

Research Article

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Is Urinary Tumor Necrosis Factor Alpha a Predictor of Urological Abnormality in Children?

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Introduction

Tumor Necrosis Factor alpha (TNF- α) is a cytokine with multiple important activities like chemotaxis, synthesis of procoagulant factors, prostaglandin release, induction of cytokines, and upregulation of adhesion molecules. This cytokine acts as a costimulatory factor for T cells and plays an important role in pathogenesis of different disorders [1-6]. TNF- α is involved in multiple metabolic pathways relevant to diabetes mellitus [7-9], IgA nephropathy [10], hemolytic uremic syndrome [11], idiopathic hypercalciuria [12], pyelonephritis [13] and chronic dialysis [14]. Recently, attention has been paid to the role of urinary TNF- α in the diagnosis and treatment of different disorders.

Introduction: The role of urinary Tumor Necrosis Factor Alpha (TNF- α) in the diagnosis and treatment of different disorders has been evaluated recently. This study was conducted to evaluate the correlation of urinary TNF- α with urological abnormalities in pediatric pyelonephritis.

Materials and Methods: This prospective study was conducted on children with acute pyelonephritis. Urine samples were tested for TNF- α (ELISA colorimetric, SANQUINE, USA) and creatinine in study group. Renal ultrasonography and voiding cystoureterography were performed in all patients, as well.

Results: One hundred pyelonephritic patients were enrolled in the study. Urinary TNF- α /Cr was in an abnormal range in 91.9% of the patients. This query revealed a significant correlation between urinary TNF-alpha and kidney ultrasound results ($r=0.59$) and grading of reflux in voiding cystoureterography ($r=0.128$). Furthermore, our study showed a significant difference between the level of urinary TNF- α /Cr in patients with and without abnormality on kidney ultrasonography (p value < 0.000).

Conclusions: The results of this study indicate the efficacy of urinary TNF- α in detection of inflammatory disorders such as pyelonephritis and pediatric urological abnormalities.

Keywords: Tumor Necrosis Factor-alpha; Urologic Diseases; Child.

Running Title: TNF Alpha a Predictor of Urological Abnormality

Previously, Mclaughlin et al showed an increased level of urinary TNF- α in post kidney transplantation acute rejection or tubular necrosis [15]. Navarro et al detected a significant relationship between urinary TNF- α and albuminuria in diabetic patients [16]. Bertini et al reported the protective effect of urinary TNF-binding protein in the treatment of septic shock [17]. Nseyo et al demonstrated the role of urinary TNF- α in the control of therapy in bladder cancer [18]. In our previous researches, we evaluated the role of urinary TNF- α in the diagnosis of acute pyelonephritis [19-20]. This study was conducted to evaluate the correlation of urinary TNF- α with urological abnormalities in acute pyelonephritis in children.

Materials and Methods

This descriptive study was conducted on children with acute pyelonephritis. Acute pyelonephritis in the study group was diagnosed based on fever (more than 38° C), leukocyturia (more than 5/Hpf), a positive urine culture, increased ESR (erythrocyte sedimentation rate > 20 mm/hr), and positive CRP (C- reactive protein ≥ 1+). The diagnosis of pyelonephritis was also confirmed by abnormal dimercaptosuccinic acid renal scintigraphy (DMSA scan). Pediatric patients with renal insufficiency or any known nephrourological disorder were excluded from the study. Pre treatment urine samples were tested for TNF- α (ELISA colorimetric, SANQUINE, USA) and creatinine (Jaffe reaction, auto analyzer, RA 1000). Renal ultrasonography and voiding cystoureterography (VCUG) were performed in all patients, as well. The ethics committee of the Pediatric Infectious Research Center approved this study. Statistical tests included Pearson's correlation coefficient and two-tailed (consider significant when $P \leq 0.05$). The SPSS software was used for statistical analyses.

Results

The authors evaluated one hundred pyelonephritic patients. The mean age of the patients was 40±25 months and with a female to male ratio of 5.2. Urinary TNF- α /Cr was in an abnormal range in 91.9% of the study group (Table 1). The ROC curve of urinary TNF- α /Cr in the study group demonstrated an area under the curve of 0.919 in comparison with DMSA scan (Fig. 1). This research revealed a significant correlation between urinary TNF-alpha and kidney ultrasound results ($r=0.59$) and grading of reflux in VCUG ($r=0.128$). Furthermore, our study showed a significant difference between the level of urinary TNF- α /Cr in patients with and without abnormality on kidney ultrasonography (p value < 0.000). The authors also found a significant difference between the level of urinary TNF- α /Cr in patients with normal and abnormal VCUG (p value < 0.001), which means that the level of urinary TNF- α /Cr was significantly higher in patients with abnormal imaging studies than those who had normal imaging results.

