Cerebral reorganization after transient focal ischemia in developing rat brain

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Purpose:

The evolution of the extent of ischemic insult areas determined by T2W and DW imaging in transient focal cerebral ischemia in P7 rats was characterized for 3h after the onset of ischemia by a large but incomplete recovery after reperfusion [1]. The remaining hyper intense areas in T2WI at 3h evolved quickly toward classical infarct area, as evidenced by histology[2], but the long term fate of the recovered areas in a developing brain tissue remain unknown. The purpose of this study was to investigate the evolution of these injured tissues by serial MRI measurements.

Materials and Methods:

This study was carried out with 7T Bruker Biospec spectrometer. Transient ischemia was induced in P7 Wistar rats (n=7) and obtained by permanent Middle Cerebral Artery occlusion (MCAo) combined with transient (50 min) right and left Common Carotid Artery occlusion (CCAo). In first hours, serial DWI (EPI sequence with b-value=1000s.mm^{-2}) was acquired. T2 map (multi echo RARE T2WI sequence, 7 echo times) and DTI data (EPI sequence, 30 directions, two b-values) were obtained at days 7, 14 and 21 after ischemia. T2WI and DTI data were acquired with a slice thickness of 1mm and an in plane resolution of 0.117 x 0.117 mm and 0.31 x 0.31 mm, respectively. The animals were anesthetized with isoflurane during surgery and MRI studies (2% and 1% respectively) in mixture 50%O_2 and 50%N_2O. At day 21 after ischemia, animals were sacrificed and the brains were fixed in 3% paraformaldehyde and processed for histology by cresyl violet-staining.

Results:

During the first hours, the evolution of edema volume, determined by DWI in each animal, was homogeneous with a sustained increase during ischemia followed by recovery (-40%) during reperfusion. From day 7 to day 21 after ischemia, the previously ischemic cortex (ipsilateral cortex) showed a significant progressive atrophy compared to the contralateral cortex volume. From day 7, this atrophy was associated with the appearance of a significant decrease of T2 value in the ipsilateral cortex compared to T2 value in contralateral cortex (ΔT2) on T2 maps. This decrease was localized in the areas of the ipsilateral cortex where there was edema area after reperfusion (3h). The T2 decrease worsened significantly with time since day 7 (mean ΔT2 = -6.8 ms) up to day 21 (mean ΔT2 = -8.9 ms). In parallel, the volume of the T2 changes decreased significantly with time from of 7% (mean value) of the brain volume down to 3%. Concerning DTI data in the corresponding areas, the trace of the diffusion tensor maps exhibited no significant change at any time. In contrast, the fraction of anisotropy (FA) maps showed heterogeneous perturbations in the same areas. These perturbations suggesting strong changes in tissue organization were more clearly evidenced on the maps of the main diffusion direction (first eigenvector of Diffusion Tensor, DT) where obvious anisotropy perturbations of the tissue were observed both in cortex and in the adjacent parts of corpus callosum (fig 1). The comparison between T2 maps and the estimation of the cell density on cresyl violet-stained slices indicated a significant increase of cell density in the areas of low T2.

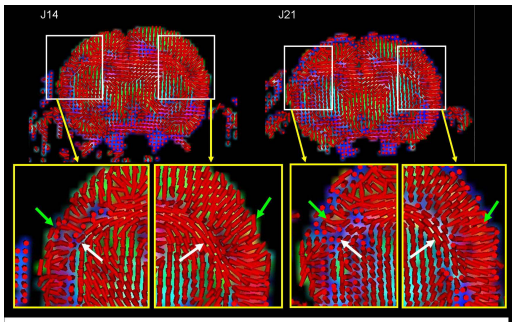

Fig1: First eigenvector of DTI representation for a same animal at day 14 and day 21 after ischemia. Perturbations of the tissue organization were appeared in cortex (green arrows) and corpus callosum (white arrows)

Conclusion:

It can be hypothesized that the long term T2 values decrease found in the previously ischemic areas would be caused by the increase of cell density evidenced by histology. According to the data provided by DTI, this increased of cell density would be associated by strong changes in the tissue architecture in these areas. These phenomena would be the results of both the delayed cerebral damage and reparation processes which take place after transient ischemic areas, such as gliosis, and the plasticity processes related to the development of the brain tissue in immature animals. These data evidenced the need of a long term monitoring by MRI, particularly by T2 and DT imaging, in models of transient focal ischemia in neonates particularly when it is used to investigate the efficiency of a putative protective treatment.

1 Fau S. et al., Experimental Neurology, in press , 2007
2 Renolleau S. et al., Stroke, 29, 1998