Platelet Counts in Children With Henoch–Schönlein Purpura—Relationship to Renal Involvement

Ahmet Taner Elmas and Yilmaz Tabel*

Department of Pediatric Nephrology, Faculty of Medicine, University of Inonu, Malatya, Turkey

Background: The aim of this study is to identify the clinical and laboratory risk factors for renal involvement and to determine the relationship between platelet counts and renal involvement in (Henoch–Schönlein purpura) HSP patients. **Methods:** We reviewed the medical records of 107 children with HSP according to Euler/Press diagnostic criteria. Clinical and laboratory parameters for renal involvement were evaluated and compared to no renal involvement. **Results:** A retrospective study consisted of 107 children, 61 boys (57%), and 46 girls (43%). Twenty-eight of the 107 patients (26.1%) had renal involvement. The mean platelet count was significantly higher in patients with renal involvement when compared to

patients without renal involvement ($P = 0.001$). The multivariate logistic regression analysis identified that age ($P = 0.022$), sex ($P = 0.037$), gastrointestinal involvement ($P = 0.019$), and platelet count ($P = 0.019$) were significantly associated with the renal involvement of HSP. The platelet count was predictive of renal involvement, which had odds ratio of 1.0, and achieved *area under the curve* of 0.66 for predicting the renal involvement within the acute stage of HSP ($P = 0.009$). **Conclusion:** Our study indicated that age, sex, gastrointestinal involvement, and platelet count were significant risk factors of renal involvement of HSP. J. Clin. Lab. Anal. 30:71–74, 2016. ©

2014 Wiley Periodicals, Inc.

Key words: child; Henoch–Schönlein purpura; platelet counts; renal involvement

INTRODUCTION

Henoch–Schönlein purpura (HSP) is one of the most common vasculitides of childhood that has major manifestations of nonthrombocytopenic purpura, arthritis/arthralgia, abdominal pain, and renal involvement (1).

Considering HSP as a systemic vasculitis with widespread endothelial damage, it should be noted that in fact certain laboratory findings either reflect the immunopathology of the disease or represent the result of a complication, depending on the extend and the grade of an impaired function. However, all these relevant tests cannot be considered as specific diagnostic markers (2). Previously, a few studies have shown that thrombocytosis is found in about 60–70% of HSP patients in the acute stage, which might be related to the severity of the illness (3). Thrombocytosis can be classified as primary (clonal) and secondary (reactive) forms. While clonal thrombocytosis is noted in myeloproliferative diseases, reactive thrombocytosis is observed in stressful or inflammatory diseases, such as acute or chronic infection, trauma, and malignancy. Thrombocytosis seen in HSP patients is a type of inflammatory reactive thrombocytosis, and that

IL-6 may also play a role in the pathogenesis of HSP (4).

The aim of this study is to evaluate the renal manifestations of HSP in unselected patients, to identify the clinical and laboratory risk factors for renal involvement, and to determine the relationship between platelet counts and the renal involvement in HSP patients.

MATERIALS AND METHODS

We reviewed the medical records of 107 children with HSP who were admitted between the time period January 2006 and December 2010. The inclusion criteria applied were the EULAR/PRESS diagnostic criteria for HSP (5). Exclusion criteria were thrombocytopenia and systemic

*Correspondence to: Yilmaz Tabel, Inonu Universitesi, Turgut Ozal Tip Merkezi, Çocuk Sagligi ve Hast. AD, 44280 Malatya, Turkey. E-mail: yilmaztabel@yahoo.com

Received 28 August 2013; Accepted 25 August 2014

DOI 10.1002/jcla.21817

Published online in Wiley Online Library (wileyonlinelibrary.com).

