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Original Article

Prediction of prognosis of upper-extremity function following stroke-related paralysis using brain imaging

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Abstract. [Purpose] Diffusion tensor imaging (DTI) has attracted attention as a method for determining prognosis following paralysis after stroke. However, DTI can assess the degree of damage to the corticospinal tract but cannot evaluate other brain regions. In this study, we examined in detail the prognosis of upper-limb function of the paralyzed side following stroke, using DTI and voxel-based morphometry (VBM). [Subjects and Methods] We studied 17 consecutive patients diagnosed with stroke, including hemorrhagic and ischemic types, who exhibited hemiparesis and were treated in our hospital. DTI and VBM were performed 14 days after admission. Outcome measurements that assessed upper limb function were Fugl-Meyer Assessment (FMA) and Motor Activity Log (MAL), which were applied after 3 months. [Results] The fractional anisotropy ratio of the bilateral cerebral peduncles (rFA) was significantly correlated with FMA, amount of use, and quality of movement 3 months after stroke. The precentral gyrus significantly degenerated as compared with the control group for a case with notable motor paralysis, for which rFA was high. [Conclusion] We suggest it may be possible to predict recovery of upper limb function following stroke by combining DTI and VBM visualization methods.
Key words: Upper-extremity function, Diffusion tensor imaging, Voxel-based morphometry

INTRODUCTION

Stroke is one of the major causes of impaired health and functional capacity, and is the most common cause of mortality or dysfunction in many developed countries[1, 2]. In recent years, various treatment options have become available, such as thrombolysis and endovascular therapy. Thus, it has become possible to avoid the most severe stroke symptoms, but the importance of functional recovery via rehabilitation remains critical[3]. Rehabilitation aims to restore the capacity to take part in daily life of the patient, i.e., his or her functionality. Recovery biomarkers acquired during the acute and subacute phases may be vital to set attainable neurorehabilitation goals and to choose proper therapeutic approaches based on the recovery capacity[4]. It has been suggested that prediction of motor recovery in the early phase of stroke may play an important role

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in tailoring neurorehabilitation therapies for each individual[5–7]. In particular, a number of recent studies have shown that neurologic biomarkers are more predictive of motor recovery than clinical behavioral biomarkers[8–10].

The severity of paralysis after stroke has a deep relationship with the extent of damage to the corticospinal tract[6, 11, 12]. In recent years, DTI has attracted attention as one of the most recent magnetic resonance image analysis methods that can confirm changed neural structures following rehabilitation of motor paralysis and recovery after stroke[13]. DTI objectively quantifies the microstructure of white matter[14]. Reports suggest that fractional anisotropy (FA) in the cerebral peduncle 14 days after stroke onset is significantly correlated with improvements in motor paralysis[15–18]. FA of the ipsilesional CST is associated with microstructural characteristics of white matter fibers[8, 19]. A lower FA value of the ipsilesional CST may indicate greater damage to the CST, which can lead to increased Wallerian degeneration of CST axons[20]. Much of the DTI research has investigated the relationship between motor paralysis and the corticospinal tract. DTI cannot evaluate relationships with other brain regions.

Fortunately, there exists a new means by which to evaluate cortex-wide neural degeneration, namely voxel-based morphometry (VBM). VBM evaluates the density and volume of gray matter and white matter for each voxel, and has been used in the context of mental illness. Tisserand et al.[21] considered changes in normal aging, with the finding that declines in cognitive function were associated with changes in gray-matter density. Chetelat et al.[22] classified patients as having mild cognitive impairment or markedly reduced cognitive function. The latter group had faster progression of atrophy in the hippocampus, gyrus temporalis medius, gyrus temporalis inferior, and posterior cingulate rear cortex, as revealed by VBM analysis. Yin et al.[23] investigated improvement in motor paralysis, using VBM to target chronic-stage stroke patients. Their study investigated the relationship between motor function, as assessed by tract-based spatial statistics (TBSS), a method of analyzing the diffusion-tensor image, in addition to VBM. TBSS and VBM revealed similar results, supporting VBM as a valid brain-imaging method, even for stroke patients.

Here, we considered whether it is possible to provide a detailed prognosis for upper-limb function following stroke paralysis, by considering the degree of degeneration of the whole brain via VBM analysis and the FA of the cerebral peduncle via DTI analysis, using MRI images taken in the sub-acute stroke phase.

