LONGITUDINAL DTI OF WHITE MATTER INJURY IN EXPERIMENTAL INTRACEREBRAL HEMORRHAGE

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Introduction

White matter injury is closely related to motor outcome after intracerebral hemorrhage (ICH)[1]. Recent clinical studies have demonstrated that DTI metrics of corticospinal tract (CST), including pyramidal tract (PY), could be utilized to predict the functional outcome of ICH[2,3]. However, such findings in patients were largely preliminary due to inconvenient follow-up investigations, small number of patients and such inter-patient variances as hemorrhage volume, physical state and treatment intervention. Previous MRI studies of experimental ICH mainly dealt with the changes of the hemorrhage and its surrounding areas[4,5], while white matter injury was poorly understood. This study aims to employ longitudinal DTI to characterize white matter injury in the well-controlled collagenase-induced ICH rodent model, which closely resembles spontaneous ICH in human[6].

Methods

Animal Preparation: Five female Sprague-Dawley (SD) rats (~15wks; 320~340g) were stereotactically infused with 0.28U collagenase (Type IV, C5138, Sigma) in 1.4μL heparinized saline (0.125μL/min) into the right basal ganglia[6]. MRI was performed in all animals at 3 to 4 hours, 1 day, 3, 7, 14, 28 and 42 days after the surgical insult. ***MRI Protocols:*** All MRI experiments were performed on a 7T Bruker MRI scanner. Under inhaled isoflurane anesthesia, the animal was kept warm by circulating water at 37°C. Diffusion-weighted images (DWIs) were acquired with a SE 4-shot EPI with 30 diffusion gradient directions and 5 b_0 using: TR/TE=3750/32ms, δ/Δ=5/17 ms, resolution=273×273×1000μm^3, b=1000s/mm^2 and NEX=3. 2D T_2-weighted images (T_2WIs) were acquired with TR/TE=3600/38.9ms, FOV=30×30mm^2, matrix=256×256, slice thickness=1.0mm, RARE factor=8 and NEX=2. T_1WIs were acquired with the same dimensions with TR/TE=400/8ms, RARE factor=4 and NEX=28. ***Data Analysis:*** Fractional anisotropy (FA), axial ($\lambda_{//}$) and radial ($\lambda_\perp$) diffusivity maps were generated from DWIs using DTIStudio for quantitative analysis. ROIs were first manually delineated in FA and $\lambda_\perp$ diffusivity maps[7] over external capsule (EC) and pyramidal tract (PY) of both hemispheres on 3 consecutive slices (Fig. 1). Paired t-test was performed for comparison of DTI metrics between ipsi- and contra-lesional EC and PY at each time point (*$p < 0.05$, **$p < 0.01$).

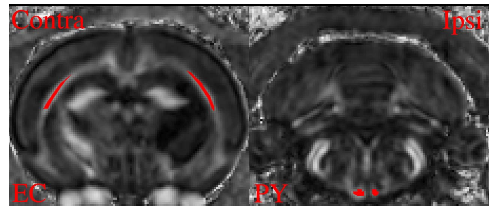

Fig.1 ROI definition of external capsule (EC) and pyramidal tract (PY) in both hemispheres.

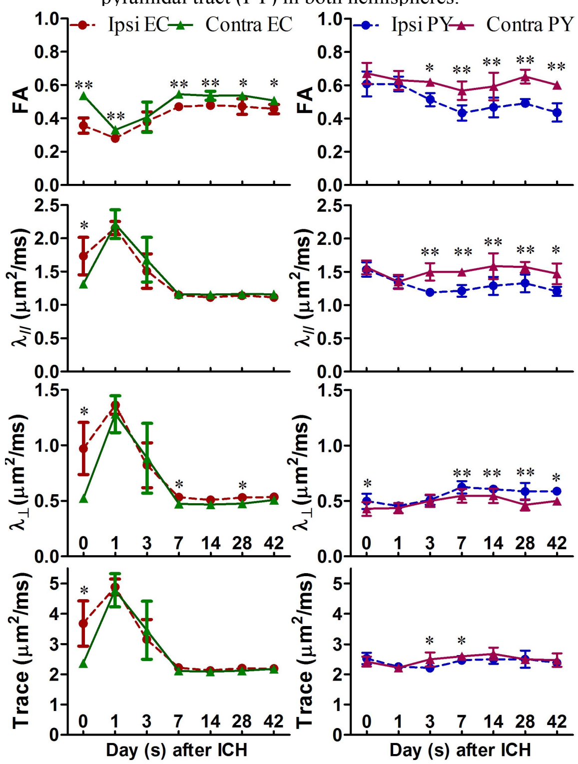

Fig.2 Comparison of DTI metrics (Mean±SD) in ipsilesional external capsule (Ipsi EC) and pyramidal tract (Ipsi PY) versus their contralesional counterparts (Contra EC and Contra PY). Two-tailed paired t-test was performed at each time point (n=5, *$p < 0.05$, **$p < 0.01$).

