Journal of Pediatric Urology (2013) 9, 856—866

Journal of Pediatric urology

Prevalence and risk factors for renal scars in children with febrile UTI and/or VUR: A cross-sectional observational study of 565 consecutive patients

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Received 24 January 2012; accepted 19 November 2012
Available online 7 March 2013

KEYWORDS
Focal renal cortical defect;
Renal scar;
Vesicoureteral reflux;
Urinary tract infection;
DMSA;
Technetium-99m dimercaptosuccinic acid renography

Abstract *Purpose:* To determine prevalence and risk factors for renal scar in children referred for urologic assessment of febrile UTI and/or VUR.
Methods: Pre-determined risk factors for renal scar were prospectively recorded in consecutive patients referred for UTI/VUR. Age, gender, VUR grade, and reported number of febrile and non-febrile UTIs were analyzed with logistic regression to determine risk for focal cortical defects on non-acute DMSA.
Results: Of 565 consecutive children, 24 (4%) had congenital renal dysplasia and 84 (15.5%) had focal defect(s). VUR, especially grades IV—V, recurrent febrile UTI, and older age increased risk. For any age child with the same number of UTIs, VUR increased odds of renal defect 5.4-fold (OR = 5.4, 95% CI = 2.7—10.6, AUC = 0.759).
Conclusions: Focal DMSA defects were present in 15.5% of 565 consecutive children referred for febrile UTI and/or VUR; 4% had presumed congenital reflux nephropathy without cortical

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1477-5131/$36 Published by Elsevier Ltd on behalf of Journal of Pediatric Urology Company.
http://dx.doi.org/10.1016/j.jpurol.2012.11.019

defect. All VUR grades increased risk for these defects, as did recurrent febrile UTIs and older age. However, 43% with grades IV–V VUR and 76% with recurrent UTI had normal DMSA.
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Introduction

One justification for the detection and management of vesicoureteral reflux (VUR) after urinary tract infection (UTI) is increased risk for renal scarring when VUR is present. However, few studies report likelihood for renal scar after UTI, with sometimes conflicting results in patient populations that may not be representative of those referred to pediatric urologists. For example, some prospective studies using dimercapto-succinic acid (DMSA) scintigraphy to diagnose renal scarring found increased risk in patients with VUR [1–3] while others found no increased risk [4–6]. Of the populations evaluated in these studies, 4 were limited to children with their first febrile UTI [1,3,5,6], 2 were limited to children less than 1 or 2 years of age [1,5], and 1 was limited to patients with unilateral VUR [3].

Previously reported meta-analyses [7–9] demonstrate an overall increased risk for "abnormal DMSA" in children with UTI and VUR ranging from 2.6 to 2.8 times. Yet the meta-analysis performed by the American Urological Association (AUA) VUR Guideline Update Committee comprised only 4 articles, 3 limited to patients with their first known febrile UTI and 2 reporting median ages younger than 9 months [7]. A subsequent meta-analysis by Shaikh et al. was also limited to children after their first UTI, did not define abnormal DMSA (focal defects, decreased function, or both), and only 2.5% of the patients had grades IV–V VUR [9]. The meta-analysis by Faust et al. was limited to patients with acute DMSA lesions to determine subsequent renal scarring, and so was not designed to evaluate scar rates among patients with and without VUR [8]. The fact that each meta-analysis reported approximately the same odds for renal scarring with VUR is not surprising since there was considerable overlap in the reviewed articles.

Given the small numbers of patients with grade-stratified VUR evaluated for renal scarring, narrow inclusion criteria, and heterogeneity between study populations in published reports, the risk for renal scarring posed by VUR remains incompletely defined. This is especially true among patients referred to pediatric urologists, who present at various ages, often after more than 1 febrile UTI, and may have proportionately higher grades of VUR than encountered in studies by primary care providers. Consequently, we obtained non-acute DMSA scintigraphy in consecutive children referred with VUR and/or febrile UTI, and now report likelihood for presumed acquired renal scarring and associated baseline risk factors in this cross sectional study of consecutive patients.

Materials and methods

Patients

Datasheets were created to capture data for predetermined factors potentially related to acquired renal scar – defined as focal cortical defect(s) on non-acute DMSA scintigraphy - including patient age, gender, VUR grade, febrile versus non-febrile UTI, the number of UTIs, and voiding habits for toilet trained children. These datasheets were then used by pediatric urology providers following a standard protocol in evaluating consecutive patients referred for febrile UTI and/or VUR between October 2008 and April 2011, with the goal of determining the percentage of referred patients with abnormal DMSA.

DMSA scintigraphy was scheduled at or beyond 3 months after the latest febrile UTI, when present. Data was prospectively entered into a database and analyzed for this report following institutional review board approval. Exclusion criteria included solitary kidney, ureteropelvic or ureterovesical junction obstruction, duplication anomalies with ectopic ureter or ureterocele, neurogenic bladder, posterior urethral valves and/or prune belly syndrome. Patients with presumed congenital reflux nephropathy (CRN), defined as $\leq$44% reduced ipsilateral function without focal cortical defects, were excluded from analysis of acquired renal defects.

Caregivers of toilet-trained children were questioned regarding bowel and bladder dysfunction (BBD), defined as presence of any of the following: infrequent voiding $\leq$3 times per day; urinary frequency $\geq$8 times per day; diurnal incontinence; and/or infrequent stooling $<$3 times per week, hard or painful stools, scybalous or excessively large stools, or bowel incontinence. BBD as a separate potential risk factor for abnormal DMSA was not assessed in our primary model since there are no standardized criteria for diagnosis and we lacked data in our large percentage of patients who were not toilet trained. Instead, we performed univariate and multivariate analysis among a subset of toilet-trained children to evaluate the risk of BBD.

Imaging

Technetium-99m DMSA (40–120 MBq) was injected intravenously, with dose calculated using Clark's rule (weight in kg/70 $\times$ standard adult dose $=$ 5 mCi), with a minimum dose of 1 mCi and a maximum dose of 5 mCi. Imaging was performed 1.5–3 h after injection. Images were obtained using parallel hole, low energy high resolution collimators on either a Phillips Prism 1500 single head camera or a Phillips Axis head camera. Planar images were magnified 1–4 times, based on the patient's size. Planar images in the anterior, posterior, and right and left posterior oblique images of both kidneys were obtained for 5 min each. Magnified posterior images were obtained at 4 times magnification. Differential activity of the kidneys was calculated from both the anterior and posterior images, with total differential function determined by averaging the percentages from the anterior and posterior images.

DMSA studies were reviewed by 2 pediatric radiologists blinded to VUR status, with discrepancies resolved by consensus. Results were graded using Randomized