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Evaluation of the Use of DMSA in Culture Positive UTI and Culture Negative Acute Pyelonephritis

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This prospective study was done to assess the frequency of acute pyelonephritis (APN) in febrile children with positive urine culture as documented by Tc^{99m} DMSA scintigraphy (DMSA) and the frequency of vesicoureteric reflux (VUR) in these children. Secondly, to determine the frequency of APN, in febrile children with supportive evidence for UTI but with negative urine culture, as documented by DMSA and frequency of VUR in them. Thirdly to stress the utility of DMSA to diagnose APN in urine culture negative febrile children and to suggest DMSA as a clinical tool in evaluation of fever of unknown origin (FUO). This study included 42 children with positive urine culture and 26 children with negative urine culture who had supportive evidence of UTI as determined by the predetermined criteria and diagnosed to have APN by DMSA. All of them had ultrasonogram (USG), DMSA and voiding cystourethrogram (VCU). They were followed up for a minimum period of 6 months. Out of the 42 children with positive urine culture 92.9% had features of APN in the DMSA of whom 82.1% had vesicoureteric relux (VUR). The DMSA was abnormal in 26 children with negative urine culture, of whom 65.4% had VUR. Ultrasound suggestive of parenchymal change was observed in 47.6% in the culture positive group and 65.4% in the culture negative group. In conclusion, it is suggested, that DMSA is a useful investigation for the diagnosis of APN in febrile UTI. DMSA is indicated in febrile children with negative urine culture but with supportive evidence of UTI and in FUO. An abnormal DMSA is a strong indication for work up for VUR.

Key words: *Acute pyelonephritis, DMSA, Fever of unknown origin, Scintigrapy, Urinary tract infection, Vesicoureteric reflux.*

URINARY tract infection (UTI) is a frequent bacterial infection in children and urine culture is a 'confirmatory gold standard' for the diagnosis. A positive urine culture indicates infection anywhere in the urinary tract. It is not synonymous with acute

pyelonephritis (APN) or acute parenchymal inflammation. Hence there is a need for a reliable investigation, which can tell the physician that there is parenchymal inflammation in a given child with bacteriuria. Further, not infrequently, urine cultures are negative in APN. Indiscriminate and inappropriate use of antibiotics has made it difficult to obtain an appropriate or adequate bacterial growth.

Urinalysis, ESR and CRP have low predictive value in the diagnosis of APN(1). Today there seems to be an answer in the use of Tc^{99m} DMSA scintigraphy (DMSA) for diagnosis of APN *vis-à-vis* UTI. DMSA can be done in the acute phase and is a rapid and relatively inexpensive test, with no need for preparation. Studies have shown the utility of DMSA scintigraphy even in culture negative febrile children for the diagnosis of APN(2).

This prospective study had three objectives. First was to assess the frequency of APN in febrile children with positive urine culture as documented by DMSA and the frequency of VUR in these children. Second was to determine the frequency of VUR in culture negative pyelonephritis diagnosed on the basis of positive DMSA in febrile children with supportive evidence for UTI. Thirdly to stress the utility of DMSA to diagnose pyelonephritis even in culture negative febrile children.

Subjects and Methods

This prospective study was conducted at the Department of Nephrology, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, Tamilnadu, India from January to June 2002.

Inclusion and exclusion criteria

For culture positive febrile UTI: Febrile children with culture positive UTI were included. Children with obstructive urological disorders as demonstrated by clinical history, examination and USG were excluded.

For culture negative febrile UTI: Inclusion criteria includes essential and supportive criteria. Three essential criteria used were (*a*) fever without focus; (*b*) persistently high fever >38°C for >5 days; and (*c*) negative urine culture. Four supportive criteria used were (*a*) pyuria; (*b*) polymorphonuclear leucocytosis; (*c*) raised acute phase reactants and (*d*) USG findings of focal or diffuse parenchymal hyperechogenicity, loss of corticomedullary differentiation, irregular outline of kidney, reduction in parenchymal thickness and renomegaly, which are considered as evidence of pyelonephritis. Children who fulfilled all 3 essential criteria and 2 supportive criteria were included in the study. Children with obstructive urological disorders as demonstrated by clinical history, examination and USG were excluded.

Methodology

For culture positive UTI: Thirty two children with first episode of febrile UTI and 10 children with recurrent febrile UTI had an USG and DMSA during the febrile episode. DMSA finding considered as pyelonephritis were single or multiple hypoactive areas or a small-deformed kidney. Presence of these findings on a repeat isotope scan after 6 months was considered as scars. A voiding cystourethrogram (VCU) was done after ensuring that the urine was sterile with appropriate antibiotic therapy followed by 2 weeks of chemoprophylaxis and one injection of Gentamicin 1 mg/kg IV one hour before VCU. Children with a VUR and/or renal parenchymal changes alone as seen in the DMSA scan were continued on chemoprophylaxis. Repeat DMSA scan was done 6-12 months later to look for persistence of the existing renal parenchymal changes, appear-

ance of new lesions and resolution of the existing lesion.

