Prediction of Motor Function Outcome after Intracerebral Hemorrhage Using Fractional Anisotropy Calculated from Diffusion Tensor Imaging

Yasutaka Kuzu a Takashi Inoue c Yoshiyuki Kanbara b Hideaki Nishimoto a Shunro Fujiwara a Kuniaki Ogasawara a Akira Ogawa a

Departments of a Neurosurgery and b Radiology, Iwate Medical University, Morioka, and c Department of Neurosurgery, Kohnan Hospital, Sendai, Japan

Key Words
Fractional anisotropy · Functional recovery · Intracerebral hemorrhage · Magnetic resonance

Abstract
Background: The efficacy of surgical evacuation in patients with intracerebral hemorrhage (ICH) remains unclear for recovery of motor function. The relationship between improvement of motor function outcome and sequential change of fractional anisotropy (FA) values was investigated in patients with ICH, to explore whether motor function outcome can be predicted in the early phase. Indication of the surgical hematoma evacuation was also considered. Methods: This prospective study included 23 patients with ICH. All patients underwent diffusion tensor imaging to measure the FA value five times: within 3 days, day 14, day 30, day 60, and day 90 after the onset. The regions of interest were determined on the b = 0 step of the echo planar imaging scans in the bilateral cerebral peduncles and were automatically transferred onto the FA images. The FA value was then calculated for each patient. Patients were divided into good and poor recovery groups according to the motor function outcome on day 90. Results: The mean FA value of the poor recovery group gradually decreased until day 90, but remained unchanged in the good recovery group. The mean FA value on day 3 was significantly higher (p < 0.001) in the good recovery group (0.745 ± 0.0073) than in the poor recovery group (0.682 ± 0.0090). Receiver operating characteristic curve analysis showed that the FA value on day 3 could predict motor function outcome with a sensitivity of 100% and a specificity of 77.8% at an FA value of 0.7 on day 3. Conclusion: The main finding of this study was that the FA values of the cerebral peduncle on the pathological side in patients with ICH on day 3 could predict the motor function outcome on day 90.

Introduction

Stroke is the third most common cause of death in the developed world, and the most common cause of disability in patients [1]. Ischemic stroke is the most common type of this disease, with approximately 13% of strokes caused by hypertensive intracerebral hemorrhage (ICH). Patients with ICH are sometimes treated with surgical evacuation of the hematoma to save life, and the surgery
could reduce the mortality [2]. ICH volume larger than 50 ml has a poor prognosis with conservative therapy [3], but the efficacy of surgical evacuation of the hematoma for recovery of motor function remains unclear.

Neuroimaging evaluation of the corticospinal tracts with methods such as computed tomography (CT) or conventional magnetic resonance (MR) imaging has been attempted. Conventional MR imaging is limited to the detection of Wallerian degeneration [4–6]. These trials were unsuccessful in predicting the motor function outcome in the acute phase. Among the various contrast methods for MR imaging, apparent anisotropic diffusion has the unique property of directional dependency [7, 8]. Diffusion-weighted (DW) MR imaging can demonstrate the diffusion, or microscopic random translational motion, of water molecules in vivo [9]. Diffusion tensor (DT) imaging has proved to be a valuable tool for investigating the integrity of the white matter microstructure that cannot be assessed by conventional MR imaging [10–12]. DT imaging provides information on both the magnitude and directionality of water diffusion, and can also probe the structural properties of tissue, such as the integrity and orientation of tracts in the brain, which cannot be imaged by other techniques. Fractional anisotropy (FA) was used as a quantitative index for DT imaging, and FA could identify white matter lesion in the acute stage [13–15]. FA values in patients with ICH detected within 5 days were reported to predict the motor function outcome [13, 15, 16]. However, those studies investigated the relationship between the initial FA values and the final motor function outcome. Therefore, which patients would benefit from surgical evacuation of the hematoma to improve motor function outcome remains unclear.

This prospective study was conducted to assess the relationship between improvement of motor function outcome and change in FA values in patients with ICH, and to explore whether the motor function outcome can be predicted in the early phase by the FA values. Indication of the surgical hematoma evacuation was also considered.

