Usefulness of Serum Procalcitonin Level for Prediction of Vesicoureteral Reflux in Pediatric Urinary Tract Infection

Fakhrossadat Mortazavi,[1] Morteza Ghojazadeh[2]

[1]Pediatric Health Research Center, Department of Pediatric Nephrology, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of physiology, Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

Keywords. child, vesicoureteral reflux, procalcitonin, urinary tract infection

Introduction. Procalcitonin is a sensitive biomarker for bacterial infections. Recent studies show a correlation between serum procalcitonin level and vesicoureteral reflux (VUR). The aim of this study was to evaluate the predictive value of procalcitonin in diagnosis of VUR in children with febrile urinary tract infection.
Material and Methods. One hundred and eight children aged 2 month to 12 years with febrile urinary tract infection were evaluated. Serum procalcitonin was measured before initiation of antibiotics. Standard voiding cystourethrography (VCUG) was performed in all children as the gold standard for detection of VUR. Sensitivity and specificity of a high procalcitonin level was evaluated using the receiver operating characteristic curve.
Results. Forty-eight patients (44%) had VUR at least in one kidney, including grade 1 to 2 in 12 patients (11.1%), grade 3 in 16 (14.8%), and grade 4 to 5 in 20 patients (18.5%). Procalcitonin level ranged from 0.05 ng/mL to 13.6 ng/mL. Procalcitonin level was significantly higher with increasing the grading of reflux. Comparing procalcitonin levels with VCUG results, a sensitivity of 97% and a specificity of 75% was obtained at a procalcitonin level of 0.59 ng/mL for diagnosis of VUR. There was a significant correlation between procalcitonin level and leukocytosis, erythrocyte sedimentation rate, and C-reactive protein.
Conclusions. A high procalcitonin level may be used for prediction of all grades of VUR in children with febrile urinary tract infection. A low procalcitonin level may be used for avoidance of unnecessary VCUG in some low-risk patients.

IJKD 2014;8:37-41
www.ijkd.org

Original Paper

INTRODUCTION

Urinary tract infection (UTI) is the most common bacterial infection in young febrile children.[1] Urinary tract infection occurs in 1% to 3% of girls and 1% of boys in the first 5 years of life.[2] About 50% of children with a febrile UTI show renal tissue involvement on dimercaptosuccinic acid scan, and approximately 50% of them will develop permanent renal scar.[2,3] Scarred kidney may result in renin-mediated hypertension, failure to thrive, chronic kidney disease, morbidity during pregnancy, and end-stage renal failure.[1-4]

Regarding the significant complications of UTI, it is very important to detect the predisposing factors of UTI. Vesicoureteral reflux (VUR) is one of the well-known risk factors that predispose children to upper UTI and scar formation. Vesicoureteral reflux is diagnosed in approximately 30% of children with UTI.[5] Voiding cystourethrography (VCUG), either as a standard contrast VCUG or radionuclide cystography, is the gold standard method for diagnosis of VUR.[2-6] However, VCUG

in children needs bladder catheterization that is painful and may result in iatrogenic UTI. In addition, VCUG procedure is expensive and irradiating for gonads.[5,7,8] Bladder catheterization is also considered as a psychiatric trauma for children. Thus, other modalities such as voiding ultrasonography have been used for diagnosis of VUR.[9] The advantage of voiding ultrasonography is significant reduction in radiation exposure. However, this modality has its own limitations and is less sensitive.[7]

Recently, procalcitonin has been proposed as a novel biomarker for prediction of VUR. Procalcitonin is a propeptide of calcitonin without hormonal activity.[1] Multiple studies performed in recent years show that serum procalcitonin is a sensitive biomarker for differentiation of upper UTI from noncomplicated lower UTI, and its level increases when renal tissue inflammation is present.[10-17] Since VUR is the most important risk factor for occurrence of pyelonephritis and renal tissue inflammation, serum procalcitonin level may have a relationship with VUR. However, there are few data about the relationship between procalcitonin level and VUR in the literature. We evaluated the predictive value of serum procalcitonin level in the diagnosis of VUR in children admitted with their first febrile UTI.

MATERIALS AND METHODS

In this cross-sectional study, all children at the age of 2 months to 12 years admitted to Children's Hospital of Tabriz, Iran, from October 2006 to October 2011, with their first febrile UTI episode were studied. The Research Ethics Committee of Tabriz University of Medical Sciences approved the study and informed consent was taken from the parents. Diagnosis of UTI was based on the presence of fever (temperature > 38°C) and urinary symptoms accompanied with pyuria and positive urine culture. Pyuria was defined as the presence of more than 7 leukocytes in high-power field of centrifuged urine. A positive urine culture was defined as more than 10^5 colony forming units of a single organism per milliliter in midstream urine sampling, greater than 10^4 colony forming units per milliliter of a single organism in urine samples obtained through bladder catheterization or any microorganism culture in samples obtained by suprapubic sampling.

