Alteration in the number and integrity of white matter tracts in the preterm: A quantitative diffusion tensor imaging and diffusion fibre tractography in children

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Abstract

Purpose: Periventricular white matter is most commonly injured in preterm babies with hypoxia. To assess white matter damage, we decided to perform diffusion tensor imaging (DTI) in preterm children with history of hypoxia and magnetic resonance imaging (MRI) features of periventricular leukomalacia (PVL) (PTH). We hypothesized that the PTH have reduced number of white matter fibres compared to age matched pre term children without hypoxia (PTHO), and also depending on the severity of PVL, there could be reduction in the number of fibres as well. **Materials and Methods:** The present study was carried out at the Government Medical College, Thiruvananthapuram. DTI was performed on 15 PTH and 15 PTHO. We measured number of fibres and fractional anisotropy of corpus callosum (CC) and optic radiations (OR). **Results:** There was significant difference between two groups with regard OR ($P < 0.001$).The mean number of OR fibres in cases and control was 104 ± 28.44 (mean ± SD) and 578 ± 286 (mean ± SD), respectively.The mean number of CC in cases was 953 ± 429 and in controls was 1625 ± 116 with a P value <0.56. No significant difference in FA was seen between cases and controls ($P = 0.94$). **Conclusions:** Preterm children with history of hypoxia and MRI features of PVL show reduced number of CC and OR compared to preterm children without hypoxia. There was significant correlation between PVL severity and number of OR fibres which could be due to the preferential involvement of periventricular white matter, in which OR has a major contribution.

Key words: Corpus callosum; diffusion tensor imaging; optic radiations; periventricular leukomalacia

Introduction

Periventricular leukomalacia (PVL) or posthypoxic leukoencephalopathy in newborn is the most common form of brain injury in preterm children (PTC) presenting with cerebral palsy. It is seen in 50–70% of the preterm children. PVL is defined as ischemia leading to infarction of white matter in the periventricular region resulting in cystic changes with appearance of white spots and softening of

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periventricular white matter (PVWM) at autopsy.[1] This was first described by Virchow in 1867 as small pale infarcts in periventricular white matter.[2]

Any hypoxic or inflammatory insult secondary to hypoxia, infection, or septicemia can trigger a variety of inflammatory mediators inducing inflammation in the white matter in preterm babies.[3,4] Characteristically PVL involves PVWM especially the parieto-occipital regions. Conventional magnetic resonance imaging (MRI) can show dilated ventricles, scalloping of ventricular margin, periventricular white matter thinning, cystic areas, white matter atrophy, and dilatation of cortical sulci.[5-7] However, white matter tract involvement can be objectively assessed only by diffusion tensor imaging (DTI) and diffusion tractography (DFT). DTI exploits the principle of Brownian movement of water molecules *in vivo* – structures such as white matter tracts due to directionality of fibers show high degree of anisotropy compared to gray matter and cerebrospinal fluid (CSF).[8,9] PVL can present with varying anomalies ranging from motor or sensory defects to impairment in attention, cognition, and development delay.[10-12]

The aim of this project was to apply the principles of DTI and DFT to (1) quantify injury to the white matter tracts in children below 2 years of age who were born prematurely and with MR evidence of PVL; (2) to inspect any morphological variation regarding fiber disruption, discontinuity, or any other changes in anisotropy as measured with DTI metrics. We planned to quantify the damage to optic radiation (OR) and corpus callosum (CC) in preterm babies with clinical history of hypoxia/presenting with spastic cerebral palsy and MR evidence of PVL using DTI and DFT.

Our hypothesis is that, depending on the severity of PVL in MRI, there could be alteration in the number of white matter fibers of CC and OR. Further, depending on the severity of MRI imaging findings, DFT could also show incongruities in the fiber anatomy and morphology. Only few studies had accomplished DTI analysis in such young children.