**Subjects and Methods**

**Eligible Patients**

This study included patients with ICH who were admitted to our hospital within 24 h of onset between April 2003 and June 2004. The diagnosis of ICH was based on CT obtained immediately after arrival at the hospital. The ICH volume was calculated from measurements of the maximum width × maximum length × thickness × 1/2 of the high-density area on the CT scans [17].

Only patients with no previous history of stroke and prestroke ability better than a modified Rankin scale score of 2 were included. Patients who required surgical evacuation in the acute phase, had severe systemic disorder (e.g. severe heart failure or malignant tumors), or had any implanted metal items (e.g. artificial pacemaker) were excluded. All patients underwent the current imaging protocol which was approved by the local ethics committee after obtaining written informed consent from the patient or responsible relatives.

**MR Imaging**

All patients underwent MR imaging five times: within 3 days, on day 8 ± 1, day 30 ± 3, day 60 ± 7, and day 90 ± 10 after the onset of the ICH. Conventional and DT imaging were performed with a 3.0-tesla scanner (Signa VH/i; General Electric Medical Systems, Milwaukee, Wisc., USA). All patients underwent T2-weighted imaging using the short inversion time inversion recovery sequence prior to DT imaging with the following parameters: repetition time (TR) 4,000 ms, echo time (TE) 25 ms, inversion time 100 ms, matrix 512 × 384, field of view (FOV) 240 mm, 6.5 mm thickness, and 2 mm gap. DT imaging was obtained using the spin echo type echo planar imaging sequence with diffusion gradients applied in six directions, and the following parameters: TR 8,500 ms, TE 68.6 ms, matrix 128 × 128, FOV 24 × 24 cm, thickness 2.5 mm (interleaved), and b value 800 s/mm². DW imaging for color-coded map was scanned using the following parameters: TR 6,000 ms, TE 80 ms, matrix 256 × 260, FOV 240 mm, 6 mm slice thickness, and b value 800 s/mm².

**Image Analysis**

All image postprocessing was performed on a workstation (ULTRA2; Sun Microsystems, Mountain View, Calif., USA) connected to the scanner, using a subprogram of the Functoll™ imaging analysis software (General Electric Medical Systems, Buc, France). The regions of interest were determined on the b = 0 step of the echo planar imaging scans (T2-weighted, but not DW) in the bilateral cerebral peduncles and were automatically trans-
ferred onto the FA images (fig. 1). The FA value was then calculated for each patient. The analyses were separately done by two of the authors (Y. Kuzu and H. Nishimoto), and the mean number was used.

Assessment of Motor Function

Motor function was evaluated immediately before each MR imaging. Motor dysfunction was classified according to the National Institutes of Health stroke scale [18]. The sum of the upper and lower extremity motor dysfunction scores was defined as motor function score (0 was best and 8 was worst). Motor function outcome was judged with the motor function score on day 90. Motor function score of 0–3 on day 90 was defined as good recovery, and motor function score of 4–8 on day 90 was defined as poor recovery [19].

Statistical Analysis

Values are expressed as mean and standard deviation. The differences in sequential FA values or other parameters between the good and poor recovery groups were compared using the repeated-measures analysis of variance or χ² tests. The receiver operating characteristic (ROC) curve and multivariate logistic analysis were established to determine significant factors for predicting the outcome. Differences were considered significant with probability values of <0.05.

Results

This study included 23 patients: 11 females and 12 males aged 44–85 years (mean 65 ± 13 years), with 19 putaminal and 4 thalamic hemorrhages. The clinical and imaging characteristics of the 23 patients are shown in table 1. The good and poor recovery groups included 14 and 9 patients, respectively.