On admission, all of the patients underwent clinical and laboratory investigations, including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ultrasonography of the urinary tract. Qualitative latex agglutination test was used for CRP evaluation. Serum procalcitonin was measured using immunoluminometric assay (318101-procalcitonin, Liaison, Diasorin, Saluggia, Italy) before antibiotic initiation. Standard contrast VCUG was performed in all patients after the urine culture became negative and before discharging the patient from the hospital. Results of VCUG were evaluated by a specialist who was blinded to procalcitonin levels. Grading of reflux was interpreted by using the International Reflux Classification.[2] Grade 1 to 2 VUR was defined as mild, grade 3 as moderate, and grade 4 to 5 as severe VUR. Dimercaptosuccinic acid renal scintigraphy was performed within the first 5 days of admission.

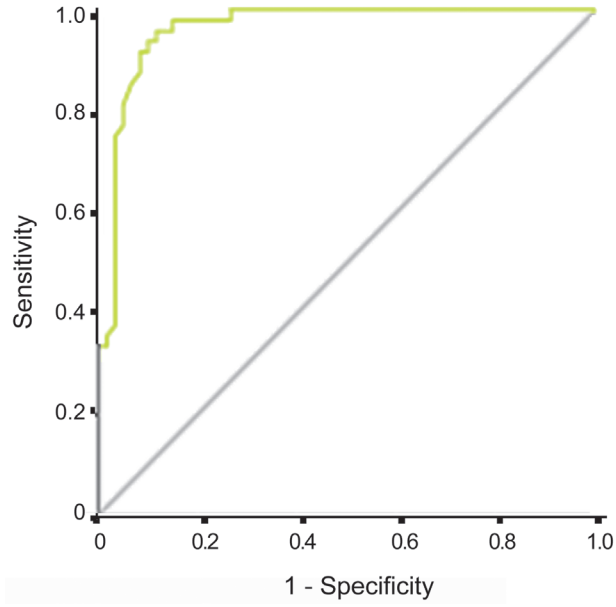
Patients with obstructive malformations and renal calculi and patients who were taking steroids and nonsteroid anti-inflammatory drugs during the 2 weeks before admission were excluded. Also, patients with insufficient data and patients suspected to have another infection besides UTI were not included. All demographic, clinical, and laboratory findings were collected.

Variable values were demonstrated as mean ± standard deviation or median (minimum to maximum) or absolute count (%).Correlation between procalcitonin level with leukocytosis and ESR was assessed with the Pearson correlation coefficient test. The statistical differences between qualitative variables were evaluated by the chi-square test or the Fisher exact probability test. The *t* test was used for comparison of quantitative variables. For comparison of leucocyte count and ESR in patients with and without reflux, the Mann-Whitney U test was used. A receiver operating characteristic (ROC) curve was obtained by plotting sensitivity against the false-positive rate (1-specificity) for all possible cutoff points of the serum procalcitonin level. The area under the ROC curve was reported as an index of the discriminating ability of the instruments. The SPSS software (Statistical Package for the Social Sciences, version 19.0, SPSS Inc, Chicago, Ill, USA) was used to determine the area under the curve. A *P* value less than .05 was considered significant.

RESULTS

A total of 123 patients with their first febrile UTI were included in the study, of whom 15 patients were excluded because of incomplete data. Demographic and clinical characteristics of the patients are shown in Table 1. Forty-eight patients (44%) had VUR at least in one kidney, including grade 1 to 2 in 12 patients (11.1%), grade 3 in 16 patients (14.8%), and grade 4 to 5 in 20 patients (18.5%).

Procalcitonin level ranged between 0.05 ng/mL and 13.6 ng/mL. Its level was significantly higher with increasing the grading of reflux ($P < .001$; Table 2). Considering VCUG results as negative or positive, the ROC curve showed a sensitivity of 97% (95% confidence interval, 92% to 99%) and a specificity of 75% at a procalcitonin level of 0.59 ng/mL (Figure). A direct significant correlation was observed between procalcitonin level and leukocytosis (r = 0.81, $P < .001$) and ESR (r = 0.62, $P < .001$). The mean procalcitonin level in patients with a positive CRP (4.02 ± 0.43 ng/mL) was significantly higher than its mean level in patients with a negative CRP (0.85 ± 0.27 ng/mL; $P < .001$). The frequencies of a positive CRP, hydronephrosis, and leucocyte count, as well as ESR level were significantly higher in patients with VUR than patients without VUR (Table 3).



The receiver operating characteristic curve of serum procalcitonin level to predict the vesicoureteral reflux.

