Marmara Medical Journal 2015; 28: 151-156
DOI: 10.5472/MMJoa.2803.05

ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Clinical importance of mean platelet volume in children diagnosed with Henoch-Schönlein purpura (Ig-A vasculitis)

Henoch-Schönlein purpurası (IgA vasküliti) tanılı çocuklarda ortalama trombosit hacminin klinik önemi

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ABSTRACT

Objectives: Henoch-Schönlein purpura (HSP) or IgA vasculitis, is the most common form of childhood vasculitis. Mean platelet volume (MPV) is a parameter of a complete blood count that shows thrombocyte function and activation. This study evaluated the link between MPV and HSP.

Patients and Methods: The data of 75 patients with a diagnosis of HSP were retrospectively evaluated. A control group was formed with 79 healthy children of similar gender and ages.

Results: The average ages were 6.8±3.02 years (44 males, 31 females) and 7.49±2.95 years (40 males, 39 females) for the patient and control groups respectively. Mean platelet volume was found to be significantly lower in the study group ($p<0.0001$). Patients' thrombocyte count were significantly higher ($p<0.0001$). Upon presentation 18 patients' faecal occult blood (FOB) test results were positive, and there was microscopic hematuria in 12 patients, MPV was found to be significantly lower in FOB positive patients ($p=0.043$).

Conclusion: Inflammation may affect MPV levels by increasing or decreasing. In our study, MPV measurements performed by a cheap and simple method, have been considered as a negative acute phase reactant. Decreased MPV measurements despite increased platelet count may be important in the prediction of hypercoagulopathy problems during the likely course of the disease and in close follow up for those with a predisposition.

Keywords: Henoch-Schönlein Purpura, Ig-A Vasculitis, Mean platelet volume, Platelet count, Hematuria, Fecal occult blood

ÖZET

Amaç: Henoch-Schönlein purpurası (HSP) ya da IgA vasküliti, çocukluk çağında en sık görülen vaskülittir. Tam kan sayımındaki parametrelerden biri olan ortalama trombosit hacmi (OTH), trombosit aktivasyonu ve fonksiyonunu gösteren bir belirteçtir. Çalışmamızda HSP ile OTH arasındaki ilişkinin araştırılması amaçlanmıştır.

Hastalar ve Yöntemler: Kliniğimizde HSP tanılı 75 hastanın verileri retrospektif olarak değerlendirildi. Cinsiyet ve yaşları benzer 79 sağlıklı çocuk ile kontrol grubu oluşturuldu.

Bulgular: Yaş ortalaması hastalarda 6,8±3,02 yıl (44 erkek, 31 kız), kontrol grubunda7,49±2,95 yıl (40 erkek, 39 kız) idi. Ortalama trombosit hacmi çalışma grubunda anlamlı derecede düşük saptandı ($p<0,0001$). Hastaların trombosit sayısı anlamlı derecede yüksek bulundu ($p<0,0001$). Başvuru anında 18 hastada gizli gaite kan (GGK) testi pozitifti ve 12 hastada mikroskopik hematüri mevcuttu, GGK pozitif olan hastalarda OTH anlamlı düşük bulundu ($p=0,043$).

Sonuç: İnflamasyon, OTH düzeyini artma/azalma şeklinde etkileyebilmektedir. Çalışmamızda ucuz ve basit bir yöntem olan OTH ölçümleri negatif akut faz reaktanı olarak değerlendirilmiştir. Henoch-Schönlein purpuralı çocuklarda, artmış trombosit sayısına karşın, azalmış OTH ölçümlerinin, yatkınlığı olanlarda, hastalık seyrindeki olası hiperkoagülopati problemlerinin önceden belirlenmesinde ve yakın takipte önemli olabileceği kanısına varılmıştır.

Anahtar kelimeler: Henoch-Schönlein purpurası, IgA vasküliti, Ortalama trombosit hacmi, Trombosit sayısı, Hematüri, Gaitada gizli kan

Introduction

Henoch-Schönlein purpura (HSP) was first defined in 1801 by Heberden in a child of five years with stomach pain, vomiting, melena, arthralgia, haematuria and purpuric rash. Later Schönlein attested that arthralgia and purpuric skin rash accompanied each other and called this peliosis rheumatic

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Submitted/Gönderilme: 21.05.2015 **Accepted/Kabul:** 13.09.2015

