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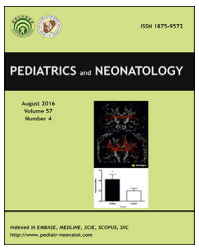

Original Article

Elevated urinary monocyte chemoattractant protein-1 levels in children with Henoch-Schonlein purpura nephritis

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Key Words
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proteinuria

Background: Chemokine monocyte chemoattractant protein-1 (MCP-1) has been proved as a potential urinary biomarker in nephropathies. The aim of this study was to investigate the urinary monocyte chemoattractant protein-1 (MCP-1) levels and clinical significance in Henoch-Schonlein purpura (HSP) children with and without nephritis and determine the association of MCP-1 with proteinuria.

Methods: A total of 261 HSP children—with or without nephritis—and 84 healthy control children were enrolled in this study. Of these, 126 HSP nephritis (HSPN) children were subdivided into three groups according to total urine protein in 24 h (TUP): Group A, mild proteinuria group with TUP $<$25 mg/kg; Group B, moderate proteinuria group with TUP $\geq$25 mg/kg and $<$50 mg/kg; Group C, severe proteinuria group with TUP $\geq$50 mg/kg. Urinary MCP-1 levels were determined by ELISA. Levels of serum creatinine (Cr), blood urea nitrogen (BUN), urinary α_1-micro globulin (α_1-MG), micro-albumin (mAlb), immunoglobulin G (IgG), transferrin (TRF) and TUP were performed to determine their associations with MCP-1.

Results: Urinary MCP-1 was significantly higher in HSPN group in comparison with HSP group and controls ($P < 0.05$), but no significant difference was found between the HSP group and the healthy group ($P > 0.05$). The levels of urinary MCP-1 increased in parallel to the enhancement of total urine protein in 24 h in HSPN patients. There were statistically significant differences among these three groups of HSPN children ($p < 0.05$). Urinary MCP-1 correlated positively with urinary α_1-MG, mAlb, IgG, TRF and TUP in HSPN, whereas no correlation was observed with serum Cr and BUN.

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Conclusions: MCP-1 was elevated in children with HSPN and correlated with proteinuria. Urinary MCP-1 could be used as a suitable, non-invasive biomarker to provide valuable information not only for the diagnosis of HSPN, but also for evaluation of severity of renal damage.

1. Introduction

Henoch-Schonlein purpura (HSP), the most frequently detected form of vasculitis in children, is an IgA-mediated small-sized vessel leukocytoclastic vasculitis predominantly affecting the skins, joints, gastrointestinal tract and kidneys.[1,2] HSP has been called IgA vasculitis after the revised nomenclature and classification of vasculitis from the 2012 International Chapel Hill Consensus Conference.[3] The consensus renamed IgA vasculitis is based on the compelling body of literature indicating that abnormal IgA deposits in vessel walls are the defining pathophysiologic feature. Henoch-Schonlein purpura nephritis (HSPN) is observed in 30%—50% of children with HSP, which follows the onset of typical rash within 6 months.[4,5] The histologic findings of this disease include mesangial cell proliferation, crescent formation, and mesangial IgA deposition.[6] The prognosis of HSP is mostly dependent on the severity of renal involvement. However, the mechanism in HSP renal damage is not fully understood.

In recent years, studies have reported that monocytes/macrophages are the main inflammatory cells that actively participate in pathophysiological process of kidney disease. The number of both intraglomerular and interstitial monocytes/macrophages was significantly correlated with the grade of mesangial matrix increase and of interstitial fibrosis.[7,8] A long-term follow-up study showed that persistent inflammation existed in glomeruli in the HSPN chronic progress phase. Chemokines are a group of small, secreted proteins that play an important role in the development of inflammatory disorders. The critical step in the development of inflammatory responses in renal diseases is that chemokines attract peripheral leukocytes, particularly monocytes/macrophages, into tissues.

The gold standard for confirmation of diagnosis and disease severity of glomerulonephritis is renal biopsy, but this procedure is invasive, with a risk of complications such as infections and hemorrhage. Thus, a non-invasive monitoring method is acceptable, especially in pediatric patients. In healthy individuals, approximately 70% of the urinary proteome originates from the kidney and the urinary tract.[9] Thus, urine is a valuable source of renal disease biomarkers. The chemokine monocyte chemoattractant protein-1 (MCP-1), a member of the C-C family of chemokines, belongs to the group of inflammatory chemokines. MCP-1 is a potent chemotactic factor for monocytes, as well as for memory T lymphocytes, natural killer cells and basophils. In addition, MCP-1 has the ability to influence the macrophage contribution to fibrosis through both direct and indirect mechanisms.[10,11]

Recently, MCP-1 has been proved as a potential urinary biomarker in nephropathies. In experimental animal models, there was a reduction in the number of glomerular macrophages, a decrease in crescent formation, and reduced interstitial fibrosis after treatment with a neutralizing antibody to MCP-1.[12] Shoukry et al.[13] reported that urinary MCP-1 may be considered as a novel potential diagnostic biomarker for the early detection of diabetic nephropathy. Wasilewska et al.[14] found increased urinary MCP-1 levels in patients with persistent proteinuria due to IgA nephropathy. Ghobrial et al.[15] proved that increased urinary MCP-1 was useful for the early diagnosis of lupus nephritis and monitoring the severity of renal involvement. Fuentes et al.[16] showed that HSP patients with nephritis had higher urinary MCP-1/creatinine levels. In addition, an elevated MCP-1/creatinine level was an indication for renal biopsy. However, it is not known whether urinary MCP-1 excretion correlates with proteinuria.

The aim of this study was to investigate the urinary MCP-1 level in HSP children with or without nephritis and to determine the association of MCP-1 with the severity of proteinuria.

2. Patients and methods

The study was approved by the Ethical Committee of the Ningbo Women and Children's Hospital, and informed consent was obtained from custodians of all participants. A total of 261 pediatric patients were recruited in this study between Jan 2013 and Dec 2015 from the Department of Pediatric Rheumatology and Immunology, Ningbo Women and Children's Hospital, China. HSP was diagnosed according to the EULAR/PRINTO/PRES criteria as follows[17]: purpura or petechiae (mandatory) with lower limb predominance and at least one of the four following criteria: abdominal pain, histopathology (typical leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposits), arthritis or arthralgia, or renal involvement (proteinuria $>$ 0.3 g/day or hematuria or red blood cell casts $>$5 red blood cells/high power field).

HSPN was clinically diagnosed according to the Subspecialty Group of Nephrology, Society of Pediatrics, Chinese Medical Association criteria as follows[18]: presence of hematuria and/or proteinuria within 6 months after the onset of rash. Hematuria was defined the presence of macroscopic or microscopic hematuria (red blood cell casts $>$5 red blood cells/high power field). Proteinuria was defined by meeting at least one of the three following criteria: 1) routine urinalysis demonstrating proteinuria 3 or more times in one week, 2) total urine protein in 24 h exceeding 150 mg, and 3) a urinary micro-albumin level higher than the normal value 3 or more times in one week. Additionally, HSPN children were subdivided into three groups according

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