WHITE MATTER ALTERATION IN BRAIN HEMISPHERE CONTRALATERAL TO LIGATION IN NEONATAL RAT MODEL OF HYPOXIC-ISCHEMIC INJURY

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INTRODUCTION

Neonatal hypoxic ischemic (HI) injury is a complex process, depending on the time and severity of insult. Diffusion tensor imaging (DTI) has been recently applied to study the white matter (WM) vulnerability in the hypoxic-ischemic encephalopathy (HIE) in neonatal rodent models[1,2]. In human neonates, the brain hemisphere contralateral to the lesion side was also found to be affected, exhibiting decreased fractional anisotropy (FA) in WM[3] and indicating possible WM damages. This study aimed to investigate whether HI injury occurs in the hemisphere contralateral to the carotid artery ligation using DTI in well-controlled neonatal rat models of severe and mild HI injuries.

METHOD

Animal model: Established HIE rat models were employed by performing unilateral left common carotid artery ligation on 7-day-old SD rats, followed by exposure to 8% oxygen-balanced nitrogen for 1 hour and 2 hours, respectively, to create mild and severe HI injuries. HIE rats were divided into 2 groups: Group A (1 hour hypoxia; n=9) and Group B (2 hours hypoxia; n=9). As normal controls, intact rats (n = 11 for D1 and D7; n=4 for D14 and D30) were scanned as normal controls.

DTI study: All experiments were performed with a 7T Bruker scanner. DTI was performed on day 1 (D1), day 7 (D7), day 14 (D14) and day 30 (D30) post injury. DT images were acquired with a respiration-gated spin echo 4-shot EPI readout sequence. An encoding scheme of 30 gradient directions homogenously distributed on the unit sphere was used to acquire DT images. The imaging parameters were: repetition time TR = 3000ms, echo time TE = 32ms, Δ = 20ms, δ = 4ms, field of view (FOV) = 32mm (for D1 and D7 post injury), 40mm (for D14 and D30 post injury), thickness = 0.5mm (for D1 and D7 post injury), 0.7mm (for D14 and D30 post injury), Matrix size = 128 x 128 (zero filled to 256 x 256), image resolution = 250 x 250 μm^2 (for D1 and D7 post injury), 313 x 313 μm^2 (for D14 and D30 post injury), acquisition time = ~8 min.

Data analysis: Fractional anisotropy (FA), axial diffusivity ($\lambda_{//}$), radial diffusivity ($\lambda_{\perp}$) and apparent diffusion coefficient (ADC) maps were generated with DTIStudio. Regions of interest (ROIs) were manually drawn in FA maps on the consecutive slices in four areas: corpus callosum (cc), cerebral cortex (CX), anterior commissure (ac) and cerebral peduncle (cp). Values of FA, $\lambda_{//}$, $\lambda_{\perp}$ and ADC were measured. T-tests were performed for any statistical differences in DTI parameters measured between the side of brain contralateral to the ligation in HIE rats and the same side of the brain in normal control rats (with $p<0.001$ considered significant).

RESULTS

Fig. 1 summarizes the findings. In Group A, transient lesion appearances were observed in ipsilateral hemisphere and there was no cyst formation, as expected in mild HI injury. Group B exhibited severe lesions in the ipsilateral hemisphere which gradually became cystic, as illustrated in Fig. 2. At day 1 after HI insult, FA decrease and axial diffusivity increase were found in the contralateral hemispheres in both Group A and Group B. At day 7, Group B continued to exhibit FA decrease, and axial and radial diffusivity increase. However, these changes gradually diminished over time and could not be detected at day 30. No consistent and statistically significant changes in FA and diffusivities were seen in other WM structures (ac and cp) studied and cerebral cortex (cc).

