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Urinary excretion of pentraxin-3 correlates with the presence of renal scar following acute pyelonephritis in children

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Abstract

Purpose Acute pyelonephritis is associated with considerable morbidity and potential for renal scarring. Pentraxin3 (PTX3) is a recently discovered mediator of inflammation. The objective of this study was to investigate the changes in serum and urine PTX3 levels in children who had a history of pyelonephritis and were diagnosed with renal parenchymal scar (RPS) and/or vesicoureteral reflux (VUR).

Methods The study included 88 children (31 males, 57 females) aged between 3 months and 18 years. The children included in the study were divided into four groups: VUR with RPS (Group 1), RPS without VUR (Group 2), VUR without RPS (Group 3), and healthy children without a history of hydronephrosis or UTI history (Group 4). After the initial evaluation, the participants were further divided into two more groups and re-evaluated: Children with RPS (Group 1 + 2), children without RPS (Group 3 + 4), children with VUR (Group 1 + 3), and children without VUR (Group 2 + 4).

Results We found that urine pentraxin 3 (uPTX3) and uPTX3/Creatinine levels were significantly higher in the groups with renal scar with or without VUR than the ones without RPS [mean uPTX3, 3.5 pg/ml (min–max 0.0022–12.3668) vs. 2.2 pg/ml (min–max 0.0022–18.5868) and uPTX3/creatinine, 10.5 pg/mg (min–max 0.0035–51.1) vs. 5.8 pg/mg (min–max 0.0004–78.7), $p < 0.01$]. uPTX3 levels were not different among the groups with and without VUR. In addition, serum PTX3 levels were not different among the groups.

Conclusions We showed that urinary PTX3 increased only in patients with scarred kidneys. These results might be helpful to predict RPS due to past pyelonephritis.

Keywords Children · Pentraxin 3 · Renal scar · Vesicoureteral reflux

Introduction

Acute pyelonephritis is one of the significant infectious diseases in children. It can lead to permanent kidney damage (renal parenchymal scar, RPS) and result in chronic kidney disease. Particularly, urinary tract infections can lead to severe inflammation that goes to focal ischemia and interstitial injury. Fibrosis and irreversible kidney damage have been shown to occur with inflammation, which is defined as RPS that can be shown by renal scintigraphic

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evaluation. Moreover, some authors showed that inflammatory processes persist even after the urinary tract infection has resolved. Vesicoureteral reflux (VUR) is defined as the pathologically backward flow of urine from the bladder into the ureter and kidneys. It is commonly observed in urinary tract malformations of the childhood. VUR is an important risk factor for the development of RPS following UTI [1–5].

Pentraxin 3 (PTX3) is a recently discovered mediator of inflammation. While PTX3 is classified in the structurally long pentraxin group, C-reactive protein (CRP) and serum amyloid p (SAP) are noted in the short pentraxin group. PTX3 is synthesized in the peripheral tissues (dendritic cells, macrophages, fibroblasts, activated endothelial cells, monocytes, neutrophils, and renal cells), whereas CRP and SAP are synthesized in the liver. Under normal conditions, pentraxins are not present or have very low expression levels. Proinflammatory cytokines stimulate the production of CRP and SAP in the liver, and PTX3 in the peripheral tissues [6, 7]. Many recent studies have shown that there is an association concerning severity and progression between PTX3 and the autoimmune, cardiovascular, and kidney diseases [8–10]. It has been suggested that this mediator is an independent indicator for the severity and activity of the disease because it is locally synthesized (different than CRP) in the inflammation area [8].

In this study, we aimed to investigate the changes in serum and urine PTX3 levels in children who had pyelonephritis and were diagnosed with renal parenchymal scar (RPS) and/or vesicoureteral reflux (VUR).

Patients and methods

The study consisted of 88 children (31 boys, 57 girls) aged between 3 months and 18 years, who visited our clinic between January 2014 and December 2016.

