

# The Diagnostic Value of Clinical and Radiologic Findings in Children after the First Episode of Acute Pyelonephritis

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= **Abstract** =

**Purpose :** Acute pyelonephritis is one of the most common causes of unexplained fever in children. It may lead to the development of progressive renal damage. However, the detection of acute pyelonephritis can be difficult, especially in infants. The objective of this study was to evaluate the diagnostic value of various lab tests and imaging studies for acute renal parenchymal changes in children with APN. We correlated the clinical and laboratory manifestations of acute pyelonephritis with the imaging studies.

**Methods :** We reviewed the records of 115 children (85 males and 30 females) who were hospitalized during the period of January 1998 to December 2002 with initial clinical symptoms suggestive of pyelonephritis. The patients' age, sex, duration of fever, laboratory findings, and causative organisms were compared with the findings of imaging studies (Technetium-99m dimercaptosuccinic acid renal scan, renal ultrasonography, intravenous pyelography, voiding cystourethrography).

**Results :** No significant relation between the number of febrile days, leukocyte count, causative organism, and the renal abnormalities in the imaging studies were observed. On the other hand, both C-reactive protein and erythrocyte sedimentation rate levels were significantly elevated in children with positive dimercaptosuccinic acid renal scan. Furthermore, females and children older than 1 year presented with significantly higher rate of abnormal dimercaptosuccinic acid renal scan findings and vesicoureteral reflux presented by voiding cystourethrography.

**Conclusion :** We recommend females and children older than 1 year who are suspected of acute pyelonephritis be evaluated carefully for renal involvement by performing imaging studies including dimercaptosuccinic acid renal scan and voiding cystourethrography. (**J Korean Soc Pediatr Nephrol 2005;9:201-212**)

**Key Words :** Acute pyelonephritis, Age, Sex, Dimercaptosuccinic acid renal scan, Vesicoureteral reflux, Renal damage

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## INTRODUCTION

Acute pyelonephritis (APN) is a common disease in children, especially in infants [1]. It has been estimated that approximately 1%

of boys and 3% of girls will experience a symptomatic UTI before the 11th year of life [2]. The diagnosis of APN rests upon clinical symptoms, pyuria and detection of bacteria from urine sample. However, in infants, the diagnosis can be difficult due to nonspecific symptoms such as jaundice, poor feeding, irritability and weight loss. In 50-65% of affected children, the inflammation from the initial insult of APN produces irreversible lesions of the renal parenchyma [3,4]. The damaged areas of renal tissue are replaced by fibrous scars and the damage can subsequently lead to arterial hypertension and in most severe cases, renal failure [5]. Studies in animals have demonstrated that inflammation has an important role in the pathological process that involves the local influx of polymorphonuclear leukocytes and the release of cytotoxic metabolites [6] and that renal lesions caused by acute febrile urinary tract infection (UTI) may be prevented or diminished by early diagnosis and treatment [7]. Therefore, it is very important that we recognize the risk factors for early renal damage in childhood pyelonephritis. Most cases have supported the fact that the susceptibility of the renal parenchyma varies with age, with infants under 1 year at greatest risk, and sex, in that underlying urological abnormalities are more often seen in males. Jakobson et al. have shown that one-third of children with radiological abnormalities have vesico-ureteric reflux (VUR) [8]. The role of intra-renal reflux (Hodson) and the Big Bang Theory (Ransley) in relation to VUR are being discussed [9], and in our previous studies, we have suggested a genetic basis

for VUR by investigating the genetic polymorphism of ACE, AT1 and AT2 subtypes of ANG II receptor genes [10]. The risk factors for renal involvement in childhood pyelonephritis are yet being debated. Since it is often difficult to determine the renal involvement in urinary tract infections by fever, flank pain, elevated C-reactive protein (CRP) values or erythrocyte sedimentation rate (ESR), which are classically associated with pyelonephritis in adults, imaging techniques including Tc-99m dimercaptosuccinic acid (DMSA) renal scan, renal ultrasonography (US), intravenous pyelography (IVP) and voiding cystourethrography (VCUG) are used to assess APN. Many reports have claimed DMSA renal scan to be the best clinically applicable standard of reference for the diagnosis of acute pyelonephritis [11,12]. Moreover, DMSA renal scan provides the opportunity to study the progression of renal damage and functional loss from the initial insult of APN to the subsequent development of irreversible renal damage.

