Evidence for abnormal venous drainage in a closed head model of pediatric mild traumatic brain injury using 9.4T MRI

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Target audience: Researchers and clinicians who are studying the pathology of mild traumatic brain injury (mTBI or concussion). Specifically those using MRI, with an interest in pediatric injury, vascular changes, and/or those interested in animal models of mTBI.

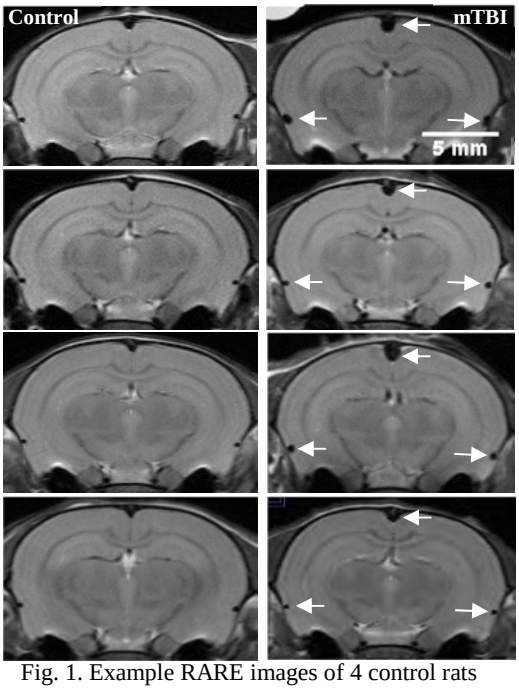

Fig. 1. Example RARE images of 4 control rats (left column) and 4 mTBI rats (right column). White arrows point towards enlarged sagittal and transverse sinuses. Bregma -4.8.

Purpose: To determine the imaging phenotype of a new pediatric closed head mTBI model and whether anatomy, perfusion or quantitative T2 could be used as a marker of injury.

Methods: Juvenile male and female Sprague-Dawley rats (P30) were anesthetized using isoflurane and exposed to a modified closed-head impact or a sham injury[1]. Control (n=5; 3 female, 2 male) and mTBI (n=12; 6 female, 6 male) rats were imaged 24h post-injury using a 9.4T Bruker Avance console with a 35mm volume coil. MRI was done using isoflurane anesthesia, spontaneously ventilating and controlling for respiration, heart rate, and body temperature. RARE had a matrix of 256x256 and a resolution of 0.1 x 0.1 x 1mm. ASL and multi-echo methods had a matrix of 128x128 and a resolution of 0.2 x 0.2 x 1mm. RARE (TE/TR: 16/4000, RARE factor: 8, NEX= 5), continuous arterial spin labeling (cASL) (TE/TR: 2.66/3000, NEX= 16, RARE factor: 36), multi-echo spin echo (TE/TR: 6/3000, NEX = 4, echo = 6 ms, 128 echoes) and multi-echo gradient echo (TE/TR/α: 3/300/30°, echo = 4 ms, 5 echoes, NEX = 10) sequences were used. Time-to-right was recorded immediately post-injury to be used as supporting evidence to show rats did experience an mTBI. For T2, T2* and perfusion, ROIs were drawn on the hippocampus, prefrontal cortex, and basal ganglia. Sinus area was calculated using ImageJ. ROIs were drawn on 3 consecutive slices at approximately bregma 3.8, -4.8 and -5.8 based on anatomical landmarks[2] for each sinus and averaged for each animal.

Results: There were significant differences in time-to-right between the groups with mTBI rats exhibiting a greater latency ($p<0.05$). Sagittal and transverse sinuses were visibly enlarged 24h post-injury (Fig. 1). mTBI rats had a significant enlargement of the sagittal sinus (mTBI: 0.60±0.2 mm^2 (mean±S.D.) vs. sham 0.38±0.07 mm^2) and a significant increase in left transverse sinus size (mTBI: 0.12± 0.04 mm^2 vs. sham: 0.07±0.02 mm^2) (Fig. 2). There was no significant difference in cerebral blood flow (CBF), T2 and T2* measurements.

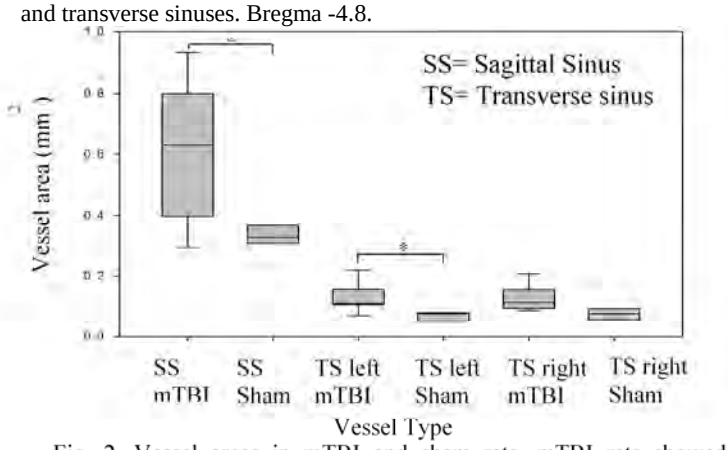

Fig. 2. Vessel areas in mTBI and sham rats. mTBI rats showed enlargement of sagittal (SS) and transverse sinuses (TS). *p<0.05. Boxes represent the 25th and 75th percentiles, error bars are the min and max values and the line the median.

Discussion: Within the brain, this model shows no abnormality based on standard T2w MRI, perfusion, T2 or T2*, even though mTBI animals exhibited an increased time-to-right. This is consistent with the lack of structural abnormalities in clinical MRI studies in pediatric mTBI patients. These results however suggest that the sagittal and transverse sinuses are affected enlarged in this model, which may be of clinical importance. These large low pressure drainage systems are not thought to have regulation, making this observation particularly interesting. Enlargement is unlikely to be caused by flow changes as there is no significant change in ASL perfusion and the trend is for reduced, not increased flow. The reason behind this increase in venous calibre is unclear and requires further investigation. The venous abnormality is consistent with evidence in human studies of abnormal perfusion and flow regulation in mTBI, which includes a report of collapsed jugular veins and an increase in flow through secondary veins[3]. As abnormal flow could directly relate to headache[4], this finding opens a new avenue of investigation (changes in venous draining) into the pathophysiology of mTBI.

Conclusion: We believe this to be the first time that enlargement of the large cerebral venous draining vessels has been reported in an animal model of mTBI. These results suggest that the pathophysiology of mTBI may involve abnormalities of cerebral venous drainage. This novel observation could provide clues as to the cause of post-traumatic headache and highlights the need for additional studies of venous drainage in mTBI patients.

References: 1] Mychasiuk R, Farran A, Esser MJ. J Neurotrauma. 2014; 31(8):749-57
2] Paxinos GP and Watson C. 1986. The rat brain in stereotaxic coordinates. London: Academic Press.
3] Pomschar A, Koerte I, Lee S, Laubender RP, Straube A, Heinen F, Ertl-Wagner B, Alperin N. PLoS One. 2013; 8(2):e55447
4] Gilkey SJ, Ramadan NM, Aurora TK, Welch KM. Headache. 1997; 37(9):583-7.