Correlation of ultrasonographical findings of hydronephrosis/atrophy with 99m technetium-dimercaptosuccinic acid in childhood: A single-center experience from Turkey

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INTRODUCTION

Hydronephrosis and atrophy are frequently detected pathologies in pediatric urinary ultrasonography (US).¹ No matter what the indication of ultrasonographic examination, dimercaptosuccinic acid (DMSA) is considered as the next step. DMSA is the most sensitive technique for the detection of renal scarring, renal agenesis, or occult duplex system.²

Materials and Methods: We retrospectively reviewed the DMSA, ultrasonography (US), micturating cystourethrogram (MCUG) findings, and medical records of pediatric patients with hydronephrosis and/or atrophy who were at follow-up between January 2013 and December 2016 in our center which is located in the southeast region of Turkey.

Results: Among 148 pediatric patients (male/female = 60/88), 66 had hydronephrosis, 72 had atrophy, and 10 patients had both. MCUG study detected VUR in 66 patients. Patients with atrophy were significantly older than patients with hydronephrosis (77.8 ± 58.6 vs. 39.3 ± 38.9 months, P = 0.002). Only 19.4% of our patients with atrophy had VUR. The rate of VUR was higher in the high-grade group than the mild-to-moderate-grade group although the difference was not statistically significant (80% vs. 61%, P = 0.199). Patients with high-grade hydronephrosis had more severe DMSA findings (73% vs. 39%). On the other side, 79% of the patients with high-grade VUR had severe DMSA findings. A total of 10 patients had both atrophy and hydronephrosis all affecting the left side. Six of them had VUR. Severe DMSA findings were more likely in toddlers (age 24–72 months) (48%). This finding was abruptly lowered after 72 months of age.

Conclusions: The presence of atrophy and cases of left-sided hydronephrosis should be closely monitored, and DMSA may not be necessary in cases with high-grade hydronephrosis before MCUG.

Keywords: Atrophy, children, hydronephrosis, severity, vesicoureteric reflux

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Moreover, the standardized evaluation for children referred for febrile urinary tract infection (UTI) includes both DMSA and ultrasonography obtained >3 months after infection to detect renal scarring since 2008.[3] In addition, micturating cystourethrogramy (MCUG) is frequently employed for the evaluation of children with UTIs and detection of urinary tract abnormalities, especially vesicoureteric reflux.[4] The National Institute for Health and Clinical Excellence (NICE) guidelines and The European Society of Pediatric Radiology also recommend a hybrid of the bottom-up and top-down approaches utilizing both DMSA and MCUG in selected cases.[5-7] In the present study, we aim to assess the association of abnormalities (hydronephrosis and/or atrophy) detected on renal ultrasound and DMSA scan with the presence of vesicoureteral reflux (VUR) on MCUG in children to find new perspectives.

MATERIALS AND METHODS

We retrospectively reviewed the DMSA, US and MCUG findings, and medical records of pediatric patients with hydronephrosis and/or atrophy who were at follow-up between January 2013 and December 2016 in our center which is located in the southeast region of Turkey. The exclusion criteria included having neurological lesions, anatomical abnormalities of the lower urinary tract, bilateral small kidneys, horseshoe kidneys, multicystic dysplastic kidney, ureteropelvic obstruction, or chronic renal failure.

A UTI was diagnosed if a child had positive nitrite and leukocyte esterase in a urine sample in the presence of typical symptoms including fever, loin tenderness, frequency, dysuria, cloudy urine or hematuria, and a positive urine culture during the course of illness. Recurrent UTI was defined according to the National Institute for Health and Care Excellence criteria.[8] Hydronephrosis on US was defined as a dilatation of the renal pelvicalyceal system. For measuring the pelvicalyceal system, the maximum axial length observable at the level of the renal hilum was recorded.[7] Hydronephrosis was graded by pelvic diameter according to the anterior–posterior diameter classification criteria as normal (0–4 mm), mild (5–9 mm), moderate (10–15 mm), and severe (>15 mm).[9] We formed two groups; the first group was composed of patients with severe hydronephrosis and the second group composed of patients with mild-to-moderate hydronephrosis.

