Can the integrity of the corticospinal tract predict the long term motor outcome in post stroke hemiplegic patients?

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Nobody has been more important to me in pursuit of this project than the members of my family. I would like to thank my parents, whose love and guidance are with me in whatever I pursue.

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ABSTRACT

Can the integrity of the corticospinal tract predict the long term motor outcome in post stroke hemiplegic patients?

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This study aimed to investigate the long-term motor outcome according to early diffusion tensor tractography (DTT) findings for the affected corticospinal tract (CST) in post-stroke hemiplegic patients

48 supratentorial subacute patients after stroke (mean age, 63.3 years; male: female, 34:14) were enrolled, who had a brain MRI scan within 6 weeks from onset, and no stroke recurrence reported within the 2 year follow-up period. Diffusion tensor images (DTI) were obtained using 3.0-Tesla scanners, and CSTs were reconstructed through selection of fibers passing through seed and target ROIs (anterior mid-pons, anterior lower-pons). The subjects were classified into four groups according to DDT findings; Type A, the CST originating from the primary motor cortex was preserved around the lesion area; Type B, the CST was similar to type A except the fiber originated from the area adjacent to the primary motor cortex; Type C, the CST was interrupted at or around the lesion area; and Type D, the CST was not shown. The Fugl-Meyer Motor Assessment (FMA), Box and Block Test (BBT), Functional Ambulation

Category (FAC), and Mini-Mental Status Examination (MMSE) were measured at baseline and at 2 years from stroke onset. These clinical outcomes were compared between the four groups.

Changes in FMA and BBT were significantly different according to DTT type at follow-up ($P<0.05$), FAC and MMSE were not. In post-hoc analysis, group A showed significantly greater improvements than group C on the BBT and on the FMA subscale of wrist (corrected $P<0.05$). Furthermore, group A showed significantly greater improvements than group D on the BBT and the FMA subscale of the shoulder/elbow, wrist and hand (corrected $P<0.05$). Group B showed significantly greater improvements on the FMA subscale of wrist than groups C and D. Additionally group B showed significant changes on the FMA subscale of shoulder/elbow and hand compared with group D (corrected $P<0.05$).

This study demonstrated the importance of corticospinal tract integrity for stoke motor recovery. The early integrity of the CST may be helpful in predicting long-term motor outcomes, specifically with upper extremity hand function. It may be helpful for clinicians to establish a proper rehabilitative strategy.

Key Words: Stroke, Corticospinal tract, Diffusion tensor tractography, Prognosis

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Ⅰ. Introduction

Stroke is one of the most common neurologic diseases resulting in a disability among adult. Motor deficit is main sequalae with about 50% of patients suffering from residual motor weakness[1]. Although difficult to accurately predict the degree of motor recovery in the early stages of stroke, it has important implications for stroke rehabilitation because it enables clinicians to set therapeutic rehabilitation goals[2].

The corticospinal tract (CST) is the primary motor pathway regulating motor activities in humans. Many studies have suggested that the preservation of the lateral CST may be associated with good recovery from motor deficits in patients with stroke[3-5]. To analyze the status of the CST, various neuroimaging approaches have been evaluated. Traditional neuroimaging such as brain computed tomography (CT) and magnetic resonance imaging (MRI) are valuable tools for the diagnoses of hemorrhage and infarction, but not for neural tract assessment[6]. Diffusion tensor imaging (DTI) is a noninvasive technique for anatomical mapping of brain axonal connections and can be used to reflect the structural tissue status[7]. DTI can also provide indirect measures of the functional integrity of white matter. Based on DTI analysis[8], diffusion tensor tractography (DTT), a 3-dimensional imaging technique can be used for investigating changes in white matter integrity[9].

Through the development of DTT, several recent studies have demonstrated that it may be a useful tool in predicting motor outcome in patients with stroke[10-15] and the validity and reliability of DTT for CST has been proven[16].

However, most previous studies of DTI have demonstrated the short-term motor outcome of patients after stroke by analyzing the state of CST at one instant, with motor outcome assessments generally taken at 3 or 6 months after stroke onset.

In this study, we determined whether at 2-year long-term motor functional outcome can be predicted in patients with stroke, using early DTI findings of the affected corticospinal tract to help clinicians set the optimal therapeutic goals and strategies.