Fifty-two patients who had past pyelonephritis in the medical history and were diagnosed with VUR and/or RPS and 36 healthy children were included in the study. Children who had more than one APN attack were included, children who had acute pyelonephritis in the 6-month follow-up period were excluded from the study. The diagnosis of acute pyelonephritis was made by positive urine culture, fever (> 39°), systemic symptoms (vomiting, side pain, etc.), increased acute phase reactants (crp sedimentation, leukocytosis).

The children were divided into four groups: Group 1, RPS with VUR (8 boys, 13 girls); Group 2 RPS without VUR (9 boys, 9 girls); Group 3 VUR without RPS (2 boys, 11 girls); and Group 4 healthy children (12 boys, 24 girls). The healthy group had no history of UTI or antenatal hydronephrosis and no abnormalities according to urinalysis and ultrasound examination results. After the initial evaluation, the participants were further divided into two groups and re-evaluated: Children with RPS (Group 1 + 2), children without RPS (Group 3 + 4), and children with VUR (Group 1 + 3), and children without VUR (Group 2 + 4).

Serum and urine samples were obtained from children at the third week after the last acute pyelonephritis attack. The children had no active UTI during the sample collection. The diagnosis was made by conventional urine microscopy, erythrocyte sedimentation rate, C-reactive protein (CRP), white cell count, and negative urine culture.

Participants with proteinuria, hypertension, chronic kidney disease, other urinary tract malformations, such as obstructive uropathy, bladder dysfunction, urinary stones, neurogenic bladder, ureterocele, or bladder diverticulum, and those with acute or chronic systemic diseases were excluded from the study.

Vesicoureteral reflux diagnosis was made based on voiding cystourethrogram (VCUG). VCUG was performed in the 1st week following APN treatment. The grading of VUR was made according to the international classification system [11] from I to V. If VUR was bilateral, then the degrees of reflux were assembled. Grade 1–2, Grade 3, and Grade 4–5 were classified as mild, moderate, and severe VUR, respectively. The diagnosis of RPS was made and graded with the 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy. All DMSA scans were performed in the Medical Faculty Nuclear Medicine Department. DMSA scans were performed according to the guidelines on 99mTc-DMSA scintigraphy in children prepared by the European Association of Nuclear Medicine. DMSA scan was administered to the children 6 months after an acute pyelonephritis attack. The renal lesions determined with DMSA scan were graded based on the DMSA grading system reported by Imperiale et al. [12] as Grade 0 (normal), Grade 1 (single lesion), Grade 2 (two lesions), and Grade 3 (diffuse damage in the kidney). The presence of renal lesions was assessed in both kidneys, and the degree of RPS was recorded.

Urine samples were taken in the morning for urine PTX3 (uPTX3) measurement, urinalysis, and urine culture. A clean-catch midstream urine sample was obtained from the children who had bladder control. From patients without bladder control, urine samples were obtained with a urine bag. Part of the obtained urine was used for urine analysis, measurements of urinary creatinine levels, and urine culture. The other part of the urine was immediately centrifuged (10 min at 4000 rpm), and the supernatant was collected and kept at − 80 °C until the measurements of PTX3 levels were done.

Also, a part of the serum samples was kept at − 80 °C until the analysis. The other parts were used to measure the level of creatinine, white blood cell count, ESR, and CRP. Urine and serum PTX3 concentrations were determined by using a sandwich high-sensitivity ELISA kit for quantitative

detection of Human PTX3/Pentraxin 3 (Boster's Human PTX3/Pentraxin 3 PicoKine™ ELISA Kit) (Boster Biological Technology, Pleasanton CA, USA, Catalog # EK0861) according to the manufacturer's instructions (Boster Biological Technology Co., Ltd.). The plates were read at a wavelength of 450 nm using an automatic ELISA reader. The sensitivity of the test for PTX-3 was < 10 pg/ml.

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) version 10.0 was used for statistical analysis. Categorical variables were expressed as percentages. Differences in categorical variables among the groups were assessed by using the Chi-square test. The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess for normality. When non-normality detected, results were presented as medians and ranges and non-parametric tests (the Mann–Whitney U and Kruskal–Wallis tests) were used to test differences among the groups. A threshold of $p < 0.05$ was considered statistically significant.

