

Risk Factors for Severe Gastrointestinal Involvement in Childhood Henoch-Schoenlein Purpura

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Abstract

Background: Henoch–Schonlein Purpura (HSP) is an IgA-mediated vasculitis of children. It is often regarded as a benign disease. Nevertheless, some patients may manifest severe renal or gastrointestinal (GI) involvement. We sought to identify the risk factors for severe GI involvement in HSP.

Methods and findings: We performed a retrospective study of all children who had Henoch-Schönlein purpura with gastrointestinal (GI) involvement admitted during a 10 years period to a single pediatric department. The GI involvement was categorized as severe in children who presented with intense abdominal pain with a score > 3 on a 0-10 self- report scale, or who presented at least one of the following items on initial presentation and/or on the whole course of the disease <10 on the Amiel-Tison scale for children younger than 3 years, the need for enteral tube feeding or corticosteroid administration, upper or lower gastrointestinal bleeding, intussusception or parietal hematoma on abdominal ultrasound data and if a surgical intervention was needed (group A). The group B included all children diagnosed with HSP without GI involvement or presented with mild abdominal pain (group B). We compared the two groups, using initially Chi square (χ^2) and student "t" tests, and thereafter, we employed logistic stepwise regression analysis.

Conclusion: Independent risk factors for severe digestive involvement were hyperleukocytosis ($p=0.004$; Adj OR: 4.5 [1.6–13]), neutrophilia ($p<10^{-3}$; Adj OR: 8.7 [3.5–26.2]) and renal involvement. The risk factors for severe gastrointestinal involvement in SHP are close to those of severe renal impairment. The identification of these risk factors could guide the indication of hospitalization and the therapeutic modalities.

Introduction

Henoch-Schonlein Purpura (HSP), also known as rheumatoid purpura, is a systemic vasculitis involving the small vessels of the skin, the gastrointestinal (GI) tract, the kidneys and the joints [1]. GI involvement occurs in 10–40% of patients [2]. In addition to abdominal pain of varying intensity and duration, it includes GI bleeding, intussusceptions, perforations, and bowel infarctions. Severe GI involvement in HSP requires several therapeutic interventions such as corticosteroid, immunoglobulin infusions, enteral tube feeding and surgical management. As a consequence, this condition can result in significant morbidity and increased length and cost of hospital stay. Despite the life-threatening risk associated with abdominal symptoms, few studies have evaluated the predictive factors for severe GI involvement. We aimed to identify predictive factors for severe GI involvement in HSP.

Material and Methods

This was a retrospective, descriptive and analytic study of a population of children hospitalized for HSP during a 10-year period (January 2007 - December 2016). The study included all children admitted for HSP. To guarantee the exhaustiveness of the study population, the cases were extracted from the hospital database. The diagnosis of HSP was based on the simultaneous existence of purpura and at least one of the three other manifestations of the disease (articular, gastrointestinal and renal) [3]. Data collected from records included: age, gender, clinical symptoms and biological findings performed on the first day of hospital admission such as serum protein, serum albumin, 24-hour urine protein test and complete blood count. We also collected abdominal ultrasound and digestive endoscopy data. The GI involvement severity was based on the clinical presentation. It was found to be severe in children who presented at least one of the following items on initial presentation and/or on the whole course of the disease: intense abdominal pain with a score >3 on a 0-10 self-report scale, or score <10 on the Amiel-Tison scale for children younger than 3 years, the need for enteral tube feeding or corticosteroid administration, upper or lower gastrointestinal bleeding, intussusception or parietal

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hematoma on abdominal ultrasound data and if a surgical intervention was needed (Group A). The group B included all children diagnosed with HSP without GI involvement or presented with mild abdominal pain (Group B).

