Diffusion tensor imaging of periventricular leukomalacia – Initial experience

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KEYWORDS
DTI: diffusion-tensor imaging;
DTT: diffusion tensor tractography (DTT);
PVL: periventricular leukomalacia;
CP: cerebral palsy

Abstract  Aim of the study: To investigate the role of MR diffusion tensor imaging (DTI) and diffusion tensor tractography (DTT) in the assessment of altered major white matter fibers in preterm infants and children with PVL.

Patients and methods: We used diffusion tensor imaging to evaluate the major white matter tract fibers in 15 children with periventricular leukomalacia in correlation with cognitive and motor disability. Mean age of the patients was 28.5 months (range: 9–84 months). 5 normal control children were recruited (mean age: 21.4, range: 11–60 months). MR imaging was obtained by using a 1.5-T, whole-body scanner. DTI was acquired after the routine sequences. Then, data post-processing and fiber-tracking method was applied.

Results: This study demonstrated the existence of the WM tract injury in PVL patients using the DTI tractography approach in correlation with neurodevelopmental delay in patients with various degrees of cognitive and motor impairment. Compared with the normal control group, the following abnormalities were detected on qualitative analysis of the white matter tracts.

Corticospinal tracts: Decreased volume and cross-sectional area on the affected side.

Ascending sensorimotor tracts: Thinning of sensory fiber tracts and posterior thalamic radiations.

Commisural and association tracts: Significant damage of the callosal fibers was reported in cases with partial agenesis of the corpus callosum.

Conclusion: DTI proved to be a promising noninvasive method for assessing the severity of white matter tract injury in patients with PVL. This is owing to the capability of fiber-tracking techniques to provide more information for understanding the pathophysiologic features of sensorimotor and...
cognitive disability associated with PVL. This will allow for the early intervention and initiation of rehabilitation programs aiming for minimizing the associated neurological deficit.

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1. Introduction

Diffusion-tensor imaging (DTI) is a powerful MR imaging method to probe tissue microstructure by using the diffusion of water molecules. Diffusion tensor tractography (DTT) is a unique method to reconstruct and visualize the three-dimensional tracts noninvasively, which has not been possible before with any other imaging modality (1).

By applying the appropriate magnetic field gradients, MR imaging may be sensitized to the random, thermally driven motion (diffusion) of water molecules in the direction of the field gradient. Diffusion is anisotropic (directionally dependent) in white matter fiber tracts, as axonal membranes and myelin sheaths present barriers to the motion of water molecules in directions not parallel to their own orientation. The direction of maximum diffusivity has been shown to coincide with the WM fiber tract orientation (2).

This information is contained in the diffusion tensor, a mathematical model of diffusion in three-dimensional space. In general, a tensor is a rather abstract mathematic entity having specific properties that enable complex physical phenomena to be quantified (3). In the present context, the tensor is simply a matrix of numbers derived from diffusion measurements in several different directions, from which one can estimate the diffusivity in any arbitrary direction or determine the direction of maximum diffusivity. The tensor matrix may be easily visualized as an ellipsoid whose diameter in any direction estimates the diffusivity in that direction and whose major principle axis is oriented in the direction of maximum diffusivity (4) (Fig. 1).

The shape of the resulting diffusion ellipsoid is described by the resulting primary eigenvectors and eigenvalues. From these indices, quantitative measures of diffusion anisotropy, such as the fractional anisotropy, can be calculated (5). This summary measure, along with other quantitative diffusion indices such as the directionally averaged mean diffusivity (also referred to as average apparent diffusion coefficient, abbreviated as MD, Dav or ADCave) have proved useful for probing the integrity and development of white matter pathways in the brain (6).