Results

Fig. 2 shows the longitudinal changes of FA, $\lambda_{//}$ and $\lambda_\perp$ in ipsilesional EC (Ipsi EC) and PY (Ipsi PY), as compared with their contralesional counterparts (Contra EC and Contra PY, respectively). At 3 to 4 hours after ICH, significant decrease in FA value (33.5%) and increase in $\lambda_{//}$ (31.6%) were observed in ipsilesional EC, while increase in $\lambda_\perp$ was observed in both ipsilesional EC (85.5%) and PY (15.9%). At 1 day after ICH, ipsilesional EC showed lower FA value than the contralesional side, while no significant difference was found in $\lambda_{//}$, $\lambda_\perp$ and trace. At 3 days after ICH, decrease in FA value and $\lambda_{//}$ were detected in the ipsilesional PY, but not accompanied by increase in $\lambda_\perp$. At 7 days and afterwards, lower FA value was observed in both ipsilesional EC and PY. In ipsilesional PY, such FA change was accompanied by $\lambda_{//}$ decrease and $\lambda_\perp$ increase at all time points. In Fig. 3, the top panel shows increased T_2W signal in both ipsi- and contra-lesional external capsules within 1 day after ICH, while ipsilesional hyperintensity was retained at 14 days after ICH; the bottom panel shows typical T_2- and T1-weighted images at 14 days after ICH, where no evident difference was observed between ipsi- and contra-lesional PY.

Discussions and Conclusion

In this study, ipsilesional EC showed a decrease in FA value within 4 hours after ICH, as a result of a dominant increase in $\lambda_\perp$ over $\lambda_{//}$. The decrease in FA value persisted from 7 days up to 6 weeks after ICH, but not accompanied by significant decrease in $\lambda_{//}$. This implied that the diffusivity changes in ipsilesional EC was mainly due to vasogenic edema after ICH[8], with characteristic increase in T_2W signal intensities[9] as shown in Fig. 3. Ipsilesional PY showed a decrease in FA and $\lambda_{//}$ at 3 days after ICH, and delayed increase in $\lambda_\perp$ at 7 days after ICH. These changes retained for up to 6 weeks. Meanwhile, no evident signal difference was observed between the ipsi- and contra-lesional PY on T_2- and T_1-weighted images, suggesting that the changes in DTI metrics was not likely due to vasogenic edema. These findings implied that Wallerian degeneration of PY may have occured, which would lead to initial axonal disintegration and subsequent demyelination and fiber tract atropy, similar to that observed in ischemic strokes[10]. In summary, this study characterized longitudinal changes of DTI metrics in white matter for the first time in a well-established experimental ICH model. Diffusivity changes in ipsilesional EC was shown to be mainly due to brain edema. Wallerian degeneration in PY was detected by DTI within 3 days after ICH, and characterized by FA and $\lambda_{//}$ decrease and $\lambda_\perp$ increase. Such degeneration could not be identified on conventional T_1- and T_2-weighted images at 2 weeks after ICH. The diffusivity changes persisted up to 6 weeks after ICH, suggesting an irreversible axonal and myelin damage. These findings provided a more comprehensive understanding of diffusivity changes in PY after ICH, and further support the utilization of DTI for early prognosis and longitudinal monitoring of this human disease. Correlation of early-phase DTI metrics and outcome of motor function will be further investigated to assess the accuracy of DTI in ICH prognosis.

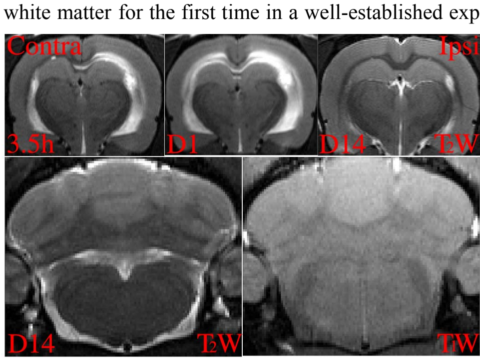

Fig.3 Top panel: T_2WIs of external capsules at 3.5 hours, 1 day and 14 days after ICH; bottom panel: T_2WI and T_1WI of pyramidal tract at 14 days after ICH.

References

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