The Evolution of Traumatic Brain Injury in a Rat Model: Implications for Cell Tracking with MRI

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Introduction: Serial MRI facilitates in vivo intra- and inter-experimental subject evolutionary analysis of traumatic brain injury (TBI) lesions1-5. MRI has been used to track the delivery of superparamagnetic iron oxide (SPIO) labeled cells in experimental TBI models6-8. However, despite the availability of MRI, the natural history of experimental TBI lesions is not well described in the literature. We performed controlled cortical impact (CCI) and MRI on rats during the acute to chronic stages after injury, demonstrate the inherent variability in the model, and raise concern in interpreting results in the absence of rigorous follow-up studies.

Methods and Materials: The motor cortex (2.5 mm left lateral, 1.0 mm anterior of Bregma) of anesthetized female Wistar rats (ages 8-12 weeks; n=34) underwent CCI with a 5 mm impactor tip driven by an electromagnetic piston (velocity 5 m/s, depth 2.0 mm, dwell time 100 msec). In vivo MRI was performed at 7T on days 2, 9, and 30 post-CCI using a T2w sequence (TR/TE 3500/40 msec, resolution of 112×112×500 μm3). Cortical and lesion volumes were determined using MEDx software.

Results: The appearance and volume of CCI-induced lesions at days 2, 9, and 30 was variable and was different than was previously reported. There was little correlation between the percent change of CCI side cortex volume to contralateral side cortex volume on Day 2 to subsequent exams on days 9 and 30 (percent change CCI cortical volume/contralateral cortex volume mean±standard deviation: Day 2 = 24.4±8.6%; Day 9 = -5.9±11.0%; Day 30 = -11.6 ±12.0%)(fig1). Hemorrhagic conversion within the CCI lesion occurred in 45% of rats between days 2 and 9 (fig 2).

Discussion and Conclusions: Some of the early variation in CCI lesions can be attributed to differences in surgical technique. However, the further divergence of similar lesions between days 2 and 30 demonstrates the inherent biological variability of the CCI rat model. The possibility of hemorrhagic evolution between days 2 and 9 raises caution in using SPIO-labeled cells to track their delivery to CCI lesions, as hemorrhage will appear identical on MRI and Prussian blue staining. Autofluorescence of antibody stained cells within the area of hemorrhage may also lead to misinterpretation of positive findings of SPIO labeled cells unless the appropriate controls are performed (fig 3). Investigators utilizing the CCI model in the rat should be aware of the higher degree of variability in results obtained with this method of inducing TBI.


Figure 1. Rats with similar amounts of injury on MRI at Day 2 could have lesions that appeared markedly different by Day 30 (right). Scatter plots of percent differences in cortical volume of the injured side versus the contralateral side demonstrated less variability at Day 2 than at Day 30 (left).

Figure 2. Hemorrhage can develop by Day 9 in rats with little evidence of hemorrhage on T2 weighted (left, right) or T2* (middle) sequences at Day 2.

Figure 3. Areas of hemorrhage are hypointense on MRI (top). Cells in these regions may stain with Prussian blue (bottom left) and exhibit autofluorescence in the absence of antibody staining (bottom right), that complicates tracking of SPIO labeled cells.