

Adult Henoch–Schönlein purpura: Clinical and histopathological predictors of systemic disease and profound renal disease

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Abstract

Background: A major challenge in the management of adult Henoch–Schönlein purpura is the difficulty in assessing the risk of systemic involvement. There is currently a paucity of data in this area.

Aims: This study sought to determine specific clinical and histopathological features associated with systemic involvement in adult Henoch–Schönlein purpura.

Methods: We reviewed the records of 99 adult Henoch–Schönlein purpura patients who presented at the National Skin Centre, Singapore, between January 2008 and May 2015.

Results: Renal involvement was found in 56 (56.6%) patients, joint involvement in 21 (21.2%) and gastrointestinal involvement in 13 (13.1%). Age > 30 years was an independent predictor of renal involvement with an adjusted odds ratio of 2.97 (95% confidence interval, 1.08–8.16; $P = 0.04$). Risk factors for significant renal involvement necessitating nephrology referral were further evaluated: the odds were approximately 60% higher for every 10-year increase in age (95% confidence interval, 1.02–2.57; $P = 0.04$) and patients with cutaneous bullae and/or necrosis had an almost six times higher risk (95% confidence interval, 1.43–25.00; $P = 0.01$).

Limitations: This study was limited by its retrospective design. We also lacked long-term data to examine how clinical and histopathological characteristics correlated with long-term disease outcomes.

Conclusions: Adult Henoch–Schönlein purpura patients older than 30 years have a threefold increased risk of renal involvement. The risk of profound renal disease necessitating nephrology referral rose significantly with age and the presence of cutaneous bullae and/or necrosis.

Key words: Adult, cutaneous, gastrointestinal diseases, Henoch–Schönlein purpura, joint diseases, kidney diseases, leukocytoclastic, retrospective studies, vasculitis

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Introduction

Henoch–Schönlein purpura is a small-vessel vasculitis that affects multiple organ systems including the skin, kidneys, joints and gastrointestinal tract. A hallmark of Henoch–Schönlein purpura is nonthrombocytopenic purpura, most commonly on the lower limbs [Figure 1]. Histopathologically, Henoch–Schönlein purpura is characterized by leukocytoclastic vasculitis associated with deposition of immunoglobulin A immune complexes in vessel walls. Childhood Henoch–Schönlein purpura has been extensively studied, but much less attention has been given to adult Henoch–Schönlein

purpura, which is known to have a significantly higher frequency of renal involvement and poorer renal outcomes.^{1–6} Renal involvement is the most serious sequela of Henoch–Schönlein purpura and can progress to end-stage renal failure requiring renal replacement therapy.

Assessing the risk of systemic involvement remains a major challenge in the management of adult Henoch–Schönlein purpura, though recent years have seen a growing interest in investigating

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predictors of systemic involvement. Some characteristics that have been described include lesions above the waist, presence of bullous and/or necrotic lesions [Figure 2], older age, absence of tissue eosinophils and presence of immunoglobulin M deposits on skin histology.⁷⁻¹⁰ However, not many studies have been published on this topic and most were limited by small sample sizes. In addition, some of the findings reported are conflicting.

There are also few studies which investigated risk factors of clinically significant renal involvement that necessitates nephrology referral. Therefore, we sought to determine whether specific clinical and histopathological features are associated with (1) the presence of renal, joint and gastrointestinal involvement and (2) significant renal involvement that necessitates nephrology referral.

Methods

Patients

Medical records of patients who presented at the National Skin Centre, the main tertiary dermatological referral center in Singapore, between January 2008 and May 2015 were reviewed. Diagnostic criteria for Henoch–Schönlein purpura were similar to those used in previous studies: (1) palpable purpura or petechiae clinically consistent with Henoch–Schönlein purpura, (2) skin biopsy showing leukocytoclastic vasculitis on histological examination and (3) immunoglobulin A deposition in vessel walls

on immunohistochemical examination.⁷⁻⁹ Inclusion required all three criteria to be satisfied and an age at diagnosis of ≥ 18 years. Patients were excluded if they had a known history of malignancy, connective tissue diseases, autoimmune diseases, viral hepatitis, cryoglobulinemia or other hematologic disorders.^{8,9,11}

