RISK FACTORS AND OUTCOME OF ATYPICAL ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS IN PEDIATRICS

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Abstract. We conducted this study to identify the clinical features and risk factors for atypical acute post-streptococcal glomerulonephritis (APSGN). Thirty-five cases of atypical APSGN treated at Srinagarind Hospital during 2002-2009 were compared with 27 typical cases. The clinical symptoms, anti-streptococcal antibody titers, and laboratory data at the first hospital visit were compared between the two groups. A marked elevation in anti-streptolysin O (ASO) titer was seen more commonly in the atypical APSGN group than in the typical APSGN group (p=0.025). Significantly more patients in the atypical APSGN group had a high urine specific gravity, hematuria and pyuria than patients in the typical APSGN group (p<0.01, p<0.031, and p<0.046, respectively). A high ASO titer, high urine specific gravity, severe hematuria and pyuria early in the illness were suggestive of a higher risk for an atypical presentation.

Keywords: APSGN, ASO, hematuria, pyuria, outcome, pediatric patient

INTRODUCTION

Acute post-streptococcal glomerulonephritis (APSGN) is the most common form of acute glomerulonephritis in children. It has been estimated that more than 470,000 cases of APSGN occur annually, with 97% occurring in less developed countries (Steer *et al*, 2007). After acquired certain serotypes of streptococcal infection of the skin or throat, the patient may develop edema, gross hematuria and hypertension. These symptoms rarely persist more than 3 weeks (Eison *et al*, 2011). APSGN usually has a good outcome in children, although a small percentage of patients progress rapidly to acute renal failure (Eison *et al*, 2011). Once the patient has passed the acute stage there is less risk of progression to renal impairment (White *et al*, 2001). However, several studies have reported APSGN patients with atypical manifestations, such as prolonged hypertension and proteinuria later in the clinical course (Baldwin *et al*, 1974; Rajajee, 1990; White *et al*, 2001). Some APSGN patients develop concomitant nephrotic syndrome (Roy and Stapleton, 1990; Becquet *et al*, 2010).

There is little information about the risk or predictive factors for atypical

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APSGN. The aim of this study was to determine the risk factors for atypical APSGN in pediatric patients.

METERIALS AND METHODS

The medical records of children aged less than 15 years with APSGN treated at Srinagarind Hospital (Khon Kaen University Hospital), Thailand between July 2002 and July 2009 were reviewed. Inclusion criteria were: 1) patients with hematuria, 2) with evidence of recent streptococcal infection [positive streptococcal culture of the skin or throat, having an anti-streptolysin O (ASO) titer >333 IU/ml, or an antideoxyribonucrease B (ADNaseB) level >200 IU/ml, 3] with a decreased serum concentration of complement protein C3 (<60 mg/dl) and 4) without any history of renal disease. Patients diagnosed as having other disease on renal biopsy or had a history of underlying renal disease were excluded from the study.

All eligible patients were divided into two groups according to their clinical course and outcome. Patients were placed in the atypical APSGN group if they met any of the following criteria: 1) having severe proteinuria (nephrotic range proteinuria or a spot urine protein ≥ 3+), 2) having a serum creatinine (Cr) > 2.0 mg/dl, 3) having oliguria (< 0.5 ml/kg/h) and/or azotemia (serum BUN ≥ 20mg/dl) lasting more than 2 weeks, 4) having a persistently low C3 level for more than 8 weeks, 5) having hypertension (defined as having a systolic and/or diastolic blood pressure for age and height greater than 95th percentile following the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents; US NIH, 2005), or having gross hematuria lasting more than 3 weeks, 6) having proteinuria (≥1+ on a urine dipstick) lasting for more than 6 months, and 7) having microscopic hematuria lasting for more than 1 year. Patients who did not meet these criteria were placed in the typical APSGN group.

