Biomarker Insights

ORIGINAL RESEARCH

Plasma Soluble Urokinase Plasminogen Activator Receptor in Children with Urinary Tract Infection

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Abstract

Objective: In this prospective study we investigated the role of plasma levels of soluble urokinase plasminogen activator receptor (suPAR) in children with urinary tract infection.

Material and methods: We measured the levels of plasma suPAR during admission in 42 children with suspected acute pyelonephritis and compared the results to acute DMSA scintigraphy.

Results: The mean level of plasma suPAR at admission was significantly elevated in children with renal involvement (7.3 ng/ml) assessed by the DMSA scintigraphy compared to children without renal involvement (4.4 ng/ml, $P = 0.010$). The positive predictive value of suPAR seems high, since all patients without renal involvement had low suPAR values. During treatment the mean level of plasma suPAR decreased.

Conclusion: We conclude that plasma suPAR could be of clinical use for the diagnosis of acute pyelonephritis and that high levels of plasma suPAR might reflect the level of renal involvement and could therefore be a new indicator for renal scarring.

Keywords: biomarker, urinary tract infection, suPAR

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Introduction

Urinary tract infection (UTI) is a very common childhood infection, which normally resolves after antibiotic therapy without further morbidity. However, in children with UTI involving the renal parenchyma, 10%–20% will develop chronic kidney disease,[1] associated with abnormal findings on dimercaptosuccinic acid (DMSA) scintigraphy six months after the infection, so called renal scarring.[2]

Soluble uPAR (urokinase plasminogen receptor activator or suPAR) is a new and promising inflammatory biomarker and has demonstrated prognostic value in various infectious diseases such as tuberculosis, HIV infection and streptococcal bacteremia.[3,4] Elevated levels have recently also been associated with increased risk of cardiovascular disease, type 2 diabetes and cancer in the general population.[5] So far only a few studies have been published on suPAR as a biomarker for infections in the paediatric population, and little is known about the kinetics of suPAR.[6] Finally, mice knockout studies have shown a crucial role of uPAR in the host defence against experimental acute pyelonephritis.[7]

We aimed to investigate whether there is a relationship between plasma suPAR and renal involvement assessed by DMSA scintigraphy in children with acute pyelonephritis. Furthermore, we wished to determine the response of plasma suPAR to relevant treatment of the infection.

Materials and Methods

Blood samples from 42 patients were analysed for this study. Inclusion criterias: Children < 15 years of age suspected of having acute pyelonephritis, ie, fever (>38.5 °C), malaise, leucocyturia and positive urine culture (more than 10^4 CFU). Blood samples were collected for suPAR measurement at admission. The children were aged 2 months—14 years (average: 7 years) with a girl:boy ratio of 34:8. The local ethical committee approved this study and informed consent was obtained from parents and/or patients. For the purpose of comparing the suPAR levels in children with UTI with a group of non-infected children, we analysed plasma suPAR levels in 19 out clinic patients with well-treated asthma.

Within 5 days of admission renal parenchymal involvement was assessed by DMSA scintigraphy. The results were evaluated on the 5 level scale of severity (proposed by Benador et al[8]) by 2 specialists, who were neither aware of the children's condition nor of test results. All patients received treatment for suspected acute pyelonephritis consisting of intravenous ampicillin 100 mg/kg/day and gentamicine 6 mg/kg/day. SuPAR levels were determined using the suPARnostic ELISA (ViroGates, Copenhagen, Denmark). Comparison of suPAR concentrations between groups was determined using Mann Whitney U-test. Changes in patient biomarker concentrations over time were determined using the paired sample t-test. Statistical analysis was carried out using SSPS v11 and graphs drawn using Graph Pad Prism. A P-value <0.05 was considered significant.

Results

Figure 1 illustrates the subgroups of the 42 patients: (1) patients with uptake defects on acute scintigrams (N = 9), (2) patients with normal acute scintigrams (N = 15) and (3) patients who did not receive acute scintigraphy, due to former UTI with scarring (N = 18). Figure 2 shows the plasma suPAR levels for the 3 subgroups. Patients with DMSA positive UTI (1) had significantly higher median plasma suPAR level (7.3 ng/ml) than patients with DMSA

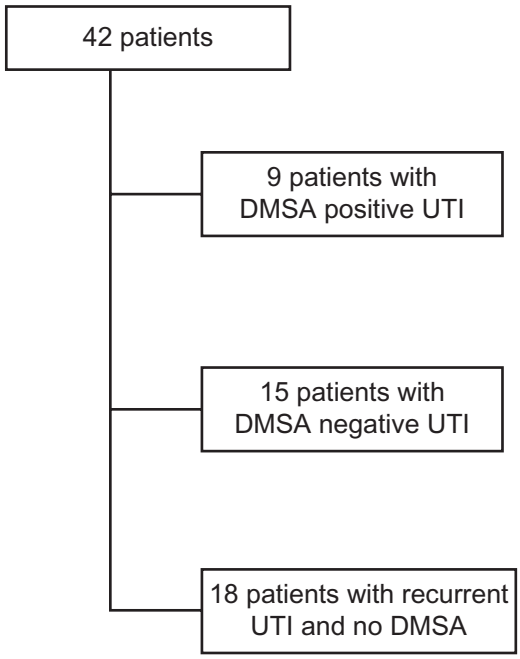

Figure 1. Flowchart of participants, who were divided into 3 groups: (1) DMSA positive UTI = uptake defects on acute scintigrams; (2) DMSA negative UTI = normal acute scintigrams; (3) patients with no acute scintigraphy due to former UTI with scarring.

