Activation of less affected corticospinal tract and poor motor outcome in hemiplegic pediatric patients: a diffusion tensor tractography imaging study

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Abstract
The less affected hemisphere is important in motor recovery in mature brains. However, in terms of motor outcome in immature brains, no study has been reported on the less affected corticospinal tract in hemiplegic pediatric patients. Therefore, we examined the relationship between the condition of the less affected corticospinal tract and motor function in hemiplegic pediatric patients. Forty patients with hemiplegia due to perinatal or prenatal injury (13.7 ± 3.0 months) and 40 age-matched typically developing controls were recruited. These patients were divided into two age-matched groups, the high functioning group (20 patients) and the low functioning group (20 patients) using functional level of hemiplegia scale. Diffusion tensor tractography images showed that compared with the control group, the patient group of the less affected corticospinal tract showed significantly increased fiber number and significantly decreased fractional anisotropy value. Significantly increased fiber number and significantly decreased fractional anisotropy value in the low functioning group were observed than in the high functioning group. These findings suggest that activation of the less affected hemisphere presenting as increased fiber number and decreased fractional anisotropy value is related to poor motor function in pediatric hemiplegic patients.

Key Words: nerve regeneration; unaffected hemisphere; hemiplegia; corticospinal tract; diffusion tensor imaging; motor function; neural regeneration

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Introduction
Brain plasticity plays an important role in the motor recovery mechanism in an injured brain (Broderick et al., 2004). In particular, immature brain of pediatric patients has greater potential for plasticity than mature brain during the recovery phase (Johnston et al., 2003). Understanding the recovery mechanism using brain plasticity is essential in terms of prediction of functional outcome and establishment of rehabilitative treatment. Several motor recovery mechanisms have been proposed in previous studies: recovery of a damaged lateral corticospinal tract (CST), subcortical peri-lesional reorganization, contributions of ipsilateral motor pathway from unaffected motor cortex to the affected extremities, and the other motor areas, and among them, the ipsilateral motor pathway is significant because it can change with time and it can be influenced by rehabilitative management (Colebatch et al., 1989; Kim et al., 1993; Chen et al., 1997; Jang, 2009a, 2011). It is also known that sustained activation of the ipsilateral motor pathway results in poor motor outcome in adult hemiplegic patients with stroke (Chen et al., 1997a, b; Netz et al., 1997; Kim et al., 2004; Serrien et al., 2004; Kwon et al., 2007). Several previous studies have reported contribution of the ipsilateral motor pathway from the unaffected hemisphere in mature brains, using transcranial magnetic stimulation (TMS) (Chollet et al., 1991; Farmer et al., 1991; Carr et al., 1993, 1996; Maegaki et al., 1995; Caramia et al., 1998), conventional magnetic resonance imaging (MRI) (Staudt et al., 2005), functional MRI (Cramer et al., 1997), positron emission tomography (Jang et al., 2001), transcranial Doppler ultrasonography (Silvestrini et al., 1995), and autopsy study (Scales et al., 1972; Schachenmayr et al., 1978).

Diffusion tensor imaging (DTI) allows the estimation of neural tracts quantitatively by virtue of its ability to quantify water diffusion properties (Basser et al., 1996; Mori et al., 1999; Arzoumanian et al., 2003; Drobyshhevsky et al., 2007; Ludeman et al., 2008; Yoshida et al., 2010). Diffusion tensor tractography (DTT), which is derived from DTI, provides three-dimensional visualization of the neural pathways (Basser et al., 1996; Mori et al., 1999; Arzoumanian et al., 2003; Drobyshhevsky et al., 2007; Ludeman et al., 2008; Yoshida et al., 2010). Some DTT studies in adult hemiplegic patients have
demonstrated the compensation of the ipsilateral CST from the unaffected hemisphere as a recovery mechanism (Jang et al., 2005a, 2009; Kwak et al., 2010). However, regarding pediatric hemiplegic patients, only two DTT studies with small numbers of patients have been reported (Thomas et al., 2005; Wakamoto et al., 2006), and no DTT studies have demonstrated the relationship between ipsilateral CST of the less affected hemisphere and motor function in pediatric patients with hemiplegia.

In this study, we investigated the relationship between the state of the ipsilateral CST and motor function in pediatric hemiplegic patients using DTT.

