Endocapillary Proliferation was Associated with Unfavorable Outcomes in Children with Henoch-Schönlein Purpura Nephritis and IgA Nephropathy

Supatjaree Chanvitan

Mahidol University Faculty of Medicine Ramathibodi Hospital

Kanchana Tangnararatchakit

Mahidol University Faculty of Medicine Ramathibodi Hospital

Pawaree Saisawat

Mahidol University Faculty of Medicine Ramathibodi Hospital

Songkiat Chantarogh

Mahidol University Faculty of Medicine Ramathibodi Hospital

Suchin Worawichawong

Mahidol University Faculty of Medicine Ramathibodi Hospital

Kwanchai Pirojsakul (✉ Kwanchai.pio@mahidol.ac.th)

Mahidol University Faculty of Medicine Ramathibodi Hospital <https://orcid.org/0000-0002-9043-6689>

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Abstract

Introduction: There are limited data on the outcomes in children with Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) in limited-resource countries. This study was aimed to evaluate the outcome of HSPN and IgAN and to evaluate the pathological findings associated with unfavorable outcomes.

Materials and methods: This was a retrospective study conducted in children (≤ 18 years) diagnosed with HSPN or IgAN, had estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² and underwent renal biopsy between year 2002 - 2018 at Ramathibodi Hospital, Bangkok, Thailand. Clinical outcomes were graded according to the outcome classification by Counahan, as follows: favorable [A, normal; B, minor urinary abnormalities (proteinuria < 1 g/1.73 m²/day)]; unfavorable [C, active renal disease (proteinuria > 1 g/1.73 m²/day and/or hypertension); D, renal insufficiency (eGFR < 60 mL/min/1.73 m² or died)]. Pathologies were graded according to Oxford classification.

Results: A total of 47 patients (28 HSPN and 19 IgAN) were included with means of age at 9.4 ± 2.8 vs 11.3 ± 4.3 years, respectively. After a median follow-up time of 50 months, proportions of favorable outcomes in the patients with HSPN and IgAN were 82.1% (23/28) and 89.5% (17/19), respectively (p -value = 0.685). In multivariate analysis, only endocapillary proliferation (E) was associated with unfavorable outcomes in both diseases with the odds ratio (95% CI) of 12.46 (1.36 - 114.51, p -value = 0.026).

Conclusion: The clinical outcomes of most patients with HSPN and IgAN were favorable and comparable. Endocapillary proliferation (E) was the only factor associated with poor outcome in both diseases.

Introduction

Immunoglobulin A nephropathy (IgAN) and Henoch-Schönlein purpura nephritis (HSPN) are common glomerular diseases in children. HSPN usually presents with involvement of skin, joints and gastrointestinal tract and approximately 20–47% of patients had renal involvement (e.g. proteinuria, hematuria)^{1–3}. However, IgAN usually presents with renal limited symptoms such as recurrent hematuria or proteinuria in which diagnosis needs to be confirmed by renal pathology showing mesangial deposition of IgA in glomeruli. Both diseases share common clinical features and pathologies². The clinical, genetic and immunologic features of these conditions are so closely linked that one could consider HSPN as a systemic form of IgAN^{4–6}. The pathogenesis of both conditions are proposed to be related with galactose-deficiency of O-linked glycans in the hinge region of IgA1 subtype. These structures are recognized by autoantibodies, resulting in the formation of immune complexes in the circulation and deposition of these immune complexes in various organs^{5, 7–9}.