Table 1. Demographic and Clinical Characteristics of Children With Febrile Urinary Tract Infection*

Characteristic	Value
Mean age, mo	29.9 ± 23.3 (2 to 78)
Sex	
Male	12 (11.0)
Female	96 (89.0)
Hydronephrosis in at least one kidney	34 (31.5)
Reduced parenchymal uptake in DMSA scan	49 (45.4)
Vesicoureteral reflux in at least one kidney	48 (44.0)

*Values in parentheses are percentages, except for mean age, which is range minimum and maximum. DMSA indicates dimercaptosuccinic acid.

DISCUSSION

Our study showed that a procalcitonin level of 0.59 ng/mL had a sensitivity of 97% and a specificity of 75% in diagnosis of all grades of VUR and serum level of procalcitonin increased significantly with increasing the grading of

Table 2. Serum Procalcitonin Level by Grading of Vesicoureteral Reflux

Reflux Severity	Median Procalcitonin Level, ng/mL	Mean Procalcitonin Level, ng/mL
No reflux	0.30 (0.50 to 6.80)	0.68 ± 1.24
Mild reflux (grade 1 to 2)	2.70 (0.57 to 6.60)	2.97 ± 1.78
Moderate reflux (grade 3)	5.59 (1.50 to 13.60)	6.69 ± 3.41
Severe reflux (grade 4 to 5)	5.00 (1.80 to 12.60)	6.36 ± 3.29

Table 3. Comparisons Between Children With and Without Vesicoureteral Reflux*

Parameter	Reflux	No Reflux	*P*
Positive C-reactive protein	40 (83.3)	29 (48.3)	< .001
Hydronephrosis	26 (54.0)	8 (13.3)	< .001
Median erythrocyte sedimentation rate, mm/h	44.50 (3 to 120)	20 (3 to 120)	.02
Median Leucocyte count, × 10^9/L	18.33 (4.35 to 30.64)	9.77 (6.36 to 35.00)	< .001

*Values in parentheses are percentages for frequencies and range minimum and maximum for continuous values.

reflux. Also, we observed a significant correlation between procalcitonin level and leukocytosis, ESR, and CRP level. Ipek and coworkers studied 66 children with their first febrile UTI to evaluate the relationship between procalcitonin and VUR. They found a sensitivity of 66.7% and a specificity of 77.1% with a procalcitonin level greater than 0.56 ng/mL for diagnosis of VUR.[18] Leroy and colleagues demonstrated a significant relationship between both all-grade and high-grade VUR and a procalcitonin level of 0.5 ng/mL and higher, with a sensitivity of 85% for all-grade and 92% for high-grade VUR.[7] Findings of our study are in accordance with results of studies performed by these authors.

It may be supposed that procalcitonin only reflects the renal parenchymal damage during a UTI and since VUR is the major risk factor of renal parenchymal damage, the relationship between procalcitonin and VUR is an indirect relationship. However, a meta-analysis study performed by Leroy and colleagues demonstrated that procalcitonin levels higher than 0.5 ng/mL were a sensitive predictor of high-grade VUR (≥ grade 3), regardless of the presence of early parenchymal involvement.[5]

Procalcitonin is secreted by C cells of the thyroid gland. Its serum level is negligible in healthy individuals (less than 0.1 ng/mL). Procalcitonin level increases up to 1700 fold in response to bacterial endotoxins.[1,17,19] It is believed that a severe bacterial infection induces the *CALCI* gene expression that results in rapid release of procalcitonin by liver and the monocyte-macrophage system.[1,19] For the first time in 1993, Assicot and coworkers described that the concentration of a substance immunologically identical to procalcitonin increased during sepsis and bacterial infection, and its level correlated with severity of tissue inflammation and bacterial invasion.[20] The significant correlation between procalcitonin level and leukocytosis, ESR, and CRP level that was found in the present study is compatible with results of their study. After Assicot and colleagues report, some studies published during last 10 years suggesting that a high procalcitonin level during UTI is associated with VUR.[11] It is believed that VCUG, which is routinely performed for diagnosis of VUR after a febrile UTI, is negative in 60% to 70% of cases.[5] Hence, regarding the high frequency of UTI, many children undergo unnecessary VCUG that is an unpleasant and problematic procedure. Leroy and colleagues showed that measurement of serum procalcitonin level during the first days of a febrile UTI might be used to reduce the number of unnecessary VCUG in children.[21] Results of our study, in accordance with some recent studies, suggest that high procalcitonin levels could be used for detection of high-risk patients who need to undergo VCUG, and a low procalcitonin level could be used for avoidance of unnecessary VCUG in low-risk patients.

CONCLUSIONS

This study showed that procalcitonin with a cutoff value of 0.59 ng/mL has high sensitivity and specificity for prediction of VUR in children with febrile UTI. However, other studies are needed for defining an accurate cutoff value for procalcitonin level in children with febrile UTI to differentiate patients who are at risk of VUR from low-risk patients.