Subjects and Methods

Subjects

Sixty hemiplegic patients were recruited in accordance with the following criteria: (1) patients with spastic hemiplegia examined by two pediatric neurologists, (2) DTT performance at physiologic age of 10–20 months, (3) patients who underwent rehabilitation therapy in our hospital for at least 6 months. The patients were excluded in accordance with the following criteria: (1) diagnosed chromosomal anomaly, congenital brain anomaly, or genetic syndrome, (2) severe mental retardation or intractable seizure, (3) history of postnatal brain injury such as traumatic event, hypoxic brain injury, brain surgery, or postnatal neonatal stroke, (4) upper limb joint contracture which may affect the function of the hand, (5) dyskinetic or hypotonic movement pattern. Three patients with chromosomal anomaly and two patients showing congenital brain anomaly such as pachygyria or schizencephaly were excluded. Three patients with intractable epilepsy and one patient who underwent brain surgery were also excluded. In addition, five patients could not be included in this study due to motion artifact on DTI images. All subjects were patients who visited Pediatric Rehabilitation Center of Yeungnam University Hospital, Korea, and they were volunteers and their parents volunteered for this study.

Hemiplegic upper extremity motor function of all patients was evaluated using functional level of hemiplegia (FxL) (House et al., 1981; Romain et al., 1999; Fluet et al., 2010) by two pediatric neurologists who did not know the results of other evaluations. The patients were divided into two age-matched groups according to the FxL. 0 (has no use), 1, use as stabilizing weight only; 2, can hold objects placed in hand; 3, can hold object and stabilize it for use in other hand; 4, can actively grasp object and hold it weakly; 5, can actively grasp object and stabilize it well; 6, can actively grasp object and manipulate it against other hand; 7, can perform bimanual activities easily and occasionally use the hand spontaneously; 8, use the hand with complete independence). The high functioning group included patients who showed FxL ≥ 6, and the low functioning group included patients who showed FxL ≤ 5. In this study, the criteria to distinguish between high functioning group and low functioning group was whether the patient can perform bimanual activities or not, because bimanual activity is usually required to perform the functional activity of hands.

One patient whose results from two neurologists did not match and five patients who were not age-matched were excluded. Therefore, 40 patients were recruited in the final analysis (Figure 1). We also recruited 40 age-matched typically developing control subjects whose parents volunteered for this study. The parents of control subjects applied for this study and the results of DTT were provided free of charge. The control subjects had no medical history or diagnosis of neurological or psychological disease including brain trauma or delayed development. Informed consents were obtained from the parents of all subjects, and this study was approved by the Institutional Review Board at Yeungnam University Hospital, Korea.

DTI

Within an interval of less than 3 days from FxL assessment, DTI scanning was performed at an average of 13.65 ± 3.0 months (range 10–20 months) using a six-channel head coil on a 1.5 Tesla Philips Gyroscan Intera unit (Philips Medical Systems, Best, The Netherlands) with single-shot echo-planar imaging. Sixty-seven adjacent slices were obtained for the 32 non-collinear diffusion sensitizing gradients. Imaging parameters were as follows: field of view = 221 × 221 mm², acquisition matrix = 96 × 96, reconstructed matrix = 128 × 128, echo time = 76 ms, repetition time = 10,726 ms, echo planar imaging factor = 59, sensitivity encoding factor = 2, b = 1,000 s/mm², number of excitations = 1, and a slice thickness of 2.3 mm. Oxford Centre for Functional Magnetic Resonance Imaging of Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl) was used to remove distorted images from Eddy current using multi-scale two-dimensional registration. Fiber Assignment by Continuous Tracking (FACT) in Philips PRIDE software (Philips Medical Systems), which is three-dimensional fiber reconstruction algorithm, was used to evaluate fiber connectivity. The termination standard of fiber tracking was fractional anisotropy (FA) threshold < 0.2 and angle change > 45°. On an FA axial color slice, a seed region of interest (ROI) was placed in the anterior mid-pons (the CST portion). On each of the FA axial color slices, another ROI was drawn in the anterior low-pons (the CST portion). The tracts passing through both ROIs were selected as final tracts. The ROI size was set between 5 and 10 voxels to include only the CST (Son, 2009) (Figure 2). Fiber number (FN), mean value of FA, and mean diffusivity (MD) of both sides of the entire CST were measured. In the control group, there was no definite difference of values between the two hemispheres; therefore, the mean values of diffusion parameters of both CSTs were measured.

Statistical analysis

For detection of the demographic differences between the patient and control groups, chi-square test was used for gender and independent t-test for age. For comparison of DTI parameters (FN, FA and MD) between the patient and control groups, one-way analysis of variance was conducted. When a significant difference was found between these two groups, Bonferroni post-hoc test was used to assess pairwise
comparisons. Independent t-test was used for comparison of DTI parameters in the less affected CST between the high functioning and low functioning groups. SPSS 18.0 software (SPSS, Chicago, IL, USA) was used. A level of $P < 0.05$ was considered statistically significant.

