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Diffusion tensor imaging detects Wallerian degeneration of the corticospinal tract early after cerebral infarction☆

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Abstract

To investigate the feasibility and time window of early detection of Wallerian degeneration in the corticospinal tract after middle cerebral artery infarction, 23 patients were assessed using magnetic resonance diffusion tensor imaging at 3.0T within 14 days after the infarction. The fractional anisotropy values of the affected corticospinal tract began to decrease at 3 days after onset and decreased in all cases at 7 days. The diffusion coefficient remained unchanged. Experimental findings indicate that diffusion tensor imaging can detect the changes associated with Wallerian degeneration of the corticospinal tract as early as 3 days after cerebral infarction.

Key Words: corticospinal tracts; Wallerian degeneration; fractional anisotropy; diffusion tensor imaging; neuroimaging; neural regeneration

Abbreviations: MRI, magnetic resonance imaging; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; ROI, region of interest

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INTRODUCTION

Recent neuropathologic studies have shown that Wallerian degeneration of the corticospinal tract can occur as early as the first week after cerebral infarction. It is manifested by distal axonal swelling, rupture, collapse, and myelin relaxation at 1 week after onset. Myelin swelling, thickening, bending, and breakdown into free lipid and neutral fat were visible at 2 weeks after injury[1]. Wallerian degeneration in the corticospinal tract after cerebral infarction viewed with conventional magnetic resonance imaging (MRI) showed abnormal signal strip distribution along the pyramidal tracts which were associated with primary lesions[2]. After a short phase of hypointensity in T2-weighted MRI, a T2-weighted hyperintensity along the affected tracts was usually found in the chronic stage, likely a result of fibrosis of the pyramidal tract. However, in the early stage, Wallerian degeneration is not detectable by conventional MRI.

Diffusion tensor imaging (DTI) may overcome the deficiency of traditional MRI examination by measuring fractional anisotropy (FA) values of the corticospinal tract. DTI may show subtle anatomical structural changes of nerve fibers, which cannot be displayed in conventional MRI. DTI detects lesions at an early stage of Wallerian degeneration and allows quantitative analysis. However, the time window for early detection of Wallerian degeneration in the corticospinal tract by DTI after cerebral infarction remains unknown.

In this study, 23 patients with middle cerebral artery infarction were enrolled within 2 weeks after onset to determine the sensitivity of early detection of Wallerian degeneration of the corticospinal tract and the time window for early detection by DTI at 3.0T.

RESULTS

Quantitative analysis of participants

A total of 23 patients with cerebral infarction were selected from Zhongshan Hospital of Fudan University, China between November 2008 and August 2009. At the same time, 10 age- and gender-matched healthy volunteers were selected as a control group.

Baseline data

The patients underwent MRI DTI examination at admission. The demographic characteristics and vascular risk factors of the patients were collected. Clinical data and statistical information of all patients are shown in Table 1. Motor function impairment

was found in all patients.

Table 1 Clinical data of 23 patients with cerebral infarction

Case	Gender	Age (year)	Previous history	Lesion sites
1	Male	33	Migraine	FL, BA/R
2	Female	62	RF ablation	CR, BA/L
3	Male	78	HT	Thalamus/R
4	Male	64	Smoking	CR, BA/R
5	Male	45	HT	IC, BA/R
6	Female	50	NRF	FL, PL, insula/L
7	Male	37	NRF	CR, BA/R
8	Male	56	Smoking	BA/R
9	Male	52	HT	FL, PL, TL, IC/R
10	Female	81	HT, diabetes mellitus, CHD	FL, PL, TL, IC/R
11	Female	59	Thyroidectomy/R	FL, PL, TL,IC/L
12	Male	69	HT, AF, CHD	Insula, PL/R
13	Female	40	NRF	CR, IC, BA/R
14	Male	58	HT	CR, BA/R
15	Female	73	HT, SLE	IC, BA/L
16	Male	42	HT, SLE	FL, PL/L
17	Male	70	HT, diabetes	FL, PL/R
18	Female	52	HT	CR, BA/R
19	Female	80	HT, diabetes	BA/L
20	Male	79	HT	Posterior limb/R
21	Male	33	NRF	CR, IC/L
22	Male	57	HT	Corpus callosum/L
23	Male	65	NRF	CR, BA/L

R: Right; L: left; BA: basal ganglia; CR: corona radiate; IC: internal capsule; FL: frontal lobe; PL: parietal lobe; TL: temporal lobe; HT: hypertension; AF: atrial fibrillation; CHD: coronary heart disease; SLE: systemic lupus erythematosus; NRF: no risk factor.

