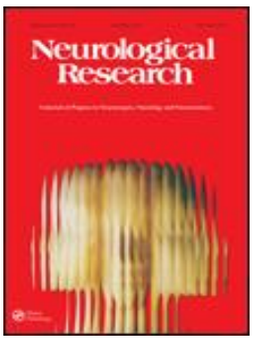

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Original Research Paper

Motor outcome of deep intracerebral haemorrhage in diffusion tensor imaging: comparison of data from different locations along the corticospinal tract

Chun-Yu Cheng[1], Chia-Yu Hsu[2], Yen-Chu Huang[2], Yuan-Hsiung Tsai[3], Hsien-Ta Hsu[4], Wei-Husn Yang[1], Hsiu-Chu Lin[1], Ting-Chung Wang[1], Wan-Chun Cheng[1], Jen-Tsung Yang[1], Tao-Chen Lee[1], Ming-Hsueh Lee[1]

[1]Department of Neurosurgery, Chang Gung Memorial Hospital at Chiayi, Chang-Gung University College of Medicine, Tao-Yuan, Taiwan, [2]Department of Neurology, Chang Gung Memorial Hospital at Chiayi, Chang-Gung University College of Medicine, Tao-Yuan, Taiwan, [3]Department of Diagnostic Radiology, Chang Gung Memorial Hospital at Chiayi, Chang-Gung University College of Medicine, Tao-Yuan, Taiwan, [4]Division of Neurosurgery, Taipei Tzu-Chi Hospital, Taiwan

Objectives: Although diffusion tensor imaging (DTI) is widely studied to assess the motor outcome after ischaemic stroke, there is paucity of data regarding outcomes of intracerebral haemorrhage (ICH). The aim of this study was to determine the DTI data from different locations along the corticospinal tract (CST) and association to motor outcome.
Methods: We prospectively recruited patients with deep ICH admitted to our hospital from November 2010 to July 2012.Diffusion tensor imaging was performed within 14 days after the onset of ICH. Fractional anisotropy (FA) was measured along the CST at corona radiata, perihaematomal oedema, cerebral peduncle and pons. Corticospinal tract integrity was classified into three types by diffusion tensor tractography (DTT): type A with preserved CST, type B with partially interrupted CST and type C with completely interrupted CST. Motor outcome was assessed by Motricity index (MI) at admission, after 1 and 3 months.
Results: Forty-eight patients were enrolled with a mean age of 62 years. The median time interval from onset of ICH to DTI study was 7 days. The patients in type C had significantly worse MI at admission ($P<0.001$), after 1 month ($P<0.001$) and after 3 months ($P<0.001$) as compared to those with type A and type B. Lower rFA at the corona radiata was significantly correlated with poorer motor outcome at admission, after 1 month and after 3 months.
Discussion: Clinical motor outcome of ICH within 2 weeks can be identified with a statistically significant decrease in rFA at the corona radiata.

Keywords: Corticospinal tract, Diffusion tensor imaging, Tractography, Intracerebral haemorrhage

Introduction

Primary intracerebral haemorrhage (ICH) is the most common type of haemorrhage and often causes severe motor weakness and functional disability.[1] Prediction of the motor prognosis in these patients is important for designing an appropriate rehabilitation programme. The corticospinal tract (CST) is the most important motor pathway, and the extent of its damage is correlated with the motor outcome after an acute ICH.[2] Therefore, an evaluation of the CST integrity after ICH may be helpful for motor outcome prediction. However, computed tomography or conventional magnetic resonance imaging (MRI) has limitations to precisely assess the microstructural damage of the CST. Diffusion tensor imaging (DTI) can detect the direction and degree of water molecule diffusion and can be used to delineate the anatomical orientation and integrity of the white matter tracts.[3] Diffusion tensor tractography (DTT) is a three-dimensional modelling technique used to visually represent neural tracts using data collected by DTI. Fractional anisotropy (FA), a widely used parameter of DTI, represents the diffusion anisotropy along specific region and has been used to

Correspondence to: Ming-Hsueh Lee, Department of Neurosurgery, Chang Gung Memorial Hospital, Chiayi Center, No. 6, West Section, Jiapu Road, Puzi City, Chiayi County, Taiwan. Email: ma2072@gmail.com

