ORIGINAL REPORT

INJURY OF THE CORTICORETICULAR PATHWAY IN SUBARACHNOID HAEMORRHAGE AFTER RUPTURE OF A CEREBRAL ARTERY ANEURYSM

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Objective: Several studies have reported on injury of the corticoreticular pathway in patients with stroke and traumatic brain injury. However, little is known about injury of the corticoreticular pathway in patients with subarachnoid haemorrhage. The aim of the current study was to investigate corticoreticular pathway injury in patients with subarachnoid haemorrhage.

Design: Comparative study.

Subjects: Among 137 patients with subarachnoid haemorrhage, 17 patients with motor weakness who showed intact integrity of the corticospinal tract were recruited.

Methods: Motricity Index was used for measurement of motor function. The fractional anisotropy value, apparent diffusion coefficient value, fibre volume, and integrity of the corticoreticular pathway were used for the diffusion tensor imaging parameters.

Results: Twelve (70.6%) of 17 patients and 18 (52.9%) of 34 hemispheres showed a discontinuation of the corticoreticular pathway at the midbrain level. The contralateral shoulder, hip, and lower extremity of the discontinued corticoreticular pathway showed lower motor functions, in comparison with those of the contralateral side of the intact corticoreticular pathway ($p < 0.05$). By contrast, the Motricity Index for distal joint, upper and total Motricity Index were not different irrespective of the state of the corticoreticular pathway ($p > 0.05$).

Conclusion: Corticoreticular pathway injury is common in patients with motor weakness after subarachnoid haemorrhage, and it appears to be related to weakness in the contralateral shoulder, hip and lower extremity.

Key words: diffusion tensor imaging; corticoreticular pathway; subarachnoid haemorrhage.

INTRODUCTION

Spontaneous subarachnoid haemorrhage (SAH) is usually caused by rupture of a cerebral arterial aneurysm (1–3). SAH commonly accompanies various neurological sequelae, including motor weakness, somato-sensory deficit, visual dysfunction, and cognitive dysfunction (1–11). In particular, visual field defects, complex visual hallucinations and memory impairment with short-term, verbal or working memory are frequently observed in patients with SAH (12–17). In terms of motor weakness, motor deficits have been reported in 14–29% of patients with SAH (1, 7–10). In addition, previous studies have reported frequent leg weakness and gait disturbance after SAH (4–6). Suggested pathogenic mechanisms of motor weakness in SAH include cerebral infarct due to vasospasm, rapidly increased intracranial pressure, direct compression of the artery to the corticospinal tract by aneurysm, and injury of the corticospinal tract (CST) (4–6, 11, 18). However, this has not yet been clearly elucidated.

In the human brain, the descending motor pathways are classified into the pyramidal and extrapyramidal tracts (19, 20). The corticoreticulospinal tract, one of the extrapyramidal tracts, consists of the corticoreticular pathway (CRP) and the reticulospinal tract (21–23). This tract innervates proximal muscles of the extremities and axial muscles; therefore, it is believed to be closely associated with gait function (21–25). Recent development in diffusion tensor imaging (DTI) has enabled investigators to estimate the state of the CRP at the subcortical level (23). Several studies have reported on injury of the CRP in patients with stroke and traumatic brain injury (21, 23–26). However, little is known about injury of the CRP in SAH.

In this study, using DTI, we attempted to investigate CRP injury and clinical characteristics of motor function in patients with SAH.

MATERIAL AND METHODS

Subjects

Among 137 patients with subarachnoid haemorrhage admitted for rehabilitation to the rehabilitation department of a university hospital, we recruited 17 patients (7 males (mean age 44.9, age range 34–53 years), 10 females (mean age 55.6, age range 51–70 years); total mean age 50.8, age range 34–70 years) disease were recruited for this study. In addition, 23 age-and sex-matched control subjects (10 males (mean age 46.8, age range 35–54 years), 13 females (mean age 52.7, age range 53–70 years); total mean age 50.1, age range 35–70 years) with no history of neurological or psychiatric disease were recruited for the control group.

