<Clinical Application of DTI in Children>
Diffusion tensor MRI and fiber tractography in developmental CNS anomalies: new method describing aberrant fiber connections

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Introduction

Diffusion tensor MRI (DTI) and fiber tractography (FT) are recently introduced techniques, which can demonstrate the white matter fiber orientation as well as the integrity in vivo (1-5), however, their clinical application is still under investigation. Previous application studies include an evaluation of the axonal damage caused by a chronic infarct or motor neuron disease (6), a direct insult to the axonal fibers such as multiple sclerosis (7, 8) or acute disseminated encephalomyelitis (9).

Developmental CNS diseases, both congenital and post-natal diseases, can be a spotlighted field of DTI due to the potentiality of generating a fiber pathway and aberrant connections in the case of a blockage of normal white matter formation.

In this review, the author examined the developmental CNS anomalies with DTI and FT, and investigated their clinical utility in describing the aberrant fiber connections to provide a better understanding of the pathogenetic mechanisms of congenital diseases.

Imaging Protocol

A short acquisition time and instant processing is essential for the clinical feasibility of a certain procedure. The authors applied single shot spin echo EPI and parallel imaging techniques to achieve motion free and higher signal-to-noise ratio (SNR)DTI. The total scan time for DTI and FT was 7 to 9 minutes according to the slice numbers, which was added to the routine MRI examinations. Informed consent was received from all patients or the participants'parents or legal guardian, and all procedures were performed under the approval by institutional review board of clinical studies.

MRI Acquisition

All studies were performed on a 1.5T Philips Gyroscan Intera system using 6-channel Sensitivity Encoding (SENSE) head coil. The diffusion weighted imaging was performed using single-shot spin echo-echo planar imaging (EPI) with a navigator echo phase correction (motion correction) and a SENSE factor 2. This study used a data matrix of 96 acquisitions, which was reconstructed to 128 over a field of view of 220mm. The imaging slices were positioned to make the slice perpendicular to the anterior commissure-posterior commissure (AC-PC) line. The slice thickness was 2.3mm without a gap (45 to 55 slices); TE = 70ms; TR = 6599-8280ms; Number of

acquisition = 2, b = 600 s/mm^2.

Data Processing

The data was processed on a Window-2000 PC equipped with Philips Research Image-processing Development Environment (PRIDE) software (Philips Medical Systems, Best, Netherlands) based on the Fiber Assignment by Continuous Tracking (FACT) method (10). Anisotropy wascalculated using orientation-independent fractional anisotropy and DT-MRI-based color maps were created from the FA values and the 3 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. Three-dimensional fiber tractography was then obtained by connecting voxel to voxel with the FACT algorithm. The threshold values for the termination of the fiber tracking were < 0.3 for FA and > 45 for the trajectory angles between the ellipsoids.

Abnormalities of corpus callosum

Between 8 and 20 weeks of gestation, the corpus callosum was formed by development of the callosal precursors and the fibers from the hemispheric cortex (11). These callosal precursors secrete the chemo-attractants, axonin-1, to guide the developing axons across the midline (12). Therefore, each region of the hemispheric fibers isconnected to the contralateral side through the corpus callosum.

Complete Agenesis of Corpus Callosum

Agenesis of corpus callosum (ACC) is characterized by typical MRI findings such as a 'cart-wheel configuration' of the interhemispheric sulcal markings, an absence of the cingulate gyrus and colpocephalic features of the lateral ventricles. On the DTI-FT, fibers from the hemispheric cortex fail to cross the midline and form a thick bundle running antero-posteriorly e.g. Probst bundle.

In some cases, ACC is an incidental finding and the patient is asymptomatic. Normal motor fibers and major interconnecting fibers in brain stem are demonstrated in such cases. Previous reports describe thickened anterior commissure in the ACC (13), although the thickness varies on a patient-by-patient basis. In the case of complex anomalies, the DTI findings vary according to the extent of the affected structures.

Partial Agenesis of Corpus Callosum

The corpus callosum develops from the genu portion followed by the body, splenium and lastly the rostrum. Therefore, the posterior part or rostrum is hypoplastic in the case of a partial ACC. A high FA value and strong fiber connection through the remaining portion of the corpus callosum were demonstrated in partial ACC (14). The white matter fibers from the parieto-occipital lobe formed a back-to-front bundle and entered into the remaining genu portion. Fibers from the frontal lobe also joined the connection through partially formed corpus callosum, formed H-shape configuration of hemispheric fibers on axial views.