Materials and Methods

Participants

The study was approved by Institutional Ethical Committee. Written informed consent was taken from parents of all participants. This study involved children born prematurely before 36 weeks of gestation. Premature children who had come to the radio diagnosis department in our hospital from September 2012 to September 2014 were retrospectively reviewed for white matter changes by DTI and DFT. Fifteen Preterm children with perinatal hypoxia and MRI showing features of PVL were selected.

Inclusion criteria for cases included preterm children born between 31 and 36 weeks gestational age and whose MRI taken when they were 2 months to 2 years of age with history of hypoxia and showed evidence of PVL. Children with metabolic disorders, meningitis, congenital malformation, and MRI with movement artefacts were excluded. Fifteen preterm infants of approximately similar term equivalent age without any history of hypoxia and with normal MRI without any evidence of metabolic, congenital, head injury, were included as controls.

Depending on the imaging findings the cases were graded[13] into mild, moderate, and severe PVL [Table 1]. This classification is based on the white matter changes, presence of cysts, corpus callosal thinning, and hydrocephalus. There were 4 children with severe PVL, 5 with moderate PVL, and 6 children with mild variant of PVL. The mean birth weight of the cases was 1.238 ± 0.734 kg and that of controls was 1.538 ± 0.562 kg, respectively.

Imaging

Magnetic resonance imaging scan

Imaging was done using Siemens 1.5 Tesla MRI (Avanto SQ engine, Siemens, Erlangen, Germany) scanner using eight channel phased array head coil. Mild sedation with oral chloral hydrate 3–50 mg/kg was given to the babies under the supervision of a pediatrician to reduce the movement inside the MR scanner, and the head was immobilized using a small pillow.

Each patient underwent conventional MRI with axial T1 and T2 followed by three-dimensional (3D) fluid-attenuated inversion recovery (FLAIR) sequences with TR/TE/TI 5000/405/1800 ms, FOV 256 mm, slice thickness 1 mm, matri × 256 × 256. A high-resolution 3D T1-weighted images of the entire head were obtained with 3D fast low angle shot (FLASH) with TR/TE 11/4.94 ms, flip angle 15°, FOV 256 mm, slice thickness 1 mm, and matri × 256 × 256.

Table 1: Grading of PVL into mild, moderate and severe variant based on conventional MRI findings

MRI	Score 1	Score 2	Score 3	
WM signal Abnormality	Nil	<2 Focal Lesions	>2 Focal Lesion	Score 7-9=Mild
WM Volume Loss	Nil	Mild	Marked	Score 10-12=Moderate
Cystic Changes	Nil	<2 mm cyst	>2 mm cyst/multiple cyst	Score 13-15=Severe
Ventricular Dilatation	Nil	Mild to Moderate	Global enlargement	
Corpus Callosal Thinning	Normal CC	Focal Thinning	Global Thinning	

All the MR images were scrutinized for the presence of white matter changes, cysts, white matter thinning, hydrocephalus, and corpus callosal thinning.

Diffusor tensor imaging acquisition

Spin-echo echo-planar DTI sequence was performed with diffusion gradients along 30 noncollinear directions using TR 3500 ms, TE 105 ms, matri × 192 × 192, FOV 230 mm^2, 2 mm slice thickness with 1.5 mm gap averaged twice and with a b factor of 0 and 1000 s/mm^2. Sixty-five contiguous sections were taken from the level of the cervicomedullary junction, covering the entire brain.

Diffusor tensor imaging postprocessing and analysis

From DTI, color-coded FA maps were scrutinized and tractography was done using fractional anisotropy (FA) threshold of 0.2 and angle threshold of 50° for tracing OR and CC. The Tractography processing was carried out using FACT algorithm using SyngoNeuro3D which is an inbuilt software in the Siemens workstation and using trackvis.[14,15] The entire CC drawn using Hand ROI and fibres regenerated. Optic tracts were traced using sphere ROIs placed in lateral geniculate body and occipital cortex with 1.2mm diameter ROI [Figures 1 and 2]. DTI indices including apparent diffusion coefficient (ADC), FA, were measured from CC, and OR bilaterally from the ROIs drawn on the color map. The same study was repeated in the age and sex-matched control group. DTI images and data were interpreted by radiologist (RMS) and a scientist (SA) who have more than 4 years' experience in DTI processing and blinded to the data.

