Dynamic contrast enhanced MRI for investigation of the blood-brain barrier in an experimental model of communicating hydrocephalus

L. Fanea[1], S. Rashid[1], J. P. McAllister[2], J. Li[3], H. Benveniste[4], M. Yu[4], and M. E. Wagshul[1]

[1]Department of Radiology, SUNY Stony Brook, Stony Brook, NY, United States, [2]Division of Pediatric Neurosurgery, Primary Children's Hospital, University of Utah, Salt Lake City, UT, United States, [3]Department of Pediatric Neurosurgery, Children's Hospital of Michigan, Detroit, MI, United States, [4]Medical Department, Brookhaven National Laboratory, Upton, NY, United States

INTRODUCTION Hydrocephalus (HC) represents the leading cause for brain surgery in children in the US. While treatment of HC with ventriculoperitoneal shunting is a well established technique with marked improvement in patient outcome, there are still numerous complications and the mean lifetime of a shunt before needing revision surgery is only a little over one year (1). The disruption of normal CSF flow and drainage in hydrocephalus is assumed to be the primary "pathology" of this disease and thus the reestablishment of CSF drainage with the shunt is the logical treatment of choice. However, with the complications associated with shunting and the lack of a clear understanding of the source of CSF blockage in many cases it may be beneficial to study other aspects of the disease. For example, it is well established that there are alterations in cerebral blood flow patterns in the brain in hydrocephalus (2). It has been hypothesized that changes in intracranial compliance in hydrocephalus may lead to changes in the distribution of intracranial pulsations, which in turn can lead to increased pulsations at the capillary level and alterations in the integrity of the blood-brain barrier (BBB) (3). It has recently been shown that transfer rates of gadolinium into normal brain can be detected using slow gadolinium infusions (4). In this study, we utilized slow-infusion, dynamic contrast enhanced MRI (DCE-MRI) to study subtle changes in the BBB in a rat model of communicating hydrocephalus.

METHODS Hydrocephalus was induced in Sprague-Dawley rats (female, n = 6, wt = 200-220 g) by injection of kaolin into the basal cistern (5). In most cases, this induction leads to mild-to-severe ventriculomegaly within a few days. At between 4-5 weeks post induction, DCE-MRI was performed on a Bruker Biospec 9.4T animal microMRI system. Animals were maintained under isoflurane anesthesia while inside the MRI scanner, lying with their head on a 3-cm surface coil. DCE-MRI was collected with a 3D spoiled gradient echo sequence with the following parameters: FOV = 4x3cm, matrix 128 x 96, TE/TR = 1.6/60 ms, FA = 40, ST = 1 mm, 50 slices. Total acquisition time was 4.8 minutes. Infusions into the tail vein were 5 ml/hr of 125 mM gadolinium (diluted in physiological saline), with the infusion lasting 45-60 minutes. Prior to and during the infusion DCE-MRI images were collected every 5 minutes, and after the infusion stopped they were collected every 10 minutes. Total acquisition time ~ 120 min.

Image analysis, signal intensity measurements and data modeling were performed in Matlab. Signal intensity curves, normalized to the pre-infusion values and to a calibration phantom, were modeled using a two-compartment model, with a fixed extravascular, extracellular space of 0.2. The arterial input function was extracted from the transverse sinus, ensuring to select voxel with minimal potential for partial volume error, and data were analyzed in tissue (thalamus and cortex), and CSF space (lateral ventricle, aqueduct and 4th ventricle) regions of interest (ROIs).

Overall infusion and elimination rates of the CA in the blood, exchange rates, k_{trans}, of the CA between the blood and the tissue through the BBB and the fractional volumes of the tissue compartments assumed: blood, parenchyma and the intracellular space were calculated by fitting the blood and tissue CA concentration curves over time to the corresponding models (3,4).

Two compartments accessible to water solutes were considered for modeling of concentration curves over time in the CSF spaces: the blood compartment (fractional volume - v_B) and the CSF compartment (fractional volume - v_C). Presence of the CA in the blood at a concentration C_B and in the CSF compartment at a concentration C_c was assumed to model concentration curves over time in the CSF spaces (Cs): $Cs = v_B C_B + v_c C_c$. CA concentration over time in the CSF compartments increases at an overall rate, k_{in} due to possible passage of the CA from the blood to the CSF compartment through the blood to CSF barrier in the choroid plexus. CA concentration in the CSF compartment (C_c) decreases over time at an overall rate, k_{out}, due to the elimination mechanisms of the CSF: $dC_c/dt = k_{in}C_B - k_{out}C_c$

RESULTS CA concentration curves over time measured in the blood (+ red), 4th ventricle (+ blue), aqueduct (+ pink) and thalamus left (+ black) and right (o black) and their corresponding fittings (continuous lines, corresponding colours) for a mildly HC animal are shown in Fig. 1. For all animals investigated, the overall infusion rates of the CA in the blood varied from 0.0427 to 0.0956 mM/min, while the overall elimination rates varied from 0.0281 to 0.0344 1/min.