The aim of this study was to evaluate the diagnostic values of various lab tests and imaging studies for early renal parenchymal changes in children first admitted for clinically suspected APN. We compared the sensitivities of imaging techniques for the assessment of renal abnormalities and correlated the clinical and laboratory manifestations of acute pyelonephritis with the imaging studies.

## MATERIALS AND METHODS

### 1. Patients' characteristics and study design

A retrospective study was undertaken with 115 consecutive patients admitted to the hospital who had taken DMSA renal scan for suggested APN. The records of the pediatric patients aged 0-15 years who were admitted to Guro Hospital and Anam Hospital, Korea University Medical Center between January, 1998 and December, 2002 were reviewed. 85 male and 30 female patients were eligible for the study. They were highly suggestive of APN (fever >38.5°C, white blood cells in urine  $\geq 5$  per high power field on microscopy and positive urine culture  $\geq 10^5$  microorganisms per mL for voided urine,  $\geq 10^3$  for suprapubic collection). To keep possible misinterpretation due to previous renal scars to a minimum, we only included children with the first symptomatic urinary tract infection. All children had undergone DMSA renal scan and renal US, 75 had IVP, and 95 had undergone VCUG. Those studies not taken were either because the physician did not order the study or the patient's guardians neglected the order. Prior to evaluating the relations of patient's age, sex, fever duration, causative organism, and laboratory results to the findings of imaging studies, the sensitivity of each imaging study was statistically compared to choose the best parameter for the detection of renal abnormalities. Children in the study were divided into two groups as follows: group I, age less than 1 year and group II, age greater than 1 year.

### 2. Clinical and laboratory assessments

The duration of fever prior to admission was evaluated for the possible risk factor of renal damage. For laboratory assessments, the causative organism confirmed by urine culture, white blood count (WBC), CRP, and ESR levels were evaluated. The result of CRP level was missing in 1 case, and ESR level in 5 cases.

### 3. Imaging studies

DMSA renal scan was performed 3 hr after injection of  $99mTc$ -DMSA, taking one posterior, one anterior, and two posterior oblique images by rectangular-headed, rotating gamma camera (SOPHA DSX; Sopher Medical Systems, Columbia, MD) with the patient in the prone position. The fractional left and right activities were calculated for each kidney after background correction. A kidney uptake of 45-55% of the total renal activity was considered normal. The criteria of renal abnormality were: focal or diffuse areas of decreased uptake of labeled DMSA or diffusely decreased uptake in an enlarged kidney. DMSA renal scan was performed no later than 15 days following the diagnosis of UTI in order to assess the acute lesion.

Renal US was performed by a certified radiologist using HDI-5000 scanner with sector C8-5 mHz probes for neonates and convex C5-2 mHz probes for older children. The criteria for renal abnormality were: focal or diffuse parenchymal hyper- or hypoechogenicity, loss of corticomedullary differentiation, pelvic dilatation, parenchymal reduction or increase in renal size.

IVP was taken with a series of radiographs of the urinary tract at 1, 3, 7, 12, 20, 25 and 30 min after intravenous injection of contrast medium, lobitridol, at the dosage of 1 mL/kg. The criteria of renal abnormality were: pelvic dilatation, distention of minor calyx and infundibulum, and loss of minor calyceal cupping.

VCUG was evaluated for the presence and grade of reflux. Iodinated contrast material was inserted into the bladder by ureteral catheterization by a pediatrician. The procedure was performed after the urine culture was evidently sterilized by at least a week of antibiotic treatment. As the child voids, radiographic cystograms, two oblique and one supine view, were taken spontaneously. Reflux severity was based on the International Study Classification: Grade I reflux was defined as reflux into a non-dilated ureter; Grade II was reflux into the upper collecting system without dilatation; Grade III was reflux into dilated ureter and/or blunting of calyceal fornices; grade IV was reflux into a grossly dilated ureter; Grade V was massive reflux with significant ureteral dilatation and tortuosity and loss of papillary impression. In this study, Grade I-III and IV-V were categorized as low and high grade, each respectively.

