MRI Characterization of Kidney Lesions in Tuberous Sclerosis Mouse Model

Y. Sun[1], S. Doshi[1], L. Lee[2], P. Sudentas[2], B. Donohue[2], K. Asrican[2], A. Worku[2], V. Walker[2], N. EL Hashemite[2], A. Lader[2], H. Onda[2], H. Zhang[2], M. S. Albert[1], F. Jolesz[1], D. J. Kwiatkowski[1], S. L. Dabora[1]

[1]Radiology, Brigham and Women's Hospital, Boston, MA, United States, [2]Hematology, Brigham and Women's Hospital, Boston, MA, United States

Introduction: Tuberous sclerosis complex (TSC) is a multisystem familial tumor disorder. Kidney benign tumors consist of blood vessels, fat cells and smooth muscle cells, and they occur in approximately 75% of TSC patients over the age of 5 years old. Kidney cysts are also common and occur in about 30% of TSC patients. There is also an increased incidence of renal cancers in TSC patients (1). Recent biomedical research and drug discovery has led to the development and wide use of small animal models of human disease. Standard approaches to the evaluation of therapeutic interventions normally require survival curves, excised tissue weights, and cell cultures established from diseased tissue. Ex vivo tissue analysis, however, requires that a large number of animals be sacrificed because of inter-animal variability of the response to treatment. Noninvasive MRI investigations of biological processes *in vivo* can provide the potential for longitudinal studies in the same animal. The conventional Tsc2+/- mouse model is the best model for renal disease as the majority of animals develop kidney cystadenomas by the age of 9-12 months. The physiological features of this model at the cellular and sub-cellular level have not, however, been well characterized by MRI. In this study, we used various MRI methods to identify the different lesions and measured the T1 and T2 characteristics of tuberous sclerosis complex disease in the mouse kidney model.

Method: 6 Tsc2+/- mice (age from 13 to 16 months) were evaluated via MRI at 4.7T. Animals were imaged with a RARE imaging sequence(TR= 3000, TEeffect= 62) in the coronal plane with a slice thickness of 0.75 mm with a slice number to cover both kidneys, and with a matrix size of 128x128, field of view (FOV) of 3x3 cm^2. With the same geometry as described above, T1 weighted images were then acquired with TR=500ms, and TE=8 ms. A combination of the T1- and T2 weighted images were used to identify the lesions in the kidney. The slice with the most of the lesions was chosen for T1 and T2 measurements. The measurements were repeated for multiple regions-of-interest (ROIs) containing lesions within both the left and right kidneys. Saturation recovery imaging was used to measure T1 with TR varied from 100 ms to 8000 ms. A Carr-Purcell-Meiboom-Gill (CPMG) imaging sequence was used for T2 measurements with TR of 3000ms and TE of 10xn ms (n=1, 2, …32).

Results: Fig. 1 shows a representativeT2 weighted images of a mouse kidney at age of 54 weeks old. This subject has numerous lesions on both the right and left kidneys. The 3D reconstruction of the kidneys of the same subject and lesions are shown in Figure 2. The total volume of all the lesions in this mouse was 11.42 mm^3. There were three types of lesions were depicted in the mice with TS, which included simple cysts, complicated cysts and solid tumors. A summary of our findings is provided in Figure 3. Simple cysts typically showed very high signal intensity on T2WI, and low signal intensity on T1WI. Complicated cysts showed low to high signal intensity on T2WI and high signal intensity on T1WI. Complicated cysts showed high signal intensity, while simple cysts showed hypointense after intraperitoneal administration of GD-DTPA. Solid tumors show slightly high signal intensity on T2WI and slightly low signal intensity on T1WI and inhomogeneous enhancement on post Gd-T1WI. There were not any cysts or solid apparent in the control mouse kidney at age matched mice (Fig 3d). There were 69 lesions in six mice; 22 simple cysts, 45 complicated cysts and two solid tumors. The average volumes of simple cysts, complicated cysts and solid tumors were 0.282 mm^3, 0.267 mm^3 and 52.628 mm^3, respectively. The range of simple cysts per mouse was one to seven (ave. 3.7). The range of complicated cysts per mouse was zero to 24 (ave. 7.5). Five mice out of six mice had bilateral kidney cysts and only one had unilateral kidney cysts. Two mice had unilateral solid kidney tumors. The above findings are in agreement with MR images from patients with TSC (3). Figure 4 shows a color-coded T1 and T2 map. Our preliminary data in the Tsc2+/- mice gives a T2 value of 50±11 ms and T1 value of 690±19 ms for normal kidney tissue respectively. For simple cysts, T1 value was 2147±31 ms, T2 value was 125±17 ms. For complicated cyst, T1 was 1696±36 ms, T2 was 253±21ms; For solid tumors, T1 was 1127±23ms, T2 was 72±14 ms.

