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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

The Relationship Between Serum IL-6 Level and Mean Platelet Volume with the Disease Severity in Pediatric Patients with Henoch Schönlein Purpura

Henoch Schönlein Purpuralı Pediatrik Hastalarda Serum IL-6 Düzeyi ve Ortalama Trombosit Hacmi ile Hastalık Şiddeti Arasındaki İlişkisi

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Abstract

Objectives: Henoch-Schönlein purpura (HSP) which is the most common childhood vasculitis, causes mortality that is generally related with severe renal and gastrointestinal symptoms. The present study aimed to investigate the relationship between serum interleukin (IL)-6 and mean platelet volume (MPV) levels and disease severity in pediatric patients.

Materials and Methods: HSP was diagnosed based on the EULAR/PRINTO/PRES criteria. Age, gender, season of disease onset, and the presence and type of infection before the attack were recorded. Systemic involvement for each patient was evaluated from the medical history, physical examination, and laboratory tests.

Results: A total of 85 patients between 2-17 years of age (median age: 8 years) were included in the study. All patients had the typical purpuric rash, with 71.8%, 74.1%, and 31.8% displaying joint, gastrointestinal system (GIS), and renal involvement, respectively. IL-6 levels were increased in 61.1%, 55.6%, and 63.3% of patients with renal, GIS, and joint involvement, respectively. MPV levels were decreased in 40.7%, 49.2%, and 49.2% of patients with renal, GIS, and joint involvement, respectively. IL-6 and MPV levels were not significantly different (p>0.05) between patients with and without renal, joint, or gastrointestinal involvement.

Conclusion: There was no prognostic relationship between MPV or serum IL-6 levels at the initial diagnosis and GIS or renal involvement in HSP. Further studies are needed to determine the relationship between inflammatory cytokines and HSP.

Key Words: Henoch-Schönlein Purpura, Interleukin-6, Mean Platelet Volume

Öz

Amaç: Çocukluk çağı vaskülitlerinin en sık görüleni olan Henoch-Schönlein purpurası (HSP), genellikle şiddetli böbrek ve gastrointestinal semptomlarla ilişkili mortaliteye neden olur. Bu çalışmada, pediatrik hastalarda serum interlökin (IL)-6 ve ortalama trombosit hacmi (MPV) düzeyleri ile hastalık şiddeti arasındaki ilişkinin araştırılmaktadır.

Gereç ve Yöntem: EULAR/PRINTO/PRES kriterlerine göre HSP tanısı konuldu. Hastaların yaş, cinsiyet, hastalığın başladığı mevsim ve önceki enfeksiyon varlığı ve türü kaydedildi. Her hasta için sistemik tutulum tıbbi hikaye, fizik muayene ve laboratuvar testleri değerlendirildi.

Bulgular: Çalışmaya 2-17 yaş arasında (ortanca yaş: 8 yıl) 85 hasta dahil edildi. Tüm hastalarda tipik purpurik döküntü vardı. Eklem tutulumu %71,8, gastrointestinal sistem (GİS) tutulumu %74,1 ve renal tutulum %31,8 oranında tespit edildi. Renal, GİS ve eklem tutulumu olan hastaların sırasıyla %61,1, %55,6 ve %63,3'ünde IL-6 seviyeleri yükselmiştir. Böbrek, GİS ve eklem tutulumu olan hastaların sırasıyla %40,7'sinde, %49,2'sinde ve %49,22sinde MPV seviyeleri düşmüştür. IL-6 ve MPV düzeyleri böbrek, eklem veya gastrointestinal tutulumu olan ve olmayan hastalar arasında anlamlı farklılık göstermedi (p>0,05).