vasculitis at onset. Pertinent data including age of the disease onset, body weight, body length, and sex were collected for all patients. The signs and symptoms of the patients were evaluated and the incidence of skin, joint, gastrointestinal, renal, and other manifestations were determined. The following laboratory data during the acute phase of the disease were analyzed: haemoglobin (Hb) (g/dl), white blood cell count (WBC) ($\times 10^3/\mu\text{L}$), platelet count ($\times 10^3/\mu\text{L}$), erythrocytes sedimentation rate (ESR) (mm/1st hr), C-reactive protein (CRP) (mg/dl), blood urea nitrogen (BUN) (mg/dl), serum creatinine (mg/dl), total protein (g/dl), albumin (g/dl), immunoglobulin A (IgA) (mg/dl), G (IgG) (mg/dl), M (IgM) (mg/dl), complement 3 (C3) (mg/dl), and 4 (C4) (mg/dl) values. The urine analyses included dipsticks, microscopy, and 24 hr collected urine protein assays.

Renal involvement was defined as the presence of proteinuria or hematuria or red blood cell casts. In the patients with renal involvement, the incidence of hematuria, proteinuria, hypertension, and nephritic and nephrotic syndrome were determined. Nephrotic syndrome was defined as the presence of proteinuria ($>40 \text{ mg/m}^2/\text{hr}$) and a serum albumin value less than 2.5 g/dl, with edema. Acute nephritic syndrome was defined as the presence of hematuria together with at least two of the conditions from the set of hypertension, raised serum urea, or creatinine and oliguria. Hypertension was defined as systolic or a diastolic blood pressure higher than the 95th percentile for the patient's age, sex, and height according to the Update on the 1987 Task Force Report (6).

STATISTICAL ANALYSIS

Data were evaluated using the Statistical Package for Social Sciences (SPSS) program for Windows version 16.0 (SPSS Inc., Chicago, IL). Numerical data are expressed as mean $\pm$ standard deviation (SD) or median (with minimum–maximum range), depending on normal distribution (Shapiro–Wilk test). Differences between two groups were assessed by using unpaired *t*-test or Mann–Whitney U test. Categorical variables were expressed as proportions or percentages. The significance of differences between proportions or percentages was determined by the Chi-square test or Fisher's exact test. Multivariate logistic regression analysis was used to determine whether a platelet counts and other variables were a predictor of renal involvement in HSP at the time of diagnosis. Inter-correlations between parameters were computed through the Pearson's correlation analysis. The diagnostic accuracy of the platelet count tested in this study was evaluated by constructing receiver operating characteristics (ROC) curves. Sensitivity and specificity were also calculated. A *P*-value, which is less than 0.05, was considered to be significant.

RESULTS

The study group consisted of 107 children, 61 boys (57%) and 46 girls (43%), the ratio of boys to girls 1.32, and the mean age was 7.56 ± 3.40 years. The incidence rates of skin, joint, gastrointestinal, scrotal, and renal involvement were 100, 67.2, 41.1, 6.5, and 26.1%, respectively.

The patients with renal involvement were classified according to the emergence time of renal involvement. Signs of renal involvement were detected in six patients at the time of diagnosis. In 18 patients, renal involvement was detected in the first month (85.7%), in three patients in 1–3 months (10.7%), and in only one patient in 4–6 months (3.5%). Finally, 28 of the 107 patients (26.1%) had renal involvement. There were 19 boys (67.8%) and nine girls (32.1%), with the boys/girls ratio of 2.1 in the group with renal involvement where no significant difference due to sex was obtained ($P > 0.05$). The mean age of the patients with renal involvements were statistically significantly higher than the patients without renal involvement (8.7 ± 4.1 and 7.1 ± 23.0 , $P = 0.033$). In addition, in the group with renal involvement, the incidence of scrotal involvement was statistically significantly higher than that of the group without renal involvement ($P = 0.004$).

The mean platelet count was significantly higher in patients with renal involvement when compared to patients without renal involvement ($483.6 \pm 120.3 \times 10^3/\mu\text{l}$ and $422.3 \pm 87.8 \times 10^3/\mu\text{l}$, $P = 0.001$). Comparison of demographic, clinical, and laboratory parameters between patients with and without renal involvement is given in Table 1.

