Diagnostic Potential of Urinary Tumor Necrosis Factor-Alpha in Children With Acute Pyelonephritis

Masoumeh Mohkam, Fahimeh Asgarian, Alireza Fahimzad, Mostafa Sharifian, Reza Dalirani, Fatemeh Abdollah Gorgi

Pediatric Infectious Research Center, Shahid Beheshti University (MC), Tehran, Iran

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Introduction. Tumor necrosis factor-alpha (TNF-α) is an important mediator of the inflammatory response in serious bacterial infections. The aim of this study was to evaluate the potential of urinary TNF-α for diagnosis of acute pyelonephritis in children.

Materials and Methods. This study was conducted from March 2006 to December 2007 on children with confirmed diagnosis of acute pyelonephritis. They all had positive renal scintigraphy scans for pyelonephritis and leukocyturia. The ratios of urinary TNF-α to urine creatinine level were determined and compared in patients before and after antibiotic therapy.

Results. Eighty-two children (13 boys and 69 girls) with acute pyelonephritis were evaluated. The mean pretreatment ratio of urinary TNF-α to urinary creatinine level was higher than that 3 days after starting on empirical treatment ($P = .03$). The sensitivity of this parameter was 91% for diagnosis of acute pyelonephritis when compared with demercaptosuccinic acid renal scintigraphy as gold standard.

Conclusions. Based on our findings in children, the level of urinary TNF-α-creatinine ratio is acute increased in pyelonephritis and it decreases after appropriate therapy with a high sensitivity for early diagnosis of the disease. Further research is warranted for shedding light on the potential diagnostic role of urinary TNF-α in pyelonephritis in children.

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INTRODUCTION

Urinary tract infection (UTI) is a common clinical problem in infancy and childhood. Cystitis and pyelonephritis are among the most prevalent infections and account for significant morbidity and medical costs in developed countries.[1] Urinary tract infection may cause inflammation of the renal parenchyma and may lead to impairment in kidney function and scar formation. Cytokines are involved in the systemic and local inflammatory response in patients with UTI. Analysis of urinary cytokines and mediators of inflammation is emerging as an important area of pediatric nephrological research.[2]

The most potent pro-inflammatory cytokines are tumor necrosis factor-alpha (TNF-α) and interleukin-1. Van der Poll and Lowry reported that TNF is elevated in sepsis.[2] The results of previous researches suggest that cytokines may be elevated in urine during UTI, as well, and may play a key role in defining pyelonephritis.[3-5] Engel and colleagues showed that TNF-α is increased in the bladder during UTI.[6] The present study focuses on the diagnostic role of TNF-α in children with acute pyelonephritis.

MATERIALS AND METHODS

We performed a quasi-experimental study on children aged between 1 month and 12 years old. They were patients presented with pyelonephritis from March 2006 to December 2007. The ethics committee of the Shahid Beheshti Medical University and Pediatric Infectious Research Center approved this study. Acute pyelonephritis was documented by dimercaptosuccinic acid (DMSA) renal scintigraphy scans in favor of pyelonephritis, accompanying by leukocyturia, and one of following signs or symptoms: fever, abdominal pain, anorexia, dysuria, positive urine culture, increased erythrocyte sedimentation rate, positive C- reactive protein. As a result, all of our patients had abnormal DMSA scan and leukocyturia. The excluding criteria were any evidence of renal insufficiency, previously known urological problems or surgical intervention, hypertension, recent history of antibiotic administration, extrarenal accompanying infections, and history of nephrologic problems.

Urinary TNF-α was assessed in samples taken before and after the treatment. Fresh random urine samples were obtained on the admission time and on the 3rd day of starting treatment (after 48 hours). Urine samples were tested for creatinine (Jaffe reaction, RA 1000, Tecnicon Autoanalyzer, Tarrytown, USA) and TNF-α using colorimetric enzyme-linked immunosorbent assay (Sanquin Research, Plesmanlaan, Netherlands). All of the patients were treated empirically with intravenous ceftriaxone, 75 mg/kg.

Data were expressed as mean ± standard deviation. In order to adjust TNF-α values with kidney function, the ratio of TNF-α to creatinine (TNF-α/C) was calculated for all measurements. The SPSS software (Statistical Package for the Social Sciences, version 11.5, SPSS Inc, Chicago, Ill, USA) was used for analyses. The TNF-α/C ratios before and after treatment were compared using the 2-tailed paired *t* test, and diagnostic analysis was done with the help of receiver operating characteristics curve. Results were considered significant if *P* was less than .05.

RESULTS

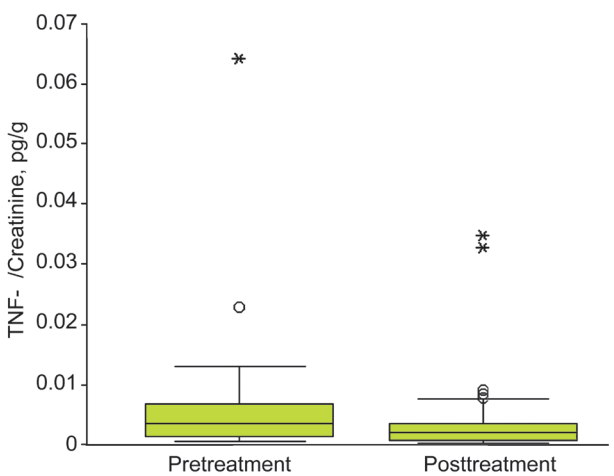
A total of 120 children admitted to our hospital were approached, of whom 38 were not eligible based on the exclusion criteria. As a result, 82 children with acute pyelonephritis were evaluated. They were 13 boys (15.9%) and 69 girls (84.1%) with a mean age of 38.1 ± 35.0 months (range, 1 to 132 months). Blood pressure was normal in all of the children and hemoglobin and kidney function tests yielded results within reference ranges. The mean blood leukocyte count was 15.83 ± 10.00 × 10^9/L (range, 3.2 × 10^9/L to 29.0 × 10^9/L). A summary of laboratory tests results is listed in the Table.