**Results**

**Demographic data**

Age at MRI scans and clinical evaluations were adjusted based on physiologic age. Out of 40 patients, 20 patients were included in the high functioning group (14 males, 6 females; mean age 13.7 ± 3.0 months; 13 full-term delivery, 7 preterm delivery) and another 20 patients in the low functioning group (14 males, 6 females; mean age 13.7 ± 3.0 months; 2 full-term delivery, 18 preterm delivery). The mean age of the control group was 13.7 ± 3.0 months (25 males, 15 females; 40 full-term delivery). There were no significant differences in demographic data between the patient and control groups (Table 1). The mean FxL score of the high and low functioning groups was 7.5 ± 0.7 and 3.7 ± 1.5, respectively. On conventional MRI, three patients had lesions (three periventricular leukomalacia) in the high functioning group, and eight patients had lesions (two intra-cerebral hemorrhages and six periventricular leukomalacia) in the low functioning group. The other patients showed no abnormal brain lesions on conventional MRI (Table 2).

**DTI parameters**

The more affected CST of the patient group showed significantly decreased FN and FA value, significantly increased MD value compared with the less affected CSTs and that of the control group ($P < 0.05$). The less affected CST of the patient group showed significantly increased FN and significantly decreased FA value compared with that of the control group ($P < 0.05$). However, there was no significant difference in MD value between the less affected CST of the patient group and the control group ($P > 0.05$) (Table 3).

The low functioning group showed significantly increased FN and significantly decreased FA value than the high functioning group ($P < 0.05$). There was no significant difference

| Table 1 Demographic data for hemiplegic patients and controls |
|-------------------|-------------------|
| **Patient group** | **Control group** |
| Patient (n)       | 40                |
| Age (month)       | 13.7±3.0          |
| Gender (male/female, n) | 28/12             |
| Age (month)       | 13.7±3.0          |
| Gender (male/female, n) | 25/15             |

Values of age are presented as the mean ± SD.

| Table 2 Demographic and clinical data for the high functioning and low functioning groups |
|--------------------------------------|--------------------------------------|
| **High functioning group**          | **Low functioning group**             |
| Patient (n)                         | 20                                   |
| Age (month)                         | 13.7±3.0                             |
| Gender (male/female, n)             | 14/6                                 |
| Full-term/preterm (n)               | 13/7                                 |
| FxL score                           | 7.5±0.7                              |
| Brain lesion                        | Periventricular leukomalacia (n)      |
| Intra-cerebral hemorrhage (n)       | 3                                    |

Values of age and FxL score are presented as the mean ± SD. FxL: Functional level of hemiplegia.

| Table 3 Diffusion parameters of CST in hemiplegic patients and controls |
|------------------------------------------------------------------------|
| **Less affected CST in the patient group** | **More affected CST in the patient group** | **Mean values of both CSTs in the control group** |
| Fiber number (n = 40)                                                   | Fiber number (n = 40)                                         | Fiber number (n = 40) |
| Fiber number                                                            | Fractional anisotropy                                        | Mean diffusivity (× 10$^{-3}$ mm$^2$/s) |
| 1,203.15±278.32                                                       | 0.4888±0.022                                                | 0.9010±0.056                                      |
| 1,394.95±343.22                                                       | 0.4658±0.026                                                | 0.9214±0.034                                      |

Values are expressed as the mean ± SD. $^*P < 0.05$, vs. the less affected side in the patient group and the control group; $^\dagger P < 0.05$, vs. control group. One-way analysis of variance followed by Bonferroni post-hoc test was used. CST: Corticospinal tract.
in MD value between the high functioning and low functioning groups (P > 0.05) (Table 4).

Discussion
In the current study, significantly increased FN and decreased FA value of the less affected CST were observed in hemiplegic patients than in the controls. The comparative result for the less affected CST showed significantly increased FN and decreased FA value in the low functioning group than in the high functioning group.

In the current study, we used FxL for functional evaluation of participants. FxL is an observational description of hemiplegic upper extremity use in pediatric patients, and has been widely used in several previous studies on the therapeutic effect of rehabilitation on motor dysfunction (House et al., 1981; Romain et al., 1999; Fluet et al., 2010). Because the CST is highly related to the fine motor coordination of the upper extremities (Jang, 2009b; Cho et al., 2012), we used FxL, which can focus on the more affected upper extremity use instead of Bayley Scales of Infant Development (BSID) or Erhardt Developmental Prehension Assessment (EDPA), which cannot assess the function of the more affected extremity, particularly in hemiplegic patients.