There were positive correlations between platelet counts and renal involvement, WBC counts, ESR, and CRP values ($r = 0.26$ and $P = 0.005$, $r = 0.32$ and $P = 0.0001$, $r = 0.28$ and $P = 0.005$, and $r = 0.24$ and $P = 0.016$, respectively). In addition, there was a negative significant correlation between renal involvement and C3 values ($r = -0.22$ and $P = 0.043$).

We also evaluated the relationship between renal involvement and various factors using a backward stepwise multivariate logistic regression analysis. The multivariate logistic regression analysis identified that age (odds ratio (OR) = 1.2; 95%CI 1.03–1.60, $P = 0.022$), sex (OR = 9.6; 95%CI 1.15–81.1, $P = 0.037$), gastrointestinal involvement (OR = 5.8; 95%CI 1.09–31.3, $P = 0.019$), and platelet count (OR = 1.0; 95%CI 1.0–1.02, $P = 0.019$) were significantly associated with the development of nephritis.

The diagnostic performance of platelet count on predicting renal involvement with HSP patients in the acute stage is assessed. The platelet count was predictive of renal involvement, having OR of 1.00, and achieving *area under the curve* of 0.66 for predicting the renal involvement within the acute stage of HSP ($P = 0.009$). We also

TABLE 1. Comparison of Demographic, Clinical, and Laboratory Parameters Between Patients with and Without Renal Involvement

Parameter	Total (n = 107)	Renal involvement (n = 28)	No renal involvement (n = 79)	<i>P</i> ^{a,b}
Age (years)	7.56 ± 3.3	8.7 ± 4.1	7.1 ± 3.0	0.033^a
Body weight (kg)	21.5 (8.6–69.5)	28.4 (10.7–65.0)	20.0 (8.6–69.5)	0.042^a
Body length (cm)	118.2 ± 25.3	128.1 ± 26.2	118.6 ± 18.8	0.042^a
Male sex (n, %)	61 (57.5%)	19 (67.8%)	42 (53.1%)	0.192 ^b
GI manifestations (n, %)	44 (41.1%)	15 (53.5%)	29 (36.7%)	0.179 ^b
Arthritis/arthritis (n, %)	72 (67.2%)	16 (57.1%)	56 (70.8)	0.241 ^b
Scrotal involvement (n, %)	4 (3.7%)	4 (14.2%)	0 (0%)	0.004^b
Anemia (n = 107)	13/107 (12.1%)	5/28 (17.8%)	8/79 (10.1%)	0.318
Leukocytosis (n = 107)	38/107 (35.5%)	14/28 (50.0%)	24/79 (30.3%)	0.070
Thrombocytosis (n = 107)	44/107 (41.1%)	17/28 (60.7%)	27/79 (34.1%)	0.024
Elevated ESR (n = 95)	58/95 (61.0%)	19/28 (67.8%)	39/67 (58.2%)	0.350
Elevated CRP (n = 95)	82/95 (86.3%)	25/28 (89.2%)	57/67 (85.0%)	0.498
Elevated IgA (n = 75)	31/75 (41.3%)	11/18 (61.1%)	20/57 (35.0%)	0.060
Elevated IgG (n = 75)	8/75 (10.6%)	2/18 (11.1%)	6/57 (8.7%)	0.671
Elevated IgM (n = 74)	0/74 (0%)	0/18 (0%)	0/56 (0%)	–
Decreased C3 (n = 85)	7/85 (8.2%)	4/23 (17.3%)	3/62 (4.8%)	0.085
Decreased C4 (n = 80)	2/80 (2.5%)	2/21 (4.7%)	0/59 (0%)	0.068

Hb, hemoglobin; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BUN, blood urea nitrogen; IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; C3, complement component 3; C4, complement component 4. Leukocytosis was defined as leukocyte count $\geq 13.5 \times 10^3/\mu\text{l}$; anemia as hemoglobin $< 11 \text{ g/dl}$; thrombocytosis, platelet count higher than $> 500 \times 10^3/\mu\text{l}$; elevated ESR, if values were higher than 20 mm/1st hr; elevated serum CRP levels, if values were higher than CRP than 3.13 mg/dl.