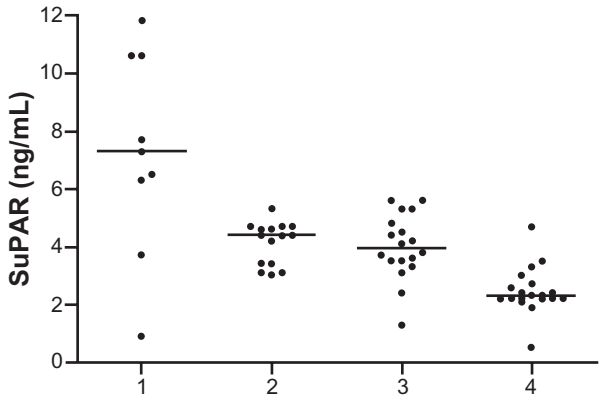

Figure 2. suPAR levels (ng/ml) at admission in patients with UTI and: positive DMSA (1), negative DMSA (2) and recurrent UTI with no DMSA (3). For comparison, the mean suPAR level of the control group is illustrated (4).

negative UTI (2) (4.4 ng/ml, $P = 0.010$) and patients with recurrent UTI and no new DMSA scintigraphy (3) (4.0 ng/ml, $P = 0.005$). The median plasma suPAR levels in these 3 subgroups were all significantly higher than in children from the out patient clinic with asthma (4) (2.3 ng/ml, N = 19, $P < 0.001$). Furthermore we analysed suPAR levels following treatment initiation and the median level was 4.4 ng/ml on day 1 (admission) falling to 3.7 ng/ml (n = 23) on day 3 and 2.9 ng/ml on day 5 (n = 8). A paired sample t-test for suPAR levels in all patients showed a trend towards a decrease in suPAR ($P = 0.053$).

C-reactive protein (CRP) and procalcitonin (PCT) were also measured at admission. Figure 3 displays the CRP levels in the 3 groups of children with UTI (n = 42) and we found a significant positive correlation of the suPAR levels with CRP, Pearson correlation = 0.492, $P < 0.01$. Comparison of suPAR and PCT levels in this group yielded a non-significant positive correlation of 0.300 (n = 14), probably because of the low sample number.

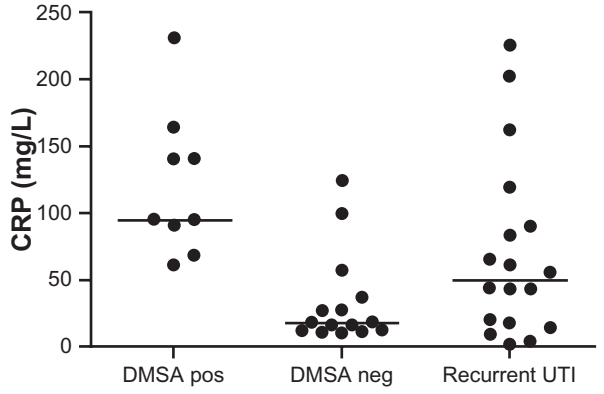

Figure 3. CRP levels (mg/l) at admission in patients with UTI and: positive DMSA, negative DMSA or recurrent UTI with no DMSA.

Discussion

Despite the relatively low number of patients included in this study, we found significant higher levels of plasma suPAR in patients with positive DMSA. This suggests that suPAR is a powerful marker of inflammation concordant with previous studies of suPAR. Noticeable for suPAR in this study and also prior, is a relatively small increase in suPAR during severe inflammation compared to the huge increases seen for CRP. The smaller increase of suPAR does not make it a poorer inflammatory marker compared to CRP. The nature of suPAR seems to be less fluctuating and a two-fold increase or more is usually enough to predict inflammation. We suggest suPAR as a possible complementary test to CRP with a promising positive predictive value.

In the group of patients with positive DMSA there are 2 outliers with rather low suPAR levels. This could be explained by for example congenital abnormalities, but we can of course not rule out the possibility of these being true false negative samples.

We conclude that plasma suPAR levels among children with positive DMSA scintigraphy were significantly elevated at admission. Since suPAR levels reflect immune activation and inflammation and our study shows an association between the suPAR level and acute DMSA scintigraphic findings, we suggest that the severity of the infection may be measured using suPAR. Further and larger studies are needed to determine whether high plasma suPAR levels are prognostic for the development of renal scarring and chronic renal disease.

Acknowledgments

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Conflict of Interest

Jesper Eugen-Olsen is a founder, shareholder and board member in ViroGates, the company that produce the suPARnostic assay. No other authors have any conflict of interest to declare.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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