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Sonuç: HSP'de başlangıç tanısında MPV veya serum IL-6 seviyeleri ile GİS veya böbrek tutulumu arasında prognostik ilişki yoktu. Enflamatuvar sitokinler ve HSP arasındaki ilişkiyi belirlemek için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Henoch-Schönlein Purpurası, Interlökin-6, Ortalama Trombosit Hacmi

Introduction

Henoch-Schönlein purpura (HSP) is a systemic small-vessel vasculitis characterized by purpuric rash, arthritis, nephritis, and gastrointestinal symptoms. It is the most common cause of non-thrombocytopenic purpura in childhood, with a community incidence of approximately 13.5-18/100,000 (1,2). HSP is reported to be triggered by infectious agents (e.g., beta-hemolytic streptococci), drugs, food, and insect bites (1,3-6). The most common, prominent sign is non-thrombocytopenic palpable purpura, particularly on the lower extremities. Severe early gastrointestinal system (GIS) and late renal system involvement are the primary factors contributing to the mortality and morbidity of HSP (7).

Although the exact etiopathogenesis of HSP is still unclear, research has focused on the potential roles of tumor necrosis factor (TNF), free oxygen radicals, leukotrienes, prostanoids, vascular cell adhesion molecules, and the C5b-9 terminal complement complex. The complement system is known to be activated by various antigenic stimuli. Activated neutrophils release free oxygen radicals and proteinases, which damage the vascular wall and tissues. Studies have shown that proinflammatory cytokines also play a role in activating the complement system. Increased levels of TNF-α and interleukin (IL)-6 have been observed in children during the acute phase of HSP as compared to healthy controls (2,8-10). This study aimed to investigate whether IL-6 and mean platelet volume (MPV) levels were associated with GIS and renal system involvement in HSP patients.

Materials and Methods

This retrospektif cohort study was performed on HSP patients under 18 years of age at Ankara Child Health and Diseases Hematology and Oncology Training and Research Hospital in Turkey and approved by the local ethical committee, performed according to the Declaration of Helsinki and Good Clinical Practice guidelines Declaration of Helsinki and Good Clinical Practice guidelines (13.3.2011-2011/51). We obtained written informed consent from all participants. The HSP diagnosis was based on the EULAR/PRINTO/PRES criteria (11).

Data Collection and Analysis

Patient clinical and demographic data were collected, including age, sex, the season of disease onset, and the presence and type of infection before the attack. Systemic involvement in each patient was evaluated from the medical history, physical examination, and laboratory tests. Normal MPV, CRP, and IL-6 levels were designated as 6.9-10 fL, 0-1.8 mg/dL, and <5.4 pg/mL, respectively. IL-6 levels were measured via immunoluminometric assay.

HSP nephritis patients were classified by the initial clinical presentation into five grades using a modified Meadow classification: grade 1, microscopic hematuria; grade 2, persistent mild proteinuria (<20 mg/m^2/h) and/or hematuria; grade 3, nephritic syndrome (hematuria, low glomerular filtration rate, oliguria, hypertension, edema); grade 4, nephrotic syndrome (proteinuria >40 mg/m^2/h, hypoalbuminemia, hyperlipidemia, edema); and grade 5, mixed nephritic-nephrotic syndrome. Indications for renal biopsy were persistent proteinuria, persistent hematuria, nephrotic or nephritic syndrome, or hematuria with renal failure (12). Renal biopsies were graded in increasing severity from I to V according to the International Study of Kidney Disease in Children classification system (13).

Statistical Analysis

We compared the data of the patient groups regarding their demographic, clinical characteristics and outcomes. All statistical analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to summarize the participants' baseline characteristics, including medians, and interquartile ranges for continuous variables and frequency distributions for categorical variables. P-values were calculated using the chi-square or Fisher's exact tests for categorical variables and the Student's t-test or Mann-Whitney U tests for continuous variables according to the normality assumption to evaluate the relationship between urinary protein content and serum factor and renal impairment in HSP patients. A p-value of <0.05 was regarded as indicative of statistical significance.

Results

A total of 85 patients between 2-17 years of age (median age: 8 years) were included in the study, of which 46 (54.1%) were male and 39 (45.9%) were female (Table 1). All patients had the typical purpuric rash, with 5 (5.8%) showing scalp edema and 61 (71.8%), 63 (74.1%), and 27 (31.8%) displaying joint, GIS, and renal involvement, respectively (Table 1). Of the 27 patients with HSP nephritis, 7 (25.9%) were grade 1, 14 (51.8%) were grade 2, and 6 (22.2 %) were grade 4 according to the modified Meadow's criteria. The six children assigned as grade 4 underwent renal biopsy, which classified 5 (83.3%) of them as grade 2 and confirmed 1 (16.6 %) as grade 4.

