Micro-MRI Methods with 3D-FIESTA to Detect Renal Micro-Cysts in Chronic Renal Failure Model Mice

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Synopsis

Mouse models of disease are powerful tools to analyze the molecular basis of disease. We evaluated if micro-MRI employing a new 3D-MR hydrography signal sequence [3D-fast imaging employing steady-state acquisition (3D-FIESTA)] can visualize chronic cystic changes without contrast enhancement. We were able to positively depict multiple renal cortical cysts of ~0.2 mm diameter in sickle cell transgenic mice and observe serial changes of renal cysts in cyclooxygenase-2 knockout mice during a 2.5 month period. We found that some cysts decreased in size over time. Micro-MRI with 3D-FIESTA can depict and monitor cyst formation in the diseased kidneys of living mice.

Introduction

Chronic kidney disease is typically diagnosed by a combination of chronic interstitial inflammation/fibrosis and tubular atrophy, and is associated with cyst formation. While serum creatinine is a useful biomarker of chronic kidney disease in humans, serum creatinine is often not elevated in mouse models of renal disease. Therefore, non-invasive detection of the changes in renal anatomy or function can play an important role in documenting chronic kidney disease in animal models. We employed a 1.5 Tesla clinical MRI system fitted with a mouse coil and used a new 3D fast imaging employing steady-state acquisition (3D-FIESTA) to visualize renal cysts in two mouse models of chronic renal disease: sickle cell transgenic (SC-Tg) mice and cyclooxygenase-2 knockout (COX-2KO) mice. The 3D-FIESTA is a relatively new water-sensitive fast sequence (MR hydrography) that detects small amounts of fluid based on its long T2 relaxation. This 3D steady-state coherent imaging pulse sequence, 3D-FIESTA, has recently become available on clinical MRI machines (Signa LX, GE, Milwaukee, WI) and permits acquisition of images with a 0.6-mm slice thickness while retaining high signal-to-noise ratios at very short scan times.

Methods

Contrast agent: A polyamidoamine (PAMAM)-G4 dendrimer (14 kD) based MRI contrast agent coupled with 2-(*p*-isothiocyanatobenzyl)-6-methyl-diethylenetriamine-pentaacetic acid (1B4M) containing 64 Gd(III) (58 kD) ions was synthesized to visualize the functional anatomy of the kidney. ***Animal models:*** Eight-month old hemizygous SC-Tg mice (n=7) containing one normal mouse beta-globin allele with numerous micro-renal cysts and 5- or 10-month old hemizygous COX-2KO mice with scattered micro-renal cysts (n=4 in each group) were used for chronic kidney disease models. Normal Balb/c mice were used as controls. ***MRI studies:*** All mice were anesthetized and injected intravenously with 0.6 μmolGd of PAMAM-G4 into the tail vein for functional anatomy studies. The non-contrast 3D-FIESTA sequence was performed with 45° flip angle [TR/TE 27.7/13.8 msec; scan time 2'29"; frequency encoding x phase encoding steps 320 x 224; 3 numbers of excitation; 16 slice encoding steps]. The coronal images for MRI were reconstructed from 0.6-mm thick sections without gap. FOV was 6 x 3 cm and the size of the matrix was 0.19 x 0.27 mm. Then, all CE-dynamic micro-MR images were obtained using a 1.5-tesla superconductive magnet unit (Signa LX, General Electric Medical System) with a 1-inch round surface coil (Birdcage type) fixed by an in-house constructed coil holder. A 3D-fast spoiled gradient echo [3D-fastSPGR (efgre3d package); TR/TE 17.4/4; TI 43 msec; 31.2 kHz, flip angle 30°, 2 NEX; scan time 1'25"] with chemical fat-suppression was used for contrast enhanced dynamic study with a G4 contrast agent 1, 3, 5, 7, 9, 11, and 13 min after injection of the contrast agents. The coronal images were reconstructed with 0.8-mm section thickness with 0.4-mm overlap (two 512 matrix Zips). FOV was 8 x 4 cm and the size of matrix was 512 x 256.

Results

The 3D-FIESTA images of sickle cell mice clearly showed bright cysts with diameters of ~0.2 mm, even when they were located near the renal capsule (**Figs. 1-2**). In contrast, whereas the dynamic MRI with G4 could detect internal cysts (dark circles), cysts near the surface of the kidney indistinctly appeared as a wavy surface contour, or were not detected (**Figs. 1-2**).

We also evaluated both MRI methods in COX-2 KO mice. The 3D-FIESTA method could detect bright cysts in the inner stripe with a diameter of ~0.2 mm. Although cysts were visible on G4 dynamic MRI, they were more easily identified using 3D-FIESTA. Serial MRI examinations at 5 and 7.5 months in one mouse revealed that 2 cysts decreased in size from 5 to 7.5 months. Serial MRI examinations in 4 mice showed that some cysts were stable, whereas others either increased or decreased in size. This decrease in size of four cysts was also found in the other COX-2 KO mice (**Fig. 3**). Images taken 3 days apart showed good reproducibility (mean differences in size ± s.d. = 0.05 ± 0.02 mm; n=19; r^2=0.63) of cyst diameter.

Conclusion

The micro-MRI method using non-contrast 3D-FIESTA enabled visualization of micro-renal cysts in living mice to monitor changes in individual cysts over time. Therefore, this micro-MRI method should greatly aid in the non-invasive investigation of chronic kidney damage in mouse models, which cause cystic disease of the kidneys.

Fig. 1 MRI of the kidney in a SC-Tg mouse.

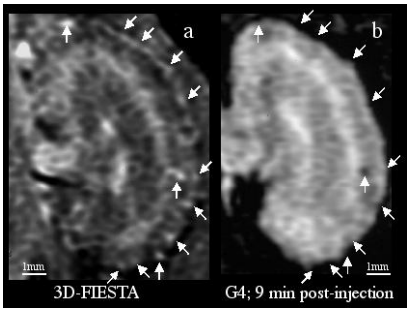

Fig. 2 Histology of the kidney shown in Fig.1.

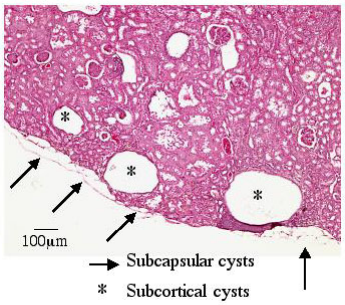

Fig. 3 Time course change of cyst sizes in COX-2KO kidney.