The study was approved by the Pamukkale University Ethics Committee (IRB number 60116787-020/549639).

Results

VUR was present in 34 children (65.3%). The degree of VUR was mild, moderate, and severe in 14 (41.1%), 11 (32.4%), and 9 (26.5%) children, respectively. RPS was present in 39 children (75.0%), and 15 (38.5) of them were Grade I, 5 (12.8%) were Grade II, and 19 (48.7%) were classified as Grade III. Demographic and clinical characteristics of the patients are shown in Table 1.

The mean level of serum PTX3 was high compared to the control group; however, the difference was not statistically significant. Moreover, the mean level of urine PTX3/creatinine (uPTX3/Cr) ratio was not different between the patients and the healthy controls (Table 2).

When the group with RPS (Group 1 + 2) and the group without RPS (Group 3 + 4) were compared, it was observed that uPTX3 and PTX3/Cr levels were statistically higher in the ones with RPS compared to the ones without RPS (Fig. 1). However, there was no correlation between the grading of RPS and urine PTX levels. The mean serum PTX3 levels were lower in the group without RPS compared to the group with RPS; however, this difference was not statistically significant either (Table 3).

Receiver operating characteristic curves of urine PTX3 and urine PTX3/creatinine ratio for diagnosing renal scar are shown in Figs. 2 and 3. Both figures demonstrate that area under curve are approximately 0.67, and p values are statically significant ($p = 0.006$).

When the group with VUR (Group 1 + 3) and the group without VUR were compared, no statistically significant difference was determined between the mean levels of uPTX3 and uPTX3/Cr. Similarly, there was no correlation between the grading of VUR and PTX3 levels.

Discussion

In this study, we observed that urine PTX3 levels and uPTX3/Cr ratio were significantly higher in the groups with renal scar compared to those without RPS. Moreover, these results were not affected by whether the scar was associated

Table 1 Clinical and demographic feature of the participants

Characteristic	Group 1 VUR+ RPS+	Group 2 VUR− RPS+	Group 3 VUR+ RPS−	Group 4 Control	Total	*p*
Age, years, mean (min–max)	5.5 (1–16)	4.9 (0–12)	7.3 (1–16)	8.5 (1–18)	6 (0–18)	0.007
Gender *n* (%)						
Male	8 (25.8)	9 (29.0)	2(6.5)	12 (38.7)	31	0.25
Female	13 (22.8)	9 (15.8)	11 (19.3)	24 (42.1)	57	
Total	21 (23.9)	18 (20.5)	13 (14.8)	36 (40.9)	88	
Grade of VUR *n* (%)						
Mild (1–2)	7 (50)		7 (50)		14	0.47
Moderate (3)	8(72.7)		3 (27.3)		11	
Severe (4–5)	6 (66.7)		3 (33.3)		9	
Grade of renal parenchymal scar *n* (%)						
0	0	0	13 (26.5)	36 (73.5)	49	0.01
1	6 (40)	9 (60)	0	0	15	
2	3 (60)	2 (40)	0	0	5	
3	12 (63.2)	7 (36.8)	0	0	19	

VUR vesicoureteral reflux; *RPS* renal parenchymal scar

Table 2 Comparison of the serum and urine PTX3 levels between groups

	Group 1 ($n=21$) VUR+ RPS+	Group 2 ($n=18$) VUR− RPS+	Group 3 ($n=13$) VUR+ RPS−	Group 4 ($n=36$) Control	p value
Serum PTX3 (pg/ml)					
Median	2045.3	1844.7	1055.5	748.7	0.29
Min–max	325.1–10363.6	325.1–10732.7	325.1–3762.3	325.1–3570.8	
IQR	983	1188.1	1363.6	615.2	
Urine PTX3 (pg/ml)					
Median	3.49	3.50	2.50	2.17	0.033
Min–max	0.0022–12.3668	0.0022–9.4632	0.0022–9.4632	0.0022–18.5868	
IQR	4.6546	3.7574	3.9526	3.3944	
Urine PTX3/cr (pg/mg)					
Median	9.9	11.3	3.5	6.7	0.052
Min–max	0.0035–51.1206	0.0035–51.1206	0.0018–17.2058	0.0004–78.7576	
IQR	11.8706	13.8325	5.7721	9.0501	