Stroke patients were recruited according to the following inclusion criteria: (*i*) first ever stroke; (*ii*) age 21–70 years; (*iii*) haemorrhage in the

subarachnoid space due to aneurysmal rupture (the anterior communicating artery (ACoA): 14 patients (82.4%), the posterior communicating artery (PCoA): 1 patient (5.88%), anterior cerebral artery (ACA): 1 patient (5.88%) and internal carotid artery: 1 patient (5.88%) confirmed by a neuroradiologist; (*iv*) DTI scanning was performed during the early stage (within 3 weeks to 3 months after onset, the mean duration from SAH onset was 6.2 weeks (range 3–10 weeks)); (*v*) patients who showed any weakness in extremities at the time of DTI scanning; (*vi*) on diffusion tensor tractography (DTT), the integrities of the CST in both hemispheres were preserved; and (*vii*) no severe somatosensory problem, apraxia, or cognitive problems. Severity of SAH was assessed according to Fisher CT grade (mean grade: 3 ± 1.3) (27).

Patients with hydrocephalus, intracerebral haemorrhage, intraventricular haemorrhage, or any lesion along the CST and CRP pathway or the CST and CRP origin areas, including the primary sensory-motor cortex, premotor cortex, supplementary motor area, prefrontal cortex, and posterior parietal cortex were excluded. This study was conducted retrospectively, and the Institutional Review Board of our hospital approved the study protocol.

Clinical evaluation

Motor function was evaluated using the Motricity Index (MI), at the time of DTI scanning. MI was used for measurement of motor function of the affected upper and lower extremities (maximum score: 100) (28). The reliability and validity of MI have been well established (28).

Diffusion tensor imaging

Diffusion weighted imaging, which for the acquisition of DTI data, were acquired at an average of 6.2 weeks using a 1.5-T Philips Gyroscan Intera system (Philips, Ltd,. Best, the Netherlands) equipped with a synergy-L Sensitivity Encoding (SENSE) head coil using a single-shot, spin-echo planar imaging pulse sequence. For each of the 32 non-collinear and non-coplanar diffusion sensitizing gradients, we acquired 60 contiguous slices parallel to the anterior commissure-posterior commissure line using a 32-direction DTI gradient encoding scheme. The imaging parameters were: matrix $= 128 \times 128$ matrix, field of view $= 221 \times 221$ mm^2, echo time $= 76$ ms, repetition time $= 10,726$ ms, SENSE factor $= 2$; echo planar imaging factor $= 67$ and b $= 1,000$s/mm^2; number of excitations $= 1$; and a slice thickness of 2.3 mm; pulse duration $= 3$ms; pulse separation $= 3.5$ ms; scan duration $= 4,021.5$ ms.

Affine multi-scale two-dimensional registration was used for reduction of eddy current-induced image distortions and motion artefacts (29). Pre-processing of DTI data-sets was performed using the Oxford Centre for Functional Magnetic Resonance Imaging of Brain (FMRIB) Software Library (FSL). DTI-Studio software (CMRM, Johns Hopkins Medical Institute, USA) was used for reconstruction of the CRP. For analysis of the CRP, the seed Region of Interest (ROI) was placed on the reticular formation of the medulla, and the target ROI on the midbrain tegmentum (21, 23). The CRP was determined by selection of fibres passing through the seed and target ROI. Fibre tracking was performed using a fractional anisotropy (FA) threshold > 0.2 and direction threshold $< 70°$. The FA value, mean diffusivity (MD) value, and fibre volume of the CRP in both hemispheres were measured.

Statistical analysis

An independent *t*-test was used for determination of the difference in each motor functions according to the type of CRP injury. Spearman's correlation test was used for determination of correlation between DTI parameters of the constructed neural tract and motor functions. Software (v.15.0; SPSS, Chicago, IL, USA) was used for statistical analyses, and statistical significance was set at $p < 0.05$.

