Serial Diffusion Tensor Tractography Studies in Term Neonates with Hypoxic Ischemic encephalopathy

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Introduction: Hypoxic-ischemic encephalopathy (HIE) is an important cause of permanent damage to neuronal cells that may result in neonatal death or be manifested later as cerebral palsy or impaired cognition. 15–20% of infants with HIE die in the neonatal period, and 25–30% of survivors are left with permanent neurodevelopmental abnormalities.[1] Insufficient delivery of oxygen and glucose to brain triggers a sequence of biochemical events, which contributes to the energy failure leading to neuronal and glial cell injury or death. In the term infants, the parasaggital cortex, cerebral neocortex, thalamus, dorsal hippocampus, and subcortical white matter are all located within watershed zones and are the primary brain regions affected by the HI insult. Documented magnetic resonance imaging (MRI) pattern of injury in moderate and severe HIE are abnormal signal intensity in posterior limb of internal capsule,[2] abnormalities in basal ganglia and thalami, and loss of grey-white matter differentiation in the hemispheres. Diffusion tensor imaging (DTI) studies of normal neonates have shown that mean diffusivity (MD) decreases with age in both grey matter and white matter, and anisotropy increases with age, especially in white matter region. Malik et al. in their region of interest (ROI)-based DTI study have shown significant differences in age-related fractional anisotropy (FA) increase in periventriculer white matter and age-related MD decrease in the caudate nuclei, and temporal white matter between controls and neonates with HIE.[3] The popular ROI–based morphometric DTI method is limited to 2 dimensional (D) that does not reflects the whole fiber bundle in 3 D space. In brain white matter, the principle diffusion direction corresponds well with orientation of major fiber in each voxel. Diffusion tensor tractrography (DTT) gives 3 D information of white matter fiber tract. The purpose of this study was to determine the change over time of the DTI measures in thalamic radiations in term neonates with HIE compared to age/sex matched healthy term neonates through their early infancy.

Materials and methods: Eleven term neonates (7 males) of 39.5 mean weeks of gestation with birth asphyxia were examined. All of the children had Sarnat satge II HIE. Eight term neonates (5 males) with normal neurological examination served as control subjects. Both patients and controls underwent DTI around 25 days and around 90 days of life. The mean age in patients group was 23.2 days (range, 15–25 days) and 85.6 days (range, 83–90 days) at the time of first and second MRI study, respectively. All studies were performed within the guidelines of institutional review board. Whole brain conventional MRI (T2, T1 and FLAIR) and DTI were performed on a 1.5-Tesla GE MRI system. DTI data were acquired using a single-shot echo-planar dual spin-echo sequence with ramp sampling. White matter fiber tracts including corpus callosum (CC), anterior (ATR), superior (STR), and posterior (PTR) thalamic radiations were generated and quantified by using in-house developed JAVA based software. The white matter fiber tracts were generated as described in detail elsewhere.[4]

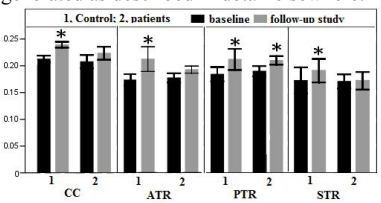

Figure 1: Bar shows change in FA values with age. * Denotes $p < 0.05$.

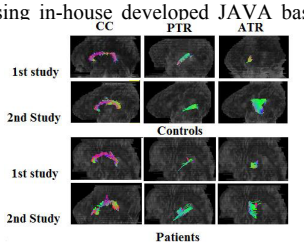

Figure 2: Projection of CC, PTR, and ATR on mid sagittal plane at both time points in controls and HIE infants shows a subsequent change in age-related FA increase between controls and patients.

Results: Nine of the eleven neonates with HIE were normal on conventional MR imaging at both study times. In controls age-related increase in FA with decrease in MD values was observed in all WM fiber bundles on comparing baseline with follow-up study. Significantly increased FA values were observed only in CC, ATR, PTR and STR. In contrast to controls in HIE group no temporal change in FA values was observed in CC, ATR and STR. In controls, significantly decreased MD values were observed in STR. In rest of the fiber bundles showed decreasing trend of MD values over time; however it did not reach the level of statistical significance.

On follow-up study, patients showed decreased FA values in CC, ATR, and STR compared to controls; but it did not reach the level of statistical significance. In neonates with HIE, significantly increased MD values were observed at both time point in all fiber bundles as compared to controls.

Discussion: In newborn with HIE, FA failed to increase significantly with time in CC as well as all the three thalamic radiations; and MD values were consistently higher in patient group compared to controls at both the time points. Abnormal pattern of changes in FA and MD values in normal appearing white matter over time in neonates with HIE may be explained by delayed myelination and documented pathological characteristics of HIE-like neuronal and glial degeneration, cellular necrosis, and apoptosis.

In our patient group concurrently happening events responsible for FA and MD changes in fiber bundles are progressive myelination (due to aging) and ongoing pathological processes. The progressive myelination in white matter fiber bundles in both patients and controls counterbalances the difference in FA values due to the effect of disease. Previous studies using rat model of perinatal HIE have shown that neuronal and oligodendroglial progenitors are highly vulnerable to perinatal hypoxic ischemic brain injury.[5] Injury to these progenitors may lead to the depletion of neurons and oligodendrocytes, contributing to low FA values following hypoxic-ischemic insult. From these observations, it can be inferred that different pattern of age-related increase in anisotropy in periventricular white matter reflects the true difference in myelination among neonates with HIE and controls observed in this study. Significantly increased MD values in patients at both time points signify the events related to disease progression. Ischemic cell death, cell lysis, and membrane disruption in newborn with HIE, result in accumulation of water in extracellular space and further increase in regional MD values. Our study suggests that abnormal FA and MD values with near normal conventional imaging may allow early and more accurate assessment of injury in neonates with HIE.

Reference: 1) Stoll BJ, et al. Nelson Textbook of Pediatrics. Philadelphia: Saunders, 2004:566–568; 2) Schneider JFL, et al. Neuroradiology 2004;46:258–266; 3) Malik GK, et al. Neuropediatrics 2006;37:337–343; 4) Trivedi R, et al. Pediatr Res 2009;66:636-41; 5) Back SA, et al. The Journal of Neuroscience 2002; 22: 455–463.