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evaluate the extent of axonal damage of a selected fibre tract.[3] Reduced FA along the CST remote from the injured site was used to index secondary axonal degeneration of the neural fibre after the axonal injury.[4] Taken together, DTI and DTT can be used to evaluate the CST integrity and quantify the extent of axonal degeneration of CST after an ICH.[5]

Recent studies using DTI and DTT have shown that reduced FA at cerebral peduncle noted 2–18 days after the putaminal or thalamic haemorrhage could predict poor short-term and long-term motor outcome.[6–9] The cerebral peduncle is distal to putamen or thalamus and reduced FA at this site is supposed to be attributed to Wallerian degeneration (WD).[10] However, in ischaemic stroke DTI study, both anterograde (WD) and retrograde degeneration occurred and were associated with poor recovery after stroke.[4] The extent and the timing of the axonal degeneration proximal or distal to the injured site may be varied, and therefore, their correlation to the motor outcome may differ. Only one study had previously evaluated the FA value in the corona radiata/internal capsule and in the cerebral peduncle within 12–18 days after deep ICH, and they found FA at the cerebral peduncle more precisely predicted 1-month motor outcome.[7] However, the FA data at internal capsule might be interfered with by haemosiderin because it was too close to the haematoma. To consider the FA data from the corona radiata, which is above and distant to the haematoma, separately may lead to different results. To the best of our knowledge, to date, there has been no study, which has evaluated the FA value above, at and below the haematoma at the same time and comparing their predictive accuracy to the motor outcome after deep ICH.

The present study aimed to compare the predictive accuracy of motor outcome by using DTI data derived from four different locations along the CST at early stage after ICH onset. We also investigated whether the CST integrity assessed by DTT is correlated with the DTI data and the motor outcome.

Materials and Methods

Patients

We prospectively recruited patients with spontaneous ICH admitted to Chiayi Chang Gung Memorial Hospital in Taiwan from November 2010 to July 2012. The inclusion criteria were: (1) first ever onset of stroke; (2) weakness of affected limbs at admission; (3) supratentorial deep haematoma; and (4) Glasgow Coma Scale >6 at admission. The exclusion criteria were: (1) marked intraventricular haemorrhage; (2) infratentorial haemorrhage; (3) lobar haemorrhage; (4) poor medical comorbidity; and (5) contraindications for magnetic resonance imaging (MRI) studies. All patients underwent routine medical treatment and 10 patients received surgical evacuation of the haematoma according to treatment guidelines.[11] Formal rehabilitation programmes were arranged for all patients soon after their condition had been stabilised. This study was performed under a protocol approved by the Institutional Review Board of the Chang Gung Memorial Hospital, and informed consent was obtained from all patients.

The weakness of the affected limb was contralateral to the side of the haematoma, either in the upper or lower extremity. Motor function of the affected side was measured at admission, and at 1 and 3 months following ICH. The Motricity index (MI), ranging from 0 (hemiplegia) to a maximum score of 100 (no deficits), was used to evaluate the motor function.[12]

Imaging

MRI data acquisition and processing

MRI scans were performed within 2 weeks following stroke. All data were collected using a 3 T Siemens Verio MRI system (Siemens Medical System, Erlangen, Germany) using a 32-channel head coil. Haematoma and perihaematomal oedema volumes were calculated accordingly.

Diffusion tensor imaging sequences were obtained using a single-shot spin-echo echoplanar imaging sequence [repetition time (TR)=9000 ms, echo time (TE)=100 ms, FOV=220 mm, matrix=88×88, 64×2.5 mm slices, b value=1000 s/mm^2, 30 directions). Standard sequences for the depiction of the anatomy, haematoma and perihaematomal extent included axial T2*-weighted gradient echo images (TR=355 ms, TE=13.81 ms, excitations=1, flip angle=18°, section thickness=6.5 mm with a gap of 1.5 mm, and matrix size=512×256), axial fluid-attenuated inversion recovery (FLAIR) images (TR=6000 ms, TE=120 ms, excitations=2, flip angle=90°, using the same section thickness and matrix size) and axial T1-weighted anatomical images with a gradient echo sequence (TR=3500 ms, TE=2.82 ms, FOV=220 mm, matrix=256×256; 160×1 mm slices, resulting in a spatial resolution of 0.9 mm $\times$ 0.9 mm $\times$ 1.0 mm).

