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Corticoreticular tract lesion in children with developmental delay presenting with gait dysfunction and trunk instability

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Abstract
The corticoreticular tract (CRT) is known to be involved in walking and postural control. Using diffusion tensor tractography (DTT), we investigated the relationship between the CRT and gait dysfunction, including trunk instability, in pediatric patients. Thirty patients with delayed development and 15 age-matched, typically-developed (TD) children were recruited. Fifteen patients with gait dysfunction (bilateral trunk instability) were included in the group A, and the other 15 patients with gait dysfunction (unilateral trunk instability) were included in the group B. The Growth Motor Function Classification System, Functional Ambulation Category scale, and Functional Ambulation Category scale were used for measurement of functional state. Fractional anisotropy, apparent diffusion coefficient, fiber number, and tract integrity of the CRT and corticospinal tract were measured. Diffusion parameters or integrity of corticospinal tract were not significantly different in the three study groups. However, CRT results revealed that both CRTs were disrupted in the group A, whereas CRT disruption in the hemispheres contralateral to clinical manifestations was observed in the group B. Fractional anisotropy values and fiber numbers in both CRTs were decreased in the group A than in the group TD. The extents of decreases of fractional anisotropy values and fiber numbers on the ipsilateral side relative to those on the contralateral side were greater in the group B than in the group TD. Functional evaluation data and clinical manifestations were found to show strong correlations with CRT status, rather than with corticospinal tract status. These findings suggest that CRT status appears to be clinically important for gait function and trunk stability in pediatric patients and DTT can help assess CRT status in pediatric patients with gait dysfunction.

Key Words: *nerve regeneration; corticoreticular tract; corticospinal tract; gait; trunk; diffusion tensor; Trunk Control Measurement Scale; Functional Ambulation Category; Growth Motor Function Classification System; cerebral palsy; motor; neural regeneration*

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Introduction
Gait dysfunction is the most frequent motor problem in the pediatric rehabilitation field. The main motor pathways are classified as the corticospinal tract (CST, pyramidal tract) and the non CST (extrapyramidal tract) (Lessek, 1948; de Oliveira-Souza, 2012). The main function of the CST is to control voluntary movements of the distal extremities (Lessek, 1948; Son et al., 2009), and in particular, the CST is known to be critically related to the fine motor activities of the hands (Son et al., 2007; Yeo et al., 2014). Interestingly, there is evidence that stroke patients are able to walk even after complete injury to the lateral CST (Cho et al., 2012), and gait function, which is mainly related to trunk and leg motor function, is less dependent on the CST than hand function (Yeo et al., 2014). Non-CSTs are more involved in gait (Matsuyama et al., 2004; Jang, 2010; de Oliveira-Souza, 2012; Yeo et al., 2014). The cortico-reticulospinal tract, one of the non-CSTs, is known to be important for locomotion control. This tract consists of the cortico-reticular and reticulo-spinal tracts, and sends signals to the spinal cord through the reticulo/vestibule/rubrospinal tracts (Shik and Orlovsky, 1976; Jang, 2010). Furthermore, the cortico-reticulospinal tract is involved in walking and postural control because it regulates proximal and axial muscles (Matsuyama et al., 2004; Yeo et al., 2014).

The corticoreticular tract (CRT) originates from the premotor cortex (PMC), descends through the corona radiata and the posterior limb of the internal capsule anterior to the CST, and passes through the tegmentum in the midbrain to terminate at the pontomedullary reticular formation in the pons (Yeo et al., 2012). Several studies have reported a strong association between PMC injury and gait dysfunc-

