

Levels of intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 in children with Henoch-Schönlein purpura

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Background and Purpose: Henoch-Schönlein purpura (HSP) is a small vessel vasculitis. Soluble adhesion molecules play a very important role in the immuno-inflammatory reaction of damaged vascular tissues. This study investigated the prognostic and diagnostic potential of soluble intracellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) in HSP.

Methods: Serum levels of sICAM-1 and sVCAM-1 were studied in 26 children with HSP. Paired blood samples (during acute and convalescent stages) were collected from 17 of the children and assayed by enzyme-linked immunosorbent assay. Correlations with clinical manifestations were examined. Seventeen healthy children served as controls.

Results: Both sICAM-1 and sVCAM-1 were significantly elevated at the acute stage compared with the remission stage of HSP patients versus controls ($p=0.006$ and $p=0.0173$, respectively).

Conclusions: Although the levels of sICAM-1 and sVCAM-1 were not correlated with the severity of clinical manifestations in HSP, these soluble adhesion molecules may serve as diagnostic markers.

Key words: Henoch-Schönlein purpura, intercellular adhesion molecule-1, vascular cell adhesion molecule-1

Introduction

Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in children. It is characterized by non-thrombocytopenic purpura, arthritis or arthralgia, abdominal pain, gastrointestinal hemorrhage, and glomerulonephritis [1]. The clinical features of HSP are a consequence of widespread leukocytoclastic vasculitis. Soluble adhesion molecules facilitate adhesion, migration, and transmigration of circulating cells into damaged vascular tissues [2], and play a very important role in the immuno-inflammatory reaction [3,4]. Recent studies have suggested the prognostic and diagnostic potential of various soluble adhesion molecules in vascular and cardiovascular diseases [2]. This study investigated the

changes of serum soluble adhesion molecules levels during the disease course of children with HSP. It also tested the correlation between levels of these soluble adhesion molecules and clinical symptoms.

Methods

The study group consisted of 26 children, including 17 boys and 9 girls aged 1 to 15 years, with a mean age of 6.3 years. All patients fulfilled the American College of Rheumatology 1990 criteria for the classification of HSP. Their serum levels of soluble intracellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured during the acute phase (3 to 5 days after the onset of symptoms). Paired sera were collected 6 months to 2 years after remission in 18 of the 26 children with HSP (11 boys and 7 girls). Eight patients with renal complications not reaching the remission stage were

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excluded. Seventeen healthy children (9 boys and 8 girls) aged 7-12 years attending the hospital for school health care examination were recruited as normal controls. All blood samples were measured with commercially available sandwich enzyme-linked immunosorbent assay kits (R & D System, Minneapolis, MN, USA). Data were expressed as mean \pm standard error of the mean. Comparisons of these data between different disease stages were analyzed using Student's *t* test. *p* values less than 0.05 were considered significant.

Results

There were 17 boys and 9 girls with a mean age of 6.3 years and age range of 1-15 years. All patients presented with the characteristic palpable purpuric lesions of HSP (Table 1). Two-thirds of patients had gastrointestinal system involvement and arthritis or arthralgia. Eight patients (31%) had renal involvement. One patient developed nephrotic syndrome. Hematuria and proteinuria were noted in 8 patients (31%) and 7 patients (27%), respectively. All patients with proteinuria had concomitant hematuria. Steroids were used in 11

patients because of either nephritis or severe abdominal pain uncontrolled with non-steroidal anti-inflammatory drugs; the dosage of steroids was 1 to 2 mg/kg with a duration ranging from 3 to 7 days; prolonged usage (2 to 5 weeks) with tapering dose was also administered in protracted or recurrent cases. Patients treated with steroids showed resolution of clinical symptoms as well as decreased levels of sICAM-1 and sVCAM-1 in remission compared with the acute stage ($p=0.001$ and $p=0.035$, respectively). This difference was not significant in patients who were not treated with steroid ($p=0.30$ and $p=0.93$, respectively) [Fig. 1, 2]. Acute phase sICAM-1 levels were significantly higher than during remission in patients with elevated anti-streptolysin O (ASLO) titers ($p=0.02$). During the acute stage, clinical symptoms such as purpura, abdominal pain, and arthralgia/arthritis were significantly associated with increased levels of sICAM-1 or sVCAM-1 (Table 1, Fig. 3). There were no age-related differences in expression of adhesion molecules, including sICAM-1 and sVCAM-1. The level of adhesion molecules was decreased in patients with renal involvement, especially patients with nephrotic syndrome.