SUBJECTS AND METHODS

We studied 17 consecutive patients diagnosed with supratentorial stroke, including hemorrhagic and ischemic types, who exhibited hemiparesis and were treated in our hospital between September 2014 and September 2015. These patients were transferred to a rehabilitation hospital soon after they were admitted. During hospitalization, they underwent physical therapy, occupational therapy, and speech therapy. Exclusion criteria were as follows (1) prior or subsequent symptomatic stroke, (2) the lesion extended to the brain stem, (3) assistance was required for daily living activities, or (4) the individual presented severely disturbed consciousness and similar complications. This study was approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences and a signed informed consent form was obtained from every subject prior to the experiment (approval number: 14062718).

An MRI was performed 14 days after admission using a 1.5-T MR scanner (Signa HD1.5, GE Healthcare, USA) with a 32-channel head coil. Using a single-shot echo-planar imaging sequence, the DTI scheme acquired 12 images with non-collinear diffusion gradients and 1 non-diffusion-weighted image. Typical acquisition parameters were as follows: repetition field of view=26 × 26, matrix=256 × 192, slice thickness=1 mm, interslice gap=1 mm, repetition time/echo time=8,300/101.9 ms, b value=1,000 s/mm^2, number of excitations=3.

DTI analysis used Functool, which is internal analysis software of the SIGNA1.5HD. The regions of interest (ROIs) were placed on axial slices at the cerebral peduncle on the right and the corresponding area on the left, which is similar to a previously described method (Fig. 1)[17]. A radiologist blinded to the aim of the present study set the ROI, measured fractional anisotropy (FA) values, and the ratio between FA values in the affected and unaffected sites (rFA) for the cerebral peduncle. The tractography was constructed using the ROIs outlined above, via one-ROI method. The pattern of tractography was divided into two groups, namely a completely disrupted type and incompletely disrupted type, by a therapist who was blinded to the patients' outcomes (Fig. 2).

VBM analysis was carried out on the 3D T1 image using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) in the MATLAB environment (The MathWorks, Natick, MA, USA). First, gray matter, white matter, cerebrospinal fluid, the skull, and soft tissue were identified. Second, to improve precision, the brain of each target person was modeled using diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL). The image was standardized to the Montreal Neurological Institute space (MNI space). Voxel smoothing reduced the individual differences that remained after anatomic standardization. The control group in statistical analyses consisted of images of physically unimpaired individuals (n=71) held by The Center for Biomedical Research Excellence (http://fcon_1000.projects.nitrc.org/indi/retro/cobre.html). In addition, we used Anatomy Toolbox (http://www.fz-juelich.de/SharedDocs/Downloads/INM/INM-1/DE/Toolbox/ Toolbox_18.html) to identify anatomical positions.

Outcome measurements that assessed upper-limb function consisted of the Fugl-Meyer Assessment (FMA)[24] and Motor Activity Log (MAL)[25, 26]. Evaluations were conducted by an occupational therapist of Nagasaki Rehabilitation Hospital and Nagasaki Memorial Hospital, 3 months after stroke onset.
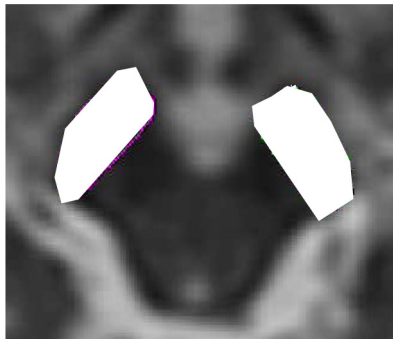
Fig. 1. The regions of interest (ROIs) were placed on axial slices over the bilateral cerebral peduncles
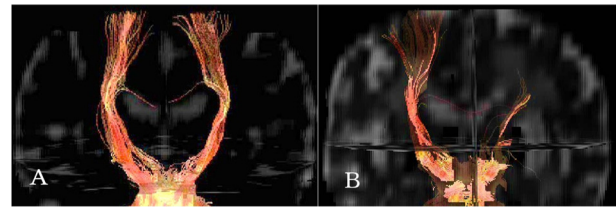

Fig. 2. Representative images of sub-population types on diffusion tensor imaging tractography
(A) The incompletely disrupted type was characterized by the presence of fibers that successfully contacted the cerebral cortex.
(B) The completely disrupted type was characterized by the presence of fibers that disappeared proximal to the lesion.