tion (Freund and Hummelsheim, 1984, 1985; Freund, 1985; Grafton et al., 1998; Miyai et al., 1999; Schubotz and von Cramon, 2003; Bestmann et al., 2010; Chang et al., 2010; Kantak et al., 2012; Sitaram et al., 2012). As the PMC is the origin site of the CRT, the CRT is suggested to be a primary neural pathway for gait function (Shik and Orlovsky, 1976; Kably and Drew, 1998; Matsuyama et al., 2004; Chang et al., 2010; Jang, 2010). The identification and function of the CRT have been demonstrated in several previous studies in animals and humans (Gloor et al., 1973; Kawamura and Chiba, 1979; Freund, 1985; Kably and Drew, 1998; Miyai et al., 1999; Chang et al., 2010). Recent development of diffusion tensor imaging (DTI) enabled CRT evaluations in the human brain. In fact, detailed quantitative visualized information on specific neural tracts can be obtained by DTI or diffusion tensor tractography (DTT) (Mori et al., 1999; Miller et al., 2002; Naganawa et al., 2004; Malik et al., 2006; Drobyshevsky et al., 2007). Yeo et al. (2012) first reported the identification of the CRT in the human brain, and several studies have described CRT injury in patients with stroke or traumatic brain injury (Jang et al., 2013; Yeo et al., 2013). However, to the best of our knowledge, there is no report on the relationship between CRT status and gait dysfunction in pediatric patients with delayed development.

In the present study, we investigated the relationship between CRT status and gait dysfunction, including trunk instability, in pediatric patients.

Subjects and Methods

Subjects

Thirty patients (21 males and 9 females; overall mean corrected age 24.6 ± 3.6 months; range 20–35 months) and 15 typically developed, age-matched children were recruited for this study. Patients were selected from 234 patients with a chief complaint of developmental delay defined as follows: (1) definite trunk instability and gait dysfunction; (2) no definite abnormal lesions possibly related to clinical symptoms as determined by conventional brain MRI; (3) absence of any diagnosed genetic syndrome or epilepsy; (4) no specific history of brain trauma or surgery; and (5) no definite severe spasticity or contracture requiring orthopedic surgery of distal extremities as determined by and diagnosed by pediatric neurologists.

In this study, 234 patients were recruited initially, 139 children with a definite lesion as confirmed by brain MRI were excluded. Of the remaining 95, 59 children with definite trunk instability and gait dysfunction were originally selected. However, 26 patients with severe spasticity or contracture in a distal extremity, two with genetic syndrome or epilepsy, and one patient with a history of traumatic brain injury were excluded. The remaining 30 subjects were enrolled in this study.

The included patients were divided into two groups based on clinical symptoms. Fifteen patients with bilateral trunk instability were assigned to group A. When these patients were asked to bear their weight, they were not able to sustain proximal stability on either right or left sides. The other 15 patients showed unilateral trunk instability, that is, they showed right or left side instability, and these patients were included in the group B. In addition, 15 age-matched, typically developed children (group TD) were enrolled as controls. The study was available with research funds for control subjects; these children were evaluated and determined to be normal healthy subjects by a pediatric neurologist. All participants in the group TD were volunteers whose parents had applied to participate in the study. Written informed consent was obtained from the parents of all participants from this study, and the study was approved by the institutional review board of Yeungnam University Hospital, Republic of Korea (IRB number: PCR-10-31).

Functional evaluation

Gross motor function level was assessed using the Growth Motor Function Classification System (GMFCS), a widely used five-level classification system (Gorter et al., 2009; El et al., 2012; Rackauskaite et al., 2012; Mayson et al., 2013). Children classified as GMFCS level I or II can walk independently both indoors and outdoors. Children classified as GMFCS levels III, IV or V have limited self-mobilities, which includes sitting or standing abilities (Wood and Rosenbaum, 2000; Palisano et al., 2006; Redekop et al., 2008; Gorter et al., 2009; Rodby-Bousquet and Hagglund, 2010).

Gait function was assessed using the Functional Ambulation Category (FAC) scale (Holden et al., 1984). This well-known scale includes six categories with scores ranging from 0 to 5 (FAC0–FAC5) is used to classify gait function according to degrees of independence in terms of ambulation, transfer, and postural stability. The FAC scale is both reliable and valid and is widely used in the clinical setting (Wade, 1992; Mehrholz et al., 2007).

