The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original Article

Risk factors of renal scars in children with acute pyelonephritis

Fahimeh Ehsanipour[*], *Minoo Gharouni*, *Ali Hoseinpoor Rafati*, *Maryam Ardalan*, *Neda Bodaghi*, *Hasan Otoukesh*

Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Article history:
Received 5 April 2011
Accepted 29 May 2011

Keywords:
Health of institutionalized children
Pyelonephritis
Vesicoureteral reflux

ABSTRACT

Objective: The aim of this study was to determine the association between previously documented risk factors such as recurrent pyelonephritis with the incidence of renal scarring after acute pyelonephritis in children.

Material and methods: Children with acute pyelonephritis who were admitted to the Department of Pediatrics of a teaching hospital during 2007-2009 were enrolled in this study. DMSA scans were obtained 4-6 months after the last episode of pyelonephritis in all patients.

Results: A total of 80 children with acute pyelonephritis were enrolled in this study. Most of them were girls (77.5%), with a median age of 12 months. Nearly half of the children (n = 44; 55%) had one or more renal scars. The distribution of gender, CRP level and leukocytosis did not differ significantly regardingthe absence or presence of renal scars ($p > 0.05$). Most of the scars occurred in children who had presented with bilateral pyelonephritis (69.4% vs. 18.2%, $p = 0.001$). Most of the patients with renal scars had a positive history of vesicoureteral reflux (VUR) (75% vs.13.6%, $p = 0.001$). The significant roles of recurrent pyelonephritis and presence of VUR were further confirmed by multivariate analysis.

Conclusions: According to our findings, presence of VUR and recurrent pyelonephritis are independently associated with a higher incidence of renal scarring.

Introduction

Urinary tract infection (UTI) is considered the most common disease of childhood. UTI may be limited to the bladder, cystitis, or may involve the renal parenchyma, acute pyelonephritis (APN), defined as fever over 38.5°C, high level of C-reactive protein or erythrocyte sedimentation rate, leucocyturia and positive urinary culture.[1] The clinical presentation of APN may be nonspecific and varies according to factors such as the patient's age and level of infection (whether the infection involves kidneys or lower urinary tract only). The renal cortical changes are acceptably detected by 99mTc-DMSA renal scintigraphy.[2] This method is applied in two ways: (1) to localize UTI during an attack to predict the risk of scarring; (2) to monitor the development of new scars; and/or (3) progression of existing scars in a serial

[*] *Corresponding author at:* Division of Infectious Diseases, Department of Pediatrics, Rasoul Akram Hospital, Tehran University of Medical Sciences, Sattarkhan St, Niayesh St, Tehran, Iran
E-mail address: ehsanipourfahimeh@yahoo.com (Fahimeh Ehsanipour)

follow-up.[3,4] The Scientific Committee of Radionuclides in Nephrourology tried to compromise on modalities of using renal scintigraphy in children with UTI[5] depending on the health-care delivery system in a specific area; there are various types of approaches for managing patients with UTI. Moreover, the pediatric nephrologist's judgment differs frequently from that of the nuclear medicine physician and considerable discrepancies exist even among the opinions of nuclear-medicine specialists. The timing of the 99mTc-DMSA scan (whether to perform an acute scan, a follow-up scan only or both) is still an issue of debate. It is actually believed that acute renal scintigraphy is unnecessary due to the temporary nature of developed lesions in half of the cases. Eventually, they disappear over time.[6,7] Also, most of the pediatric nephrologists prefer to rely on clinical and biological findings in case of complicated UTI rather than scintigraphy.[8,9] However, it sometimes happens that clinical findings and equivocal urine cultures do not favor diagnosis, even though the patient may already have UTI and renal damage.[10,11] This prospective clinical study was carried out to indicate any correlation between the incidence of renal scarring following acute pyelonephritis and previously well-known risk factors such as vesicoureteral reflux (VUR), age and recurrent urinary tract infections.

Material and methods

Subjects

The patient sample included all children diagnosed with acute pyelonephritis (APN) in the pediatric section of a teaching hospital during 2007-2009. Each diagnosis was confirmed by a pediatric nephrologist, based on clinical and laboratory examinations and DMSA.

For analytical purposes, the patients were divided into three age groups:

Group I: < 12 months;
Group II: 12-48 months;
Group III : > 48 months.

