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Are Mean Platelet Volume and Neutrophil-to-Lymphocyte Ratio Valuable in The Early Detection of System Involvements in Henoch-Schönlein Purpura?

Ortalama Trombosit Hacmi ve Nötrofil-Lenfosit Oranı Henoch-Schönlein Purpurası'nda Sistem Tutulumlarının Erken Saptanmasında Değerli mi?

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Abstract

Aim: Henoch-Schönlein purpura (HSP) is the most common type of vasculitis in childhood, and severe complications due to intestinal and renal involvement can be observed. In this study, it was planned to investigate the value of mean platelet volume (MPV) and neutrophil-to-lymphocyte ratio (NLR) in early detection of system involvement in HSP.

Methods: A total of 119 patients diagnosed with HSP and 75 healthy controls were included in the study. Data on age, gender and physical examination as well as complete blood count, complete urine examination and faecal occult blood test were obtained from the files of the patients.

Results: Gastrointestinal system (GIS) involvement was detected in 41 patients (34.45%), renal involvement in 35 patients (29.41%) and arthritis was detected in 21 patients (17.65%). It was determined that the mean hemoglobin (p=0.02) and MPV values (p=0.0001) o were significantly lower and the mean leukocyte (p=0.0001), platelet (p=0.0001), neutrophil (p=0.0001) count and NLR value (p=0.0001) were significantly higher in patients than in controls. No statistically significant difference was observed in the MPV and NLR values between patients with and without GIS involvement, renal involvement and arthritis.

Conclusion: It is thought that MPV and NLR cannot be used as laboratory parameters in the early detection of system involvement in HSP.

Keywords: Henoch-Schönlein purpura, mean platelet volume, neutrophil-to-lymphocyte ratio

Öz

Amaç: Henoch-Schönlein purpurası (HSP) çocukluk çağının en sık görülen vasküliti olup intestinal ve renal tutuluma bağlı ağır komplikasyonlar görülebilir. Çalışmamızda HSP'nin sistem tutulumlarını erken saptamada ortalama trombosit hacminin (OTH) ve nötrofil lenfosit oranının (NLO) değerlendirilmesi amaçlanmıştır.

Yöntemler: HSP tanısı alan 119 hasta ve 75 sağlıklı kontrol çalışmaya alındı. Hastaların yaşı, cinsiyeti, fizik muayene bulguları, tam kan sayımı, tam idrar incelemesi, dışkıda gizli kan tetkiki dosyalarından kaydedildi.

Bulgular: Hastaların 41'inde gastrointestinal sistem (GİS) tutulumu (%34,45), 35'inde renal tutulum (%29,41), 21'inde artrit (%17,65) tespit edildi. Hastaların hemoglobin (p=0,02) ve OTH (p=0,0001) değeri ortalaması anlamlı derecede düşük, lökosit (p=0,0001), trombosit (p=0,0001), nötrofil (p=0,0001) sayısı ve NLR değeri (p=0,0001) ortalaması anlamlı derecede yüksek bulunmuştur. GİS tutulumu, renal tutulumu ve artriti olan ve olmayan hastaların ortalama OTH ve NLO değeri arasında istatistiksel olarak anlamlı farklılık gözlenmemiştir.

Sonuç: HSP'de sistem tutulumlarını erken saptanmada OTH ve NLO'nun laboratuvar parametresi olarak kullanılamayacağını düşünmekteyiz.

Anahtar Sözcükler: Henoch-Schönlein purpura, ortalama trombosit hacmi, nötrofil lenfosit oranı

Introduction

Henoch-Schönlein purpura (HSP), which is the most common childhood vasculitis, usually improves without treatment; complications rarely occur in the course of the disease, and long-term renal outcomes depends on the initial clinical presentation (1). HSP is a systemic

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vasculitis characterized by palpable purpura without thrombocytopenia, colic-like abdominal pain, joint involvement in the form of arthritis and/or arthralgia, and renal involvement varying from microscopic haematuria to acute glomerulonephritis. It is most frequently observed between the ages of three and 15 years and 1.5 times more commonly among males than in females (2).

The emergence of the disease exhibits seasonal differences, and it is observed more frequently during the autumn and winter months, and after an upper respiratory tract infection. It is known that infectious agents, especially beta-haemolytic streptococci, trigger the disease. Apart from this, *Mycoplasma pneumoniae*, *Bartonella henselae* and vaccines are other most frequently blamed predisposing factors (3,4).