Values are median (range)

PTX3 pentraxin 3, *VUR* vesicoureteral reflux, *RPS* renal parenchymal scar, *IQR* interquartile range

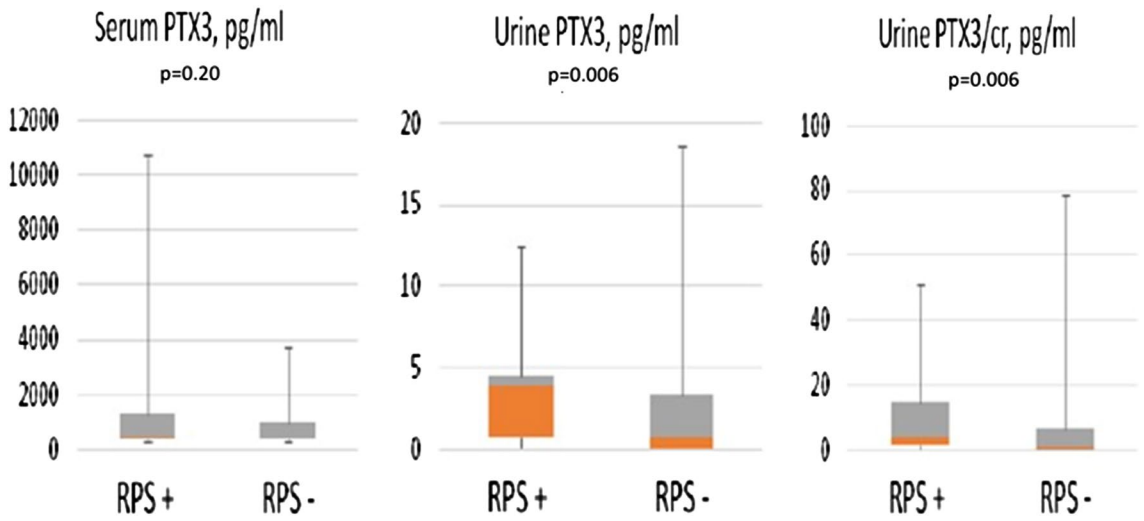


Fig. 1 Serum and urine PTX3 levels in patients with and without RPS. *PTX3* pentraxin 3, *RPS* renal parenchymal scar

with reflux. To our knowledge, this is the first study evaluating the relationship between RPS and serum and urine levels of PTX3.

The levels of the different cytokines in serum and urine and their association with renal scarring were studied by some of the researchers. The potential role of the inflammatory processes in renal scar development and recovery after UTI was elucidated [5, 13–17]. It has been shown in many studies that urine IL-8 levels increase in patients with VUR and renal scar. In addition, it has been suggested that high levels of IL-8 could be a sign of continued inflammation after infection in patients with VUR and renal scarring during the period without UTI [5, 13–15]. Besides IL-8, it was reported that IL-6, TNF-alpha, and TGF-beta levels were increased, respectively, in VUR and reflux nephropathy [14–17].

