The Value of Platelet Indices in Henoch-Schönlein Purpura

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Abstract

Background: Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood and is usually associated with thrombocytosis. Platelet indices, mean platelet volume (MPV) and platelet distribution width (PDW) have recently been described as markers of platelet activation and function. The aim of this retrospective study is to investigate the value of platelet indices in HSP.

Methods: The study was conducted in 117 HSP patients diagnosed with HSP and 68 age- and sex-matched healthy controls with a retrospective design. The data for both patient and control groups were extracted from the hospital’s computerized database following approval by the local ethics committee.

Results: The mean leukocyte and platelet counts were significantly higher in HSP patients than in the control group (p<0.01), while mean MPV and PDW values did not differ in the two groups. Furthermore, the platelet indices did not differ between patients with and without multisystemic involvement.

Conclusions: The results of our study suggest that platelet indices cannot be used as a laboratory markers either in diagnosis of HSP or predicting severe multisystemic disease in HSP.

Key words: Henoch-Schönlein purpura, platelet, mean platelet volume, platelet distribution width

Introduction

Henoch-Schönlein purpura (HSP), also known as anaphylactoid purpura, is a vasculitis of small vessels commonly seen in children with cutaneous and systemic involvement [1]. It is characterized by a clinical triad of non-thrombocytopenic palpable purpura, abdominal pain, and arthritis [2] and is almost self-limited except for severe complications of intestinal or renal involvement.

The pathologic lesions in the skin, intestines and synovium are leukocytoclastic angitis, and inflammatory damage to the endotelium of the capillary and postcapillary venules mediated by leukocytes and macrophages [3]. The diagnosis of HSP depends on clinical findings and although leukocytosis, thrombocytosis and mild anemia elevated erythrocyte sedimentation rate and C-reactive protein levels are reported to accompany the disease,
no laboratory finding is diagnostic of HSP [4]. Furthermore, there is no laboratory finding in predicting severe multisystemic involvement in HSP. Some recent studies reported that thrombocytosis is associated with severe disease in HSP [5,6], but this issue is still controversial.

There is convincing evidence that platelets are important components of the inflammatory response. Platelets contain more dense granules when they become activated and secrete multiple inflammatory factors including chemokines, cytokines and coagulation factors resulting in an increase in platelet size and pseudopodia formation [7]. Mean platelet volume (MPV) reflects the platelet size, while platelet distribution width (PDW) reflects the change in the number and size of the pseudopodia of platelets [8]. The aim of this study is to evaluate the diagnostic value of platelet indices in HSP Henoch-Schönlein Purpura, arthritis in HSP and predicting multisystemic involvement in affected individuals.

**Methods**

Patients records of the Behcet Uz Children’s Hospital, a reference hospital for the pediatric population, were screened for this study. Patients diagnosed with HSP between January 2007 and December 2011 were evaluated retrospectively. Age and sex-matched healthy children who were admitted to outpatient clinics for routine controls and pediatric surgery outpatient clinics for preoperative evaluation before elective surgery were considered as the control group. The children with acute or chronic illnesses, anemia, leukocytosis/leukopenia, thrombocytosis/thrombocytopenia were excluded from the control group. The demographical and laboratory data for both patient and control groups were extracted from the hospital's computerized database. After the blood samples were collected in standard tubes containing EDTA, the complete blood count (CBC) analysis was performed on a Symex XT 2000, calibrated monthly by central laboratory. The laboratory reference values were 7.0-11.0 fL and 9.0-15.0 fL for MPV and PDW, respectively.

The patients presenting with cutaneous involvement and/or arthritis were classified as Group 1, while the patients with multisystemic disease (at least two organ system involvement of gastrointestinal and/or renal and/or other less common manifestations of the disease such as neurologic and pulmonary involvement) were included in Group 2. Gastrointestinal involvement defined gastrointestinal disease such as intestinal perforation, gastrointestinal bleeding (melena, hematochesia) or at least occult blood in stool + abdominal pain. Renal involvement was considered to exist if clinical classification is ≥ stage 2 according to Meadow et al [9] (at least minimal proteinuria + microscopic hematuria) during the acute phase of the purpura.

Hemoglobin (g/dl), number of leukocytes (/mm$^3$), number of platelets (/mm$^3$), mean platelet volume (fL), platelet distribution width (fL) were compared between patient and control groups, and additionally between Group 1 and 2 in order to evaluate the diagnostic value these parameters in HSP patients and to predict the multisystemic involvement. The difference between erythrocyte sedimentation rate (ESR) (mm/h) and C-reactive protein (CRP)(mg/dl) levels were not evaluated because data were missing in the control group.