#### 4. Statistical analysis

The results were analyzed with chi-square test, Fischer's exact test, t test, and rank sum test. The relations of sex and age with the imaging studies were mainly tested using chi-square test, while the other risk factors were tested by t test and rank sum test, as

needed. A *P*-value of less than 0.05 was considered statistically significant. The Sigstat version 2.0 for Windows was used.

## RESULTS

### 1. Patients' characteristics (age and sex)

A total of 115 Korean children, 85 males and 30 females, were enrolled in the study. The mean age was 12 months. 96 (80 males and 16 females) were less than 1 year in age; 19 (5 males and 14 females) were older than 1 year. In children younger than 1 year, the frequency of first documented APN was significantly higher in males than in females (83.3% in males vs. 16.7% in females,  $P < 0.05$ ). On the contrary, females were predominant in children older than 1 year (26.3% in males vs. 73.7% in females,  $P < 0.05$ ).

### 2. Clinical and laboratory data in relation to imaging studies

The mean fever duration prior to admission was  $2.6 \pm 3.9$  days (range 1-30). Leukocyte count measured was  $13,766 \pm 5,697/\text{mm}^3$  (range 3,200-30,500). CRP measured in 114 of the 115 patients was  $63 \pm 58$  mg/L (range 0-222), while ESR measured in 110 of the 115 patients was  $44 \pm 32$  mm Hg (range 1-134). No significant differences in the number of febrile days and leukocyte count in relation to the renal abnormalities in the imaging studies (renal US, IVP, DMSA renal scan, VCUG) were observed. CRP and ESR levels were not in relation to the renal abnormalities in renal US, IVP, and VCUG. However, both CRP and ESR levels were significantly elevated in children with posi-

tive DMSA renal scan ( $P < 0.001$ ,  $P = 0.044$ , respectively) (Table 1). The fever duration, leukocyte count, CRP, and ESR levels showed no relation to the positive findings of follow-up DMSA renal scan which suggests scarring of renal parenchyma as opposed to acute transient inflammation.

### 3. Bacterial pathogen in relation to imaging studies

The causative organisms of APN were evaluated to compare the influence of each organism's virulence on renal damage. *E. coli* was the infecting agent in 105 (91.3%) children and *K. pneumoniae* in 5 (4.4%), *Enterobacter* in 2 (1.7%), *K. oxytoca* in 2 (1.7%), *Enterococcus* in 1 (0.9%) composed the rest. The organisms were divided into two groups; *E. coli* group and non-*E. coli* group. No significant relation, however, was found between the two groups and the findings of imaging studies. Age and sex were not in relation to the causative organisms, as well.

### 4. Renal US in relation to age and sex

Of the 115 children who had taken renal US, 37 (32.1%) showed renal abnormalities. 28 of 85 (32.9%) males and 9 of 30 (30%) females had positive sonographic findings. 34 of 96 (35.4%) in age group I and 3 of 16 (18.7%) in group II had positive findings.

The findings on renal US had no relation to age or sex.

### 5. IVP in relation to age and sex

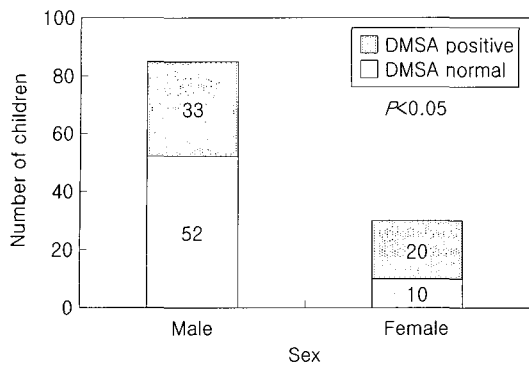
Of the 75 children who had taken IVP, 21 (28.0%) had abnormal findings. 14 of 55 (23.6%) males and 8 of 20 (40.0%) females had positive findings. 13 of 58 (22.4%) in age group I and 8 of 17 (47.0%) in group II had positive findings. The findings on IVP had no relation to age or sex.