However, the present study included some patients who could not walk due to severe trunk instability, and the FAC cannot identify the laterality of proximal or trunk instability, and therefore, the Trunk Control Measurement Scale (TCMS) was used to provide a clinical assessment of trunk instability (Heyrman et al., 2011, 2013). The TCMS has been reported to have high validity and reliability in previous studies (ICCs from 0.91 to 0.99) (Heyrman et al., 2011), and a significant correlation has been reported between the TCMS score and GMFCS level in pediatric patients (Heyrman et al., 2013). The TCMS can even be used to evaluate proximal stability in patients unable to stand or walk independently. In the present study, the TCMS was applied under three conditions, that is, during static sitting, dynamic sitting, and dynamic reaching. Laterality of trunk instability was evaluated by assessing lateral right and left sides, which showed which side was more unstable. Functional evaluations of all subjects, including application of the GMFCS, FAC, and TCMS, were performed independently by two pediatric neurologists unaware of mutual results at the time of DTI scanning.

DTI acquisition and analysis

DTI data were acquired using a synergy-L Sensitivity Encoding (SENSE) head coil on a 1.5-T Philips GyroscanIntera system (Hoffmann-La Roche, Best, The Netherlands)

equipped with a 6-channel head coil and a single-shot spin echo planar imaging sequence. Sixty-seven contiguous slices were acquired parallel to the anterior commissure (AC)–posterior commissure (PC) line. Imaging parameters were as follows: matrix = 128 × 128, field of view = 221 mm × 221 mm, echo time = 76 ms, repetition time =10,726 ms, SENSE factor (parallel imaging reduction factor) = 2; echo-planar imaging factor = 67 and b = 1,000 mm^2/s, number of excitations = 1 and thickness = 2.3 mm (acquired isotropic voxel size 2.3 × 2.3 × 2.3 mm^3).

Diffusion-weighted imaging data was analyzed using the Oxford Center for Functional MRI of the Brain (FMRIB) Software Library (FSL; www.fmrib.ox.ac.uk/fsl). Head motion and image distortion due to eddy currents were resolved by affine multi-scale two-dimensional registration. Fiber tracking was performed using a probabilistic tractography method based on a multifiber model utilizing tractography routines implemented in FMRIB diffusion (5,000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2). CSTs and CRTs were identified by selecting fibers passing through regions of interest (ROIs). Briefly, a CST seed ROI was placed on the area of the lower pons on the color map. Target ROIs were located according to known anatomy of the precentral knob and the mediodorsal part of the primary motor cortex for the upper and lower extremities, respectively (Kunimatsu et al., 2004). Fiber tracts passing through the ROIs were designated final tracts of interest. To reconstruct CRTs, a seed ROI was positioned on the reticular formation of the medulla. The first target ROI was positioned on the midbrain tegmentum and the second target ROI on the PMC (Brodmann area 6) (Yeo et al., 2012). Fractional anisotropy (FA), apparent diffusion coefficient (ADC), and fiber number (FN) of the CST and CRT were measured.

Statistical analysis

Data analysis was performed using SPSS 17.0 software (SPSS, Chicago, IL, USA). One-way analysis of variance and the chi-square test were used to compare demographic and functional GMFCS and FAC data between groups. The Kruskal-Wallis test with the *post hoc* Mann-Whitney *U* test was used to analyze TCMS results, and the Wilcoxon's rank test was used to compare right and left side mean TCMS results between groups. The inter-rater intraclass correlation (ICC) value of TCMS between the two pediatric neurologists was 0.998 to 0.999, indicating excellent reproducibility. The independent *t*-test was used to compare right and left side DTI parameters in each group. One-way analysis of variance with Bonferroni's *post hoc* test was used to compare DTI parameters between patients and TD groups. In addition, Pearson's correlation coefficients were used to evaluate statistical correlations between functional data and DTI parameters including FA, ADC, and FN. Statistical significance was accepted for P values < 0.05.