C-reactive protein (CRP) and IL-6 levels were increased in 34 (40%) and 38 (53.5%) of the patients, respectively, while 40 (47.1%) patients had decreased MPV. At the time of diagnosis, when leucocyte count and serum IL-6, CRP, and MPV levels were evaluated, only the serum leukocyte count and CRP level were positively correlated (r=0.223; p=0.03). Urinary protein content did not correlate (p>0.05) with leucocyte count or serum IL-6, CRP, and MPV levels. Although patients with and without joint involvement showed significant differences in the rate of leukocytosis (p=0.01) and CRP levels (p=0.02), these parameters did not significantly differ (p=0.05) for patients with or without renal or GIS involvement.

The median (minimum-maximum) IL-6 levels in patients with renal, GIS, or joint involvement were 5.6 pg/mL (0-30 pg/mL), 5.7 pg/mL (0-45 pg/mL), and 6.8 pg/mL (0-45 pg/mL), respectively. Patients without renal, GIS, or joint involvement had IL-6 levels of 6.5 pg/mL (0-45 pg/mL), 4 pg/mL (0-16.8 pg/mL), and 1 pg/mL (0-39 pg/mL), respectively. The median (minimum-maximum) MPV levels in patients with renal, GIS, or joint involvement were 7.4 fL (5.4-9.1 fL), 6.9 fL (5.3-9.3 fL), and 6.9 fL (5.3-10 fL), respectively. Patients without renal, GIS, or joint involvement had MPV levels of 6.8 fL (5.3-10 fL), 7.2 fL (5.4-10 fL), and 7 fL (5.9-9 fL), respectively (Figure 1). IL-6 and MPV levels did not significantly differ (p>0.05) between

Table 1: Demographic and clinical data of patients with Henoch Schönlein purpura

	Total patients (n=85)	Patients with renal involvement (n=27)	Patients without renal involvement (n=58)	p-value
Age (years) (median, min-max)	8 (2-17)	9 (2-18)	8 (2-17)	0.21
Sex, male/female	46/39	17/10	29/29	0.26
Seasonal pattern (%)				
Spring	21 (24.7)	7 (25.9)	14 (24.1)	
Winter	23 (27.1)	8 (29.6)	15 (25.9)	0.94
Autumn	29 (34.1)	9 (33.3)	20 (34.5)	
Summer	12 (14.1)	3 (11.1)	9 (15.5)	
Possible etiological factors (n, %)				
Respiratory tract infections	51 (64)	15 (55.6)	36 (62)	0.70
Acute gastroenteritis	3 (3.5)	2 (7.4)	1 (1.7)	NA
Drug usage	2 (2.3)	0	2 (3.4)	NA
Urinary tract infection	2 (2.3)	2 (7.4)	0	NA
Epstein-Barr virus infection	1 (1.1)	1 (3.7)	0	NA
No factor	26 (30.5)	7 (25.9)	19 (32.7)	0.52
Clinical features (n, %)				
Cutaneus lesions	85 (100)	27 (100)	58 (100)	NA
Palpable pupura	85 (100)	27 (100)	58 (100)	NA
Scalp edema	5 (5.8)	1 (3.7)	4 (6.9)	0.81
Gastrointestinal involvement	63 (74.1)	21 (77.8)	42 (72.4)	0.59
Abdominal pain	63 (74.1)	21 (77.8)	42 (72.4)	0.59
Melena/positive stool guaiac test	25 (29.4)	7 (25.9)	18 (31)	0.09
Joint involvement	61 (71.8)	19 (70.4)	42 (72.4)	0.84
Laboratory findings (median, min-max)				
IL-6 (pg/mL)	**5.6 (0-45)**	**5.6 (0-30)**	**6.5 (0-45)**	**0.88**
WBC (10^3/µL)	11 (5-21.7)	10.8 (7-20)	11.4 (5-21.7)	0.74
Platelet (10^3/µL)	346 (112-899)	333 (156-654)	363 (112-899)	0.37
Mean platelet volume (fL)	**6.9 (5.3-10)**	**7.4 (5.4-9.1)**	**6.8 (5.3-10)**	**0.55**
Hemoglobin (g/dL)	13 (7.7-17.1)	12.8 (8.3-17.1)	13.1 (7.7-16.6)	0.08
Sedimentation (mm/h)	28 (0-13)	35 (0-99)	28 (8-133)	0.40
C-reactive protein (mg/dL)	1.2 (0-21)	0.9 (2-12)	1.5 (0-21)	0.22
Urea (mg/dL)	23 (9.6-146)	24 (9.6-146)	23 (13-42)	0.21
Creatinin (mg/dL)	0.3 (0.2-0.9)	0.4 (0.2-0.9)	0.3 (0.2-0.9)	0.10

