# Five-Year Experience of Henoch-Schönlein Nephritis in Thai Children: A Single Center Report

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Background: The risk of Henoch-Schönlein nephritis (HSN) is well-established, however, the existing data validating this concept remains limited.

Materials and Methods: A retrospective 5-year chart review was conducted at Queen Sirikit National Institute of Child Health.

**Results**: Ninety patients were diagnosed with Henoch-Schönlein purpura, with a mean age of 6.9±2.8 years. Among them, 25 cases (27.7%) presented with renal involvement or HSN. Among the HSN cases, 17 were classified as mild and eight as severe. Symptom presentation included hematuria in ten cases (40%), proteinuria with hematuria in six cases (24%), nephrotic range proteinuria with hematuria in four cases (16%), acute nephritis syndrome with proteinuria in three cases (12%), proteinuria in one case (4%), and nephrotic range proteinuria in one case (4%). Significant associations were observed between HSN incidence and patients older than eight years, (p=0.03) and those with purpura lasting more than three weeks, (p=0.02). The onset of renal involvement ranged from 1 to 315 days (mean of 45.4 days and median of 24 days). Three cases (12%) had mild HSN after six months of the onset of disease. There were no reported cases of mortality or chronic kidney disease.

**Conclusion**: The majority of HSN cases manifest as mild and are associated with favorable outcomes. To achieve early diagnosis of HSN in all instances, it is imperative to conduct timely and regular urinary examinations for all affected patients.

Keywords: Henoch-Schönlein purpura; Henoch-Schönlein nephritis; Nephrotic syndrome; Hematuria

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Henoch-Schönlein purpura (HSP) is a systemic inflammation of small vessels, characterized by the tissue deposition of immunoglobulin A (IgA) containing immune complexes, also known as IgA vasculitis (IgAV). However, aberrant IgA antibodies may not be confirmed in all patients<sup>(1)</sup>. Although it can occur at any age, the peak incidence is between four and six years old, and more than 90% of the patients are under ten years of age<sup>(2-4)</sup>. Many studies have shown a seasonal pattern in the disease, with a higher prevalence of HSP found in late autumn and winter, suggesting a possible viral infection-related etiology<sup>(5)</sup>.

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Department of Dermatology, Queen Sirikit National Institute of Child Heath, 420/8 Ratchawithi Road, Thung Phayathai, Bangkok 10400, Thailand.

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Rujimethapass N, Kietkajornkul C, Chaninvanich S, Limpongsanurak W, Singalavanija S. Five-Year Experience of Henoch-Schönlein Nephritis in Thai Children: A Single Center Report. J Med Assoc Thai 2023;106:925-31. DOI: 10.35755/jmedassocthai.2023.10.13895 The classic presentations of HSP include skin purpura, arthritis, abdominal pain, and renal involvement. Typically, HSP is considered to be self-limiting, although renal involvement as Henoch-Schönlein nephritis (HSN) is a well-known cause of morbidity from the disease, with its prevalence varying between 20% and 60% of patients<sup>(6,7)</sup>. Renal involvement, which is not necessarily related to the severity of extrarenal involvement, significantly impacts the overall long-term prognosis of the disease. The onset of renal involvement is typically noted within a few days or one to six months after the onset of systemic symptoms and rarely occurs after the improvement of clinical manifestations<sup>(2,8-11)</sup>.

Renal involvement in HSP typically includes findings of microscopic hematuria and mild proteinuria, with rare occurrences of acute nephritis or nephrotic syndrome. Although the majority of renal involvement cases are mild and self-limited, it has been reported that approximately 1% of patients may progress to end-stage renal disease (ESRD)<sup>(12-16)</sup>.

The objective of the present study was to determine the incidence of renal involvement in HSP patients and to identify the initial clinical signs and symptoms that most accurately associate with HSN in a cohort of children with HSP.