In IgAN, the previous studies in pediatric patients indicated that 5-year and 20-year renal survival rates were 94–100% and 70–89%, respectively^{10–14}. Several factors have impact on the prognosis in patients

with IgAN, such as elevated serum creatinine, heavy proteinuria, and hypertension¹⁵. However, the outcome of IgAN in children is generally a complete resolution of clinical signs and symptoms^{4, 13, 14}. Children with IgAN who have a normal urinalysis after treatment usually do not progress to end-stage renal disease (ESRD)⁴. In HSPN, mild cases usually show a complete resolution of nephritis. However, some studies reported the recurrence rate between 2.7–30%^{16–18}. Data from unselected cohorts showed that 5-year renal survival rates were between 82–95%^{19–21}. The unfavorable prognosis of HSPN usually links to severe clinical symptoms or pathology at the initial presentation. There are several studies regarding the outcomes of treatment and pathological findings in adults with IgAN and HSPN. However, there are limited data on pathological findings and outcomes of treatment in children in Thailand. The aims of this study were to evaluate the outcomes of HSPN and IgAN and to evaluate the pathological findings associated with unfavorable outcomes.

Materials And Methods

We performed a retrospective single-center study by reviewing the medical records and renal biopsy results of children aged ≤ 18 years, diagnosed with HSPN or IgAN from years 1998–2018 at Ramathibodi Hospital, Bangkok, Thailand. HSPN was diagnosed according to criteria defined by the American College of Rheumatology¹. IgAN was diagnosed based on the results of pathology findings without the presence of extrarenal symptoms at initial diagnosis and during the follow-up period. Secondary IgAN, eg. liver disease, inflammatory bowel disease and infection-induced IgAN were excluded. All medical records were reviewed with emphasis on baseline characteristics, clinical presentation, laboratory data, pathological findings, treatments, and outcomes. Ethical permission was obtained from the Ethics Committee in Human Research of the Faculty of Medicine, Ramathibodi Hospital (ID 09-61-59 for IgAN and ID 09-61-29 for HSPN).

Hypertension was diagnosed if blood pressure (BP) $\geq$ the 95th percentile for age, gender and height on repeated measurements²². Proteinuria was defined as a positive protein in urine dipstick testing or urine protein-to-creatinine ratio (UPCr) ≥ 0.2 g/g. Hematuria was defined as positive blood in urine dipstick testing or ≥ 5 red blood cells per high-power on microscopic examination of a centrifuged urine specimen. Estimated glomerular filtration rate (eGFR) was calculated by the bedside CKiD equation as follows²³:

$$\text{eGFR} = 0.413 \times \text{height (cm)} / \text{serum creatinine (mg/dl)}$$

All renal biopsies were performed prior to the initiation of treatment and reviewed by the two experienced renal histopathologists. Stains used for assessment were H&E, PAS, Jones and Masson's trichrome. All specimens were examined by light microscopy, immunofluorescence staining and electron microscopy. MEST-C criteria in the updated Oxford classification were used to describe pathological data which were standardized for classification in IgA nephropathy²⁴. The MEST-C criteria comprise of mesangial hypercellularity (with M0 and M1) corresponding to $\leq 50\%$ and $> 50\%$ of the glomeruli showing

hypercellularity, respectively), endocapillary proliferation (defined as E0, absence or E1, presence), segmental glomerulosclerosis (defined as S0, absence or S1, presence), tubular atrophy/interstitial fibrosis (with T0, T1, and T2 corresponding to $\leq 25\%$, 26%-50%, and $> 50\%$ of cortical area involvement, respectively), cellular/fibrocellular crescents (with C0, C1, and C2 corresponding to their absence, presence in ≥ 1 and $< 25\%$ of glomeruli, and presence in $\geq 25\%$ of the glomeruli, respectively). This classification has been validated for use in HSPN in previous adults and pediatric studies^{25,26}. However, patients who had missing data, no glomerulus presented in the renal biopsy specimens or an initial eGFR < 60 mL/min/1.73 m² were excluded.

The treatment regimen was decided by the attending nephrologists at the time of consultation. Patients who had proteinuria with or without microscopic hematuria received enalapril with the doses ranging from 0.1–0.6 mg/kg/day. If nephrotic-range proteinuria was detected, corticosteroid therapy (prednisolone or intravenous methylprednisolone) was prescribed with the maximum dose of 2 mg/kg/day or not exceeding 60 mg/day. Immunosuppressive agents were also prescribed in corticosteroid-resistant cases.

