SWI monitoring iron tagged dextran transportation in normal and hydrocephalus rat brains via intrathecal delivery

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INTRODUCTION: Hydrocephalus can be experimentally induced by producing a sustained increase in CSF osmolarity. This implies that the macromolecular content in the CSF is critical in determining the ventricular volume. Therefore we hypothesized that macromolecular transport is altered in the presence of hydrocephalus. We have previously shown that macromolecules (Dextran) are transported from the ventricles into the brain tissue and are rapidly concentrated in the perivascular space surrounding microvessels throughout the brain.[1] In addition, the dextrans were distributed along the olfactory pathways.[1] Dextrans distribute through brain parenchyma along brain-wide paravascular pathway.[2] Gd-based positive contrast-enhanced MRI was used to capture these pathways.[3] This work was designed to use SWI with the negative contrast agent (iron tagged Dextran, 10kD, 10nm, nanomag®-CLD-redF) to monitor the intraventricularly delivered tracer transportation in normal and communicating hydrocephalus rat brains.

MATERIALS AND METHODS: Adult female SD rats were divided into two groups: normal (n=3) and hydrocephalus (n=3). Hydrocephalus was induced by using subarachnoid space blockage with kaolin injected into the basal cistern.[4] The MRI scans were performed on a 7 T magnet (ClinScan). The following sequences were performed: fast dual echo 2D gradient echo data were collected dynamically for the first 20 minutes, followed by two flip angle 3D FLASH, multi-echo (ME) spin echo, ME susceptibility weighted imaging (SWI) for about 50 minutes. The dynamic scans were performed every 15 seconds and repeated 80 times. After collecting 9 time point baseline data, the Fe- Dextran was infused into the right-lateral ventricle (LV) via a PE micro-catheter. The T1, T2 mapping and SWI were performed once before tracer injection, and then were repeated twice after the dynamic scanning.

RESULTS: (1) Two normal rats were used to determine the dose of Fe-Dextran via cisterna magna injection. The localizer images showed cerebral vessel enhanced (T1 reducing effect) after 20 minutes at low dose 7.5 µg Fe-dextran (30µL at 0.25g/L). Fig 1 showed the tracer temporal course of T2* effect till 2h10m for another normal rat at high dose 100 µg (20µL at 5g/L). Tracer was found in para-arterial (Virchow-Robin) space, i.e. from basal cistern transported along the circle of Willis, the olfactory arterial complex into olfactory bulb; along the posterior choroidal arterial complex upward to the pineal recess. The tracer showed peak concentration outside the circle of Willis (row 1, 3) at 1h when it reached the azygos pericallosal artery (azpa), a black ring around azpa (row 2) at 1h40m. The dark pituitary recess returned to normal at 2h10m and there was a dark layer between superior sagittal sinus (sss) and cortex (row 4). Slight enhancement in signal intensities in brain parenchyma indicated there was lower concentration Fe-Dextran. SWIM (susceptibility maps) (row 5) showed susceptibility of a cortical penetrating vein changed from 40 (pre) to 126, 112, and 91 part per billion. (2). A moderate dose 20 µg Fe-dextran (20µL at 1g/L) was chosen for right ventricle injection in the remaining rats. From the dynamic scan data (first 20m), the half-life times of tracer clearance (ΔR2* reduced to half of maximum value) for normal rats were about 7s in right-LV, 60s in left-LV, 5m15s in 4th ventricle; those for hydrocephalic rats were 7m30s in right-LV and longer than 20m in left-LV and 4th ventricle. SWI scans also showed that there was a difference in the presence of Fe-Dextran in the LVs at 1 h and 1.5 h (Fig 2). Normal rats showed rapid clearance from LVs and the brain into the venous system and eventually into the sss (Fig 2 row 2). The hydrocephalic rats showed a very slow clearance from LVs and evidence of a build-up of Fe-Dextran in the brain tissue although this eventually also cleared in time (Fig 2 row 1). Tracer might have been absorbed by capillaries and veins. Inferior sagittal sinus showed major drainage on dorsal brain. However, there was no evidence of tracer clearance directly into the sss in hydrocephalic animals. Also there was no obvious para-arterial pathway showing up in hydrocephalic rats as the high dose normal rat. Venous susceptibility enhancement was stronger in hydrocephalic rats (Fig 3).