The sequential changes in the FA values of the pathological side are shown in figure 2. The mean FA value gradually decreased until day 90 in the poor recovery group, but not in the good recovery group, showing a significant difference (p < 0.001). The mean FA value on day 3 was significantly higher (p < 0.001) in the good recovery group (0.745 ± 0.0073) than in the poor recovery group (0.682 ± 0.0090; fig. 3). Fourteen of the 16 patients with FA values of greater than 0.7 on day 3 were included in the good recovery group. On the other hand, all 7 patients with FA values of less than 0.7 on day 3 were included in the poor recovery group. The ROC curve which predicts good recovery based on the FA value on day 3 is shown in

Table 1. Characteristics and FA values of patients with ICH

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F = Female; G = good outcome; M = male; MFS = motor function score; P = poor outcome; Pt = putamen; T = thalamus.
The area under the curve was 0.933, and the 95% confidence interval was 31.6–162.7, with a sensitivity of 100% and specificity of 77.8% at the FA value of 0.7 on day 3.

The hematoma volume was significantly smaller ($p = 0.008$) in the good recovery group (12.1 ± 8.8 ml) than in the poor recovery group (23.8 ± 11.4 ml). The ROC curve which predicts good recovery based on the hematoma volume is shown in figure 4b. The area under the curve was 0.798, with a sensitivity of 92.9% and specificity of 66.7% at the hematoma volume of 20 ml.

The mean motor function scores on day 3 was significantly lower ($p < 0.001$) in the good recovery group (3.3 ± 1.4) than in the poor recovery group (7.1 ± 0.9). All patients with a motor function score of under 6 on day 3 were included in the good recovery group, and all patients with a motor function score of over 7 on day 3 were included in the poor recovery group. The ROC curve which predicts good recovery based on the motor function score on day 3 is shown in figure 4c. The area under the curve was 0.988, with a sensitivity of 92.9% and specificity of 100% at the motor function score of 5 on day 3.

Age, sex, and location of the hematoma were not significantly correlated with the motor function outcome. The results of multivariate logistic analysis are shown in table 2. The FA value and the motor function score on day 3 were independent factors for predicting the motor function outcome ($p = 0.03$ and $p = 0.006$, respectively). Two patients with FA values of greater than 0.7 and motor function score of 6 or greater on day 3 were included in the poor recovery group (fig. 5, arrow).

**Exceptional Case (Case 18)**

A 68-year-old female suffered sudden onset of left hemiparesis and consciousness disturbance. CT on admission showed right putaminal hemorrhage with a cal-
culated volume of 23 ml. Three-dimensional anisotropy contrast imaging demonstrated that the right pyramidal tract remained intact (fig. 6). Her motor function score was 6 and the FA value of the pathological cerebral peduncle was 0.74 on day 3. She received conservative treatment and rehabilitation, but motor function score was 4 on day 90, so she was considered to have poor recovery.

**Discussion**

The main finding of this study was that the FA values of the cerebral peduncle on the pathological side in patients with ICH on day 3 could predict the motor function outcome on day 90. Patients with an FA value of greater than 0.7 can be expected to obtain good motor function outcome.
Direct injury depicted by DW imaging was previously reported to correlate with motor function outcome in patients with ICH [20]. DW or DT imaging in the acute phase have the potential to predict motor function outcome in patients with ischemic or hemorrhagic diseases [13–15, 21]. Decreased FA values in the remote pyramidal tract after stroke are associated with Wallerian degeneration. Motor neurons will be irreversibly damaged by 3 months after stroke even if not directly destroyed by hematoma in the acute stage [14, 22, 23]. In the present study, FA values in the poor recovery group gradually decreased until day 90, suggesting that neural tracts in the poor recovery group had undergone progressive Wallerian degeneration for 90 days.

The present study found that the FA values in the cerebral peduncle on day 3 already showed significant differences between the good and poor recovery groups. Although it is difficult to estimate the exact reason of this phenomenon, one of the most likely reasons is that this FA value change means direct damage of the pyramidal tract by the hematoma. The cytotoxic edema along the tracts not visible on T2-weighted images might be depicted on DT imaging. Conventional MR imaging can detect Wallerian degeneration by a few months after stroke onset [5, 24, 25]. On the other hand, DT imaging can demonstrate Wallerian degeneration as decreased FA value in patients with ischemic stroke within a few days or weeks [26–28]. Reduction of anisotropy mirrors disintegration

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**Fig. 5.** Relationship between FA values and motor function scores. Two patients with FA values of higher than 0.7 and motor function score of 6 or greater were included in the poor outcome group (arrows).