[1,2]. It is reported to have an annual incidence of between 14-20/100.000 [2,3], while this is higher in males [2-4] (male/female ratio 1.4-1.8). Clinical findings are significant in diagnosis, skin or kidney biopsy is often not necessary. Diagnostic criteria of HSP, together with other childhood vasculitis were presented by Özen et al in 2006, and the final edited version was published in 2010 under the name of 2008 Ankara final classification criteria (Table I) [5,6], Henoch-Schönlein purpura, was renamed as IgA vasculitis with the "*International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides*" statement in 2012. In the course of the disease, palpable purpura mostly over the lower extremities with the skin, stomach pain, bleeding, invagination in the gastrointestinal system, arthritis or arthralgia in the joints and in renal involvement hematuria or varying degrees of proteinuria may occur. Less often, signs and symptoms may be seen in many other systems [2,3]. While HSP, progresses without complications in mild cases, in severe cases complications in the gastrointerstinal system in acute phase, and renal complications in chronic phase determine the prognosis [2]. While some publications have reported that the determination of nephrotic range proteinuria during first presentation or the deterioration of kidney function is a risk factor for renal failure within 20 years following diagnosis [2-8], in an Italian cohort study, the authors showed that early symptoms are not significant in determining the prognosis [2,9,10].

Platelet volume has been identified as a marker of platelet activation and function and mean platelet volume (MPV) is one of the routine parameters in complete blood count test. Diseases such as myocardial infarction, pulmonary embolism, acute pancreatitis, familial mediterranean fever, diabetic retinopathy and chronic obstructive pulmonary disease associated with inflammation, hypoxia, vascular injury, thrombosis and atherosclerosis were found to be associated with MPV [11-15]. Our study aimed to investigate the relationship between HSP and MPV.

Table I. Final EULAR/PRINTO/PRES HSP criteria (with glossary) and classification definition (sample 973) [6]

Criterion	Glossary	Sensitivity (%)	Specificity (%)	AUC (%)
Purpura (mandatory criterion)	Purpura (commonly palpable and in crops) or petechiae, with lower limb predominance, * not related to thrombocytopenia	89	86	87.5
1. Abdominal pain	Diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding	61	64	62.2
2. Histopathology	Typically leucocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit	93	89	91.1
3. Arthritis or arthralgias	Arthritis of acute onset defined as joint swelling or joint pain with limitation on motion Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion	78	42	59.9
4. Renal involvement	Proteinuria >0.3 g/24 h or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample Haematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick	33	70	51.4
HSP EULAR/PRINTO/PRES Ankara 2008 classification definition: κ 0.90 (95% CI 0.84 to 0.96)	Purpura or petechiae (mandatory) with lower limb predominance* and at least one of the four following criteria: Abdominal pain Histopathology Arthritis or arthralgia Renal involvement	100	87	93.5

*For purpura with atypical distribution a demonstration of an IgA deposit in a biopsy is required.
AUC, area under the curve; EULAR, European League Against Rheumatism; HSP, Henoch–Schönlein purpura; PRES, Paediatric Rheumatology European Society, PRINTO, Paediatric Rheumatology International Trials Organisation.

Patients and Methods

In this study, the data of patients presenting between January 2008-December 2013 to the pediatric nephrology clinic and pediatric emergency unit with HSP diagnosis was reviewed retrospectively. Our study was approved by our Hospital Clinical Research Ethics Committee on 15.09.2014 with the decision numbered 2014/12/10. Patients with missing information were excluded from the study. Seventy-five patients were included in the study. Patient presentation, age, gender, platelet count (in cubic millimetre), MPV (fL), plateletcrit (PCT), urinalysis, positive fecal occult blood (FOB), liver and kidney function test results were recorded from patient files. Calculation of the number of platelets were over /1000 value (PLT/1000). To create the control group, 79 healthy children were included in the study. In the automatic complete blood count, EDTA containing tubes were used and studied within one hour, and data obtained from LH 750, Beckman Coulter, England system was evaluated.

Statistical analysis was performed with SPSS 20 program. In the evaluation of quantitative data, in addition to descriptive statistical methods (mean, standard deviation), depending on distribution property in comparison between groups Student's-t or Mann-Whitney-U tests, and in the comparison of qualitative data chi-square and Fisher's exact tests were used. As a final consequence, $p< 0.05$ was considered for statistically significant values.