Ⅱ. Subject and Method

1. Subject

Forty-eight patients with first ever post-stroke hemiplegia who were admitted at the Department of Rehabilitation Medicine, Yonsei University College of Medicine from April 2010 to January 2013 were recruited. Criteria for inclusion in the study were as follows: (1) first-ever acute hemiplegic stroke; (2) unilateral supratentorial lesion; (3) age≥19 years at onset of stroke; (4) DTI scanning performed within 6 weeks after onset; and (5) moderate-to-severe stroke deficit defined by a total Fugl-Meyer Assessment(FMA) score≤79.

The exclusion criteria for this study were as follows: (1) previous neurologic or orthopedic disorders; (2) contraindication to magnetic resonance imaging; (3) refusal of DTI; (4) recurrence of stroke; (5) refusal of follow-up 2 years after onset of stroke.

In total, 34 male and 14 female patients after stroke with a mean age of 63.3 years were enrolled. Of these 48 patients, 40 had cerebral infarction, 8 had intracranial hemorrhage, 19 had a lesion in the left hemisphere, and 29 in the right hemisphere. Stroke motor severity was determined by FMA scores; moderate 35-79, severe<35. At baseline, there were no significant differences for age, sex, lesion side, type of stroke, days when MRI were taken from onset, and severity of motor function among four groups. A summary of the demographic and clinical data of the patients is shown in Table 1.

The study protocol was approved by the Institutional Review Board of Yonsei University, and informed consent for the study was obtained from each subject.

Table 1. Baseline Characteristic of Subjects (n=48)

	Group A (n=16)	Group B (n=15)	Group C (n=8)	Group D (n=9)
Age (year)	64.0±12.7	63.9±12.4	57.9±14.7	65.6±19.2
MRI from onset (day)	19.8±9.8	14.8±5.3	16.6±4.5	12.6±4.2
Sex (M:F)	12:4	9:6	7:1	6:3
Lesion side (Rt:Lt)	10:6	10:5	5:3	4:5
Stroke type (I:H)	15:1	12:3	7:1	6:3
Motor severity				
Moderate (n)	10	10	2	0
Severe (n)	6	5	6	9

I, infarction; H, hemorrhage

2. DTI data acquisition and analysis

DTIs were acquired using 3.0-Tesla scanners (GE Healthcare Horizon, Philips Gyroscan Intera, or Siemens Magnetom Trio) with standard eight-channel phased array head coil with a single-shot spin-echoplanar imaging 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. The imaging parameters used included the following: matrix=120×120 matrix, field of view=240×240 mm^2, TE (echo time)=84 ms, TR (repetition time)=16,000 ms, b=800 mm^2 s^{-1}, and slice thickness=2 mm.

DTI analyses of CST were performed by an experienced medical doctor using DTI studio software (www.mristudio.org, Johns Hopkins Medical Institute, Baltimore, MD). Fiber tracking was performed using the fiber assessment by continuous tracking algorithm, a brute-force reconstruction approach, and multiple-regions of interest (ROIs) approach. The seed ROI was drawn in the CST portion of the anterior mid-pons on a number of 2-dimensional fractional anisotropy color maps. The target ROI was drawn in the CST portion of the anterior lower-pons. Tract fibers passing through both regions of interest were designated as final tracts of interest.

The termination criteria used were fractional anisotropy (FA) < 0.2, and an angle change >60° consistent with a previous study for the optimal trackability threshold of FA[6,17].

The DTI findings were classified into four groups, which Cho et al had suggested[10]. (1) Type A, the CST was preserved around the infarction or hemorrhage, namely, the tract originating from the affected hemisphere including the primary motor cortex and passing around the lesion; (2) Type B, the CST was similar to type A, except the fiber originated from other cortex other than the primary motor cortex (e.g., primary sensory cortex, posterior parietal cortex, premotor cortex, prefrontal cortex, somatosensory cortex and etc.); (3) Type C, the CST was interrupted at the lesion; and (4) Type D, CST could not be found (Fig. 1)

