Stem Cell Treatment of Hemorrhagic Lesions Investigated by Longitudinal DTI Study of a Monkey Model

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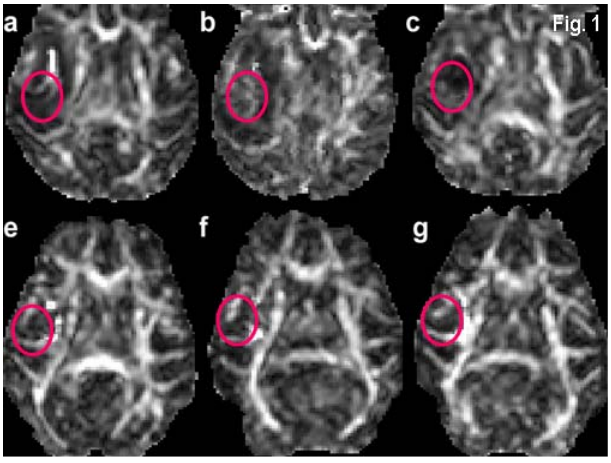
Introduction: Neural transplantation is a novel and promising approach for ameliorating functional deficits caused by CNS diseases or brain trauma injuries [1-3]. Cellular labeling approaches are commonly used for tracking the migration of the transplanted cells in the studies of animal models of rodents by using microscopic imaging. In this study, a more realistic model based on larger animal of monkeys was investigated longitudinally using a routine clinical 3T MRI system. Such studies are very important for eventual clinical applications of the neural transplantation techniques. We used diffusion tensor imaging (DTI) techniques to study how the transplantation of the neural stem cells (NSCs) into the hemorrhagic lesions could improve the neuronal repair and fiber track regeneration in a period of 8 weeks.

Materials and methodS: A reliable intracerebral hemorrhage model based on cynomolgus monkeys was applied for the study. Five young (3 years old, ~5 kg) cynomolgus monkeys were investigated. In each animal a large hemorrhagic lesion was produced by injecting slowly 1.5ml autologous blood into the right basal ganglia nuclei. The NSCs were incubated with ferumoxide-PLL one day before the transplantation. The five monkeys were divided the three groups: high-dose group (n=2), low-dose group (n=2) and control group (n=1). The high-dose group was treated by injecting 0.5ml (5×10^8cells) NSCs around the lesion a week after the hemorrhagic insult. Low-dose group received 0.5ml(1×10^6cells) NSCs treatment at the same region and the same time point. The control animal received no NSCs administration. For the MRI measurements, the animals were anaesthetized with pentobarbital (100mg/Kg i. p.). All measurements were conducted by using a Philips 3T clinical MRI scanner (Achieve Intera) equipped with an 8-channel phased array head coil. Together with other conventional anatomical MRI scans including T1-, T2- and T2*-weighed contrasts, DTI measurements were performed at day 1 and longitudinally at 5, 11,19, 27 and 40 days after NSCs transplantation. The DTI measurements were based on a single-shot echo-planar imaging (EPI) sequence and the essential acquisition parameters included the followings: 15 transverse slices of 4 mm thick and 1 mm slice gap, TE/TR=68/1445ms; FOV=100mm×100mm; matrix size 128×128, one measurement at b=0, and 15 diffusion-weighted measurements at b=1000 s/mm^2 with different diffusion-weighting gradient directions. Parallel imaging acquisition based on SENSE techniques was also used to reduced EPI artifacts. The DTI data were analyzed off-line by using the AFNI software. Before the tensor calculation, eddy current correction was performed by using the algorithm implemented in FSL. White matter fiber tracts around the lesion were also examined using the software DTI-Query (http://graphics.stanford.edu/projects/dti/software). To access the longitudinal changes of the white matter structure in the region near the lesion, The values of the diffusion tensor eigenvalues as well as the derived fraction anisotropy (FA) and mean diffusivity (<D>) were estimated by applying a region of interest (ROI) approximately to the same anatomical locations.

Results: All treated animals showed significant behavior and neurological recovery as expected from the neuronal regeneration observed in the longitudinal DTI measurements. As shown in Fig.1 which shows the FA images for one of the monkeys treated with the high-ose NSCs transplantation, the shrinkage of the hemorrhagic lesion and regeneration of the white matter tracts were apparently substantial over the time period of 40 days. Quantitative evaluation of the ROI values indicated that that FA was significantly decreased in the first week followed by the gradual recovery, while the mean diffusivity was initially increased. An analysis of the individual eigenvalues suggests that the initial FA reduction was due to the increase of the smallest eigenvalue. This is very likely caused by the swelling of the axonal diameter. The animals received lower dose NSCs showed also similar development.



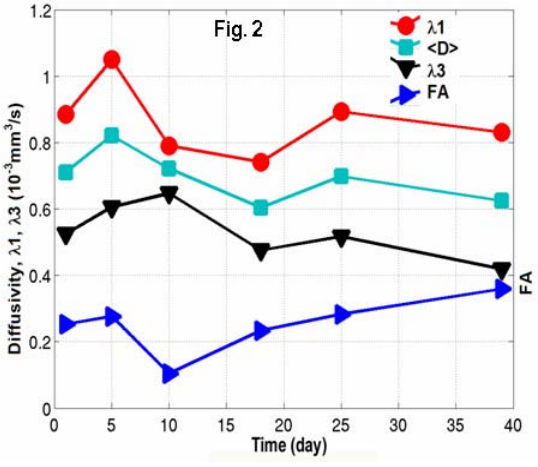


Fig. 1: The FA maps for one of the monkeys treated with the high-dose of NSCS at day 1 (a) and 5 (b), 11 (c),19 (e), 27 (f), and 40 (g) days following the NSCs transplantation.

Fig. 2: The time course of the FA, mean diffusivity, largest (λ1) and smallest (λ3) eigenvalue for the select ROI, as indicated by the circled region in Fig. 2.

Conclusion: (1) NSCs treatment with 0.5-2.5 million cell dosage is very effective for the hemorrhagic lesion as studied by the monkey model; (2) DTI is a useful tool to monitor the time course of the neuronal repair and fiber track regeneration process followed by the NSCs procedure. (3) Cell labeling with ferumoxide-PLL for imaging on clinical MRI system provides quite limited contrast.

References:1) Roy A. E. Bakey, M.D. et al *J Neurosurg* 103:6, 2005; 2) Arbab AS, Yocum GT, Kalish H, et al. *Blood*.;104:1217, 2004; 3) Dong Q, Welsh RC, Chenevert TL, et al. J Magn Reson Imaging, 19: 6, 2004.