Results

The mean age of 44 male and 31 female children assessed within the HSP group was 6.8±3.02 years. Of the children in the control group, 40 were male and 39 female, and the mean age was found to be 7.49±2.95 years. There was no statistically significant difference between age and gender distribution between the groups (p=0.154, p=0.073). In the study and control groups, MPV was found to be 7.28±0.73 fL; 8.42±0.67 fL respectively, MPV was found to be significantly lower in the study group (p=0,0001). The PLT/1000 average of the study group was found to be statistically significantly higher than the control group (p=0.0001) (Table II). Of the patients with HSP, 18 were FOB positive upon presentation, and microscopic hematuria was found in 12 patients. Other clinical manifestations of the patients are shown in Table III. While MPV average was 6.97±0.48 fL in patients with positive FOB, it was found to be 7.36±0.76 fL in those with negative FOB. The difference was statistically significant (p=0.043) (Table IV). The mean age of patients with hematuria was 9.4 ± 2.86 years and 6.3 ± 2.8 years in those without. There was a statistically significant difference between them (p = 0.0001) (Table V). No significant difference was determined between those with and without hematuria in terms of MPV, PCT and PLT/1000 averages. In three of our patients invagination, and one acute appendicitis developed. Sixteen patients were admitted to hospital for treatment. There was no statistical difference between the age, MPV, PLT/1000 and PCT averages of the patients admitted and those treated as outpatients. When considering gender, it was determined that while 70.5% of male patients were admitted to hospital, 90.3% of female patients were admitted. The difference was statistically significant (p <0.05) (Table VI).

Renal biopsy was carried out on two patients due to persistent massive proteinuria during outpatient follow ups. The histopathological examination results were interpreted as mesengio-proliferative glomerulonephritis in one patient, and IgA cumulative minimal glomerular lesions in the other patient. Glomerular crescent formation was not observed in either patient.

Table II. Comparison of the data of the patient group and control group

		Control Group n= 79		Patient Group n= 75		p
Age (years)		7.49±2.95		6.8±3.02		0.154
Gender n (%)	**Male**	44	57.89	40	50.63	0.073
	Female	32	42.11	39	49.37	
MPV (fL)		8.42±0.67		7.28±0.73		**0.0001**
PCT (%)		0.26±0.04		0.27±0.06		0.360
PLT/1000 (/mm^3)		314.09±60.59		371.93±82.91		**0.0001**

MPV: mean platelet volume; PCT: plateletcrit; PLT: platelet count

Table III. Clinical and laboratory findings of patients

Findings	Patients with findings	Patients without findings	Ratio (%)
Skin rash	74	0	100
Abdominal pain	39	36	52
Arthritis	16	59	21.3
Soft tissue oedema	38	37	50.7
Proteinuria	3	72	4
Hematuria	12	63	16
Fecal occult blood	18	56	24.3

Table IV. A comparison of patients with and without fecal occult blood positive

	FOB positive patients n=18	FOB negative patients n=56	p
Age (years)	6.39±2.75	6.81±3.0	0.6
MPV (fL)	6.97±0.48	7.36±0.76	**0.043**
PCT (%)	0.26±0.05	0.27±0.06	0.76
PLT/1000 (/mm^3)	382.94±71.79	369.46±86.86	0.55

FOB: fecal occult blood, MPV: mean platelet volume; PCT: plateletcrit; PLT: platelet count

Table V. Comparison of patients with and without hematuria

	Patients with microscopic hematuria n=12	Patients without microscopic hematuria n=63	p
Age (years)	9.4±2.86	6.3±2.8	**0.001**
MPV (fL)	7.27±0.68	7.28±0.75	0.923
PCT (%)	0.25±0.06	0.27±0.06	0.237
PLT/1000 (/mm^3)	347.83±92.6	376.52±80.93	0.275

MPV: mean platelet volume; PCT: plateletcrit; PLT: platelet count

Table VI. Comparison of patient data for those admitted to hospital and those with outpatient follow up

		Those admitted to hospital n=59	No hospital admissions n=16	p
Age (years)		7.13±2.97	5.59±2.97	0.066
Gender n (%)	**Male**	31 (70.5)	13 (29.5)	**0.048**
	Female	28 (90.3)	3 (21.3)	
MPV (fL)		7.24±0.71	7.43±0.82	0.592
PCT (%)		0.27±0.06	0.26±0.64	0.732
PLT/1000 (/mm^3)		375.66±80.18	358.19±93.8	0.233