Discussion

In this descriptive study, the authors sought to gain more insight into the predictive role of urinary TNF- α in the diagnosis of urological

abnormalities in children with pyelonephritis. The results showed a significant correlation between the levels of urinary TNF- α and abnormal reports of kidney ultrasonography and VCUG. It seems that this factor might be useful in the detection of hydronephrotic changes and vesicoureteral reflux beside pyelonephritis in children. There are currently no larger studies on the role of this factor in pyelonephritis and the correlation between its level and other variants of pyelonephritic patients such as imaging studies. Urinary biomarkers have recently become a focus of clinical research in pediatric nephrourological diseases. Biomarkers are the laboratory tests that help to distinguish between two or more disorders and serve as a guide for further clinical decision making. A number of studies have shown the relationship between nephrourological diseases and production of cytokines. Indeed, the measurement of urinary and plasma levels of cytokines has been used to monitor and diagnose various urological diseases [21-26]. Cytokines like TNF- α and chemokines as CCL2/MCP-1, macrophage inflammatory protein-2, and γ -interferon-inducible protein have been previously evaluated in experimental studies on models of hydronephrosis [21, 27-29]. TNF- α may play an important role in initiating tubulointerstitial injury in patients with obstructive uropathy. The increased levels of TNF- α at early stages of obstruction in obstructive kidney diseases may stimulate the production of chemoattractants and infiltrate monocytes and leukocytes [21]. For instance, Misseri et al. evaluated the expression of TNF- α mRNA in rats with left ureteral obstruction and concluded that TNF- α might participate in initiating tubulointerstitial damage in the obstructed kidney by producing leukocytes infiltration [30]. Previously, in a clinical trial, Davidoff et al investigated urinary TNF- α in patients with microscopic hematuria and demonstrated that urinary TNF- α was significantly elevated in patients with microhematuria when compared to the control group but they did not evaluate the associated urological abnormalities directly [31]. More recently, Muller et al. reported that fetal serum ss2-microglobulin and cystatin C were good markers for detection of postnatal renal function in bilateral renal hypoplasia and dysplasia [32]. After that, Mersobian et al. evaluated urinary proteome in pediatric patients with ureteropelvic junction obstruction (UPJO) and found a statistically significant difference in the expression of urinary proteins and polypeptides

between patients with and without UPJO [33]. In this regard, Almodhen et al evaluated the urinary concentrations of transforming growth factor-beta (TGF-β) in patient with urinary tract anomalies and revealed that this cytokine might be useful in detecting urological anomalies associated with urinary tract obstruction [34].

Table 1 Paraclinical features of study group [↑](#)

Para Clinical features	Frequency (%)
Positive urine culture	85.7
Abnormal DMSA scan	100
Abnormal Urinary TNF-α/Cr	91.9
Abnormal kidney ultrasonography	32.4
Hydronephrosis	25.4
Renal stone	7
Abnormal VCUG	12.2
VUR GI	2
VUR GII	6.1
VUR G III	3.1
VUR G IV	1

[↑](#)

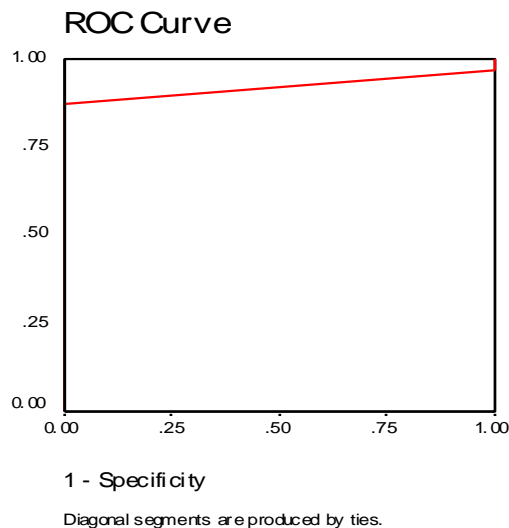


Figure 1 ROC curve of urinary TNF-α /Cr in study group (Area under the curve: 0.919) in comparison with DMSA scan

Jutley studies the serum cytokine levels of TNF-α, interleukin-6, soluble TNF receptor-1, and interleukin-8 in patients with vesicoureteral reflux and revealed a significant difference in the levels of TNF-α, interleukin-6, and soluble TNF receptor-1 between the study and the control group [35]. Ninan et al reported the usefulness of

urinary cytokines, soluble TNF-α, and TNF receptor-1 in detection of reflux associated renal damage. They showed that urinary levels of the cytokines IL-6 and soluble TNF receptor-1 were significantly elevated in pediatric patients with vesicoureteral reflux associated with reflux nephropathy [36]. In this regard, Klahr et al demonstrated that cytokines were involved in the pathogenesis of interstitial fibrosis due to obstructive nephropathy [37].

Conclusions

Although few studies have been conducted in this area, their results indicate the efficacy of urinary TNF-α/Cr in detection of inflammatory disorders such as pyelonephritis and pediatric urological abnormalities. These findings fundamentally question the real role of urinary TNF-α in better and faster diagnosis of pyelonephritis and related urological problems and follow-up of these patients. The authors recommend more investigations to obtain more information for better understanding of this fact.

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Conflict of Interest

None declared

Financial Support

None declared

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