The mean urinary TNF-α/C ratio was 0.0051 ± 0.0008 pg/g (0.0041 pg/g to 0.064 pg/g) before treatment which reduced to 0.0031 ± 0.0005 pg/g (0.0014 pg/g to 0.0350 pg/g) 3 days after starting antibiotics (*P* = .03; Figure). The sensitivity of urinary TNF-α/C ratio for diagnosis of acute pyelonephritis regarding DMSA scan results as the golden standard test was 91.0% with an area under the curve of 0.919.

Demographic and Clinical Data of Children With Acute Pyelonephritis

Parameter	Value*
Age, mo	38.1 ± 35.0 (1 to 132)
Body weight, kg	13.81 ± 9.46 (3 to 47)
Blood leukocyte count, × 10^9/L	15.83 ± 10.00 (3.2 to 29.0)
Hemoglobin, g/dL	11.39 ± 1.60 (7.4 to 16.8)
ESR, mm/h	45.2 ± 31.5 (2 to 102)
Blood Urea Nitrogen, mg/dL	10.8 ± 8.7 (2 to 26)
Creatinine, mg/dL	0.66 ± 0.10 (0.1 to 0.8)
Urine leukocyte, /HPF	19.5 ± 10.8 (2 to 30)
Urine erythrocyte, /HPF	5.1 ± 4.0 (0 to 25)
Urine Specific gravity	1014.0 ± 5.0 (1011 to 1035)
Urine pH	5.4 ± 0.8 (5 to 8)

*Values are demonstrated as mean ± standard deviation (range). ESR indicates erythrocyte sedimentation rate and HPF, high-power field.



Pretreatment and posttreatment ratio of urinary TNF-α to creatinine in children with acute pyelonephritis (*P* = .03).

DISCUSSION

The early defense against bacterial infections is anticipated to depend primarily on resident tissue cells and innate immune effectors such as macrophages and granulocytes.[7] Cytokines and cytokine receptors are involved in the systemic and local inflammatory response in patients with UTIs. Urine and serum concentrations of cytokines and granulocyte colony-stimulating factor increase in acute pyelonephritis, during the subsequent episode of cystitis or asymptomatic bacteriuria. It has been shown that concentrations of cytokines and granulocyte colony-stimulating factor are related to the expression of 5 virulence markers of *Escherichia coli*.[8] Of particular interest is that cytokines are involved in the systemic and local inflammatory response in patients with UTIs. Analysis of urinary cytokines and mediators of inflammation is emerging as an important area of new researches. The most potent pro-inflammatory cytokines are TNF-α and interleukin-1. Among the cytokines studied interleukin-1α, interleukin-1ß, interleukin-6, and TNF-α are differentially elevated during an episode of UTI.[9] Tumor necrosis factor-alpha and inducible nitric oxide synthase-producing dendritic cells rapidly recruit to the bladder in UTI.[6] As a matter of fact, TNF-α implies a potent inflammatory response involving macrophages and neutrophils. In a study on rats, Biyikli and colleagues showed that blood urea, serum creatinine, serum TNF-α, and kidney tissue malondialdehyde and myeloperoxidase levels are elevated in acute and chronic pyelonephritis.[10]

In the present study, we sought to gain more insight into the urinary cytokine response in children before and after antibiotic therapy. We concluded that urinary TNF-α/C ratio was elevated in acute pyelonephritis and decreased after empirical treatment. We also showed that sensitivity of TNF-α/C ratio for diagnosis of acute pyelonephritis is 91%. Davidoff and coworkers showed that TNF-α was significantly elevated in patients with cystitis compared to healthy individuals.[7] Sadeghi and colleagues revealed an increased level of urinary cytokines including TNF-α during bacteriuria in kidney transplant patients.[11]

In contrast to the abovementioned study results, Olszyna and coworkers reported that concentrations of TNF in serum and urine were below the limit of detection in the vast majority of controls and pyelonephritic patients, and no significant differences between these two groups were found.[12] They showed that only TNF receptors had higher concentrations in urine of pyelonephritic patients. Kim and colleagues showed the same results, too.[13]

CONCLUSIONS

The discrepancies in investigations on urinary TNF-α levels in patients with acute pyelonephritis shows that the studies in this field are not conclusive yet. Some findings fundamentally question the real role of urinary TNF-α in diagnosis and follow-up of pyelonephritic patients, while in children, we documented elevated TNF-α in the beginning of the disease. The authors recommend more research on larger samples to accumulate enough information for better understanding of the process related to cytokines such as TNF-α during the course of pyelonephritis.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Masoumeh Mohkam, MD
Mofid Children's Hospital, Shariati Ave, Tehran 15468, Iran
Tel: +98 21 2288 7529
Fax: +98 21 2222 0254
E-mail: mohkamm@yahoo.com

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