DTT and region of interest analysis

Neuro 3D software (Siemens Syngo) was used for the post-processing of the DTI data. The DTI map was co-registered to the T1-weighted anatomical images. Following co-registration, the CST was reconstructed with the seed region of interest (ROI) being the CST portion of the pontomedullary junction and the target ROI being the CST portion of the anterior midpons. Fibre tracts passing through both ROIs were designated as the final tracts of interest. An FA threshold of >0.2 and direction threshold $<60°$ were used for the performance of fibre tracking.

The ROIs was selected according to the DTT information with reference to the anatomic atlas in T1-MPRAGE sequence. The size range was 1.5–2.5mm^2 and depended on the location of each ROI. Voxel-based ROIs were drawn on T1-weighted images in the middle corona radiata, the perihaematomal oedema area, the cerebral peduncle and the pons along the CST pathway. In cases that the CSTs were completely disrupted and could not be tracked to the level of corona radiata, the lesion site ROIs were created based on anatomic imaging and the reference from contralateral normal CST. All the haematoma and its perihaematomal oedema areas were within basal ganglion without extension to the brainstem. The perihaematomal ROIs were selected on imaging voxels that the CSTs passed through in the perihaematomal oedema area. In cases that CSTs were disrupted by the haematoma and oedema, the perihaematomal ROIs were selected on the voxels that CST terminated. Mean FA and mean apparent diffusion coefficient (ADC) values were measured for each ROI at the lesion side and the corresponding ROIs at the contralateral side (Fig. 1). The ratios of FA and ADC between the affected side and the unaffected side for each ROI were calculated and defined as relative FA (rFA) and relative ADC (rADC).

DTT classification

The patients were classified into three groups according to the integrity of the CST on DTT (Fig. 2): type A, the CST was preserved around the haematoma; type B, the fibres of the CST were partially interrupted and type C were completely interrupted at or around the haematoma. The CST integrity was defined by visual inspection by an experienced neuroradiologist (Yuan-Hsiung Tsai) and a neurosurgeon (Ming-Hsueh Lee) into three types, who were blind to the patient's clinical information. The inter-rater reliability was 0.742, which was of substantial agreement ($P<0.001$).

Statistical analysis

The Statistical Program for Social Sciences (SPSS) statistical software (version 18, Chicago, IL, USA) was used for all statistical analyses. Descriptive statistics of scores are presented as mean values with standard deviation (SD). The difference for demographic data among the three DTT types was analysed by one-way analysis of variance (ANOVA) test or Kruskal–Wallis test after testing for normalisation. Categorical data were analysed by Fisher's exact or Person's Chi-Square test, as appropriate. The Kruskal–Wallis test was used to analyse the differences in motor function among the three DTT types, and Spearman correlations were used to analyse the associations between rFA or rADC values and motor outcomes of the patients. Significant differences were considered with probability values of <0.05.

Results

A total of 85 patients were evaluated and we excluded 33 patients according to the exclusion criteria: (1) marked intraventricular haemorrhage ($N=12$); (2) infratentorial haemorrhage ($N=6$); (3) lobar haemorrhage ($N=3$); (4) poor medical comorbidity ($N=5$); and (5) contraindications for magnetic resonance imaging (MRI) studies ($N=7$). Forty-eight patients were finally enrolled, including 29 with pure putaminal haemorrhages, 15 with pure thalamic haemorrhages and four with combined haemorrhages. The demographic data of these patients among three groups were shown in Table 1. The median time interval from onset of ICH to MRI study was 7 ± 5 days. Twenty-one patients (44%) had the ICH in the left hemisphere, and 27 (56%) in the right hemisphere. The mean haematoma and perihaematomal oedema volume were 18.1 ± 14.3 ml (0.8–52.5 ml) and 20.3 ± 19.6 ml (89.1–0.1 ml), respectively.