Results

Demographic and functional data

Demographic data for the groups A, B, and TD are provided in **Table 1**. No significant intergroup differences were observed for demographic data, including corrected age, sex, gestational age, or birth weight (P > 0.05).

Table 1 Demographic data of subjects in the three study groups

	Group A (n = 15)	Group B (n = 15)	Group TD (n = 15)	P value
Corrected age (month)	24.5±3.1	24.5±4.2	24.6±2.8	0.994
Sex (n, male/female)	10/5	11/4	8/7	0.507
Gestational age at birth (week)	38.20±1.37	38.73±1.34	39.20±0.78	0.083
Birth weight (kg)	3.17±0.36	3.08±0.302	3.18±0.25	0.595

Values are expressed as the mean ± SD with n = 15 in each group. Group A: Patients with bilateral trunk instability; group B: patients with unilateral trunk instability; group TD: typically developed children.

Significant differences in mean GMFCS, FAC, and TCMS scores were observed between the three groups (P < 0.05). Mean GMFCS level was 3.4 in the group A (bilateral trunk stability), 2 in the group B (unilateral instability), and 1 in the group TD. Mean FAC score was 0.2 in the group A, 1.27 in the group B, and 5 in the group TD. Mean TCMS score was highest in the group TD (27 for the right side/27 for the left side), followed by the group B (12.86 for the less affected side/10.07 for the more affected side), and the lowest in the group A (1.8 for the right side/1.67 for the left side) (P < 0.05). Mean TCMS scores for each category showed the same order (P < 0.05). No significant intragroup differences were observed between the right and left TCMS scores in the groups A and TD (P > 0.05), but in the group B, TCMS scores of more affected sides were significantly lower than those of less affected side (P < 0.05) (**Table 2**).

Diffusion tensor imaging

DTI results for CST

In all three groups, DTT showed preserved integrity of both CSTs (**Figure 1**) and no significant intragroup difference was observed between CST DTI parameters of right and left hemispheres (P > 0.05), and comparative analysis failed to reveal any significant intergroup differences (P > 0.05). Group CST parameters are summarized in **Table 3**.

DTI results for CRT

CRT variables were found to depend on clinical manifestations (**Table 4** and **Figure 1**). In the group B, mean CRT FA and FN values were significantly lower for more affected sides (P < 0.01). Intragroup analysis of right and left side DTI parameters showed no significant difference in any parameter in group A or group TD (P > 0.05). Right and left side CRT ADC values were not significantly different in any group. However, FA values in the group A and those in the other two groups were significantly different (P < 0.01). Similarly, there were significant differences in FN values between group A and the other two groups (P < 0.01), except between group A and the more affected side of group B (P > 0.05). Furthermore, the affected sides of group B had significantly lower FA and FN values than the group TD. No significant difference in

Table 2 Participant function

				P value		
	Group A	Group B	Group TD	A–TD	B–TD	A–B
GMFCS	3.40±0.52	2.00±0.00	1.00±0.00	0.000*	0.000*	0.000*
FAC	0.20±0.41	1.27±0.46	5.00±0.00	0.000*	0.000*	0.000*
TCMS (right - less affected)	1.80±1.21	12.86±1.73	27.00±0.00	0.000*	0.000*	0.000*
TCMS (left - more affected)	1.67±1.18	10.07±1.58	27.00±0.00	0.000*	0.000*	0.000*

Values are expressed as the mean ± SD. *$P < 0.05$. The Kruskal-Wallis test with the *post hoc* Mann-Whitney *U* test was used to analyze TCMS results, and the Wilcoxon's rank test was used to compare right and left side mean TCMS results between groups. GMFCS: Growth Motor Function Classification System; FAC: Functional Ambulation Categories; TCMS: Trunk Control Measurement Scale; group A: patients with bilateral trunk instability; group B: patients with unilateral trunk instability; group TD: typically developed children, R: right side, L: left side.