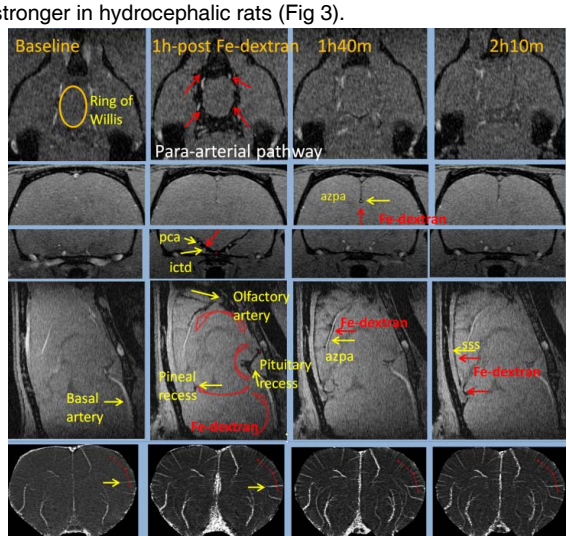
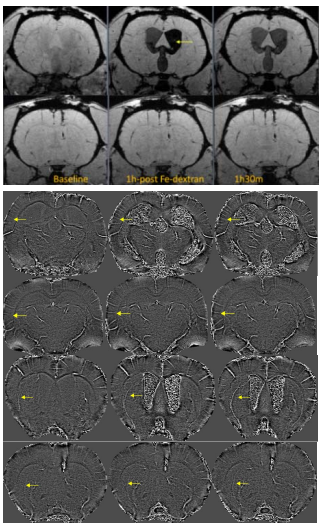


Figure 1 (left) Pre/post Fe-Dextran SWI (TE=2.7ms) at 1h, 1h40m and 2h10m (left-right) for a normal rat at a high dose of 100 µg. Row 1, horizontal; row 2-3, coronal; row 4, sagittal; row 5, SWIM (thick=1.28mm) coronal

Figure 2 (upper right) Pre/post Fe-Dextran SWI (TE=7.71ms) at 1h and 1h30m (left-right) for hydrocephalic (top) and normal (bottom) rats. Dose of 20 µg

Figure 3 (lower right) Pre/post Fe-Dextran SWIM at 1h and 1.5h (left-right) showed hydrocephalic subcortical penetrating vessels (row 1) and striate arteries (row 3) enhanced more than those of normal rat (row 2, 4). Res=41.6× 41.6×160 µm^3. Dose of 20 µg



CONCLUSIONS: SWI can be used to monitor Fe-Dextran whose clearance time from brain depends on the amount of its content. Distribution kinetics of Fe-Dextran in the ventricle as well as in the brain parenchyma is clearly different in hydrocephalus compared to normal rats. For normal rats, the Fe-Dextran entering the brain tissue via para-arterial pathways is rapidly cleared and does not build up in the brain parenchyma or vessel wall while for hydrocephalic rats there is an obvious delay in clearance with a significant increase in Fe-Dextran in the veins. This study confirms that intraventricularly injected Fe-Dextran is transported into the brain tissue prior to clearance into the vascular system.

REFERENCES 1. Satish Krishnamurthy, Jie Li, Transl Pediatr 2014;3(3):185-194. 2. Iliff JJ, Wang M, Liao Y, et al. Sci Transl Med 2012; 4:147ra111. 3. Iliff JJ, Lee H, Yu M, et al. J Clin Invest 2013;123:1299-309. 4. Jie Li et al. Exp Neurol 2008; 211(2):351-361