Table 1. Clinical profiles of patients with Henoch-Schönlein purpura

Symptoms and signs	No. of patients (%)	sICAM-1 (ng/mL) ^a		sVCAM-1 (ng/mL) ^a	
		Acute phase	Remission	Acute phase	Remission
Control	17	227 \pm 54.9		307.1 \pm 79.1	
Purpura	26 (100)	266.3 \pm 84.3	173.2 \pm 58.5 $p<0.001$	224.8 \pm 82.9	170.6 \pm 63.1 $p=0.017$
Abdominal pain	20 (77)	248.9 \pm 72.8	131.8 \pm 63.0 $p<0.001$	214.4 \pm 86.2	133.1 \pm 26.7 $p=0.044$
Arthritis/arthralgia	19 (73)	253.4 \pm 64.7	164.8 \pm 46.1 $p=0.0028$	208.4 \pm 56.9	157.9 \pm 61.9 $p=0.044$
Renal involvement	8 (31)	231.05 \pm 78.9		206.2 \pm 85.1	
Hematuria	8 (31)	205.1 \pm 115.8		127.4 \pm 64.2	
Proteinuria	7 (27)	217.3 \pm 138.7		113.8 \pm 51.0	
Nephrotic syndrome	1 (4)		62.2		78.1
Elevation of ASLO ^b	9 (35)	374.6 \pm 182.2	155.6 \pm 39.0 $p=0.02$	213.8 \pm 121.1	232.5 \pm 225.6 $p=0.46$
Treatment with steroid	11 (42)	261.7 \pm 90.1	140.6 \pm 60.4 $p<0.001$	206.2 \pm 85.1	120.7 \pm 37.5 $p=0.035$
Treatment without steroid	15 (58)	243.9 \pm 72.2	192.6 \pm 33.0 $p=0.30$	203.2 \pm 70.6	197.9 \pm 107.7 $p=0.93$
Allergic rhinitis	12 (46)	174.9 \pm 88.5	159.1 \pm 56.3 $p=0.72$	151.4 \pm 96.5	184.6 \pm 53.9 $p=0.41$
Acute sinusitis	7 (27)	221.5 \pm 153.9	209.3 \pm 11.5 $p=0.92$	209.9 \pm 94.9	211.8 \pm 14.9 $p=0.97$

Abbreviations: sICAM-1 = soluble intracellular adhesion molecule-1; sVCAM-1 = soluble vascular cell adhesion molecule-1; ASLO = antistreptolysin O

^aValues are presented as mean \pm standard error of the mean.

^bASLO level >58 U/mL was considered as elevated.

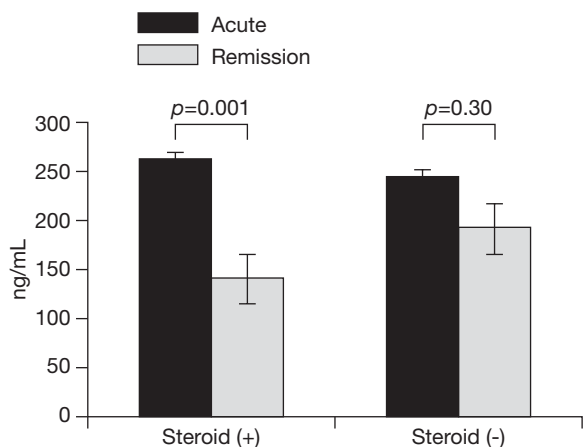


Fig. 1. Remission levels of soluble intracellular adhesion molecule in patients treated with steroid were significantly decreased in the acute stage compared with those not treated with steroid; $p=0.001$ and $p=0.30$, respectively.