Familial Spastic Paraplegia with Thin Corpus Callosum (HSP-TCC)

Hereditary spastic paraplegia (HSP) is a heterogeneous group of neurodegenerative diseases, and a subtype of complicated HSP has been reported in Japan and Korea (15). HSP presents a progressive spastic gait in the second decade, anddementia, muscle rigidity, and cerebellar ataxia can occur in combination. On MRI, a thinning of the corpus callosum is demonstrated, particularly in the anterior part, which suggests progressive atrophy after the complete formation of the corpus callosum.

On DTI and FT, the decreased fibers through anterior part of corpus callosum aredemonstrated with intact splenial fibers. Patients with HSP-TCC usually show an upper motor neuron signs. However, the gross morphology of corticospinal tract is within the normal limits on fiber tractography.

Malformations of cortical development

Normal Development of Cortex

In the developing brain, neuronal migration occurs from the ependymal portion to the cortex by a radial growth pattern with the guidance of theradial glial fiber system (16). In a premature brain, a high anisotropic cortical ribbon appears, which reflects the directivity of neuronal migration (17).

Cortical Dysplasia

DTI has a powerful ability to describe the white matter integrity, and can detect abnormalities of the brain tissue in the earlier stage than conventional T2 or T1 weighted imaging. Although DTI can be used to assess gray matter abnormalities like a cortical infarction (18) or MCD (19), evaluating the gray matter by DTI is not of great value because of the nature of a low FA of the gray matter and a partial volume effect by CSF in the sulcus. Furthermore, some Eddy current artifacts may ruin the exact measurement of the FA at the surface of the brain. Instead, DTI and FT can be used to evaluate the white matter integrity adjacent to the dysplastic cortex. DTI and FT can perfectly visualize decreased fractional anisotropy around the cortico-medullary junction and fiber connection between deep white matter and dysplastic cortex in comparison to the normal contralateral side. In the case of severe dysplastic white matter, an aberrant course of the underlying white matter tract can be detected by DTI-FT.

Heterotopia

In the case of heterotopic gray matter in the white matter, the arrested neurons exist in the white matter bundles, and might have some degree of directivity like the normal white matter tracts and show increased anisotropy. Gray matter in the white matter, i.e. nodular or band heterotopia showed a higher anisotropic value compared to the normal cortex with statistical significance (0.280.07 vs 0.180.02, p=0.0003). Subependymal gray matter showed slightly lower FA values without statistical significance (0.16 0.01, p=0.0859). In the case of band heterotopia, failure of connection between deep white matter and cortex was clearly demonstrated on fiber tractography.

This study suggests that increased anisotropy of the heterotopic gray matter results from the histological nature and embryogenetic mechanism i.e. gray matter tissue in white matter bundles and a radial growth pattern of neuronal migration. The partial volume effect by the surrounding white matter also plays a role in the increasing anisotropy in the case of nodular heterotopia.

Cerebral palsy

Cerebral palsy (CP) is a non-progressive disorder with various motor dysfunctions with a diverse cause. The most common cause of childhood cerebral palsy is hypoxic brain injury and periventricular leukomalacia (PVL) in premature births (20). Before the era of DTI, an impairment of the corticospinal tract was believed to be responsible for the motor dysfunction. A recent study by Hoon et al (21)reported that sensory fibers were the problems in PVL and they showed a normal descending corticospinal tract by DTI and FT. The results were well correlated by a previous study of CP with SPECT, which described a thalamic hypoperfusion in PVL and suggested that the spasticity of CP may be associated with a dysfunction of the inhibitory stimuli from the thalamus (20).

In PVL, either with spastic quadriplegia or diplegia, severe atrophy of the periventricular fibers is demonstrated on DTI and FT due to previous germinal matrix hemorrhage. Corticospinal tract is usually normal and sensory fibers are decreased in comparison to age matched controls. The connecting fibers between the thalamus and parietal cortex, posterior thalamic radiations, are also absent. A thinning of the corpus callosum due to volume loss of periventricular white matter (PVWM) can be observed. Until now, the severity of spasticity (diplegic vs quadriplegic) is not well correlated with the degree of PVWM volume loss, which requires further investigation. In hemiplegic CP, their motor dysfunction is well correlated with the DTI and FT. The atrophied lesional side corticospinal tract is clearly depicted on FT.

