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Serum Levels of Interleukin (IL)-1 β , sIL-2R, IL-6, IL-8 and TNF- α in Children with Idiopathic Nephrotic Syndrome*

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Abstract

The pathogenesis of idiopathic nephrotic syndrome (INS) is still controversial. Lymphocytic dysfunction and increased cytokine production have been suggested to be pathogenetic mechanism for renal injury in childhood INS. In order to investigate the role of certain cytokines, 23 children with steroid sensitive INS, aged 2-8 years, and 29 healthy controls were included in the study. Blood samples of patients were taken both at remission and relapse phases of the disease. Cytokines were measured by the chemiluminescent immunometric assay. Interleukin (IL)-1 β was undetectable in serum samples of all children. Serum levels of soluble interleukin-2 receptor (sIL-2R), IL-6, IL-8, and tumor necrosis factor- α (TNF- α) were significantly higher in relapsing phase of INS compared to remission and controls. Significant correlation was found between sIL-2R and 24-hour proteinuria.

In conclusion, sIL-2R, IL-6, IL-8 and TNF- α may have a role in the pathogenesis of renal injury in childhood steroid sensitive INS.

Key Words: Children, cytokines, nephrotic syndrome, pathogenesis

Çocukluk Çağı İdyopatik Nefrotik Sendromunda Serum İnterlökin (IL)-1 β , sIL-2R, IL-6, IL-8 ve TNF- α Düzeyleri

Özet

İdyopatik nefrotik sendrom (INS) patogenezi halen tartışmalı bir konudur. Lenfosit fonksiyon bozukluğu ve artmış sitokin üretimi çocukluk çağı nefrotik sendromunda patogenetik mekanizma olarak ileri sürülmüştür. Bazı sitokinlerin INS patogeneziindeki rolünü araştırmak üzere, yaşları 2-8 yıl arasında değişen 23 INS'li çocuk ile benzer yaş grubundan 29 sağlıklı çocuk çalışmaya alındı. Hem relaps hem de remisyon dönemlerinde hastalardan kan örnekleri alındı. Sitokinler 'chemiluminescent immunometric' yöntemle çalışıldı.

İnterlökin-1 β düzeyleri hasta ve kontrol grubunda saptanabilir değerin altında bulundu. Solubl IL-2 reseptörü (sIL-2R), IL-6, IL-8 ve tümör nekroz faktör-alfa (TNF- α) düzeyleri INS'li çocukların relaps fazında remisyon fazına ve kontrollere göre anlamlı yüksek bulundu. Yirmi dört saatlik idrar proteini ile sIL-2R düzeyi arasında anlamlı korelasyon bulundu. Sonuç olarak çocukluk çağı steroid duyarlı INS'sinde sIL-2R, IL-6, IL-8 ve TNF- α 'nin böbrek hasarlanmasında rolü olabilir.

Anahtar Kelimeler: Çocuklar, sitokinler, nefrotik sendrom, patogenezi

It has been suggested that idiopathic nephrotic syndrome (INS) in children is related to a lymphocytic dysfunction (1). A decreased proportion of T helper (CD4+) cells and an increased proportion of T suppressor (CD8+) cells have been reported in the active phase of steroid sensitive INS (2). However, Tejani et al (3) found no significant difference of T cells in relapse phase of nephrotic syndrome from controls or INS patients in remission. In a number of studies, some authors have suggested that the cytokines

produced by monocytes/macrophages (IL-1 α , IL-1 β , IL-8 and TNF- α) and by T cells (IL-2, IFN γ , IL-4, IL-6 and IL-10) may induce proteinuria in idiopathic nephrotic patients (4-6). The role of these cytokines and their receptors for the pathogenesis of INS is still controversial, but in progressive glomerulonephritis the role of certain cytokines (e.g. IL-1 β , sIL-2R, IL-6, IL-8 and TNF- α) is well established (7,8). In this study, we have assessed the cytokine spectrum of patients

with INS during active and inactive disease to find evidence for the roles of cytokines in renal injury during relapse.

Patients and Methods

Our study population consisted of 23 pediatric patients (15 males, 8 females), aged 2-8 years, with steroid sensitive INS and 29 healthy controls of similar age while undergoing routine assessment prior to elective surgery or routine check-up. Patients with acute infection or who had blood transfusion during the last month were excluded from participation in the study.

No patients with INS had undergone renal biopsy, since they were all steroid sensitive patients, ages ranging between 2 and 8 years. Blood samples of patients were taken both at remission, at least after two months of steroid discontinuation and at relapse while not initiated steroids. For the determination of cytokines blood was kept for 10 minutes at room temperature then was centrifuged and serum samples were preserved at -20°C. Cytokines were measured by two-site sequential chemiluminescent immunometric assay (Immulite, EURO/DPC Ltd, UK). In

the same blood samples creatinine, urea, total proteins, albumin and cholesterol were determined by routine methods.

Statistical analysis: Data were expressed as geometric mean and standard error of mean. Due to highly skewed distribution of interleukin values, nonparametric Wilcoxon Signed Rank test and Mann-Whitney U test were performed to compare data belonging to paired and unpaired groups. P value less than 0.05 was accepted as significant.