Discussion

HSP is the most common acute vasculitis affecting children. The vast majority of patients with HSP are children between the ages of 3 and 15 years. The mean age of the patients in our study was 6.3 years and all patients were younger than 15 years. Symptom onset followed an upper respiratory tract infection in 40% of our patients. Many studies have proposed infection, particularly beta-hemolytic streptococcal disease, as a trigger for HSP [5]. al-Sheyyab et al reported that a significantly higher proportion of children with HSP had increased ASLO titers (49%) compared with controls (16%) [6]. Elevated ASLO was found in 35%

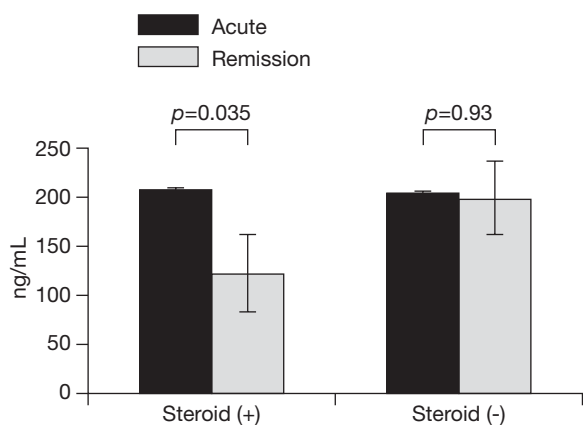


Fig. 2. Remission levels of soluble vascular cell adhesion molecule in patients treated with steroid were significantly decreased in the acute stage compared with those not treated with steroid; $p=0.035$ and $p=0.93$, respectively.

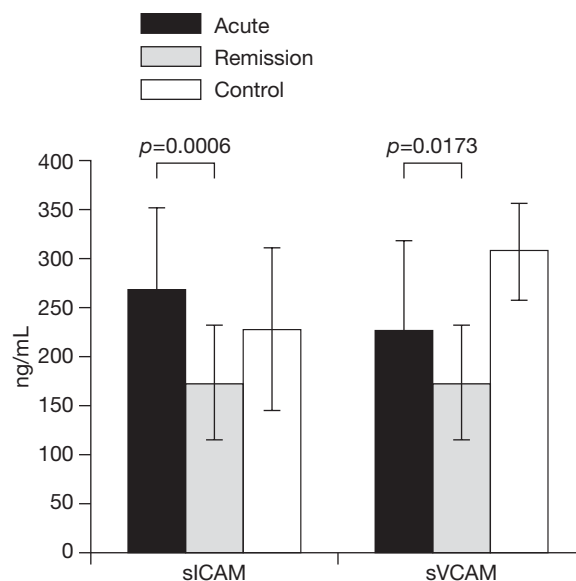


Fig. 3. Comparison of serum levels of soluble intracellular adhesion molecule (sICAM) and soluble vascular cell adhesion molecule (sVCAM) in acute and remission stages in patients with Henoch-Schönlein purpura and the control group. Serum sICAM and sVCAM concentrations were significantly higher in the acute stage than in remission; $p=0.0006$ and $p=0.0173$, respectively.