Assessment of systemic involvement was also done as in previous studies.⁷⁻⁹ Patients were considered to have joint involvement if arthralgia and/or joint swelling were present on clinical history and examination. Gastrointestinal involvement was considered to be present if there was abdominal pain and/or gastrointestinal bleeding during the development of cutaneous lesions. Renal involvement was determined through the detection of microscopic hematuria (red cell casts or >5 red blood cells per high power field) and/or proteinuria (urine protein $\geq 1+$) on microscopic urinalysis. Microscopic hematuria in association with proteinuria of variable range is the earliest and most sensitive sign of nephropathy in Henoch–Schönlein purpura.¹²

Significant renal involvement necessitating nephrology referral was defined as the presence of at least one of the following: (1) new onset hypertension, (2) macroscopic hematuria for ≥ 5 days, (3) microscopic hematuria for ≥ 12 months, (4) proteinuria (\geq protein 2+ on microscopic urinalysis) for ≥ 4 weeks, (5) abnormal renal function as indicated by creatinine clearance <60 mL/min,



Figure 1: Characteristic nonthrombocytopenic purpura in Henoch–Schönlein purpura



Figure 2: Cutaneous bullae in Henoch–Schönlein purpura

(6) nephrotic syndrome (proteinuria >3.5 g/day and plasma albumin <2.5 g/dL) or (7) acute nephritic syndrome (microscopic or macroscopic hematuria and two other signs including proteinuria, edema, hypertension, oliguria, and raised serum creatinine or urea). Since there are no guidelines available on the indications for nephrology referral in adult Henoch–Schönlein purpura patients, the criteria used were adapted from recommendations for pediatric Henoch–Schönlein purpura.^{1,13-17}

Table 1: Patient demographics and clinical characteristics

Characteristics	n=99 (%)
Sex	
Male	32 (32.3)
Female	67 (67.7)
Age	
Mean±SD	39.6±15.6 year
Median (range)	37 (18-72) year
Race	
Chinese	71 (71.7)
Malay	3 (3.0)
Indian	19 (19.2)
Others	6 (6.1)
Systemic involvement	
Renal	56 (56.6)
Joint	21 (21.2)
Gastrointestinal	13 (13.1)
Distribution of skin lesions	
Lower limbs	99 (100.0)
Buttocks	22 (22.2)
Above waist (trunk, upper limbs or head)	41 (41.4)
Presence of bullous and/or necrotic lesions	25 (25.2)
Histological and immunohistochemical findings	
Eosinophils	25 (25.2)
IgM	14 (14.1)
IgG	3 (3.0)
C3	66 (66.6)
Fibrinogen	20 (20.2)

SD: Standard deviation, IgM: Immunoglobulin M, IgG: Immunoglobulin G, y: Years. All values are presented as number and percentage of patients unless specified otherwise

Statistics

Chi-square tests or Fisher's exact tests were used to test for the association of each categorical variable with systemic involvement. Wilcoxon rank-sum test was performed to assess the relationship between age and systemic involvement. Multivariate logistic regression models were used to adjust for confounders. Odds ratios and their corresponding 95% confidence intervals were calculated. $P < 0.05$ was considered statistically significant. Statistics were generated using STATA version 14.0 (STATA Corporation, College Station, TX, USA).

Results

A total of 99 patients were included in the study [Table 1], of whom 32 (32.3%) were men. Their median age was 37 years (range, 18–72 years) and the mean follow-up duration was 15 months (range, 1 week–5.9 years). The ethnicity distribution of our cohort is similar to that of the local population, except that there was a higher percentage of Indians (19.2% vs. 9.1%) and a lower percentage of Malays (3.0% vs. 13.3%).¹⁸

Renal involvement was found in 56 (56.6%) patients, joint involvement in 21 (21.2%) and gastrointestinal involvement in 13 (13.1%). None of the 56 patients with renal involvement had a previous history of renal disease. A large majority, 50 (89.3%) of the 56 patients, developed hematuria and/or proteinuria within one month of diagnosis of Henoch–Schönlein purpura, including 34 (60.7%) who had hematuria and/or proteinuria at diagnosis. The longest interval from diagnosis of Henoch–Schönlein purpura to the development of hematuria and/or proteinuria was 3.9 years. Nineteen patients with renal involvement met our criteria for significant renal involvement requiring nephrology referral.