For culture negative acute pyelonephritis: Children with fever without obvious cause were subjected to a thorough physical examination and investigations to rule out common infections in various medical units of our hospital. Children with persisting high-grade cryptogenic fever, pyuria, polymorphonuclear leucocytosis, elevated acute phase reactants, ultrasonographic features of pyelonephritis and negative urine culture, were included in the study and were subjected to a DMSA in the medical units. Children with positive DMSA only are included in this study after registration in Nephrology Department and VCU was done after control of fever and adequate chemoprophalaxis.

Results

Culture positive UTI

Forty two children with UTI formed the study material and were evaluated for the first time. Nineteen (45.2%) children were less than 2 years of age and 10 (23.8%) were above 5 years. Twenty-five (59.5%) children were girls. *E. coli* (88.1%), *Pseudomonas aeruginosa* (7.1%) and *Klebsiella* (4.8%) were the causative organisms. USG was normal in 22 (52.4%) and abnormal in 20 (47.6%) children (*Table I*). VUR was absent in 9 (21.4%) and present in 33 (78.6%) children (*Table I*), of which 17 (51.5%) had unilateral VUR and 16 (48.5%) had bilateral VUR. All the 42 children had DMSA scan of which 39 (92.9%) had abnormal DMSA and 3 (7.1%) had normal DMSA. Of 39 children with abnormal DMSA finding, VUR was present in 32 (82.1%) and there was no VUR in 7 (17.9%) children (*Table II*). Amongst 3 children with normal DMSA, 2 (66.7%) children had no VUR while one (33.3%) child had VUR (*Table II*). Sixteen (38.1%) of the 42 children alone could be followed up for a minimum period of 6 months. In 10 children with recurrent UTI there was no change in DMSA in 5 (50.0%), in 2 (20.0%) there was new scars and in the other 3 (30.0%) there was resolution of the parenchymal changes. In 6 children with the first episode of febrile UTI, resolution of nucleopenic areas was noted in 4 (66.7%) and absence of resolution in 2 (33.3%). Thirty percent of children with recurrent UTI showed resolution of parenchymal change while 66.7% of children with first episode of febrile UTI showed resolution. Seventy percent of children with recurrent UTI developed scars while 33.3% of children with first episode of febrile UTI had persistent parenchymal changes suggestive of scars.

Culture negative acute pyelonephritis

Twenty six children formed the study material. Six (23.1 %) children were less than 2

TABLE I--*Imaging Evaluation and Observation in Culture Positive and Negative Children.*

Imaging modality	Culture positive (n = 42)				Culture negative (n = 26)			
	Normal		Abnormal		Normal		Abnormal	
	No.	%	No.	%	No.	%	No.	%
USG	22	52.4	20	47.6	9	34.6	17	65.4
DMSA	3	7.1	39	92.9	0	0	26	100.0
VCU	9	21.4	33	78.6	9	34.6	17	65.4

USG - Ultrasonogram; DMSA - Tc^{99m} DMSA scintigraphy; VCU - Voidinig cystourethrogram.

TABLE II–*Comparison of DMSA and VCU in Culture Positive and Negative Children*

DMSA	Culture positive (n = 42)					Culture negative (n = 26)				
	No.	VUR present		No VUR		No.	VUR present		No VUR	
		No.	%	No.	%		No.	%	No.	%
Abnormal	39	32	82.1	7	17.9	26	17	65.4	9	34.6
Normal	3	1	33.3	2	66.7	0	–		–	

years of age and 6 were above the age of 5 years (23.1%). Sixteen (61.5%) children were girls. Fever was the only manifestation in 3 children. Other clinicobiological features were vomiting (50.0%), abdominal pain (23.1%), polymorpholeucocytosis (88.5%), elevated ESR and a positive CRP (42.3%). USG was normal in 9 (34.6%) and abnormal in 17 (65.4%) children (*Table I*). Obviously, DMSA was abnormal in all 26 children as it was the diagnostic tool used to diagnose APN in those febrile children. Among them VUR was absent in 9 (34.6%) and present in 17 (65.4%) children (*Table II*). Of the 17 children, 13 (76.4%) had unilateral VUR and 4 (23.6%) had bilateral VUR. Ten (38.5%) children alone could be followed up for a minimum period of 6 months. None of the children developed new scars. No change in DMSA was seen in 2 (20.0%) and 8 (80.0%) had resolution of the nucleopenic areas.

