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ORIGINAL PAPER

Hitomi Sano · Michiko Izumida · Hiroshi Shimizu
Yunosuke Ogawa

Risk factors of renal involvement and significant proteinuria in Henoch-Schönlein purpura

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Abstract Risk factors of renal involvement and significant proteinuria in patients with Henoch-Schönlein purpura (HSP) were retrospectively evaluated by univariate and multivariate analyses. The analysis was performed in 134 patients with HSP. Renal involvement was found in 65 patients (49%) and 97% of the renal involvement was found within 3 months of disease onset. Moderate or severe proteinuria was recognised in 25 patients. A univariate analysis revealed that an age of more than 4 years at the onset, severe abdominal pain with gastrointestinal bleeding, persistent purpura over a month, coagulation factor XIII activity $<80\%$, and treatment with factor XIII concentrate were associated with developing renal involvement. A multivariate analysis showed that severe abdominal symptoms, an age of more than 4 years, and persistent purpura increased the risk of renal involvement. Risk factors of moderate or severe proteinuria were also examined. The risk factors in a univariate analysis were severe abdominal symptoms, persistent purpura, decreased factor XIII activity, treatment with steroids, and treatment with factor XIII concentrate. Of those, persistent purpura, treatment with factor XIII concentrate, and factor XIII activity $<80\%$ were associated with significant proteinuria in a multivariate analysis. Among the patients with severe abdominal symptoms, factor XIII activity was significantly decreased in patients with significant proteinuria compared to other patients without significant proteinuria. *Conclusion:* Long-term prognosis of Henoch-Schönlein purpura is dependent on the severity of renal involvement. In those patients who have the risk factors of renal involvement, especially significant proteinuria, close attention should be paid to a urinalysis for at least 3 months from the onset of the disease.

Keywords Children · Factor XIII · Henoch-Schönlein purpura · Purpura nephritis

Abbreviation *HSP* Henoch-Schönlein purpura

Introduction

Henoch-Schönlein purpura (HSP) is the most common acute systemic vasculitis affecting children. The dominant clinical characteristics are purpura, abdominal pain, gastrointestinal bleeding, arthritis, and renal involvement. Since HSP is a self-limited disease in general, the long-term prognosis is dependent on the severity of renal involvement. Although most of the patients with renal involvement in HSP have a good prognosis, some with significant proteinuria progress to end-stage renal disease [3, 9]. A number of studies have therefore focused on the prognostic factors of developing renal involvement, but the results were not totally consistent. The first multivariate analysis based on a Cox regression model has recently shown that severe abdominal symptoms, persistent purpura, and decreased coagulation factor XIII activity were significant risk factors of renal involvement in HSP [12]. Those patients with isolated haematuria or with mild proteinuria have a uniformly good prognosis [4, 19]. We therefore sought to define the risk factors of not only development of renal involvement in HSP but also development of moderate or severe proteinuria. In the present study, we evaluated 134 patients with HSP and examined the risk factors by using univariate and multivariate analyses.

Subjects and methods

A total of 134 patients with HSP were admitted to our hospital between January 1991 and December 2000. The diagnosis of HSP was made if a typical purpura without thrombocytopenia was

H. Sano · M. Izumida · H. Shimizu (✉) · Y. Ogawa
Department of Paediatrics,
Saitama Medical Centre,
Saitama Medical School,
1981 Kamoda-Tsujido,
Kawagoe, 350-8550 Japan
E-mail: hirosmz@saitama-med.ac.jp
Tel.: +81-49-2283617
Fax: +81-49-2261424

recognised. Other accepted features included abdominal pain, gastrointestinal bleeding, arthritis or renal involvement. Arthritis was defined as swelling of the joints or painful periarticular soft tissue oedema, and the patients who could not walk due to arthritis were determined to have severe arthritis. The patients manifesting abdominal pain with gastrointestinal bleeding such as guaiac-positive stools or grossly bloody stools were defined to have severe abdominal symptoms. Persistent purpura was determined as purpura persisting over 1 month. Renal involvement was defined by the presence of gross or microscopic haematuria (> 5 red blood cells per high-power microscopic field in a centrifuged specimen) with or without proteinuria [12,19]. Mild, moderate or severe proteinuria was defined as proteinuria less than 0.1 g/m^2 per day, greater than 0.1 g/m^2 per day but less than the nephrotic range, or nephrotic range (more than 1.0 g/m^2 per day), respectively. The factor XIII activity was examined in 129 patients by a chromogenic substrate method using a commercial coagulation system (Dade Behring Marburg GmbH, Marburg, Germany). The factor XIII activity of less than 80% was defined to be decreased. The serum IgA level was examined in 120 patients by nephelometric immunoassay using a Behring nephelometer analyser II (Dade Behring). An IgA level of more than 300 mg/dl was classed as increased.