The data were analysed using a statistical software package (SPSS version 18.0). G Power (version 3.1.7) software was used to find the required sample size. We computed that at least 64 cases are needed for each group to detect an existing difference between groups, with 80% power, 0.05 type alpha error level and 0.5 effect size, by predicting means and standard deviations similar to those of previous studies. The distribution of the data was tested by Kolmogorov Smirnov test and if the data were normally distributed, Student t test was used, otherwise Mann-Whitney U test was used for evaluations. The $p$ values <0.05 were considered to indicate statistical significance. The study was carried out after appropriate approval by the local ethics committee (24/11/2011-23) and therefore it was performed in accordance with ethical standards declared in 1964 and updated in 2008, Declaration of Helsinki [10].

**Results**

A total of 117 patients diagnosed with HSP (Male/Female:60/57) and 68 healthy controls (Male/Female : 37/31) were evaluated for the study. The mean age was 7.0 ±2.9 and 7.1 ±3.1 in patient and control groups, respectively. There was no significant difference between patients and controls considering age and gender. All of the patients had palpable purpura. The most common clinical involvement to cutaneous lesions was arthritis (56%), followed by gastrointestinal involvement.
Table 1. Clinical characteristics of HSP patients.

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpura</td>
<td>117 (100)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>66 (56)</td>
</tr>
<tr>
<td>Gastrointestinal involvement *</td>
<td>46 (39)</td>
</tr>
<tr>
<td>Renal involvement **</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Isolated cutaneous involvement</td>
<td>39 (33)</td>
</tr>
<tr>
<td>Multisystemic disease ***</td>
<td>58 (49)</td>
</tr>
</tbody>
</table>

Gastrointestinal involvement*, at least occult blood in stool + abdominal pain. Renal involvement**, at least minimal proteinuria + microscopic hematuria. Multisystemic disease***, at least two organ involvement in addition to purpura and arthritis.

(39%) and renal involvement (10%). There was no patient in the study group with uncommon manifestations of the disease such as neurologic or pulmonary involvement. The clinical characteristics of the patients are presented in Table I.

In the HSP group, the mean leukocyte count was 10.6±3.1×10^3 /μL and the mean platelet count was 386±103×10^3/μL, which were both higher than in the control group (leukocyte count: 8.0±2.1×10^3/μL; platelet count: 318±69×10^3/μL). The difference was statistically significant (p<0.01 in both). The mean MPV values in the HSP and control groups were 8.9±1.1 fL and 9.0±1.2 fL, respectively; there was no significant difference between groups. The mean PDW value was 11.0±2.0 fL in the HSP group and 11.3±1.7 in the control group; there was no significant difference in PDW values, either (Table II).

In HSP patients, hemoglobin, leukocyte and platelet counts, platelet indices, ESR and CRP values of subgroups are given in Table III. There were no statistical differences between two groups in all comparisons, except for MPV. MPV was found to be higher in patients with multisystemic involvement (mean±SD: 9.3±0.9) (Group 2) than in Group 1 (mean±SD: 8.8±1.1) (p = 0.04).

Discussion

Although MPV and PDW are easily measured platelet indices that increase during platelet activation, the results of this study indicate that platelet indices cannot be used as an activation marker either in diagnosis or to predict multisystemic disease in HSP, the most common vasculitis of childhood. Furthermore, we suggest that there is no laboratory marker to predict multisystemic involvement in HSP patients.

Clinical evidence has accumulated suggesting an important role of MPV as a marker of inflammation, disease activity and efficacy of antiinflammatory treatment in several chronic inflammatory disorders. The size of circulating platelets is dependent on the intensity of systemic inflammation, with contrasting features of MPV in high- and low-grade inflammatory disorders [11]. The mean platelet volume (MPV) is probably the most extensively studied platelet activation marker in hypertension, diabetes mellitus, ischemic cerebrovascular events and myocardial infarction [12-15]. Recently, novel platelet indices such as mean platelet component (MPC) and platelet component distribution width (PCDW) have been investigated as prospective platelet activation markers [16-17]. However, most hematology analyzers are not able to examine such indices. Thus, there is interest in finding simple and widely used platelet activation criteria and this relies on the observation that platelet activation leads to morphologic changes including spherical shape and pseudopodia formation. Platelets’ volume increases when platelets become activated. Larger platelets contain more dense granules, have higher thrombotic potential and are able to start the inflammation. Therefore, higher MPV levels predict platelet activity and thus intensity of inflammation [18]. Platelets with increased number and size of pseudopodia differ in size, possibly affecting PDW. PDW is recently reported to be more specific marker of platelet activation, because it does not increase during simple platelet swelling [7]. On the contrary, Beyan et al. reported that platelet indices should not be used alone as direct indicators of platelet activation [19]. Their observation was derived from the lack of correlation of MPV and PDW with optical platelet aggregation responses in healthy volunteers. They reported that large platelets did not show more intense activation in aggregometer. Moreover, platelets shape and volume are variable, even in healthy persons. Thus, they reported that serial measurements of MPV and PDW would be more useful than simultaneous measurements.