Posterior fossa malformation

Posterior fossa malformations such as Arnold Chiari syndrome or a Dandy Walker malformation did not show remarkable findings on DTI and FT. Joubert syndrome is a subtype of a posterior fossa malformation and consists of vermian hypoplasia and a derangement of the cerebello-brain stem connections or cerebello-cortical connections. On MRI, the typical 'molar-tooth appearance'of the superior cerebellar peduncle (SCP) is diagnostic, and a partial or complete absence of the vermis is demonstrated. On DTI and FT, a thickened and elongated SCP with horizontal configuration can be seen. Three patients with Joubert syndrome received a DTI and FT examination, and all of them showed a thickened SCP and a connection to the pre-motor and motor cortex. In age-matched controls, a visual inspection showed that the SCP was smaller than Joubert syndrome there were few fibers to the cortex. This suggests that there is some modified connection from the cerebellum to the cerebral cortex in Joubert syndrome. There have been many reports on the shape of the brain stem and SCP (22). However, a detailed description of the fiber itself was impossible by conventional imaging. DTI and FT are the only methods that can describe such aberrant fiber connections in the diseased state and provide a better understanding of a malformed brain.

Technical considerations and conclusions

This study applied the DTI procedure using single shot spine echo EPI and SENSE. Since its first introduction to the clinical field by Pruessmann et al (23), SENSE has provided a fast imaging time, less susceptibility and motion artifacts. The total scan time was 7 to 9 minutes with a 2-signal averaging, which was tolerable for all patients. The DTIprocessing time was less than 5 minutes. The major fiber tracts were produced within a few seconds, and the radiologists or neurologists easily performed all procedures. The ten-minute DTI and fiber tracking protocol used in this study is a simple procedure and can be added to a routine sequence,i.e. it is no longer a research tool but is a strong clinical modality that describes the white matter pathology. Furthermore, pediatric patients may have more potential to form a modified fiber connection, particularly in the case of congenital diseases, which is a challenging field of DTI-FT for a future clinical study.

Some problems in DTI-FT need to be considered. First, DTI-FT is a powerful anatomic imaging tool that can describe the gross fiber architecture, not the functional or synaptic connection. With a clinical 1.5T scanner, or even with a high field system, the spatial resolution of DTI-FT is 1~2 mm. In that voxel, there must be plenty of synaptic connections and crossing fibers. However, these could not be detected in them. Therefore, major fiber bundles such as the corticospinal tract or corpus callosum on DTI-FT can be the real fiber pathways, relaying fibers like the cerebello-thalamo-cortical circuits, which cannot be depicted by DTI-FT, and is a limitation of DTI-FT.

Second, the fiber tracking technique is quite operator dependent and the operator should be aware of the detailed knowledge of the neuroanatomy. The standard ROI location and settlement of the adequate threshold value for fiber tracking is essential for making an objective and uniform fiber tracking result. Another important consideration in fiber tractography is setting the threshold values of FA and trajectory angles for termination of tracking. For example, we applied different values for fractional anisotropy and trajectory angles between ellipsoidsin drawing corticospinal tract, e.g. from 0.2 to 0.3 for FA and 0.75 to 0.85 for angles (0 = full deflection, 1 = no deflection). High threshold values for FA showed less fibers and only straight corticospinal tract from precentral gyrus to brain stem, while low threshold for FA demonstrated more fiber connections to lateral aspect of precentral gyrus and contralateral hemisphere through corpus callosum. Large threshold for deflection angle depicted more fibers to distant areas.

With our results, we can postulate that the operator can make more fibers by intention or ignore intact tracts according to threshold setting for fiber tracking termination. This is quite important because modified or aberrant fiber connections do occur in diseased conditions, and the modified fiber tracts can be exaggerated or underestimated by various threshold values. Therefore, the results of this study should be repeatedly reproduced by other scientists in the future by fiber tracking techniques other than described here.

Third, DTI-FT still depends on a qualitative visual analysis by radiologist and requires further development of the quantification and standardization methods. Nevertheless, the ability of DTI-FT in describing the white matter architecture is unparalleled by any other imaging modality and further active clinical applications are required.

In conclusion, this study obtained additional or unique findings from CNS developmental

disease using DTI-FT, which could not be obtained by conventional MRI. Future studies will be focused on determining the meaning of the aberrant fiber connections and their relationship with the clinical manifestations of the CNS anomalies.

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