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Diffusion Tensor Imaging–Demonstrated Differences between Hemiplegic and Diplegic Cerebral Palsy with Symmetric Periventricular Leukomalacia

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ABSTRACT

BACKGROUND AND PURPOSE: Patients with cerebral palsy have variable clinical presentations such as hemiplegic, diplegic, or quadriplegic patterns though they have PVL on conventional MR images. The authors investigated whether DTT can differentiate between hemiplegic and diplegic CP in patients presenting with symmetric PVL on conventional MR images.

MATERIALS AND METHODS: One hundred thirteen consecutive pediatric patients with definite hemiplegic (59 patients; 30 boys, 29 girls; mean age, 34.19 months; range, 24–52 months) or diplegic (54 patients; 27 boys, 27 girls; mean age, 31.07 months; range, 24–48 months) symptoms and bilateral symmetric PVL on conventional brain MR imaging were recruited. The states of CSTs were examined by using DTT, and the asymmetries of right and left CSTs in the hemiplegic and diplegic groups were compared by using asymmetric anisotropy indexes and asymmetric mean diffusivity indexes.

RESULTS: All patients in the hemiplegic group with asymmetric results exhibited disrupted integrities of more affected CSTs and sparing of less affected CSTs. However, diplegic patients revealed symmetric disrupted findings of the right and left CSTs at the upper periventricular level. Asymmetric anisotropy index and asymmetric mean diffusivity index values were significantly higher in the hemiplegic group than in the diplegic group ($P < .05$), and these results of DTT significantly corresponded with their typical clinical manifestation.

CONCLUSIONS: DTT may be very useful for the detailed estimation of the CST state in patients with bilateral symmetric PVL.

ABBREVIATIONS: CP = cerebral palsy; CST = corticospinal tracts; DTT = diffusion tensor tractography; FA = fractional anisotropy; PVL = periventricular leukomalacia

PVL is the common cause of chronic motor disability in preterm-born children. The vascular susceptibility of periventricular WM between 24 and 34 weeks of gestation is known to be related to PVL lesion formation.[1,2] CST injury due to PVL may lead to spastic diplegic, quadriplegic, or hemiplegic CP.[3-5] Patients with PVL can have variable clinical presentations of abnormal tone and movement patterns, and these clinical problems may be associated with the extent of white matter damage due to PVL.[6,7] Clarification of the states of neural tracts in patients with PVL is important in terms of elucidating the causes of neurologic deficits, the setting of scientific rehabilitative strategies, and the prediction of prognoses. Some authors have demonstrated PVL by using methods, such as brain CT, brain MR imaging, cranial ultrasonography, and biologic and neuropsychologic methods. However, these evaluation tools are limited in that they do not allow the direct estimation or visualization of neural tracts; therefore, determination of the presence and extent of neural injury has been limited.[8-13]

DTI is a recently introduced technique that allows the integrities of WM tracts to be estimated by virtue of its ability to visualize the diffusion characteristics of water. DTT is a 3D visualized version of DTI and thus provides concrete descriptions of the architecture and integrity of the CST.[14-17] Several previous studies have demonstrated that DTI provides a powerful means of detecting white matter lesions and evaluating the states of neural tracts.[6,7,18-24] In the current study, we sought to determine whether DTT can differentiate between hemiplegic and diplegic CP in patients who display symmetric PVL on conventional MR imaging.

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Comparison of hemiplegic and diplegic groups

	Hemiplegia (n = 59)	Diplegia (n = 54)	P Value
GA at birth (wk)	31.31 ± 1.80	30.91 ± 2.08	.61
Age at exam (mo)	34.19 ± 8.59	31.07 ± 6.34	.38
Male	30	27	.55
PROM[a]	47	44	.30
PIH[b]	18	12	.17
Placenta problem	18	15	.88
ROP	32	29	.12
Heart problem	31	27	.12
GMFCS	2.74 ± 0.93	3.14 ± 0.77	.09
AA	46.78	8.21	.00
AD	20.14	6.72	.00

Note:—PROM indicates prolonged rupture of membranes; ROP, retinopathy of prematurity; PIH, pregnancy-induced hypertension; AA, asymmetric anistropy index; AD, asymmetric mean diffusivity index; GA, gestational age; GMFCS; Gross Motor Function Classification System.

[a] Defined as rupture for ≥18 hours.

[b] Defined as a systolic blood pressure of >140 mm Hg and a diastolic blood pressure of >90 mm Hg plus proteinuria with or without edema.