Clinical studies report controversial results. MPV values are reported to increase in FMF [20] and to decrease in
Table 2. Comparison of laboratory parameters including platelet indices between HSP patients and healthy controls.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HSP Group</th>
<th>Control Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb*</td>
<td>12.2±1.1</td>
<td>12.3±0.9</td>
<td>0.41</td>
</tr>
<tr>
<td>WBC*</td>
<td>10.6±3.1</td>
<td>8.0±2.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plt*</td>
<td>386±103</td>
<td>318±69</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MPV *</td>
<td>8.9±1.1</td>
<td>9.0±1.2</td>
<td>0.75</td>
</tr>
<tr>
<td>PDW*</td>
<td>11.0±2.0</td>
<td>11.3±1.7</td>
<td>0.32</td>
</tr>
<tr>
<td>ESR**</td>
<td>31 (25)</td>
<td>N/A</td>
<td>-</td>
</tr>
<tr>
<td>CRP**</td>
<td>0.9 (1.6)</td>
<td>N/A</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data are presented as mean±Standard Deviation. **Data are presented as median (interquartile range)

Table 3. Comparison of laboratory parameters including platelet indices in HSP patients with and without multisystemic involvement.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Multisystemic Involvement</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n:84)</td>
<td>Yes (n:33)</td>
</tr>
<tr>
<td>Hb*</td>
<td>12.1±1.2</td>
<td>12.4±1.0</td>
</tr>
<tr>
<td>WBC**</td>
<td>10.1(4.1)</td>
<td>9.8(4.3)</td>
</tr>
<tr>
<td>Plt*</td>
<td>381±94</td>
<td>398±122</td>
</tr>
<tr>
<td>MPV*</td>
<td>8.8±1.1</td>
<td>9.3±0.9</td>
</tr>
<tr>
<td>PDW*</td>
<td>11.0±2.1</td>
<td>11.0±1.7</td>
</tr>
<tr>
<td>ESR**</td>
<td>31(25)</td>
<td>25(18)</td>
</tr>
<tr>
<td>CRP**</td>
<td>0.9(1.6)</td>
<td>0.9(2.9)</td>
</tr>
</tbody>
</table>

*Data are presented as mean±Standard Deviation. **Data are presented as median (interquartile range)

Table 1-2: Hb, Hemoglobin (g/dl) - PDW, Platelet Distribution Width, fL - WBC, White Blood Cell (×10^3/μL) - ESR, Erythrocyte sedimentation rate (mm/h) - Plt, Platelet (×10^3/μL) - CRP, C reactive protein (mg/dl) - MPV, Mean Platelet Volume, fL

ulcerative colitis, Chron’s disease, rheumatoid arthritis and anklylosing spondilitis [21-22]. It was also reported that MPV values during the attack period are significantly lower than in the attack-free period in FMF [23]. Henoch Schönlein Purpura, usually presenting with purpuric bruises, hematemesis, melena, hematochexia or hematuria may suggest platelet function disturbances. Culic et al. reported abnormal aggregation curves in HSP [24]. Makay et al. reported the first study investigating MPV values in HSP [25]. They reported that decreased MPV values are related with gastrointestinal bleeding in HSP and speculated that low MPV is related to IL-6, based on reports indicating elevated serum IL-6 levels in HSP [26] and a decrease in MPV in cancer patients who were administered IL-6 [27]. The results of this study do not support the recent study reported by Makay et al. This may be because of differences in study populations as our patient group includes all HSP patients, with and without gastrointestinal bleed. Furthermore, our study is the first study investigating PDW values in HSP and documented no difference compared to healthy controls.

Another clinical issue is to predict multisystemic disease when a patient is diagnosed with HSP. Clinicians usually need to decide to follow-up the patient at home or refer him/her to a hospital. However, there is no report to predict the multisystemic involvement in HSP. In our study, although the MPV level of individuals with systemic involvement (mean ± SD: 9.0±1.2) seems to be higher than in other patients (mean ± SD: 8.7±1.3) (p: 0.046), the clinical significance of this differ-
ence is not clear since the mean MPV values are close to each other and in normal reference range for both groups. The retrospective design is the limitation of the study, which makes it impossible to study platelet values in different time points. In addition, renal involvement can be delayed in some patients and we only studied the platelet values during the acute phase of the disease; hence, we might have missed the late onset changes. Thus, prospective evaluation at different time points may provide different results.

In conclusion, the results of our study indicate that platelet indices cannot be used as laboratory markers either in diagnosing or predicting severe multisystemic disease in the acute phase of HSP. Moreover, there is no other laboratory marker to predict multisystemic involvement in HSP patients. Clinicians need to follow up the patients carefully in order to predict multisystemic disease.

**Declaration of interest**
The authors have no conflicts of interest to declare.

**References**