

## Early MRI characterization of cerebral edema following diffuse traumatic brain injury in rat

Y. van de Looij<sup>1,2</sup>, H. Lahrech<sup>1,2</sup>, G. Francony<sup>1,2</sup>, O. Carle<sup>1,2</sup>, R. Farion<sup>1,2</sup>, C. Segebarth<sup>1,2</sup>, J-F. Payen<sup>1,2</sup>

<sup>1</sup>INSERM U594, Grenoble, France, <sup>2</sup>Univ Joseph Fourier, Grenoble, France

### Introduction

Posttraumatic cerebral edema represents the leading cause of death and neurological sequels. However, early characterization of this edema is poorly documented, although it could affect the early management of patients with severe Traumatic Brain Injury (TBI). The objective of this work was to characterize early brain edema in a model of diffuse traumatic injury in rat brain using diffusion, quantitative T<sub>1</sub> and quantitative T<sub>2</sub> MR Imaging. Furthermore, Blood-Brain-Barrier (BBB) permeability was also analyzed by MRI after the administration of Gd-Dota and manganese Contrast Agents (CA). Histology and microgravimetry [1] were performed in order to confirm MRI results.

### Materials and methods

22 Adult male Wistar rats (300-400g) were divided into two groups: a control group (n=10) and a trauma group (n=12). Rats were anesthetized, tracheotomized and artificially ventilated. Two catheters were inserted into the femoral artery and vein to monitor arterial blood pressure, blood gases and for intravenous administration of anesthetic agents ( $\alpha$ -chloralose, pancuronium) and CA. Diffuse TBI was induced according to the impact acceleration model [2]. Two independent MRI protocols were performed post-trauma using a 7T magnet and a homogeneous RF coil for signal excitation and detection. During all of these experiments, rat body temperature, mean arterial blood pressure and arterial blood gases (PaO<sub>2</sub>, PaCO<sub>2</sub>, arterial pH) were maintained constant. The first protocol consisted in the acquisition of diffusion tensor, T<sub>1</sub> and T<sub>2</sub> quantitative images each hour up to six hours post-trauma. At the end of the experiment (6 hours after trauma), brains were extracted for the both groups (control: n = 6, trauma: n = 8) and Cerebral Water Content (CWC) was determined by the microgravimetric method [1]. The second protocol was performed in order to assess the BBB permeability. Quantitative T<sub>1</sub> images after CA administration (0.2 mmol/kg of Gd-Dota followed by an infusion of manganese 9  $\mu$ mol/ kg/min) were performed during 3 hours post-trauma (control: n = 4, trauma: n = 4). This second protocol included histology, performed at the end of MRI experiments, using tissue coloration with intravenously injection of 50 mg/kg of Evans blue dye at the moment of trauma. For diffusion measurements, diffusion gradients were set in 6 different orientations. Diffusion gradient duration and diffusion time were 9 ms and 17 ms respectively leading to a gradient *b*-factor equal to 500 s/mm<sup>2</sup>. The quantitative T<sub>2</sub> sequence was a multi-slice/multi-echo sequence with 8 different echo times (from 25 to 200 ms). For these two MRI sequences, 5 slices were acquired with a 128x64 matrix. An IR-snapshot sequence was used for quantitative T<sub>1</sub> measures (1 slice, 12 inversions times from 50 to 6000 ms). All images were acquired with a FOV of 40 mm and a thickness of 1.5 mm. Maps of T<sub>1</sub>, T<sub>2</sub> and the Apparent Diffusion Coefficient (ADC: average of the three eigenvalues) were made with in house software using the IDL (Interactive Data language) programs. Four regions of interest were analyzed: dorsoparietal cortex, corpus callosum, basal nuclei, and extracerebral tissue. Results (mean  $\pm$  SD) were analyzed by Student test and ANOVA.