ACKNOWLEDGMENTS

The authors would like to thank the Pediatric Health Research Center and the research vice chancellor of Tabriz University of Medical Sciences for financial support of this study.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Leroy S, Gervaix A. Procalcitonin: a key marker in children with urinary tract infection. Adv Urol. 2011;2011:397618.
2. Elder JS. Urinary tract infections. In: Kliegman RM, Stanton BF, editors. Nelson textbook of pediatrics. 19th ed. Philadelphia: Saunders; 2011. p. 1829-36.
3. Mohammadjafari H, Aalaee A, Salehifar E, Shiri A, Khademloo M, Shahmohammadi S. Doppler ultrasonography as a predictive tool for permanent kidney damage following acute pyelonephritis: comparison with dimercaptosuccinic acid scintigraphy. Iran J Kidney Dis. 2011;5:386-91.
4. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. Pediatrics. 2010;126:1084-91.
5. Leroy S, Romanello C, Galetto-Lacour A, et al. Procalcitonin is a predictor for high-grade vesicoureteral reflux in children: meta-analysis of individual patient data. J Pediatr. 2011;159:644-51.
6. Ilyas M, Mastin ST, Richard GA. Age-related radiological imaging in children with acute pyelonephritis. Pediatr

Nephrol. 2002;17:30-4.

7. Leroy S, Adamsbaum C, Marc E, et al. Procalcitonin as a predictor of vesicoureteral reflux in children with a first febrile urinary tract infection. Pediatrics. 2005;115:e706-e709.
8. Mohkam M, Maham S, Rahmani A, et al. Technetium Tc 99m dimercaptosuccinic acid renal scintigraphy in children with acute pyelonephritis: correlation with other imaging tests. Iran J Kidney Dis. 2010;4:297-301.
9. Darge K. Diagnosis of vesicoureteral reflux with ultrasonography. Pediatr Nephrol. 2002;17:52-60.
10. Prat C, Dominguez J, Rodrigo C, et al. Elevated serum procalcitonin values correlate with renal scarring in children with urinary tract infection. Pediatr Infect Dis J. 2003;22:438-42.
11. Benador N, Siegrist CA, Gendrel D, et al. Procalcitonin is a marker of severity of renal lesions in pyelonephritis. Pediatrics. 1998;102:1422-5.
12. Zaffanello M, Brugnara M, Franchini M, Fanos V. Is serum procalcitonin able to predict long-term kidney morbidity from urinary tract infections in children? Clin Chem Lab Med. 2008;46:1358-63.
13. Bressan S, Andreola B, Zucchetta P, et al. Procalcitonin as a predictor of renal scarring in infants and young children. Pediatr Nephrol. 2009;24:1199-204.
14. Kotoula A, Gardikis S, Tsalkidis A, et al. Procalcitonin for the early prediction of renal parenchymal involvement in children with UTI: preliminary results. Int Urol Nephrol. 2009;41:393-9.
15. Mantadakis E, Plessa E, Vouloumanou EK, Karageorgopoulos DE, Chatzimichael A, Falagas ME. Serum procalcitonin for prediction of renal parenchymal involvement in children with urinary tract infections: a meta-analysis of prospective clinical studies. J Pediatr. 2009;155:875-81.
16. Nikfar R, Khotaee G, Ataee N, Shams S. Usefulness of procalcitonin rapid test for the diagnosis of acute pyelonephritis in children in the emergency department. Pediatr Int. 2010;52:196-8.
17. Pecile P, Miorin E, Romanello C, et al. Procalcitonin: a marker of severity of acute pyelonephritis among children. Pediatrics. 2004;114:e249-e254.
18. Ipek IO, Sezer RG, Senkal E, Bozaykut A. Relationship between procalcitonin levels and presence of vesicoureteral reflux during first febrile urinary tract infection in children. Urology. 2012;79:883-7.
19. Nanda N, Juthani-Mehta M. Novel biomarkers for the diagnosis of urinary tract infection-a systematic review. Biomark Insights. 2009;4:111-21.
20. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet. 1993;341:515-8.
21. Leroy S, Romanello C, Galetto-Lacour A, et al. Procalcitonin to reduce the number of unnecessary cystographies in children with a urinary tract infection: a European validation study. J Pediatr. 2007;150:89-95.

Correspondence to:
Fakhrossadat Mortazavi, MD
Children's Hospital of Tabriz, Sheshgelan St, Tabriz, Iran
Fax: +98 411 526 2279
Tell: +98 411 526 2280
E-mail: Mortazavi_fakhri@yahoo.co.uk

Received December 2012
Revised June 2013
Accepted July 2013