All analyses were performed using SPSS software version 19.0. We compared categorical variables with chi-square test or Fisher's exact test and continuous variables with the student t test. In all statistical tests, the significance level was set to 0.05. Univariate odds ratio was calculated as an approximation of relative risk factors by simple cross-tabulation, with 95% confidence intervals (95% CI). We have transformed the quantitative variables into categorical variables. To determine the threshold at which it must "cut", we have established ROC (Receiver Operating Characteristics) curve. After verifying that the area under the curve was significantly >0.5 , we have chosen the threshold value of the variable as corresponding to the best couple "sensitivity-specificity". In order to identify risk factors independently

related to the event, we conducted a logistic regression analysis in descending order.

Results

There were a total of 80 observations of HSP over the 10 years period of the study. Forty-seven children (58.75) had GI involvement. Digestive manifestations were considered severe in 37 cases (46.3%) (Group A). The remaining 43 belonged to group B with 10 children with mild GI involvement and 33 cases of HSP without digestive manifestations.

The annual admission rate varied between 4 and 11 cases per annum with an important resurgence of the disease in autumn and winter. In fact, 65.8% of the patients were hospitalized during these seasons. The mean age was 5.6 ± 2.3 years (range 2-12 years). The ratio of boys to girls was 1.58. No significant differences were observed among GI-involvement groups for any of the patient characteristics (**Table 1**).

Table 1 Comparison of baseline characteristics and biological parameters in the two groups.

Variables	Total population (N=80)	Group A	Group B (N=43)	p-value
		(N=37)		
Mean age \pm SD (years)	5.6 \pm 2.3	5.95 \pm 2.25	5.35 \pm 2.32	0.24
Gender (Male/female)	1.58	2	1.3	0.282
Digestive symptoms	47	37 (100%)	10 (21.3%)	-
Arthralgia	44 (55%)	15 (34.1)	29 (65.9%)	0.016
Arthritis	13 (16.3%)	3 (8.1%)	10 (23.3)	0.067
Hematuria	25 (31.3%)	16 (43.2%)	9 (20.9%)	0.032
Proteinuria	22 (27.5%)	18 (48.6%)	4 (9.3%)	$<10^{-3}$
Hematuria and Proteinuria	12 (15%)	11 (29.7%)	1 (2.3%)	0.001
Nephrotic syndrome	4 (5%)	4 (10.8%)	0	0.027
Mean hemoglobin level \pm SD (g/dl)	9.4 \pm 2.4	7.45 \pm 2	11.9 \pm 1.2	0.001
Mean WBC \pm SD $\times 10^3/\text{mm}^3$	10.2 \pm 3	11.5 \pm 3	9.1 \pm 3	0.001
Mean neutrophil count \pm SD $\times 10^3/\text{mm}^3$	6.3 \pm 2	7.4 \pm 5	5.2 \pm 2	$<10^{-3}$
Mean Serum sodium \pm SD (M Eq/L)	136 \pm 3	135 \pm 3	137 \pm 4	0.2
Mean Serum potassium \pm SD (M Eq/L)	4.1 \pm 0.6	4. \pm 0.7	4.2 \pm 0.7	1.6
CRP (mg/L)	24 \pm 18	26.8 \pm 21	21 \pm 14	0.165

A trigger was identified in 71 cases (89%). It was an infectious episode in 47 cases (59%) and medication in 24 cases (30%). The purpura was first sign of the disease in 59 cases (73.8%). Digestive disorders such as abdominal pain or digestive hemorrhage revealed HSP in 15 patients (18.8%). In the remaining cases, the revealing symptom was arthralgia. During the hospital stay, skin rash has been observed in all patients. Abdominal Pain was intense in all cases in group A. It was present in 10 children included in group B and was considered mild. Eight patients belonging to group A had lower gastrointestinal bleeding. At the time of admission, arthritis was detected in 13 cases (16.3%) without difference between

the two groups (8.1% versus 23.3%; $p=0.067$). The first examination revealed renal edema in six children one of whom had confirmed hypertension. Otherwise, urine test strips, performed the first day of hospital stay, detected hematuria in 25 cases (31.3%) and proteinuria in 22 cases (27.5%). Acute renal failure was found in four children in group A. Similarly four children in this group have been diagnosed with nephrotic syndrome. As illustrated in **Table 1**, renal involvement was more severe in group A. Complete blood count was performed in all cases. The mean hemoglobin level was 9.4 ± 2.4 g/dl (95% CI: 2.8-13). The mean white blood cell count (WBC) was $10247 \pm 3455/\text{mm}^3$ (range: 5100-18000). The mean neutrophil