Results of conventional MRI

Of the 23 cases with cerebral infarction, 14 had right middle cerebral artery occlusion and nine had left right middle cerebral artery occlusion. Three cases developed large cerebral infarction of the middle cerebral artery trunk (all involved the posterior limb of the internal capsule) (Figure 1), while the remaining 20 cases had a small cerebral infarction in a branch of the middle cerebral artery (four cases involved the posterior limb of the internal capsule) (Figures 2, 3).

Hypointense areas were seen in the lesions of the cerebral infarcts on T1-weighted images and apparent diffusion coefficient map. Hyperintense areas were seen in the lesions of the cerebral infarcts on T2-weighted images, fluid-attenuated inversion recovery images and diffusion-weighted images. No abnormalities were seen in the corticospinal tract beside the lesions on conventional MRI (Figures 1–3).

FA and mean diffusivity (MD) values of the corticospinal tract

DTI images showed that there was no significant difference in the FA and MD values in the area of cerebral infarction, ipsilateral posterior limb of the internal capsule, cerebral peduncle, corticospinal tract or the corresponding parts of the contralateral region (Table 2, Figures 1–3). The FA and MD values in the posterior limb of the internal capsule, cerebral peduncle and corticospinal tract were similar between the left and right sides of healthy subjects ($P > 0.05$).

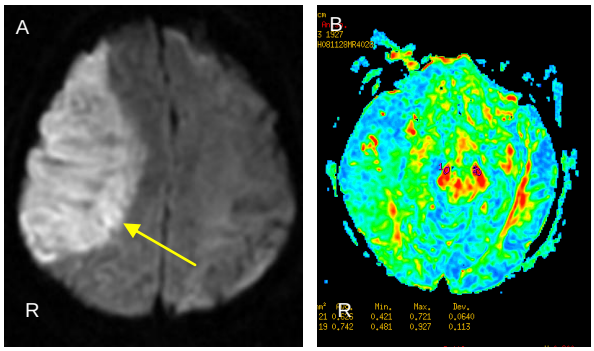

Figure 1 Large cerebral infarction of the right middle cerebral artery at 3 days after onset. R: Right.

(A) Hyperintensity on the diffusion-weighted image was seen in the large cerebral infarction (arrow) of the right middle cerebral artery.

(B) A reduced fractional anisotropy value was found in the ipsilateral cerebral peduncle of the cerebral infarction and the ratio of lesion/normal fractional anisotropy values was 0.626/0.742 by the regions of interest method.

The infarct area had significantly reduced FA and MD values (Figures 2B, C). The average ratios of lesion/normal FA and MD were 0.65 ± 0.31 ($P < 0.01$) and 0.73 ± 0.21 ($P < 0.01$), respectively, as determined by the regions of interest (ROI) method.

A significantly reduced FA value was seen in the posterior limb of the ipsilateral internal capsule and in the cerebral peduncle of the cerebral infarction (Figures 2D, 2F, Figure 3B). The ratios of lesion/normal FA were 0.90 ± 0.08 ($P < 0.05$) and 0.89 ± 0.12 ($P < 0.05$), respectively. However, no significant changes in MD values were found in the posterior limb of the ipsilateral internal capsule and in the cerebral peduncle of the cerebral infarction (Figure 2E). The ratios of lesion/normal MD were 0.99 ± 0.11 ($P > 0.05$) and 0.96 ± 0.14 ($P > 0.05$), respectively.

A significantly reduced FA value was seen in the ipsilateral corticospinal tract of the cerebral infarction, and the ratio of lesion/normal FA was 0.89 ± 0.09 ($P < 0.05$). However, no significant changes in the MD value were found in the ipsilateral corticospinal tract of the cerebral infarction. The ratio of lesion/normal MD was 0.96 ± 0.10 ($P > 0.05$).