Each patient with APN underwent renal ultrasound and voiding cysto-ureterography (VCUG) 4-6 weeks later as part of the initial investigation. DMSA scans were obtained at least 4-6 months after the last pyelonephritis episode in all patients. The grade of VUR was categorized according to the International Reflux Committee classification.[12] All patients were treated with appropriate antibiotic therapy and kept on prophylaxis as indicated.

Statistical analysis

The descriptive analysis was performed as appropriate (median and range for non-parametric data). Chi-square test or Fisher's exact test were used to analyze categorical data and Mann-Whitney test was used to compare two non-parametric variables. Logistic regression analysis was planned considering kidney scar as the dependent variable, and testing the covariates resulting significant in the previous univariate analysis. $p < 0.05$ was considered statistically significant.

Results

Demographic findings

A total of 80 children with acute pyelonephritis were enrolled in this study. Most of the patients were girls, 77.5%, with a median age of 12 months (range 1-156) and more than half of them were younger than 1-year-old (n = 45; 56.2%). Almost half (n = 44; 55%) reported having APN at least once in their past history; however, APN occurred twice and three times in 25 (31.2%) and 11 (13.8%) children, respectively, during their previous admissions.

The gender distribution did not differ significantly according to categorized age groups ($p > 0.05$).

Clinical and paraclinical findings

One or more renal scars were found in 44 (55%) children. VUR was not reported in the majority of the patients (n = 47; 58.8%); however, grades I-II VUR were seen in 26 (32.5%) patients and the remaining (n = 7; 8.8%) had grades III-V VUR. Only 16 (20%) children had neurogenic bladder. The median duration of fever was 3 days (range 1-14). Other paraclinical findings were as follows: CRP level of more than 6 mg/dL was reported in 61 (76.2%) children; leukocytosis in 42 (52.5%); and positive culture for *Escherichia coli* was obtained from 69 (86.2%) and the rest of the patients had other urinary microbial profiles.

As shown in Table 1, the distribution of gender, CRP level, leukocytosis and urine culture results did not differ significantly in relation to the absence or presence of renal scars ($p > 0.05$). A substantial number of patients with renal scars had a positive history of VUR in comparison to patients with a negative history of VUR (75% vs. 13.6%, respectively, $p = 0.001$). The frequency of children with neurogenic bladder was higher among patients with renal scar compared to their counterpart group (30.6% vs. 11.4%, respectively, $p = 0.049$). Furthermore, regarding other variables such as the median age (months) of the children, duration of fever (days), recurrences of pyelonephritis were significantly higher among patients with renal scars ($p < 0.05$) (Table 1).

As summarized in Table 2, the roles of the recurrences of pyelonephritis and presence of VUR were further confirmed by the multivariate analysis.

Discussion

Identifying children with UTI who are at increased risk of renal damage is one of the major clinical challenges. Several complications of renal scarring have been reported including hypertension, chronic renal failure and ultimately failure to thrive.[13]

Renal scars are present in 6.1% of children with UTI.[14] Children with APN are substantially vulnerable to renal scarring due to the necrosis and fibrosis associated with acute inflammation. Actually, it has been shown that 80% of defects in APN tend to remain unchanged at least 6 months after onset;[15] in fact the defects in a binary manner resolve or eventually turn into scars.

Table 1 - Comparison of clinical and paraclinical data according to the presence renal scar

Variable	Renal scar		p-value
	Present	Absent	
Gender			
Boy	5 (13.9%)	13 (29.5%)	0.09*
Girl	31 (86.1%)	31 (70.5%)	
CRP level			
< 6 mg/dL	7 (19.4%)	12 (27.3%)	0.41*
> 6 mg/dL	29 (80.6%)	32 (72.7%)	
Leukocytosis			
Positive	17 (47.2%)	21 (47.7%)	0.96*
Negative	19 (52.8%)	23 (52.3%)	
Urine culture results			
Escherichia coli	28 (77.8%)	41 (93.2%)	0.057*
Others	8 (22.2%)	3 (6.8%)	
VUR grades			
No VUR	9 (25%)	38 (86.4%)	0.001*
Grades I-II	21 (58.3%)	5 (11.4%)	
Grades III-V	6 (16.7%)	1 (2.3%)	
Neurogenic bladder			
Present	11 (30.6%)	5 (11.4%)	0.049*
Absent	25 (69.4%)	39 (88.6%)	
Age (months)			
Median (range)	22 (1.5-156)	9 (1-96)	0.02**
Duration of fever (days)			
Median (range)	3 (1-14)	2 (1-5)	0.019**
Recurrences of pyelonephritis			
Median (range)	2 (1-3)	1 (1-2)	0.001**

