Diffusion-tensor magnetic resonance imaging in children with language impairment

Jinna Kim[a], Yong Wook Kim[b], Chang-il Park[b], Eun Sook Park[b], Hyang-Hee Kim[b], Seung-Koo Lee[a] and Dong Ik Kim[a]

[a]Department of Radiology and Research Institute of Radiological Science and [b]Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, Seoul, Korea

Correspondence and requests for reprints to Dr Yong Wook Kim, MD, Department and Research Institute of Rehabilitation Medicine, Yonsei University College of Medicine, 134 Shinchondong, Seodaemungu, Seoul 120-752, Korea
Tel: +82 2 2228 3716; fax: +82 2 363 2795; e-mail: ywkim1@yumc.yonsei.ac.kr

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We evaluated the integrity of the white matter tract using diffusion-tensor magnetic resonance imaging in children with language impairments who exhibited a structurally normal brain on conventional magnetic resonance imaging, and compared it with age-matched normal children. After generating fractional anisotropy and color-coded vector maps, fractional anisotropy values of the major white matter tracts were measured in six locations and compared between the two groups. Compared with the normal control group, the fractional anisotropy values of children with language impairments showed a statistically significant reduction in the genu of the corpus callosum, which is rarely revealed on conventional magnetic resonance images. Our results suggest that delayed maturation of the white matter plays a partial role in the pathophysiological mechanisms of language impairments. *NeuroReport* 17:1279–1282 © 2006 Lippincott Williams & Wilkins.

Keywords: children, diffusion tensor imaging, language impairment

Introduction

Language impairment (LI), a common developmental difficulty in childhood, refers to inadequate language acquisition at the expected age in children with otherwise ostensibly normal development [1,2]. LI encompasses deficits in comprehension, expression, and use of language that is not in keeping with a child's mental age, usually accompanied by normal or near-normal nonverbal cognitive skills. While the prevalence of LI varies from 1 to 15% depending on inclusion criteria, it is thought that, on average, approximately 6% of children may have LI [3].

For several decades, research has mainly focused on the language-specific nature of LI, particularly on lexical semantics or morphosyntax [4]. These studies suggest that the language learning system is intact in LI, showing that the language performance of younger children with LI is similar to that of age-matched control children. As a result of the recent development in advanced magnetic resonance (MR) technology, various neuroimaging studies have reported structural brain abnormalities in children with LI to date [1,5–8]. Although some quantitative morphometric analyses of MR images suggested subtle structural abnormalities of the specific brain regions, most children presenting the mildest form of LI have normal brain MR imaging findings.

The recently introduced diffusion tensor imaging (DTI) has the powerful ability to demonstrate altered white matter fiber integrity, and its clinical feasibility has been proven in the evaluation of various brain pathologies such as stroke, tumor, diffuse axonal injury, and congenital migration anomalies [9–11]. Many studies with DTI revealed that so-called 'normal appearing white matter' on conventional MR imaging shows altered white matter integrity with a low fractional anisotropy (FA) value compared with normal white matter. The aim of this study was to use DTI to demonstrate FA changes in the white matter tract of children with LI prior to structural alteration, and to evaluate the utility of DTI for assessment of children with LI.

Materials and methods

Selection of study participants and controls

Seven pediatric patients with LI were prospectively evaluated by DTI. The study participants consisted of five boys and two girls, with ages ranging from 30 to 79 months (mean age, 46 months). Children with abnormal birth history or delayed developmental milestones (i.e. head control, turning, sitting, crawling, standing, and walking) were excluded. Seven age-matched, normal controls showing normal developmental milestones were recruited from among patients who received an MR examination for simple febrile convulsions (n=3) or headaches (n=4). None of the patients in this study had discernible brain abnormalities