Statistical analysis

Statistical analysis was done with SPSS software – Statistical Package for Social Science Version 19.0.1 for windows (SPSS 19, SPSS Inc. Chicago, Illinois, USA). To assess consistency among raters an interrater reliability was assessed by using kappa statistics. The interrater reliability was found to be 0.78 and 0.82 for DTI-OR ($P < 0.05$) and DTI-CC, respectively ($P < 0.01$). Chi-square analysis was done to assess the difference between patients' age and sex. Student's *t*-test was done to assess difference between cases and controls with respect to number of fibres in OR and CC.

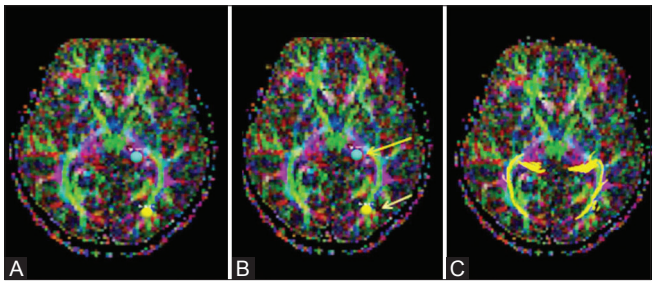

Figure 1 (A and B): (A) MRI template showing "sphere" ROI placement in lateral geniculate body (green ROI) and occipital cortex (yellow ROI); B and C shows optic radiations (yellow in C) from lateral geniculate body to occipital cortex (yellow arrows in B)

Results

A total of 25 children underwent DTI and DFT [Table 2]. Chi-square analysis for difference between patient age was not significant ($P = 0.642$) and sex was also not significant ($P = 0.745$). Mean age of the cases was 12 months and 5 days (12 males and 8 females), ranging from 2 months to 24 months. The mean age of controls was 11 months 6 days, (7 males and 5 females) ranging from 2 months to 23 months. The mean birth weight of the cases was 1.238 ± 0.734 kg and that of controls was 1.538 ± 0.562 kg, respectively.

Of the 15 babies with PVL, there were 4 children with severe PVL, 5 with moderate PVL, and 6 children with mild variant of PVL. Two patients had multiple periventricular cysts, 3 children had corpus callosal thinning, 5 patients had WM thinning, 4 patients had hydrocephalus.

DTI showed reduced number of fibres involving both OR and CC compared to controls [Figures 3-5]. In patients with CC thinning, there were reduced number of CC fibres and the morphology of the tract was also altered. There was twisting and irregularity of tracts [Figure 4]. Average

Table 2: DFT findings in cases and controls showing number of fibers in the optic radiations (OR) and corpus callosum (CC)

No	Cases		Controls	
	OR	CC	OR	CC
1	100	1369	1369	3567
2	120	543	542	2387
3	48	132	232	972
4	123	1293	1260	642
5	89	1640	1569	2071
6	120	899	723	3211
7	136	920	733	2311
8	56	975	747	631
9	121	1459	701	562
10	108	1430	734	691
11	101	957	1790	754
12	71	583	2341	643
13	93	734	1874	942
14	142	968	890	3452
15	132	48	476	1543