It is well known from studies of animals (7) and adult humans (8) that DTI can serve as an early indicator of stroke, often demonstrating image abnormalities on water diffusion maps well before conventional MRI. Early detection of injury is particularly critical in the context of administration of neuroprotective therapies to infants. These therapies must be initiated quickly in order to interrupt the cascade of irreversible brain injury (9). Water diffusion maps derived from DTI may provide the means for this early detection of injury. Changes in diffusion characteristics further provide early evidence of both focal and diffuse brain injury in association with

![Fig. 1](image-url)  
Top left, Fiber tracts have an arbitrary orientation with respect to scanner geometry (x, y, z axes) and impose directional dependence (anisotropy) on diffusion measurements. Top right, The three-dimensional diffusivity is modeled as an ellipsoid whose orientation is characterized by three eigenvectors ($\xi_1, \xi_2, \xi_3$) and whose shape is characterized by three eigenvalues ($\lambda_1, \lambda_2, \lambda_3$). The eigenvectors represent the major, medium, and minor principle axes of the ellipsoid, and the eigenvalues represent the diffusivities in these three directions, respectively. Bottom, This ellipsoid model is fitted to a set of at least six noncollinear diffusion measurements by solving a set of matrix equations involving the diffusivities (ADCs) and requiring a procedure known as matrix diagonalization. The major eigenvector (that eigenvector associated with the largest of the three eigenvalues) reflects the direction of maximum diffusivity, which, in turn, reflects the orientation of fiber tracts. Superscript T indicates the matrix transpose. Quoted from: Brian et al. (4).
periventricular leukomalacia, the most common form of white matter injury in the preterm infant (10).

Periventricular leukomalacia (PVL) is now recognized as one of the most important causes of cerebral palsy (CP) in preterm infants. The incidence of intraventricular hemorrhage and associated complications has declined recently, and PVL has become the dominant neuropathologic condition in premature infants. PVL is the major neurologic basis of spastic motor deficits and cognitive abnormalities observed later in such infants (11).

Cerebral palsy (CP) is defined as a group of non-progressive motor disorders of movement and posture due to a defect or lesion of the developing brain. The motor disorders of CP are often accompanied by disturbances in sensation, perception, cognition, communication, and behavior, and by epilepsy and secondary musculoskeletal problems. Early accurate evaluation of individuals with CP is critical because certain developmental intervention programs can be initiated, and these offer the possibility of improving the neurological outcome (12).

Our study thus aimed to investigate the role of MR diffusion tensor imaging (DTI) and Diffusion tensor tractography (DTT) in the assessment of altered major white matter fibers in preterm infants and children with PVL.

2. Patients and methods

This study was approved by the ethics committee of our university, and informed consent was obtained from the parents of each patient. MRI was performed between January 2013 and January 2014. 15 children (9 males and 6 females) were included. Mean age was 28.5 months (range: 9–84 months). 5 normal controls, 3 males and 2 females, were recruited (mean age: 21.4, range: 11–60 months).

Based on clinical history and neurologic examination, 7 patients were diagnosed as PVL with CP. They suffered severe complications e.g. spastic paraplegia or quadriplegia, mental retardation, and/or epilepsy. The remaining 8 children presented with neurodevelopmental delay, without paralysis or seizures. Functionally non-impaired children were categorized as PVL without CP (Table 1).

MR imaging was obtained by using a 1.5-T, whole-body scanner (Achieva; Philips Medical Systems, Best, Netherlands). All children underwent routine pulse sequences, including axial fast spin echo T1, T2 and FLAIR images & coronal T2 and sagittal T1 images; 5 mm slice thickness, no interslice gap; T1-weighted sequences (repetition time 450 ms, echo time 15 ms), T2-weighted sequences (repetition time 3960 ms, echo time 110 ms) and FLAIR (repetition time 6000 ms and echo time 120 ms and inversion time 1800 ms).

DTI was acquired after the routine sequences and consisted of a single-shot echo-planar imaging technique (repetition time: 6000 ms; excitation time: 88 ms), with a motion-probing gradient in 15 orientations, a field of view of 230 mm, b values of 0 and 1000 s/mm².