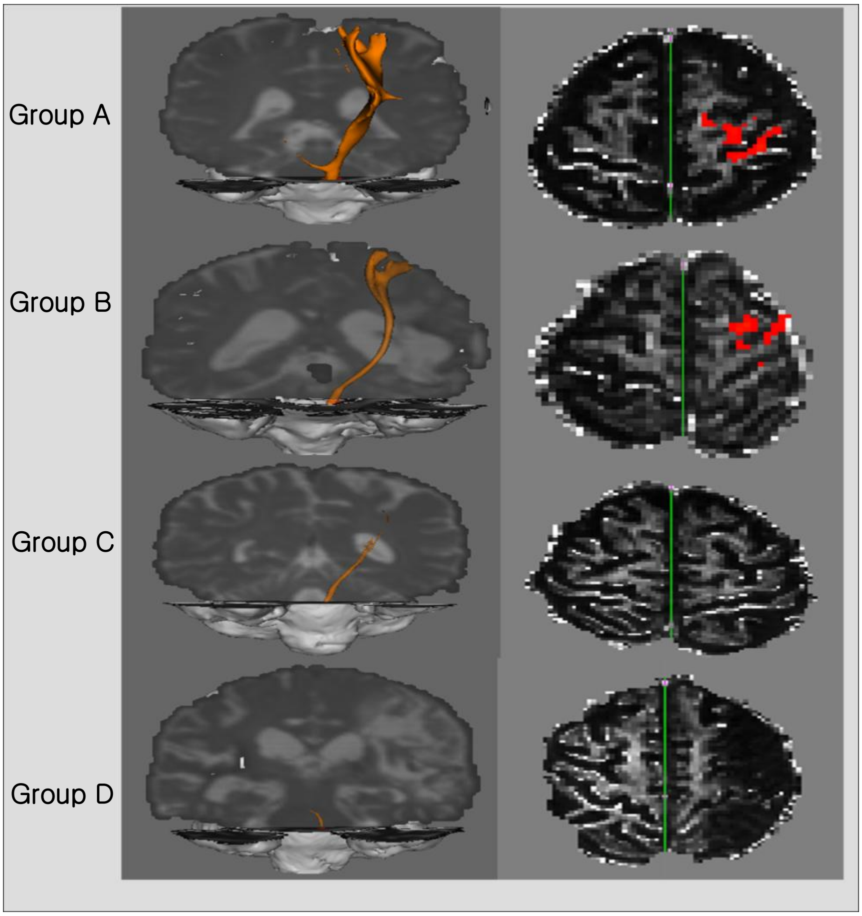

Figure 1. Classification of diffusion tensor tractography

3. Clinical outcomes

Clinical outcomes were measured at baseline (within 1 week from DTT) and at 2 years after stroke onset using the Fugl-Meyer Assessment (FMA)[18], Functional Ambulation Category (FAC)[19], Box and Block Test (BBT)[20,21] and Mini-Mental State Examination(MMSE)[22] to assess gross motor function, walking ability, hand dexterity and cognitive status, respectively.

The FMA, one of the most widely-used quantitative measures of motor impairment[23] is an index for evaluating motor recovery and is comprised of five subscales that measure movement, coordination, and reflex actions of the shoulder/elbow, wrist, hand, hip, knee, and ankle. The FAC[24] is the most common functional test that evaluates ambulation ability in accordance with the amount of physical support required and scope of walking. BBT[25] measures gross manual dexterity and is scored in accordance with the number of wooden blocks that can be moved from one compartment of a box to another within 1 -minute. MMSE[26] is a 30-point questionnaire that is used extensively in clinical settings to measure cognitive impairment.

4. Statistical analysis

Data analyses were performed using SPSS version 23.0 software (SPSS Inc., Chicago, IL). Baseline characteristics (sex, lesion side, type of stroke, severity of motor function) were compared by the chi-square test. The Kruskal-Wallis test, a non-parametric signed-rank test, was used to compare the baseline characteristics (age, days when MRI were taken from onset) and clinical outcomes between four groups. In post-hoc analysis, Mann-Whitney U tests were used. The p- values less than 0.05 in the Kruskal-Wallis test and less than 0.008 (Bonferroni corrected p-value < 0.05) in the Mann-Whitney U test were considered statistically significant.

Ⅲ. Results

The 48 subjects were divided into four groups by DTT findings with 16, 15, 8 and 9 patients in CST Groups A, B, C, and D, respectively.

In the FMA score at baseline, a significant difference existed between groups A and D as well as, groups B and D (corrected $P<0.05$). At 2 years follow-up, FMA score showed a significant difference between groups A and C, groups A and D, and groups B and D (corrected $P<0.05$).

At baseline, none of the patients in group C and D were able to perform the BBT. At 2 years follow-up, we found a significant difference in BBT scores between groups A and C as well as, groups A and D (corrected $P<0.05$). In FAC, groups A and C and, groups B and D showed a significant difference at baseline and at a 2-year follow-up (corrected $P<0.05$). In MMSE, a significant difference existed between groups A and C and, groups A and D at baseline and between groups A and D at 2 years follow-up(corrected $P<0.05$, Table 2).