Pentraxin3 was first described as a cytokine-inducible gene in the endothelial and fibroblast cells. Besides, it was shown that dendritic cells and macrophages produce high amounts of PTX3. Inflammatory cytokines (IL-1α, TNF-α) are locally synthesized in the inflammatory regions in response to microbial products like toll-like receptor activation and lipopolysaccharide. Expression of PTX3 in the peripheral tissues is the most essential feature and distinguishes it from short pentraxins. Pentraxins are important components of immune regulation, opsonization of

Table 3 Serum and urine PTX3 levels in groups with and without RPS

	RPS+ Group 1 and 2	RPS− Group 3 and 4	*p*
Serum PTX3 (pg/ml)			
Median (min–max)	1952.7 (325.1–10732.7)	830.16 (325.1–3762.3)	0.20
Urine PTX3 (pg/ml)			
Median (min–max)	3.5 (0.0022–12.3668)	2.2 (0.0022–18.5868)	0.006
Urine PTX3/cr (pg/mg)			
Median (min–max)	10.5 (0.0035–51.1)	5.8 (0.0004–78.7)	0.006
N	39	49	

PTX3 pentraxin 3, *RPS* renal parenchymal scar

Values are median (range)

microorganisms, activation or inhibition of complement, recognition and clearance of apoptotic cells, deposition of extracellular matrix, tissue remodeling, and angiogenesis [6, 7, 18].

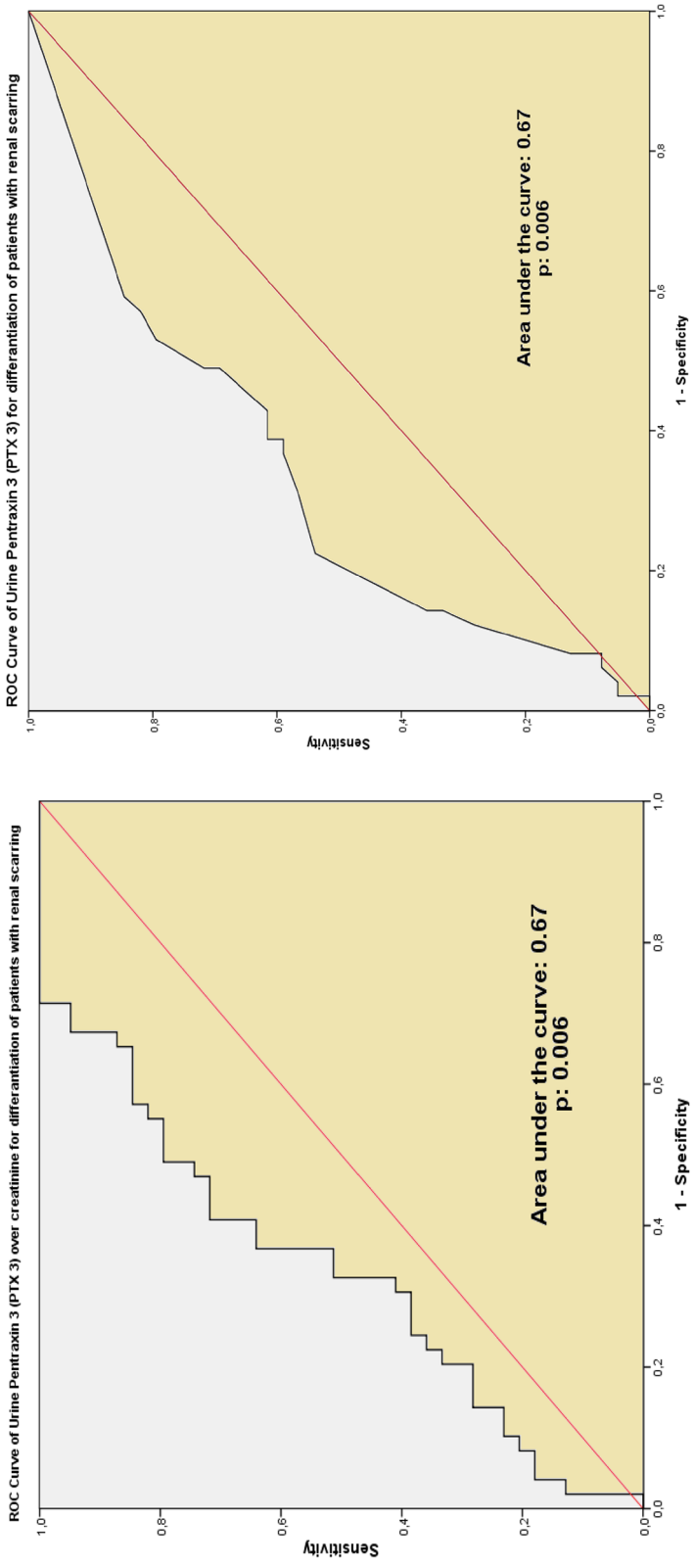
Pentraxin is important in the host defense during some fungal, bacterial, and viral infections. It has been found that the production of PTX3 is increased and the activity of the disease is related to the prognoses in various infectious disorders including sepsis [19, 20]. Jaillon et al. [21] reported that PTX3 was determined in the urine of patients with UTI and the amount of the urine PTX3 correlated with the severity of the disease. In the same study, PTX3 was shown to be an essential component of the natural defense against UTI [21]. It has been observed that septic pulmonary disease and myocardial infarction were intensified in a mouse model with PTX3 deficiency [22, 23]. Similarly, post renal inflammation and acute kidney damage have been shown to be increased in the absence of PTX3. Based on these data, PTX3 may have a regulatory role in the inflammatory response and may limit tissue damage caused by excessive inflammation [23]. It has been suggested that there is a possible association between PTX3 and kidney involvement in some autoimmune diseases (e.g., systemic lupus erythematosus). On the other hand, it is believed that PTX3 has a complex regulatory role on complement. PTX3 binds to C1q; however, the relationship between C1q and PTX3 is not understood entirely. It may play a role in the inhibition or activation of the classical complement pathway [24–26].