# **Materials and Methods**

The investigation was a retrospective review of pediatric patients, aged less than 15 years, who fulfilled the validated EULAR/PRINTO/PRES criteria for HSP, treated at both the inpatient and outpatient pediatric dermatology, nephrology, and gastroenterology clinics at the Queen Sirikit National Institute of Child Health. The follow-up duration for these patients was at least six months, over a 5-year period between January 2012 and December 2016. During each monthly follow-up, all patients underwent routine urinary examination, which hematuria was defined as the presence of red blood cells (RBCs) exceeding 5 cells/HPF (high-power field), proteinuria defined as urine protein exceeding 1+, or a urine protein/creatinine ratio (UPCR) of 0.2 or greater. Acute nephritis syndrome was defined as hematuria plus two or more of the following 1) hypertension, 2) increased serum levels of blood urea nitrogen (BUN) or creatinine, and 3) urine output less than 0.5 mL/kg/hour.

The severity of HSN was categorized as mild and severe HSN. Mild HSN was defined as patients who had hematuria and/or proteinuria at less than nephrotic-range proteinuria, and severe HSN was defined as patients who had nephrotic-range proteinuria and/or acute nephritis<sup>(15)</sup>. A kidney biopsy was performed in patients with nephrotic syndrome, acute nephritis, and gross hematuria with nonnephrotic-range proteinuria during the first month of presentation. However, according to the KDIGO 2021 guidelines, treatment may proceed without a kidney biopsy confirmation of the diagnosis<sup>(17)</sup>.

The chi-square test was used to determine the relationship between initial manifestations and the development of renal involvement. A p-value of less than 0.05 was considered significant. The analysis was conducted using IBM SPSS Statistics, version 23.0 (IBM Corp., Armonk, NY, USA).

The present study was approved by the Research Ethics Review Committee of the Queen Sirikit National Institute of Child Health (REC.020/2561). The retrospective chart review was approved for the collection of clinical data, including age, sex, and the presence of renal, gastrointestinal (GI), or other systemic involvement.

# Results

Ninety patients who fulfilled the validated EULAR/PRINTO/PRES criteria for HSP were

examined over a 5-year period. Among them, 46 patients (51.1%) were male, with a male-to-female ratio of 1.05 to 1. The mean age of the patients was 6.9±2.8 years, ranging from 1 to 13 years old. The peak incidence occurred between 4 to 6 years for 31 cases (34.4%), followed by the age group from 7 to 9 years for 29 cases (32.2%). The mean follow-up duration was 19.4±8 months, ranging from 6 to 72 months. Of the patients, 16 (17.8%) were obese, and 13 (14.4%) were underweight. The highest incidence was observed in June for 15 cases (16.7%), along with May and August for 10 cases (11.1%). Purpura, starting on both lower legs, was the most common presenting symptom in all patients in 66 cases (73.3%). Among them, 62 cases (94%) had mild purpura on both lower legs, while four cases (6%) had severe skin manifestations, such as hemorrhagic blebs or necrotic lesions (Figure 1A, B). Abdominal pain was present in 18 cases (20%), and six cases (6.7%) presented with arthralgias or joint swelling. All patients had a purpuric rash, with the most common location being on both lower extremities. Forty-three cases (47.8%) had abdominal pain, and 14 cases (15.5%) had GI bleeding. Joint tenderness was observed in 40 cases (44.4%), predominantly in the ankle joint. Renal involvement (HSN) was present in 25 cases (27.8%), and other manifestations, such as orchitis and subcutaneous edema, were observed in 16 cases (17.8%) (Table 1).

Laboratory investigations included complete blood count (CBC), with hematocrit ranging from 28.2% to 46.8% (mean  $37\pm3.4$ ), white blood cell count (WBC) ranging from 6,540 to 36,820/ cu mm (mean 12,550±5,211), and platelet count ranging from 154,000 to 759,000/cu mm (mean 414,188±122,530). Complement (C3 and C4) levels in 31 cases (34.4%) were all within the normal range. Antinuclear antibodies in 42 cases (46.6%) turned out to be unremarkable. ASO titer was sent in 51 cases, showed a high titer in 11 cases (21.6%). Erythrocyte sedimentation rate (ESR) was done in 28 cases, showing an increased rate in 24 cases (85.7%).