Table 3 Mean diffusion parameters of CST in the three groups

				P value		
CST	Group A	Group B	Group TD	A–TD	B–TD	A–B
FA						
Right - Less affected	0.454±0.046	0.446±0.028	0.471±0.026	0.583	0.171	1.000
Left - More affected	0.447±0.043	0.454±0.032	0.474±0.042	0.221	0.495	1.000
ADC						
Right - Less affected	0.933±0.069	0.918±0.065	0.911±0.054	1.000	1.000	1.000
Left - More affected	0.954±0.072	0.927±0.039	0.915±0.106	0.553	1.000	1.000
FN						
Right - Less affected	569.27±182.3	537.47±128.7	620.86±255.3	1.000	0.750	1.000
Left - More affected	558.53±175.1	527.20±131.7	635.53±226.7	0.760	0.332	1.000

Values are expressed as the mean ± SD with $n = 15$ in each group. One-way analysis of variance with Bonferroni's *post hoc* test was used to compare DTI parameters between groups A and B and group TD. FA: Fractional anisotropy; ADC: apparent diffusion coefficient; FN: fiber number; CST: corticospinal tract; TD: typically developed. Right - Less affected: right side for groups A and TD - Less affected side for group B; Left - More affected: left side for groups A and TD - more affected side for group B; group A: patients with bilateral trunk instability; group B: patients with unilateral trunk instability; group TD: typically developed children.

Table 4 Mean diffusion parameters of CRT in the three groups

					P value		
CRT	Group A	Group B	Group TD	Less affected-More affected in group B	A–TD	B–TD	A–B
FA							
Right - Less affected	0.394±0.033	0.442±0.037	0.447±0.030	0.000**	0.000**	1.000	0.001**
Left - More affected	0.387±0.042	0.325±0.055	0.458±0.036		0.000**	0.000**	0.002**
ADC							
Right - Less affected	0.964±0.124	0.926±0.124	0.903±0.047	0.998	0.355	1.000	0.993
Left - More affected	0.980±0.194	0.940±0.075	0.895±0.050		0.172	0.949	1.000
FN							
Right - Less affected	75.47±29.14	364.73±112.5	529.86±270.6	0.002**	0.000**	0.054	0.000**
Left - More affected	84.66±36.0	128.33±57.8	561.73±256.0		0.000**	0.000**	1.000

Values are expressed as the mean ± SD with $n = 15$ in each group. FA: Fractional anisotropy; ADC: apparent diffusion coefficient; FN: fiber number; CRT: corticoreticular tract; TD: typically developed. Right - Less affected: right side for groups A and TD - Less affected side for group B; Left - More affected: left side for groups A and TD - more affected side for group B. For the comparison of DTI parameters between less affected and more affected sides in the group B, the independent *t*-test was used, and for the comparison between groups A and B and group TD, one-way analysis of variance with Bonferroni's *post hoc* test was used (**$P < 0.01$). Group A: Patients with bilateral trunk instability; group B: patients with unilateral trunk instability; group TD: typically developed children.

CRT ADC values was found between groups ($P > 0.05$).

Correlation between DTI parameters and functional data

Results of correlation analyses performed between diffusion parameters and functional GMFCS, FAC, and TCMS data are shown in **Table 5**. All CRT parameters, except ADC, showed significant correlations with functional data ($P < 0.05$). In particular, FN values showed an extremely strong positive correlation with FAC scores and less affected side TCMS scores (R: Pearson correlation coefficients ≥ 0.7), and moderate negative correlations with GMFCS scores ($R =$