Table 1. Patient profiles

ID	Age	Gender	Stroke type	Stroke side	DTI Tractography type	FA (R)	FA (L)	rFA	FMA	MAL AOU	QOM
1	58	F	I	L	B	0.38	0.4	0.97	4	0	0
2	48	F	I	L	B	0.31	0.3	0.95	4	0	0
3	91	F	I	R	A	0.48	0.5	0.97	59	4.1	3.6
4	64	M	I	L	B	0.4	0.4	0.96	5	0	0
5	83	F	I	R	B	0.3	0.3	0.94	9	0.1	0.2
6	68	M	I	L	A	0.34	0.2	0.68	4	0	0
7	75	F	I	R	A	0.31	0.5	0.66	4	0	0
8	83	F	I	R	A	0.38	0.4	0.93	61	4.2	3.8
9*	56	M	I	R	A	0.32	0.4	0.73	59	2.4	3.1
10	93	M	I	R	B	0.34	0.3	0.82	4	0	0
11	52	M	I	L	A	0.39	0.4	0.98	65	4.3	4
12*	64	M	I	L	A	0.36	0.4	0.93	19	0.5	1
13	69	M	H	L	A	0.45	0.4	0.92	66	5	5
14	65	M	H	L	A	0.42	0.4	0.94	59	2	2.3
15	40	F	H	L	A	0.44	0.4	0.88	66	5	5
16	86	M	H	L	A	0.45	0.5	0.85	63	2	1.5
17	62	F	H	R	A	0.45	0.4	0.92	62	3.7	3.5

M: male; F: females; H: cerebral hemorrhage; I: cerebral infarction; Tractography typeA: the incompletely disrupted type was characterized by the presence of fibers that successfully contacted the cerebral cortex; Tractography typeB: the completely disrupted type was characterized by the presence of fibers that disappeared proximal to the lesion; rFA: ratio fractional anisotropy; FMA: Fugl-Meyer Assessment; MAL: Motor Activity Log
*VBM analysis patient

We first assessed the correlation between rFA and FMA, AOU, and QOM after 3 months, using Pearson rank correlations. In VBM analysis was conducted for two sample t-test between motor paralysis and rFA contradict case and control group. The initial voxel threshold was set to p<0.001, uncorrected. Clusters were considered significant if cluster-corrected p (FDR)<0.001. All statistical analyses were performed using SPSS version 19.0 (IBM, USA) and SPM12 in the MATLAB environment.

RESULTS

The 17 patients screened between September 2014 and September 2015 had a mean age of 68 years (range 40–93). Average scores were as follows: FMA 36 (4–66), AOU 1.95 (1–5), and QOM 1.93 (1–5) 3 months after stroke onset. The basic attributes are shown in Table 1.
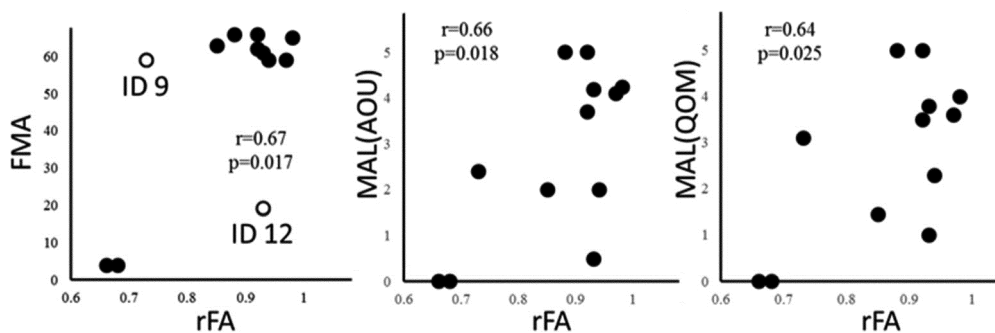
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Fig. 3. Correlations between rFA and upper limb function 3 months after stroke
ID 9 exhibited improved motor paralysis but low rFA as compared with ID 12, who exhibited considerable motor paralysis but high rFA.
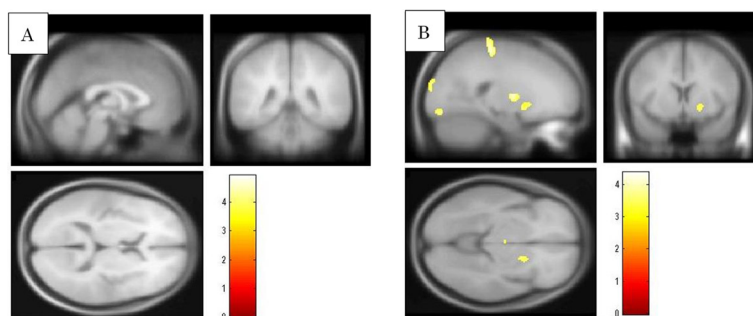

Fig. 4. VBM analysis comparing the control group with ID 9 and ID12
(A) Degeneration was not observed for ID 9 versus the control group. (B) Degeneration was
observed for ID 12 versus the control group in the precentral gyrus, prestrite cortex, and V3.

