Research Article

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An evaluation of biomarkers indicating endothelial cell damage, inflammation and coagulation in children with Henoch-Schönlein purpura

Henoch-Schönlein Purpura'lı çocuklarda endotel disfonksiyonu, inflamasyon ve koagülasyon biyobelirteçlerinin değerlendirilmesi

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Abstract

Objective: Henoch-Schönlein purpura (HSP) is characterized by generalized vasculitis. The etiopathogenesis of the disease is unknown, but inflammation and endothelial dysfunction have been held responsible. Therefore, herein we investigated serum levels of biomarkers indicating endothelial cell damage, inflammation and coagulation in children with HSP.

Materials and methods: Twenty six patients with HSP and 26 healthy children were included in the study. Routine biochemical tests and laboratory parameters showing inflammation, coagulation, and endothelial cell damage were examined in all subjects.

Results: White blood cell (WBC) number, C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), neutrophil/lymphocyte rate (NLR), triglyceride, immunoglobulin A (IgA), and C₃ were significantly higher in children with HSP than the controls. HDL and albumin levels were lower in the patients with HSP. Endocan levels were not significantly different between the HSP and control

groups ($p=0.884$). Serum endocan levels in patients with HSP were inversely correlated only with activated partial thromboplastin time (APTT) ($r=-0.485$, $p=0.012$).

Conclusion: Coagulation abnormalities and increased acute phase reactants were present in patients with HSP while no difference was determined in endocan levels.

Keywords: D-dimer; Endocan; Endothelial dysfunction; Inflammation; Henoch-Schönlein purpura.

Öz

Amaç: Henoch-Schönlein purpurası (HSP) jeneralize vas-külit ile karakterizedir. Hastalığın etiopatogenezi bilinmemekte olup inflamasyon ve endotel disfonksiyon sorumlu tutulmaktadır. Bu nedenle çalışmamızda HSP'li çocuklarda endotel hücre hasarı, inflamasyon ve pıhtılaşmayı belirten bazı biyobelirteçlerin serum düzeyleri araştırılmıştır.

Gereç ve Yöntem: Çalışmaya HSP'li 26 hasta ve kontrol grubu olarak 26 sağlıklı çocuk dahil edildi. Tüm olgularda rutin biyokimyasal testler ve inflamasyon, koagülasyon ve endotel hücre hasarını gösteren laboratuvar verileri analiz edildi.

Bulgular: HSP'li çocuklarda beyaz kan hücresi (WBC) sayısı, C-reaktif protein (CRP) düzeyi, eritrosit sedimentasyon hızı (ESH), nötrofil/lenfosit (NLR) oranı, trigliserit, immünoglobulin A (IgA) ve C₃ kontrol grubundan anlamlı olarak yüksek bulundu. HDL ve albümin düzeyleri ise HSP'li hastalarda daha düşüktü. Endocan düzeyleri açısından gruplar arasında anlamlı farklılık saptanmadı ($p=0.884$). Serum endocan düzeyleri sadece aktive parsiyel tromboplastin zamanı (APTT) ile ters korele bulundu ($r=-0.485$, $p=0.012$).

Sonuç: HSP'li çocuklarda koagülasyon anormallikleri ve artmış akut faz reaktanları gözlenirken, bir endotel disfonksiyon belirteci olan endocan düzeylerinde anlamlı farklılık saptanmadı.

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Anahtar Kelimeler: D-dimer; endoksan; endotel disfonksiyonu; inflamasyon; Henoch-Schönlein purpurası.

Introduction

Henoch-Schönlein purpura (HSP) is one of the most common vasculitic syndromes. The clinical manifestation is variable and characterized by non-thrombocytopenic cutaneous palpable purpura, joint manifestations, gastrointestinal (GI) findings, and hematuria/proteinuria [1]. The disease is usually self-limiting, but can rarely cause severe renal disease. Although HSP has been known for many years, the etiopathogenesis is not still clear. However, it has been proposed that vascular inflammation and endothelial dysfunction may play an important role in the pathogenesis [2–4].

HSP is an immune-mediated inflammatory disease. IgA deposition in vessel walls leads to endothelial cell damage and cytokines secretion [1]. The coagulation system and fibrinolysis are thus activated. Several studies have reported biochemical markers indicating endothelial cell damage or hemostatic parameters in HSP patients [5–10].