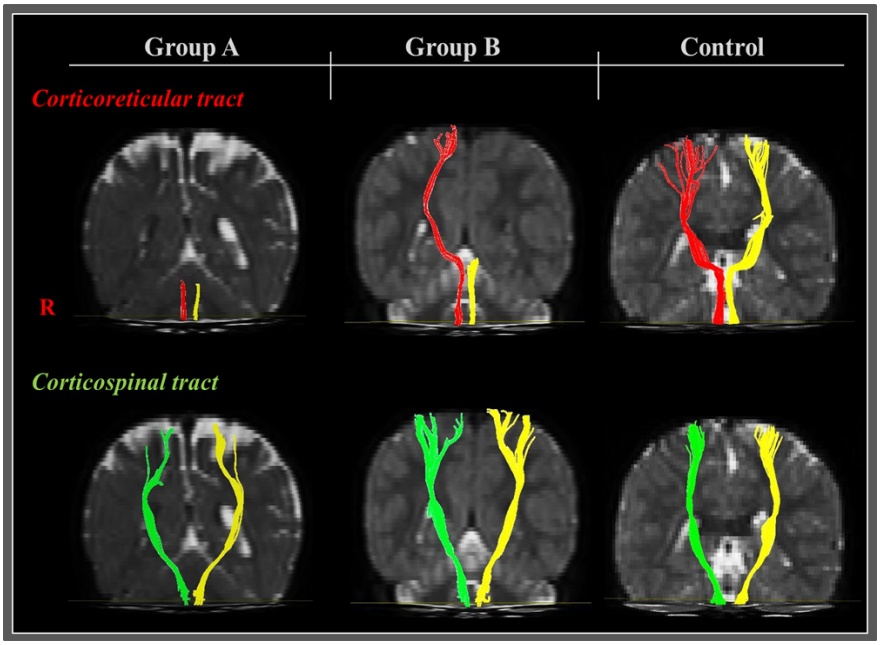

Figure 1 Diffusion tensor tractography results for the corticospinal and corticoreticular tracts of the participants.
All three study groups show patent corticospinal tracts in both hemispheres. Corticoreticular tracts in the group A were disrupted bilaterally at the brainstem level; whereas unilateral disruption was observed in the group B. Corticoreticular tracts in the group TD were normal. Group A: Patients with bilateral trunk instability; group B: patients with unilateral trunk instability; group TD: typically developed children; red color: right or less affected corticoreticular tract; green color: right or less affected corticospinal tract; yellow color: left or affected corticoreticular tract/left or affected corticospinal tract.

Table 5 Pearson's correlation coefficients between functional data and diffusion parameters of CST and CRT

	GMFCS	FAC	Less affected side of TCMS	More affected side of TCMS
CST				
FA	–0.219	0.184	0.226	0.070
ADC	0.124	–0.226	–0.136	0.044
FN	–0.247*	0.151	0.126	0.170
CRT				
FA	–0.410**	0.491**	0.503**	0.642**
ADC	–0.109	–0.012	–0.207	0.001
FN	–0.405**	0.879**	0.700**	0.339*

Pearson's correlation coefficients were used to evaluate statistical relationship between functional data and DTI parameters. *P < 0.05, **P < 0.01. CST: Corticospinal tract; CRT: corticoreticular tract; GMFCS: Growth Motor Function Classification System; FAC: Functional Ambulation Categories; TCMS: Trunk Control Measurement Scale; FA: fractional anisotropy; ADC: apparent diffusion coefficient; FN: fiber number.

–0.405, P < 0.01) and more affected side TCMS scores (R = 0.339, P < 0.05). FA values showed a moderate correlation with all functional data; GMFCS (R = –0.410, P < 0.01), FAC (R = 0.491, P < 0.01), and TCMS (R = 0.503 for less affected sides and 0.642 for more affected sides, P < 0.01). However, similar correlation analysis of CST parameters only showed TV values were mildly correlated with GMFCS scores (R = –0.247, P < 0.05).

Discussion

Results from this study showed that the clinical manifestations of patients with trunk instability were significantly related to CRT status as determined by DTI. We believe that gait dysfunction and trunk instability in our patients were related to CRT status for the following reasons.