Elevated serum IgA levels when $> 159 \text{ g/l}$ for children < 5 years and $> 236 \text{ g/l}$ for children aged 5–15 years.

Elevated serum IgG levels when $> 1235 \text{ mg/dl}$ for children < 5 years, $> 1572 \text{ mg/dl}$ for children aged 5–15 years.

Elevated serum IgM levels when $> 207 \text{ mg/dl}$ for children 2–8 years, $> 242 \text{ mg/dl}$ for children aged 9–15 years.

Decreased C3 and C4 levels; low C3 when $< 90 \text{ mg/dl}$ and C4 $< 10 \text{ mg/dl}$.

Data were presented as mean $\pm$ SD, median (minimum–maximum) or percentages; *P*-value is for comparison between control and patients and $P < 0.05$ is significant.

^aUnpaired *t*-test or Mann–Whitney U test.

^bChi square test or Fisher's exact test.

calculated the cutoff value for platelet count to predict the renal involvement in the acute stage of HSP. At the values of platelet count $\geq 565.000 \times 10^3/\mu\text{l}$, the sensitivity (%) and specificity (%) for detecting renal involvement in the acute stage of HSP were 36 and 49%, respectively.

DISCUSSION

One manifestation of HSP that can continue to cause lifelong problems is renal involvement. In the literature, renal involvement in patients with HSP varies between 20 and 80% (7). In our study, renal involvement ratio was 26.1%, which is in agreement with the literature. The sex ratio shows a male preponderance (male to female ratio, 1.4–1.7:1) and renal involvement in HSP is most frequent between 6 and 10 years of age (8). Previous studies (9, 10) showed that the renal involvement in HSP occurred more frequently in older children than the younger children. This study suggests that the older age at onset was one of the significant risk factors of renal involvement based on multivariate logistic regression analyses.

Platelets have major roles in acute and chronic inflammation, including release of proinflammatory mediators, display of surface molecules that have inflammatory func-

tions, and interactions with leukocytes and endothelial cells (11, 12). During an acute attack, thrombocytosis is frequently observed in children with HSP, which might be related to the severity of the illness (13, 14). Our data showed that increased platelet counts in 60.7% of patients with renal involvement. As HSP is a systemic vasculitis, some proinflammatory cytokines such as tumor necrosis factor- α , interleukin (IL)-6, and IL-8 have been found to be involved in the pathogenesis of the disease (15–17). It is known that IL-6 is an important proinflammatory cytokine that induces thrombocytosis (18, 19). A recent study showed that thrombocytosis in HSP patients is a type of inflammatory reactive thrombocytosis, and that IL-6 may also play a role in the pathogenesis of HSP (4). In our study, platelet counts were significantly higher in patients with renal involvement when compared to the patients without renal involvement, which is consistent with previous studies (4, 15–17, 20). Our study indicated that the platelet count was one of the significant risk factors of renal involvement based on multivariate analyses. According to our findings; thrombocytosis is identified as an independent risk factor for renal involvement in HSP and we hypothesize that thrombocytosis in HSP may be related to IL-6.

In conclusion, we speculated that thrombocytosis might be an early and useful parameter as an indicator of renal involvement in HSP. The use of this parameter adds no extra cost and technical effort. We think that further prospective studies to investigate the factors affecting the platelet count is required to obtain whether thrombocytosis might be employed as an indicator for renal involvement in HSP.