RESULTS

Twelve (70.6%) of the 17 patients showed a discontinuation of the CRP; in detail, bilateral discontinuations of the CRPs were observed in 6 patients and unilateral discontinuations
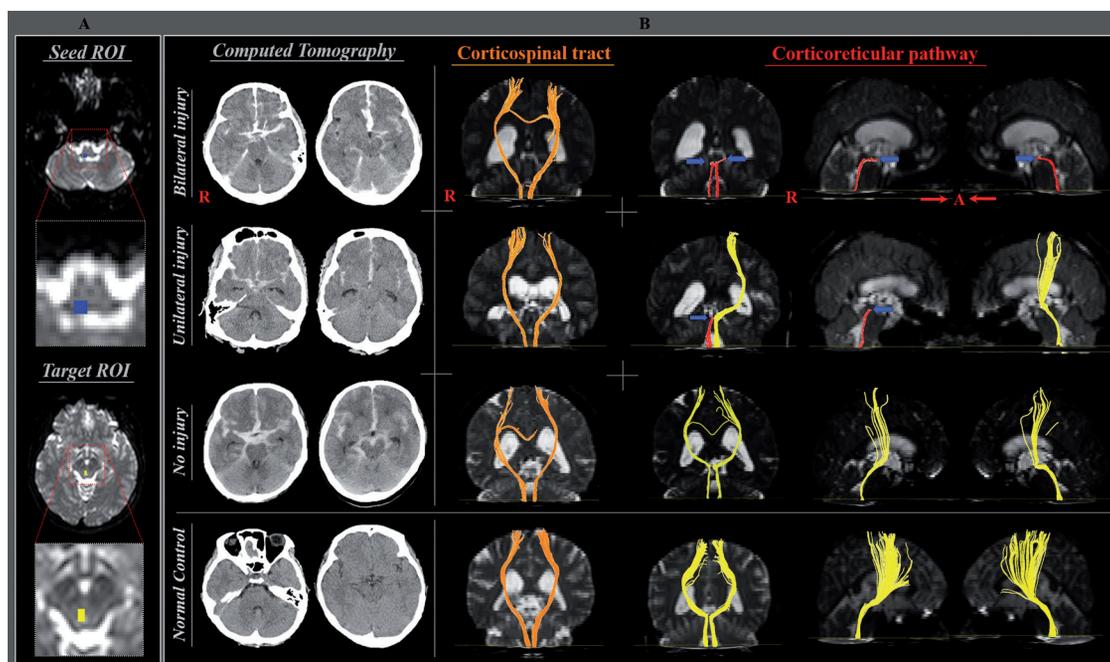

Fig. 1. (A) Seed region of interest (ROI) was given on the medullary reticular formation (*blue rectangle*), and the target ROI was placed on the midbrain tegmentum (*yellow rectangle*). (B) Computed tomography (CT) and diffusion tensor tractography (DTT) of the corticospinal tract and corticoreticular pathway (CRP) in patients with subarachnoid haemorrhage (SAH) and control subject (52-year-old female). The CRP originating from the premotor cortex was preserved to the medullary reticular formation in 5 patients; however, 12 patients showed unilateral (6) and bilateral (6) discontinuations of the CRP at the midbrain level due to SAH (*blue arrows*).

