OUTCOMES AND FACTORS ASSOCIATED WITH ACUTE RENAL FAILURE AMONG CHILDREN WITH ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS

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Abstract. Acute post-streptococcal glomerulonephritis (APSGN) is the most common type of acute glomerulonephritis in children. Acute renal failure (ARF) is an uncommon but serious complication in children with APSGN. The aims of this study were to identify outcomes and factors associated with ARF among children with APSGN so that patients presented with these factors should be closely monitored. We conducted a single-centered, case-control study by reviewing the medical records of children aged < 18 years with APSGN at Srinagarind Hospital between 2008 and 2017. Out of a total of 128 patients, 43 (33.6%) developed ARF. The mean ages in the ARF and non-ARF groups were 9.2±2.9 and 9.2±2.6 years, respectively. On univariate analysis, nephrotic-range proteinuria, severe hematuria and hypoalbuminemia were significantly associated with ARF (p <0.05). On multivariate analysis, hypoalbuminemia was significantly associated with ARF (adjusted odds ratio = 7.87; 95% confidence interval (CI): 2.82-21.93; p <0.001). The median time to normalization of renal function in the ARF group was 3.4 (95% CI: 1.4-5.5) weeks. The median time to resolution of proteinuria in the ARF group was 20.7 (95% CI: 15.1-26.4) weeks and in the non-ARF group was 6.9 (95% CI: 5.1-8.6) weeks. The median time to resolution of hematuria in the ARF group was 27.1 (95% CI: 21.9-32.4) weeks, twice as long as the non-ARF group (14.0; 95% CI: 11.4-16.6 weeks). No end-stage renal disease was found in this study. Hypoalbuminemia was the only factor significantly associated with ARF in children with APSGN. Therefore, APSGN patients who had hypoalbuminemia should be aware of severe disease.

Keywords: Post-streptococcal glomerulonephritis, acute glomerulonephritis, associated factor, acute renal failure, children

INTRODUCTION

Acute post-streptococcal glomerulonephritis (APSGN) is the most common type of glomerulonephritis in children (Ayoob and Schwaderer, 2016; Demircioglu Kilic *et al*, 2018). The incidence of APSGN in less developed countries (24.3 per 100,000 person-years) is more than the incidence in more developed countries (6.0 per

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100,000 person-years) (Carapetis *et al*, 2005). The severity of APSGN varies from subclinical disease to rapidly progressive glomerulonephritis (RPGN) (Ayoob and Schwaderer, 2016; Becquet *et al*, 2010; Demircioglu Kilic *et al*, 2018; Takeno *et al*, 2013; Wong *et al*, 2009). The outcomes of APSGN are excellent in children, although a small percentage of patients may progress to acute renal failure and require acute dialysis (Chugh *et al*, 1987; Eison *et al*, 2011).

Acute renal failure (ARF) is not uncommon in children with APSGN (Ali *et al*, 2014; Becquet *et al*, 2010; Takeno *et al*, 2013; Wong *et al*, 2009). The definition of acute kidney injury in children is based on the pediatric RIFLE classification (an acronym for the symptoms ranging from Risk for renal dysfunction to Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal disease, respectively) (Akcan-Arikan *et al*, 2007). ARF is also defined as a reduction in creatinine clearance of at least 75% from baseline or a creatinine clearance <35 ml/min/1.73 m^2 (Akcan-Arikan *et al*, 2007). The definition of ARF varies by study, some of which include both adults and children (Baldwin *et al*, 1974; Becquet *et al*, 2010; Chugh *et al*, 1987; Garcia *et al*, 1981; Potter *et al*, 1982). There are few published studies of outcomes and predictive factors for ARF among children with APSGN. The aims of this study were to identify associated factors and outcomes of acute renal failure among children with APSGN at Srinagarind Hospital, a tertiary care university hospital in northeastern Thailand.

MATERIALS AND METHODS

This study was conducted retrospectively by reviewing the medical records of children diagnosed with APSGN at Srinagarind Hospital between 2008 and 2017. This study was approved by the Ethics Committee, Khon Kaen University. All patients aged <18 years at the time of APSGN diagnosis who were followed up at Srinagarind Hospital, Department of Pediatrics during the study period were included. Patients with a history of underlying disease, such as heart failure, liver failure or other renal diseases, were excluded from the study as were patients who had received nephrotoxicity drugs during the month prior to APSGN diagnosis or whose medical records were lost were also excluded from the study.

The diagnosis of APSGN was having either a) symptoms of acute nephritis such as anasarca, gross hematuria, hypertension, oliguria, and evidence of streptococcal infection confirmed by a high ASO titer or an anti-deoxyribonuclease B (anti-DNaseB) titer); or b) pathology on renal biopsy consistent with APSGN.