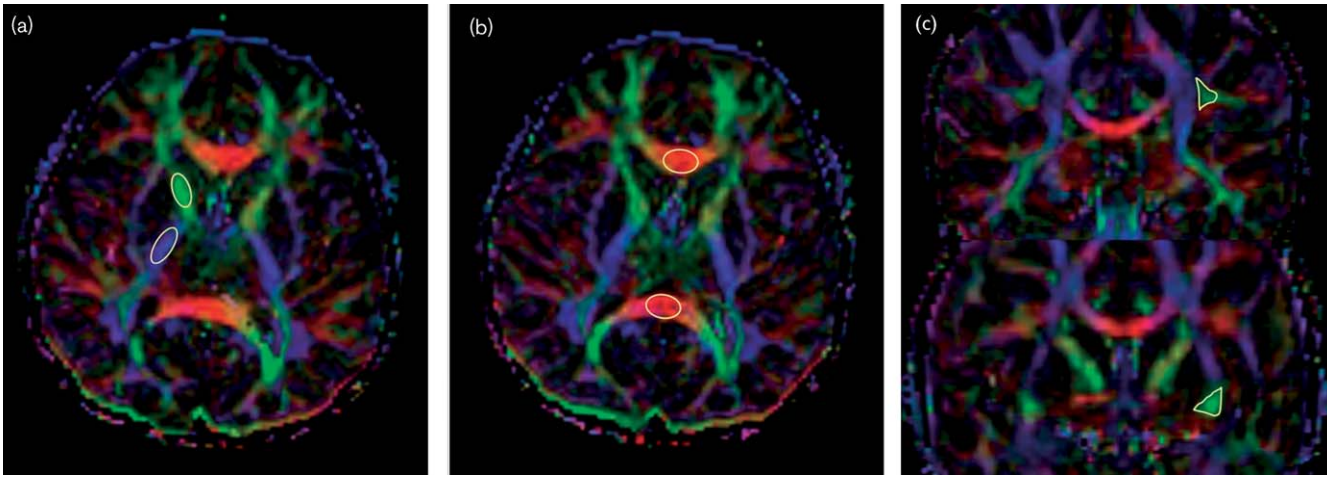

Fig. 1 Region of interest (ROI) location for diffusion tensor magnetic resonance imaging of the major white matter tracts. Fractional anisotropy (FA) values of the internal capsule were measured in a ROI located on anterior and posterior limbs on axial color maps (a). FA values of corpus callosum were also measured in a ROI located on the genu and splenium on axial color maps (b). The superior and inferior longitudinal fasciculi are generated from a single ROI on coronal color maps (c).

upon conventional T2-weighted MR imaging. Informed consent was received from all the participant's parents or legal guardians, and all procedures were performed with the approval of the Institutional Review Board for Clinical Studies.

The diagnosis of LI in the children was done by a speech pathologist using the SELSI (Sequenced Language Scale for Infants) [12] or PRES (Preschool Receptive Expressive Language Scale) [13] linguistic tests. SELSI is a test designed to evaluate children aged between 0 and 3 years and PRES is for 2- to 6-year-olds. A child was diagnosed as having LI if they manifested a combined language age (CLA) of 2 standard deviations lower than the mean score at SELSI. CLA indicated the mean value of both receptive and expressive language ages. In PRES, if the difference between the chronological age and CLA was more than 2 years, a child was diagnosed as having LI. None of the children exhibited any abnormal articulation, deviant speech mechanism, hearing impairment, or fluency disorders.

Magnetic resonance data acquisition

DTI was performed using a 1.5-T system (Intera; Philips Medical Systems, Best, The Netherlands) with a six-channel sensitivity encoding (SENSE) head coil. Diffusion-weighted imaging was performed using single-shot spin-echo echo-planar imaging and navigator echo phase correction (motion correction), and a SENSE factor of 2. The imaging sections were positioned to make the section perpendicular to the anterior commissure–posterior commissure line. DTI parameters were as follows: a data matrix of 96 over a 22-cm field of view, zero-filled to 128 matrices, 2.3-mm section thickness without a gap, TE=70 ms, TR=6599–8280 ms, SENSE factor=2; number of acquisitions=2, b=600 s/mm^2 with 32 directions, and a total imaging time of less than 10 min.

Data processing and statistical analysis

The data was processed on a PC equipped with the Philips Research Image-processing Development Environment (PRIDE) software package (Philips Medical Systems), based on the Fiber Assignment by Continuous Tracking method described by Mori *et al.* [14]. Anisotropy was calculated by orientation-independent FA, and DTI-based color maps were created from the FA values and the three vector elements. The vector maps were assigned to red (x element, left–right), green (y, anterior–posterior), and blue (z, superior–inferior) with a proportional intensity scale according to the FA. FA values were measured in the major white matter tracts, including projection, commissural and association fibers. On the basis of the previously published fiber tract-based atlas of human white matter anatomy [15], the region of interest (ROI) on the color maps was applied in the following six locations: the genu and splenium of the corpus callosum, the anterior and posterior limbs of the internal capsule, and the superior and inferior longitudinal fasciculi (bilaterally). The ROIs were placed according to the anatomical delineation of the structure of interest, and the plane of the ROI was varied according to the running direction of the white matter fibers (e.g. internal capsule and corpus callosum on the axial views, superior and inferior longitudinal fasciculi on the coronal views) (Fig. 1). The procedures were each repeated three times by two experienced neuroradiologists (J.K. and S.K.L.), and the results were averaged. Using a two-tailed paired t-test, the average FA values for children with LI were compared with those for healthy children, and a P value of less than 0.05 was considered statistically significant.

Results

Table 1 shows a summary of the FA values derived from DTI in the children with LI and the controls. Mean measurements of FA values and standard deviations are given for each white matter structure that was assessed. Results for the right and left cerebral hemispheres were averaged.