Statistical analysis was performed using the chi-squared test and Student's *t* test for a univariate analysis, and the stepwise forward and backward models for a multivariate logistic regression analysis. A *P* value of less than 0.05 was considered as significant.

Results

Clinical and laboratory features

The major clinical and laboratory features of the 134 patients are shown in Table 1. The patient population consisted of 71 boys (53%) and 63 girls and 49 (37%) manifested purpura persisting for more than 1 month. Abdominal pain was evident in 96 (72%), and severe abdominal symptoms were recognised in 80 of them. Arthritis was present in 99 (74%) patients, of whom 24 had severe symptoms. Factor XIII activity was determined in 129 patients, of whom 79 (61%) had a decreased activity under 80%. The mean (± SD) factor XIII activity was 70.2 ± 28.6%. An increased serum IgA level was recorded in 26 (22%) of 120 patients examined. The mean IgA level was 241.6 ± 34.9 mg/dl. A total of 25 patients (19%) were treated with corticosteroids in order to reduce abdominal symptoms. Oral or intravenous prednisolone, initially 1 to 2 mg/kg per day, was administered for 12.5 days (median) ranging from 2 to 54 days. Factor XIII concentrate at a dose of 30 to 50 units/kg per day for 3 days was also administered to 31 patients (23%) for relief of the symptoms.

Renal involvement was found in 65 patients (49%) which manifested as isolated haematuria in 28 (21%), mild proteinuria with or no haematuria in 12 (9%), and moderate proteinuria in 14 (10%). Nephrotic syndrome was diagnosed in ten patients (7%). One patient manifested acute glomerular nephritis. The mean interval from the appearance of the purpura to the onset of renal involvement was 26 days. Of the patients with renal involvement, 49 (76%) manifested urinary abnormalities within 4 weeks and 97% of the renal involvement was found within 3 months of the appearance of purpura. The renal involvement resolved in 51 patients during the observation periods (8 months to 9 years), and 86% of those became free of urinary abnormalities within 2 years. In patients with moderate or severe proteinuria, the renal involvement persisted significantly longer; the mean duration of urinary abnormalities was 469 days in those patients in contrast to 217 days in patients with isolated haematuria and/or mild proteinuria ($P = 0.027$). During the observation periods, no patient had yet developed end-stage renal disease.

Table 1 Clinical and laboratory features in 134 children with HSP

Feature	Number (*n*) (%)
Boys	71 (53%)
Persistent purpura	49 (37%)
Abdominal pain	96 (72%)
Severe abdominal symptoms	80 (60%)
Arthritis	99 (74%)
Severe arthritis	24 (18%)
Renal involvement	65 (49%)
Haematuria alone	28 (21%)
Mild proteinuria and/or haematuria	12 (9%)
Moderate proteinuria and/or haematuria	14 (10%)
Nephrotic syndrome	10 (7%)
Acute glomerular nephritis	1
Decreased factor XIII activity[a] ($n = 129$ patients)	79 (61%)
Increased serum IgA level ($n = 120$ patients)	26 (22%)
Treatment with steroids	25 (19%)
Treatment with factor XIII concentrate	31 (23%)

[a]Factor XIII activity < 80%

Risk factors of renal involvement

A univariate analysis was performed to examine the relationship between renal involvement and various factors (Table 2). Age at disease onset ranged from 2 to 15 years, with a mean of 6.3 ± 2.4 years. Patients with renal involvement were significantly older than those without renal involvement (6.7 ± 2.4 years versus 5.9 ± 2.4 years, $P = 0.042$) (Fig. 1). Data analysis at various cut-off values of age revealed that an age more than 4 years ($P = 0.005$) was a significant factor. Severe abdominal symptoms ($P = 0.0004$) and persistent purpura ($P = 0.04$) were also significant in patients with renal involvement. In addition, factor XIII activity in patients with renal involvement was significantly decreased ($P = 0.024$), and the treatment with factor XIII concentrate was significantly more often prescribed ($P = 0.023$). Concerning factor XIII activity, the mean activity of factor XIII was more obviously decreased in patients with severe abdominal symptoms (62.6 ± 29.3%, $n = 80$) than in others (82.6 ± 22.9%, $n = 49$) ($P < 0.0001$). Among the patients with severe abdominal symptoms, the mean factor XIII activities were not significantly different between the patients with or without renal involvement (Table 3).