Immune complexes in the systemic circulation formed by various antigenic stimuli accumulate in the capillary wall and activate the complement system, chemotaxis occurs, polymorphonuclear leukocyte migration takes place, polymorphonuclear leukocytes disintegrate as a result of degranulation, and this leads to the deconstruction of and around the blood vessel wall (5). The frequent immunoglobulin (Ig) A accumulation in blood vessels gives rise to the thought that the immune system response in relation to IgA may play a role in the pathogenesis of the disease. Nevertheless, the exact pathogenesis of the disease is not known (4).

The diagnosis of HSP is based on clinical findings. While thrombocytosis, leucocytosis, moderate anaemia, C-reactive protein (CRP), elevated sedimentation are the laboratory findings of HSP, they are not specific to HSP (6,7). Furthermore, there is no unique laboratory that estimates multisystem involvement in HSP. Hemogram parameters have started to be frequently used in recent years in the diagnosis of HSP and other inflammatory diseases, and in the assessment of the severity of clinical findings since assessment of neutrophil-to-lymphocyte ratio (NLR) and mean platelet volume (MPV) is cheap and easily-accessible (8-12).

In this study, we investigated the value of MPV and NLR in the early detection of system involvement in patients with HSP.

Methods

Medical records of 119 patients diagnosed with HSP between January 2013 and December 2016 in the Pediatrics Clinic at University of Health Sciences, Bağcılar Training and Research Hospital and 75 healthy children of the same age and gender were investigated in this retrospective study.

HSP diagnosis was made according to the "EULAR/PRINTO/PRES" criteria (13). There was at least one another system [joint, gastrointestinal system (GIS) or renal] involvement that accompanied typical palpable purpura in all the patients. The epidemiological, clinical and laboratory findings and treatment information in children with HSP were obtained by examining their records. Patients who used drugs due to a chronic disease that would affect platelet functions and those who received oral steroid treatment before admission were excluded from the study.

Patients' age, gender and physical examinations in terms of system involvement on the day of admission, complete blood count, complete urine examination and faecal occult blood (FOB) test were recorded.

Arthritis was defined as limited movement in the joint or painful periarticular, soft tissue oedema. Gastrointestinal involvement was defined as the presence of abdominal pain and/or GIS bleeding. GIS bleeding was defined as a positive FOB test and presence of haematochezia or melena. Nephritis was defined as "macroscopic" or microscopic haematuria (microscopically >5 erythrocytes in every area of centrifuged urine), with proteinuria The present study was approved by the Ethics Committee of Bağcılar Training and Research Hospital (approval number: 2016/497). Study participants and/or their parents provided written informed consent.

Statistical Analysis

Statistical analyses were performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA). In the data evaluation, in addition to descriptive statistical methods (mean, standard deviation), the independent t-test was used in the comparison of the paired groups of variables exhibiting a normal distribution, the Mann-Whitney U test was used in the comparison of the paired groups of variables that did not exhibit a normal distribution, and the chi-square test was used in the comparison of qualitative data. The results were evaluated at a significance level of $p<0.05$.

Results

Seventy-five of 119 patients diagnosed with HSP were male and 44 were female. The mean age of the patients was 7.82±3.01 years. The control group consisted of 75 children with an mean age of 8.55±3.09 years, 37 of whom were female and 38 were male. No statistically significant difference was observed in mean age and gender distribution between the control and HSP groups ($p>0.05$) (Table 1).

Upon examining the hemograms in the patient and control groups, the mean hemoglobin value in the patients was found to be significantly lower ($p=0.02$), the mean leukocyte count was found to be significantly higher ($p=0.0001$), the mean platelet count was found to be significantly higher ($p=0.0001$), the mean MPV value

was found to be significantly lower (p=0.0001), the mean neutrophil value was found to be significantly higher (p=0.0001) and the mean NLR value was found to be significantly higher than in controls (p=0.0001) (Table 1).

GIS involvement was determined in 41 (34.45%) patients, renal involvement in 35 (29.41%), and arthritis was determined in 21 patients (17.65%). While all the patients with GIS involvement had abdominal pain, FOB was determined in 36 (30.25%), proteinuria in 10 (8.4%), and haematuria was determined in 32 patients (26.89%) (Table 2).