Table I. *Diffusion tensor image parameters of the corticospinal tract and the corticoreticular pathway in patient and control subjects*

	Corticospinal tract			Corticoreticular pathway			
	FA	MD	FV	FA	MD	FV	ICV
Patient (*n*=17)	0.55 (0.04)	0.81 (0.03)	1,015.03 (426.61)	0.48 (0.04)	0.87 (0.08)	416.41 (350.17)	176,172.88 (82,013.83)
Control (*n*=23)	0.56 (0.03)	0.82 (0.05)	1,037.57 (404.20)	0.50 (0.03)	0.81 (0.05)	992.54 (588.65)	167,688.74 (104,724.94)
p	0.079	0.556	0.812	0.017*	0.000*	0.000*	0.776

*$p < 0.05$. FA: fractional anisotropy; MD: mean diffusivity; FV: fibre volume; ICV: intracranial volume. Values represent mean (standard deviation).

were observed in 6 patients (Fig. 1). As a result, 18 (52.9%) of 34 hemispheres in 17 patients showed a discontinuation of the CRP and all discontinuations of the CRPs were observed at the midbrain level. In addition, the patient group showed significantly decreased FA value and fibre volume and significantly increased MD value, compared with those of the control group ($p < 0.05$) (Table I). MIs for the contralateral shoulder, hip, and total lower extremity of the discontinued CRP were significantly lower, compared with those of the intact CRP ($p < 0.05$). By contrast, the MIs for total, upper, and distal joints as elbow, hand, knee, and ankle were not different irrespective of the state of the CRP ($p > 0.05$) (Fig. 2, Table II).

A summary of the results of the correlations between DTI parameters of the CRP and motor functions is shown in Table III. FA values of the CRP showed moderate positive correlation with the shoulder MI ($r=0.342$, $p=0.041$) and hip MI ($r=0.348$, $p=0.038$), but did not show correlation with distal (elbow, hand, knee, and ankle), upper, lower, and total MIs ($p > 0.05$). By contrast, the MD values and fibre volumes of the CRP did not show correlation with all types of MIs ($p > 0.05$) (Table III).

DISCUSSION

This study investigated CRP injury in patients with SAH, and evaluated associations with the motor function of patients. The results can be summarized as follows: (*i*) 12 (70.6%) of 17 patients and 18 (52.9%) of 34 hemispheres showed a discontinuation of the CRP at the midbrain level. The contralateral shoulder, hip and lower extremity of the discontinued CRP showed lower motor functions, compared with those of the contralateral side of the intact CRP, without differences in other distal joints and upper extremity. Consequently, approximately 70% of patients with motor weakness after SAH showed discontinuation of the CRP, and the discontinued CRP appeared to show a close association with motor weakness of the contralateral proximal joint and lower extremity; (*ii*) motor functions of the shoulder and hip joint showed positive correlations with the FA value of the CRP. The FA value indicates the degree of directionality of water diffusion, which represents the white matter organization: in detail, the degree of directionality and integrity of white matter microstructures, such as axon, myelin, and microtubule (30, 31). In contrast, the MD value indicates the magnitude of water diffusion (30, 31). In addition, the
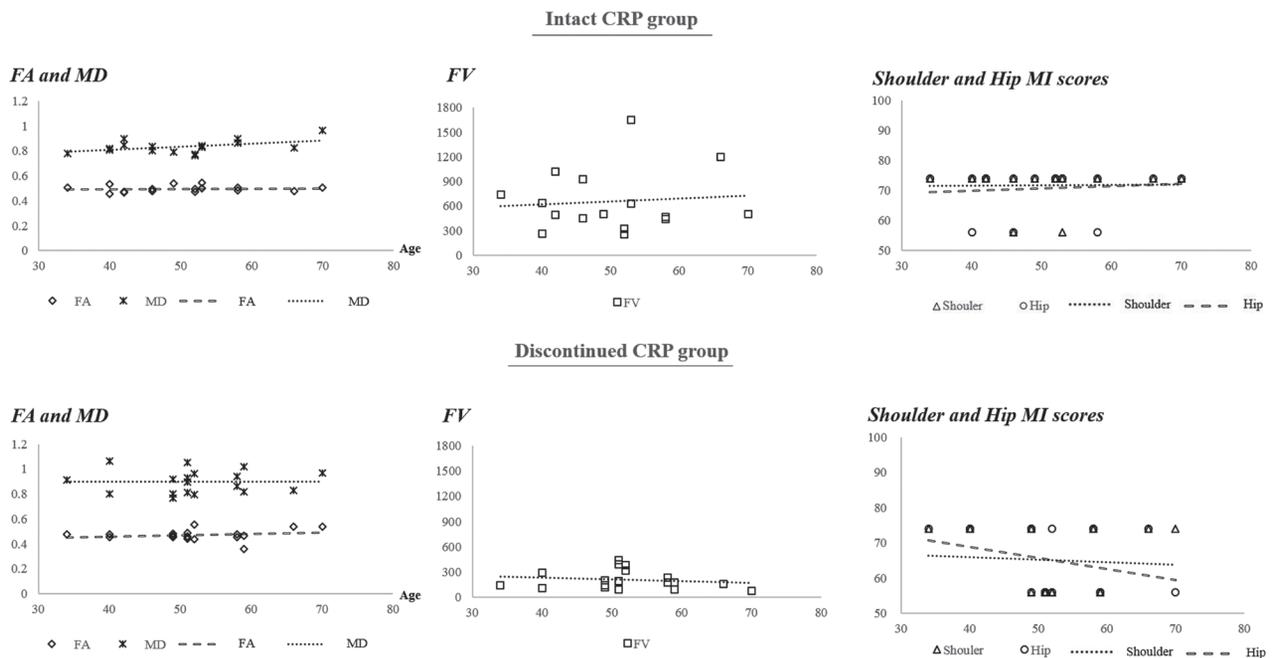