Discussion

In this study, in both culture positive and culture negative UTI, females outnumbered males. In Biggi A *et al*(3) report of 101children with APN, 60 were females and 41 were male. *E.coli* was the commonest organism, which is comparable to other studies(4). In 42 culture positive children 39 (92.9%) had features of APN by DMSA, of whom, only 20 (51.2%) had USG abnormalities. None of the children with normal DMSA had USG abnormalities. Vanderfiellie, *et al.*(5) showed that USG was normal in half the number of kidneys with an abnormal DMSA and indicated that USG is a poor investigation to diagnose APN(5). Morin, *et al.*(6) observed that renal USG scan using high resolution technique was found to be as near sensitive as DMSA scan in diagnosing unobstructive APN and in predicting VUR. In his study with 70 children using high frequency transducer by a trained radiologist, abnormal sonographic finding was seen in 61 (87.1%). This study has limitations, as there is a need for high resolution USG and a specially trained person. The author does not report how many children with normal USG had APN as shown by a DMSA. He also adds that the DMSA might be reserved, if necessary, for detection of APN in those children with a normal USG. The author does not express the specificity of an abnormal USG to diagnose APN and adds that the diagnosis can be missed in 20% of children(6).

VUR as been reported to be present in 30-50% of the children with UTI(7). In our study 33 (78.6%) children had VUR, possibly due to the captive subjects included as our department is a referral center in a tertiary care hospital. Further, our study also included children with recurrent UTI.

Of 39 children with an abnormal DMSA 32 (82.1%) had VUR. In 3 children with a normal DMSA, VUR was present in 1 (33.3%). Out of 33 children with VUR 32 (96.6%) had DMSA findings of APN. Majid,

Key Messages

- DMSA is the gold standard and sensitive investigation to diagnose acute pyelonephritis in febrile culture positive UTI and febrile culture negative acute pyelonephritis
- DMSA followed by VCU to diagnose VUR if DMSA is positive should form part of the protocol for evaluation of every child with 'fever of unknown origin'.

et al.(8) have observed that DMSA scan finding of APN were present in 79% of children with VUR and in 60% of children with no demonstrable VUR. VUR was present in 19% of kidneys with normal scan finding(8). The possibility of VUR is high if there is abnormal DMSA and absence of VUR does not rule out APN. The association of APN, as suggested by DMSA and the presence of VUR can be of value to prognosticate for subsequent scarring. Biggi A *et al*(3) have classified them into various groups: (*a*) Low risk group (normal kidney with or without VUR) in whom the risk of scarring is zero; (*b*) Intermediate risk group (mild lesion with or without VUR and extensive lesions without VUR) have 14-30% risk of scarring-and (*c*) High-risk group (extensive lesion with VUR) the risk of scarring is 88%. Thus the presence of VUR and APN is necessary to prognosticate the risk of scarring. Quantifying the risk of scarring would help in planning for the prevention of progression of parenchymal damage in terms of efficient control of infection, prevention of relapses and correction of VUR. Parkhouse et al(9) reported that DMSA to have a sensitivity of 89% and specificity of 100% for diagnose of APN. Thus DMSA at present is the best available modality to diagnose APN and could be considered the 'gold standard'.

The value of DMSA is further strengthened by the demonstration of APN by the DMSA in 26 febrile children with a negative urine culture but with clinicobiological features to suggest UTI. In these children the USG was abnormal in 17 (65.4%) and normal in 9 (34.6%). In all the 9 children the DMSA was abnormal, hence reiterating that USG is a poor investigatory tool to diagnose APN. Of the 26 children with abnormal DMSA only 17 (65.4%) had VUR. In 9 children with an abnormal DMSA there was no VUR. Absence of VUR does not rule out APN. Levtchenko, *et al*.(2) have shown the utility of DMSA in the diagnosis of APN in children with negative urine cultures. In this study it was pointed out that VUR was present in 60% of children with an abnormal DMSA. Hence, VUR could have been missed in this good number of children with culture negative pyelonephritis and this would have resulted in the possibility of scarring and progressive renal damage. It is suggested by the author that DMSA should be done in children with severe infection without clear etiology especially in those with abnormal urine analysis(2). Ten children were followed up. In 8 of these children a repeat DMSA showed resolution. This is in accordance to the study where parenchymal changes were found reversible in more than 50% of children in the first episode(4,7,10). However, in 10 children with recurrent UTI, 7 (70%) had scars signifying that recurrent infections are prone for scars and need to have followed up.

From this study, we feel a DMSA is essential in children with febrile UTI to diagnose APN, the presence of which will play a principal role in the therapy and follow up

evaluation. Children with APN need to have a VCU done to decide for chemo-prophylaxis and its duration. In view of the high possibility of false negative urine culture in children with UTI a DMSA should form part of the protocol in the evaluation of FUO particularly when supportive evidence for UTI is present.

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