Discussion

While HSP was defined at the beginning of the 19th century, its exact etiology remains unclear. It is much more common in children than in adults. It is reported that it generally occurs between the ages of 5-15, on average around 5-6 years of age [4,16-19]. As palpable purpuric rash of different sizes from small petechiae to large ecchymoses which are more dominant on the lower extremities is characteristic in HSP, it is generally diagnostic. Gastrointestinal involvement is the third most commonly affected area after the skin and joint involvement. It occurs in approximately two-thirds of children. In a multicenter study conducted in our country by Peru et al, FOB involvement in children with HSP was found in 50% of patients, and renal involvement was found in 30% of patients [20]. Oedema and bleeding due to vasculitis developing on the intestinal wall; may lead to invagination, gangrene or perforation [3,4,21]. Surgical complications are rare in adults and children under the age of three. The most common surgical complication in patients with gastrointestinal involvement is invagination, and its incidence is known to be less than 1% [3,4,22-24]. In our study, three patients have been operated due to invagination (0.04%). Henoch-Schönlein purpura nephritis is usually seen as spontaneously resolving microscopic hematuria and / or mild proteinuria. If there are initial findings of massive proteinuria and nephrotic or nephritic syndrome symptoms, it may progress rapidly. Publications report 15-62% renal involvement with HSP in the early period, and between 1-2% in the long term, however late stage renal failure incidence is between 0-3% [3,25-27]. In our patient group, hematuria was detected in 12 patients, and proteinuria was detected in three patients. In two of these both hematuria and proteinuria, and in one isolated proteinuria was present. Renal involvement in a total of 13 patients was found to be 17.3% of total patients. The detection of longstanding proteinuria in two patients (2.6%) was consistent with literature. Platelets, hemostasis and endothelial repair has a vital role, and also plays a significant role in the development of atherothrombosis [28]. Platelet volume is an indicator of platelet function and activation [29]. It has been reported that platelet count increases and MPV decreases in many inflammatory diseases [30,31]. In contract, in many prothrombotic disorders, MPV was determined to be high [32].

While there are studies showing that MPV is higher in rheumatoid arthritis, there are also studies showing that it is lower [33,34]. Gasparyan has reported that MPV average is higher in patients with hypertension together with rheumatoid arthritis [33]. In a study by Kısacık et al, in patients with active ankylosing spondylitis and rheumatoid arthritis, platelet volume has been found to be lower and with treatment an increase in MPV levels and normalizing has been seen [34]. Uysal et al., have reported that MPV is lower in cystic fibrosis patients during acute attack in comparison with those not in attack, and in those outside of acute attack, a lower MPV has been determined in comparison with healthy patients [35]. In many other studies, MPV has been found to be low during active disease in adult ulcerative colitis patients, while platelet number has found to be high [30-32]. MPV levels have been reported to be significantly lower in patients with gastrointestinal bleeding in a study by Makay et al[36]. In a majority of prothrombotic diseases, MPV has been found to be high and to be associated with disease activity [32]. MPV value prior to percutaneous coronary angiography in acute coronary syndrome has been found to be a similar indicator of prognosis as troponin [37]. It has been reported that MPV increases in chronic renal patients proportionally to the decrease in estimated glomerular filtration rate (eGFR), and that MPV is higher in patients with coronary artery disease than those without [38]. There are publications available showing that thrombotic events are more frequent in vasculitis [39,40]. MPV has been reported to be high in Behçet's disease patients with thrombosis [41].

In our study, MPV levels were found to be significantly lower in patients with HSP in comparison with the control group, while platelet counts were found to be significantly higher. No difference was determined between the groups in terms of PCT value impacted in the opposite direction by these two parameters.

The increase in platelet count in order to balance the

decrease in platelet activity as a result of the decrease of MPV levels may be a measure taken by the organism for the proper operation of the hemostasis system. In HSP patients, MPV levels were also found to be decreased in gastrointestinal system involvement. In contrast, the increase in platelet count determined in patients in comparison with the control group was not observed in patients with GI bleeding. The decreased MPV and increased platelet count in patients with gastrointestinal bleeding suggests that a reduction in platelet activity may have been caused.

Henoch Schönlein purpura, generally has a much better prognosis than most other vasculitis and most patients recover uneventfully [3,42]. When considering the relationship between increased platelet activity and vascular damage, the prognosis being better with this disease may be related to the vascular damage induced by platelets being less severe. In our study, the MPV average of HSP patients was found to be significantly lower in comparison with healthy controls. MPV being found to be higher in the course of other vasculitis and diseases with thrombosis supports the contribution of platelet activation in the formation of vascular complications. Due to the low number of patients in our study, the relationship between renal involvement and MPV was not evaluated, and broader studies are required in this regard.

In conclusion our study showed that MPV may be a guide in the disease activity in the follow up of patients with HSP. Care must be taken in terms of vascular complications in patients whose MPV decrease could not be determined as expected in normal course. There is a need for further studies with larger number of patients with long term follow up.

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