Among DTI parameters, FN represents the quantitative information on connectivity within a white matter tract (Wilson-Costello et al., 2005; Son et al., 2009; Faria et al., 2010; Jang, 2010; Kwak et al., 2010; Yoshida et al., 2010). FA value represents the degree of unidirectionality of a well-organized white matter tract (Basser et al., 1996; Mori et al., 1999; Assaf et al., 2008; Neil, 2008). MD value represents the magnitude of water diffusion (Basser et al., 1996; Mori et al., 1999; Assaf et al., 2008; Neil, 2008). Therefore, increased FN and decreased FA value of the less affected CST appear to indicate a regenerative activation for compensatory action following brain injury (Kawk et al., 2010). Although the mechanism of activation of the unaffected motor cortex after brain damage has not been fully addressed, disinhibition hypothesis is currently the most acceptable (Netz et al., 1997; Liepert et al., 2000; Manganotti et al., 2002; Duque et al., 2005). Normal motor cortices in both hemispheres are balanced by interhemispheric transcallosal inhibition against each other. However, brain injury in one hemisphere can cause off-balance between two hemispheres due to the decreased power of inhibition from the injured hemisphere. As a result, unaffected motor cortex can be activated more than the balanced state. This hypothesis is believed to be the scientific basis for the recovery mechanism through the ipsilateral motor pathway.

In the comparative analysis according to motor function, the low functioning group showed significantly increased
FN and significantly decreased FA value of the less affected CST than the high functioning group. This finding indicates greater activation of the less affected motor cortex in the low functioning group than in the high functioning group. Although the ipsilateral motor pathway is a momentous motor recovery mechanism, many previous studies in adult stroke patients have reported that patients who had ipsilateral motor pathway recovery showed poor motor (hand) function, and sustained activation of the unaffected hemisphere is related to poor motor function (Tourtou et al., 1996; Jang et al., 2005b; Jang, 2007, 2009b; Netz et al., 1997; Kim et al., 2004; Serrien et al., 2004; Kwon et al., 2007). Other studies in adult stroke patients showed that the ipsilateral motor pathway was less effective compared to other recovery mechanisms such as the recovery of damaged lateral CST or peri-lesional reorganization (Colebatch et al., 1989; Kim et al., 1993; Chen et al., 1997; Jang, 2009a, 2011). Our results are consistent with those of previous studies. We demonstrated the relationship between the state of the less affected CST and motor function. In detail, high contribution from the ipsilateral motor pathway also showed relevance to poor motor (hand) function in pediatric patients with hemiplegia. Therefore, suppression of less affected motor cortex and facilitation of more affected motor cortex could be a scientific rehabilitative strategy for better motor outcome in pediatric patients with hemiplegia.

Regarding pediatric patients with hemiplegia, Wakamoto et al. (2006) performed a study based on seven patients who experienced hemisphericectomy and age matched normal control subjects, indicating no significant change of the unaffected CST. Another DTT study by Thomas el al. (2005) showed significant increase of fiber count of the unaffected corticobulbar tract in five hemiplegic pediatric patients compared with those of age- matched control subjects. However, these studies recruited a small number of heterogeneous patients, and did not evaluate clinical motor function either. Therefore, for more homogeneous recruitment of subjects, we recruited a larger number of subjects and set a narrower range of subject age. In addition, we demonstrated the relationship between motor (hand) function and the contribution of the ipsilateral motor pathway. However, limitations of this study should be considered. First, the onset time of brain lesions such as periventricular leukomalacia and intra-cerebral hemorrhage was unclear. We evaluated patients during the recovery phase, so that recruitment of homogeneous subjects was very important. However, it was impossible to confirm the duration time after onset in cases of perinatal or prenatal injury. Therefore, to reduce bias from heterogeneity of duration time and to maintain homogeneity of the subjects, we recruited the subjects according to the physiologic age of 10–20 months rather than corrected age. DTT is a valuable neural imaging modality which can show false positive and false negative results because of volume effect or crossing fiber (Yamada et al., 2009; Fillard et al., 2011). Further functional MRI and/or TMS guided complementary studies will be required. Finally, other clinical evaluations that may influence motor function such as sensory or cognitive dysfunction were not conducted. Further complementary studies involving more detailed clinical parameters will be warranted.

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