Upon examining the hemogram parameters in patients diagnosed with HSP with and without GIS involvement, the MPV in patients with and without GIS involvement was found to be 428.11±163.86 (x1000/μL) and 341.98±104.71 (x1000/μL), respectively. The MPV in patients with GIS involvement was found to be statistically significantly higher than in patients without GIS involvement (p=0.0001).

The mean MPV value in patients with and without GIS involvement was 6.58±1.05 and 6.88±1.17, respectively. No statistically significant difference was observed in MPV values between patients with and without GIS involvement (p=0.170).

The mean NLR value in patients with and without GIS involvement was found to be 2.86±1.89 and 2.17±1.27, respectively and no statistically significant difference was observed in the mean NLR value between patients with and without GIS involvement (p=0.060) (Table 3).

The mean MPV value in patients with and without renal involvement was 6.66±1.08 and 6.83±1.16, respectively. No statistically significant difference was observed in MPV values between patients with and without renal involvement (p=0.461).

The mean NLR value in patients with and without renal involvement was 2.55±1.46 and 2.34±1.58, respectively and no statistically significant difference was observed in the mean NLR value between patients with and without renal involvement (p=0.503) (Table 4).

The mean MPV value in patients with and without arthritis was 6.83±1.1 and 6.77±1.15, respectively.

Table 1. Demographic characteristics and hemogram parameters of the patient and control groups

		Control group n=75	HSP group n=119	p
Age* (Years)		8.55±3.09	7.82±3.01	0.104
Gender, n (%)	Male	38 (50.67)	75 (63.03)	0.089
	Female	37 (49.33)	44 (3.97)	
Hemoglobin* (g/dL)		13.08±0.9	12.71±1.15	0.02
Leukocyte* (10^3/μL)		8.47±2.02	12.34±4.64	0.0001
Platelet* (10^3/μL)		281.41±65.42	367.62±133.96	0.0001
MPV* (fL)		7.77±1.64	6.78±1.14	0.0001
Neutrophil* (10^3/μL)		4.19±1.51	7.62±4.1	0.0001
Lymphocyte* (10^3/μL)		3.28±1.02	3.75±2.28	0.318
NLR* (10^3/μL)		1.38±0.57	2.41±1.54	0.0001

MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, HSP: Henoch-Schönlein purpura
*Mean ± standard deviation

Table 2. Clinical features of the patients

		n	%
GIS involvement	Negative	78	65.55
	Positive	41	34.45
Renal involvement	Negative	84	70.59
	Positive	35	29.41
Arthritis	Negative	98	82.35
	Positive	21	17.65
FOB	Negative	83	69.75
	Positive	36	30.25
Proteinuria	Negative	109	91.60
	Positive	10	8.40
Haematuria	Negative	87	73.11
	Positive	32	26.89

GIS: Gastrointestinal system, FOB: Faecal occult blood

Table 3. Comparison of the hemogram parameters in Henoch-Schönlein purpura patients with and without gastrointestinal system involvement

	GIS (-) n=78	GIS (+) n=41	p
Platelet* (10^3/μL)	341.98±104.71	428.11±163.86	0.0001
MPV* (fL)	6.88±1.17	6.58±1.05	0.170
Neutrophil* (10^3/μL)	7.11±3.74	8.57±4.61	0.092
Lymphocyte* (10^3/μL)	3.78±2.16	3.7±2.5	0.504
NLR* (103/μL)	2.17±1.27	2.86±1.89	0.060

MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, GIS: Gastrointestinal system *Mean ± standard deviation

Table 4. Comparison of the hemogram parameters in Henoch-Schönlein purpura patients with and without renal involvement

	Renal involvement (-) n=84	Renal involvement (+) n=35	p
Platelet* (10^3/μL)	363.61±147.30	390.98±172.76	0.229
MPV* (fL)	6.83±1.16	6.66±1.08	0.461
Neutrophil* (10^3/μL)	7.56±3.86	7.76±4.68	0.811
Lymphocyte* (10^3/μL)	3.96±2.57	3.24±1.2	0.116
NLR* (103/μL)	2.34±1.58	2.55±1.46	0.503

MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, HSP: Henoch-Schönlein purpura *Mean ± standard deviation