According to the CST integrity on DTT, 14 patients (29.2%) were type A (preserved CST), 20 (41.6%) were type B (partially interrupted CST) and 14 (29.2%) were type C (completely interrupted CST). A comparison of demographics and DTI indices in the three groups are shown in Table 1. Age, sex, lesion sides and timing from stroke onset to MRI were not significantly different in the three groups. There was no significant difference in rFA values among the three types except rFA at the corona radiata ($P<0.001$). The rADC values at the four regions were also not significantly different among the three types. Patients in type C had significantly larger haematoma volume and perihaematomal oedema volume ($P=0.002$ and $P<0.001$, respectively). The motor outcomes in the three groups are compared in Table 2. Patients in type C had significantly worse MI at admission ($P<0.001$), at 1 month ($P<0.001$) and at 3 months follow-up ($P<0.001$) comparing to patients in type A and type B. After calculating the change in MI at admission compared to 3 months later, 27 patients had clinical improvement, seven patients became worse and 14 patients had stationary motor outcome.

The association of the rFA and the rADC in the different portions of CST with the motor outcomes is shown in Tables 3 and 4, respectively. The rFA at the corona radiata was significantly positively correlated with the MI at admission ($r=0.443$, $P=0.002$), at 1 month ($r=0.433$, $P=0.002$) and 3 months ($r=0.405$, $P=0.004$) (Table 3). However,

