Functional kidney MRI with a dendrimer-based nano-size contrast agent, G4, as a diagnostic and prognostic biomarker of sepsis-induced acute renal failure in aged mice.

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Synopsis

Mouse models of disease are powerful tools to investigate the pathogenesis and experimental therapy of disease. We evaluated use of micro-MRI employing a nano-size contrast agent G4 of 6 nm in diameter for early diagnosis of the acute renal failure (ARF) induced by sepsis. We were able to diagnose the severity of ARF prior to increased serum creatinine and monitor therapeutic response with ethyl pyruvate. The appearance of renal dysfunction by dynamic MRI with G4 correlated well with survival (r2 = 0.88). Dynamic MRI with G4 is a novel surrogate marker that provides information for the early diagnosis, drug responsiveness, and prognosis of sepsis-induced ARF.

Introduction

Acute renal failure (ARF) is a relatively common life-threatening illness occurring in 5–20 % of ICU patients. Sepsis is a major cause and sepsis-induced ARF has a particularly poor outcome with a mortality of 50-80%. If therapies are to be effectively tested in human studies, renal impairment needs to be diagnosed early in a septic patient and the cause be differentiated from other insults such as ischemia and nephrotoxins. Development of a non-invasive biomarker which can detect renal injury early, locate the site of injury and determine the cause would be extremely valuable. For drug monitoring, the biomarker should track successful drug treatment and serve as an intermediate end-point. This study describes the results using one such biomarker: a novel MRI imaging study employing a dendrimer nanoparticle.

Methods

Contrast agent: A polyamidoamine (PAMAM)-G4 dendrimer (14 kD) based nano-size MRI contrast agent coupled with 2-(*p*-isothiocyanatobenzyl)-6-methyl-diethylenetriamine-pentaacetic acid (1B4M) containing 64 Gd(III) (58 kD; 6nm in diameter) ions was synthesized to visualize the functional anatomy of the kidney. ***Animal models:*** A fluid- and antibiotic- treated cecal ligation and puncture (CLP) sepsis model was made with aged (42 to 44 weeks) male C57BL/6 mice. In brief, a silk ligature was placed at the cecal tip. The cecum was punctured twice. After surgery, pre-warmed normal saline was given intraperitoneally. All animals received a broad-spectrum antibiotic. ***MRI studies:*** All mice were anesthetized and injected intravenously with 0.6 μmolGd of PAMAM-G4 into the tail vein for functional anatomy studies. All 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 1'52"] with chemical shift fat-suppression was used for contrast enhanced dynamic study with a G4 contrast agent. Serial mages were obtained at pre-injection and 1, 3, 5, 7, 9, 11, 13, 15, and 17 min post-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. The severity of renal injury was scored by 3 criteria: Presence of stripes in outer medulla/cortex; Contrast in pelvis; and Kidney tissue 'brightness' compared to renal vein.

Results

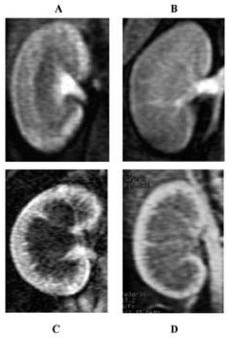
Twenty hours post-CLP, aged mice have a distinct pattern of renal injury using G4-enhanced dynamic MRI. This pattern is different from renal injury induced by either cisplatin or ischemia/reperfusion (I/R) (Fig. 1). G4-enhanced dynamic MRI detects renal dysfunction 6 hours post-CLP, a time when serum creatinine remains normal. Ethyl pyruvate (EP) reverses the renal dysfunction detected by G4-enhanced dynamic MRI at 20 hours, but not at 6 hours post-CLP (Fig. 2). The appearance of renal dysfunction on G4-enhanced dynamic MRI at 6 hours post-CLP accurately correlates to severity of illness and survival (Fig. 3).

Conclusion

Dynamic MRI with G4 is a novel surrogate marker that provides information for the early diagnosis, drug responsiveness, and prognosis of sepsis-induced ARF.

Fig. 1 MRIs of ARF kidneys by various causes. Fig. 2 3DMRI at 20 hr post-CLP (A: EP therapy+; B: No therapy). Fig. 3 severity score on MRI versus survival span (r2=0.88)

A: sham, B: Sepsis, C: I/R, D: cisplatin



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