Sixty-five cases (72.2%) had no renal involvement (non-HSN), 60 cases (92.3%) treated with systemic corticosteroids and others with supportive care for including bed rest, non-steroidal anti-inflammatory drugs (NSAIDs). Indication for systemic steroids was GI involvement in 43 cases (71.6%), subcutaneous edema and orchitis in 13 cases (21.6%), severe skin manifestation in four cases (6.6%). The mean duration of systemic corticosteroids treatment was 3.7±1 weeks, ranging from 1 to 8.5 weeks. Most



Figure 1. (A) Symmetrical palpable purpura on both legs. (B) Severe purpura, hemorrhagic vesicles and crust over bilateral legs and feet.

Table 1. Demographic clinical and laboratory data (n=90)

Characteristics	Values*
Age (year); mean±SD	$6.9{\pm}2.8$
Sex; n (%)	
Male	46 (51.1)
Female	44 (48.9)
Sign and symptoms; n (%)	
Purpura	90 (100)
Arthralgia/arthritis	40 (44.4)
Abdominal pain	43 (47.0)
GI bleeding	14 (15.5)
Renal involvement (HSN); n (%)	
Mild HSN	17 (18.8)
Severe HSN	8 (8.8)
Others; n (%)	
Orchitis	5 (5.5)
Subcutaneous edema	12 (13.3)
Follow-up (months); mean (range)	19.4 (6 to 72)

\* Values are mean  $\pm$  standard deviation for quantitative variables and number (percent) of patients for dichotomous ones

patients improved within seven days of systemic corticosteroids treatment.

HSN was diagnosed in 25 cases (27.7%). Among those who had HSN, 17 cases (68%) had mild HSN, and eight cases (32%) had severe HSN. The age range was from 3 to 13 years (mean  $7.7\pm3$ ). There was 15 males and 10 females, thus, a male-to-female ratio of 1.5 to 1. Symptoms included hematuria for ten cases (40%), proteinuria with hematuria for six cases (24%), nephrotic range proteinuria with hematuria for four cases (16%), acute nephritis syndrome with proteinuria for three cases (12%), proteinuria in one case (4%), and nephrotic range proteinuria also in one case (4%). We found renal involvement, HSN, in 25 cases (27.8%), and the patients above eight years and those who had skin manifestations for more than three weeks were significantly associated with the incidence of HSN (p<0.05). The other factors such as gender, other associated symptoms, laboratory investigation, and systemic steroids treatment were not significantly associated with the incidence of HSN as shown in Table 2. The onset of renal involvement ranged from 1 to 315 days (mean of 45.4 and median of 24 days). We found three cases (12%) had mild HSN after six months of the onset of disease. Among the patients with mild HSN, 15 cases (88.2%) were treated with systemic corticosteroids, the treatment duration ranging from 1 to 12 weeks (mean 3.7±2.8 weeks). Other treatments included angiotensin-converting enzyme inhibitors (ACEIs). All cases of mild HSN showed recovery without any serious renal sequelae.

Severe HSN was found in eight cases, of which five cases (62.5%) had nephrotic-range proteinuria, and three cases (37.5%) had acute nephritis syndrome with proteinuria. All patients with severe HSN

Table 2. Factor	· associated	with	Henoch	-Schönlein	nephritis
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Factors	HSN (n=25) n (%)	Non-HSN (n=65) n (%)	p-value
Sex			0.295
Male	15 (32.6)	31 (67.4)	
Female	10 (22.7)	34 (77.3)	
Age			0.030*
≤8 years old	12 (20.3)	47 (79.7)	
>8 years old	13 (41.9)	18 (58.1)	
Symptoms			
Purpura >3 weeks	6 (60.0)	4 (40.0)	0.025*
Abdominal pain	31 (72.1)	12 (27.9)	0.979
GI bleeding	4 (28.6)	10 (71.4)	1.000
Laboratory			
White cell count			0.274
• <15,000/cu mm	17 (24.3)	53 (75.7)	
• >15,000/cu mm	7 (36.8)	12 (63.2)	
Platelet count			0.891
• <500,000/cu mm	17 (26.6)	47 (73.4)	
• >500,000/cu mm	7 (28.0)	18 (72.0)	
ESR >20	3 (12.5)	21 (87.5)	0.135
Treatments			1.000
Corticosteroids	23 (27.7)	60 (72.3)	
Non-corticosteroids	2 (28.6)	5 (71.4)	