Endocan is excreted from vascular endothelial cells, renal distal tubule cells, and bronchi [11–13]. Endocan has recently been investigated in various pathological processes, such as cancer, infections and rheumatological diseases [11–15]. Tumor necrosis factor alpha (TNF- α) and vascular endothelial growth factor (VEGF) stimulate endocan expression and secretion from endothelial cells [13]. Increased levels of both have been observed in patients with HSP [10, 16]. We therefore presumed that endocan may be a vascular endothelium damage biomarker for HSP.

Our aim in this study was to investigate various inflammation and coagulation parameters and endocan as endothelial dysfunction markers in children with HSP and to compare these with healthy children. We also examined the relationship between endocan and clinical findings and laboratory tests in patients with HSP.

Materials and methods

Patient selection

This case-control study was performed in the pediatric clinic of our hospital between February, 2016, and January, 2017. The study included 26 patients (mean age 7.4 ± 3.3 years) with HSP and 26 healthy children (mean age 6.7 ± 2.8 years) as a control group. Diagnosis of HSP was

based on European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PRES) classification criteria for HSP [17]. HSP was diagnosed in patients with non-thrombocytopenic palpable purpura as mandatory criterion and in the presence of at least one of diffuse abdominal pain, any biopsy showing IgA deposition, joint findings or renal involvement. Patients' clinical characteristics (age, gender and clinical course) are summarized in Table 1.

Patients with other forms of systemic vasculitis, diabetes mellitus, hypertension, thyroid dysfunction, hematological disorders, known malignancy, infection, liver or kidney disease were not taken into the study. The control

Table 1: Demographic features and clinical findings in patients with HSP and control subjects.

Parameters	HSP (n = 26)		Controls (n = 26)		p-Value
	n	%	n	%	
Gender					
Male	14	53.8	16	61.5	0.575 ^a
Female	12	46.2	10	38.5	
	Median (min–max)		Median (min–max)		
Age					
Years		7 (2–17)		7 (2–13)	0.555 ^b
Season					
Spring	3	11.5			
Summer	7	26.9			
Fall	9	34.6			
Winter	7	26.9			
Clinical findings rash					
Absent	0	0.0			
Present	26	100.0			
Arthralgia/arthritis					
Absent	17	65.4			
Present	9	34.6			
GI manifestations					
Absent	5	19.2			
Abdominal pain					
Present	12	46.2			
GI bleeding					
Present	9	34.6			
Renal involvement					
Absent	20	76.9			
Present	6	23.1			
Other					
Present	2	7.7			
Treatment					
NSAID	20	76.9			
Steroid	11	42.3			

HSP, Henoch-Schönlein purpura; Min, minimum; Max, maximum; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug. ^a χ^2 test, ^bMann-Whitney U test.

group was selected from patients with no known acute or chronic disease attending our pediatric clinic for other reasons. The study was accordance with the Helsinki Declaration. It was approved by the local Ethics Committee (Approval No. 03/02/2016-328). All participants provided written informed consent.

Renal involvement was defined as the presence of any hematuria and/or proteinuria. Arthralgia or arthritis were determined as joint manifestations. GI manifestations were diffuse abdominal pain and/or GI bleeding, or a positive test for occult blood in faeces.

Biochemical analysis

Blood samples were collected (without stasis after morning fasting) from all participants and placed into tubes with gel, and tubes containing K2EDTA (Becton Dickinson, UK) on the first day of admission. Serum samples placed into tubes with gel were allowed to clot before centrifugation. Following centrifugation for 10 min at 1000 g, the serum was aliquoted and kept at -70°C until the day of study.