of our patients and was associated with significant elevation of sICAM-1. Several microorganisms have been reported to be associated with the development of HSP, including *Mycoplasma pneumoniae* [7], varicella [8], and mumps virus [9]. However, adenovirus was isolated in 2 of our patients. Cutaneous purpura is a sine qua non for the diagnosis of HSP [10]. Palpable purpuric lesions are typically seen on dependent or pressure-bearing areas, especially around the malleoli of dorsal surface of the leg, and buttocks [11]. Arthritis is the second most frequent clinical manifestation of HSP, and was found in 73% of our patients. Although the arthritis in patients with HSP may be incapacitating, it is self-limited and non-deforming. Similar to purpura in HSP, arthritis tends to abate with bed rest and exacerbate with ambulation [12]. Abdominal pain has been reported to occur in more than 50% of children, and is potentially the most serious complication of HSP [12]. In this study, abdominal pain was noted in 77% of children. Our finding that 31% children with HSP had renal involvement is within the reported range of 20 to 34% [1]. The spectrum of renal manifestations ranges from fairly typical symptoms of hematuria and proteinuria to the less common but more severe conditions of nephrotic syndrome and renal failure. These clinical symptoms

have incidences compatible with the renal manifestations in our patients. Proteinuria was always associated with hematuria in this study. Previous study of skin and kidney biopsies revealed the immunopathogenesis of HSP. Immune complexes, mainly immunoglobulin A, and immunoglobulin G, C3, properdin, and fibrin were deposited in vessel walls [13]. The trapping of immune complexes in vessel walls initiates local complement activation and adhesion molecule expression that result in migration and adhesion of neutrophils and macrophages to endothelial cells [13,14]. The subsequent release of proteolytic enzymes, leukotrienes, nitric oxide, and reactive oxygen molecules damages the vessel walls and surrounding tissues [15,16]. Therefore, adhesion molecules are believed to play a very important role in the immuno-inflammatory reaction. Increased circulating sICAM-1 levels were also demonstrated in the acute stage of HSP patients when compared to the remission stage [3]. In our study, sICAM-1 and sVCAM-1 were significantly increased in the acute stage compared to the remission stage.

The sICAM-1 levels of the control group were higher than in the remission stage of HSP patients, while the sVCAM-1 levels in the control group were higher than those of patients in both the acute and remission stages. One possible explanation is that increased production of adhesion molecules is noted in autoimmune diseases, and cardiovascular diseases. Previous study also found that asthmatic children had higher levels of sICAM-1, and that serum level of sICAM-1 increased in asthmatic children when air pollution exacerbated [17]. These diseases may have been present in the children in the control group and overlooked by the school health examination. This might explain why the allergic rhinitis and acute sinusitis seen in our HSP patients were not associated with differences in levels of adhesion molecules between acute and remission stages (Table 1).

Determination of whether these complications impact on the level of adhesion molecules may require careful interpretation. Correlation of sICAM-1 and sVCAM-1 levels with the clinical symptoms revealed that levels of these 2 adhesion molecules significantly decreased when clinical symptoms such as purpura, abdominal pain, and arthritis/arthralgia improved (Table 1, Fig. 3). The only patient with associated nephrotic syndrome had significantly decreased levels of both sICAM-1 and sVCAM-1. Mrowka et al reported progressive glomerulosclerosis in patients with severe immunoglobulin A nephropathy who had impaired renal

function associated with markedly lower sICAM-1 levels than in patients with mild or medium lesions [18]. Another of our patients with renal involvement who had an elevated ASLO titer and suspected poststreptococcal glomerulonephritis also had a very low level of sICAM-1. Determination of whether a high level of sICAM-1 implies previous Group A streptococcal infection or if extremely low levels of adhesion molecules are a risk factor for renal impairment requires further investigation. More research on the value of adhesion molecules as a diagnostic or risk factor for HSP is needed.

Although the patients who received steroid treatment had relatively severe clinical symptoms, they did not have higher soluble adhesion molecular levels. Both sICAM-1 and sVCAM-1 levels were significantly decreased in the remission stage ($p=0.001$ and $p=0.035$, respectively) compared with the acute stage in the steroid-treated patients. This may reflect the anti-inflammatory and immunomodulatory effects of steroids.

In summary, this study has demonstrated the significant correlation of both sICAM-1 and sVCAM-1 levels with the acute and remission stages. Whether adhesion molecules can be used as a specific diagnostic markers for HSP or a severity marker for renal involvement requires further investigation.

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