IL-6: Interleukin-6, WBC: White blood cell, min: Minimum, max: Maximum, NA: Not applicable

patients with and without renal, GIS, or joint involvement (Table 2). Furthermore, these levels were not significantly different (p>0.05) when considering the grade of renal involvement (Table 3).

Of the 85 patients, 11 (12.9%) received supportive care, 33 (38.8%) received non-steroidal anti-inflammatory drugs (NSAIDs), 30 (35.8%) were treated with steroids, and 8 (9.4%) received both steroids and NSAIDs. One patient with severe renal involvement was treated with pulse steroid and pulse cyclophosphamide. The two remaining patients had severe GIS involvement and were treated with pulse steroid and plasmapheresis or with pulse steroid, pulse cyclophosphamide, and plasmapheresis.

Discussion

HSP is an acute, systemic vasculitis of unknown etiology, although several studies have implicated cytokines in its pathogenesis (14-16). The role of IL-6 in HSP renal, GI, and joint involvement has been of particular interest (17-21). IL-6 which is a cytokine important for inducing the fever response, stimulates the production of acute-phase proteins and induces leukocytosis, fever, and angiogenesis, can be released from vascular endothelial cells to initiate and propagate the inflammatory response. Once the inflammatory mechanisms are activated, IL-6 facilitates autoimmune phenomena and amplifies acute inflammation (22). Besbas et al. (17) reported a significant increase in TNF, IL-6, and IL-1 levels in HSP-patient skin specimens. Serum IL-6 levels were also found to be significantly higher during the acute stage of HSP and lower in patients with glomerulonephritis or gastrointestinal hemorrhage (23). Interestingly, Rostoker et al. (20) observed that the serum IL-6 levels of HSP patients did not correlate with proteinuria. In our study, IL-6 levels were increased in 53.5% of the HSP patients; however, there was no significant prognostic relationship between the serum IL-6 level at the initial diagnosis and GIS or renal involvement. These findings may reflect differences between serum and local tissue concentrations of IL-6. Serum concentration is likely not representative of cytokine production rate or local tissue concentration. Moreover, serum cytokine levels are influenced by a variety of interactions involving cytokines, their specific receptors, the soluble receptor fraction, and antagonists (18,24,25).

HSP is characterized by inflammation of small blood vessels via leukocytic infiltration of tissue, hemorrhage, and ischemia. Platelet activation plays a major role in the pathophysiology of diseases presenting with thrombosis and inflammation (26). Platelet volume is known to be correlated with platelet activation and function, with smaller platelets displaying decreased functional capabilities (27,28). Although there are limited studies investigating the role of MPV in HSP etiopathogenesis, decreased MPV levels have been suggested to be involved in HSP-related inflammation (29). Makay et al. (30) reported that low MPV levels could contribute to gastrointestinal bleeding in HSP. MPV has also been suggested to be a useful marker for identifying active disease in HSP patients (31). However, other studies did not observe similar dependencies, and findings concerning the importance of MPV in other inflammatory diseases are conflicting (10,32). Our study found no relationship between decreased MPV levels and GIS or renal involvement in HSP patients.