**Chi square test (Fisher's exact test); **Mann-Whitney test; VUR, vesicoureteral reflux.

Table 2 - Logistic regression model

Variables	B	S.E.	Wald	df	p-value	Exp (B)	95% CI for Exp(B)	
							Lower	Upper
VUR grades	2.204	0.565	15.195	1	0.000	9.064	2.992	27.456
Recurrences of pyelonephritis	1.118	0.466	5.755	1	0.016	3.059	1.227	7.627
Constant	-2.956	0.804	13.522	1	0.000	0.052		

Method: Forward conditional ; Nagelkerke R Square: 0.496; dependent variable: Kidney scar (present: 1, negative: 0); VUR, vesicoureteral reflux.

There is a wide variety of factors that might contribute to renal damage in children. For this purpose, nephrologists generally take some specific clinical signs, such as high fever, serious enough to order a diagnostic imaging test.[15] Other known factors[7] that increase the likelihood of renal damage in children have been shown to be reflux, CRP and body temperature. Obviously, the probability of renal damage in children suffering from UTI and high levels of CRP, high fever and dilating reflux is up to ten times higher than their counterpart with normal or slightly elevated CRP levels, no or mild fever, and no reflux. In contrast, this study and another similar study[16] did not support these results; clearly we did not find any significant difference between th two groups of children, with and without scars, regarding the levels of CRP and cell counts at the time of APN. Despite significantly longer duration of fever in children with scars, this variable did not turn out to play an independent role in further multivariate analysis.

The advantages of using 99mTc-DMSA renal scintigraphy to evaluate renal sequela after APN have been confirmed in various studies.[17-19] They demonstrated the efficiency of this imaging modality for clinical use in comparison with conventional imaging techniques such as ultrasound, CT and MRI methodology. Comparatively, ultrasound has not a high sensitivity for APN and spiral CT and MRI, with equal sensitivity, are not routinely recommended. Further, an abnormal DMSA in children was associated with a higher frequency of VUR.[19]

There is some evidence that confirm the predominant role of high grades VUR (grades IV and V) in the development of renal parenchymal damage[15,20,21] which strongly predicts the extent of renal lesion after an APN.[21] Nevertheless, renal lesions have been found in lower grades or even in the absence of VUR.[21] Our results support the latter findings and that is why although some follow-up studies considered VUR as a poor predictor of renal damage,[22] in this study, all of our patients had APN. Therefore, high association of VUR and renal scar might be partly due to the fact that children with APN and established VUR are more vulnerable to renal damage [odds ratio: 9.064; 95% CI: 2.99 to 27.45].

Among our patients, VUR was detected in 41.2% of the children. Most of the patients with kidney scars had a positive history for VUR (75%). Abnormal DMSA changes were found in 45% of patients with potential renal scarring, which was higher in comparison to data previously reported (5% to 15%).[23,24]

In addition to the studied factors, there are some other risk factors that largely account for the development of renal parenchyma scarring which include the route of antibiotics administration, the time elapsed before the onset of symptoms and initiation of therapy.[20] Though we did not evaluate in this study, it has been observed that other factors such as bacterial virulence, immunodeficiency and anatomic or functional abnormalities make children with UTI vulnerable to renal scarring.[23]

Furthermore, we showed that the recurrence of APN is independently associated with increased risk for future renal scarring. Apart from the presence of VUR, parenchymal damage and subsequent scarring following repeated APN is almost unavoidable. However, no one can ignore the higher probability of scarring triggered by coincident occurrence of APN and higher grades of reflux.[25]

Conclusion

Our study suggests that incidence of renal scarring is higher in children with presence of VUR and recurrant pyelonephritis. We recommend performing DMSA scan in all children with recurrences of pyelonephritis and lower grades of vesicoureteral reflux.

Conflict of interest

All authors declare to have no conflict of interest.