The left/right FA and MD values of the posterior limb of the internal capsule (0.651 ± 0.085 *vs.* 0.653 ± 0.093, $P > 0.05$; 7.35 ± 0.79 $\times 10^{-3}$ mm^2/s *vs.* 7.40 ± 0.86 $\times 10^{-3}$ mm^2/s, $P > 0.05$), cerebral peduncle (0.699 ± 0.05 *vs.* 0.701 ± 0.06 $\times 10^{-3}$, $P > 0.05$; 8.87 ± 1.10 mm^2/s *vs.* 8.91 ± 1.07 $\times 10^{-3}$ mm^2/s, $P > 0.05$), and corticospinal tract (0.696 ± 0.093 *vs.* 0.698 ± 0.055, $P > 0.05$; 8.31 ± 0.89 $\times 10^{-3}$ mm^2/s *vs.* 8.34 ± 1.04 $\times 10^{-3}$ mm^2/s, $P > 0.05$) were obtained successfully in the normal control group and no significant differences were found.

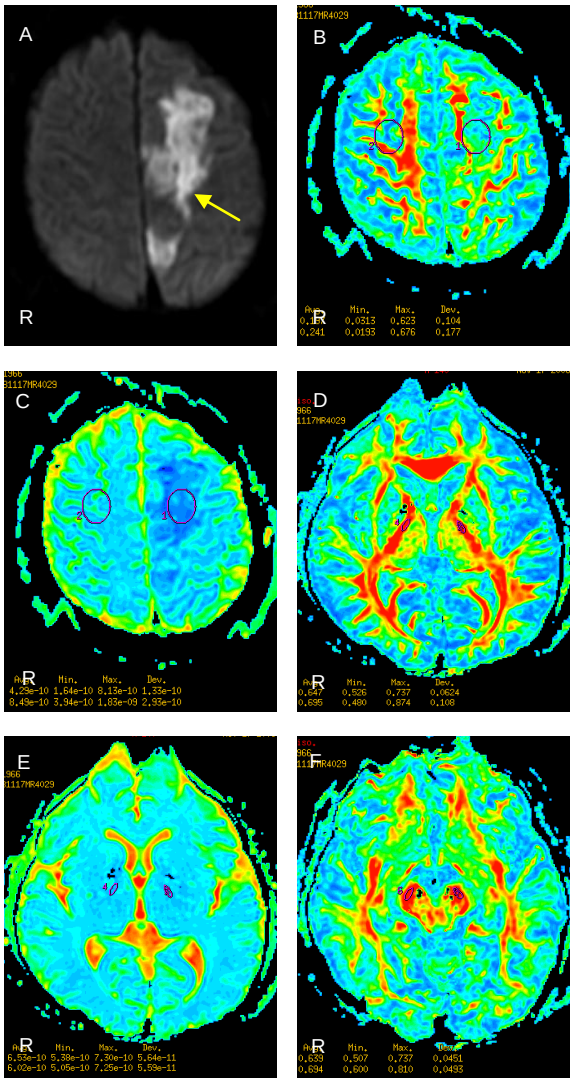

Figure 2 Cerebral infarction of the left middle cerebral artery at 7 days after onset. R: Right.

(A) Hyperintensity (arrow) on the diffusion-weighted image was seen in the cerebral infarction of the left middle cerebral artery.

(B–C) The significantly reduced fractional anisotropy (FA) value (B) and mean diffusivity value (C) was found in the ipsilateral regions of interest (circles) of the cerebral infarction.

(D) A significantly reduced FA value was found in the ipsilateral posterior limb of the internal capsule and the FA value in the left was much smaller than that in the right.

(E) No significant difference on the mean diffusivity value was found in the posterior limb of the internal capsule between the left and right sides.

(F) A significantly reduced FA value was found in the corticospinal tract of the left cerebral peduncle.

Case analysis

Lesions involving the frontal, temporal, parietal and internal capsule were found in three patients who had a large cerebral infarction of the middle cerebral artery.

The interval from onset to DTI examination was 5 hours, 3 days or 7 days in these cases. The earliest time for a significantly reduced FA value on DTI to be seen in the ipsilateral corticospinal tract of the cerebral infarction was at 3 days after onset, and the ratio of lesion/normal FA was reduced by 16% (Figures 3A, B) according to the ROI method. A reduced FA value was also found in the ipsilateral cerebral peduncle of the cerebral infarction in two cases, and the interval from onset to DTI detection was 3 days and 7 days, and the ratio of lesion/normal FA values was reduced by 16% and 19%, respectively, as measured by the ROI method.