Data Postprocessing and Fiber-Tracking Method
Anisotropy at each voxel was calculated, and color maps were created. A two-dimensional visualization approach was used to identify specific white matter (WM) tracts. In this approach, image brightness represents diffusion anisotropy, with a red–green–blue color scheme indicating tract orientation (red, revealing fibers with lateral orientation; green, anterior–posterior; and blue, cranio-caudal). The procedure for mapping neural connections started through multiple fiber tracking of 3 arbitrary ROIs. We determined ROIs on axial slices of the color vector map for all cases. For the anatomical regional measurement of fractional anisotropy of major WM fibers, all fibers were identified on axial, sagittal and coronal slices of directional color-coded maps. The threshold chosen for FA was 0.15 and the angle threshold 60.

3. Results

On conventional MRI, all patients had evidence of diffuse PVL, including scanty deep periventricular white matter, bilateral periventricular hyperintensities on T2-weighted images, various degrees of ventricular dilatation, scalloped ventricular contours and thinning of the corpus callosum (Fig. 2a and b). 4 cases were associated with partial agenesis of the corpus callosum, one of them was with interhemispheric arachnoid cyst (Fig. 4).

Normal anatomical tractography was first established on the control children to provide a baseline for qualitative analysis of WM tract fibers and comparison with abnormal findings in the affected children (Fig. 1). We followed the white matter tract identification protocol provided by Nagae et al., (13).

On qualitative analysis of the white matter tracts, DTT revealed (Table 2): Corticospinal tract: (CST) four cases with spastic hemiplegia revealed decreased volume and cross-sectional area of the CST on the affected side (Fig. 3). Ascending sensorimotor tracts: seven cases with variable degrees of cognitive impairment and spastic quadriplegia demonstrated thinning of sensory fiber tracts and posterior thalamic radiations (PTR) (Fig. 4). Commissural and association tracts: significant damage of the callosal fibers was reported in all four cases with partial agenesis of the corpus callosum (Fig. 5).

4. Discussion

PVL is defined as focal necrosis in the periventricular WM of the cerebral hemispheres, associated with diffuse gliosis in adjacent WM, a common finding after perinatal asphyxia, particularly in preterm infants (14). This study demonstrated the existence of the WM tract injury in PVL patients using the
diffusion tractography (DTT) approach in correlation with neurodevelopmental delay in patients with various degrees of cognitive and motor impairment.

This is attributed to the fact that the microstructures of widespread WM tract fibers were significantly impaired in patients with PVL whose cause may be impairment of axonal development or in oligodendroglial ensheathment or both (15). The microstructure impairment of these projection, commissural and association tracts directly reduces the speed and capability of the information exchange among multiple cortical regions (16).

Projection tracts, namely, corticospinal tract (CST), corona radiata (CR), posterior limb of the internal capsule (ICPL) and posterior thalamic radiation (PTR) encompass large areas of the brain and are responsible for the disturbance of motor and sensory functions. CST is a descending pathway mainly from the precentral motor cortex into the brain stem. ICPL contains connections between thalamus and motor, somatosensory, and other parietal cortex. CR mainly contains pyramidal tracts (17).

In this study, we assessed the integrity of CST fibers in comparison to the age matched control children. Four cases with spastic hemiplegia demonstrated decreased volume and cross-sectional area of the CST on the affected side. This finding reflects impairment of motor projection fibers causing motor problems (Fig. 3). Similar results were also described by previous studies (18–21). They used diffusion tensor imaging to identify the CST and assess symmetry of properties between ipsilateral and contralateral tracts in spastic hemiplegia. Asymmetry was demonstrated in cross-sectional area (20) and number of tracts (21).

However, one study showed no significant correlation between CST asymmetry and impaired limb function but did show significant correlation with sensorimotor thalamic
In recent research, PTR has been considered as an important tract reflecting the degree of both sensory and motor deficits. The PTR connects the thalamus to the posterior parietal and occipital cortices. The posterior parietal cortex is involved with complex upper limb function and visuo-spatial performance (22).

In our study, seven cases with variable degrees of cognitive impairment and spastic quadriplegia demonstrated thinning and distortion of sensory fiber tracts and posterior thalamic radiations (Fig. 4). These findings are in agreement with two previous studies which reported the PTR to be among the most injured tracts qualitatively (17,23). Accordingly, both

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**Table 2** Qualitative analysis of the white matter tracts.