Clinical outcomes were graded according to the outcome classification by Counahan²⁷, as follows: A, normal (normal physical examination with normal urine and renal function); B, minor urinary abnormalities (proteinuria < 1 g/1.73 m²/day with or without microscopic); C, active renal disease (proteinuria > 1 g/1.73 m²/day and/or hypertension); D, renal insufficiency (eGFR < 60 mL/min/1.73 m² or died). However, some patients who had no 24-hour urine collection at the last follow up visit, we used protein-to-creatinine ratio > 1 g/g instead of 1 g/1.73/m²/day. Outcome A or B were considered as a favorable outcome and outcome C or D were considered as an unfavorable outcome.

The IBM SPSS program version 24 was used for analysis. Data were presented as percentages, mean and standard deviation or median and interquartile range (IQR), as appropriate. Categorical data and proportions were compared using Chi-square test or Fisher's exact test, as appropriate. Student's t-test or Mann-Whitney U test was used for comparison of continuous data between the two groups, as appropriate. Bivariate logistic regression analysis was used to identify the factors associated with the unfavorable outcome. A *p*-value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics and pathological findings

A total of 75 patients diagnosed with HSPN and IgAN over a 17-year period were reviewed. Twenty-eight patients were excluded from the study due to no renal pathological data or no glomerular presented in the specimen (14), missing data (3) and eGFR < 60 mL/min/1.73 m² (10 from IgAN, 1 from HSPN). Therefore, 28 patients (16 males) with HSPN and 19 (12 males) with IgAN were included in the final analysis. The demographic, clinical, and pathological data are summarized in Table 1. The median number of glomeruli from the renal biopsies was 14 glomeruli ranging from 5 to 44 glomeruli.

Table 1

Baseline characteristics, clinical presentation and renal pathological findings of groups of patients with HSPN and IgAN

Characteristics	HSPN (N= 28)	IgAN (N= 19)	p-value
Age (years), mean $\pm$ SD	9.4 $\pm$ 2.8	11.3 $\pm$ 4.3	0.078
Male, n (%)	16 (57.1)	12 (63.2)	0.680
Weight z-score, median (IQR)	0.20 (-0.61-1.18)	0.36 (-0.91-1.59)	0.991
Height z-score, median (IQR)	0.20 (-0.30-1.18)	0.20 (-1.70-1.30)	0.594
BMI (kg/m ²), median (IQR)	16.8 (14.3–21.0)	17.2 (16.0-19.8)	0.467
Percentile of systolic BP, mean $\pm$ SD	83.9 $\pm$ 13.0	78.1 $\pm$ 23.0	0.272
Percentile of diastolic BP, mean $\pm$ SD	79.9 $\pm$ 19.8	79.1 $\pm$ 25.1	0.903
Initial investigation			
Serum sodium (mmol/L), mean $\pm$ SD	137.5 $\pm$ 3.2	138.0 $\pm$ 2.6	0.599
eGFR (mL/min/1.73 m ²), mean $\pm$ SD	123.0 $\pm$ 32.1	111.2 $\pm$ 30.1	0.214
Albumin (g/L), mean $\pm$ SD	30.3 $\pm$ 6.1	34.2 $\pm$ 7.4	0.052
UPCr (g/g), median (IQR)	4.5 (2.0-5.7)	2.0 (0.9–7.2)	0.270
Clinical presentation, n (%)			
Edema	10 (35.7)	6 (31.6)	0.769
Hypertension	8 (28.6)	3 (15.8)	0.485
Acute kidney injury	1 (3.6)	1 (5.3)	1.000
Microscopic hematuria	18 (64.3)	3 (15.8)	0.001
Gross hematuria	10 (35.7)	16 (84.2)	0.001
Proteinuria	27 (96.4)	19 (100)	1.000
Nephrotic-range proteinuria	21 (75.0)	8 (42.1)	0.023
Renal pathological findings			
Total glomeruli, median (IQR)	14 (9.3–23.5)	14 (11.0–20.0)	0.965
Crescent (C1 + C2), n (%)	10 (35.7)	2 (10.5)	0.052