Results

Serum IL-1 β levels were undetectable (<5 pg/ml) in all children with INS both in remission and relapse and in controls. Serum levels of sIL-2R, IL-6, IL-8 and TNF- α of all subjects are shown at Table 1. There were significant differences between relapsing and remission phases of INS and controls in sIL-2R, IL-6, IL-8 and TNF- α levels. Levels of these cytokines were higher in relapsing INS compared to remission and controls. There were no significant differences in IL-1 β , sIL-2R, IL-6 and TNF- α levels between remission phase of INS and controls (Table 1).

Table 1. Serum cytokine levels in children with idiopathic nephrotic syndrome and control group (geometric mean $\pm$ SEM)

Cytokines	INS patients (n=23)		Controls (n=29)	Significance		
	Relapse	Remission		*P ₁	**P ₂	**P ₃
sIL-2R (IU/L)	1347 $\pm$ 127	799 $\pm$ 78	901 $\pm$ 73	<0.001	<0.001	NS
IL-6 (pg/ml)	3.9 $\pm$ 0.5	2.4 $\pm$ 0.4	1.9 $\pm$ 0.4	0.010	0.001	NS
IL-8 (pg/ml)	21.9 $\pm$ 8.8	10.4 $\pm$ 3.2	5.2 $\pm$ 0.4	0.016	<0.001	0.001
TNF- α (pg/ml)	23.7 $\pm$ 1.6	16.1 $\pm$ 1.8	13.8 $\pm$ 0.5	0.010	<0.001	NS

*According to Wilcoxon Signed Rank test, and **Mann-Whitney U test; P₁: between relapse and remission; P₂: relapse-controls; P₃: remission-controls; NS: not significant

Table 2. Spearman correlation coefficients of cytokines, serum albumin and urinary 24 hour protein excretion in children with idiopathic nephrotic syndrome.

	Serum albumin	sIL-2R	IL-6	IL-8	TNF- α
Proteinuria	-0.61*	0.462**	0.198	-0.094	0.200
Serum albumin		-0.152	0.018	0.015	-0.118
sIL-2R			0.357*	0.089	0.295*
IL-6				0.364*	0.626**
IL-8					0.404**

*Correlation is significant at the 0.05 level, **Correlation is significant at the 0.01 level

With Spearman's correlation analysis we found significant correlations between serum levels of sIL-2R and 24 hour-proteinuria, between sIL-2R and IL-6, between IL-6 and IL-8, and between IL-8 and TNF- α (Table 2). There were no significant correlations between cytokines and serum albumin, total protein, cholesterol, urea or

creatinine (data not shown, p>0.05).

Discussion

The assessment of cytokines as a possible pathogenetic factor in the nephrotic syndrome may increase our understanding about mechanism of renal injury. While interpreting the results of

cytokines and their receptors, it is important to consider that serum levels can only partially reflect the local in vivo production of these substances in the kidney. This means all cytokines produced in the kidney are not necessarily secreted into the circulation or circulated levels of cytokines may be too low to detect.

Monokines (e.g. IL-1, IL-8 and TNF- α) are the first mediators induced in the immune response. They are involved both in T cell and natural killer cell activation. The monokines IL-1, IL-8 and TNF- α are involved in kidney diseases since they are expressed in normal mesangial and glomerular epithelial cells (8). Conflicting results have been published on IL-1 production in INS. Suranyi et al (9) observed that plasma levels of IL-1 β were similar to controls in minimal change nephrotic syndrome (MCNS) patients. However Saxena et al (1) have found an increased IL-1 production by stimulated peripheral monocytes in children. In this study serum levels of IL-1 β were lower than 5 pg/ml, minimum detectable value according to our method, in relapse and remission phase of INS and controls.

The IL-2 receptor has a unique role for local cell to cell signal transduction and is an activity marker of the immune system (10). Neahaus et al (11) in children and Mandreali et al (12) in adult patients with INS reported higher urine/plasma ratios of sIL-2R in relapse vs remission. In our study we found higher levels of sIL-2R in relapse compared to remission phase of INS and controls. Although we have found no correlation between age and sIL-2R levels, some studies have reported that sIL-2R levels depend on age and previous immunosuppressive medication (10).

The serum levels of IL-6 was higher in relapse than remission phases of INS and controls. Although, the role of IL-6 is well established in mesangial proliferative glomerulonephritis, this cytokine was not detected in the urine of patients with MCNS (13). Daniel et al. (10) have found similar serum IL-6 levels in relapse and remission phases of children with INS.

Interleukin 8 has rarely been investigated in patients with glomerular disorders. Garin et al (4) and Neahaus et al (11) have reported higher serum levels of IL-8 in INS children in relapse vs remission or controls. Our own finding of increased IL-8 serum levels in relapsing INS patients compared to remission phase is in accordance with previous studies.

Variable findings have been reported about

TNF- α in patients with INS. Egido et al. (14) observed an increased production of TNF- α by peripheral monocytes and high plasma and urine levels in relapsing INS compared to remission and controls. However Özen et al (5) have failed to find such significant difference in the urinary TNF- α excretion of INS children compared to controls. Our finding of higher TNF- α in relapsing INS indicates that TNF- α production may play a role in the pathogenesis of INS in children.

In conclusion, we found higher sIL-2R, IL-6, IL-8 and TNF- α levels in relapsing children with INS compared to remission and controls. However serum levels of IL-1 β was unchanged in all groups. Thus sIL-2R, IL-6, IL-8 and TNF- α may have a role in the pathogenesis of INS in children.

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