### 6. DMSA renal scan in relation to age and sex

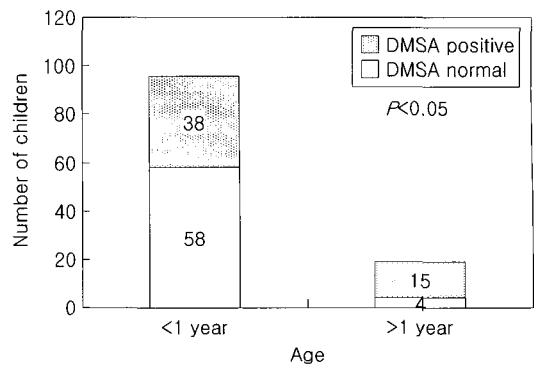
Of the 115 children who had taken DMSA renal scan during the acute phase, 53 (46.0%) had findings consistent with APN; 40 had unilateral, 13 had bilateral changes on renal scan. Follow-up DMSA renal scan was performed within 6 months in 44 of 115 children for the evaluation of prolonged renal damage or scar; 13 of 44 (29.5%) children with initial renal damage showed persistent lesions. On the initial DMSA renal scan, 33 of 85 (38.8%) males and 20 of 30 (66.6%) females had positive findings; females had a significantly higher proportion of renal parenchymal damage on DMSA renal scan ( $P = 0.014$ ) (Fig. 1). 38 of 96 (39.5%) children in age group I and 15 of 19 (78.9%) in group II were positive for APN by DMSA renal scan;

**Table 1.** Summary of Laboratory and Clinical Data Expressed as Mean and Standard Deviation in Comparison to Tc-99m Dimercatposuccinic Acid Renal Scan

	DMSA positive	DMSA normal	P value
Number of patients	53	62	
Duration of fever (days)	2.9±5.0	2.3±2.8	>0.05
C-reactive protein (mg/dL)	88±65	43±40	<0.001
Erythrocyte sedimentation rate (mm/h)	51±34	38±28	0.044
White blood count (WBC/mm <sup>3</sup> )	14,243±6,129	13,358±5,317	>0.05



**Fig. 1.** Comparison of Dimercaptosuccinic acid (DMSA) renal scan findings by sex in children with clinically suggested APN.

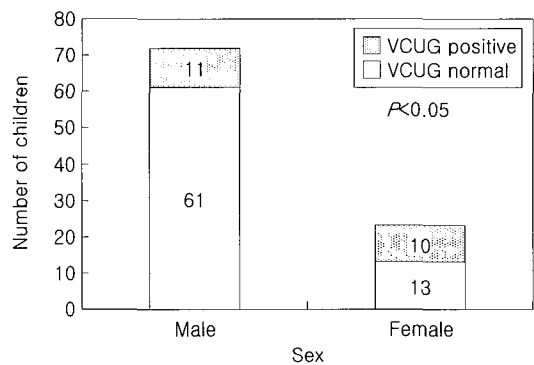


**Fig. 2.** Comparison of DMSA renal scan findings by different age groups in children with clinically suggested APN.

older groups had significantly higher proportion of positive findings ( $P=0.004$ ) (Fig. 2). However, positive findings on follow-up DMSA renal scan were not related to age or sex. Furthermore, the DMSA renal scan findings were evaluated in 4 different combinations of groups by sex and age. As a result, the rate of positive findings on the initial DMSA renal scan was significantly higher in the group of children who are concurrently female and older in age (age group II); 12 of 14 (85.7%) children who are female and in age group II, 3 of 5 (60.0%) who are female and in age group II, 8 of 16 (50.0%) who are male and in age group II, and 30 of 80 (37.5%) who are male and in age group I, showed positive findings consistent with APN in DMSA renal scan ( $P=0.008$ ). The positive findings on follow-up DMSA renal scan, however, were not significantly related to such combination groups.