Study Limitations

Several limitations affect the generalizability of our findings. As the study was performed in a single center, the number of participants was limited. Additionally, there was no healthy control group. Finally, we were unable to evaluate IL-6 levels in

Table 2: IL-6 levels (pg/mL) and MPV (fL) in groups with or without system involvement

	Renal involvement			GIS involvement			Joint involvement		
	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
IL-6 (pg/mL) median (min-max)	5.6 (0-30)	5.6 (0-45)	0.88	5.7 (0-45)	4 (0-16.8)	0.33	6.8 (0-45)	1 (0-39)	0.27
MPV (fL) median (min-max)	7.4 (5.4-9.1)	6.8 (5.3-10)	0.55	6.9 (5.3-9.3)	7.2 (5.4-10)	0.21	6.9 (5.3-10)	7 (5.9-9)	0.50

IL-6: Interleukin-6, MPV: Mean platelet volume, GIS: Gastrointestinal system

Table 3: IL-6 levels (pg/mL) and MPV (fL) in groups according to the grade of renal involvement

	Patients without renal involvement (n=58)	Grade 1 renal involvement (n=7)	Grade 2 renal involvement (n=14)	Grade 4 renal involvement (n=6)	p-value
Laboratory findings (median, min-max)					
IL-6 (pg/mL)	6.5 (0-45)	5.7 (2.4-30)	3.9 (0-12)	6 (4.5-7.6)	0.83
Mean platelet volume (fL)	6.8 (5.3-10)	7.7 (6.8-9.1)	6.8 (5.4-8,1)	7 (5.4-8.3)	0.09