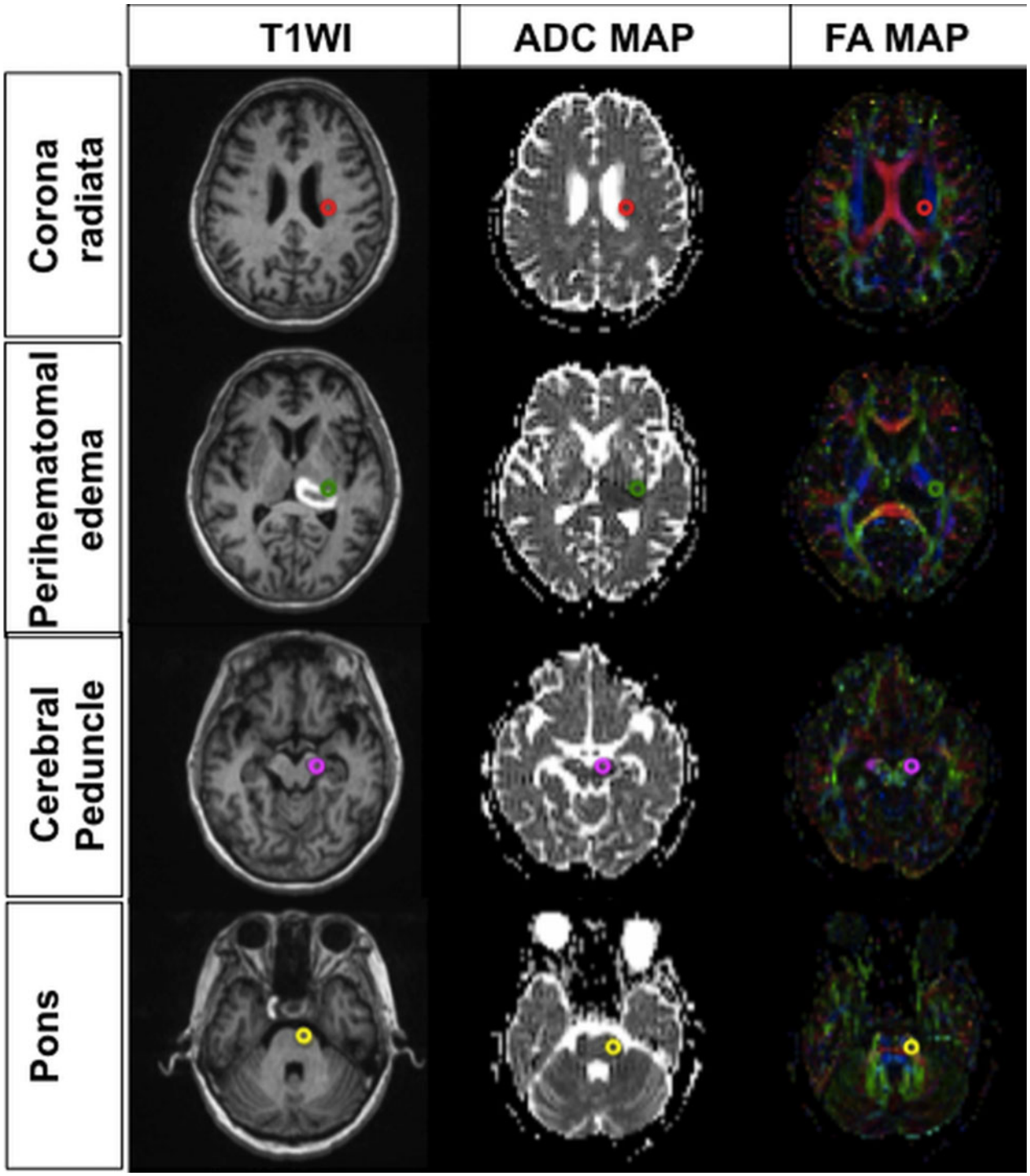

Figure 1 Diffuse tensor image of four regions of interest. The small circles indicate the regions of interest over the damaged corticospinal tract (CST) in axial T1-weighted imaging (T1WI), apparent diffusion coefficient (ADC) map and FA map images. The regions of interest are shown in red (corona radiata), green (perihaematomal oedema), purple (cerebral peduncle) and yellow (pons).

the ADC ratio at each location was not correlated with motor function at admission, 1 or 3 months after onset (Table 4).

Discussion

In this study, we presented the feasibility of DTI as an imaging biomarker to assess CST injury and to predict motor outcomes of ICH patients. We found that the FA ratio within the corona radiata in the early stage could predict the long-term prognosis and that this early signal change in the corona radiata was likely due to the early phase of WD. However, the relationship between FA ratio change and motor outcome was not observed in the perihaematomal oedema area. The predicative effect near the haematoma may be affected by structural destruction, mixed vasogenic and cytotoxic oedema or haemosiderin susceptibility effect.