BMI, body mass index; eGFR, estimated glomerular filtration rate; UPCR, urine protein to creatinine ratio; M, mesangial hypercellularity; E, endocapillary proliferation; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis; C, cellular/fibrocellular crescents

Characteristics	HSPN (<i>N</i> = 28)	IgAN (<i>N</i> = 19)	<i>p</i> -value
Segmental sclerosis (S1), n (%)	13 (46.5)	9 (47.4)	0.949
Tubular atrophy/interstitial disease (T1 + T2), n (%)	5 (17.9)	6 (31.6)	0.312
Endocapillary proliferation (E1), n (%)	11 (39.9)	8 (42.1)	0.847
Mesangial hypercellularity (M1), n (%)	8 (28.5)	5 (26.3)	0.865
BMI, body mass index; eGFR, estimated glomerular filtration rate; UPCr, urine protein to creatinine ratio; M, mesangial hypercellularity; E, endocapillary proliferation; S, segmental glomerulosclerosis; T, tubular atrophy/interstitial fibrosis; C, cellular/fibrocellular crescents			

Treatment

Corticosteroids, immunosuppressive agents, and ACEIs and/or ARBs were usually prescribed in both groups. The proportion of patients receiving corticosteroids were higher in HSPN compared to IgAN (96.4% vs 63.2%, $p = 0.003$) but the proportion of patients receiving cyclophosphamide, cyclosporine, azathioprine, ACEIs and/or ARBs were not significantly different between the two groups.

Outcomes

Medians of follow-up duration were 50.4 (20.5-100.1) months in the HSPN group and 49.2 (25.6-105.2) months in the IgAN group. The outcomes of both diseases are shown in Table 2. There was no significant difference in the proportion of patients who had remission of proteinuria in HSPN vs IgAN (89.3% vs 73.7%), presence of hematuria (28.6% vs 31.6%), and presence of hypertension at last visit (10.3% vs 20.7%). Outcome A or B was seen in 23/28 (82.1%) in HSPN, and 17/19 (89.5%) in IgAN ($p = 0.685$). None of the patients in either group had developed ESRD, required renal replacement therapy or died at the last follow-up.

Table 2
Treatment, complication, and outcome of HSPN and IgAN

	HSPN (N= 28)	IgAN (N= 19)	<i>p</i> -value
Treatment			
Steroids, n (%)	27 (96.4)	12 (63.2)	0.003
Cy, n (%)	17 (60.7)	7 (36.8)	0.108
Cy accumulation dose (mg/kg/day)	138.5 ± 44.6	129.8 ± 31.7	0.647
ACEIs and/or ARBs, n (%)	24 (85.7)	15 (78.9)	0.697
Cyclosporine, n (%)	0 (0)	1 (5.3)	0.404
Azathioprine, n (%)	2 (7.1)	2 (10.5)	1.000
Outcome			
Duration of follow in months, median (IQR)	50.4 (20.5-100.1)	49.2 (25.6-105.2)	0.461
Remission of proteinuria, n (%)	25 (89.3)	14 (73.7)	0.240
Presence of hematuria at last visit, n (%)	8 (28.6)	6 (31.6)	0.825
Hypertension, n (%)	3 (10.3)	6 (20.7)	0.470
Last eGFR (mL/min/1.73 m ²), mean ± SD	115.9 ± 24.7	118.2 ± 22.5	0.748
Last UPCr (g/g), median (IQR)	0.20 (0.19–0.87)	0.20 (0.18–0.88)	0.692
Last serum albumin (g/L), median ± SD	35.6 ± 6.4	41.7 ± 5.5	0.012
Outcome A or B, n (%)	23 (82.1)	17 (89.5)	0.685
Cy, cyclophosphamide; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; UPCr, urine protein to creatinine ratio.			