The ratio between atypical and typical APSGN patients at Srinagarind Hospital was 1.7:1. The incidence of proteinuria with typical APSGN was about 10%, lower than the atypical cases with an odds ratio of 8. To reach a confidence level of 95% and a power of 80%, the sample size for atypical cases was 38 and of typical cases was 22.

The clinical course, anti-streptococcal antibody titer and other laboratory data at the first hospital visit were recorded. Statistical analysis, including the Mann-Whitney test, chi-square test and Fisher's exact test were conducted using GraphPad Prism, version 5.0. The statistical significance was set at $p<0.05$. This study had ethical approval from the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University and the Faculty of Medicine, Khon Kaen University.

RESULTS

During the 7-year study period, 103 patients were clinically diagnosed with having APSGN. Of those, 42 patients were excluded for the following reasons: in 3 patients renal biopsy showed a disease other than APSGN, 38 had no confirmed group A streptococcus (GAS) infection and/or no decreasing C3 level and 1 had bilateral renal hypoplasia. Sixty-one patients, all children, were enrolled in the study: 35 were diagnosed with having atypical APSGN and 26 wih typical APSGN; therefore, the number of atypical cases did not reach the goal of 38 cases, but typical cases reached the goal of 22 cases.

The demographic features of the pa-

Table 1
Demographic characteristics and underlying diseases of subjects.

Demographic data	Total (*n*=61)	Atypical (*n*=35)	Typical (*n*=26)	*p*-value
Male : female ratio	44:17	28:7	16:10	0.112
Age (years), median (IQR)	9 (7-11)	10 (8-11)	9 (6-10)	0.260
Underlying diseases, *n* (%)				
Tetralogy of Fallot	1 (1.6)	1 (2.9)	0	
Patent ductus arteriosus	1 (1.6)	0	1 (3.8)	
Thalassemia	2 (3.3)	1 (2.9)	1 (3.8)	
Bronchial asthma	2 (3.3)	1 (2.9)	1 (3.8)	
Cerebral palsy, epilepsy	1 (1.6)	1 (2.9)	0	
Drug allergy	1 (1.6)	1 (2.9)	0	
Hypospadias	1 (1.6)	0	1 (3.8)	
Peptic ulcer	1 (1.6)	0	1 (3.8)	

Table 2
Selected laboratory findings among subjects.

Laboratory values	*n* (%)
Serum Cr >2.0 mg/dl	11 (31.4)
Severe proteinuria	29 (82.9)
Oliguria >2 weeks	2 (5.7)
Hypertension >3 weeks	18 (51.4)
Gross hematuria >3 weeks	13 (37.1)
Proteinuria >6 months	6 (17.1)

tients are shown in Table 1. Most (72.1%) of the patients in this study were male; 77.0% were older than 7 years. There were no significant differences in gender or age between the atypical and typical APSGN groups. Table 2 shows the presences of selected laboratory findings among atypical APSGN cases. Severe proteinuria was the most common selected laboratory finding among atypical APSGN cases followed by hypertension lasting more than 3 weeks. None of the atypical APSGN patients in this study had a continuous decrease in C3 level or microscopic hematuria lasting more than 1 year.

Table 3 shows selected signs and symptoms among typical and atypical APSGN patients. Hypertension and edema were the most common selected findings, found in 90.2% of all subjects, followed by gross hematuria in 72.1%. The percentages of subjects with gross hematuria, oliguria and dyspnea were significantly higher among subjects with atypical APSGN than typical APSGN ($p<0.01$, $p<0.038$ and $p<0.033$, respectively), while the percentage of subjects with fever was significantly higher among subjects with typical APSGN than atypical APSGN ($p=0.033$). There were no significant differences in the percentages of subjects with sore throat and pyoderma between the two groups.

The mean laboratory results among atypical and typical APSGN patients are shown in Tables 4 and 5. Patients in the atypical APSGN group were significantly more likely to have a high ASO titer than patients in the typical APSGN group ($p=0.019$). Patients with an ASO titer

Table 3
Selected signs and symptoms among study subjects.