Technetium (Tc)-99m-DMSA renal scan was performed following a standard protocol. Renal scintigraphy was performed 1.5–3 h after intravenous administration of an age-appropriate dose of DMSA, 3–5 mCi/1.73 m2 body surface area, or 50–100 mCi/kg body weight (minimum dose 0.5–1 mCi). Administered activity was scaled according to the dose chart of EANM Dosimetry guide.[10] Posterior and posterior-oblique renal images were acquired. Differential renal function was calculated on the posterior image by subtracting background counts and calculating for each kidney the percentage of total counts for both kidneys. The results were considered normal if the uptake of the radioisotope was homogeneous with no evidence of scarring and relative uptake within the normal range. Renal scarring was defined as the presence of photon-deficient areas along with deformation of renal outline or the presence of cortical thinning with reduced volume. Scarring, decreased uptake of 99mTc-DMSA in one or more sites, and abnormal differential function considered as a pathologic DMSA. Differential renal function was considered abnormal if renal uptake of the kidney was <45%.[11] The findings of DMSA were classified as normal, mild (i.e., decreased uptake in one or two foci), and severe (i.e., scar).

MCUG was used for detection and grading of VUR. VUR was graded and defined according to the recommendations of the International Reflux Study in Children.[12] Only the patients with VUR were evaluated. For the purposes of comparing the grading of VUR and the association of renal damage, Grades I, II, III VUR were grouped together as low-grade VUR, Grade IV to V as high-grade VUR. Patients with bilateral VUR were assigned to the high-grade group.

The interpretations of the DMSA, US, and MCUG were made by experienced a nuclear medicine consultant and experienced radiologist who were blinded to all the other clinical and imaging data.

The patients were divided into three age groups: <24, 24–72, and >72 months. We chose 24 months and 72 months as the boundary to identify whether significant differences exist in the accuracy of DMSA in predicting severe VUR between these groups.

Statistical analysis

Study data were analyzed by the Statistical Package for the Social Science 16.0 software package. Statistical analyses were performed with Chi-square test and Mann–Whitney U-test. Correlations between certain parameters were assessed by Pearson or Spearman’s correlation analyses. The level of significance was set at \( P < 0.05 \).

RESULTS

Among 148 pediatric patients (male/female = 60/88), 66 had hydronephrosis, 72 had atrophy, and 10 patients had
showed abnormal results in a total of 58 children with hydronephrosis. Among patients with hydronephrosis, 8 patients had normal DMSA findings, 22 patients had mild finding, and 36 had severe findings. Patients with high-grade hydronephrosis had more severe DMSA findings (73% vs. 39%). None of the patients with high-grade hydronephrosis had normal DMSA findings. On the other side, 79% of the patients with high-grade VUR had severe DMSA findings. None of the patients with high-grade VUR had a normal DMSA scan [Table 3].

A total of ten patients had both atrophy and hydronephrosis all affecting the left side. Six of them had VUR. Among these patients, 2 had high-grade VUR.

Fifty-two patients were under 24 months of age, 48 were above 72 months of age, and the remaining 48 patients were between 24 and 72 months of age. Our study revealed that atrophy was more likely in older children than younger children (50%) whereas high-grade hydronephrosis and high-grade VUR were more likely in younger children (50% and 58%, respectively) [Table 4]. Severe DMSA findings were more likely in toddlers (age 24–72 months) (48%). This finding was abruptly lowered after 72 months of age.

High-grade hydronephrosis and high-grade VUR groups had a 9-time (95% confidence interval [CI] 1.38–58.44) and 7.5-time (95% CI 0.92–61.04) higher likelihood of having severe DMSA findings compared to patients who had low-to-moderate-grade hydronephrosis and low-grade VUR, respectively.

**DISCUSSION**

The role of imaging in the evaluation of VUR has been addressed by multiple guidelines. Previous studies have suggested that DMSA scanning can eliminate the need for MCUG examination in infants and younger children presenting with the first febrile UTI.[13] DMSA had a high sensitivity in both acute and chronic pyelonephritis compared with ultrasonography and intravenous urography.[14] However, performing all imaging studies for all of patients would place an economic burden on health resources.