### Results

Temperature (control T = 37  $\pm$  0.3  $^{\circ}$ C and trauma T = 36.9  $\pm$  0.3  $^{\circ}$ C), mean arterial blood pressure (control = 112  $\pm$  15 mmHg and trauma = 99  $\pm$  24 mmHg) and arterial blood gases (control PaO<sub>2</sub> = 206  $\pm$  56 mmHg and trauma PaO<sub>2</sub> = 174  $\pm$  29 mmHg; control PaCO<sub>2</sub> = 34  $\pm$  9 mmHg and trauma PaCO<sub>2</sub> = 32  $\pm$  6 mmHg; control arterial pH = 7.38  $\pm$  0.05 and trauma arterial pH = 7.36  $\pm$  0.07) analyses were similar in the two groups. Figure 1 shows that the ADC value in the cortex was significantly lower (16 %; p < 0.05) in the trauma group compared with the control group. Overall, the ADC decrease was significant in corpus callosum and in basal nuclei throughout the experiment. T<sub>1</sub> variations between the two groups were only significant in basal nuclei at 4 hours post-trauma (control T<sub>1</sub> = 1610  $\pm$  50 ms versus trauma T<sub>1</sub> = 1780  $\pm$  50 ms; p < 0.05) while intracerebral T<sub>2</sub> values were not significantly different in the two groups (control T<sub>2</sub> = 45  $\pm$  5 ms and trauma T<sub>2</sub> = 43  $\pm$  5 ms; p > 0.05). Microgravimetric analysis confirmed cerebral edema 6 hours after trauma in cortex and basal nuclei since an increase of 0.9% CWC was detected in trauma group (CWC: 78.5% in control group versus 79.4% in trauma group; p = 0.02). Changes in T<sub>1</sub> values in cortex and basal nuclei were positively correlated with the increase in CWC (r<sup>2</sup> = 0.51). Figure 2 shows three plots of T<sub>1</sub> behavior after MRI CA injection. The plot from muscle region of interest is shown as a reference for a tissue with high permeability. The temporal evolutions of the two plots from cerebral tissue corresponding to trauma group plot and control group plot are similar and are very different from that of muscle. This demonstrates the absence of BBB breakdown. This result was confirmed by histological analysis in which no presence of Evans blue dye was found in the interstitial space.

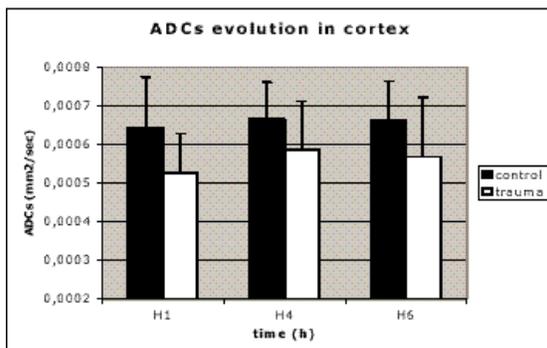


Fig. 1

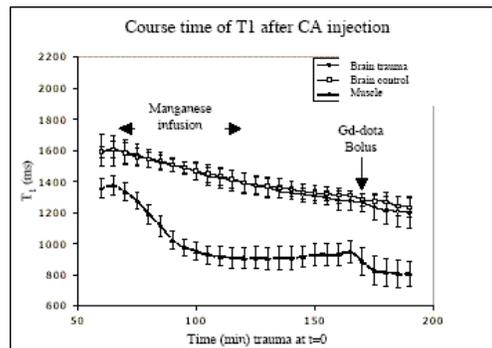


Fig.2

### Conclusion

The diffusion results revealed that ADC is a promising parameter for the early detection of post-traumatic cerebral edema. However, quantitative T<sub>1</sub> and T<sub>2</sub> MRI parameters are not sensitive. The early ADC decrease (already observed at one hour post-trauma) is in agreement with others [3], and provides evidence that cellular edema is predominant following diffuse traumatic brain injury. This result is confirmed by the CA MRI results where the BBB is found intact, showing the absence of a vasogenic edema three hours post-trauma. Such findings could be of interest for the early management of patients with severe traumatic brain injury.

[1] Marmarou A *et al*, J Neurosurg 56: 246-253, (1982); [2] Marmarou A *et al*, J Neurosurg 80: 291-313, (1994); [3] Barzo P *et al*, J Neurosurg 8 : 900-907, (1997).