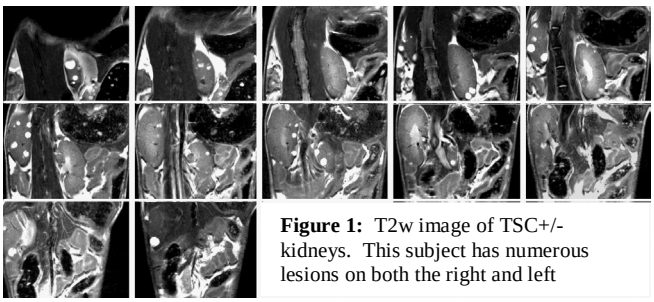

Figure 1: T2w image of TSC+/- kidneys. This subject has numerous lesions on both the right and left

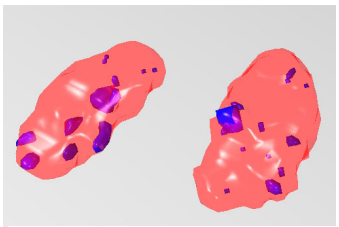

Figure 2: 3D reconstructions of the kidneys in Figure 1. Lesions are shown in blue

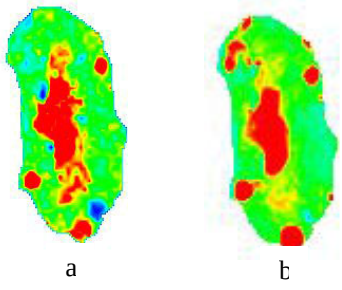

Figure 4: Color-coded map of T1 (a) and T2 (b).

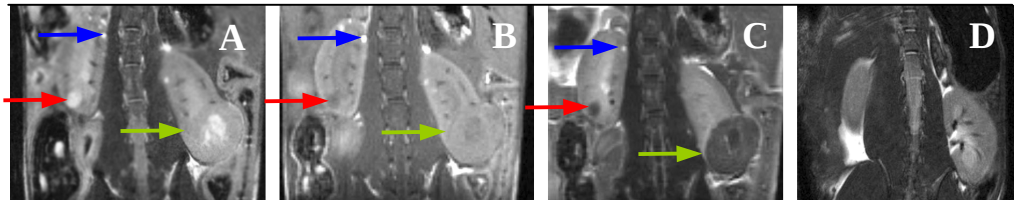

Figure 3: Various MR images of a 14 month old TSC +/- mouse (A, B, C) depicting the typical intensities for simple (red arrows) and complex (blue arrows) cysts, and solid tumors (green arrows). On a T2WI (A) simple cysts present a high signal intensity, while complex cysts can present low to high signal intensity. Solid tumors present high signal intensity on a T2WI. Typically, only complex cysts show high signal intensity on a T1WI (B). Post Gd-enhancement (C) complex cysts show bright enhancement, while simple cysts show little to no enhancement. Solid tumors show inhomogeneous enhancement. Image D was taken from a 14 month old control normal mouse. Note the lack of any cysts or solid tumors on this T2WI.

Discussion: Our results indicate that three types of lesions were present in the kidneys of Tsc2+/- mice : simple cysts, complicated cysts, and solid tumors. These findings are consistent with the description of the histolopathologic findings (2) and in agreement with MR images from patients with TSC (3). Prolonged T1 and T2 values are a common feature of cysts. Changes in T1 and T2 relaxation times due to therapeutic response have been observed in other animal models. The utility of various MRI imaging sequence as a diagnosis tool as well as relaxation times measurements, offers valuable information in characterization of the renal lesions and would be used for the for the evaluation of new therapeutic approaches.

References: 1. Gomez M, *etc.* , (1999). Oxford, England, Oxford University Press. **2**.Casper KA, *etc*., (2002), Radiology 225: 451-6. **3**. Onda H, (1999), J Clin Invest 104: 687-95.