We further examined the risk factors of renal involvement by using a multivariate analysis (Table 4). When analysed by a multivariate logistic regression analysis using a stepwise backward method, severe abdominal

Table 2 Univariate analysis of the factors associated with renal involvement in HSP

Factor	*P*
Boys	0.080
Age at onset	0.042*
Age ≥4 years	0.005*
Severe abdominal symptoms	0.0004*
Severe arthritis	0.93
Persistent purpura	0.040*
Factor XIII activity	0.024*
Factor XIII activity <80%	0.18
Serum IgA level	0.72
Treatment with steroids	0.54
Treatment with factor XIII concentrate	0.025*

*$P < 0.05$

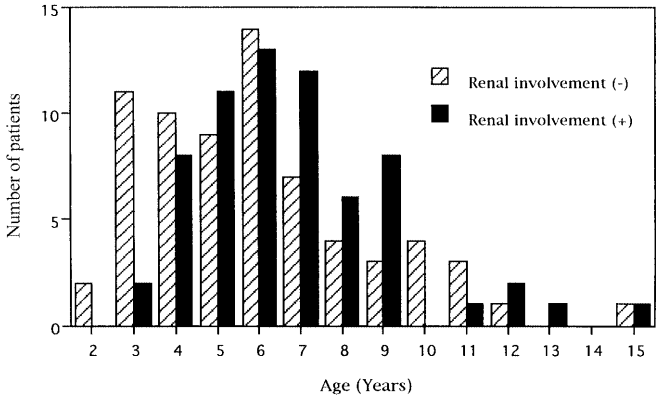

Fig. 1 Age distribution of 134 patients with HSP

Table 3 Factor XIII activity in patients with HSP and severe abdominal symptoms ($n = 80$)

Renal features		Number of patients (*n*)	Mean factor XIII activity (SD) (%)	*P*
Renal involvement	(+)	49	60.8 (30.6)	0.49
	(−)	31	65.5 (27.3)	
Moderate or severe proteinuria	(+)	21	45.5 (22.1)	0.0015*
	(−)	59	68.6 (29.3)	

*$P < 0.05$

symptoms, persistent purpura, and age over 4 years were found to be independent risk factors of renal involvement with significance. Their odds ratios were 1.74, 2.07, and 4.94, respectively. In addition, the stepwise forward analysis method defined severe abdominal symptoms and age over 4 years as significant risk factors of renal involvement with odds ratios of 1.87 and 5.10, respectively.

Risk factors of moderate or severe proteinuria

Moderate or severe proteinuria was evident in a total of 25 patients (19%). As shown in Table 5, a univariate analysis showed that severe abdominal symptoms ($P = 0.033$) and persistent purpura ($P = 0.024$) were significantly associated with moderate or severe proteinuria. Factor XIII activity ($P < 0.0001$) was also significantly associated with moderate or severe proteinuria. Thus, we segregated our patients into two groups at various cut-off values of factor XIII activity. The analysis revealed that the factor XIII activity of less than 80% ($P = 0.003$) was a significant factor in patients with moderate or severe proteinuria. The treatment with steroids ($P = 0.027$) and treatment with factor XIII concentrate ($P < 0.0001$) were also significant factors.

Table 4 Multivariate analysis of the factors associated with renal involvement in HSP

Method	Factor	Odds ratio	95% confidence interval	*P*
Backward	Severe abdominal symptoms	1.74	1.12–2.70	0.014
	Persistent purpura	2.07	0.94–4.58	0.071
	Age ≥4 years	4.94	1.00–24.34	0.049
Forward	Severe abdominal symptoms	1.87	1.21–2.88	0.0046
	Age ≥4 years	5.10	1.05–24.9	0.044

Table 5 Univariate analysis of the factors associated with moderate or severe proteinuria in HSP

Factor	*P*
Boys	0.103
Age at onset	0.41
Age ≥4 years	0.78
Severe abdominal symptoms	0.033*
Severe arthritis	0.93
Persistent purpura	0.024*
Factor XIII activity	<0.0001*
Factor XIII activity <80%	0.003*
Serum IgA level	0.72
Treatment with steroids	0.041*
Treatment with factor XIII concentrate	<0.0001*

