Fractional Anisotropy Changes Following Blood Brain Barrier Disruption

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Introduction

DWI describing net diffusion is becoming extensively used in clinical neurosciences. For example, it is widely used in ischemic stroke detection. DTI is a more complex method to describe diffusion, as the directionality of water diffusion can also be described. The apparent diffusion coefficient (ADC) is a quantitative measure of the net diffusion that can be derived from either DWI or DTI. Fractional anisotropy (FA) describes the level of directionality associated with diffusion and can only be calculated from DTI. FA is higher in white matter (WM) than in grey matter (GM) because the structure of myelin greatly hinders the diffusion of water perpendicular to WM tracts, while water in GM is less hindered and there is little directionality associated with diffusion. With disease, changes in FA are not well characterized, particularly as there are many factors that can alter water diffusion properties (*i.e.*, demyelination, atropy, *etc*.)

In this study, ADC and FA evolution was studied in canines during blood brain barrier (BBB) disruption by hypertonic mannitol solution. The canine model is advantageous, as canines have anatomical similarities to humans, specifically the WM and GM proportions, as FA is influenced by tissue cytoarchitecture. The results indicate FA may be useful to examine BBB integrity.

Methods

Under x-ray guidance, a micro-catheter was placed in a randomly selected left or right internal carotid artery. Baseline MR imaging included five DTI acquisitions (TR/TE = 5000 ms/90.3 ms, 144 × 144 matrix reconstructed to 256 × 256, 24 cm × 14.4 cm field-of-view, 5 mm slice thickness, 15 diffusion directions, b = 1000 s mm^{-2}). At the beginning of the sixth DTI acquisition, 60 ml of 1.4 M mannitol solution was injected into the internal carotid artery over 45 s.[3] Imaging was performed for 2.5 h after mannitol administration, initially every 5 min and this was decreased to every 15 min after 1 h.

FA and ADC maps were constructed using FSL (FMRIB, http://www.fmrib.ox.ac.uk/fsl/). All maps were registered to the first DTI acquisition based on the T2-weighted (b = 0 s mm^{-2}) images using SPM (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/). Any voxels that had an ADC value of >1.0 ×10^{-3} mm^{2}s^{-1} or <0.1 10^{-3} mm^{2}s^{-1} on any of the baseline maps were considered CSF or noise and were subsequently removed from future analysis. Based on the baseline FA maps, WM voxels were defined by FA > 0.35, and GM based on the FA < 0.20. Voxels with an FA between these two thresholds was defined as MIX. On the registered data, the hemisphere in which the mannitol was injected was segmented by hand for serial data analysis. Repeated measures ANOVA examined the ADC and FA values over time across the 10 canines in each tissue type.

Results

ADC did not show any changes with time in any tissues. FA showed time-dependent changes in all three tissues (WM: p = 0.003, MIX: p < 0.001 and GM: p < 0.001); however, the Greenhouse-Geisser correction maintained significant changes in MIX and GM tissues (WM: p = 0.1, MIX: p = 0.02 and GM: p = 0.002). There were also differences in the evolution pattern of FA between the different tissues. In WM, FA showed a transient decrease that reached the minima within the first hour of study and then returned toward baseline. Conversely, GM and MIX tissues FA increased throughout the study. Fig 1 summarizes the FA changes in all three tissues at the time of maximum response.

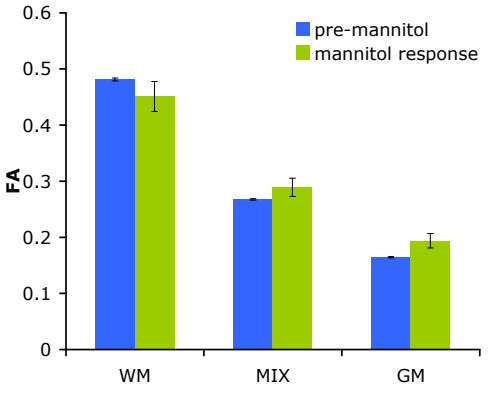

Fig 1. Pre-mannitol and maximum mannitol response FA values for each tissue. All tissues showed time-dependent changes (see text). WM showed a transient FA decrease after mannitol administration, and the minimum values for each animal within 30 min to 60 min after mannitol administration were pooled. MIX and GM showed a constant increase after mannitol administration, so the maximum response time was the final (150 min) observation. Error bars are of the standard error.

Discussion

Here the diffusion responses to BBB disruption with a hypertonic mannitol solution in a gyrencephalic species were examined. In this setting, ADC did not show a response, likely indicating the BBB disruption was not severe enough to cause an ADC change. FA, however, showed different responses depending on the tissue. WM showed a transient decrease, which is on the time scale of the maximum BBB disruption.[4] GM showed an increase throughout the experiment and thus the maximum response time was taken as the final time-point. The MIX tissue is an artificially defined tissue as it is a mixture of WM and GM. The results here indicate that the MIX response is dominated by the GM response. These results may help to understand the FA response in various diseases. For example, we propose that the transitions in FA may assist in determining stroke patients who are good candidates for thrombolysis as there appears to be FA responses before the ADC increase that is indicative of BBB integrity loss.

References:

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[3]Culver *et al.* Am J Vet Res. 1998; **59**: 1503 [4]Neuwelt *et al.* J Clin Invest 1979; 64: 684