Complete blood count parameter analysis was performed using the Sysmex XE-2100 hematology system (TOA Medical Electronics, Kobe, Japan). The neutrophil/lymphocyte ratio (NLR) was calculated as a ratio between absolute neutrophil and absolute lymphocyte counts. Serum C-reactive protein (CRP) levels, immunoglobulin and complements (C3, C4) were measured using an immune turbidimetric method with an AU-2700 autoanalyzer (Beckman Coulter, USA). Other biochemical tests were determined using a spectrophotometric method with an AU-2700 autoanalyzer (Beckman Coulter, USA). Blood samples for coagulation tests were provided using 3.2% concentration citrate anticoagulant. Plasma was prepared shortly after blood collection by centrifugation at 1000 g for 10 min, and was then tested. Coagulation tests were measured by chromogenic assay using the ACL TOP 500 autoanalyzer (Beckman/Instrumentation Laboratory). Stool occult blood was assessed using the immunochromatographic rapid test (Standard Diagnostics Inc., South Korea). After centrifugation for 5 min at 600 g, urine samples were tested using a Urised II & Labumat II autoanalyzer (77 ElektronikaKft, Budapest, Hungary).

Human endocan measurements

Endocan concentrations were evaluated with the sandwich enzyme-linked immunosorbent assay (ELISA) method. The manufacturer's recommendations were properly

applied for tests. Evaluations were performed using a Bio-tek Synergy HT (BioTek Instrument Inc., Winooski, VT, USA) ELISA plate reader. The results were expressed as pg/mL. The reference range of serum endocan was 15.63 to 1000 pg/mL. The coefficients of variation were 10% and 12% for intra- and inter-assay precision, respectively. The lower limit of detection for endocan was 6.9 pg/mL.

Statistical analysis

Statistical analysis was carried out on SPSS 15.0 software. Numbers and percentages were used to express categorical variables, and mean and standard deviation or median (minimum–maximum) were used for numerical variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the normal distribution. The Mann-Whitney U test or Student t test were for comparisons between two groups, depending on the sample distribution. Comparisons between more than two groups were carried out using the Kruskal-Wallis test again depending on the sample distribution. Multivariate logistic regression analysis was performed to determine odds ratio at 95% confidence interval (CI). Categorical variables were compared using the χ^2 test. Monte Carlo simulation was performed in boundary conditions. Pearson and Spearman correlation analysis were used to evaluate relations between variables. $p < 0.05$ was regarded as the alpha (α) significance level.

Results

Patient characteristics

The mean age of the patients was 7.4 ± 3.3 years, and the mean age of the controls 6.7 ± 2.8 years. The difference was not statistically significant ($p = 0.555$). The HSP group consisted of 14 boys (53.8%) and 12 girls (46.2%), and the control group of 16 boys (61.5%) and 10 girls (38.5%). Sex distributions were similar between the groups ($p = 0.575$). Disease onset occurred in all seasons, but with the highest incidence being reported during the fall (34.6%). The second highest incidence was observed during summer and winter (26.9%) (Table 1).

Clinical manifestations

Of the children with HSP, rash was present in 26 (100%), arthralgia/arthritis in 9 (34.6%), abdominal pain and GI

bleeding in 9 (34.6%), abdominal pain only in 12 (46.2%), renal findings in 6 (23.1%). Twenty children were treated with non-steroidal anti-inflammatory drugs and 11 received steroids. Participants' clinical characteristics are presented in Table 1.

Laboratory tests

Following laboratory evaluation, significant mean erythrocyte sedimentation rate (ESR) ($p=0.030$), CRP ($p=0.001$), white blood cell (WBC) ($p=0.025$), NLR ($p=0.02$), D-dimer ($p<0.001$), triglyceride ($p=0.043$), globulin ($p=0.014$), IgA ($p=0.001$), and C_3 ($p<0.001$) value elevations were determined in the patients compared to the healthy controls. Mean HDL and albumin values were significantly

lower in the patients than in the healthy controls. Patients' mean endocan levels were 809.4 ± 430.4 pg/mL, and were similar to those of the control group (775.6 ± 374.1 pg/mL; $p=0.884$). Differences in other parameters between the groups were not significant. The results of these comparisons are given in Table 2.

The receiver operating characteristic (ROC) curves for biochemical parameters are shown in Figure 1. The areas under the curve of D-dimer, NLR, IgA and C_3 were 0.94, 0.74, 0.74 and 0.89, respectively. Our multivariate analysis, increased IgA, NLR, CRP, C_3 , D-dimer levels, and decreased albumin level were not related to HSP (Table 3). Serum endocan concentrations were inversely correlated with activated partial thromboplastin time (APTT) ($r=-0.485$, $p=0.012$), but did not correlate with other parameters.