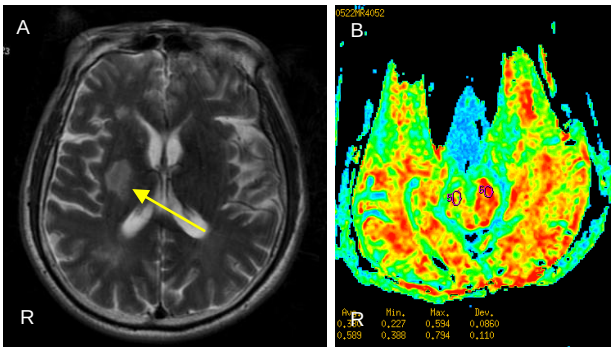

Figure 3 Cerebral infarction in the right basal ganglia at 6 days after onset. R: Right.

(A) Cerebral infarction (arrow) involving the right internal capsule of the basal ganglia shown on T2-weighted imaging.

(B) A significantly reduced fractional anisotropy (FA) value was found in the right corticospinal tract. The FA value in the right side was much smaller than that in the left side, and the ratio of lesion/normal FA was 0.227/0.388.

Table 2 Fractional anisotropy and mean diffusivity ($\times 10^{-3}$ mm^2/s) values of the lesion and contralateral area detected by diffusion tensor imaging

Item	Side	Lesion	Internal capsule
Fractional anisotropy	Ipsilateral	0.28±0.11[b]	0.59±0.09[a]
	Contralateral	0.46±0.17	0.66±0.09
Mean diffusivity	Ipsilateral	5.81±1.78[b]	7.22±1.35
	Contralateral	7.97±1.07	7.33±0.87

Item	Side	Cerebral peduncle	Corticospinal tract
Fractional anisotropy	Ipsilateral	0.62±0.10[a]	0.62±0.08[a]
	Contralateral	0.70±0.05	0.69±0.06
Mean diffusivity	Ipsilateral	8.46±1.28	7.93±1.29
	Contralateral	8.86±1.04	8.29±0.74

Data are expressed as mean ± SD, $n = 23$. [a]$P < 0.05$, [b]$P < 0.01$, *vs.* contralateral side (Student's *t*-test).

The average FA values in the corticospinal tract on DTI examination in all cases are shown in Figure 4. Significantly reduced ratios of lesion/normal FA values in the corticospinal tract were observed in all cases when

measured at different days after onset (Figure 5).

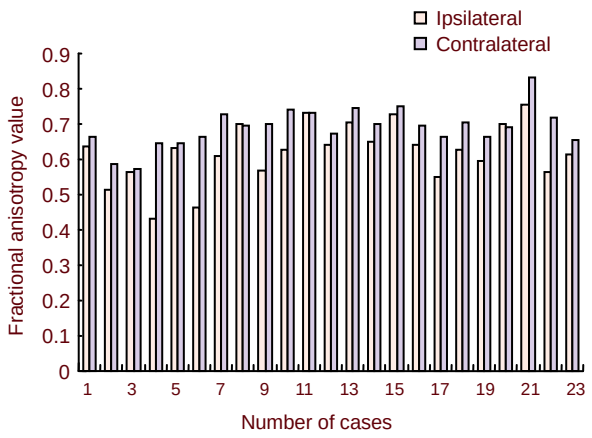

Figure 4 Fractional anisotropy values in the corticospinal tract ipsilateral and contralateral to the cerebral infarction.

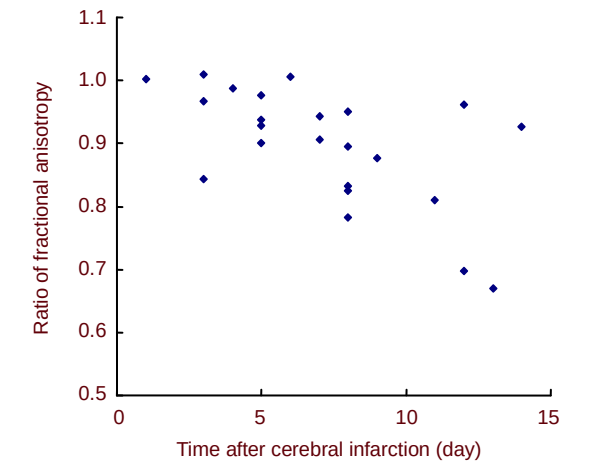

Figure 5 Ratio of lesion/normal fractional anisotropy values in the corticospinal tract at different days after cerebral infarction.