Comparing the degree of changes in clinical outcomes, the changes of FMA and BBT scores from baseline to 2 years follow-up were significantly different between the four groups ($P<0.05$), but not with MMSE and FAC scores. The improvement of FMA scores in groups A and B was significantly greater than that in groups C and D (corrected $P<0.05$). In addition, the improvement of BBT scores in group A was significantly greater than that of BBT in groups C and D (corrected $P<0.05$; Table 2, Fig 2).

Regarding FMA, the change of upper FMA score from baseline to 2-year follow-up was significantly different between the four groups ($P<0.05$); however, that of lower FMA score was not. The improvement of upper FMA in groups A and B was significantly greater than that of FMA in groups C and D (corrected $p<0.05$, Table 3). Changes in the shoulder/elbow, wrist, and hand subscales of the FMA were significantly different between the four groups ($P<0.05$), but were not for the hip, knee, and ankle subscales (Table 3).

The improvement of shoulder/elbow, wrist, and hand subscale score in groups A and B was significantly greater than in group D (corrected $P<0.05$, Table 3)

Table 2 Comparison of Changes of FMA, BBT, FAC, MMSE between DTT groups

Variables	DTT group	Baseline	2 years	Change
FMA	A	45.4±20.4	82.6±19.6	37.1±22.4
	B	32.4±19.9	67.7±28.7	35.5±24.5
	C	23.5±18.0	34.5±19.9*	9.4±11.0*†
	D	11.7±4.9*†	18.2±6.5*†	6.6±5.7*†
BBT	A	2.1±5.6	27.9±20.2	25.8±18.7
	B	2.6±7.1	17.8±21.6	15.2±19.7
	C	0±0	0±0*	0±0*
	D	0±0	0±0*	0±0*
FAC	A	1.3±1.2	4.3±1.0	2.9±1.7
	B	1.5±1.5	4.7±0.8	3.2±1.5
	C	1.0±1.8	3.5±1.7	2.5±1.6
	D	0.1±0.3*†	1.7±1.1*†	1.6±0.9
MMSE	A	15.4±12.1	19.2±11.7	3.8±8.1
	B	22.4±10.9	24.8±7.3	2.4±4.8
	C	9.5±13.2†	16.3±13.7	7.7±10.6
	D	9.2±9.0†	14.1±11.3†	3.9±7.3

*, corrected $p<0.05$ vs. group A; †, corrected $p<0.05$ vs. group B; F/U, follow-up; FMA, Fugl-Meyer motor assessment; BBT, Box and Block test; FAC, Functional ambulation category; MMSE, Mini-mental status examination