Signs and symptoms *n* (%)	Total (*n*=61)	Atypical (*n*=35)	Typical (*n*=26)	Odds ratio (95%CI)	*p*-value
Hypertension	55 (90.2)	32 (91.4)	23 (88.5)	1.39 (0.26-7.53)	1.000
Edema	55 (90.2)	31 (88.6)	24 (92.3)	0.65 (0.11-3.83)	1.000
Gross hematuria	44 (72.1)	31 (88.6)	13 (50.0)	7.75 (2.12-28.29)	0.001
Fever	35 (57.4)	16 (45.7)	19 (73.1)	0.31 (0.10-0.93)	0.033
Cough	25 (41.0)	14 (40.0)	11 (42.3)	0.91 (0.32-2.55)	0.856
Oliguria	16 (26.2)	13 (37.1)	3 (11.5)	4.53 (1.13-18.10)	0.038
Headache	16 (26.2)	7 (20.0)	9 (34.6)	0.47 (0.15-1.50)	0.199
Pyoderma	15 (24.6)	7 (20.0)	8 (30.8)	0.56 (0.17-1.82)	0.334
Sore throat	12 (19.7)	6 (17.1)	6 (23.1)	0.69 (0.19-2.45)	0.564
Dyspnea	6 (9.8)	6 (17.1)	0	11.68 (0.63-217.5)	0.033
Nausea/vomiting	5 (8.2)	4 (11.4)	1 (3.8)	3.27 (0.34-30.74)	0.382
Convulsion	2 (3.3)	2 (5.7)	0	3.96 (0.18-86.02)	0.503
Hemoptysis	1 (1.6)	1 (2.9)	0	2.30 (0.09-58.91)	1.000
Blurred vision	1 (1.6)	1 (2.9)	0	2.30 (0.09-58.91)	1.000

CI, confidence interval

Table 4
Comparison of laboratory findings between atypical and typical APSGN groups.

Profile, mean (IQR)	Total	Atypical	Typical	*p*-value
ASO titer	431 (356-858)	579 (399-947)	368 (238-550)	0.019
Anti Dnase B	911 (486-1,511)	835 (414-1,740)	976 (553-1,492)	0.425
C3 level	17.9 (<17.5-27.8)	<17.5 (<17.5-25.8)	20.0 (<17.5-30.2)	0.257
C4 level	20.3 (14.8-27.6)	21.0 (15.5-29.7)	18.9 (13.3-22.5)	0.252
Complete blood cell count				
WBC in cells/ l	10,600 (8,795-12,750)	10,625 (8,803-13,475)	10,500 (8,795-12,700)	0.782
Hematocrit in g/dl	31.3 (28.2-34.7)	32.5 (29.7-35.2)	30.6 (26.4-34.1)	0.160
Platelets in 10^3/ l	351 (272-429)	337 (246-429)	361 (314-432)	0.409
Neutrophils per l	6,958 (4,967-7,995)	7,329 (5,880-8,694)	6,000 (4,409-7,632)	0.073
Electrolytes				
Serum sodium in mEq/l	138 (135-141)	138 (135-141)	140 (137-141)	0.247
Serum potassium in mEq/l	4.6 (4.2-4.9)	4.6 (4.2-5.0)	4.5 (4.3-4.9)	0.820
Urine analysis				
Urine specific gravity	1.016 (1.010-1.020)	1.020 (1.015-1.025)	1.012 (1.009-1.018)	0.011
Urine RBC/HPF	50-100 (20->100)	>100 (30->100)	30-50 (10->100)	0.026
Urine WBC/HPF	5-10 (1-30)	5-10 (2-50)	3-5 (1-20)	0.038

APSGN, acute post-streptococcal glomerulonephritis; ASO, antistreptolysin O; WBC, white blood cells; RBS, red blood cells; HPF, high power field.

Table 5
Factors predictive for development of atypical APSGN.