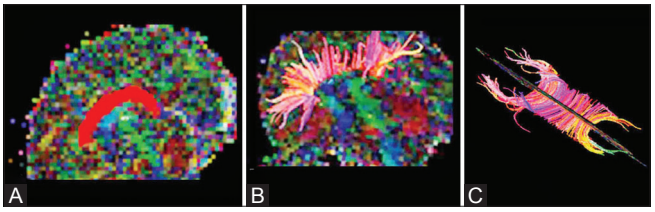

Figure 2 (A-C): (A and B) MRI template with "hand" ROI placement for drawing corpus callosum (red) and (C) showing normal corpus callosum tract

number of fibres of OR in cases were 104 ± 28.44 (mean ± SD) and of CC were 953 ± 429 (mean ± SD). In controls, the mean number of fibres of OR were 578 ± 286 (mean ± SD) and CC were 1625 ± 116 (mean ± SD).

There were statistically significant difference in the number of fibres of OR in cases compared to controls ($P < 0.001$). For CC, there was reduction in the number of fibers with increasing severity, though it was not statistically significant ($P < 0.56$). With increasing severity of PVL, there was a trend towards decrease in the number of fibres [Figure 6]. The FA value of OR in cases was 0.22 ± 0.02 (mean ± SD) with minimum value of 0.19 and maximum value of 0.26. The average FA of CC in patients were 0.27 ± 0.05 (mean ± SD) with a range of 0.21–0.34. No significant difference in FA value was seen between patients and controls with regard to ORFA and CCFA ($P = 0.724$ and 0.334, respectively).

Discussion

DTI has become one of the most prevalent MR imaging technique to analyze white matter *in vivo* and have been extensively utilized for research and clinical evaluation. Though many DTI studies in preterm patients have been reported in literature in school age and adolescents, few reports have investigated white matter analysis of preterm babies with PVL at this young age. We used standardized DTI techniques which were extensively used in the literature for gauging WM tracts. It provided unique image contrast and information on white matter and 3D visualization of neuronal pathways, with overlay of the fibres with FA, ADC map, or 3D T1WI.

In the present study, all patients with one or more features of PVL were evaluated with DTI and DFT. We had 4 children with severe PVL, 5 with moderate PVL, and 6 children with mild PVL according to the classification. We got significant correlation between MR imaging findings with DTI findings with regard to the OR in PVL patients. There were reductions in number of OR and CC and volume compared to the control group. OR were more significantly involved compared to CC. This could be due to the preferential involvement of periventricular WM in PVL. Many studies have demonstrated the preferential involvement of posterior thalamic radiations, retrolenticular part of internal capsule compared to the control group.[12] In our study, the mean FA value for OR and CC were also less in patients compared to controls though not statistically significant. Reduction in FA was also more with OR compared to CC, which can be explained by the significantly reduced number of OR in cases compared to controls.

No significant difference in FA value was seen between patients and controls with regard to ORFA ($P = 0.724$) and CCFA ($P = 0.334$), though we got high mean FA for CC and OR in controls. This could be due to small sample size we used for analysis and also because of the fact that we calculated FA for the entire tract and not region of interest (ROI) analysis as it delineated the tensor characteristics of the entire tract. Anjari *et al*. using TBSS also showed reduced FA involving centrum semiovale, frontal white matter, and the genu of the CC in preterm babies.[16] Our findings of involvement of PWM also agrees with other studies on preterm children.

Liu *et al*. described DTI findings in preterm neonates and demonstrated reduction in tract volumes and diffusion indices in children with moderate and severe PVL, especially in CST, CC, and SLF.[17] They did not describe the findings in OR. Glass *et al*. demonstrated abnormal DTI metrics in OR and correlated with visual evoked potential amplitude in preterm infants. They found a correlation between DTI indices and VEP function measured 1.5 years later showing early microstructural changes were related to long-term clinical outcome in these patients.[18]

Bassi *et al*. studied the relationship of visual function in preterm infants with microstructural changes in the Optic Radiation using DTI and compared the FA of the tracts to visual function.[19] Tracts were created using a seed mask placed in the white matter lateral to the lateral geniculate nucleus. Their findings were suggestive of direct