<table>
<thead>
<tr>
<th>White matter tract</th>
<th>Findings in DT tractography</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>CST</td>
<td>Decreased volume and cross sectional area on the affected side as compared with the contralateral side and control case of the same age group</td>
<td>4</td>
</tr>
<tr>
<td>Sensorimotor fibers</td>
<td>Mild, moderate, moderate to marked thinning and interruption of sensory fiber tracts and PTR</td>
<td>7</td>
</tr>
<tr>
<td>Callosal fibers</td>
<td>Partial agenesis with interrupted to absent or amputated fibers</td>
<td>4</td>
</tr>
</tbody>
</table>

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**Fig. 3** 21 month old child with PVL presented with spastic hemiplegia demonstrates: (A) and (B) Conventional MRI images reveal: scanty deep periventricular white matter, more evident in the parieto-occipital regions with serrated outline of the occipital horns of both lateral ventricles. (C) tractography: decreased volume and cross-sectional area of the CST (yellow) on the affected side. (D) and (E) Tractography of another 18 month old infant, showing decreased number and interrupted cortical fibers in the affected side (yellow).

**Fig. 4** Examples of fiber tracking (oblique views) in 3 children with (A) mild (B) moderate and (C) marked sensorimotor impairment: disrupted, scanty PTR fibers, as well as anterior and superior thalamic radiation fibers, mostly evident in case (C) as compared with the mild case (A) with more abundant fibers.
descending corticomotor and ascending sensorimotor tracts are involved in the pathogenesis of CP and both are clinically significant. It is not yet possible to determine which is more significant; however, descending corticomotor tracts have been studied more comprehensively (24).

On fiber tracking maps, Corpus Callosum (CC), by far the largest WM fiber bundle, is a massive accumulation of fibers connecting corresponding areas of cortex between the hemispheres (5). The corpus callosum develops from the genu portion, followed by the body, the splenium, and lastly the rostrum. Therefore, the posterior part or rostrum is hypoplastic in the case of partial agenesis of CC (25).

In our study, significant damage of the callosal fibers was noted in the four cases with partial agenesis of the corpus callosum. They presented with severe sensorimotor impairment and seizures. One of them demonstrated interhemispheric fissure arachnoid cyst. The ipsilateral right optic radiation was compressed with reduction in the number of its fibers as compared with the contralateral side (Fig. 5,c). In previous studies, altered FA in both genu and splenium of CC was reported to be associated with significant negative correlations to the cognitive level, especially in splenium of CC, which carries the fibers connecting the parietal, occipital, temporal regions between two hemicerebrums (26). The transcallosal motor fibers in particular have been shown to be involved in participants with spastic diplegia. Further research is warranted in this area (27,28).

Consequently, we can deduce that, qualitative assessment of the white matter tract fibers, particularly the descending CST and ascending sensorimotor tracts, in particular the PTR is a useful measure of white matter tract integrity, which correlate with the clinical severity of PVL. Moreover, estimation of the full extent of commissural fiber interruption and partial agenesis can be clearly delineated.

A limitation of our study was the decreased number of cases and that we relied only on qualitative analysis of the WM tracts. This results in operator dependant interpretation. Quantitative assessment of fractional anisotropy and mean diffusivity for a larger scale of patients are highly recommended for more reliable data and for comparison of results with other studies.

Moreover, long-term follow-up studies are recommended by us and Wang et al. (26) who proposed the fact that children’s development of cognitive functions is a dynamic process. It is not merely a consequence of an early brain lesion but also the result of the ongoing interaction between the child and his or her environment (26). Therefore, long-term follow-up studies will be necessary to clarify the relationship between altered WM anatomy and clinical outcome of cognitive function in children with PVL.

5. Conclusion

DTI proved to be a promising noninvasive method for assessing the severity of white matter tract injury in patients with periventricular leukomalacia. This is owing to the capability of fiber-tracking techniques to provide more information for understanding the pathophysiologic features of sensorimotor and cognitive disability associated with PVL. This will allow for the early intervention and initiation of rehabilitation programs aiming for minimizing the associated neurological deficit.

Conflict of interest

We have no conflict of interest to declare.
References