Factors associated with unfavorable outcome

Possible risk factors associated with an unfavorable outcome such as gender, age, hypertension, initial acute kidney injury, diagnosis of HSPN or IgAN and pathological findings are presented in Table 3. In univariate analysis, the only factor associated with unfavorable outcome was the presence of endocapillary proliferation (E1) in the initial renal biopsy. Initial eGFR and acute kidney injury tended to be associated with unfavorable outcome ($p < 0.3$). In multivariate analysis, we selected the presence of endocapillary proliferation and AKI in the analysis, E1 remained the only factor associated with outcome C or D with the odds ratios (95%CI) of 9.96 compared to E0 (1.05–94.80, $p = 0.046$) as shown in Table 4.

Table 3
Factors associated with unfavorable outcome

Characteristic	Favorable outcome (A, B) (N= 40)	Unfavorable outcome (C, D) (N= 7)	p-value
Male, n (%)	23 (57.5)	5 (71.4)	0.685
Age (years), mean $\pm$ SD	10.3 $\pm$ 3.7	9.2 $\pm$ 4.1	0.436
Hypertension (mmHg), n (%)	8 (20.0)	3 (42.9)	0.330
Initial albumin (g/L), mean $\pm$ SD	31.4 $\pm$ 7.1	30.5 $\pm$ 6.5	0.554
Initial eGFR (mL/min/1.73 m ²), mean $\pm$ SD	119.5 $\pm$ 33.8	100.8 $\pm$ 13.0	0.107
Initial UPCr (g/g), median (IQR)	3.5 (1.7–6.6)	2.8 (2.1-7.0)	0.723
Diagnosis of HSPN, n (%)	23 (57.5)	5 (71.4)	0.685
Acute kidney injury, n (%)	1 (2.5)	1 (14.3)	0.278
Nephrotic-range proteinuria, n (%)	24 (60.0)	5 (71.4)	0.692
Crescent (C1 + 2), n (%)	11 (27.5)	1 (14.3)	0.659
Endocapillary proliferation (E1), n (%)	13 (32.5)	6 (85.7)	0.008
Tubular atrophy/interstitial fibrosis (T1 + 2), n (%)	9 (22.5)	2 (28.6)	0.659
Segmental sclerosis (S1), n (%)	19 (47.5)	3 (42.9)	1.000
eGFR, estimated glomerular filtration rate; UPCr, urine protein to creatinine ratio; HSPN, Henoch-Schönlein purpura nephritis.			

Table 4
Univariate and multivariate analyses of factor associated with unfavorable outcome

Factors	Univariate model HR (95% CI)	p-value	Multivariate model β (95% CI)	p-value
Endocapillary proliferation	12.46 (1.36-114.51)	0.026	9.96 (1.05–94.80)	0.046
Initial eGFR	0.97 (0.94–1.01)	0.123	0.98 (0.95–1.02)	0.282
AKI	6.50 (0.36–118.4)	0.206		
eGFR, estimated glomerular filtration rate; AKI, Acute kidney injury				

Discussion

In this study, the factor associated with an unfavorable outcome (C or D) in HSPN and IgAN was the presence of endocapillary proliferation in the initial renal biopsy with the odds ratios (95%CI) of 12.46 compared to E0 (1.36-114.51, $p = 0.026$). In this regard, Yang et al. reported that endocapillary proliferation was an independent pathological factor in children with HSPN presenting with nephrotic-range proteinuria but it did not correlate with the outcome C or D during a follow-up period of 1–4 years²⁸. However, recent publication by Inagaki et al. found that E was significantly associated with renal outcome in adult patients with HSPN. It showed that event-free renal survival was significantly shorter in patients with endocapillary proliferation than without endocapillary proliferation ($p = 0.0072$)²⁹. In IgAN, Halling et al. found that endocapillary proliferation was a significant predictor of poor outcome in children with IgAN and it could predict the composite endpoint of progression to ESRD or reduction of eGFR. In addition, the latter study also found that mesangial hypercellularity, tubular atrophy/interstitial fibrosis and crescents but not segmental sclerosis, were significant predictors for poor outcome¹¹. Although a systematic review and meta-analysis of 16 retrospective cohort studies with 3893 IgAN patients and found that endocapillary proliferation was not associated with renal failure [HR 1.4 (95%CI 0.9-2.0), $p = 0.1$]³⁰, there were only four studies that included children under 18 years of age and the population included all stages of chronic kidney disease.