Table 2: Comparison of laboratory parameters between patients and controls.

	Patients (n=26)	Controls (n=26)	p-Value
Endocan (pg/mL) median (min–max)	698 (118–1867)	717 (236–1722)	0.884 ^a
CRP (mg/L) mean $\pm$ SD	8.5 (0.0–34.2)	0.7 (0.1–19.3)	0.001
ESR (mm/h) mean $\pm$ SD	27 $\pm$ 13	20 $\pm$ 8	0.030
Leucocyte (/mm ³) median (min–max)	10,435 $\pm$ 3410	8430 $\pm$ 2745	0.025^a
Neutrophil/lymph, median (min–max)	1.88 (0.59–6.96)	1.01 (0.35–4.21)	0.002^a
HCT (%) mean $\pm$ SD	35.5 $\pm$ 2.7	36.8 $\pm$ 2.4	0.067
HB (g/L) mean $\pm$ SD	12.1 $\pm$ 1.1	12.6 $\pm$ 0.7	0.069
PLT (/mm ³) mean $\pm$ SD	344,384 $\pm$ 64,670	307,961 $\pm$ 82,944	0.084
MPV (fL) mean $\pm$ SD	9.6 $\pm$ 0.8	10.0 $\pm$ 0.9	0.121
PDW (%) mean $\pm$ SD	10.9 $\pm$ 1.6	11.8 $\pm$ 1.7	0.076
PTT (s) mean $\pm$ SD	11.8 $\pm$ 1.0	11.7 $\pm$ 0.7	0.837
INR (s) mean $\pm$ SD	0.98 $\pm$ 0.08	0.99 $\pm$ 0.06	0.790
APTT (s) mean $\pm$ SD	25.1 $\pm$ 3.3	26.3 $\pm$ 2.8	0.150
Fibrinogen (mg/dL) mean $\pm$ SD	329 $\pm$ 68	307 $\pm$ 69	0.258
D-dimer (ng/mL) median (min–max)	1540 (324–6960)	280 (92–635)	<0.001^a
Urea (mg/dL) median (min–max)	24 (12–47)	21 (11–37)	0.134 ^a
Creatinine (mg/dL) mean $\pm$ SD	0.38 $\pm$ 0.12	0.44 $\pm$ 0.17	0.336
Cholesterol (mg/dL) mean $\pm$ SD	150 $\pm$ 23	159 $\pm$ 30	0.282
Triglyceride (mg/dL) median (min–max)	94 (37–413)	71 (36–173)	0.043^a
LDL (mg/dL) mean $\pm$ SD	84 $\pm$ 18	89 $\pm$ 24	0.377
HDL (mg/dL) mean $\pm$ SD	44 $\pm$ 9	53 $\pm$ 13	0.008
Albumin (g/dL) mean $\pm$ SD	3.97 $\pm$ 0.33	4.41 $\pm$ 0.31	<0.001
Globulin (g/dL) mean $\pm$ SD	2.94 $\pm$ 0.43	2.64 $\pm$ 0.42	0.014
IgG (mg/dL) median (min–max)	1002 (545–1859)	943 (431–1564)	0.142 ^a
IgE (IU/mL) median (min–max)	64 (7–1133)	65 (4–862)	0.585 ^a
IgM (mg/dL) median (min–max)	89 (40–176)	109 (52–249)	0.407 ^a
IgA (mg/dL) mean $\pm$ SD	169 $\pm$ 59	112 $\pm$ 50	0.001
C_3 (mg/dL) mean $\pm$ SD	148 $\pm$ 15	123 $\pm$ 15	<0.001
C_4 (mg/dL) median (min–max)	31 (8–234)	29 (10–44)	0.095 ^a

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HCT, hematocrit; HB, hemoglobin; PLT, platelet; MPV, mean platelet volume; PDW, platelet distribution width; PTT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Ig, Immunoglobulin; C, complement. All variables are showed as mean $\pm$ SD (Standard Deviation) or median (minimum–maximum) for continuous data with or without a normal distribution, respectively. ^aMann-Whitney U test. All other Student t test. Bold values indicate statistical significance at the $p<0.05$ level.

