Dynamic Contrast Enhanced MRI to Detect Vascular Injury in a Rat Model of Traumatic Brain Injury

Matthew D Budde[1], L. Christine Turtzo[2], Eric Gold[2], Lindsay Janes[3], Bobbi Lewis[3], and Joseph A Frank[2,3]

[1]*Neurosurgery, Medical College of Wisconsin, Milwaukee, Wisconsin, United States,* [2]*Center for Neuroscience and Regenerative Medicine, Bethesda, MD, United States,* [3]*Clinical Center, National Institutes of Health, Bethesda, MD, United States*

Introduction

Traumatic brain injury (TBI) is an important public health problem, with 1.4 million incidents annually in the US[1]. While computed tomography remains the standard of care for acute TBI management, MRI-based measures are being investigated as potential markers of injury and as specific markers for a variety of therapeutic interventions. Direct brain trauma causes injury to both the brain tissue as well as the related vasculature. We sought to investigate whether interferon-Beta 1, a drug that stabilizes the blood brain barrier (BBB) and has anti-inflammatory properties[2], would be effective in a rat model of TBI and whether dynamic contrast enhanced (DCE) MRI could be used to monitor its effect on BBB disruption[3].

Materials and Methods

Rats were exposed to a controlled cortical impact (CCI) centered over the left motor cortex (1.1 mm Bregma, 2.5 mm lateral) at a depth of 2 mm, and underwent in vivo MRI within 30 minutes of injury. A multi-echo spin echo sequence was used for T_2 mapping at a resolution of 118 μm^2 and slice thickness of 0.5 mm. T_1 was measured from a series of T_1-weighted gradient echo images with variable flip angles. DCE was performed using a T_1-weighted gradient echo sequence at a temporal resolution of 10 s and a spatial resolution of 234 μm^2 and 0.5 mm slice thickness centered over the lesion before and during a intraveneous bolus injection of Gd-DTPA (Magnevist). A post-contrast T_1-weighted spin echo was acquired at the completion of the DCE assessment at the same resolution as the T_2 image. DCE was analyzed using the reference region model[4], assuming a K^{trans} of 0.1 min^{-1} and V_e of 0.1 for muscle. A cohort of rats (n=8) were administered interferon beta-1b (Betaseron; 1 µl/g body weight i.v.) within 6 hours post injury for 3 consecutive days. Saline was administered similarly to control rats (n=9). Rats underwent MRI again at 3, 7, and 30 days post-injury. All images were registered to a common space using ANTS software and quantified with a region of interest analysis. The fractional injured volume (greater than 2 s.d. of the contralateral hemisphere) was quantified for T_2, post-contrast T_1 (Gd), K^{trans}, and V_e).

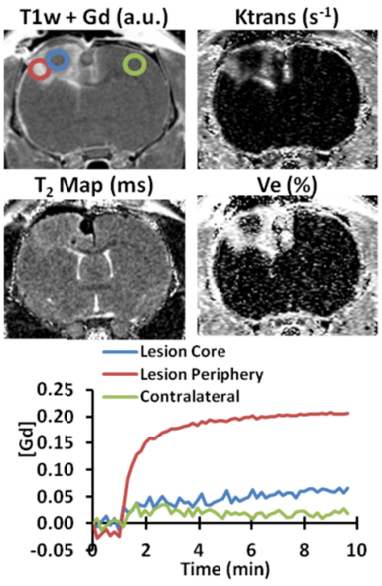

Figure 1. BBB disruption in a saline-treated animal at 30 minutes post-injury is high in the periphery of the lesion, with minimal T2 edema.

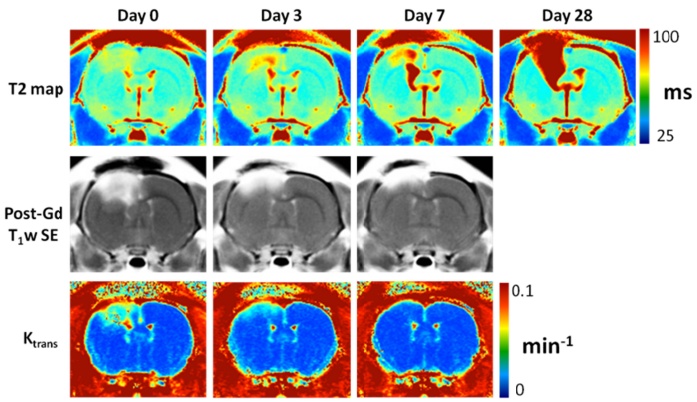

Figure 2. Group-averaged images from saline treated rats (n=9) show the evolution of edema and BBB disruption following severe TBI.

Results

Within 30 minutes of injury, extensive BBB disruption was the most striking feature in the lesioned cortex, with less visible edema. Spatially, Gd leakage coincided with the periphery of the lesion, suggesting greater vascular shearing in these areas. By day 28 post-injury, the lesion consisted of a fluid-filled cavity. Interferon-Beta treated animals were not significantly different than control animals in any of the measures at any time point. In saline-treated animals, T_2 in the acute phase was a greater predictor of eventual lesion volume than either semi-quantitative (enhancing volume) or quantitative (K^{trans}, V_e) indicators of BBB disruption. On the other hand, acute neuroimaging markers were poor predictors of sub-chronic to chronic functional abnormalities (foot faults), although the lesion volume at the endpoint (day 28) had a significant correlation with foot faults at the same time point.

Day	Measure	Day 28 T_2	Day 28 FF
0	T_2	0.80	0.02
	T_1w+Gd	0.48	-0.11
	K^{trans}	-0.59	0.10
	V_e	-0.52	0.09
3	T_2	0.67	0.44
	T_1w+Gd	0.55	0.42
	K^{trans}	-0.11	-0.29
	V_e	0.37	-0.09
7	T_2	0.62	0.76
	T_1w+Gd	0.44	0.42
	K^{trans}	-0.21	-0.39
	V_e	-0.18	-0.20
28	T_2	-	0.52

Correlations (R) between imaging measures and endpoint lesion volume (T_2) or foot faults (FF).

Discussion and Conclusions

Although the BBB was severly disrupted in the hyperacute and acute phases of injury, it was uncorrelated with either the T_2 lesion volume at day 28 or foot faults, and interferon beta-1b did not alter the course of injury. It is possible that the vascular shearing in this model is too great for pharmacological intervention. Moreover, compared to conventional contrast-enhanced T_1-weighted imaging, DCE MRI did not seem to offer significantly greater pathological insight or sensitivity. In severe TBI, conventional T_2 weighted imaging and post-contrast T_1-weighted imaging may be sufficient to determine tissue and vascular injury severity, respectively.

References: [1]Center for Disease Control, 2006. [2]Veldhuis et al. JCBFM 2003. [3]Shlosberg et al. Nat. Rev Neurol. 2010. [4]Faraneshl and Yankeelov, Phys. Med. Biol 2008.