According to tractography, 12 individuals were classified as type A and 5 as Type B. Type B were excluded from analysis because a completely disrupted corticospinal tract is associated with poor prognosis. We examined correlations between rFA and upper extremity function 3 months after stroke onset for the type A group. There were significant correlations between rFA and FMA (r=0.67, p=0.017), AOU (r=0.66, p=0.018), and QOM (r=0.64, p=0.025; Fig. 3).

In the DTI analysis, one individual (ID 9) had a low rFA value but a high FMA score (ID 9), and another (ID 12) had a high rFA value and a low FMA score (ID 12). VBM analysis was performed to compare each of these individuals against the control group. ID 12 exhibited significant degeneration as compared with the control group in the precentral gyrus (p=0.003). However, ID 9 did not suffer significant degeneration as compared with the control group (Fig. 4).

DISCUSSION

This study was conducted to provide more details of prognosis following stroke-related paralysis, using a combination of DTI and VBM. We found that rFA was significantly correlated with FMA, MAL (AOU), and MAL (QOM) 3 months after stroke for the incompletely disrupted type of tractography.

FA is related to the collapse of decreased cell means the degree of orientation the collapse of decreased cell means[27]. Reduced FA in the cerebral peduncle indicates damage to the corticospinal tract, which consists of white-matter microstructural damage due to Wallerian degeneration[28]. Therefore, DTI can reveal the relationship between motor paralysis and the corticospinal tract. Some prior research has reported a relationship between motor paralysis and the corticospinal tract after stroke, while others have used DTI to illustrate this relationship[11, 15–17, 29, 30]. The FA results of the present study confirm the outcomes of previous studies in relation to prognosis following motor paralysis. However, the FA value can be influenced by a number of other factors, such as white matter architecture. Therefore, one must interpret with caution DTI-derived FA values as neurologic biomarkers of brain impairment[4]. Accordingly, in the present study we evaluated tractography before evaluating FA. Jang et al. used tractography to examine the relationship between motor paralysis and fiber continuity to the cerebral cortex for three groups. Continuity as assessed by tractography has been reported as significantly related to recovery from motor paralysis. Therefore, initially performing tractography could minimize errors in predictions made by FA.

However, there were contradictory results when evaluating recovery from motor paralysis via tractography and FA. In a participant with low rFA values but a high FMA score, there was significant degeneration in the precentral gyrus in the VBM analysis as compared to the control group. The precentral gyrus plays a role in the relationship between motor function and the primary motor cortex. In monkeys, rehabilitation after damage to the corticospinal tract involves the primary motor cortex, as evidenced by changes in brain activity during recovery of hand function[31, 32]. In addition, fMRI studies have investigated the relationship between recovery of motor function after stroke and brain activity, with findings including negative correlations between activity in the primary motor cortex and premotor area, and cerebellum, whereby decreased overactivity was associated with restoration of motor function. That is, recovery of motor function is associated with normalization of activity in overactive brain regions[33–35]. In addition, fMRI studies of Grefkes et al. illustrated interhemispheric inhibition of the injured side of the primary motor cortex by the undamaged side in stroke patients by exercising the paralyzed hand about the suppression of recovery[36, 37]. VBM-confirmed degeneration is useful in predicting prognosis following motor paralysis because the primary motor cortex is critical in exercise-related recovery from paralysis.

Regarding limitations of the present study, first, the number of subjects was small. Therefore, moderate levels of paralysis could not be studied. Additionally, some cases could not be analyzed because it was impossible to distinguish between cerebral ischemic injury and cerebral hemorrhage. Further, the ages of subjects were not restricted and thus results may have included age-related brain degeneration. A larger subject-pool would be necessary to derive detailed predictions of prognosis for different age groups.

In conclusion, DTI allows prediction of prognosis following an initial evaluation by assessing corticospinal tract fiber continuity to the cerebral cortex and by obtaining rFA values via tractography. We suggest that improved predictions of recovery of upper limb function are provided by also assessing whole-brain degeneration by VBM. In the sub-acute stroke phase, being able to predict recovery of upper limb function may improve rehabilitation approaches by suggesting more appropriate therapies.

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