Study subjects were categorized as having either ARF or not according to the pediatric RIFLE classification (Akcan-Arikan *et al*, 2007). Patients with a glomerular filtration rate (GFR) <35 ml/min/1.73 m^2 following the Schwartz equation were classified as being in the ARF group (Schwartz *et al*, 2009). The GFR at presentation was used to classify all study subjects.

Categorical data were presented as percentages. Normally distributed data were analyzed using an independent sample T-test and presented as means ± standard deviations (SD). Non-normally distributed data were analyzed using a Mann-Whitney U test and presented as medians with interquartile ranges (IQR). Factors potentially associated with ARF were analyzed first with univariate analysis and presented as crude odds

ratios (OR) with 95% confidence intervals (95% CI). Variables with a *p*-value <0.3 on univariate analysis were included in multivariate analysis. Multivariate analysis was performed using multiple logistic regression. A *p*-value <0.05 was considered statistically significant.

RESULTS

A total of 128 patients were included in the study of whom 43 (33.6%) had ARF. The mean (SD) ages of subjects in the ARF and non-ARF groups were 9.2 (±2.9) and 9.2 (±2.6) years, respectively. Sixty-seven point four percent and 65.9% of the ARF and non-ARF patients were male. The two groups did not differ significantly in terms of mean age, percentages by sex, nutritional status, or history of underlying disease (Table 1).

A history of throat and skin infection in the two groups were not significantly different. Generalized edema (89.1%) and hypertension (78.9%) were the two most common clinical presentations in both groups (Table 2). Proteinuria and hypoalbuminemia were significantly more common in the ARF group than in the non-ARF group (Table 3). The median GFRs (IQR) at diagnosis in the ARF and non-ARF groups were 15.4 (10.9 - 22.0) and 81.4 (63.5 - 99.1) ml/min/1.73 m^2, respectively (Table 3). Steroids were given in most of the ARF group (83.7%) whereas only 20.0% in the non-ARF group received steroids.

Nephrotic-range proteinuria, severe hematuria, and hypoalbuminemia were significantly more common in the ARF group on univariate analysis (Table 4). Hypoalbuminemia was the only factor significantly associated with ARF on multivariate analysis (adjusted odds ratio = 7.87; 95% CI: 2.82-21.93; p <0.001) (Table 5). Twelve patients in the ARF group (27.9%) required acute dialysis. Three patients (7.0%) developed chronic kidney disease (CKD): one developed stage 2 CKD and two developed stage 3 CKD. None of the patients required long-term renal replacement therapy during the

Table 1
Demographic of study subjects.

Data	ARF (*n*=43)	Non-ARF (*n*=85)	*p*-value
Sex, *n* (%)			
Female	14 (33)	29 (34)	0.860
Male	29 (67)	56 (66)	
Mean age ± SD in years	9.2±2.9	9.2±2.6	0.967
Weight, *n* (%)			
Underweight	5 (12)	4 (5)	0.297
Normal	27 (63)	65 (77)	
Overweight	9 (21)	11 (13)	
Obese	2 (5)	5 (6)	
History of underlying disease, *n* (%)	5 (12)	10 (12)	0.982

APSGN: acute post-streptococcal glomerulonephritis; ARF: acute renal failure; SD: standard deviation.

Table 2
Clinical characteristics of study subjects.

Characteristics	ARF (n=43)	Non-ARF (n=85)	p-value
Recent infection, *n* (%)			0.229
None	3 (7)	18 (21)	
Skin	19 (44)	30 (35)	
Throat	18 (42)	31 (37)	
Both	3 (7)	6 (7)	
Edema, *n* (%)	40 (93)	74 (87)	0.381
Gross hematuria, *n* (%)	16 (37)	39 (46)	0.405
Hypertension, *n* (%)			0.279
None	8 (19)	19 (22)	
Stage I	10 (23)	29 (34)	
Stage II	25 (58)	37 (44)	
Oliguria/anuria, *n* (%)	25 (58)	18 (21)	<0.001*
Hypertensive encephalopathy, *n* (%)	1 (2)	8 (9)	0.271
Congestive heart failure, *n* (%)	8 (19)	10 (12)	0.296

APSGN: acute post-streptococcal glomerulonephritis; ARF: acute renal failure; *$p < 0.05$.

study period. The median length of time the subjects were followed was 23.9 (IQR: 39.5) weeks.

The median time to normalization of renal function in the ARF group was 3.4 (95% CI: 1.4-5.5) weeks. The median times to resolution of proteinuria in the ARF and non-ARF groups were: 20.7 (95% CI: 15.1-26.4) and 6.9 (95% CI: 5.1-8.6) weeks, respectively. The median times to resolution of hematuria in the ARF and non-ARF groups were 27.1 (95% CI: 21.9-32.4) and 14.0 (95% CI: 11.4-16.6) weeks, respectively.