count was $6300 \pm 2239/\text{mm}^3$ (range: 2800 -13000). The two parameters cited above were significantly higher in the first group (**Table 1**). The platelet count varied between $130000/\text{mm}^3$ and $503000/\text{mm}^3$ with an average of $253000/\text{mm}^3$ without difference between the two groups. The mean serum sodium level was similar between the two groups ($135 \pm 3 \text{ mEq/L}$ versus $137 \pm 4 \text{ mEq/L}$; $p=0.2$). The mean serum potassium levels were $4 \pm 0.72 \text{ mEq/L}$ and $4.25 \pm 0.75 \text{ mEq/L}$ respectively in the two groups ($p=0.16$). C-reactive protein was carried out in all patients. The serum concentration ranged between 0 and 83 mg/L without significant difference between the two groups ($p=0.165$). Abdominal ultrasound was performed at least once in all cases in group A. It revealed bowel wall thickness in 7 cases, parietal hematoma in 5 cases and intestinal intussusception in 3 children. Digestive endoscopy was performed in 26 cases (32.5%). It was normal in 14 cases and revealed a duodenal mucosal hemorrhage in 12 cases. Moreover, HSP was complicated with orchitis, pancreatitis and volvulus in 3, 2 and 1 children respectively. So, in summary all cases in group A had intense abdominal pain. In this group, 8 patients had lower GI bleeding, US revealed bowel wall thickness, parietal hematoma and intestinal intussusception respectively in 7, 5 and 3 cases and endoscopy was abnormal in 12 patients. Bed rest was the only therapeutic procedure in children belonging

to Group B. For Group A, in addition to bed rest, intravenous fluids administration was indicated in 24 cases (64.9%) with an average duration of 3.5 days (range 24 hours-5 days). Enteral tube feeding was recommended in 13 children (35%) for an average duration of 8.7 days (range 5-14 days). Corticosteroids were prescribed in 14 children who had no contraindications such as haemorrhage at endoscopy. Surgical treatment was performed in the three cases of intussusception and in the case of volvulus. All children with renal impairment were referred to the pediatric nephrology department. The average length of hospital stay was 6.3 ± 4.6 days, with a range between 1 and 18 days. It was of 10.22 ± 4.17 days (range 3-18 days) in group A and 2.93 ± 1 days (range 1-5 days) in group B ($p<10^{-4}$). Mortality was zero in this study.

In univariate analysis, the factors associated with severe GI involvement were hematuria ($p=0.032$, OR=2.8, 95% CI=1.1-7.6), proteinuria ($p<10^{-3}$, OR=9.2, 95% CI=2.7-31.1), the association of hematuria and proteinuria ($p=0.004$, OR=17.2, 95% CI=1.8-43.5), nephrotic syndrome ($p=0.001$, OR=17.7, 95% CI=2.1-45.7), $\text{WBC} > 10000 \text{ cells/mm}^3$ ($p=0.001$, OR=4.7, 95% CI=1.8-12.5) and neutrophil count greater than 6000 cells/mm^3 ($p<10^{-3}$, OR=8.8, 95% CI=3.1-25.1). Independent risk factors for severe digestive involvement (multivariate analysis) are illustrated in the **Table 2**.

Table 2 Multivariate analysis: Adjusted risk factors for severe GI involvement.

