correlation coefficient = .641, P = .010). Although not statistically significant (P = .084), additional analysis indicated a tendency for higher mRS scores to be associated with lower rFA values (correlation coefficient = −.461, data not shown).

Discussion

DTI has been recently applied to patients after stroke to assess neural degeneration. Most previous studies in this area have employed tractography of corticospinal tracts and have classified the integrity of affected neural fibers in relation to motor outcome. In contrast, we assessed FA values and interval measurements in this study in relation to motor outcomes. The results indicated that FA values within cerebral peduncles are moderately correlated with extremity functions.

In the image processing employed in this study, we defined ROIs and calculated FA values using a fully computer-automated methodology to ensure that FA values are consistently and accurately reproducible. In the group analysis, rFA values were moderately correlated with BRS (Fig 3), implicating their use as outcome predictors for ischemic stroke patients with corona radiata lesions. However, BRS level 5 data for wrist/hand portion revealed that FA values ranged from .868 to .985 (patients 2, 3, 5, 7, 9, and 12; Table 1, Fig 3). Accordingly, careful consideration should be taken for the interpretation of FA values when using them for outcome prediction in individual cases.
Because FA values are thought to index the degree of Wallerian degeneration, some time has to elapse before clinically significant changes are detectable. Previous studies have indicated a requirement of 2 weeks for the reliable detection of signal changes.\textsuperscript{3,4,9} Accordingly, we collected DTI data on days 14-18 from stroke onset. The database for this study consisted of 3 cardioembolic and 12 arteriothrombotic stroke cases (Table 1). Time courses of neural degeneration because of ischemic change may differ between these 2 etiologies, but we did not analyze potential differences in the present study. Therefore, future studies are needed to clarify this issue.

In this study, we applied a simple correlation modeling to the dataset and then revealed statistically significant relationships between motor outcome and FA values acquired using DTI. The findings in the present study may be useful when planning rehabilitative therapies for groups of similar patients. For example, in patients with rFA values greater than .95, it would be most beneficial to focus on rehabilitative training of the affected

Table 1. Patient profiles

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Age (y)</th>
<th>M/F</th>
<th>Type of stroke</th>
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Abbreviations: AT, atherothrombotic; CE, cardioembolic; F, female; FA, fractional anisotropy; L/E, lower extremity; M, male; mRS, modified Rankin Scale; Pt No., patient number; rFA, ratio between FA value in affected and unaffected hemispheres within the region of interest; S/E/F, shoulder, elbow, and forearm; W/H, wrist and hand.

Patients are sequenced according to rFA value (highest to lowest).

Because FA values are thought to index the degree of Wallerian degeneration, some time has to elapse before clinically significant changes are detectable. Previous studies have indicated a requirement of 2 weeks for the reliable detection of signal changes.\textsuperscript{3,4,9} Accordingly, we collected DTI data on days 14-18 from stroke onset. The database for this study consisted of 3 cardioembolic and 12 arteriothrombotic stroke cases (Table 1). Time courses of neural degeneration because of ischemic change may differ between these 2 etiologies, but we did not analyze potential differences in the present study. Therefore, future studies are needed to clarify this issue.

In this study, we applied a simple correlation modeling to the dataset and then revealed statistically significant relationships between motor outcome and FA values acquired using DTI. The findings in the present study may be useful when planning rehabilitative therapies for groups of similar patients. For example, in patients with rFA values greater than .95, it would be most beneficial to focus on rehabilitative training of the affected

Figure 2. Diffusion-weighted images and diffusion tensor imaging-fractional anisotropy images of cerebral peduncles. Arrowheads indicate ischemic lesions within the corona radiata. Abbreviation: rFA, ratio of fractional anisotropy in affected and unaffected hemispheres within the region of interest.
extremities for use in daily life. However, in patients with rFA values less than .80, in whom a poorer outcome is predicted for the affected extremities, resources would be better used in compensative strategies.

This study has a number of limitations. First, the sample size was relatively small (N = 15). Regardless, our analysis yielded statistically significant findings, suggesting that the sample size was statistically sufficient. Second, we only recruited subjects with corona radiata infarct, which is not a true reflection of daily clinical practice, where ischemic stroke patients with cortical and brainstem/cerebellar lesions are commonly encountered. To generalize the present findings, such patients should be included in future studies. Third, we limited our inclusion criteria to patients who were functionally independent. Partially because of this, our samples showed relatively good recovery in terms of independence in ADL (median mRS score = 3). Careful consideration should be taken when applying our findings to geriatric patients who required assistance with ADL before they experienced stroke. Fourth, we sampled outcome data only for 1 month after onset. This limits the applicability of our findings to within this period. Quite a few patients, however, continue to recover beyond the first month.22

In summary, quantitative assessment of DTI-FA values by a computer-automated method showed that FA values within cerebral peduncles are moderately correlated with motor outcome for ischemic stroke patients with corona radiata lesions. This observation suggests that DTI-FA may be a useful reference for outcome prediction for these patients in daily clinical practice.

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