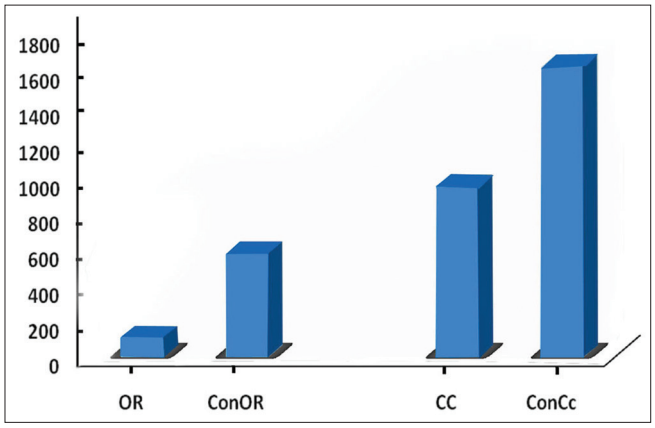

Figure 3: Bar chart shows reduced number of corpus callosum fibres (CC) and optic radiation fibres (OR) compared to controls-con CC (CC fibres in controls) and con OR (OR fibres in controls)

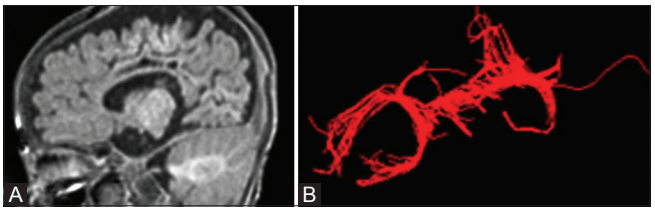

Figure 4 (A and B): Case 1 (A) MRI in a patient with PVL showing periventricular cysts and corpus callosal dysgenesis. (B) DFT of the same patient shows twisting and irregularity of corpus callosal fibers in a child with dysgenesis of corpus callosum