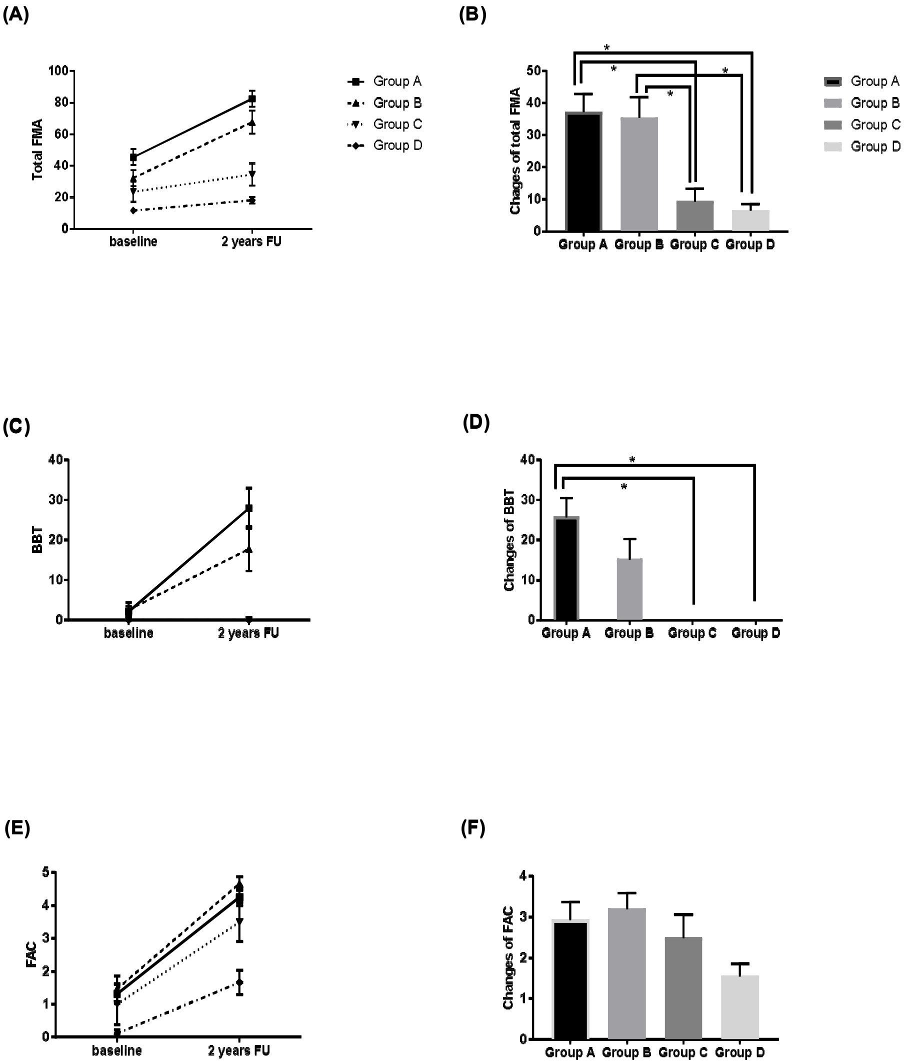

Figure 2. Changes of motor recovery according to DTT groups (A) FMA at baseline and 2 years follow up (B) Difference of FMA (C) BBT at baseline and 2 years follow up (D) Difference of BBT (E) FAC at baseline and 2 years follow up (F) Difference of FAC

Table 3. Comparison of changes of subscales of FMA between DTT groups

	DTT group	Baseline	2 years F/U	Change
Upper FMA	A	26.6±15.7	51.9±16.7	25.3±16.3
	B	14.5±12.6	41.8±22.1	27.3±19.6
	C	10.4±10.1	15.9±11.8*	5.5±7.3*†
	D	5.7±4.2*	7.8±3.9*†	2.1±3.1*†
shoulder/elbow	A	17.6±8.6	28.3±7.9	10.7±10.1
	B	11.1±8.6	22.7±13.0	11.6±10.6
	C	8.3±6.2	10.5±7.0*	2.3±5.2
	D	6.0±3.9*	5.8±4.0*†	-0.2±1.8*†
Wrist	A	3.7±3.5	7.2±3.6	3.5±3.3
	B	1.3±2.4	5.0±4.1	3.7±4.1
	C	1.3±2.3	0.8±1.4*	-0.5±0.9*†
	D	0.0±0.0*	0.0±0.0*†	0.0±0.0*†
Hand	A	4.3±4.7	11.3±4.8	7.0±4.6
	B	2.0±3.3	8.6±5.7	6.6±5.8
	C	0.9±2.1	2.5±4.8*	1.6±2.9
	D	0.0±0.0*	0.1±0.3*†	0.1±0.3*†
Lower FMA	A	18.9±8.2	30.7±4.0	11.8±8.4
	B	17.9±8.5	26.1±6.7	8.2±6.8
	C	13.1±8.6	18.6±8.8*	4.8±4.8
	D	6.0±1.3*†	10.4±3.4*†	4.4±3.2
Hip	A	8.0±2.9	10.7±2.0	2.7±3.0
	B	8.5±2.3	10.1±1.9	1.6±2.2
	C	6.6±2.4	7.8±2.4*	1.3±1.3
	D	4.8±1.3*†	5.8±2.2*†	1.0±1.1
Knee	A	4.3±2.6	7.5±1.3	3.2±2.3
	B	4.4±2.6	7.1±1.5	2.7±2.3
	C	2.9±2.6	4.9±3.3	2.0±1.7
	D	1.0±2.0*†	2.2±2.0*†	1.2±1.5
Ankle	A	3.7±3.0	6.0±2.4	2.3±2.7
	B	2.3±2.8	4.7±2.7	2.5±1.9
	C	1.0±1.9	2.9±2.9	1.9±2.9
	D	0.8±1.2	1.1±1.4*†	0.8±1.6

*, corrected $p<0.05$ vs. group A; †, corrected $p<0.05$ vs. group B; F/U, follow-up; FMA, Fugl-Meyer motor assessment; BBT, Box and Block test; FAC, Functional ambulation category;
MMSE, Mini-mental status examination

Ⅳ. Discussion

This study aimed to determine whether early DTT findings for the CST in the patients with post-stroke hemiplegia could be used to predict the long-term motor outcome 2 years after stroke onset. It is the first study regarding long-term motor functional outcome to be predicted by CST integrity.

