Acutely Elevated Diffusion Anisotropy in a Nonhuman Primate Stroke Model

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Introduction: While there have been a large number of studies of the changes of apparent diffusion coefficient (ADC) in the brain during and after stroke, in humans as well as in model systems, there has been much less attention paid to changes in the diffusion tensor, particularly the anisotropic diffusion component. Studies of evolving stroke in rats and in humans suggest that anisotropy (typically the fractional anisotropy, FA) *decreases* in chronic stroke lesions but is slightly *elevated* in the acute phase (1-7). While decreased anisotropy in the later stage of stroke is likely due to the breakdown of cellular structure in the infarct (8) the causes of acutely elevated anisotropy are less clear. Since the commonly used FA index is a combination of the 3 eigenvalues of the tensor, there are many permutations leading to increased FA such as an increase in the largest eigenvalue relative to the smaller ones, or a decrease in all components such that the anisotropic tensor components decrease less than the isotropic components (9). In any event, the observed early FA increase during stroke indicates a change in the shape of the diffusion tensor and this is additional, potentially useful information to add to the diffusion trace and other MRI indices of acutely ischemic brain. In this study we have used a nonhuman primate model of stroke to generate acute and chronic DTI data up to 30 days after stroke induction. While nonhuman primate models of stroke are complex and expensive, they have the advantage of a much more human-like cerebral structure than rats (especially in the white matter). In addition, they allow for more frequent and accurately timed (relative to stroke onset) MRI scanning than is possible with human stroke patients, as well as permitting postmortem analysis of the brain sections at the end of the study.

Methods: Four male adult macaques (macacca fasicularis, 8-10kg) were subjected to focal cerebral ischemia using an endovascular approach (10). Briefly, the model involves advancing an MRI compatible micro-infusion catheter under X-ray fluoroscopic guidance from a femoral artery sheath up into the common carotid artery and thence into the middle cerebral artery (MCA). In two animals the catheter was further advanced to occlude a distal MCA branch for 3 hours, followed by reperfusion by removal of the catheter. The other two animals received permanent MCA occlusion by injection of a small volume of glue. Animals were transferred immediately to a 1.5T GE MRI scanner. Initial diffusion scans were acquired approx. 30 minutes after MCAo. Scanning continued up to 3 hours (6 hours for transient MCAo), after which animals were recovered and scanned again at 1, 3, 6, 10, 17 and 30 days. MRI scans included EPI diffusion tensor, gradient-echo EPI perfusion, FLAIR, T2-FSE, T1-wt, standard GRE and MRA (typically at 12cm FOV, 2.5mm slice thickness). A close fitting receive only surface coil was used. At 30 days, animals were euthanized and the brains removed and fixed in formalin. Fixed brains were gross sectioned at 2.5mm intervals, paraffin embedded, and 5μm thin sections stained with H&E, Luxol Fast Blue and for Myelin Basic Protein. DTI data were processed to generate trace, FA and eigenvalue maps (MRVision software) and the data at each of the 7 timepoints were coregistered using FSL tools.

Results: Figure 1 shows examples of coregistered images from one transient ischemia animal showing the change in lesion appearance over 30 days. Figure 2 shows T2-wt intensity, ADC and FA from an ROI in the lesion core, normalized to contralateral brain in the same animal. The low->normal->elevated ADC progression mirrors that seen in human stroke, although ADC pseudonormalization and T_2 elevation occur earlier than in nonreperfused human stroke. In this example, FA was significantly elevated only at day 0. One other permanent occlusion animal showed slightly elevated FA on day 0, the other 2 animals demonstrated normal FA. By day 3 and later, FA was decreased compared to normal in all animals in the stroke lesion.

Conclusion: We have confirmed the finding of elevated diffusion anisotropy in hyperacute stroke using a nonhuman primate model but FA elevation was only seen in 2 of 4 animals. Acquisition of data in primates at well defined times, as well as addition of the histological analysis, allows for regional identification of the evolution and ultimate fate of tissues, and may help to guide predictive models of tissue outcome in human stroke.

References: 1) Maier et al. 5th ISMRM, 573 ('97). 2) Wu et al. Radiology 212;3:785 ('99). 3) Yang et al. Stroke 30:2382 ('99). 4) Zelaya et al. MRI 17:331 ('99). 5) Carano et al. JMRI 12:842 ('00). 6) Wu et al. 8th ISMRM, 778 ('00). 7) Wu et al. Stroke 33;1:17 ('02). 8) Jones et al. Stroke 30;2:393 ('99). 9) Green et al. Stroke 33:1517 ('02). 10) deCrespigny et al. 9th ISMRM, 354 ('01).

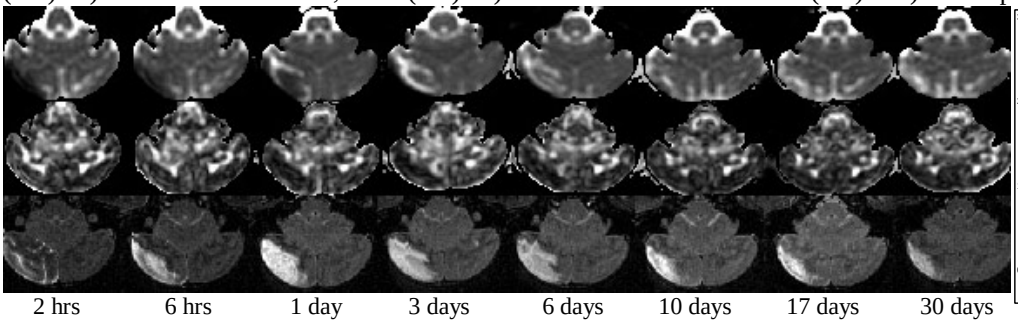

Figure 1. ADC (top), FA (middle), FLAIR (bottom) images during (2hrs) and after (6hrs+) transient MCA occlusion in one monkey.

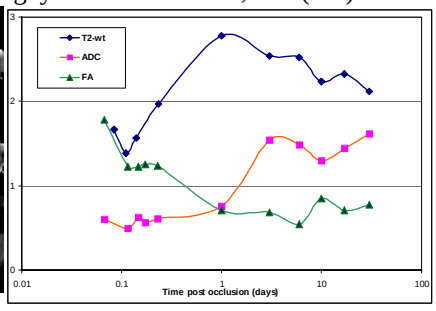

Figure 2: normalized lesion T2-wt, ADC and FA from animal in Fig. 1.