There is renal production and expression of PTX3 in primary mesangial cells, primary tubular epithelial cells, and renal fibroblasts. This expression is increased with the stimulation of IL-1 and TNF-alpha [27]. The expression of PTX3 is increased in immunoglobulin A nephropathy, type 1 membranoproliferative glomerulonephritis, diffuse proliferative lupus nephritis, Henoch-Schönlein purpura nephritis, and focal segmental glomerulosclerosis [27, 28]. Although we have limited knowledge about the role of PTX3 in kidney diseases, there is widespread idea that PTX3 has a role in the immunopathology of these patients. Previous studies reported a negative correlation between the plasma PTX3 concentrations and kidney function.

We found that there is a close correlation between the presence of kidney scar and increased urinary PTX3 excretion. UTI and renal dysfunction were absent in both the patient as well as the control groups. Diagnostic support was ensured by sterile urine culture, normal levels of white blood cell count, CRP, ESR, serum creatinine, and normal urine analysis. Detection of high levels of uPTX3 levels in patients with scar suggests that PTX3 might have a role in the scar development. Increased production of PTX3 by the renal tubular epithelial cells under inflammatory conditions was reported [29]. Hung et al. [30] suggest that PTX3 has an important role and may be a critical factor in the promotion of renal fibrosis. In this study, while PTX3 was not determined in the serum, high levels were found in the urine of patients with RPS. This finding may be associated with the local tubulointerstitial inflammation and fibrosis and expression of PTX3 locally, in the scarred kidney.

There are several limitations of this study. The small size of the study population and age differences among study groups are the limitations of this study. Further studies with bigger sample sizes will need to accomplish multivariable regression analyses in order to see all predictors for renal scarring.

In conclusion, similar to other studies on cytokines [5, 13–15, 31], the high levels of urine PTX3 observed in patients with scar may be an indicator of inflammation in the kidney. However, more studies are needed to link the levels of PTX3 with kidney inflammation.



Figs. 2 and 3 ROC curves of urine PTX3 and urine PTX3/creatinine ratio for diagnosing RPS. *ROC* receiver operating characteristic, *RPS* renal parenchymal scar

Author contributions TB conceptualized and designed the study, drafted the initial manuscript. TB, HE, and YE carried out the initial analyses, reviewed, and revised the manuscript. AE supervised the statistics. SY made critical revision of the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Compliance with ethical standards

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Ethical approval The study was approved by the Pamukkale University Ethics Committee (IRB number 60116787-020/549639).

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