**Table 1: Results of renal ultrasonography and voiding cystourethrogram**

| Atrophy | Hydronephrosis | P |
|---------|----------------|---|
| Number of patients | 72 | 66 |
| Male/female | 30/42 | 20/46 |
| Mean age (month)* | 77.8±58.6 | 39.3±38.9 |
| Urinary tract infection, n (%) | 38 (52) | 64 (96) |
| VUR, n (%) | 14 (19.4) | 46 (69.9) |

*Mean±SD. SD: Standard deviation

**Table 2: Comparison of patients with low- and high-grade hydronephrosis**

| Mild-to-moderate hydronephrosis | High-grade hydronephrosis | P |
|-------------------------------|--------------------------|---|
| Number of patients | 36 (54) | 30 (46) |
| Male/female | 10/26 | 10/20 |
| Mean age (month)* | 49.5±42.9 | 25.5±30.2 |
| Urinary tract infection, n (%) | 34 (87) | 28 (93) |
| VUR, n (%) | 22 (61) | 24 (80) |

*Mean±SD. SD: Standard deviation

**Table 3: Comparison of dimercaptosuccinic acid findings with hydronephrosis and VUR grades**

| DMSA findings | High-grade hydronephrosis | Mild-to-moderate hydronephrosis | High-grade VUR | Low-grade VUR |
|---------------|---------------------------|-----------------|---------------|--------------|
| Normal, n (%) | 0                         | 8 (22)          | 0             | 2 (9)        |
| Mild, n (%)   | 8 (27)                    | 14 (39)         | 5 (21)        | 10 (45.5)    |
| Severe, n (%) | 22 (73)                   | 14 (39)         | 19 (77)       | 10 (45.5)    |
| Rate of abnormal DMSA, n (%) | 30 (100)        | 28 (78)         | 24 (100)      | 20 (91)      |

DMSA: Dimercaptosuccinic acid
Our study was performed with the objective of determining whether the routine use of DMSA in pediatric patients with abnormal renal US findings can obviate the need for routine MCU examination and hence its associated drawbacks.

Atrophic kidney, also known as kidney atrophy or kidney shrinkage, refers to loss of nephrons causing a smaller sized kidney. Likewise, if the kidneys have already been affected, further examinations would be needed to identify whether risk factors such as VUR exist. The rate of VUR in our patients with hydronephrosis was significantly higher than patients with atrophy. We also found that the patients with atrophy were significantly older than patients with hydronephrosis. The current data also showed that older patients were more susceptible to the development of atrophy. Many causes could be responsible for atrophic kidney, renal ischemia, damage to the renal parenchyma as a result of obstruction of the urinary system, renal thrombosis, compression of blood vessels as a result of renal cysts, long-standing kidney infections such as pyelonephritis, polycystic kidney, and other chronic renal diseases that can affect the nephrons or reflux nephropathy. Only 19.4% of our patients with atrophy had VUR. Hence, there may other possibilities for the etiology of atrophy: one explanation is that a previously existing low-grade VUR may have spontaneously resolved because it is already known that low-grade VUR can spontaneously resolve in as high as 80% of cases. Another explanation could be vascular factors. Hence, therefore, it suggests that in case of renal atrophy, focusing solely on VUR may misleading and one should evaluate renal vascular system with renal Doppler US and/or renal angiography.

We found no significant difference between high- and low-moderate-grade hydronephrosis with respect to the presence of VUR. However, it was shown in a study that the presence and degree of preoperative hydronephrosis were closely related to VUR grade. However, in that study, all of 308 patients underwent antireflux surgery with different indications, and the guideline of Society for Fetal Urology for hydronephrosis was used, which categorized hydronephrosis as mild (Grade 1–2) or moderate/severe (Grade 3–4). Hence, the perspective here is important in evaluation of the relation of hydronephrosis with VUR.

