Pathophysiological changes in contusions post traumatic brain injury: insights from diffusion tensor imaging

Virginia Newcombe1,2, Guy Williams2, Joanne Outtrim1, Doris Chatfeld1, Giulia Abate1, Thomas Geeraerts1, Anne Manktelow1, Hywel Room1, Leela Mariappan1, Peter Hutchinson1, Jonathan Coles1, and David Menon1,2

1Division of Anaesthesia, Cambridge University, Cambridge, Cambridgeshire, United Kingdom, 2Wolfson Brain Imaging Centre, Cambridge University, Cambridge, Cambridgeshire, United Kingdom, 3Academic Department of Neurosurgery, Cambridge University, Cambridge, Cambridgeshire, United Kingdom

Introduction: Traumatic brain injury (TBI) is often exacerbated by secondary events that lead to secondary brain injury, and represent potentially modifiable cause of mortality and morbidity post TBI. One potential means of improving such translation is to characterise tissue at risk using early imaging studies, and define markers of injury progression in these tissue compartments to use as biomarkers. Diffusion tensor imaging (DTI) may provide better characterisation of such pathophysiology and allow contusion growth to be used as an imaging biomarker of treatment efficacy in early drug development.

Methods: Thirty-five patients with moderate-to-severe TBI who required ventilation and sedation for their injury underwent MR imaging while in the Neurosciences Critical Care Unit (NCCU) at a median of 49.5 (range 14 to 359) hours post injury. Eighteen underwent a second scan while still in NCCU at a median of 230 (range 66 to 618) hours post injury. Ethical approval was obtained from the Local Research Ethics Committee, and written assent from next-of-kin were obtained in all cases. MR imaging was performed using a 3 Tesla Siemens TIM Trio, and included a 3D T1-weighted structural sequence (MP-RAGE), as well as spin echo echoplanar diffusion weighted imaging (DWI); acquired using 12 non-collinear directions, 5 b-values equally spaced from 300 to 1500 s/mm² with 4 b = 0 images). A sequence with multiple b-values was chosen to allow accurate characterization of edema in the acute phase, as it has been shown that the use of multiple b-values for a smaller number of unique gradient directions provides ADC results that are more robust than ones obtain with a higher number of sampling directions but only one b-value. FDT (FMIRB’s Diffusion Toolbox) was used to fit a tensor at each voxel and create ADC maps. Regions of interest were manually drawn using Analyze 7.0 around contusions on ADC maps for each scan. Regions included a core with restricted diffusion, a surrounding zone of high diffusivity, and an external rim of restricted diffusion. A rim of normal appearing brain parenchyma three voxels wide surrounding Region 2/3 was also defined. A corresponding ROI was also drawn, where possible, in normal appearing tissue on the contralateral side with the same volume as the index contusion, so as to provide a “control region” with a similar mix of grey and white matter. Mean FA and ADC for the different ROIs were calculated.

Results: All contusions within the first few days of injury showed two main regions; a core of restricted diffusion surrounded by an area of raised ADC (Figure 1, A). While some lesions showed these regions more clearly than others, this pattern was universal. Surrounding the area of raised ADC a thinner rim of hypointensity was observed in 20 of 22 (91%) patients scanned within the first three days post injury. The cytotoxic rim volume was not identifiable on scans obtained more than 3 days following TBI. Both the original core ROI and original cytotoxic rim showed an increase in ADC at the second scan (Figure 1, B). The corresponding change in ADC for the vasogenic ROI was more variable. The total contusion volume increased from 9.9 (2.2 to 81.8)mm³ to 26.9 (5.7 to 90.8)mm³.

Discussion: This study documents the progression of contusions over time, providing an imaging biomarker for use in interventional studies. However, more importantly, our data provide insights into the physiology that underpins such expansion. We show that, within the first three days after injury, DTI can detect three distinct regions within traumatic contusions in the majority of patients; a core, an area of raised ADC around the core, and a thin rim of hypointensity. It is likely the areas of increased ADC represent vasogenic edema and decreased cytotoxic edema implying that two forms of edema coexists during this period around contusions. The area of cytotoxic edema may represent a “traumatic penumbra” of at risk tissue following TBI which may be rescued by effective therapy.

Conclusions: A more complete understanding of contusions, particularly the potentially reversible “traumatic penumbra” around such lesions may allow MR (including DTI) to be used as in vivo biomarkers of tissue outcome, and help provide proof of principle of the potential efficacy of specific interventions as well as an improved understanding of therapeutic windows. Such data may help refine selection of agents for subsequent outcome trials. These techniques may also aid the assessment of the adequacy of treatment in individual patients, and may therefore potential guide individualized and targeted therapy after TBI.

References:
2. FSL. www.fmrib.ox.ac.uk/fsl/