The results of the study indicated the long-term motor outcome of patients with stroke may differ in accordance with early DTT findings of CST in the affected hemisphere. Especially, DTT findings of CST may in fact predict the motor recovery of upper limb and hand dexterity.

These findings are concurrent with those of previous studies that upper extremity functional outcomes can be predicted through CST integrity. Watanabe et al. reported that in the early stages of stroke, 3-dimentional axonography may be useful in predicting motor function related disorders in patients with stroke[27]. Cho et al[10] showed early DTT findings for CST can be used to predict the motor outcome of the affected extremities in hemiparetic patients with intracerebral hemorrhage. Other studies found that upper extremity functional recovery can be evaluate through different CST integrity types among patients with thalamic hemorrhage, pontine infarction and lacunar infarction[12,28]. Jang et al. classified CST integrity into two groups; preserved around infarct and interrupted by the infarct, and reported that the patients for whom the integrity of the CST was maintained after pontine infarct showed better outcomes for both hand and gait function. However, these previous studies were limited to the patients with subcortical stroke, such as those with lacunar infarction and thalamic hemorrhage, and assessed the motor outcomes at short-term follow-up times of 30-60 days, 3 months and 6 months[12,15,28]. No previous study revealed long term functional outcome.

My results also support the theory that preservation of the integrity of the CST on the affected side is determinant of recovery of upper limb movement[29]. The hierarchical motor system in which the primary motor cortex projects via the CST is affected by the premotor and supplementary motor areas.

Interestingly, lower limb motor function and walking ability could not be predicted by the integrity of the CST in this study. In groups C and D, some of the patients were able to walk despite interrupted or completely damaged CST. This finding was in line with the suggestion that walking ability has greater potentials for recovery than hand function because the motor function of the leg is less dependent on the CST than that of hand function[30]. CST is mainly involved in the control of movement of distal extremities, particularly fine motor movement of the hand[5,31,32]. The other motor pathway that is responsible for walking ability may be the ipsilateral CST, which originates from the intact primary motor cortex, and dose not cross at the medulla. It may also be related with the unmasking of the ipsilateral motor pathway from the unaffected motor cortex after brain damage[33-35].

In addition, the extrapyramidal tract such as the reticulospinal, vestibulospinal and rubrospinal tract has been suggested as other motor pathway to play an important role in walking ability. Among them, the corticoreticulospinal tract, which originates mainly from the premotor cortex activates the axial muscles and proximal muscles[36]. Thus it involves trunk control and locomotion. It is consistent with a previous study reported that walking may be associated with activation of the premotor cortex and supplementary motor area in the affected hemisphere[37].

This study also revealed that no significant difference of motor function improvement was not found group A and group B. It means that the motor function may not be affected by the origin of CST after stroke if intact CST pathway was evident in DTT findings. This may be explained by functional reorganization adjacent to the lesion after brain damage[33-35]. In this study, the secondary motor cortex was responsible for reorganization rather than the primary motor cortex in group B, indicating that in the recovery of a damaged CST, peri-lesional reorganization at the cortical level were sufficiently evoked in partially damaged CST[38].

The result of this study showed that upper limb function and hand dexterity could be predicted by DTT findings, which coincide with previous studies. Most patients after stroke had fine motor problems associated with the affected hand. To improve fine hand dexterity, an important factor in activities of daily living, many patients after stroke spend a lot of time and money during rehabilitation. Systematic planning of a proper rehabilitative treatment plan may be developed through CST analysis in the early phases after stroke, thereby offsetting some of the time and cost lost.

This study had several limitations. First, the subjects of this study enrolled the whole supratentorial stroke patients regardless of cortical involvement. For more accurate predictions of clinical outcomes, stroke type and lesion location must be more homogeneous in future studies. Second, the time of baseline assessment was within 6 weeks after onset. It is broad, and affected the outcomes because the recovery is very rapid in acute phase despite the time taken MRI were not different between groups. Third, the amount and types of rehabilitation after discharge from our hospital were not controlled which may have an impact on patients' functional recovery. To minimize the influences of these factors, we tried to follow-up with patients at 2 years after stroke onset.