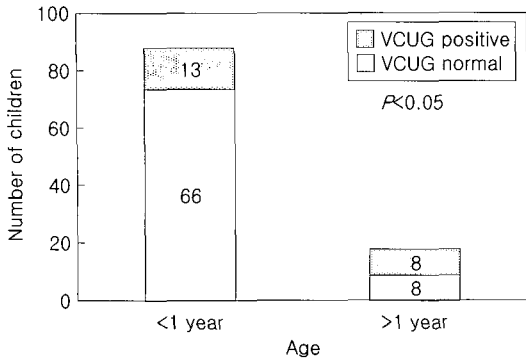
### 7. VCUG in relation to age and sex

Of the 95 children who had taken VCUG, 21 (22.1%) had VUR; high and low grade reflux in 13 (13.6%) and 8 (8.4%), each respec-

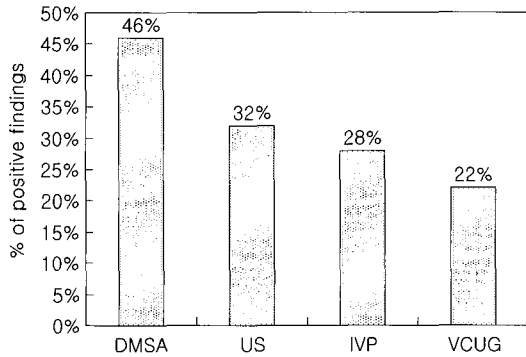


**Fig. 3.** Comparison of VCUG findings by sex in children with clinically suggested APN.

tively. 11 of 72 (15.2%) males and 10 of 23 (43.4%) females had positive findings; females had a significantly higher proportion of renal abnormality on VCUG ( $P=0.018$ ) (Fig. 3). 13 of 79 (16.5%) in age group I and 8 of 16 (50%) in group II had positive findings; children older than 1 year had significantly higher proportion of renal abnormality ( $P=0.013$ ) (Fig. 4). VCUG findings were further evaluated in 4 different combination groups by sex and age. As a result, 7 of 13 (53.8%) children who are female and in age group II, 3 of 10 (30.0%) who are male and in age group II, 1 of 3 (33.3%) who are female and in age group I, and 10 of 69 (14.5%) who are male



**Fig. 4.** Comparison of VCUg findings by different age groups in children with clinically suggested APN.



**Fig. 5.** Comparison of positive finding rates of different imaging studies in children with clinically suggested APN.

and in age group I, showed positive findings. The results, however, were not significantly related to such combination groups.

### 8. Comparison of imaging studies

From the imaging studies, DMSA renal scan presented with the highest rate of positive findings in children with clinically suggested APN (Fig. 5). The DMSA renal scan findings were each compared with other imaging studies by chi-square. As a result, not much relation was found with renal US or IVP. Of the children who had undergone both studies, only 19 of 115 (16.5%) and 14

of 75 (18.6%) were positive for both studies, respectively. On the other hand, 17 of 95 (17.8%) children had positive findings for both DMSA renal scan and VCUg and their findings were significantly related ( $P < 0.05$ ). Moreover, DMSA renal scan findings were significantly related to VCUg by grade ( $P < 0.05$ ). Of the 13 children who had low-grade reflux by VCUg, 9 (69.2%) had positive findings of DMSA renal scan, whereas, of the 8 children who had high-grade reflux, all 8 (100%) had positive findings. 31 of 74 (41.8%) children without reflux had positive findings on DMSA renal scan.

## DISCUSSION

As the diagnosis of APN is often difficult in neonates and infants, the risk factors of pyelonephritis, reliability of the diagnostic parameters, and the "gold standard" method for diagnosis are still being debated. The retrospective study we present was addressed to evaluate the risk factors of early renal damage in childhood after first APN.