IL-6: Interleukin-6, MPV: Mean platelet volume, min: Minimum, max: Maximum

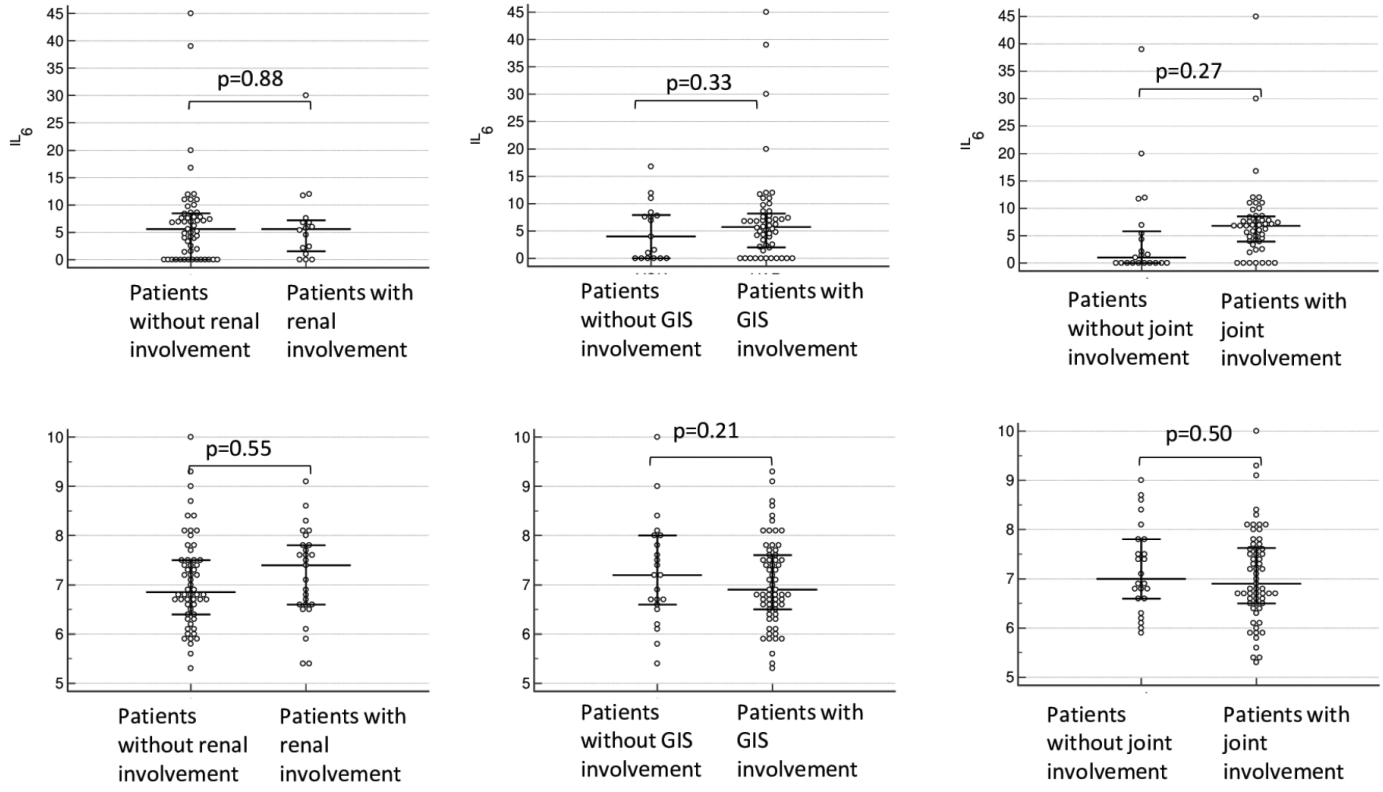

Figure 1: IL-6 levels (pg/mL) and MPV (fL) in groups according to system involvement. There was no statistically significant difference between groups (p>0.05).

IL-6: Interleukin-6, MPV: Mean platelet volume, GIS: Gastrointestinal system

sequential blood samples during the follow-up period and upon completion of the treatment.

Conclusion

In conclusion, this study found no prognostic relationship between MPV or serum IL-6 levels at the initial diagnosis and GIS or renal involvement in HSP. Due to the possibility of differences between serum and local tissue concentrations of IL-6, physicians should take account the clinical status of patients than laboratory results.

Ethics

Ethics Committee Approval: Ankara Child Health and Diseases Hematology and Oncology Training and Research Hospital in Turkey and approved by the local ethical committee, performed according to the Declaration of Helsinki and Good Clinical Practice guidelines Declaration of Helsinki and Good Clinical Practice guidelines (2011/51, 3.03.2011).

Informed Consent: We obtained written informed consent from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., Design: K.A., N.Ç., Data Collection or Processing: K.A., Analysis or Interpretation: K.A., N.Ç., Literature Search: K.A., N.Ç., Writing: K.A., N.Ç.

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References

1. Kraft DM, Mckee D, Scott C. Henoch-Schönlein purpura: a review. Am Fam Physician. 1998;58:405-411.
2. Dillon MJ. Henoch-Schönlein purpura (treatment and outcome). Cleve Clin J Med. 2002;69 Suppl 2:SII121-SII123.
3. Trapani S, Micheli A, Grisolia F, et al. Henoch Schonlein purpura in childhood: epidemiological and clinical analysis of 150 cases over a 5-year period and review of literature. Semin Arthritis Rheum. 2005;35:143-153.
4. Yano S. Henoch-Schönlein purpura associated with pulmonary Mycobacterium avium-intracellulare complex. Intern Med. 2004;43:843-845.
5. Pimentel MI, Vasconcellos Ede C, Cerbino-Neto J. Henoch-Schönlein purpura following influenza A H1N1 vaccination. Rev Soc Bras Med Trop. 2011;44:531.