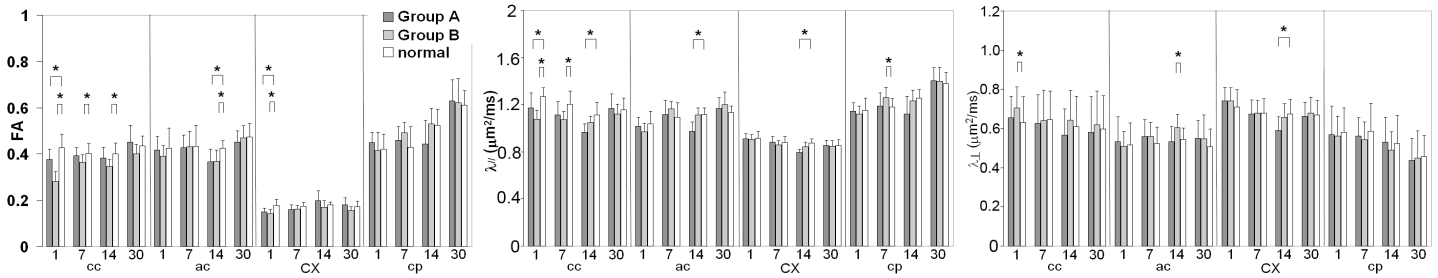

Fig.1 DTI parameters in corpus callosum (cc), anterior commissure (ac), cerebral cortex (CX) and cerebral peduncle (cp) on contralateral hemisphere among Group A (rats with 1 hour hypoxia for mild injury, n=9), Group B (2 hour hypoxia for severe injury, n=9) and normal control group (no injury, n=11) at different time points (i.e., day 1, 7, 14 and 30 after the initial HI insult at day 7).

DISCUSSIONS AND CONCLUSIONS

Lower FA and change of directional diffusivities were observed in the white matter on the contralateral hemisphere, particularly in corpus callosum, during the acute and subacute stage in neonatal P7 rats with severe or mild HI injuries. The extent of changes was in accordance with the severity of HI insult, and they fully normalized at day 30. These findings are similar to those recently reported in human HIE neonates[4]. Decrease in FA and diffusivity alterations can result from the breakdown of white matter organization[3], or on the other hand, due to the smaller number of or less well organized neurons. The exact cause of these changes found on the seemingly normal hemispheres remains unclear, though one might attribute this to the global hypoxia or intracranial pressure increase. Periventricular WM is known to be vulnerable in neonates. Our findings indicated that WM on contralateral hemisphere was indeed adversely affected, which may impact the long-term brain development. Our experimental observation should be taken into consideration in HIE investigation where the contralateral hemisphere is often used as the controls to study the ipsilateral hemisphere.

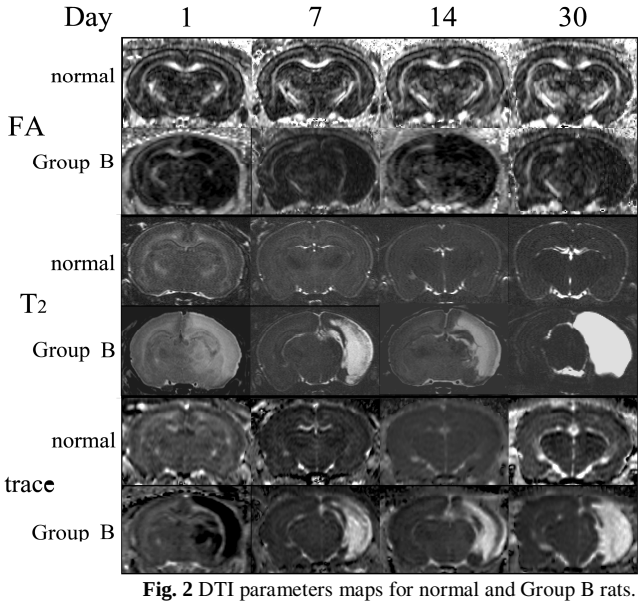

Fig. 2 DTI parameters maps for normal and Group B rats.

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