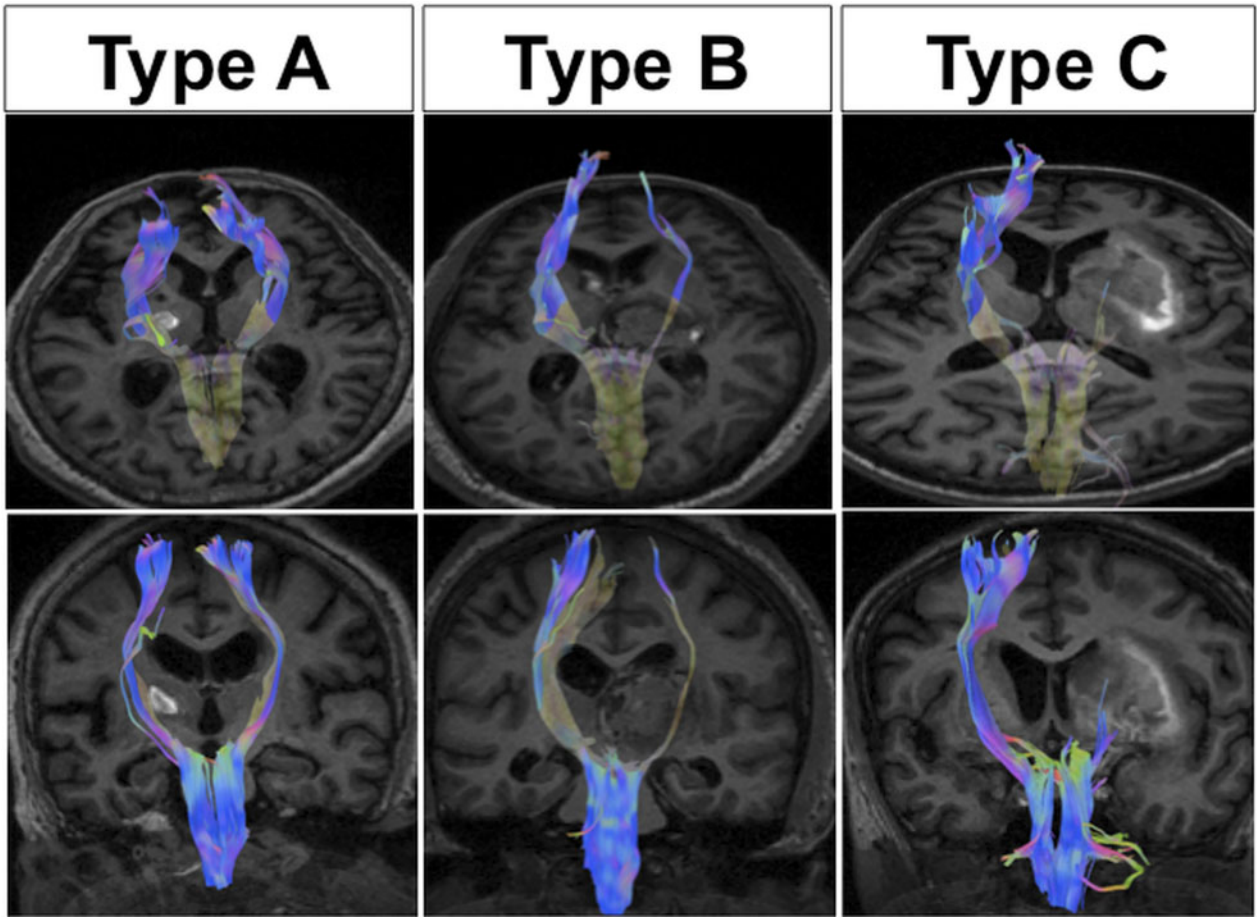

Figure 2 Classification of diffusion tensor tractography (DTT) for an injured corticospinal tract (CST). T1-weighted brain MR images, axial images and coronal images of DTT at the cortex level (showing the integrity of DTT). Type A, the CST originating from the cerebral cortex was preserved around the haematoma; type B, the CST was partially interrupted; type C, the CST was completely interrupted around the haematoma.

Table 1 Demographic data of the patients with intracranial haemorrhage

	Patients (n=48)	Type A (n=14)	Type B (n=20)	Type C (n=14)	P value
Age (years)	62±14	61±10	65±16	60±15	0.547
Sex (male)	31 (65%)	8 (57%)	13 (65%)	10 (71%)	0.951
Lesion side (right)	27 (56%)	10 (71%)	10 (50%)	7 (50%)	0.750
Haematoma location					
Putamen	29 (60%)	2 (14%)	15 (75%)	12 (86%)	–
Thalamus	15 (31%)	9 (64%)	5 (25%)	1 (7%)	–
Combined	4 (9%)	3 (21%)	0 (0%)	1 (7%)	–
Timing of MRI (days)	7±5	5±4	6±3	10±7	0.063
rFA					
Pons	1.0±0.2	1.0±0.2	0.9±0.3	1.0±0.2	0.540
Cerebral peduncle	1.1±0.9	1.1±0.3	0.9±0.3	1.3±1.5	0.285
Oedema	0.6±0.3	0.7±0.3	0.6±0.4	0.6±0.3	0.498
Corona radiata	0.8±0.4	1.2±0.4	0.7±0.3	0.7±0.3	<0.001*
rADC					
Pons	1.0±0.2	1.1±0.3	1.1±0.2	1.0±0.2	0.543
Cerebral peduncle	1.0±0.3	0.9±0.2	1.1±0.4	0.9±0.2	0.129
Oedema	1.4±0.4	1.3±0.3	1.5±0.4	1.3±0.5	0.074
Corona radiata	1.1±0.3	1.0±0.1	1.2±0.3	1.1±0.4	0.127
Haematoma volume (ml)	18.1±14.3	7.6±7.8	20.8±14.3	24.6±14.3	0.002*
Peri-haematoma oedema volume (ml)	20.3±19.6	6.2±10.5	19.0±12.4	36.4±23.6	<0.001*

All data were expressed as mean±standard deviation or number (percentage).
* P<0.05.
MRI: Magnetic resonance imaging; rFA: the ratio of fractional anisotropy of the affected side to the unaffected side; rADC: the ratio of apparent diffusion coefficient of the affected side to the unaffected side.

Table 2 Motor outcomes among the three types of DTT

DTT type	Type A (*N*=14)	Type B (*N*=20)	Type C (*N*=14)	*P* value
MI at admission	75.7±34.5	49.9±35.3	17.9±26.8	*P*<0.001*
MI at 1 month	83.3±24.4	47.8±38.7	22.8±29.0	*P*<0.001*
MI at 3 months	84.8±20.5	53.5±38.2	29.3±32.8	*P*<0.001*

All data were expressed as mean±standard deviation.
DTT: diffusion tensor tractography; MI: Motricity index.
* $P<0.05$ when groups compared with the Kruskal–Wallis test.