There have been various imaging studies performed for the evaluation of APN in children, including renal US, IVP, DMSA renal scan, and VCUg. In this study, the children with clinical and laboratory manifestation of pyelonephritis showed the highest positive rate of abnormal findings in DMSA renal scan, suggesting DMSA renal scan to be the most sensitive imaging study to assess renal parenchymal lesion (DMSA renal scan 46.0%, renal US 32.1%, IVP 28.0%, VCUg 22.1%).

DMSA renal scan has emerged as the imaging study of choice for the early detection

and evaluation of APN in many recent studies [13, 14].

The relation of patients' laboratory results with the findings of imaging studies were evaluated, and as a result, both CRP and ESR levels were significantly elevated in children with positive DMSA renal scan. Ghiro et al [15] reported that children with evidence of scars on DMSA scan had significantly higher levels of CRP, therefore suggesting a high risk of parenchymal involvement and the development of scar lesions in febrile children with UTI and increased CRP.

It has been generally accepted that the inflammatory reactions are especially harmful in children during the period when the growth of the kidney is most rapid and that infants are more prone to develop permanent renal damage [16-18]. The resistance of renal parenchyma increases and the formation of scar is thought to be less common in the older children [19-21]. Recent data, including the study results that we propose, however, call in question our previous knowledge in this field. In studies most often referred to in this respect, renal sequelae from various pathophysiological entities may have been lumped together under the terms of renal scarring and reflux nephropathy [22, 23].

Benador et al [24] reported that scarring was more common in children above 1 year of age than in those below this age. Lin et al [25] reported that APN was more common in older children with equal prevalence of renal scarring after APN in three different age groups. Our study revealed a significantly high positive rate of abnormal DMSA

findings in older children who were clinically suspected for APN, particularly in those older than 1 year. This may be due to the duration required for scars to develop or because renal scars have developed as a result of previously unrecognized pyelonephritis that were mistaken for other febrile illnesses. The different criteria for admission in infants and older children might be another contributing factor to the result. Ilyas et al [26] reported that APN correlates better with the DMSA renal scan finding in older children than in younger children, and that it may be due to the fact that older children are better able to relate their symptoms. We suggest the possibility that all children with APN run a risk of renal scarring. It seems appropriate to perform DMSA renal scan in all children clinically suggestive of APN, regardless of age. Moreover, our study showed a higher rate of reflux in children over 1 year in age.

Lin et al [25] reported that although severe renal infection can result even in the absence of VUR and the presence of VUR by itself does not necessarily imply an acute renal infection, VUR, especially high grade reflux, continues to be one significant risk factor in the etiology of childhood pyelonephritis. Howard et al [27] reported the presence of VUR in 39% of symptomatic Chinese children with UTI. In addition, the results of our study were in accordance with many other reports that noted the increased risk of renal scarring with the grade of VUR [28]. The positive rate of DMSA renal scan increased as the grade of VUR increased (VUR; no reflux 41.8%, grade I-III 69.2%, grade IV-V 100%,  $P < 0.05$ ).



The highest incidence of urinary tract infection is known to occur in the first year of life, with a strong male predominance [29]. In our study, the frequency of first documented febrile UTI in children younger than 1 year was higher in males, whereas in older children, the frequency was higher in females. Lin et al [27] reported that both febrile UTI and APN were more prevalent in males under 1 year and females over 1 year. Different contributing factors may play roles in such phenomenon. Rushton and Majd [30] showed a disproportionately high frequency of uncircumcised male infants among the male infants with febrile urinary tract infection. Host factors, such as the inner nonkeratinized epithelium of the foreskin, create a moist reservoir for uropathogens and once the prepuce is colonized, the bacteria can ascend the urinary tract infection and cause UTI. Other studies have reported that male infants have a higher incidence of urodynamic abnormalities [31, 32]. Gobet et al. [33] explained this finding by the higher resistance of the long male urethra and the narrower male meatus as well as anatomical differences in the configuration of the external urethral sphincter. The short urethra and voiding habits of females may contribute to the higher incidence of UTI in older age.