Ⅴ.Conclusions

This study demonstrated the importance of corticospinal tract integrity for stoke motor recovery, specifically with hand function. Early prediction of motor recovery of the hemiplegic hand has considerable value in stroke rehabilitation. We suggested that early DTT in the clinical setting may provide detailed information of the corticospinal tract to help clinicians establish a proper rehabilitative strategy.

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ABSTRACT(IN KOREAN)

피질척수로의 상태에 따라 편마비 뇌졸중 환자의 장기적 운동 기능의 예측

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김 애 령

뇌졸중 이후 손상된 운동기능의 회복은 뇌졸중 재활에 있어 핵심 목표 중 하나이다. 편마비 뇌졸중 환자를 대상으로 아급성기에 피질척수로(corticospinal tract)의 상태를 확산 텐서 신경다발 추적방법(diffusion tensor tractography)을 이용하여 분석하여 뇌졸중 발병 이후 2년 시점의 운동 기능 회복 정도와 비교하여 피질 척수로 상태에 따라 장기적 운동 기능의 예측이 가능한지 알아보고자 하였다.

연세대학교 의과대학 세브란스병원 재활의학과에 입원한 발병 6주 이내의 천막상(supratentorial) 초발 뇌졸중 환자 48명이 연구에 참여하였다. 2년간 추적 관찰하는 동안 재발이 없는 경우만을 포함하였다. 이들은 남자 34명, 여자 14명이었고, 평균 나이는 63.3세였다. 연구 참여자들은 발병 6주 이내에 3.0 tesla 뇌 자기공명영상(magnetic resonance imaging, MRI)을 촬영하였고, MRI 통하여 확산 텐서 영상(diffusion tensor

image)를 얻어, DTI software 프로그램을 사용하여 피질척수로를 재구성하였다. 피질 척수로는 관심영역(region of interest)인 anterior mid pons와 anterior lower pons를 지나는 섬유(fiber)를 재구성하여, 피질척수로의 상태에 따라 4 그룹으로 분류하였다. A군은 피질척수로가 일차 운동 피질로부터 기원하며 병변 주위에서도 보존된 경우, B군은 A군과 비슷하지만 피질 척수로가 일차 운동 피질 인근의 영역에서 기원한 경우, C군은 병변 또는 그 인근에서 피질척수로가 중단된 경우, D군은 피질 척수로가 보이지 않는 경우로 구분하였다. 임상적 지표는 운동 기능 회복을 보기 위해 푸글-마이어 점수 (Fugl-Meyer motor assessment), 손의 기민성을 보기 위해 상자와 나무토막검사 (Box and Block test), 보행 기능을 보기 위해 기능적 보행 단계 (Functional ambulation category), 인지 기능을 보기 위해 간이정신상태검사 (Mini-mental status examination) 를 MRI 촬영 1주일 이내의 기준시점(baseline)과 발병 2년 이후의 시점에 두 차례 평가하였다. 4 그룹간의 차이를 SPSS 23(SPSS Inc., Chicago, IL, USA)을 사용하여 Kruskal-Wallis test와 post hoc Mann-Whitney U tests 로 분석하였다.

FMA와 BBT 의 변화량이 4 그룹 사이에 유의미한 차이가 있었다. ($p<0.05$) 또한 사후분석에서 A군과 B군은 C군과 D군에서 상지 FMA 점수, 총 FMA 점수, 손목 FMA 점수에서 유의미한 차이가 있었다 ($p<0.05$). A군과 D군, B군 D군에서 어깨, 팔꿈치의 FMA 점수, 손의 FMA 점수에서 사후분석에서

유의미한 차이가 있었다($p<0.05$). BBT의 그룹간의 사후분석에서 A군과 C군, A군과 D군 유의미한 차이가 있었다($p<0.05$). FAC와 MMSE는 4 그룹간의 유의미한 차이는 없었다.

DTT를 통한 피질 척수로의 상태를 분석함으로써 뇌졸중 환자의 장기적 운동기능을 예측하는데 도움이 되며, 특히 상지 손기능을 예측하는데 도움이 될 수 있을 것으로 기대된다.

핵심되는 말: 뇌졸중, 피질척수로, 확산 텐서 신경다발 추적방법, 예측