Table 3 Association between rFA at each location and motor outcome

	MI at admission		MI at 1 month		MI at 3 months	
rFA location	*r*	*P* value	*r*	*P* value	*r*	*P* value
Pons	0.276	0.057	0.138	0.349	0.217	0.138
Cerebral peduncle	0.197	0.180	0.149	0.314	0.189	0.198
Perihaematomal oedema	0.203	0.166	0.150	0.307	0.145	0.324
Corona radiata	0.443	0.002*	0.433	0.002*	0.405	0.004*

MI: Motricity index; rFA: the ratio of fractional anisotropy of the affected side to the unaffected side.
* $P<0.05$.

Table 4 Association between rADC at each location and motor outcome

	MI at admission		MI 1 month		MI 3 months	
rADC	*r*	*P* value	*r*	*P* value	*r*	*P* value
Pons	−0.033	0.826	0.079	0.594	0.018	0.904
Cerebral peduncle	0.088	0.552	0.094	0.526	0.151	0.306
Perihaematomal oedema	0.040	0.790	0.043	0.773	−0.047	0.753
Corona radiata	0.088	0.553	0.053	0.721	0.028	0.851

ADC: apparent diffusion coefficient; MI: Motricity index.
rADC indicates the ratio of ADC of the affected side to the unaffected side.

Our results revealed that the integrity of the CST on DTT in the early stage after ICH could predict motor recovery, and that DTI could be a reliable imaging tool to assess the CST injury in ICH patients. Although haematomas resolve over time, the patients with completely interrupted CST still initially had worse motor recovery at 3 months after onset, which suggests that profound nerve injuries had occurred when the CST was destroyed by the haematoma or oedema. On the other hand, we found that motor function improved over time among groups of patients in whom the CST had been destroyed and also in those whom the CST was intact (Table 2). This suggests that a CST either partially or completely injured by haematoma can be restored.[13–15]

Most previous studies have used only the cerebral peduncle as the ROI for FA and ADC measurements to predict motor outcomes.[9,10,16] Our study is unique in that we assessed four sites along the CST, to measure DTI indices including the corona radiata, perihaematomal oedema area, cerebral peduncle and pons. Different from previous studies, this showed that injured CST could change during the motor recovery stage among patients with ICH.[17] Unfortunately, repeated MRI data were not available for all subjects in our study because some patients declined to undertake the repeated exams. If we could perform DTI at 1 and 3 months, the changes with regards to CST would be shown more clearly. The study by Jung *et al.* divided the patients into three types according to the tractography. They also observed the longitudinal change of CST. The results were impressive and valuable. However, our study provides a unique viewpoint, in that we investigated different sites over the CST in correlation to motor outcomes, which is relatively innovated as compared to previous studies. In addition, our result indicated the early microscopic fibre change at the corona radiata after the ICH, and this was not shown in prior reports.

In our study, we found that a reduction in rFA within 14 days of ICH onset at the corona radiata predicted a worse long-term motor recovery. A reduction in FA after a CST injury has been suggested to be due to WD.[18] Wallerian degeneration refers to a process of anterograde degeneration in distal axons and breakdown of myelin sheaths following damage to proximal axons or death of the cell body.[19] This process changes the microstructural

properties of tissue and leads to altered water diffusion in fibre tracts.[18,20] Similar to anterograde degeneration, the retrograde degeneration also involves axonal injury and nerve sheath demyelination. Both WD and retrograde degeneration have been detected in the site of CST injury by DTI.[18,21,22] In the present study, a reduction in FA at the acute stage following ICH appeared at the corona radiata rather than at the cerebral peduncle or pons, presumably reflecting the presence of early secondary degeneration. Recently, Koyama *et al.* reported that the decline of FA value after thalamic or putaminal haemorrhage was more prominent in the corona radiata/internal capsule than in cerebral peduncle and was supposed due to direct injury of CST by the haematoma.[7] Our results also showed that the mean rFAs of CSTs were lowest in perihaematomal ROIs, followed by corona radiata which were two regions closest to the haematoma (Table 1). The haematoma and perihaematomal oedema can lead to torsion or stretching of the fibre tracts in early stage and is more easily to be observed in the regions nearby the haematoma. Besides, this early retrograde degeneration remote from the lesion area has also been observed following stroke in other DTI studies.[4,22] Therefore, we speculate that the early changes in FA at the corona radiata might indicate direct injury of CST by the haematoma and oedema, as well as an early stage of WD or a pre-WD change.