MATERIALS AND METHODS

Patients

One hundred thirteen consecutive pediatric patients were recruited according to the following criteria: 1) evaluation by 2 pediatric neurologists and diagnosis with definite hemiplegic (59 patients) or diplegic (54 patients) symptoms, 2) bilateral symmetric focal PVL by conventional brain MR imaging confirmed by a pediatric neuroradiologist, 3) gestational age of <34 weeks at birth, 4) the absence of any diagnosed genetic syndrome or severe mental retardation, 5) no history of trauma or brain operation, and 6) the same diagnosis 1 year after the first physical and radiologic evaluations. The study population was selected from 175 hemiplegic and 192 diplegic patients who visited the department of pediatrics or the department of physical medicine and rehabilitation. Two pediatric neurologists assessed the patients independently, and all patients were evaluated by both neurologists. The 4 participants whose diagnosis was in disagreement between 2 neurologists were excluded. One hundred twenty-five hemiplegic patients and 133 diplegic patients who were born before 34 weeks' gestational age were originally selected. However, 8 hemiplegic and 6 diplegic patients were excluded due to a brain operation or trauma history, and another 12 hemiplegic and 19 diplegic patients were excluded due to a diagnosis of severe mental retardation. Two hemiplegic patients and 1 diplegic patient were also excluded because clinical diagnoses were changed at follow-up evaluations. Of the remaining subjects, 59 hemiplegic and 54 diplegic patients with symmetric PVL on conventional MR images were eligible. MR imaging findings were interpreted by a pediatric neuroradiologist unaware of clinical information. The pediatric neurologists were also unaware of MR imaging findings. Medical charts were reviewed for frequent risk factors in preterm infants (Table). Informed consent was obtained from the parents of all participants, and the study was approved by the institutional review board at our hospital.

Gross Motor Function

To evaluate clinical gross motor function, the Gross Motor Function Classification System was used (Table). The Gross Motor Function Classification System is a 5-level scale that classifies gross motor function according to the degree of independence in ambulation, transfer and postural stability, and the need for mobility devices. It is a reliable and valid method for classifying function among children with CP and is widely used in the clinical setting.[25-27] Children who are classified in Gross Motor Function Classification System levels I and II have the potential to walk independently both indoors and outdoors and in the community as well. In contrast, children classified in Gross Motor Function Classification System levels III-V are limited in their self-mobility. They walk with a mobility device and are potential wheelchair users.[25,28]

DTI Acquisitions and Analysis

DTI data were acquired by using a 1.5T Gyroscan Intera system (Philips Healthcare, Best, the Netherlands) equipped with a sensitivity encoding head coil by using a single-shot spin-echo-planar imaging sequence. For each of the 32 noncollinear and noncoplanar diffusion-sensitizing gradients, we acquired 60 contiguous sections parallel to the anterior/posterior commissure line. Imaging parameters were matrix = 128 × 128 matrix, FOV = 221 × 221 mm^2, TE = 76 ms, TR = 10,726 ms, sensitivity encoding factor = 2, EPI factor = 67, b = 1000 mm^2 s^{-1}, NEX = 1, and section thickness = 2.3 mm.

The Oxford Centre for Functional Magnetic Resonance Imaging of Brain software (www.fmrib.ox.ac.uk/fsl) was used to preprocess DTI datasets. Eddy current–induced image distortions and motion artifacts were removed by using affine multiscale 2D registration. DTIStudio software (Center for Magnetic Resonance Microimaging; Johns Hopkins University, Baltimore, Maryland) was used for CST evaluations. Fiber tracking was performed by using the fiber assignment continuous tracking algorithm, a brute-force reconstruction approach, and a multiple-ROIs approach. A seed region of interest was drawn on the CST region in the anterior midpons on a number of the 2D FA color maps of each patient. A target region of interest was drawn on the CST portion of the anterior lower pons. Fiber tracts passing through both ROIs were designated as the final tracts of interest. The termination criteria used for fiber tracking included an FA of <0.2 and an angle change of >45°.[29] We evaluated diffusion tensor tractography by using mean FAs and mean ADCs of entire CSTs. Age at the time of brain MR imaging was adjusted on the basis of corrected age for prematurity—that is, by subtracting weeks born prematurely from postbirth age.

The DTI data of each subject were analyzed by 2 authors (S.H.J. and Y.H.K.) and were included as DTT data when the results of each analyzer were the same. All the results were the same, and all the data of the 113 subjects recruited in this study were included as the DTT data. To measure the interobserver and intraobserver variation, the DTT analysis was performed randomly by 2 authors (H.K.C. and S.M.S.) who were blinded to clinical diagnosis. Each author analyzed the data of each patient twice randomly with a 1-week interval between examinations. The consistent rate of the interobserver analysis was 98%. The 2 observations made by each analyzer were the same for 110 of 113 patients. This finding shows a high rate of reproducibility. Therefore, this technique is reliable for evaluating the integrity of CSTs in patients with periventricular leukomalacia.