In the present study, the baseline characteristics of both groups were similar except for the clinical presentation of hematuria and nephrotic-range proteinuria. As IgAN is renal limited disease, patients usually present with gross hematuria, which is self-detectable and brings the patients to the hospital. However, microscopic hematuria was found incidentally in some patients (15.8%). Apart from hematuria, a larger proportion of patients with HSPN than IgAN had nephrotic-range proteinuria. As HSPN patients were usually diagnosed by skin manifestation and other systemic organ involvement, a renal biopsy was performed only in those patients with HSPN who presented with a significant amount of proteinuria. Therefore, HSPN patients in this study tended to receive corticosteroids more than IgAN due to having significant proteinuria or nephrotic-range proteinuria ($p = 0.003$).

After treatment, the outcomes of both diseases were not significantly different. None of the patients with HSPN or IgAN required renal replacement therapy or died during the medians follow-up time of 50.4 (20.5-100.1) and 49.2 (25.6-105.2) months, respectively. Outcomes A or B in this study, considered as a favorable outcome, was found in 23/28 (82.1%) patients with HSPN and 17/19 (89.5%) patients with IgAN ($p = 0.685$). Compared to other studies, Kawasaki et al. investigated 114 HSPN children with renal failure during an average observation period of 23 years and reported that 82.5% had favorable outcomes after treatment⁸. Goldstein et al. studied 78 HSPN patients during a median follow-up time of 23.4 (19-35.1) years; showed that outcomes A or B were 64/78 (82.1%) in 1971 and 56/78 (71.8%) in 1990³¹. Fu et al. also reported that there were 148/159 (93.1%) of patients who had normal or mildly abnormal urinary finding (outcomes A or B) after treatment during a follow up period 6 months to 14 years. The latter study also found the association of higher pathological grading with unfavorable outcomes³². Mir et al.

followed 141 HSPN children, and showed outcomes A or B in up to 90.2% with 1-year follow-up. Nephrotic and/or nephritic syndrome were found to be an unfavorable predictor for both short and long-term outcomes ($p < 0.05$)³³. In IgAN, Bulut IK et al. studied 29 children included some patients with renal failure during mean follow-up time of 10.4 ± 3.51 years and reported that 84.6% had outcomes A or B³⁴. All of these studies showed that the overall prognosis of both diseases in general was comparable and had a good prognosis consistent with our findings.

This study had some limitations. Firstly, it was a retrospective study with a limited number of cases and a short duration of follow-up. Secondly, some other factors could affect the outcome such as different regimens of treatment, different baseline characteristics and different severities of pathological findings. Therefore, further studies with more cases, subgroup analysis, and longer follow-up time are warranted. In conclusion, the clinical outcomes of most pediatric patients with HSPN and IgAN were favorable and comparable. The presence of endocapillary proliferation in the initial renal biopsy was the only independent factor associated with poor outcomes in both diseases.

Declaration Section

Ethical permission was obtained from the Ethics Committee in Human Research of the Faculty of Medicine, Ramathibodi Hospital (ID 09-61-59 for IgAN and ID 09-61-29 for HSPN).

Consent for publication:

not applicable

Conflicts of interest:

The authors declare no potential conflicts of interest with respect to this study.

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Author contribution:

S.C. and K.P. designed the study. S.C, K.T., P.S., S.C., S.W. and K.P. performed the research. S.C and K.P. analyzed the data. S.C. and K.P. wrote the paper. S.C, K.T., P.S., S.C., S.W. and K.P. have read and approved the final manuscript.

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