REFERENCES

1. Narchi H. Risk of long term renal impairment and duration of follow up recommended for Henoch-Schonlein purpura with normal or minimal urinary findings: A systematic review. *Arch Dis Child* 2005;90:916–920.
2. 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.
3. Saulsbury FT. Henoch-Schönlein purpura in children: Report of 100 patients and review of the literature. *Medicine* 1999;78:395–409.
4. Lin CY, Yang YH, Lee CC, Huang CL, Wang LC, Chiang BL. Thrombopoietin and interleukin-6 levels in Henoch-Schönlein purpura. *J Microbiol Immunol Infect* 2006;39(6):476–482.
5. Ozen S, Ruperto N, Dillon MJ, et al. EULAR/PRoS endorsed consensus criteria for the classification of childhood vasculitides. *Ann Rheum Dis* 2006;65:936–941.
6. National High Blood Pressure Education Program. Working Group on Hypertension Control in Children and Adolescents. Update on the 1987 task force report on high blood pressure in children and adolescents: A working group report from the National High Blood Pressure Education Program. *Pediatrics* 1996;98:49–58.
7. Saulsbury FT. Henoch-Schönlein purpura in children: Report of 100 patients and review of the literature. *Medicine* 1999;78:395–409.
8. Calvino MC, Llorca J, Garcia-Porrúa C, Fernandez-Inglesias JL, Rodriguez-Ledo P, Gonzalez-Gay MA. Henoch-Schönlein purpura in children from north western Spain: A 20-year epidemiologic and clinical study. *Medicine* 2001;80:279–290.
9. Chang WL, Yang YH, Wang LC, Lin YT, Chiang BL. Renal manifestations in Henoch-Schönlein purpura: A 10-year clinical study. *Pediatr Nephrol* 2005;20(9):1269–1272.
10. Jauhola O, Ronkainen J, Koskimies O, et al. Renal manifestations of Henoch-Schonlein purpura in a 6-month prospective study of 223 children. *Arch Dis Child* 2010;95(11):877–882.
11. Elstad MR, McIntyre TM, Prescott SM, Zimmerman GA. The interaction of leukocytes with platelets in blood coagulation. *Curr Opin Hematol* 1995;2(1):47–54.
12. McIntyre TM, Prescott SM, Weyrich AS, Zimmerman GA. Cell-cell interactions: Leukocyte-endothelial interactions. *Curr Opin Hematol* 2003;10(2):150–8.
13. Keskin N, Civilibal M, Elevli M, Koldas M, Duru NS, Ozturk H. Elevated plasma advanced oxidation protein products in children with Henoch-Schonlein purpura. *Pediatr Nephrol* 2011;26(11):1989–1993.
14. Lin SJ, Huang JL, Hsieh KH. Clinical and laboratory correlation of acute Henoch-Schönlein purpura in children. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1998;39:94–98.
15. Yang YH, Wang SJ, Chuang YH, Lin YT, Chiang BL. The level of IgA antibodies to human umbilical vein endothelial cells can be enhanced by TNF-alpha treatment in children with Henoch-Schonlein purpura. *Clin Exp Immunol* 2002;130:352–357.
16. Besbas N, Saatci U, Ruacan S, et al. The role of cytokines in Henoch Schonlein purpura. *Scand J Rheumatol* 1997;26:456–460.
17. Yang YH, Huang YH, Lin YL, et al. Circulating IgA from acute stage of childhood Henoch-Schonlein purpura can enhance endothelial interleukin (IL)-8 production through MEK/ERK signalling pathway. *Clin Exp Immunol* 2006;144:247–253.
18. Kaser A, Brandacher G, Steurer W, et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: Role in inflammatory thrombocytosis. *Blood* 2001;98:2720–2725.
19. van Gameraen MM, Willemse PH, Mulder NH, et al. Effects of recombinant human interleukin-6 in cancer patients: A phase III study. *Blood* 1994;84:1434–1441.
20. Fretzayas A, Sionti I, Moustaki M, Papadimitriou A, Nicolaidou P. Henoch-Schönlein purpura: A long-term prospective study in Greek children. *J Clin Rheumatol* 2008;14(6):324–331.