Statistical Analysis

Statistical analysis was performed in 2 steps. In the first step, Pearson χ^2 and Fisher exact tests were used to compare the demographic characteristics and the prenatal and perinatal medical histories of the hemiplegic and diplegic groups. In the second step, we assessed the significance of asymmetric differences in the hemiplegic and diplegic groups. Degrees of asymmetry between the right and left CSTs were obtained by dividing the absolute difference between the means of the 2 sides by the means of the 2 sides. Relative asymmetry values were calculated by using the following equation: [(Value of the More Affected Hemisphere − Value of the Less Affected Hemisphere)/(Value of the More Affected Hemisphere + Value of the Less Affected Hemisphere)/2) × 100], and these were calculated for both asymmetric anisotropy indexes and asymmetric mean diffusivity indexes of the CSTs in the hemiplegic and diplegic groups. A paired *t* test was used to compare the asymmetric anisotropy index and asymmetric mean diffusivity index of the 2 groups. Statistical significance was accepted for *P* values of $< .05$, and the analysis was performed by using the Statistical Package for the Social Sciences, Version 18.0 (SPSS, Chicago, Illinois).

RESULTS

Perinatal Factors and Gross Motor Function Classification

The 59 hemiplegic patients had a median gestational age of 31.31 ± 1.80 weeks (range, 27–34 weeks) and a median age at DTI scanning of 34.19 ± 8.59 months (range, 24–52 months), whereas the 54 diplegic patients with CP had a median gestational age of 30.91 ± 2.08 weeks (range, 25–34 weeks) and a median age at DTI scanning of 31.07 ± 6.34 months (range, 24–48 months). Perinatal complications in the hemiplegic and diplegic groups are indicated in the Table. In particular, prolonged rupture of membranes was the most frequent perinatal complication in both groups (hemiplegic, $n = 47$; and diplegic, $n = 44$). The frequencies of perinatal factors—that is, of male sex, prolonged rupture of membranes, pregnancy-induced hypertension, placenta problem, retinopathy of prematurity, and heart problem—did not differ significantly in the 2 groups. The comparative data of the Gross Motor Function Classification System levels were statistically insignificant.

DTI and Relative Asymmetry Values

The DTT results of all patients in the hemiplegic group revealed asymmetric findings between more affected and less affected CSTs. The more affected side revealed disrupted integrity of the CST, but less affected fiber tracts through the known CST pathway and integrity was preserved to the cortex level. By contrast, all patients in the diplegic group showed symmetric disrupted DTT results at the upper periventricular level for both CSTs (Fig 1). Additionally, FA asymmetry and ADC differences between both CSTs were more noticeable in the hemiplegic group, and the mean asymmetric anisotropy index was higher in the hemiplegic group (46.78 versus 8.21). Furthermore, a significant difference was observed between the asymmetric mean diffusivity index values of CSTs in both groups (20.14 for the hemiplegic group and 6.72 for the diplegic group, $P = .00$ for both).

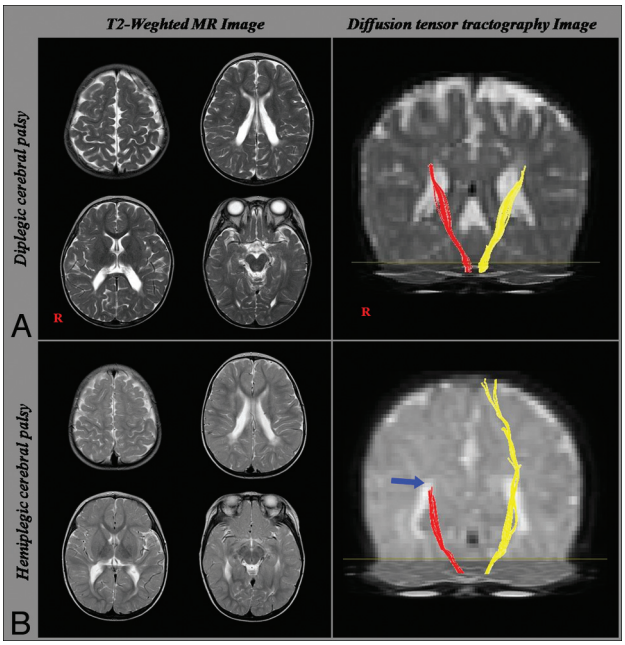

FIG 1. Results of conventional MR imaging and DTT. *A*, Conventional MR images show symmetric PVL in the hemiplegic and diplegic study groups. *B*, DTT results of CSTs (right, red). Patients with diplegic cerebral palsy were found to be associated with symmetrically disrupted CSTs at the PVL level. On the other hand, hemiplegic cerebral palsy revealed disruption of the more affected CST at the PVL level and sparing of the less affected CST through the cortex.