Parameters	Group A (N=37)	Group B (N=43)	p	A or (IC 95%)
Hematuria	16 (43.2%)	9 (20.9%)	0.034	2.6 (1-7.4)
Proteinuria	18 (48.6%)	4 (9.3%)	<10 ⁻³	8.7 (2.2-29.8)
Hematuria and proteinuria	11 (29.7%)	1 (2.3%)	0.004	17.2 (1.8-43.5)
Nephrotic syndrome	4 (10.8%)	0	0.03	2 (1.5-3)
Leukocytes count > $10000/\text{mm}^3$	28 (75.7%)	17 (39.5%)	0.004	4.5 (1.6-13)
Neutrophil count > $6000/\text{mm}^3$	30 (81.1%)	14 (32.6%)	<10 ⁻³	8.7 (3.5-26.2)

Discussion

Independent risk factors for severe gastrointestinal involvement in HSP were WBC greater than $10000/\text{mm}^3$, neutrophil count exceeding $6000/\text{mm}^3$ and presence of renal involvement at admission including hematuria, proteinuria and nephrotic syndrome. In the present study, we found a male predominance in both groups without significant difference. The male predominance is almost constant in the literature with a sex ratio ranging in value from 1.2 to 1.5 [1,4,5]. The few papers comparing severe and mild to moderate GI involvement in HSP had studied mainly biological findings. Nagomori et al. [6] compared the demographic characteristics of HSP with mild and severe GI manifestations. They didn't find any significant differences for any of the patient characteristics whereas they observed a significant correlation between the development of HSP nephritis and gender with males more likely to develop renal involvement. HSP usually occurs in children aged 2-10 years, mostly in those aged 4-6 years [3-5]. In the comparative study cited above, no

difference in age was found between SHP with severe or moderate digestive manifestations [6]. Blanco et al. [7] examined whether the age at onset of HSP reflects definable clinical characteristics of the disease. They observed a more severe GI involvement in patients older than 20 years. Instead, this paper compared the disease in children and adults and had not studied the correlation between severity of GI involvement and age in children. Otherwise, papers analyzing the effect of age on the severity of gastrointestinal disease in HSP are rare.

In the present study, precocious renal involvement, regardless of its severity, was a predictive factor of severe gastrointestinal disease. In contrast to the digestive manifestations, the predictive factors of severe nephritis in SHP are widely studied in the literature. Severe renal impairment is observed mainly in children older than 10 years, male gender, severe GI involvement, $\text{WBC} > 15 \times 10^9/\text{L}$ platelets $> 500 \times 10^9/\text{L}$, and in the case of a significant decrease in coagulation factor XIII [8-12]. Our results suggest

that the predictive factors for severe nephropathy are also related to severe GI disease. Leukocytosis and polynucleosis, without proven infection, are reported frequently in SHP [6,8]. In 2014, Nagomori et al. [6] developed a severity score for the assessment of gastrointestinal involvement in SHP. WBC exceeding 15000/mm³ and/or polynucleosis exceeding 10000/mm³ was risk factors for severe disease. The mechanism may be a tissue injury induced by inflammatory agents secreted by neutrophils [10]. In addition, a clinical trial reported that leukocytapheresis could not only ameliorate gastrointestinal symptoms, but also prevent HSP nephritis [13]. The above-cited score also included decreased serum albumin, serum sodium lower than 136 mmol/L, reduced coagulation factor XIII activity and increased D-dimers [6]. These parameters have not been evaluated in the present study. Thus, other studies are necessary for the identification of children at risk for severe GI involvement, requiring hospitalization, more attention and intervention such as corticosteroids, intravenous immunoglobulin therapy and factor XIII infusions despite the fact that the efficacy of these molecules remains controversial.

The major strength of this study was its importance for practitioners. Most studies on HSP have focused on renal involvement. Focusing on GI involvement is novel. Seeking risk factors for severe GI involvement could guide the therapeutic decisions such as the use of corticosteroids or enteral nutrition and regular US monitoring to reduce the risk of complications during the whole course of the disease. However our study has several limitations. It was a single-center study and the generalization of our results would be difficult. Some parameters were not studied due to the lack of data. Thereby, further large-scale and prospective studies are needed to overcome these limitations

Conclusion

As of today, no consensus exists regarding the management and follow-up of GI involvement in HSP. The identification of risk factors for severe digestive disease could guide the therapeutic strategy despite the fact that the effectiveness of different molecules remains controversial until today.

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