DISCUSSION

The clinical manifestations of APSGN range from subclinical disease to rapidly progressive glomerulonephritis (RPGN). Although RPGN is uncommon, some studies have reported the prevalence of ARF in APSGN to be 26.0-43.7% (Ali *et al*, 2014; Becquet *et al*, 2010; Takeno *et al*, 2013; Wong *et al*, 2009), comparable to the 33.6% seen in our study.

Patients with only mild APSGN usually require only symptomatic treatment. In more severe cases, some nephrologists have suggested treatment with steroid such as methylprednisolone but the effectiveness of such treatment remains unproven (Wong *et al*, 2009; Zaffanello *et al*, 2010). The short-term prognosis of APSGN is good in children (Becquet *et al*, 2010; Demircioglu Kilic *et al*, 2018), but the long-term prognosis may vary (Baldwin *et al*, 1974; Clark *et al*, 1988; Garcia *et al*, 1981; Potter *et al*, 1982). These difference in prognosis may be due

Table 3
Laboratory results of study subjects.

Laboratory results	ARF	Non-ARF	*p*-value
ASO titer, *n* (%)	(*n*=43)	(*n*=85)	0.796
Negative (≤200 IU/ml)	7 (16)	18 (21)	
High (>200-400 IU/ml)	14 (33)	27 (32)	
Very high (>400 IU/ml)	22 (51)	40 (47)	
Anti-DNaseB titer, n (%)	(*n*=43)	(*n*=83)	0.414
Positive (>200 U/ml)	11 (26)	16 (19)	
Negative (≤200 U/ml)	32 (74)	67 (81)	
C_3 level, *n* (%)	(*n*=42)	(*n*=80)	0.381
Low	25 (60)	54 (68)	
Normal	17 (41)	26 (33)	
C_4 level, *n* (%)	(*n*=42)	(*n*=77)	0.321
Low	11 (26)	27 (35)	
Normal	31 (74)	50 (65)	
Hematuria, *n* (%)	(*n*=43)	(*n*=85)	0.068
RBC <5/HPF	0 (0)	4 (5)	
RBC 5-50/HPF	13 (30)	38 (45)	
RBC >50/HPF	30 (70)	43 (51)	
Proteinuria, *n* (%)	(*n*=42)	(*n*=85)	0.001*
<1+ or UPCR <0.2	1 (2)	16 (19)	
1-2+ or UPCR 0.2-2	10 (24)	34 (40)	
>2+ or UPCR >2	31 (74)	35 (41)	
Serum albumin level, *n* (%)	(*n*=43)	(*n*=79)	<0.001*
<3 g/dl	31 (72)	19 (24)	
≥3 g/dl	12 (28)	60 (76)	
Platelet count, *n* (%)	(*n*=43)	(*n*=77)	>0.999
Low (<140,000/mm^3)	1 (2)	2 (3)	
Normal (≥140,000/mm^3)	42 (98)	75 (97)	
Mean (±SD) hemoglobin level in g/dl	10.3±1.8	10.5±1.5	0.665
Median (IQR) BUN level in mg/dl	74.9 (57-97)	17.7 (12-24)	<0.001*
Median (IQR) Cr level in mg/dl	3.7 (3-5)	0.7 (1)	<0.001*
Median (IQR) GFR in ml/min/1.73 m^2	15.4 (10.9- 22.0)	81.42 (63.5-99.1)	<0.001*

APSGN: acute post-streptococcal glomerulonephritis; ARF: acute renal failure; ASO: anti-streptolysin O; anti-DNaseB: anti-deoxyribonuclease B; GFR: glomerular filtration rate; HPF: high power field; IQR: interquartile range; RBC: red blood cell; SD: standard deviation; UPCR: urine protein creatinine ratio; *$p < 0.05$.

Table 4
Assessment of factors potentially associated with ARF among study subjects on univariate analysis.

Factors	AKI (%)	Non-AKI (%)	Odds ratio	95% CI	*p*-value
Age >12 years	16	7	2.56	0.80-8.16	0.113*
Female gender	33	34	0.93	0.43-2.03	0.860
Weight					0.297*
Underweight	12	5	3.01	0.75-12.07	
Normal	63	76	1		
Overweight	21	13	1.97	0.73-5.29	
Obese	5	6	0.96	0.18-5.27	
Recent skin infection	51	42	1.43	0.68-2.98	0.345
Hypertension					0.276*
Normal	19	22	1		
Stage I	23	34	0.82	0.27-2.45	
Stage II	58	44	1.06	0.61-4.23	
Low C_4 level	26	35	0.66	0.29-1.51	0.317
Nephrotic-range proteinuria	74	41	4.03	1.79-9.07	<0.001*
Severe hematuria (Urine RBC >50 cells/HPF)	70	51	2.25	1.04-4.90	0.036*
Very high ASO titer (>400 IU/ml)	51	47	1.18	0.57-2.46	0.661
Positive anti-DNaseB titer (>200 U/ml)	74	81	0.70	0.29-1.67	0.418
Hypoalbuminemia (<3 g/dl)	72	24	8.16	3.51-18.95	<0.001*
Thrombocytopenia (<140,000/mm^3)	2	3	0.89	0.08-10.14	0.927
Complications of APSGN					
Congestive heart failure	19	12	1.71	0.62-4.72	0.302
Hypertensive encephalopathy	2	9	0.23	0.03-1.90	0.107*