DISCUSSION

The current study demonstrates that DTT can detect asymmetry in hemiplegic CP, even when conventional MR imaging reveals just symmetric PVL lesions.

Preterm infants with PVL usually present with major neurodevelopmental problems and achieve variable motor outcomes, which include diplegia, quadriplegia, hemiplegia, or an extrapyramidal pattern. Previous studies have advocated assessing physical functional status and motor skills in preterm infants with PVL.[3-5,30] However, the accurate diagnosis of pediatric patients is often difficult, and some confusion about clinical type exists, though an accurate diagnosis is essential for predicting outcomes and for setting rehabilitative management strategies. In the current study, clinical diagnoses were changed at evaluations conducted 1 year after the first assessments in 3 patients. Similarly, in our previous study conducted in 2009, 2 infants who initially showed delayed development and not a hemiplegic pattern displayed definite hemiplegic symptoms during follow-up.[31] Although a hemiplegic pattern was not evident at the initial visit in these 2 patients, DTT at initial visits revealed a unilateral discontinuity, and these findings coincided with evident clinical hemiplegia at follow-up. This diagnostic confusion may have been caused by poor functional capacities and poor compliance during the physical examination in the young patients with CP and may have adversely affected treatment and prognosis; this problem suggests that radiologic evaluations can be used additionally to provide a more detailed understanding of young patients with CP.

Recent DTI studies have investigated the microstructural state of white matter in children with PVL with various neurologic deficits in attempts to reveal the micropathologic conditions of

neural tracts beyond the macrostructural abnormalities of sulcation and gyration.[6,7,23,24,32] In 2005, a DTI study was performed on 5 spastic hemiplegic patients with CP who showed unilateral periventricular white matter injury on conventional MR images. DTI results demonstrated that the affected CSTs of patients exhibited significantly reduced FA values and an increased mean diffusivity compared with unaffected CSTs.[23] Another study on 24 patients with CP and PVL found that patients had variable white matter injury patterns, and the authors concluded that DTI is potentially a more sensitive diagnostic tool than conventional MR imaging.[24]

Another recent study of patients with spastic diplegic CP with diffuse periventricular leukomalacia showed significantly decreased FA values of major white matter tracts compared with healthy control subjects.[7] These previous results correspond to our results. In the current study, all patients had symmetric PVL by conventional MR imaging, but DTI revealed decreased FA and increased ADC values of CSTs associated with their clinical conditions. In addition, we used asymmetric values such as asymmetric anisotropy index and asymmetric mean diffusivity index to investigate degrees of asymmetry between the right and left CSTs. Another study conducted in 2007 investigated asymmetric properties in hemiplegic CP and found that asymmetric anisotropy index and asymmetric mean diffusivity index values were higher in hemiplegic patients than in age-matched controls[14]; their findings correspond to our results. Originally, we believed that relative asymmetric values provide a more appropriate means of revealing differences between right and left CSTs than FA or ADC values because patients of the same age exhibit growth and developmental differences. The present study verifies the existence of significantly different pathophysiologies in hemiplegic and diplegic patients with CP based on relative asymmetry values.

In the present study, obviously different patients with CP followed up by pediatric neurologists for >1 year were recruited, and these patients were then divided into 2 groups based on confirmed clinical diagnoses. The results of this DTI study demonstrate detailed differences between hemiplegic and diplegic CP, despite the presence of symmetric PVL lesions on conventional MR images.

CONCLUSIONS

DTT was found to be very useful for precise determinations of the presence and severity of CST injury in patients with bilateral symmetric focal PVL. Furthermore, the current study confirms that DTT depicts noticeable asymmetry in hemiplegic CP. As far as we know, no previous study using DTT has reported on the pathophysiologies of clinically different symptoms in hemiplegic and diplegic patients with CP with bilateral symmetric PVL on MR images. These results have important implications for the early diagnosis, prognosis, and rehabilitation of preterm infants with PVL.

However, the study was limited by patient numbers and a lack of detailed clinical data. Also, the young age of subjects can be another limitation because their brain diffusivity has strong time dependence due to rapidly ongoing myelination.[33] Because the subjects were so young, the full examination for visual acuity, whole electromyograph/nerve conduction velocity examinations to rule out the possibility of an abnormal peripheral nerve system, and an MR imaging examination of the spinal cord could not performed in all participants. Therefore, further complementary studies involving larger case numbers and more detailed clinical parameters are warranted.

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