Area under the curve

Test result variable(s)	Area	SE	p-Value	95% Confidence interval	
Endocan	0.550	0.084	0.556	0.384	0.715
Fibrinogen	0.616	0.084	0.170	0.451	0.781
D-dimer	0.944	0.030	<0.001	0.886	1.003
Neutrophil/lymphocyte	0.743	0.072	0.004	0.602	0.884
IgG	0.603	0.084	0.219	0.440	0.767
IgE	0.529	0.085	0.733	0.363	0.695
IgM	0.432	0.085	0.421	0.265	0.599
IgA	0.746	0.073	0.003	0.604	0.888
C3	0.895	0.044	<0.001	0.809	0.981
C4	0.681	0.078	0.032	0.528	0.834

Figure 1: Receiver–operating characteristic (ROC) curve of the RDW for predicting HSP Henoch-Schonlein purpura. Areas under the curve of D-dimer, NLR, IgA and C3 are indicated by bold values.

Table 3: Logistic regression analysis of some biomarkers.

Risk factor	p-Value	OR	95% CI
IgA increase	0.422	1.097	0.875–1.375
NLR increase	0.364	56.539	0.009–341257.247
CRP increase	0.517	1.167	0.731–1.863
C3 increase	0.583	0.925	0.702–1.220
D dimer increase	0.393	1.041	0.950–1.141
Albumin decrease	0.544	0.045	0.000–990.097

CI, Confidence interval; CRP, C-reactive protein; NLR, neutrophil/lymphocyte rate; OR, odds ratio.

No relation was determined between endocan and clinical findings in patients with HSP (Table 4).

Discussion

HSP is a small vessel vasculitis drew on by IgA-immune deposits, complement proteins and neutrophil infiltration

Table 4: Relationships between endocan and clinical findings in patients.

	n	Endocan (pg/mL)	p-Value
Gender			
Male	14	959 ± 491	0.046
Female	12	634 ± 271	
Season			
Spring	3	814 ± 206	0.733 ^a
Summer	7	810 ± 616	
Autumn	9	709 ± 265	
Winter	7	934 ± 500	
Clinical findings rash			
Present	26	807 ± 405	
Arthralgia/arthritis			
Absent	17	813 ± 500	0.975
Present	9	690 ± 518	
Abdominal pain			
Absent	5	812 ± 445	0.649 ^a
Abdominal pain without GI bleeding			
Present	12	856 ± 412	
Abdominal pain with GI bleeding			
Present	9	752 ± 368	
Renal			
Absent	20	1000 ± 595	0.223
Present	6	765 ± 409	
Treatment NSAİ			
Absent	6	629 ± 380	0.251
Present	20	863 ± 438	
Steroid			
Absent	15	738 ± 362	0.339
Present	11	905 ± 511	
Urine analysis			
Normal	20	753 ± 339	0.710
>5 Erythrocyte hematuria			
Present	6	808 ± 525	
Fetal occult blood			
Negative	17	807 ± 436	0.979
Positive	9	812 ± 445	

GI, Gastrointestinal; NSAİD, nonsteroidal anti-inflammatory drug. All variables are showed as mean ± SD. ^aKruskal-Wallis test – all other Student t test. Bold value indicate statistical significance at the p < 0.05 level.

[2]. IgA is the most important component of the immune deposits in HSP. IgA is able to activate complements by inducing the alternative complement pathways and mannan-binding lectin. It is also capable of binding to some receptors, the most important of which is FcαRI, which is capable of inducing pro-inflammatory reactions such as phagocytosis, neutrophil migration, formation of reactive oxygen species (ROS), cytokine secretion and the release of neutrophil extracellular traps [2]. Proinflammatory factors, such as TNF-α, interleukin-1, interleukin-6, transforming growth factor (TGF)-b, VEGF, and

chemokines are secreted as a result of inflammation and endothelial cell damage in HSP [8, 10, 16, 18].

Studies have shown high D-dimer levels in patients with HSP [5, 9]. Hyperfibrinolysis secondary to endothelial damage has also been reported in patients with HSP [10]. Activation of inflammation causes the coagulation system to be activated. There are two suppositions on this subject; the one of them is that the circulating immune complexes act on the endothelial cells, and plasminogen proactivators are secreted. The other supposition is that proteolytic enzymes are secreted from inflammatory tissue cells, and these increase D-dimers [5, 19].