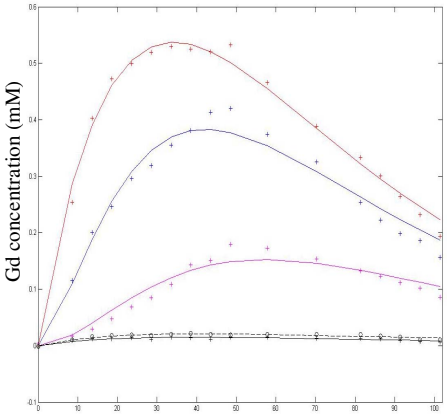

Fig 1CA concentration curves over time

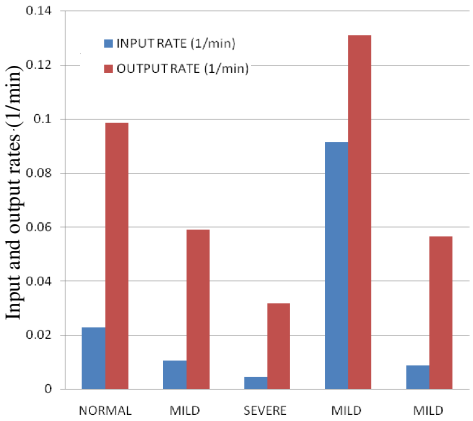

Fig. 2 Overall rates of the CA in the 4th ventricle

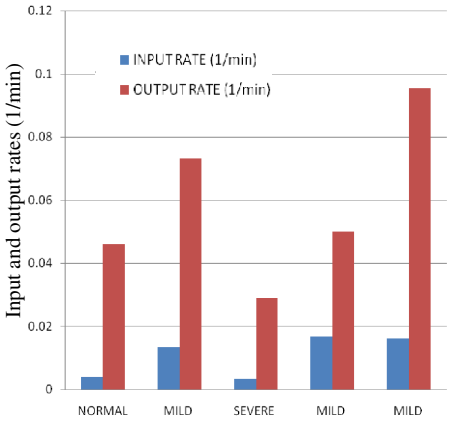

Fig 3 Overall rates of the CA in the aqueduct

Overall input and output rates of the contrast agent in the following CSF spaces: lateral ventricle (left and right hemisphere), 4th ventricle (Fig. 2) and aqueduct (Fig. 3) were calculated by fitting the CSF data in the normal, mildly and severily HC rat brain to the two-compartment model presented in the Methods section.

The blood compartment was only detected in the lateral ventricle and the 4th ventricle and its values ranged from 9.4 to 16.5 %. The largest fractional blood volumes were detected in the normal rat brain and, therefore, these values can only reflect presence of the blood compartment in small CSF spaces due to MRI data being affected by partial volume and noise effects.

For a fractional volume of the extracellular compartment of 20 %, the fractional volumes of the blood compartment in the tissue (cortex and thalamus left and right) ranged from 0.05 to 7.98 % while the fractional intracellular volumes ranged from 72 to 77 %. The maximum k_{trans} values calculated were 0.0005 1/min, while, for most cases ananlyzed, ktrans values were 0, suggesting that the SI changes in these regions were produced only by the blood compartment.

CONCLUSIONS Results in this study show that DCE-MRI provides quantitative information on the permeability of the BBB (ktrans, vb) and/or B-CSF-B (kin, vb). The dynamics of a contrast agent through the CSF spaces and tissue of the normal and hydrocephalic rat brain were also quantitatively evaluated in this study. DCE-MRI might, therefore, represent an important imaging technique for the quantitative evaluation of the mechanisms of brain diseases, including hydrocephalus and/or for responses to new therapies

REFERENCES 1. Drake JM *et al*, Neurosurg 43:294-303 (1998); 2. Owler BK *et al*, JCBF&M 24:17-23 (2004); 3. Greitz D, Neurosurg Review 27:145-165 (2004). 4. Pike, MM *et al*, Proc ISMRM, 1878, p 241 (2008); 5. Li, J *et al*, Exp Neurol 211:351-361 (2008)