*$P < 0.05$

The results of a multivariate analysis are summarised in Table 6. When analysed by a multivariate analysis using a stepwise backward method, the factors associated with moderate or severe proteinuria included persistent purpura, treatment with factor XIII concentrate, and decreased factor XIII activity with odds ratios of 2.66, 6.31 and 2.46, respectively. The stepwise forward analysis method defined persistent purpura and treatment with factor XIII concentrate as significant risk factors of moderate or severe proteinuria with odds ratios of 3.22 and 8.09, respectively. Factor XIII activity was remarkably decreased in patients with moderate or severe proteinuria; in 64% of the patients with moderate or severe proteinuria, factor XIII activity was below 50%, and none of these patients had an activity above 90% (Fig. 2). The lower activity of factor XIII in these patients was independent of severe abdominal symptoms, since the mean factor XIII activity was signifi-

Table 6 Multivariate analysis of the factors associated with moderate or severe proteinuria in HSP

Method	Factor	Odds ratio	95% confidence interval	*P*
Backward	Persistent purpura	2.66	0.97–7.24	0.056
	Treatment with factor XIII concentrate	6.31	2.28–17.44	0.0004
	Factor XIII activity < 80%	2.46	0.87–12.90	0.079
Forward	Persistent purpura	3.22	1.21–8.56	0.019
	Treatment with factor XIII concentrate	8.09	3.01–21.75	< 0.0001

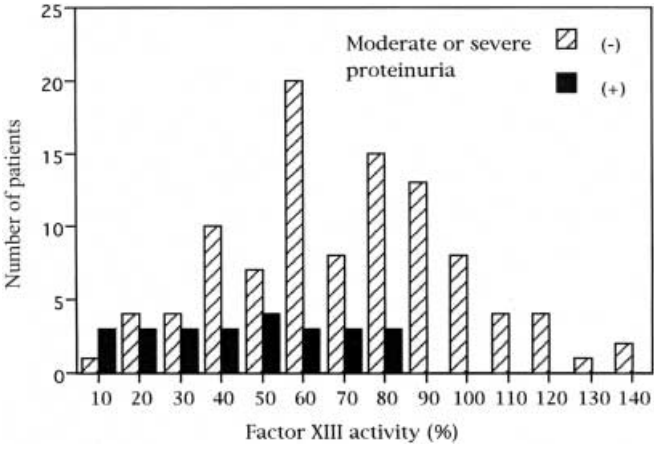

Fig. 2 Factor XIII activity in 129 patients with HSP

cantly decreased in patients with moderate or severe proteinuria ($45.5 \pm 22.1\%$, $P = 0.0015$) compared to other patients with severe abdominal symptoms (Table 3).

Discussion

Although most patients with HSP and renal involvement have a favourable prognosis, 1%–7% progress to end-stage renal disease [4, 21,23]. The patients with haematuria but without proteinuria have an almost completely benign prognosis, while ascending amounts of proteinuria are associated with progressively worse outcome [9]. It has been described that some patients, especially those with significant proteinuria, have persistent urinary abnormalities on long-term follow-up [8,21]. In the present study, the renal involvement persisted significantly longer in patients with moderate or severe proteinuria. We therefore sought to examine the risk factors of moderate or severe proteinuria as well as renal involvement. We could demonstrate that severe abdominal pain with gastrointestinal bleeding, an age of more than 4 years at onset, and persistent purpura for more than 1 month were the significant risk factors for the development of renal involvement in HSP. Furthermore, a factor XIII activity of less than 80% and treatment with factor XIII concentrate were demonstrated to be significantly associated with moderate or severe proteinuria in addition to persistent purpura.

Renal involvement was present in 49% of the patients with HSP in the present study. The result seems to be in agreement with previous studies in which approximately 30%–60% of patients with HSP manifested renal involvement [9]. In contrast to abdominal pain or arthritis in HSP, the onset of renal involvement may be delayed for weeks or months after the appearance of the purpura. The mean interval from the appearance of the purpura to the onset of renal involvement was 26 days in the present study, and 97% of the renal involvement was found within 3 months of the appearance of purpura. These results were quite consistent with other studies [19] and suggest that close attention should be paid to a urinalysis for at least 3 months from the onset of the disease in HSP patients who have the risk factors of renal involvement including significant proteinuria.