DISCUSSION

Wallerian degeneration in the corticospinal tract following cerebral infarction appears about 1 week after onset. Wallerian degeneration might be detected with DTI earlier than previously thought possible. Thus quantitative DTI analysis was used to observe Wallerian degeneration of the corticospinal tract in cerebral infarction of the middle cerebral artery in this study. The results showed that Wallerian degeneration was found from 3 days to 2 weeks after cerebral infarction, and the detection by DTI was earlier than in conventional MRI. In the human central nervous system, the diffusion rate in the direction parallel to the fiber is much larger than that in the perpendicular direction because of the barrier of the axon membrane and myelin sheath, and is the anatomical and physiological basis of DTI in MRI. This diffusion of water could be visualized in MRI, and was named as DTI. DTI is a technique that uses diffusion sensitizing gradients applied in at least six non-collinear directions to determine the full diffusion tensor. The diffusion tensor provides information on the predominant direction and degree of water diffusion and gives clues as to the microstructural properties of tissue[3]. DTI is particularly interesting for *in vivo* visualization of white matter tracts. In cerebral white matter, water diffusion is fast along the main direction of the fibers and is slow perpendicular to the fibers, resulting in anisotropic diffusion.

In this study, the diffusion gradient in 25 directions in DTI was measured to form the anisotropy map and to construct a three-dimensional map. Thus the water diffusion characteristics of brain tissue could be displayed in a three-dimensional picture.

Wallerian degeneration in distal nerve fibers of the corticospinal tract following focal cerebral infarction has been confirmed in animal experiments and in pathological examination at autopsy[4-6]. In this study, regardless of the involvement of the internal capsule, significantly reduced FA and MD values in the area of the cerebral infarction were found in all patients, while reduced FA values and unchanged MD values were found in the ipsilateral corticospinal tract of the cerebral infarction. The results indicated that changes in diffusion were seen in the area of cerebral infarction and distal nerve fibers of the corticospinal tract following focal cerebral infarction. The changes in diffusion of the corticospinal tract were similar to that of Wallerian degeneration of the optic nerve in animal experiments[7]. The secondary decomposition of the corticospinal tract occurred gradually. Since the movement of water molecules along the direction of the fiber bundles was hindered by the barrier resulting from the fragments formed by axonal disintegration, and the perpendicular movement of water molecules was increased by myelin disintegration, FA values were significantly reduced with no changes in MD values in the corticospinal tract. In a study of middle cerebral artery infarction, the reduced FA values were found in the ipsilateral cerebral peduncle at 2 weeks after onset[8]. Thomalla *et al* [9] reported that the reduced FA value in the ipsilateral corticospinal tract after cerebral infarction was found at 5 days after onset. Wallerian degeneration of the corticospinal tract could be detected with DTI as early as the third day after onset in our study. The reduced FA values were found at 7 days after onset and no changes in MD values were detected in the ipsilateral corticospinal tract by DTI in all patients with cerebral infarction. The results showed that the occurrence of reduced FA values in our study was earlier than that reported in previous studies[8-10]. Our finding was consistent with the results of animal experiments. Song *et al* [11] reported that reduced FA values in the rat optic nerve in DTI and disintegrated optic nerve axons pathologically were detected at 2–7 days after retinal ischemia. The disintegration of myelin and infiltration of

astrocytes were seen at 2 weeks after onset, which resulted in little changes in MD values on DTI.

This study showed that DTI could detect Wallerian degeneration of the corticospinal tract at an early stage after cerebral infarction. The significantly reduced FA values of the lesion area were found in three patients with a large infarction of the middle cerebral artery at an early stage after onset, which indicated serious Wallerian degeneration of the corticospinal tract. The proximal axons of the corticospinal tract, primary motor cortex of the frontal precentral gyrus and subcortical white matter fibers were involved in all three cases. Significantly reduced FA values of the lesion area were found in the remaining 20 cases, which had a small cerebral infarction in a branch of the middle cerebral artery, at 7 days after onset. The lesion areas were located in the basal ganglia, internal capsule, corona radiata, centrum semiovale and thalamus. The proximal axons and upper motor neurons of the corticospinal tract were not simultaneously involved.