Using bivariate analysis, age at diagnosis was found to be associated with renal involvement ($P < 0.01$). Multivariate analysis further demonstrated that age > 30 years was an independent predictor of renal involvement with an adjusted odds ratio of 2.97 (95% confidence interval: 1.08–8.16, $P = 0.04$) [Table 2]. The occurrences of joint and gastrointestinal involvement were associated with each other ($P < 0.01$) [Table 3]. No association was found between systemic involvement and the distribution of cutaneous lesions, presence of bullous and/or necrotic lesions, presence of tissue eosinophils, immunoglobulin M, immunoglobulin G, C3 or fibrinogen on skin histology and immunofluorescence studies [Table 4].

Table 2: Association between age and renal involvement

Age	Bivariate analysis			Multivariate analysis		
	Without renal involvement, n=43 (%)	With renal involvement, n=56 (%)	P	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P
Mean	35.2±15.4 year	42.9±15.0 year	<0.01	1.03 (1.01-1.06)	1.03 (1.00-1.07)	0.06
Median (range)	28 (18-68) year	45 (18-72) year				
≤30 year	24 (55.8)	17 (30.4)	0.01	2.90 (1.27-6.64)	2.97 (1.08-8.16)	0.04
>30 year	19 (44.2)	39 (69.6)				
≤40 year	28 (65.1)	24 (42.9)	0.03	2.49 (1.10-5.65)	2.78 (0.97-8.01)	0.06
>40 year	15 (34.9)	32 (57.1)				
≤50 year	34 (79.1)	37 (66.1)	0.06	1.94 (0.77-4.87)	1.73 (0.57-5.21)	0.33
>50 year	9 (20.9)	19 (33.9)				
≤60 year	39 (90.7)	37 (66.1)	1.00	1.17 (0.31-4.44)	0.67 (0.14-3.31)	0.62
>60 year	9 (20.9)	19 (33.9)				

CI: Confidence interval, OR: Odds ratio, y: Years. All values are presented as number and percentage of patients unless specified otherwise

Characteristics associated with significant renal involvement necessitating nephrology referral were further evaluated. Bivariate analyses yielded significant results for older age ($P < 0.01$), presence of cutaneous lesions on the trunk ($P = 0.03$) and upper limbs ($P = 0.04$), presence of cutaneous bullae and/or necrosis (including

erosions and/or ulceration) ($P = 0.01$) and presence of fibrinogen in immunofluorescence studies ($P = 0.01$). Multivariate analysis revealed two of these factors, age and the presence of cutaneous bullae and/or necrosis, to be independent predictors of significant renal involvement. The adjusted odds ratio for each 10-year increase in age was 1.62 (95% confidence interval, 1.02–2.57; $P = 0.04$) and that for cutaneous bullae and/or necrosis was 5.98 (95% confidence interval, 1.43–25.00; $P = 0.01$) [Table 5].

Of the 56 patients with renal involvement in our patient cohort, 33 (58.9%) were referred to a nephrologist for suspicion of IgA nephropathy. Three of these patients underwent a renal biopsy and histological findings confirmed immunoglobulin A (IgA) nephropathy in all three. Among the 21 patients with gastrointestinal

Table 3: Association between joint and gastrointestinal involvement

Gastrointestinal involvement	Joint involvement		P
	No n=78 (%)	Yes n=21 (%)	
No	73 (93.6)	13 (61.9)	<0.01
Yes	5 (6.4)	8 (38.1)	

Table 4: Clinical and histopathological associations of systemic involvement in Henoch-Schonlein purpura