**Fig. 6.** Case 18. A 68-year-old female who suffered sudden onset of left hemiparesis and consciousness disturbance. CT on admission showed right putaminal hemorrhage with calculated volume of 23 ml. a T2-weighted magnetic resonance image. b Three-dimensional anisotropy contrast image demonstrating the intact right pyramidal tract (red area, arrow). Motor function score was 6 and FA value of the pathological cerebral peduncle was 0.73 on day 3. She received conservative treatment and rehabilitation, but motor function score was 4 on day 90, so she was considered to have poor recovery.
of the axonal structures, which occurs in the early phase of Wallerian degeneration, and DT imaging detects changes in water diffusion related to such beginning of pyramidal tract degeneration within the first 2 weeks after stroke, which are not yet detectable by conventional MR imaging [26]. Conventional MR imaging also fails to detect signal intensity changes until 4 weeks after stroke, whereas DT imaging reveals changes related to Wallerian degeneration after only days in stroke patients [27].

We accepted the direct measurement of FA values in this study. The ratio to the contralateral side of FA values is also useful and sometimes a better indicator than direct measurement [15]. However, the ratio of FA values is difficult to assess the patients who had had any previous stroke in the contralateral side. So we did not use the ratio of FA values in the present study.

The present study included 2 patients with FA value of greater than 0.7 in the poor recovery group (cases 18 and 22). In these patients, the pyramidal tract was not directly damaged by the hematoma on day 3, and the FA values of greater than 0.7 suggested good recovery. However, the FA values gradually decreased and motor function score did not recover (table 1). Although the exact reasons are difficult to explain, the pyramidal tract might have been gradually damaged after the onset. Further assessment is needed to answer the efficacy of surgical evacuation, and it might be needed by 3 days.

The present study found that hematoma volume was correlated with the motor function score, but was not an independent predictor. Hematoma volume should be considered if ICH is likely to develop. Hematoma volume larger than 50 ml suggested a poor prognosis with conservative therapy [3]. On the other hand, motor function score on day 3 was a strong predictor for motor function score on day 90. All patients with motor function score of lower than 6 had good recovery. This finding suggests that such patients do not require surgical evacuation of the hematoma for recovery of motor function, although blood pressure lowering and adequate rehabilitation are needed [29]. The early motor function score is useful in these meanings. However, the early motor function score could not always predict the motor function score after 3 months. Some patients who had a poor motor function score in the acute phase would improve the score in the chronic phase. Some patients with a motor function score of 6 or higher will require surgical evacuation of the hematoma for recovery of motor function. Measurement of the FA value may help to select eligible patients for surgery. Multivariate analysis also showed that FA value and motor function score on day 3 were independent factors to predict the motor function score on day 90.

One of the limitations of this study is that no patients who underwent surgical evacuation of the hematoma were included. Therefore, the effect of surgical evacuation of the hematoma on the FA values remains unclear. Another limitation is the use of the measured FA value on the pathological side, not the ratio with the contralateral side. FA values can be affected by the MR imaging sequence or parameters [22, 26, 30]. The ratio of FA values between pathological and nonpathological sides has been used previously [13, 15]. However, patients with previous contralateral stroke are difficult to assess using the ratio of FA values. Therefore, standardization of the parameters of the DT imaging or region of interest settings is needed. We applied the diffusion gradients in six directions. Larger numbers of directions might be better to reduce the artifacts and to increase the signal to noise ratio. We accepted the part of NIHSS to assess the motor function. This scale is widely used for evaluating the acute-phase patients, for example, to select the eligible patients to administrate the intravenous tissue plasminogen activators. We might choose other motor function scales to only estimate the motor function in this study.

**Conclusion**

No randomized trial or meta-analysis has proven the efficacy of surgical evacuation of the hematoma in patients with ICH [31–33]. The present study suggests that measurement of the FA value can predict motor function outcome. Patients with an FA value of greater than 0.7 can be expected to obtain good motor function outcome. Patients with severe motor paresis of a motor function score of 6 or greater might be considered for surgical evacuation of the hematoma.

**References**