REFERENCES

1. Jakobsson B, Nolstedt L, Svensson I. Tc-99mDMSA scan in the diagnosis of acute pyelonephritis in children: relation to clinical and radiological findings. Pediatr Nephrol. 1992;6:328-34.
2. Craig JC, Irwig LM, Howman-Giles RB. Variability in the interpretation of dimercaptosuccinic acid scintigraphy after urinary tract infection. J Nucl Med. 1998;38:1428-32.
3. Centre for Reviews and Dissemination, NHS R&D Health Technology Assessment Programme. Effective health care diagnosing urinary tract infection (UTI) in the under fives. Bull Effect Health Serv Interv. 2004;8:1-12.
4. Rossleigh MA, Farnsworth RH, Leighton DM, et al. Technetium-99m dimercaptosuccinic acid scintigraphy studies of renal cortical scarring and renal length. J Nucl Med. 1998;391280-5.
5. Piepsz A, Blaufox MD, Gordon I. Consensus on renal cortical scintigraphy in children with urinary tract infection. Sem Nuclear Med. 1999;29:160-74.
6. Stokland E, Hellström M, Jacobson B. Early Tc-99m DMSA scintigraphy in symptomatic first-time urinary tract infection. Acta Paediatr. 1996;85:430-6.
7. Stokland E, Hellström M, Jacobson B. Renal damage one year after first urinary tract infection, role of DMSA scintigraphy. J Pediatr. 1996;129:815-20.
8. Stark H. Urinary tract infection in girls: the cost effectiveness of currently recommended investigative routines. Pediatr Nephrol. 1997;11:174-7.
9. Deshpande PV, Verrier Jones K. An audit of RCP guidelines on DMSA scanning after urinary tract infection. Arch Dis Child. 2001;84:324-7.
10. Rosenberg AR, Rossleigh MA, Brydon MP. Evaluation of acute urinary tract infection in children by DMSA scintigraphy: a prospective study. J Urol. 1992;148:1746-9.
11. Conway JJ, Cohn R. Evolving role of nuclear medicine for the diagnosis and management of urinary tract infection. J Pediatr. 1994;124:87-90.
12. International Reflux Study Committee. Medical versus surgical treatment of primary vesicoureteral reflux, Pediatrics. 1981;67:392.
13. Andrich M, Majd M. Diagnostic imaging in the evaluation of the first urinary tract infection in infants and young children. Pediatrics. 1992;90:436-41.
14. Ditchfield MR, De campo JF, Nolan TM. Risk factors in the development of early renal cortical defects in children with urinary tract infection. AJR. 1994;162:1393-7.
15. Ditchfield MR, De campo JF, Cook DJ. Vesicoureteral reflux: an accurate predictor of acute pyelonephritis in childhood urinary tract infection? Radiology. 1994;190:413-15.
16. Simsek E, Kologlu N, Yugunt I, et al. Comparison of imaging studies and diagnostic tests for the diagnosis and follow-up of recurrent urinary tract infection in children. Int Pediatr. 2004;19:109-13.
17. Majd M, Nussbaum Blask AR, Markle BM. Acute pyelonephritis: comparison of diagnosis with 99mTc DMSA SPECT, spiral CT, MR imaging and power Doppler US in an experimental pig model. Radiology. 2001;218:101-8.
18. Camacho V, Estorch M, Fraga G. DMSA study performed during febrile urinary tract infection: a predictor of patient outcome? Eur J Nucl Med Mol Imag. 2004;31:862-6.
19. Lin KY, Chiu NT, Chen MJ. Acute pyelonephritis and sequelae of renal scar in pediatric first febrile urinary tract infection. Pediatr Nephrol. 2003;18:362-5.
20. Gonzales E, Papazyan JP, Giardin E. Impact of vesicoureteral reflux on the size of renal lesions after an episode of acute pyelonephritis. J Urol. 2005;173:571-4.
21. Hoberman A, Charron M, Hickey RW. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med. 2003;348:195-202.
22. Williams G, Fletcher JT, Alexander SI, et al. Vesicoureteral reflux. J Am Soc Nephrol. 2008;19(5):847-62.
23. Piepsz A. Cortical scintigraphy and urinary tract infection in children. Nephrol Dial Transplant. 2002;17:560-2.
24. Dick PT, Feldman W. Routine diagnostic imaging for childhood urinary tract infections: a systematic overview. J Pediatr. 1996;128:15-22.
25. Skoog SJ, Belman AB, Majd M. A nonsurgical approach to the management of primary vesicoureteral reflux. J Urol. 1987;138(4):941-6.