Characteristics	Renal involvement		P	Joint involvement		P	Gastrointestinal involvement		P
	No n=43 (%)	Yes n=56 (%)		No n=78 (%)	Yes n=21 (%)		No n=86 (%)	Yes n=13 (%)	
Age									
Mean±SD	35.2±15.4 year	42.9±15.0 year	<0.01	40.1±16.0 year	37.4±14.3 year	0.54	40.5±16.0 year	33.4±11.7 year	0.17
Median (range)	28 (18-68) year	45 (18-72) year		39 (18-72) year	35 (18-67) year		41 (18-72) year	35 (18-51) year	
≤30 year	24 (55.8)	17 (30.4)	0.01	32 (41.0)	9 (42.9)	0.88	34 (39.5)	7 (53.8)	0.33
>30 year	19 (44.2)	39 (69.6)		46 (59.0)	12 (57.1)		52 (60.5)	6 (46.2)	
Gender									
Male	12 (27.9)	12 (27.9)	0.41	27 (34.6)	5 (23.8)	0.35	28 (32.6)	4 (30.8)	1.00
Female	31 (72.1)	36 (64.3)		51 (65.4)	16 (76.2)		58 (67.4)	9 (69.2)	
Race									
Chinese	29 (67.4)	42 (75.0)	0.76	54 (69.2)	17 (81.0)	0.46	61 (70.9)	10 (76.9)	0.54
Malay	2 (4.7)	1 (1.8)		2 (2.6)	1 (4.8)		2 (2.3)	1 (7.7)	
Indian	9 (20.9)	10 (17.9)		16 (20.5)	3 (14.3)		17 (19.8)	2 (15.4)	
Others	3 (7.0)	3 (5.4)		6 (7.7)	0		3 (5.4)	0	
Renal involvement									
No		NA		34 (43.6)	9 (42.9)	0.95	39 (45.3)	4 (30.8)	0.38
Yes				12 (57.2)	44 (56.4)		47 (54.7)	9 (69.2)	
Joint involvement									
No	34 (79.1)	44 (78.6)	0.95		NA		73 (84.9)	5 (38.5)	<0.01
Yes	9 (20.9)	12 (21.4)					13 (15.1)	21 (61.5)	
Gastrointestinal involvement									
No	39 (90.7)	47 (83.9)	0.38	73 (93.6)	13 (61.9)	<0.01		NA	
Yes	4 (9.3)	9 (16.1)		5 (6.4)	8 (38.1)				
Lesions above waist									
No	27 (62.8)	31 (55.4)	0.46	46 (59.0)	12 (57.1)	0.88	52 (60.5)	6 (46.2)	0.33
Yes	16 (37.2)	25 (44.6)		32 (41.0)	9 (42.9)		34 (39.5)	7 (53.9)	
Bullous and/or necrotic lesions									
No	35 (81.4)	39 (69.6)	0.18	60 (76.9)	14 (66.7)	0.34	64 (74.4)	10 (76.9)	1.00
Yes	8 (18.6)	17 (30.4)		18 (23.1)	7 (33.3)		22 (25.6)	3 (23.1)	
Eosinophils on routine histology									
No	34 (79.1)	40 (71.4)	0.38	57 (73.1)	17 (81.0)	0.58	65 (75.6)	9 (69.2)	0.73
Yes	9 (20.9)	16 (28.6)		21 (26.9)	4 (19.1)		21 (24.4)	4 (30.8)	
IgM on immunohistology									
No	35 (81.4)	50 (89.3)	0.26	69 (88.5)	16 (76.2)	0.15	74 (86.1)	11 (84.6)	1.00
Yes	8 (18.6)	6 (10.7)		9 (11.5)	5 (23.8)		12 (14.0)	2 (15.4)	

Contd...

Table 4: Contd...

Characteristics	Renal involvement		P	Joint involvement		P	Gastrointestinal involvement		P
	No n=43 (%)	Yes n=56 (%)		No n=78 (%)	Yes n=21 (%)		No n=86 (%)	Yes n=13 (%)	
IgG on immunohistology									
No	42 (97.7)	54 (95.4)	1.00	77 (98.7)	19 (90.5)	0.11	83 (96.5)	13 (100.0)	1.00
Yes	1 (2.3)	2 (3.6)		1 (1.3)	2 (9.5)		3 (3.5)	0	
C3 on immunohistology									
No	16 (37.2)	17 (30.4)	0.47	25 (32.1)	8 (38.1)	0.60	29 (33.7)	4 (30.8)	1.00
Yes	27 (62.8)	39 (69.6)		53 (68.0)	13 (61.9)		57 (66.3)	9 (69.2)	
Fibrinogen on immunohistology									
No	35 (81.4)	44 (78.6)	0.73	61 (78.2)	18 (85.7)	0.55	70 (81.4)	9 (69.2)	0.29
Yes	8 (18.6)	12 (21.4)		17 (21.8)	3 (14.3)		16 (18.6)	4 (30.8)	

SD: Standard deviation, GI: Gastrointestinal, NA: Not available, IgM: Immunoglobulin M, IgG: Immunoglobulin G, y: years. All values are presented as number and percentage of patients unless specified otherwise

Table 5: Associations with significant renal involvement necessitating nephrology referral