In our study, contrary to the high prevalence of male infants with clinically suggested APN, females presented with significantly higher rate of abnormal DMSA findings and vesicoureteral reflux (VUR) presented by VCUG. Previous studies related age below 1 year and male gender to an increased frequency of VUR [34, 35]. However, Zaki et al

reported that males had a lower risk profile than females, the latter having a higher rate of reflux as well as a higher rate of abnormal DMSA scans [36]. Notably, performing DMSA scans and VCUG according to the assumption that male infants are more likely to show abnormal findings may lead to incorrect interpretations of the patient's status. The small number of older female patients may have had some influence over the results in our study, but such results were statistically significant and should be taken into consideration more or less.

In conclusion, this study demonstrates that children who have DMSA renal changes on initial scanning, whether they were congenital or acquired in origin, were more likely to develop APN and that DMSA renal scan and VCUG showed higher positive rates of abnormalities in females and in older children. The radiological evaluation of urinary tract after the clinical suspicion of APN should not be limited to male infants or children of younger age, particularly if CRP or ESR level is markedly increased. We recommend female infants and children older than 1 year who are suspected of having APN be evaluated for renal involvement by performing imaging studies including DMSA renal scan and VCUG.

#### 한 글 요 약

### 소아에서의 첫 번째 급성 신우신염에 따른 임상 소견 및 방사선학적 검사의 진단적 유용성

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**목 적** : 본 연구에서는 급성 신우신염으로 진단 받은 환아에서 여러 임상 증상 및 검사 결과와 방사선학적 검사에서 확인된 신실질 손상의 관계를 알아보기 위하여 DMSA 신 스캔, 신장 초음파, IVP, VCUG 등의 방사선학적 검사의 유용성과 방사선학적 검사의 결과에 따른 환아들의 임상 증상 및 검사 소견을 비교 분석하였다.

**방 법** : 1998년 1월부터 2002년 12월까지 열성 요로 감염으로 처음 진단되어 입원 치료받았던 환아 115명을 대상으로 연구를 실시하였다. 이들은 DMSA 신 스캔, 신장 초음파, IVP, VCUG를 포함한 방사선학적 검사를 시행하였으며 각 검사의 양성률을 통하여 그 유용성을 비교하였다. 또한, 환아들의 연령, 성별, 발열 기간, 원인 균, 혈액학적 소견(백혈구 수, CRP, ESR)을 방사선학적 검사 결과와 비교 분석하였다. 연령에 따라 1군(1세 미만)과 2군(1세 이상)으로 분류하였으며, 각 군간의 검사 양성률 비교를 위해 chi-square test를 이용하여 통계 분석하였다.

**결 과** : 방사선학적 검사 중 DMSA 신 스캔이 가장 높은 양성률을 보였다(DMSA 신 스캔 46%, 신장 초음파 32%, IVP 28%, VCUG 22%,  $P < 0.05$ ). 환아의 발열 기간, 백혈구 수, 원인균은 방사선학적 검사 결과와 관련이 없었으나 CRP, ESR이 DMSA 신 스캔의 양성률과 밀접한 관계를 보였다. 연령별로 비교했을 때 1군에 비해 2군에서 DMSA 신 스캔 양성률이 증가하였으며(1군 40%, 2군 79%,  $P < 0.05$ ), VCUG 역시 2군에서 높은 양성률을 보였다(1군 16%, 2군 50%,  $P < 0.05$ ). 그러나 신장 초음파와 IVP는 각 군간 유의한 차이를 보이지 않았다. 성별로 비교했을 때 남아에 비하여 여아에서 DMSA 신 스캔 및 VCUG의 양성률이 높았으나(DMSA; 남아 39%, 여아 67%, VCUG; 남아 15%, 여아 43%,  $P < 0.05$ ) 신장 초음파와 IVP는 성별에 따른 유의한 차이를 보이지 않았다.

**결 론** : 급성 요로 감염에 이환된 환아는 신 손상 여부의 확인을 위하여 DMSA 신 스캔을

시행하는 것이 가장 도움이 되며, DMSA 신 스캔과 VCUG의 이상은 여아와 2세 이상에서 양성률이 높으므로, 이와 같은 경우에는 이 두 가지 검사를 반드시 시행하여야 할 것으로 사료된다.

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