6. Inal A, Yılmaz M, Kendirli SG, et al. Henoch-Schönlein purpurası tanısı alan çocukların klinik özellikleri. Erciyes Tıp Dergisi. 2009;31:153-161.
7. Arslan Ş, Saatçi Ü. Henoch-Schönlein Purpurası. Katkı Pediatri Dergisi. 1995;2:165-174.
8. Ralli M, Campo F, Angeletti D, et al. Pathophysiology and therapy of systemic vasculitides. EXCLI J. 2020;19:817-854.
9. Topaloglu R, Sungur A, Baskin E, et al. Vascular endothelial growth factor in Henoch-Schonlein purpura. J Rheumatol. 2001;28:2269-2273.
10. Jaszczura M, Góra A, Grzywna-Rozenek E, et al. Analysis of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio and mean platelet volume to platelet count ratio in children with acute stage of immunoglobulin A vasculitis and assessment of their suitability for predicting the course of the disease. Rheumatol Int. 2019;39:869-878.
11. Ozen S, Pistorio A, Iusan SM, et al. EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis. 2010;69:798-806.
12. Meadow SR, Glasgow EF, White RH, et al. Schönlein-Henoch nephritis. Q J Med. 1972;41:241-258.
13. Counahan R, Winterborn MH, White RH, et al. Prognosis of Henoch-Schönlein nephritis in children. Br Med J. 1977;2:11-14.
14. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. Nat Clin Pract Rheumatol. 2006;2:619-626.
15. Mahajan N, Kapoor D, Bisht D, et al. Levels of interleukin-18 and endothelin-1 in children with Henoch-Schönlein purpura: a study from northern India. Pediatr Dermatol. 2013;30:695-699.
16. Sun DQ, Zhang QY, Dong ZY, et al. [Levels of IL-12 produced by dendritic cells and changes of TH1/TH2 balance in children with Henoch-Schonlein purpura]. Zhongguo Dang Dai Er Ke Za Zhi. 2006;8:307-310.
17. Besbas N, Saatci U, Ruacan S, et al. The role of cytokines in Henoch Schonlein purpura. Scand J Rheumatol. 1997;26:456-460.
18. Yuan L, Wang Q, Zhang S, et al. Correlation between serum inflammatory factors TNF-α, IL-8, IL-10 and Henoch-Schonlein purpura with renal function impairment. Exp Ther Med. 2018;15:3924-3928.
19. Del Vecchio GC, Penza R, Altomare M, et al. Cytokine pattern and endothelium damage markers in Henoch-Schönlein purpura. Immunopharmacol Immunotoxicol. 2008;30:623-629.
20. Rostoker G, Rymer JC, Bagnard G, et al. Imbalances in serum proinflammatory cytokines and their soluble receptors: a putative role in the progression of idiopathic IgA nephropathy (IgAN) and Henoch-Schönlein purpura nephritis, and a potential target of immunoglobulin therapy? Clin Exp Immunol. 1998;114:468-476.
21. Amoli MM, Thomson W, Hajeer AH, et al. Interleukin 1 receptor antagonist gene polymorphism is associated with severe renal involvement and renal sequelae in Henoch-Schönlein purpura. J Rheumatol. 2002;29:1404-1407.
22. Amoli MM, Thomson W, Hajeer AH, et al. Interleukin 8 gene polymorphism is associated with increased risk of nephritis in cutaneous vasculitis. J Rheumatol. 2002;29:2367-2370.
23. Lin CY, Yang YH, Lee CC, et al. Thrombopoietin and interleukin-6 levels in Henoch-Schönlein purpura. J Microbiol Immunol Infect. 2006;39:476-482.
24. Sayinalp N, Ozcebe OI, Ozdemir O, et al. Cytokines in Behçet's disease. J Rheumatol. 1996;23:321-322.
25. Gehr G, Braun T, Lesslauer W. Cytokines, receptors, and inhibitors. Clin Investig. 1992;70:64-69.
26. Gasparyan AY, Ayvazyan L, Mikhailidis DP, et al. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17:47-58.
27. Martin JF, Trowbridge EA, Salmon G, et al. The biological significance of platelet volume: its relationship to bleeding time, platelet thromboxane B2 production and megakaryocyte nuclear DNA concentration. Thromb Res. 1983;32:443-460.
28. Thompson CB, Eaton KA, Princiotta SM, et al. Size dependent platelet subpopulations: relationship of platelet volume to ultrastructure, enzymatic activity, and function. Br J Haematol. 1982;50:509-519.
29. Varol E. Mean platelet volume and neutrophil-to-lymphocyte ratio in patients with Henoch-Schonlein purpura. Rheumatol Int. 2014;34:1329-1330.
30. Makay B, Türkyilmaz Z, Duman M, et al. Mean platelet volume in Henoch-Schönlein purpura: relationship to gastrointestinal bleeding. Clin Rheumatol. 2009;28:1225-1228.
31. Shi X, Li WC, Mo LJ, et al. Altered mean platelet volume in children with Henoch-Schonlein purpura and its association with disease activity. Ann Clin Biochem. 2018;55:368-372.
32. Ekinci RMK, Balci S, Sari Gokay S, et al. Do practical laboratory indices predict the outcomes of children with Henoch-Schönlein purpura? Postgrad Med. 2019;131:295-298.