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Elucidation of Renal Scars in Children With Vesicoureteral Reflux Using Contrast-Enhanced Ultrasound: A Pilot Study

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Introduction: Vesicoureteral reflux is a common disorder in children but can result in kidney scarring following acute pyelonephritis. The gold standard diagnostic to detect renal scars in children is ^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy. DMSA has a number of limitations including radiation exposure, need for sedation, and radiotracer supply shortages. Contrast-enhanced ultrasound (CEUS) is a technique whereby biocompatible microspheres of inert gas are administered i.v. that reflect ultrasonography sound waves and do not involve radiation. Because the contrast agent is rapidly cleared, contrast images must be obtained within minutes of administration. CEUS has been used in a variety of organ systems, but its use in pediatric kidney diseases is limited.

Methods: In this study, we performed CEUS in 7 children with documented renal scars by radiographic imaging consistent with reflux nephropathy.

Results: In all subjects, CEUS detected all previously known radiologic abnormalities as well as detecting new areas of hypoenhancing renal parenchyma. None of the patients experienced any serious adverse events.

Discussion: This study represents the first report of using CEUS to characterize renal scars in children with reflux nephropathy. We conclude that CEUS is a highly sensitive, rapid, and cost-effective diagnostic imaging modality for detecting and monitoring renal scars in children with vesicoureteral reflux.

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Vesicoureteral reflux (VUR) affects 1% to 2% of all children, and up to one-third of these patients will experience urinary tract infection (UTI). Acute pyelonephritis associated with VUR can lead to renal scarring and ultimately chronic/end-stage kidney disease known as reflux nephropathy.[1] The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial, a randomized, placebo-controlled trial in children with VUR and a history of UTI, demonstrated a rate of new scarring of almost 12% during the 2-year study period.[2] Classically, acquired reflux nephropathy scars arise following an episode of acute pyelonephritis. The pathognomonic scar in acquired reflux nephropathy fans out from the entry point in the medulla to the cortical segment in a wedge-shaped fashion. A number of imaging modalities have been used to identify and to characterize these cortical scars in children with VUR.

^{99m}Tc-dimercaptosuccinic acid (DMSA) scintigraphy is a radionuclide scan performed to detect pyelonephritis and renal scars and is considered the gold standard. The study involves a peripheral IV line and injection of radiotracer. To allow for cortical uptake, most centers wait 1 to 4 hours before imaging.[3] In the multicenter RIVUR study, 90% of centers used

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sedation to obtain images.[4] Although less than in an abdominal computed tomography (CT) scan, a substantial amount of radiation is involved in DMSA scanning and amounts to roughly 10 times the radiation exposure of pulsed fluoroscopy voiding cystourethrograms and 50 chest X-rays.[5,6] Finally, in the United States, we have experienced 2 major shortages of DMSA radiotracer in the past 10 years. Due to DMSA's unavailability since 2014, clinicians must consider other options to detect and to monitor renal scars. Magnetic resonance (MR) urography has also shown promise, but this modality frequently requires sedation and is expensive compared to other imaging modalities.[7] Conventional ultrasound's sensitivity is low as 37% to detect renal scars.[8] A rapidly obtained, cost-effective modality that is highly sensitive, does not require sedation, and does not expose the patient to radiation does not exist currently for detection of kidney scars.

Contrast-enhanced ultrasound (CEUS) is a technique that has the potential to replace imaging studies that involve radiation.[9] Ultrasound contrast agents comprised phospholipid or protein microspheres that encase an inert gas. The microspheres approximate the size of a red blood cell and remain within the vascular space. These agents are not filtered or secreted by the kidneys, and therefore allow visualization of the renal parenchyma without interfering with enhancement of the collecting system. Unlike other imaging contrast agents that cannot be administered to patients with renal insufficiency, ultrasound contrast agents are safe for use in this patient population. Because gas is highly reflective on ultrasound imaging, these agents can be administered i.v. in very small doses (0.3–2.5 ml) and are detectable down to the capillary level. In pediatrics, CEUS has been used to improve visualization of the heart, liver, and bladder.[10] Lumason (Bracco, Milan, Italy) is a contrast agent that consists of sulfur hexafluoride gas surrounded by a thin phospholipid shell roughly 2.4 μm in size. The sulfur hexafluoride gas has an extremely short half-life, and 82% is expired by the lungs unchanged within 20 minutes of administration.[11] Given that reflux nephropathy scars are areas of kidney parenchyma with abnormal blood flow, we hypothesized that CEUS would elucidate areas of abnormal parenchyma (scars) in children with known reflux nephropathy.

METHODS

Patient Population

Eight children, adolescents, and young adults aged 8 to 21 years of age were enrolled in the pilot study between May and August 2016 at Le Bonheur Children's Hospital in Memphis, TN. Two healthy adults were imaged at the beginning of the study to optimize image acquisition and contrast administration. The study was approved by the Institutional Review Board of the University of Tennessee Health Science Center and was performed under U.S. Food and Drug Administration investigational new drug application number 129000.

Inclusion and Exclusion Criteria

Patients who were 8 years or older and were eligible for renal scar detection via DMSA were approached. All patients were required to have a history of previous abnormal renal parenchyma via an imaging modality suggestive of renal scarring and/or evidence of reflux nephropathy by an abnormal serum creatinine value. All patients and legal representatives gave informed consent and assent prior to the study. Exclusion criteria included allergy to sulfur hexafluoride or other related products, known cardiac congenital abnormalities, abnormal baseline electrocardiogram (ECG), or a history of open-heart surgery, retinopathy, emphysema, or pregnancy.

Image Acquisition and Contrast-Enhanced Ultrasound Technique

After consent and pretesting screening, a 20-gauge peripheral IV line was placed. All patients underwent conventional nonenhanced renal ultrasound initially using a LOGIQ General Electric E9 version 5 (Milwaukee, WI) ultrasound machine and curved 1-6 transducer. The study radiologists and nephrologist reviewed previous images and study day images to plan study image acquisition. For the CEUS examinations, the LogicE9 contrast-specific software version R4, 3.0 was used, and dynamic imaging during renal perfusion was obtained, followed by static imaging. The ultrasound transducer was held in a single longitudinal plane that best depicted the suspected renal scar on grayscale imaging and was held in that position throughout the dynamic phase of imaging. Dynamic imaging was recorded beginning with the contrast injection and continued for 30 to 60 seconds afterward. Following the dynamic phase, additional transverse and longitudinal static images of the entire kidney were obtained for an additional 3 to 5 minutes until enhancement waned. All subjects received Lumason sulfur hexafluoride contrast agent through the 20-gauge peripheral IV line. Subjects received 0.03 ml/kg per manufacturer's recommendations up to a maximum of 1.5 ml per injection. Each injection was immediately followed by a 5-ml sterile normal saline solution flush. Subjects received a separate injection