This study measured various biomarkers in patients with HSP and healthy controls – inflammatory factors as CRP, ESR, WBC, NLR, albumin and globulin, immunological markers including IgA, IgM, IgE and IgG, vascular permeability-related biomarkers such as C3 and C4, coagulation parameters including platelets, MPV, PDW, PT, APTT, D-dimer and fibrinogen, and endothelial dysfunction markers such as endocan and lipid profiles, and also performed other routine tests such as urea and Hb. CRP, ESR, WBC, NLR, globulin, C3 and IgA values were significantly higher, while albumin values were lower in patients with HSP than in the controls. CRP, ESR and WBC are non-specific markers of inflammatory activity. Previous studies have reported high levels of inflammatory parameters in patients with HSP [7, 20–22]. The NLR is a useful marker in inflammatory diseases. Various studies have reported that high blood NLR is associated with HSP [23–25]. Lymphocyte apoptosis lead to decreased lymphocytes and increased NLR in inflammation [25]. NLR may be useful in predicting organ involvement in HSP [23, 24]. However, contradictory have been reported on the role of the NLR in HSP [25]. Further investigations are therefore needed to assess its true value.

We also observed a significant increase in serum levels of D-dimer in HSP patients. However, platelets, PT and aPTT, standard coagulation tests, were within reference ranges. These results suggest that activated coagulation is secondary to the endothelial inflammation stimulated by IgA immune deposits in patients with HSP [10]. Wang et al. [19] reported raised D-dimer level as a risk factor for renal damage in patients with HSP. Our multivariate logistic regression analysis did not showed an association between raised D-dimer level and HSP. However, our patient group included all HSP patients with and without renal involvement. The number of patients with renal involvement was low and no multivariate logistic regression analysis could be performed in this group.

Recent studies have showed that IgA autoantibodies, which are cross-reactive with endothelial cells, are present in patients with HSP [7]. Only a few studies to date

have investigated parameters that may show endothelial cell damage [3, 6, 10, 26]. These studies have frequently investigated Factor XIII and von Willebrand factor as markers of endothelial damage [3]. One previous study reported high von Willebrand antigen and low Factor XIII levels in patients with HSP [3, 6]. Söylemezoglu et al. [6] reported significantly increased von Willebrand factor during the acute phase of HSP and that this correlated well with CRP in the active phase, suggesting that this maybe a good indicator of vascular inflammation and endothelial damage.

The present study investigated endocan, a marker of epithelial cell damage, in patients with HSP. Endocan is associated with endothelial dysfunction [13]. Interaction between endocan and adhesion molecules causes transport of leukocytes to regions of inflammation and subsequent endothelial dysfunction [14]. High levels of endocan have been showed in the rheumatological diseases, including Behçet's disease, systemic lupus, and systemic sclerosis [13–15]. Balta et al. [13] observed significantly higher serum endocan levels in patients with Behçet's disease. CRP, ESR and disease activity correlated positively with endocan in these patients [13].

In our study, endocan levels were similar in the patients with HSP and the controls. We observed no correlation between endocan and other laboratory parameters. However, positive correlation was determined between APTT and endocan. No relation was determined between endocan and clinical findings.

HDL-C levels in our study were lower in patients with HSP than in the control group, but no correlation was determined with endocan. HDL exhibits anti-inflammatory, antithrombotic, and antioxidant effects. It also protects against atherosclerosis and endothelial dysfunction [14].

There are some limitations of our study. First, it is the small sample size. This may explain why no difference was determined between endocan levels in the two groups. Second, most of the HSP patients in our study were mild cases. Lastly, Factor XIII and von Willebrand Factor could not be determined due to our financial limitations.

In conclusion, endocan may be a useful predictor of endothelial dysfunction in patients with HSP. However, our results do not provide supportive evidence for an association between endocan and HSP. To the best of our knowledge, this is the first study to investigate endocan in children with HSP. Further studies of endocan involving a larger sample population are now needed. This will help clarify the possible role of endocan in the pathogenesis of HSP.

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Conflict of interest: The authors have no conflict of interest.

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