First, CRTs in the groups A and B had significantly lower FA and FN values than those in the group TD. Injured white matter tracts have been reported to have different diffusion characteristics, usually lower FA and FN values (Song et al., 2002; Son et al., 2007, 2009). Furthermore, decreased FA values are related to the disruption of directional structures, such as, axonal microfilaments and myelin sheaths (Liu et al., 2007; Seme-Ciglenecki, 2007; Assaf and Pasternak, 2008; Hong et al., 2010). Therefore, the significantly reduced FA and FN values of CRTs observed in our patients suggest CRT disruption. In addition, these results are in accordance with clinical manifestations, in particular, the group A (bilateral trunk instability) showed significantly lower FA and FN values of both CRTs than the group TD, and the group B (unilateral trunk instability) showed significantly lower FA and FN values for only CRTs contralateral to clinical manifestations than the group TD.

Second, DTT showed disruption of both CRTs in the group A and disruption of only unilateral CRTs in the group B. Yeo and colleagues reported that improvements of proximal and axial motor weakness were related to recovery of an injured CRT in a patient with intracerebral hemorrhage (Yeo and Jang, 2013) and suggested that proximal weakness is due mainly to CRT injury, rather than CST injury, in patients with traumatic brain injury (Yeo et al., 2013). Similarly, in the present study, assessments of CRT integrity were found to be compatible with clinical manifestations. This agreement implies an association between CRT status and clinical findings.

Third, diffusion parameters (FA and FN) of CRTs were significantly correlated with all functional data, including GMFCS, FAC, and TCMS scores, which provide measures of trunk stability or gait function. In addition, in the present study, these functional parameters had high validities and reliabilities, and our results were consistent with clinical manifestations. However, only for CSTs, we only detected a minimal significant correlation between FN values and GM-

FCS scores.

Finally, despite definite differences between clinical manifestations, no significant CST differences in FA, ADC, or FN were observed between patients and healthy controls. A few previous studies have reported nonsignificant correlations between CST status and gait function. Hoon et al. (2009) reported no significant correlation between CST injury and gait function in 21 pediatric patients, and during the study they found no significant correlation between quantitative measures of sensation or strength and CST injury. Furthermore, in another DTT study on the characteristics of CST injury, 56% of stroke patients with complete CST injury were able to walk independently despite complete CST injury (Cho et al., 2012). These previous studies demonstrate the clinical importance of the CRT rather than the CST with respect to gait function, and their findings concur with our results.

In conclusion, we investigated relationship between CRT parameters and gait dysfunction, including trunk stability, in pediatric patients. Comparative analysis of DTT data revealed a significant association between the DTI determined characteristics of CRT lesions and trunk instability laterality and gait dysfunction in pediatric patients. These results suggest that the CRT has an important role in gait function and that DTT is likely helpful for assessing CRT status in pediatric patients with gait dysfunction and trunk instability. To the best of our knowledge, this is the first study to demonstrate the radiologic difference of the CRT by DTT in pediatric patients with trunk instability. However, the present study is limited by the small number of subjects enrolled due to the application of strict inclusion criteria. In addition, detailed clinical data regarding cognitive function or sensory function, which can influence motor performance indirectly, could not be obtained (Floel et al., 2004; Landau and Wetzel, 2005; Pichierri et al., 2011; Mizuguchi et al., 2012). Because of the age of our subjects, full examinations of visual acuity, whole electromyography/nerve conduction examinations (to rule out the possibility of an abnormal peripheral nervous system), and MRI examinations of the spinal cord could not be performed in all participants. Thus, we suggest additional complementary larger-scale studies with detailed clinical assessments be undertaken.

Author contributions: *SMS and JR designed this study. YMK and ARK performed the experiments. SMS and YMK wrote the paper. All authors approved the final version of this paper.*
Conflicts of interest: *The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.*
Research ethics: *Written informed consent was obtained from the parents of all participants from this study, and the study was approved by the institutional review board of Yeungnam University Hospital, Republic of Korea (IRB number: PCR-10-31) and performed in accordance with the guidelines of the Declaration of Helsinki.*
Declaration of participant consent: *The authors certify that they have obtained all appropriate participant consent forms. In the form the participants have given their consent for their images and other clinical information to be reported in the journal. The particiants understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*
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