Kaku et al. [12] first reported a multivariate analysis based on a Cox regression model, and indicated severe abdominal symptoms, persistent purpura, and decreased factor XIII activity to be significant risk factors of renal involvement in HSP. Severe abdominal symptoms and persistent purpura were consistent with our results. As for factor XIII activity, we found that the mean activity of factor XIII was significantly decreased in patients with severe abdominal symptoms, however, among the patients with severe abdominal symptoms, factor XIII activity was not different between patients with or without renal involvement. From these results, it was considered that factor XIII activity was not independently related to renal involvement but was associated with severe abdominal symptoms. We also found that renal involvement was uncommon in patients under 3 years of age and an age of more than 4 years at onset was apparently associated with developing renal involvement. The result was in agreement with a previous report indicating that children less than 2 years of age were less likely to have renal involvement or abdominal complications [2]. Kaku et al. [12] indicated that an age more than 7 years at onset was one of the risk factors of renal involvement based on a univariate analysis, but a multivariate analysis did not show that the age was associated with renal involvement. Our results indicated that they should have used a lower year of age as a cut-off value.

Coagulation factor XIII is a transglutaminase which cross links fibrin monomers thereby forming the stable insoluble fibrin clot [14, 20]. Factor XIII circulates in plasma in a tetrameric form, i.e., two subunit A (Mr 75000) showing enzyme activity and two subunit B (Mr 88000) which is considered to be the carrier protein. A decreased level of factor XIII activity has been described to be associated with abdominal pain and gastrointestinal

bleeding in HSP [5, 11, 13], which was in agreement with the present result indicating the significantly decreased factor XIII activity in patients with severe abdominal symptoms. The mechanism of the decreased level of factor XIII activity in HSP has not yet been clarified, but a hypothesis has been proposed that factor XIII may be broken down by proteases of infiltrating leucocytes or be excessively consumed during fibrin formation around affected vessels. The hypothesis is supported by the finding of decreased levels of factor XIII in leukaemia [6], erosive gastritis [16], and Weber-Christian disease [10]. It was interesting that the present study indicated that the patients with moderate or severe proteinuria had apparently lower factor XIII activity even among those with severe abdominal symptoms. Moreover, severe abdominal symptoms by themselves were not defined to be significant risk factors of moderate or severe proteinuria by the present multivariate analysis. Taken together, the decreased factor XIII activity seemed to be an independent risk factor of moderate or severe proteinuria.

The therapeutic use of factor XIII concentrate has been reported to be effective for the improvement of abdominal and joint symptoms in HSP in Japanese children [7,22]. The role of factor XIII concentrate treatment in HSP is postulated that extrinsic factor XIII stabilises the fibrin clot, improves the active vasculitis, and subsequently decreases the degradation or consumption of intrinsic factor XIII rather than simply compensates for the reduced level of factor XIII activity. The effectiveness of factor XIII concentrate for the relief of severity of abdominal and joint involvement may reflect severity of vasculitis as a common pathogenetic factor. Fukui et al. [7] described that factor XIII concentrate administration improved both proteinuria and haematuria in HSP. In contrast, Kaku et al. [12] could not demonstrate the effectiveness of factor XIII concentrate administration in preventing the renal involvement in HSP. We found in the present study that the treatment with factor XIII concentrate was a significant risk factor for moderate or severe proteinuria. However, we considered that this is due to the fact that the treatment with factor XIII concentrate was significantly performed in those patients with moderate or severe proteinuria because of their remarkably decreased factor XIII activity. The treatment by itself did not seem to be a risk factor of significant proteinuria, since five patients with normal factor XIII activity had received factor XIII concentrate and only one of them developed moderate proteinuria. Further studies must be required to clarify the relation between factor XIII activity and significant proteinuria. In addition, although factor XIII treatment is translated into therapeutic strategies in Japan, a possible genetic or racial influence on the efficacy of factor XIII concentrate treatment remains to be elucidated.

Previous studies described that the use of corticosteroids gave the patients with HSP an earlier resolution of their abdominal and joint symptoms [1, 17]. In contrast those findings, it has been under discussion whether early corticosteroid administration prevented delayed renal involvement [15, 18]. Although Kaku et al. [12] reported that treatment with steroids had a hazard ratio of 0.36 and was considered to decrease the risk of renal involvement, our results were not able to indicate the beneficial effect of steroids on developing renal involvement in HSP. A univariate analysis in our study suggested that treatment with steroids was associated with moderate or severe proteinuria, but it might be due to severe abdominal symptoms in these patients.

In summary, 49% of our patients with HSP manifested renal involvement and 19% had moderate or severe proteinuria. Based on a multivariate analysis, the present study indicated that severe abdominal symptoms, persistent purpura, and age over 4 years were significant risk factors of renal involvement in HSP, and in addition to persistent purpura, decreased factor XIII activity was highly associated with the development of significant proteinuria. HSP patients who have the risk factors for renal involvement, especially significant proteinuria, should be closely observed for the development of renal involvement for at least 3 months after disease onset.

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