Profile *n*/*N* (%)	Total	Atypical	Typical	Odds ratio (95%CI)	*p*-value
Anti-streptococcal antibodies and inflammatory mediators					
ASO ≥500 IU/ml	26/61 (42.6)	19/35 (54.3)	7/26 (26.9)	3.22 (1.08-9.61)	0.033
Anti-Dnase B ≥500 IU/ml	39/53 (73.6)	19/28 (67.9)	20/25 (80.0)	0.53 (0.15-1.86)	0.365
C3 <30 mg/dl	47/57 (82.5)	28/31 (90.3)	19/26 (73.1)	3.44 (0.79-15.00)	0.160
C4 <17 mg/dl	21/54 (38.9)	12/31 (38.7)	9/23 (39.1)	0.98 (0.32-2.97)	0.975
Complete blood cell count					
WBC ≥10,000/ l	32/53 (60.4)	17/28 (60.7)	15/25 (60.0)	0.96 (0.34-3.10)	0.957
Hemotocrit <30.0g/dl	18/54 (33.3)	8/29 (27.6)	10/25 (40.0)	0.57 (0.18-1.79)	0.335
Platelet count <300,000/ l	15/52 (28.8)	11/28 (39.3)	4/24 (16.7)	3.24 (0.87-12.05)	0.124
Neutrophil count ≥10,000/ l	7/52 (13.5)	5/27 (18.5)	2/25 (8.0)	2.61 (0.46-14.91)	0.422
Electrolyte					
Sodium <135 mEq/l	12/60 (20.0)	10/35 (28.6)	2/25 (8.0)	4.60 (0.91-23.26)	0.059
Potassium ≥5.5 mEq/l	11/60 (18.3)	8/35 (22.9)	3/25 (12.0)	2.16 (0.51-9.19)	0.332
Urine analysis					
Urine specific gravity ≥1.020	18/46 (39.1)	14/24 (58.3)	4/22 (18.2)	6.30 (1.62-24.40)	0.007
Urine ≥50 RBC/HPF	32/58 (55.2)	22/32 (68.8)	10/26 (38.5)	3.52 (1.18-10.45)	0.021
Urine ≥20 WBC/HPF	17/57 (29.8)	13/32 (40.6)	4/25 (16.0)	3.59 (1.00-12.94)	0.079

ASO, anti-streptolysin O titer; WBC, white blood cells; RBC, red blood cells; HPF, high power field; *n*, number with characteristic; *N*, total number with value available.

≥500 IU/ml were more likely to have atypical APSGN than typical APSGN with an odds ratio of 3.22 (p=0.033). Significantly more subjects in the atypical APSGN group had an elevated urine specific gravity, hematuria and pyuria than subjects in the typical APSGN group (p=0.011, p=0.026, and p=0.038, respectively). The odds ratios of subjects in the atypical APSGN group of having a urine specific gravity >1.020 and >50 RBC/HPF in the urine were 6.30 and 3.52, which were significantly higher than subjects in the typical APSGN group (p<0.007 and 0.021, respectively). However, no significant differences were observed in complement titers, complete blood cell counts and electrolytes between the two groups.

Two patients in atypical group had a renal biopsy confirming the diagnosis of APSGN. One had crescent formations in 2/15 glomeruli. A garland pattern was not observed in either of these patients.

Most of the patients recovered completely from APSGN and followed up for one year after discharge. Serum creatinine levels returned to normal in the subjects by 6 months. Microscopic hematuria resolved in all the patients by 1 year, only 2 patients with atypical APSGN had prolonged hypertension and proteinuria for more than 1 year after onset of the illness.

DISCUSSION

Patients with atypical APSGN were

more likely to have a high ASO titer, a high urine specific gravity, severe hematuria and pyuria at the onset of disease. Since there is little information about the risk for developing atypical APSGN in children, this information should be helpful in recognizing patients at higher risk for developing atypical APSGN. More agressive therapy may be considered in these patients. Further studies are needed to determine if more aggressive therapy can reduce the risk of developing atypical APSGN.