The children with LI showed mean FA values of 0.5145 ± 0.0741 in all six white matter tracts and normal children showed mean FA values of 0.5244 ± 0.0717. Between the two groups, there was no significant difference of FA values in the semi-quantitative analysis of the major

Table 1 Anisotropy measurements in children with and without language impairment (LI)

Region of measurement	Children with LI (n=7)	Children without LI (n=7)	P value
Anterior limb of internal capsule	0.4759±0.0276	0.5018±0.0329	>0.05
Posterior limb of internal capsule	0.5394±0.0080	0.5390±0.0086	>0.05
Genu of corpus callosum	0.5674±0.0117	0.5893±0.0142	<0.01
Splenium of corpus callosum	0.6226±0.0140	0.6194±0.0064	>0.05
Superior longitudinal fasciculus	0.4422±0.0226	0.4403±0.0233	>0.05
Inferior longitudinal fasciculus	0.4392±0.0251	0.4563±0.0385	>0.05

white matter fiber tracts, except in the genu of the corpus callosum. In the children with LI, the average FA value in the genu of the corpus callosum was 0.5674±0.0117, which was significantly reduced compared with the FA values of the age-matched normal controls (0.5893±0.0142) (two-tailed paired t-test, P=0.0085).

Discussion

DTI is an emerging noninvasive modality that is often used in research and applied to the study of white matter fiber tracts. DTI is also a powerful modality that yields information about the developing brain, based on the fact that normal brain maturation and myelination result in reduced water diffusion and increased diffusion anisotropy [16,17]. The decreased anisotropy in DTI has been thought to be related to complex interrelated processes of white matter maturation, such as hypomyelination, decreased numbers of normal neurons, decreases in axonal diameter, or decreased synaptic density [18–20]. Although further neuropathological studies of a broader range of developmental disorders are necessary to clarify these issues, alterations in anisotropy in white matter fiber tracts may be sensitive markers of previous white matter injury or other disruptions in children's brains. Like a recent DTI study in children with developmental delays [18], the DTI findings in this study show a decrease in FA value in some major white matter pathways, and might reflect faint structural changes in the brain, which cannot be identified by conventional MR imaging.

The recent development of advanced MR technology enables one to perform large numbers of in-vivo imaging studies on brain anatomy in children with LI. Some quantitative morphometric analyses of MR images have suggested subtle structural abnormalities such as ventricular enlargement, central volume loss, and focal cortical/subcortical white matter abnormalities, especially in the planum temporale of the perisylvian regions [1,5–8]. The planum temporale is considered to be a crucial structure in the language process because it serves as the auditory association cortex and a component of the temporal speech region of Wernicke's area [5]. Although the results of brain imaging studies have been inconsistent, variation in asymmetry of the planum temporale has been claimed to be of functional significance in dyslexia persistently [5,6]. Several studies have looked for structural corpus callosum abnormalities with regard to both size and shape in individuals with LI, but their exact significance is still under investigation [21–23].

Preis *et al*. [21] found that, in the morphometric analysis of four segments of the corpus callosum, there were no significant differences between children with developmental language disorder and age-matched normal control groups. In our study, there were no significant differences of FA values between children with LI and normal controls. A significant difference in anisotropy measurements, however, was observed in the genu of the corpus callosum between the two groups. It is well established that myelination of the central nervous system progresses from an inferior to superior location, from a posterior to anterior location, and from a central to peripheral (i.e. centrifugal) location [24]. Therefore, we thought that our finding could be explained by the relatively late maturation of the genu of the corpus callosum during normal myelination. Of course, it is still unclear whether our findings are possible results of permanent injury to the brain at critical times of early neurogenesis, leading to further lagging or transient phenomena during their development with delayed catch-up. At the time of this writing, follow-up MR imaging had not been performed in either the controls or the children with LI. We expect that the longitudinal study of these children will be continued for the evaluation of prognosis and future function.

Numerous researchers have found that many children with developmental LI have accompanying, generalized 'neurodevelopmental' dysfunction. These findings suggest that developmental LI is not an isolated finding but is indicative of more widespread nervous system dysfunction [1,25]. The results of our DTI study may also support previous reports about children with developmental LI, by showing more white matter damage on a microscopic level than is suspected clinically or can be seen by conventional MR imaging. Thus, children with LI may not only need early recognition of language and other neurological impairments, but also more comprehensive intervention programs than language therapy alone.

Some shortcomings remain to be resolved. First, this study encompasses a small sample with a wide range of patient ages. Further study with a larger population that also considers sex differences is necessary to validate our results. We also did not observe significant differences in FA values related to regional variation or between the right and left hemispheres, especially in the dominant areas related to language function. Normative data for DTI should also be acquired, as FA values measured in the brain parenchyma are age dependent. As measurement of anisotropy has not been standardized to date, further technical investigations such as voxel-based analysis and statistical assessment of FA values are needed to increase the utility of DTI in the clinical setting.

Conclusion

In children with LI, DTI can show decreases in FA in some of the white matter fiber tracts and can visualize an altered white matter integrity, which are hardly demonstrated by conventional MR images. Our results suggest that delayed maturation of the white matter plays a partial role in the pathophysiological mechanisms of developmental LI. Further longitudinal studies are needed to determine whether the abnormalities detected by DTI correlate with therapeutic or functional outcomes and long-term prognoses.

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