In the current study, the rFA value in the perihaematomal oedema area was low and rADC was high; however, neither rFA nor rADC in the perihaematomal oedema area could predict motor outcomes. Theoretically, the formation of perihaematomal oedema is related to blood–brain barrier breakage and inflammatory responses after ICH. However, some studies have shown that cytotoxic oedema also exists in the perihaematomal oedema.[23–25] We also hypothesise that mixed cytotoxic and vasogenic oedema, although close to the lesion site, confounds the measurements of ADC and FA in the perihaematomal oedema area, leading to an inaccurate outcome prediction. Furthermore, the mass effect of the haematoma and perihaematomal oedema may compress or distort the surrounding CST fibres, and cause them to become non-perpendicular to the axial plane. Therefore, selecting an ROI exactly on the CST would be difficult in the perihaematomal oedema area. Another possibility is that the DTI indices in the perihaematomal oedema may be affected by deoxyhaemoglobin around the haematoma, which is a paramagnetic molecule with potential magnetic susceptibility.[26] As a result, DTI is limited in the assessment of CST injuries at the perihaematomal oedema area. Further advances in imaging techniques are needed to improve the understanding of perihaematomal oedema and its influence on motor recovery in ICH patients.

Table 5 Multivariate logistic regression to access predictors for motor outcome

	MI 1 month		MI 3 months	
	Odds ratio	*P* value	Odds ratio	*P* value
MI at admission	1.092	0.001*	1.100	0.000*
rFA corona radiata	0.204	0.408	2.458	0.689
Haematoma size	0.922	0.094	1.063	0.210

MI: Motricity index; rFA: the ratio of fractional anisotropy of the affected side to the unaffected side.
* $P<0.05$.

This study has three major limitations that are worth highlighting. First, after correcting for the baseline MI and haematoma size with multi-variate analysis, the rFA value at the corona radiata showed no significant difference with regards to motor outcome (Table 5). This is reasonable that those patients with better baseline MI had less influence on their CST by the haematoma and had better motor outcome. Since FA can reflect the integrity of organisation, the rFA value at the corona radiata may be masked by the baseline MI. Regardless of the above findings, our result is that the early fibre change at the corona radiata that has not been mentioned before should be emphasised. Second, ensuring all locations of the ROIs are within the CST in the perihaematomal oedema area is restrictive and is likely to result in a systematic bias. Third, because WD is a dynamic process that involved axon, myelin and microglia sequentially, the heterogeneity in the timing of MRI after the onset of stroke in this study may have had an influence on the statistical results.

The strength of this study is that we selected the corona radiata that is far from the haematoma and avoided the interference caused by the haematoma or perihaematomal compression. The timing of the MRI being performed and clinical outcome evaluation are comparable with those of previously published reports, but we were able to recruit more cases than previous studies.[9,10,16] In addition, this is the first report to evaluate the relationship between the FA ratio in four different areas along the CST and motor outcomes after ICH, and the results may imply the value of microstructural change over the CST. However, further investigations are necessary to clarify the fibre change in an injured CST after ICH.

Conclusion

Clinical motor outcome of ICH within 2 weeks can be identified with a statistically significant decrease in rFA at the corona radiata. This phenomenon may be assumed to be due to the early stages of

WD. However, larger-scale long-term studies are warranted to confirm the microstructural change of CST after intracerebal haemorrhage.

Disclaimer Statements

Contributors Conceived and designed the study: M-HL and Y-HT. Data collection: H-TH, W-HY, H-CL, T-CW, W-CC and J-TY. Analyzed the data: Y-HT and Y-CH. Wrote the paper: C-YC. Paper modification: C-YH and Y-CH.

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Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was approved by the Chang Gung Medical Foundation Institutional Review Board, 6 August 2010 (CGMH IRB 101-1014C).

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