Severe proteinuria was observed in 82.9% of atypical APSGN patients, much higher than previous studies reporting percentages of APSGN patients with nephrotic range proteinuria of 25 to 27.3% (Roy and Stapleton, 1990; Becquet *et al*, 2010). This may because Srinagarind Hospital is a referral center. Patients in this study may not reflect the general population. In this study having a previous history of pharyngitis or pyoderma was not associated with an increased risk of developing atypical APSGN. The results are consistent with the findings of Roy and Stapleton (1990) who found no significant association was seen between nephrotic range proteinuria and patients with sore throat or pyoderma. Significantly higher percentages of patients with atypical APSGN had gross hematuria, oliguria and dyspnea than patients with typical APSGN. This may be due to the higher presence of renal insufficiency and volume overload among atypical APSGN patients. The lower percentage of patients with fever in the atypical APSGN group may reflect a more insidious onset among patients in this group.

A higher percent of patients in the atypical APSGN group had a high ASO titer than in the typical APSGN group, which is contrary to the findings of Wong *et al* (2009). The relationship between a high ASO titer and the severity of APSGN is unclear. ASO begins to rise about 1 week following onset of infection and peaks 3-5 weeks after the onset (Blyth and Robertson, 2006). This may indicate atypical APSGN has a longer incubation period than typical APSGN. This may indicate a difference in antibody response between the two groups, since peak titers do not exceed the upper limits of normal in some patients (Johnson *et al*, 2010). The pathophysiology of APSGN is believed to be a type 3 hypersensitivity reaction (Rodríguez-Iturbe *et al*, 1980). Patients who have an excessive immune response to streptococci may develop more severe symptoms, such as severe proteinuria and gross hematuria. The percent of patients with an abnormal urinalysis results was higher in the atypical APSGN group than in the typical APSGN group, perhaps due to more damage to their kidneys. The typical light microscopy findings among APSGN patients are diffuse hypercellularity of mesangial cells and infiltration of the glomerular tuft with polymorphonuclear leukocytes (Nordstrand *et al*, 1999). In some cases, epithelial crescents are seen in severe APSGN (Roy *et al*, 1981), leading to the clinical picture of rapidly progressive glomerulonephritis (Wong *et al*, 2009). Baldwin *et al* (1974) reported glomerular sclerosis was present in 10 of 22 patients with APSGN and this correlated with a reduction in glomerular filtration rate. Although the clinical outcome in APSGN is generally thought to be good, some patients demonstrate severely abnormal laboratory findings, have more severe renal damage which can lead to reduced renal function.

These laboratory findings may predict the progression of renal insufficiency in the future. Brenner *et al* (1982) found the

mechanisms contributing to renal disease are: 1) inflammation with a reduction in the number of nephrons during disease, and 2) hyperperfusion of a reduced number of intact nephrons in order to maintain a normal GFR, leading to further renal damage and nephron loss. Therefore, among APSGN patients, recovery from the acute phase may not mean complete recovery. Patients who have suffered from APSGN in the past may develop hypertension or proteinuria later in life. Some studies have documented chronic renal impairment years after having APSGN (Baldwin *et al*, 1974; Becquet *et al*, 2010).

A strength of the present study is that a large number of atypical APSGN patients were investigated, increasing the power of the study. This information may guide future studies. The present study also had some limitations. Some information about the clinical features and laboratory data in these patients was not available. The available laboratory findings might reflect different clinical phases in each patient. Most patients did not have long term follow-up because they recovered relatively quickly.

In conclusion, a high ASO titer, a high urine specific gravity, severe hematuria and pyuria during the early phase of illness with APSGN are possible risk factors for an atypical presentations. Prospective cohort study is needed to confirm these findings and to determine if more aggressive intervention in atypical APSGN patients makes a difference in the clinical course.

ACKNOWLEDGEMENTS

We would like to express our greatest thanks to Ms Pornnipa Harnlakorn, who assisted in the English stranslation of the information gathered for this study.

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