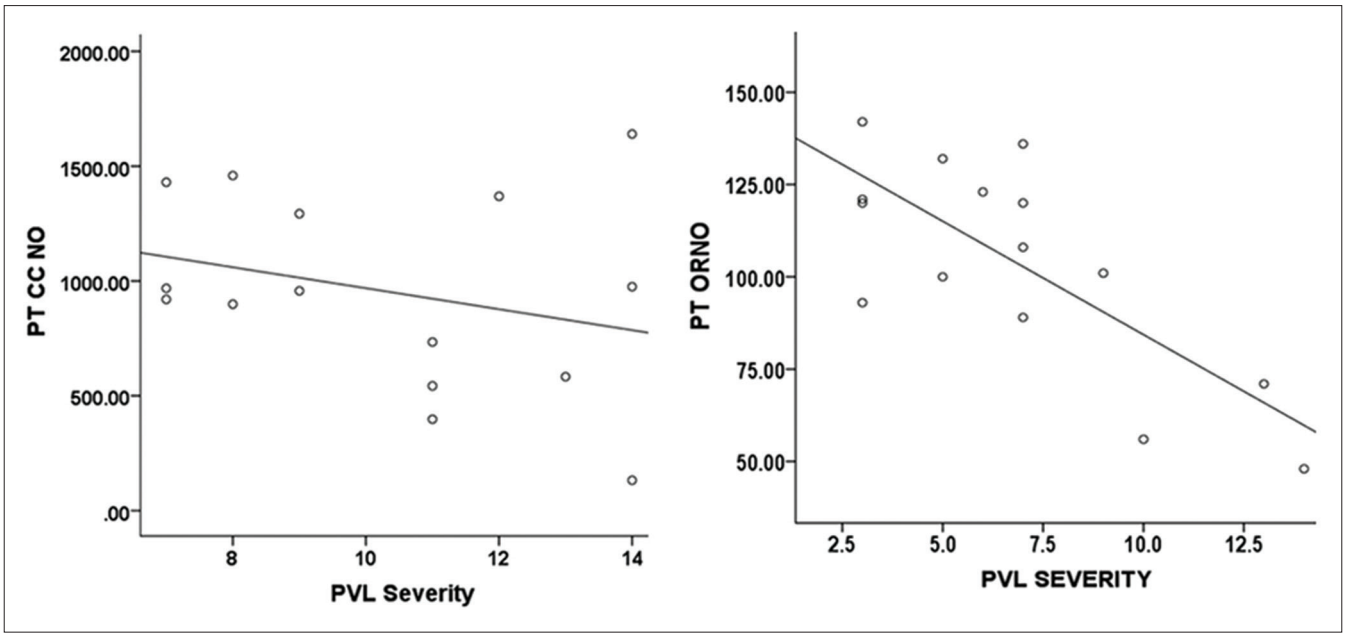

Figure 5 (A and B): Scatter plots showing (A) negative correlation between patients corpus callosal number (PT CCNO) and severity of PVL (Severity PVL) ($P = 0.56$) (B) significant correlation between patients optic radiation number (PT ORNO) and severity of PVL (Severity PVL) ($P = 0.01$)

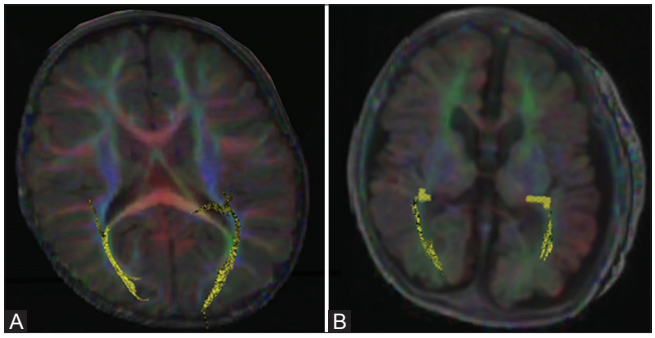

Figure 6 (A and B): DFT showing reduced number of optic radiation fibres (OR) in (A) Mild variant of PVL and (B) Severe variant of PVL

relationship between visual function and OR diffusion metrics in preterm infants at term equivalent age.

We were able to demonstrate a correlation between severities of PVL based on conventional MRI findings with tractography findings. In conventional MRI, abnormal signal intensity areas in preterm babies could be due to many factors such as hypomyelination, white matter injury, hemorrhage, or due to underlying metabolic conditions. However, only DTI and DFT can delineate WM involvement in terms of number or alteration in the FA values. We were also be able to demonstrate abnormal track morphology in severe PVL. Moreover, with DFT we could differentiate between severe CC thinning and agenesis, which was difficult with conventional MRI.

The study had several limitations. The sample size was small and we studied only two main WM tracts of the brain, even though others can also be affected. OR and CC are the 2 major tracts involved in PVL. Moreover, we did not perform an ROI analysis of the tracts or segmental analysis of the tracts. Nevertheless, we were able to quantify and correlate WM injury in preterm babies with history of hypoxia with conventional MRI features. However, *in-vivo* WM involvement can be assessed only by DTI and DFT. Though the techniques of DTI with regard to image processing, analysis, and interpretation have been refined constantly through all these years, it has inherent limitations as it is highly sensitive to movement artefacts, which is common with pediatric population.

Conclusion

DTI and DFT can quantify white matter injury in preterm babies with PVL. With increasing grade of PVL injury, there appears to be more reduction in the number of fibres as evident by DFT. With diffusion fibre tractography, we could accurately delineate microstructural alteration based on variation of diffusivity of water molecules *in vivo*. This is not possible with conventional MRI which demonstrates only T2 hyperintensity in these areas, however, cannot be quantified.

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Nil.

Conflicts of interest
There are no conflict of interest.

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