Characteristics	Bivariate analysis			Multivariate analysis		
	Nephrology referral not indicated n=43 (%)	Nephrology referral indicated n=56 (%)	P	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P
Age (10-year increase)	NA	NA	<0.01	1.56 (1.10-2.21)	1.62 (1.02-2.57)	0.04
Lesions on trunk	68 (85.0)	12 (63.2)	0.03	3.31 (1.08-10.09)	4.80 (0.85-27.15)	0.08
	12 (15.0)	7 (36.8)				
Lesions on upper limbs	54 (67.5)	8 (42.1)	0.04	2.86 (1.03-7.95)	1.90 (0.46-7.91)	0.38
	26 (32.5)	11 (57.9)				
Cutaneous bullae and/or necrosis	64 (80.0)	10 (52.6)	0.01	3.60 (1.25-10.33)	5.98 (1.43-25.00)	0.01
	16 (20.0)	9 (47.4)				
Fibrinogen on immunohistology	68 (85.0)	11 (57.9)	0.01		NA*	
	12 (15.0)	8 (42.1)				

*Fibrinogen on immunohistology was found to correlate with age and hence removed from the multivariate logistic regression model. SD: Standard deviation, CI: Confidence interval, OR: Odds ratio, NA: Not available. All values are presented as number and percentage of patients unless specified otherwise

involvement, 5 were referred to a gastroenterologist due to symptoms suggestive of gastrointestinal involvement. Four of these patients underwent endoscopic examination which revealed hemorrhagic duodenitis in 1, chronic gastritis in 2 and duodenal ulcer in 1. It was not certain if these endoscopic findings were a result of gastrointestinal involvement of Henoch–Schönlein purpura.

Discussion

Till now, this study comprises the largest retrospective cohort of adult Henoch–Schönlein purpura patients being studied for systemic manifestations. Our patient demographics were unlike that in another local study which found a preponderance of Malays,¹⁹ though that study too found renal involvement in 56% of patients, a figure similar to that in our study.

In our patients, age >30 years was shown to be an independent predictor of renal involvement with an almost threefold higher risk in this older age group. This is in concurrence with the findings of Poterucha *et al.* that patients older than 40 years were significantly more likely to have renal involvement, though they did not perform a multivariate analysis.⁹ Furthermore, we found that age was also a strong predictor of profound renal involvement that warrants referral to a nephrologist, with an approximately 60% increase in risk with every 10-year increase in age. We did not find any previous study that investigated predictors of nephrology referral

in adult Henoch–Schönlein purpura patients. A study on childhood Henoch–Schönlein purpura using similar criteria for nephrology referral however did find that older children were at higher risk of requiring referral ($P < 0.01$).¹⁴

Belli and Dervis¹⁰ noted an association between the presence of bullous and/or necrotic lesions and the development of renal and gastrointestinal involvement, which was in contrast to an earlier study by Tancrede-Bohin *et al.*²⁰ Our study did not find such an association. However, when we used significant renal involvement necessitating nephrology referral as the outcome, the presence of cutaneous bullae and/or necrosis was found to be a strong independent predictor, conferring an almost six times higher risk.

Another new positive finding in this study is the association between joint and gastrointestinal involvement ($P < 0.01$) which should prompt physicians to monitor more closely for symptoms of gastrointestinal involvement when patients present with joint symptoms and vice versa.

Renal involvement occurs after a variable period from the onset of Henoch–Schönlein purpura. Current data in adult patients is insufficient to guide the frequency of follow-up to detect renal disease. Among the 56 patients with renal involvement in our study,

a large majority (89.3%) developed hematuria and/or proteinuria within 1 month of diagnosis. Therefore, we recommend that adult patients with newly diagnosed Henoch–Schönlein purpura be more closely followed up in the first month.

This study was limited by its retrospective design. Patients were followed up for varying durations and we lacked long-term data to examine how clinical and histopathological characteristics correlated with long-term disease outcomes.

Conclusions

This study analyzed the demographic features, cutaneous and systemic manifestations of 99 adult Asian patients with Henoch–Schönlein purpura. We found that age >30 years at diagnosis conferred a nearly threefold higher risk of renal involvement. The risk of profound renal involvement necessitating nephrology referral rose by approximately 60% with every 10-year increase in age and was almost six times higher if patients had cutaneous bullae and/or necrosis. These findings can serve as a guide to stratify risk in adult patients with Henoch–Schönlein purpura, and those at higher risk can be accorded closer monitoring.

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Conflicts of interest

There are no conflicts of interest.

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