Fig. 2. Scatter diagram for diffusion tensor imaging parameters of the corticoreticular pathway and each motor function in intact and discontinued corticoreticular pathway group. CPR: corticoreticular pathway; FA: fractional anisotropy; MD: mean diffusivity; FV: fibre volume; MI: Motricity Index.

Table II. *Differences of motor functions according to the state of the corticoreticular pathway*

MI scores	Upper extremity				Lower extremity				Total Mean (SD)
	Shoulder Mean (SD)	Elbow Mean (SD)	Hand Mean (SD)	Total Mean (SD)	Hip Mean (SD)	Knee Mean (SD)	Ankle Mean (SD)	Total Mean (SD)	
Intact CRP (n=16)	73.38 (9.37)	74.50 (8.15)	73.19 (9.36)	73.69 (9.88)	73.38 (9.37)	72.25 (10.32)	72.50 (11.51)	72.71 (9.34)	68.74 (7.11)
Discontinued CRP (n=18)	66.00 (9.20)	72.44 (9.71)	76.28 (7.48)	71.57 (7.68)	66.00 (9.20)	69.00 (8.30)	62.72 (18.06)	65.91 (8.62)	73.20 (8.89)
p-value	0.028*	0.512	0.535	0.489	0.028*	0.317	0.067	0.035*	0.115

*$p < 0.05$. MI: Motricity Index; SD: standard deviation; CRP: corticoreticular pathway.

fibre volume is determined by the number of voxels contained within a neural tract (32, 33). Consequently, the directionality of the CRP appears to be related to motor control of proximal joints, such as shoulder and hip. By contrast, the mild motor weakness, which was represented in the distal joints, appears to be related to mild injury of the other neural tracts for motor function, especially the lateral CST (18, 34).

Although no study on the pathophysiological mechanism of CRP injury in patients with SAH has been reported, we make this assumption based on a previous study reporting that the CST was injured at the midbrain in SAH (18). Findings of this study suggested that frequent occurrence of SAH into perimesencephalic cisterns could be ascribed to injury of the CST, which is located in close proximity to the cistern at the midbrain through mechanical (increased intracranial pressure or direct mass) or chemical mechanisms (a blood clot itself can cause extensive damage) (35–37). However, the CRP passed through the deeper area (tegmentum) at the midbrain than the CST, which is exposed to the cistern. In 2007, Liu et al reported that SAH may cause global mild vasogenic oedema in white matter and deep grey matter, which was undetectable on T2-weighted and diffusion-weighted MR images, but was detectable by measuring the MD value in the subacute stage

of SAH (11). Therefore, although it is located more deeply than the CST in the midbrain, the CRP at the midbrain could be damaged mechanically or chemically by haemorrhage on the subarachnoid area (37).