GI=gastrointestinal; ESR=erythrocyte sedimentation rate; HSN=Henoch-Schönlein nephritis

received systemic corticosteroids duration of treatment ranging from 5.5 to 27 months (mean  $10.8\pm7.2$  months), and ACEIs, with the treatment duration ranging from 3 to 27 months (mean  $13.6\pm8.3$  months). Additionally, five cases received cyclophosphamide for 2 to 4 months (mean  $2.8\pm0.8$  months), and one case received cyclosporine A for

2 years. Renal biopsy was performed in two cases, which showed focal segmental glomerulosclerosis with mesangial IgA deposits in both cases (Table 3).

The mean duration of follow-up for patients with non-HSN was  $16.2\pm 2$  months, ranging from 6 to 72 months, while for those with HSN was  $33.4\pm 4.1$ months, ranging from 7 to 72 months. Twenty-two cases (24.4%) showed recurrence, with 15 cases in the non-HSN group and seven cases in the HSN group. The time of recurrence ranged from 1 to 31 months (mean  $6.6\pm 3.2$  months). Recurrence symptoms included purpura with GI involvement in 19 cases (86.3%) and purpura with hematuria in three cases (13.6%). Recurrence cases were treated with systemic corticosteroids, with a mean treatment duration of  $1.1\pm 0.27$  months. All cases showed recovery without any serious renal sequelae.

# Discussion

The renal involvement associated with Henoch-Schönlein purpura (HSP/IgAV) commonly referred to as HSN is a significant concern extensively documented in nephrological literature. Although HSN is generally considered more benign in children than in adults, with up to 90% experiencing disease resolution and only 2% to 13% eventually developing renal failure<sup>(18-20)</sup>, early identification of HSN is crucial. Early renal damage can be asymptomatic, and if left untreated, it may lead to irreversible renal damage. Therefore, pediatricians and pediatric dermatologists, as the first healthcare providers to encounter patients with purpura and/or severe abdominal pain, play a critical role in making the diagnosis and assessing the risk of systemic involvement, particularly renal involvement, in their

Table 3. Characteristics of patients with severe Henoch-Schönlein nephritis (HSN)

Number	Age at first visit (year)	Sex	Manifestation	Treatment	Renal Biopsy	Follow up (month)
1	6	Female	Proteinuria and acute nephritis	Prednisolone, cyclosporine A	-	30
2	13	Male	Proteinuria	Prednisolone, cyclophosphamide, cyclosporine A	Focal segmental glomerulosclerosis with mesangial IgA deposition	15
3	10	Female	Proteinuria	Prednisolone, cyclophosphamide	Focal segmental glomerulosclerosis with mesangial IgA deposition	14
4	13	Male	Proteinuria and acute nephritis	Prednisolone, cyclophosphamide	-	12
5	4	Male	Proteinuria	Prednisolone, dapsone	-	12
6	4	Male	Proteinuria	Prednisolone	-	64
7	3	Female	Proteinuria	Prednisolone	-	14
8	3	Male	Proteinuria and acute nephritis	Prednisolone, cyclophosphamide	-	69

patient population. They should advocate for early and frequent urinary screening.

Regarding the unknown etiology of HSP, several potential triggers have been proposed in various studies, including infections, medications, and vaccines. Upper respiratory tract infections have been frequently implicated as triggers, with peak incidence often observed during the winter months<sup>(4)</sup>. Interestingly, the present study findings showed that the peak incidence occurred during the rainy season in Thailand, from June to September with 40 cases (44.4%), which could possibly be linked to viral infections. Additionally, evidence of concomitant or recent group A Streptococcus infection, as indicated by ASO titer, was documented in 21.6% of the present study participants, consistent with other reports<sup>(21-24)</sup>. Clinical presentations found in the present study revealed the majority of patients presented with skin purpura or 66 cases (73.3%). Furthermore, 43 cases (47.8%) presented with abdominal pain, 40 cases (44.4%) had joint pain, and 25 cases (27.8%) had renal involvement, which is consistent with the findings of Pengpis and García studies<sup>(24,25)</sup>.