It appears that Wallerian degeneration of the corticospinal tract was closely related to the site and degree of cerebral infarction. This study showed that the FA values gradually decreased over time after cerebral infarction. The degradation in structure was followed by gradual Wallerian degeneration, which was consistent with pathological findings[12-13]. In addition, the Wallerian degeneration of the corticospinal tract after middle cerebral artery infarction in our study was detected earlier than in previous studies[14]. DTI appears to be a sensitive method for measurement of the microstructure of white matter and may detect the lesions of Wallerian degeneration in the corticospinal tract earlier than conventional MRI. DTI may be useful to evaluate pathophysiological processes in brain tissue and to determine the relationship between structural integrity and function.

SUBJECTS AND METHODS

Design

A block-design neuroimaging observation with DTI.

Time and setting

This study was performed at Zhongshan Hospital of Fudan University in Shanghai, China, from November 2008 to August 2009.

Subjects

A total of 23 right-handed patients with unilateral middle cerebral artery infarction were selected from Zhongshan Hospital of Fudan University in China. They included 14 males and nine females, aged 33–81 years, mean 58 ± 15 years. All cases were recruited within 2 weeks after symptom onset, and had impaired movement. No other signal abnormalities were seen in the areas beside the lesions of cerebral infarction on T1-weighted and T2-weighted images and fluid-attenuated inversion recovery (FLAIR) images in the brain. Patients with a history of brain or spinal disease were excluded.

Ten healthy, age- and gender-matched teachers from Zhongshan Hospital of Fudan University were selected as a control group. All subjects were right-handed. None reported a history of neurological disorders. Both oral and written informed consent was obtained from all participants. All procedures were conducted according to the *Administrative Regulations on Medical Institutions*, formulated by the State Council of China[15]. The pilot study was consistent with the ethical requirements of the Declaration of Helsinki.

Methods

Conventional MRI examination

Conventional MRI examination was performed using a GE 3.0T MR scanner (GE, Bethesda, MD, USA) to identify abnormal structures and signals in the brain. The interval from onset of cerebral infarction to MRI examination was 5 hours to 14 days. Typical acquisition parameters of the T1-weighted imaging FLAIR sequence were: TR = 2 000 ms, TE = 719 ms, flip angle = 90°, slice thickness = 5 mm, pitch = 1.5 mm, FOV = 240 mm × 240 mm, Matrix = 256 × 256. FSE sequence T2-weighted imaging: TR = 3 600 ms, TE = 90 ms, slice thickness = 5 mm, pitch = 1.5 mm, FOV = 240 mm × 240 mm, Matrix = 256 × 256.

DTI examination

A single-shot SE echo planar imaging sequence was performed for DTI data collection using the GE 3.0T MR scanner. The first DTI was completed in the first week and repeated in the second week. Acquisition parameters of DTI were: TE = minimum; b value = 0 and 1 200 s/mm^2, in 25 diffusion gradient directions; slice thickness = 5 mm; spacing = 1.5 mm; FOV = 28 cm; 26 original images were available on each DTI layer, and a total of 486 original images were collected.

DTI post-processing

The DTI data were transferred to a workstation (Advantage Workstation, GE), and the DTI parameters were calculated on a pixel-by-pixel basis. Using Functool Software (Advantage Workstation, GE), ROIs were manually defined as an ellipse with an area of 30–45 mm^2 on the FA and MD maps (Figures 1–3). Referring to anatomical knowledge and MR scan baseline, ROIs were symmetrically placed on axial slices in the left and right sides along the pathway of the pyramidal tract at three levels: the central area of the cerebral infarction, the posterior internal capsule and the cerebral peduncle of the cerebral infarction. Each ROI consisted of one slice only.

The average FA and MD values of the posterior internal capsule and cerebral peduncle were taken as the FA and MD values of corticospinal tract. If the infarction involved the posterior internal capsule, the average FA and MD values of the cerebral peduncle only were taken as the FA and MD values of the corticospinal tract.

The ratios of FA and MD values in the corticospinal tract of the cerebral infarction and the contralateral areas were calculated for the following: cerebral infarction area, posterior internal capsule, cerebral peduncle. These

measurements were also performed in the normal control group.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS, Chicago, IL, USA) and expressed as mean ± SD. FA and MD values of the bilateral corticospinal tract at different levels were compared using the Student's *t*-test. $P < 0.05$ was considered statistically significant.

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Conflicts of interest: None declared.

Ethical approval: The research protocol was approved by the Ethics Committee of Fudan University in China.

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