APSGN: acute post-streptococcal glomerulonephritis; ARF: acute renal failure; ASO: anti-streptolysin O; anti-DNaseB: anti-deoxyribonuclease B; CI: confidence interval; HPF: high power field; RBC: red blood cell; *$p < 0.30$.

to inclusion of adults in those studies (Baldwin *et al*, 1974; Garcia *et al*, 1981; Potter *et al*, 1982), since the prognosis of APSGN in children is better than adults (Becquet *et al*, 2010; Chugh *et al*, 1987; Garcia *et al*, 1981; Luo *et al*, 2010). Persistent urine abnormalities have been reported in 3.5- 60% of cases (Baldwin *et al*, 1974; Clark *et al*, 1988; Garcia *et al*, 1981; Potter *et al*, 1982). The reported proportions of APSGN patients who develop long term end-stage renal disease

Table 5
Assessment of factors potentially associated with ARF among study subjects on multivariate analysis.

Factors	Adjusted odds ratio	95% CI	*p*-value
Age >12 years	1.33	0.33-5.36	0.692
Nutrition status			0.184
Underweight	4.91	0.91-26.53	
Overweight	1.95	0.50-7.61	
Obese	3.63	0.41-32.22	
Hypertension			0.095
Stage I	1.25	0.30-5.23	
Stage II	3.27	0.92-11.58	
Nephrotic-range proteinuria	2.18	0.80-5.97	0.129
Severe hematuria	2.17	0.79-5.98	0.133
Hypoalbuminemia	7.87	2.82-21.93	<0.001*
Hypertensive encephalopathy	0.09	0.01-1.07	0.057

APSGN: acute post-streptococcal glomerulonephritis; ARF: acute renal failure; CI: confidence interval; *$p < 0.05$.

also vary (Baldwin *et al*, 1974; Garcia *et al*, 1981).

A few studies have examined the factors associated with ARF in patients with APSGN (Demircioglu Kilic *et al*, 2018; Takeno *et al*, 2013). A previous study (Takeno *et al*, 2013) reported the factors significantly associated with ARF among APSGN patients were: high urine specific gravity, high ASO titer, severe hematuria and pyuria. A previous study reported the factors significantly associated with decreased glomerular filtration rate (GFR) in children were: hypoalbuminemia, a decreased serum C_4 level and elevated inflammatory markers (C-reactive protein, white blood cell count, neutrophil count, and neutrophil/lymphocyte ratio) (Demircioglu Kilic *et al*, 2018).

Previous studies have reported children and adults with APSGN have a persisting urine abnormalities in 3.5-60.0% (Baldwin *et al*, 1974; Clark *et al*, 1988; Garcia *et al*, 1981; Potter *et al*, 1982). In our study, 12 patients (9.4%) had persistent microscopic hematuria and/or proteinuria. Previous studies reported the mean time to achieve a normal urine protein level among APSGN patients regardless of severity of disease is about 4 months (Becquet *et al*, 2010; Luo *et al*, 2010). In our study, this length of time was 7 weeks in the non-ARF patients and 5 months in the ARF patients.

Previous studies have reported the mean time to resolution of microscopic hematuria among APSGN patients regardless of APSGN severity is approximately 2.0-7.7 months (Becquet *et al*, 2010; Luo *et al*, 2010). In our study, the length of time was 3.5 months in the non-ARF patients and 7 months in the ARF patients.

Previous studies reported the proportion of children with APSGN who go on to develop ESRD is approximately 1-6% (Chugh *et al*, 1987; Garcia *et al*, 1981). In our study, no patients developed ESRD or died but 1 patient did develop stage 2 CKD and two patients developed stage 3 CKD.

A limitation of this study was incomplete data in some cases due to the retrospective study design. Some patients were referred back to local community hospitals before complete resolution of their urine abnormalities.

In conclusion, hypoalbuminemia was significantly associated with ARF among our study subjects but long term outcomes were good. APSGN children with hypoalbuminemia should be closely followed as severe illnesses may occur.

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