Table 5. Comparison of the hemogram parameters in Henoch-Schönlein purpura patients with and without arthritis

	Arthritis (-) n=98	Arthritis (+) n=21	p
Platelet* (10^3/μL)	363.12±127.26	411.49±159.11	0.104
MPV* (fL)	6.77±1.15	6.83±1.1	0.833
Neutrophil* (10^3/μL)	7.36±3.9	8.82±4.84	0.711
Lymphocyte* (10^3/μL)	3.83±2.42	3.39±1.44	0.163
NLR* (103/μL)	2.27±1.39	3.06±2.04	0.351

MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio,
* Mean ± standard deviation

No statistically significant difference was observed in MPV values between patients with and without arthritis (p=0.833). The mean NLR value in patients with and without arthritis was 3.06±2.04 and 2.27±1.39, respectively and no statistically significant difference was observed in the mean NLR value between patients with and without arthritis (p=0.351) (Table 5).

Discussion

HSP is a leukocytoclastic systemic vasculitis involving small vessels, affecting the GIS, kidneys, joints, and less rarely, other organs and systems, and especially the skin, and of which the aetiology is not exactly known. The disease is especially observed between the ages of five and 15 years (1,2). The mean age of the patients in this study was 7.82±3.01 years. It has been reported that HSP was more common among boys, and the male-to-female ratio was 1.5-2/1 (14). In this study, 75 of patients were male, 44 were female, and the male-to-female ratio was found to be 1.7/1, compatible with the literature.

HSP is characterized by purpuric rashes that are concentrated in the lower extremities and vary from small petechiae to wide ecchymosis. As in this study, it has been reported in various publications in the literature that nonthrombocytopenic palpable purpura was the only finding observed in all cases (14,15). Arthritis is the second most prevalent clinical picture in HSP. The joint involvement rates vary between 62 and 82% (15-17). Arthritis was detected in 17.65% of patients in this study, and this does not comply with other studies.

GIS involvement is found in 45-75% of HSP cases. It is the most prevalent finding after rash and joint pain (10,18). There was GIS involvement in 41 of our patients (34.45%). The most important finding suggesting GIS involvement in HSP is accepted to be abdominal pain that can be accompanied by nausea, vomiting and bleeding (19,20). In approximately 40% of patients, pain has been reported to be severe (21). All our patients with GIS involvement had abdominal pain.

The frequency of renal involvement in HSP has been reported to be between 15% and 62%, and the prognosis is generally good (22). The involvement may vary from isolated microscopic haematuria to rapidly progressive glomerulonephritis. It is believed that the long-term prognosis of the disease is related to this involvement (15,23). In our cases, renal involvement was defined according to the presence of haematuria and proteinuria, and renal involvement did not have a progressive course in any of our cases.

HSP is accompanied by thrombocytosis, leukocytosis, moderate anaemia, and elevated CRP and erythrocyte sedimentation rate (6,7). As it was also expected in this study, it was observed that leukocyte and platelet counts were significantly higher in the patient group with HSP when compared to the control group. However, the hemoglobin level was significantly lower in patients than in controls.

The hemogram parameters NLR and MPV have started to be widely used in the diagnosis of HSP and other inflammatory diseases and assessment of the severity of clinical findings in recent years since their measurement is cheap and easily accessible (8-12). Studies on the use of MPV as an indicator in pediatric patients with HSP are quite limited in the literature (11,12). While platelets play a significant role in haemostasis and endothelial repair, they are also important in the formation of atherothrombosis (24). Platelet volume is an indicator that determines platelet functions and activation (25). It has been reported that platelet count increased while MPV decreased in inflammatory diseases (26,27). In this study, it was observed that platelet count increased and MPV decreased in patients with HSP when compared controls, in line with other studies. It has been reported that MPV decreased in the active periods of ulcerative colitis and Crohn's disease, which are other inflammatory diseases affecting the GIS (26,28). It was also reported that MPV was lower in patients with ankylosing spondylitis and rheumatoid arthritis when compared to that in healthy controls (29).