The inflammatory marker, elevated ESR, was remarkably elevated in 85.7% of the cases, indicating the active inflammatory process of the disease. All cases had normal serum complement levels, while some studies reported that 10% to 20% had low serum C3 levels<sup>(4)</sup>.

The incidence of renal involvement varies in different studies. The prevalence of HSN in the García study was up to 67%, in the Jauhola study 46%, and in the Nickavar study 39%<sup>(15,25,26)</sup>. According to the SHARE initiative, renal involvement in IgAV/HSN occurs in 20% to 80% of children and can manifest with isolated microscopic or macroscopic hematuria with or without proteinuria, and nephritic or nephrotic syndrome<sup>(27)</sup>. The variation in prevalence among studies is partly due to different criteria used to define renal involvement and the variability in the length of follow-up after the onset of acute illness. For instance, Jauhola's study described hematuria as more than 5 RBC/HPF or a positive dipstick in urine, while Assadi's study defined hematuria as more than 3 RBC/HPF<sup>(15,28)</sup>. In the present study, 40% of cases had transient hematuria, which might not have been detected at the time of the initial examination. Additionally, various types of proteinuria were observed, including proteinuria with hematuria, nephrotic-range proteinuria with hematuria, acute nephritis syndrome with proteinuria, proteinuria, and nephrotic-range proteinuria.

Renal involvement of IgAV (HSN) was observed in 97% of the patients within the first six months, and only 3.3% were diagnosed after ten months. Based on these findings, the authors propose that regular urine examinations for at least 12 months would be more appropriate than examinations at six months, as observed in three cases (12%) with mild HSN diagnosed after six months from the onset of the disease<sup>(12)</sup>. The present study also indicated that patients over eight years old with prolonged skin manifestations had a higher risk of renal involvement. Similar findings were reported by Chan's study, which showed a higher risk of renal involvement in HSP in males, those aged over ten years, those with severe GI involvement, and those with prolonged joint and skin symptoms<sup>(29)</sup>. Studies by Jauhola et al. and García et al. also found a higher likelihood of developing HSN in patients aged over eight years<sup>(15,24)</sup>. Systemic corticosteroids were used in the non-HSN, mild HSN, and severe HSN groups, with mean durations of 3.7±1 week,  $3.7\pm2.8$  weeks, and  $10.8\pm7.2$  months, respectively. The present study demonstrated that the use of systemic corticosteroids did not significantly prevent nephritis in children with IgAV, which is consistent with other studies<sup>(12,30-34)</sup>. Among the cases without renal involvement, the recurrence rate was 20% in the non-steroid treatment group and 23.3% in patients received systemic steroid treatment. However, the recurrence rate in both groups is incomparable due to the severity of the disease. Patients who received steroid treatment had more severe symptoms than those who did not. Audemard and Hung studied HSP in adult patients and found that adults tended to have a higher incidence of chronic renal disease and more severe renal involvement/ESRD compared to pediatric populations<sup>(5,27)</sup>. Similar to the present study, all cases with renal involvement (HSN) responded well to treatment without serious or permanent renal disease. However, Goldstein et al. followed patients with HSN for 23 years and found that 15% of cases developed nephritis or heavy proteinuria, while 40% of cases with nephrotic syndrome progressed to renal failure<sup>(28,34)</sup>. Therefore, the authors recommend longterm follow-ups for all severe HSN patients.

# Conclusion

HSN remains a well-known and significant complication of HSP. Regular urine examinations for all cases of HSP and diligent, long-term followup for patients diagnosed with HSN are of utmost importance to ensure timely detection and effective management to prevent serious renal complications.

# What is already known on this topic?

Renal involvement in HSP is remarkable.

# What does this study add?

Risks of having renal involvement in HSP were patients older than eight years of age and those who have purpura for more than three weeks. Regular urine examinations for all cases of HSP and diligent, long-term follow-up for patients diagnosed with HSN are important. The authors propose that regular urine examinations for at least 12 months would be more appropriate than examinations at six months, as the authors observed cases with mild HSN diagnosed after six months from the onset of the disease.

# **Conflicts of interest**

The authors declare no conflict of interest.

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