The clinical characteristics of motor weakness in SAH have been reported as quadriparesis, hemiparesis, or paraparesis (1, 4–10). In particular, several previous studies have reported that paraparesis, which is concerned with proximal and lower extremity weakness, occurred occasionally after rupture of ACoA or ACA aneurysm (4–6). In 1986, Maiuri et al.(4) reported on a patient who showed sudden paraplegia as the first symptom after rupture of an ACoA aneurysm. In 1995, among 101 patients with SAH from a ruptured ACoA aneurysm, Greene et al. reported on 7 patients with weakness of the lower extremities and suggested that the vasospasm was the most likely aetiology for this (5). Subsequently, Endo et al. (6) reported on 4 patients with paraparesis after SAH from rupture of an ACA aneurysm. They suggested that all patients showed abnormal finding in the ACA territories associated with leg motor function on diffusion-weighted MR images (6). Recently, using DTI, Yeo et al. reported mild hemiparesis or quadriparesis of patients with SAH by CST injury at the midbrain level (18). On the other hand, several previous studies using DTI have reported on proximal weakness due to injury of the CRP in patients with stroke or traumatic brain injury (24–26). In 2013, Yeo & Jang reported on patients who showed proximal weakness (shoulder and hip) without injury of the CST following traumatic brain injury and intracerebral haemorrhage (24, 25). In 2013, among 247 patients with cerebral infarct, Do et al. reported on 4 hemiparetic patients who showed more severe proximal weakness compared with distal joints of the affected extremities (26). These results from previous studies appear to be compatible with the results of the current study, which showed proximal weakness of the patient after injury of the CRP by SAH.

Table III. *Correlation between motor function and diffusion tensor imaging parameters of the corticoreticular pathway*

MI		FA	MD	FV
Shoulder	r	0.342*	−0.241	0.105
	p	0.041*	0.156	0.541
Elbow	r	0.212	−0.130	0.061
	p	0.214	0.450	0.724
Hand	r	0.205	−0.123	0.014
	p	0.230	0.476	0.937
Total upper	r	0.302	−0.186	−0.078
	p	0.073	0.277	0.651
Hip	r	0.348*	−0.183	0.227
	p	0.038*	0.285	0.183
Knee	r	−0.021	−0.145	0.069
	p	0.903	0.399	0.688
Ankle	r	−0.003	0.037	0.143
	p	0.988	0.829	0.406
Total lower	r	0.110	−0.037	−0.124
	p	0.523	0.832	0.472
Total	r	0.138	−0.037	0.122
	p	0.423	0.830	0.478

*$p < 0.05$. MI: Motricity index; FA: fractional anisotropy; MD: mean diffusivity; FV: fibre volume.

In conclusion, we investigated CRP injury following SAH, and the functional roles of the CRP in relation to control of proximal joints. To the best of our knowledge, this is the first study to demonstrate injury of the CRP at the subcortical area after SAH. According to our findings, injury of the CRP appears to be related to weakness in the proximal joints (shoulder and hip) and lower extremity. Therefore, we believe that patients with SAH who show unexplained proximal weakness or leg weakness on conventional brain MRI should be evaluated using DTI. However, limitations of this study should be taken into

account. DTI analysis is operator dependent and, due to fibre complexity, it may cause false-positive or false-negative results for the fibre tracks (38). Another limitation is that we recruited the patients from those with SAH who had been admitted for rehabilitation. Therefore, it is possible that, among all patients with SAH, we recruited patients with severe clinical manifestations. Further studies with larger patient numbers are needed to clarify injury of the CRP following SAH.

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