Patients with high-degree hydronephrosis had more severe DMSA findings than the patients with mild-moderate hydronephrosis. Several studies have supported our finding that an abnormal renal ultrasonography had a good correlation with abnormal DMSA renal scintigraphy. In contrast, Ilyas et al. reported that ultrasonographic parameters did not identify children with renal damage in any age group. Some previous studies have shown that normal and abnormal renal ultrasonography results of the patients with acute pyelonephritis indicated that ultrasonography had poor sensitivity for the detection of renal scarring, whereas another study showed that ultrasonography was efficient in detecting renal scars.

The percentage of VUR was greater in the high-grade hydronephrosis group than the mild-moderate hydronephrosis group although the difference was not significant. Ozen et al. reported that 62% of patients with hydronephrosis had VUR. However, they did not specify the threshold measurement of hydronephrosis in that study. Hence, DMSA may not be necessary in cases with high-grade hydronephrosis before MCU, even there is UTI.

Relatively, a high proportion of patients with VUR had severe DMSA findings. Compared with children with low-grade or no VUR, patients with high-grade VUR are more likely to have their kidneys affected. All patients with high-grade hydronephrosis and high-grade VUR had abnormal DMSA findings. The greater severity of VUR in our study also may have contributed to these results. Another study confirmed that renal parenchymal damage was observed only when VUR was Grade III and above.

The common practice of early circumcision of males in our country may explain the relatively lower numbers with UTI in comparison to females. There was no meaningful difference between the right and left side in respect to hydronephrosis and atrophy.

All cases with both hydronephrosis and atrophy were left-sided. Sixty percent of them had VUR. Ghasemi et al. similarly showed that the frequency of positive scans was also significantly higher in the left kidney (65.7%) in comparison with the right kidney (14.2%), and the frequency of renal scarring was much higher (66.6%) in the left kidney than that in the right kidney (23.8%). The presence of hydronephrosis on the left side may be a risk...
factor for atrophy. Left renal atrophy may be significantly higher than the right side in humans. Aortic pressure induced flow disorders and the structural anomalies of the left renal vein and possibly the higher arterial pressure of the left kidney due to the shorter distance to the heart as an underlying cause of atherosclerosis may be some of the possible causes of this occurrence.\(^{(27)}\)

Controversy still exists regarding whether a normal DMSA scan could obviate MCUG. Two patients with a normal DMSA had low-grade VUR; none of the patients with normal DMSA had high-grade VUR. In a study with 753 pediatric patients, Zhang et al.\(^{(28)}\) showed that 12 patients with normal DMSA scan had low-grade VUR and 2 patients had high-grade VUR. The likelihood of the presence of dilating VUR on MCUG is low when the result of DMSA is negative.

Severe DMSA finding was more likely in toddlers (24–72 months of age) with a percentage of 48%. Mattoo et al.\(^{(29)}\) showed that renal scarring was more likely in older children than younger children; however, the upper limit of their study age was 71 months. Hence, we showed that after 6 years of age, scars were relatively a rare finding. Hence, we may not need a DMSA after 6 years of especially in cases of hydronephrosis with or without UTI. Recent studies have already questioned this conventional wisdom by reporting that younger age may not be a risk factor for renal scarring;\(^{(30)}\) the risk in older children may even be higher.\(^{(31)}\) In addition, the recommendation by the American Academy of Pediatrics and National Institute for Health and Clinical Excellence guidelines\(^{(6,22)}\) to delay MCUG until the second episode of UTI may need to be reviewed.

Our study has some limitations. The retrospective nature of data collection could be seen as a limitation. Furthermore, the total number of patients was relatively low in comparison with previous correlation studies.\(^{(30)}\) There was no need for a control group of healthy patients since we aimed to assess and compare pathologic groups.

**CONCLUSIONS**

The presence of atrophy and cases of left-sided hydronephrosis should be closely monitored and DMSA may not be necessary in cases with high-grade hydronephrosis before MCUG. A finely designed diagnostic accuracy study is needed to validate the findings of this study.

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**Conflicts of interest**

There are no conflicts of interest.

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