It is believed that certain cytokines that increase throughout the inflammatory process in HSP affect platelet count and volume. Interleukin (IL)-6 is the most important proinflammatory cytokine that causes an increase in platelets and affects the platelet volume (30,31). It has been reported that administration of IL-6 increased platelet count and MPV in cancer patients (31,32). It is believed that IL-6 is responsible for changes in platelets in HSP. Lin et al. (33) reported that serum IL-6 levels were higher in patients with HSP when compared to the controls. Nevertheless, it was observed that the

level of IL-6 was significantly lower in patients with GIS and renal involvement in HSP when compared to those without organ involvement. This was explained in the literature by the fact that IL-6 is consumed in the early phase of the disease (in the early period of inflammation), and it was protective against internal organ involvement and other complications (12). In line with the present study, in a study by Benzer et al. (34), the level of MPV in patients with HSP was found to be lower when compared to healthy controls. In a study by Makay et al. (12), it was reported that the MPV was significantly lower in patients with GIS involvement in HSP when compared to those without GIS involvement. Again, in the study of Benzer et al. (34), it was observed that MPV was significantly lower in patients with GIS involvement. Differently from these two studies, it was observed in the present study that there was no significant difference in MPV between HSP patients with and without GIS involvement. However, the MPV value was significantly lower in patients with HSP when compared to controls, in line with the literature. This can be explained by the fact that IL-6 is protective against internal organ involvement and other complications by being consumed in the early phase of the disease (in the early period of inflammation), as it is explained above.

No study evaluating the relationship between other system involvements apart from GIS involvement and MPV in HSP was encountered in the literature. However, no significant difference in terms of MPV was observed in HSP patients with and without arthritis and in HSP patients with and without renal involvement.

NLR is used as a beneficial indicator that shows the clinical course in inflammatory diseases (35-37). NLR is used in cardiovascular diseases, malignancies, cystic fibrosis and familial Mediterranean fever (35-38). In the study of Makay et al. (11), NLR was found to be significantly higher in HSP children with GIS bleeding when compared to those without GIS involvement. In their study, Gayret et al. (10) found that NLR was significantly higher in patients with HSP when compared to controls, however, no significant difference was observed between HSP children with and without GIS involvement. Similarly, in the present study, NLR was found to be higher in children with HSP than in healthy controls group, and no significant difference was observed between those with and without GIS involvement. NLR is calculated by dividing neutrophil count by lymphocyte count. Increased neutrophil and decreased lymphocyte count can be observed in various infectious diseases or certain inflammatory conditions and stressful situations (39,40). Decreased lymphocyte count is observed in sepsis and lymphocyte apoptosis in inflammatory diseases (40). In the present study, it was observed that neutrophils were significantly higher in the patient group with HSP, but the lymphocytes were not very low. Nevertheless, no significant increase was observed in NLR in patients with GIS involvement, although NLR is high in HSP patients.

Steroid treatment is used in HSP with GIS involvement. Early steroid treatment reduces HSP-related GIS complications (41). It has been reported that patients with GIS bleeding had higher NLR values when compared to patients without GIS bleeding but with abdominal pain (11). It was found out that the detection of high NLR may result in fewer complications by ensuring that the use of steroids is started early with the early detection of the possibility of GIS bleeding in HSP. In the present study, it was observed that there was no difference in NLR between HSP patients with GIS and other system involvements and those without organ involvement.

Study Limitations

The retrospective design and small sample size were the limitations of this study.

Conclusion

When compared to other studies, it is observed that MPV and NLR were significant bioindicators in patients with HSP. HSP is an inflammatory condition, and it was observed that MPV was low and NLR was high, indicating inflammation. However, it was observed that MPV and NLR were not very significant in patients diagnosed with HSP with and without GIS or other organ involvement. Low MPV and high NLR values are expected in patients with GIS involvement, however, in the present study, it was observed that there was no difference in these parameters between patients with and without GIS involvement. Therefore, prospective studies are required. Again, in the literature, we found no study investigating the relationship between MPV and NLR in patients with renal involvement and arthritis. In the present study, it was observed that there was no difference in MPV and NLR values between patients with renal involvement and arthritis and those without involvement.

Authorship Contributions

Surgical and Medical Practices: A.Ö., Ö.B.G. Concept: A.Ö., Ö.B.G. Design: A.Ö., Ö.B.G. Data Collection or Processing: A.Ö., Ö.B.G. Analysis or Interpretation: Ö.B.G., M.E., Ö.Y., F.M. Literature Search: Ö.B.G., M.E., Ö.Y., F.M. Writing: Ö.B.G., M.E., Ö.Y., F.M.

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