Turkish Journal of Pediatric Disease

Original Article

Changing Face of Pediatric Acute Poststreptococcal Glomerulonephritis in the Pre and Post Pandemic Period: A Comparison Study

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ABSTRACT

Objective: Acute poststreptococcal glomerulonephritis (APSGN) is the leading cause of acute glomerulonephritis in children. APSGN often develops after pharyngitis due to the activation of antibodies and complement proteins to streptococcal antigens by an immune complex-mediated mechanism. In this study, we aimed to analyze APSGN patients diagnosed before and after the pandemic, with their demographic characteristics , clinical and laboratory findings.

Material and Methods: In this study, patients diagnosed with APSGN in a tertiary children's hospital between October 2022 and March 2023 were retrospectively analyzed. The patients were compared with a large cohort followed up with the same diagnosis between 2010-2022. The patients were divided into two groups: group I (n=153, pre-pandemic) and group II (n=28, post-pandemic). Clinical, radiologic, and laboratory findings were compared between the two groups.

Results: The mean age at diagnosis in the group I (2010-2022) was 7.36±2.92 years, and in the group II 8.69±2.51 years. More than three-fourths of the cases [group I/group II; 106 (69.3%) / 21 (71.4%)] were male in both studies. As macroscopic hematuria was the most common finding in the group I, hypertension was the most common finding in group II. Complement 3 (C3) levels were significantly lower in the group I and C3 recovery time was significantly shorter in the group II. Five (19.4%) of patients in group I and only one patient in group II progressed to RPGN.

Conclusion: The incidence of APSGN increased rapidly after the Covid-19 pandemic when the use of face masks was discontinued. Although the patients presented with a serious clinic, their prognosis was better.

Key Words: Acute, Child, COVID-19, Pandemic, Poststreptecoccal glomerulonephritis

INTRODUCTION

Acute poststreptococcal glomerulonephritis (APSGN) is an immune-complex mediated glomerular disease triggered by group A β-hemolytic streptococcus (GAS) or streptococcus pyogenes infections. APSGN primarily affects children aged between 5 and 12 years, and is uncommon among children aged below 3 years (1). The clinical presentation varies from asymptomatic, microscopic or macroscobic hematuria (30-50%) to the acute nephritic syndrome characterized by smoky, and tea or cola colored urine, proteinuria (which can reach the nephrotic range), edema, hypertension (50-90%) and elevation of serum creatinine level. However most children are asymptomatic (2). Rarely, rapidly progressive glomerulonephritis (RPGN) occurs in less than 0.5% of cases and progressed with damage to more than 50% of the glomeruli and formation of crescent formation, and acute kidney injury (AKI) occurs with >50% loss of kidney function within a few days to weeks (3,4). Hypertension has been reported in 50-

Conflict of Interest: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval: This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the Clinical Research Ethics Committee No. 1 of Ankara Etlik City Hospital (2020-KAEK-141/123).

Contribution of the Authors : ***UZUN KENAN B:*** Constructing the hypothesis or idea of article. Analyzed the results. Planned the methodology to reach the results, examined the patient data. Interpreted the results and discussed them with the current literature. ***ÇAKICI KARGIN E:*** Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***GÜNGÖR T:*** Conducted statistical analysis of the data. ***KARAKAYA D:*** Assisted in collecting patient data. ***ÇELİKKAYA E:*** Assisted in collecting patient data. ***YILMAZ ÇALTİK A:*** Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite: Uzun Kenan B, Çakıcı Margın E, Güngör T, Karakaya D, Çelikkaya E and Yılmaz Çaltik A. Changing Face of Pediatric Acute Poststreptococcal Glomerulonephritis in the Pre and Post Pandemic Period: A Comparison Study. Turkish J Pediatr Dis 2025;19(1): 25-30.

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Received : 04.06.2024
Accepted : 26.08.2024
DOI: 10.12956/tchd.1494473

90% of cases in various series. in various series (5). Hypertensive encephalopathy is a rare but serious complication (5,6). These patients require emergent intervention.

The estimated global incidence of APSGN is 470.000 cases per-year and APSGN often occurs in regions of the world with poor socio-economic status, with an annual incidence ranging from 9.5 to 28.5 per 100.000 individuals (7). The rate of APSGN has decreased over the last few decades in high-income countries due to the use of antibiotics, improved socio-economic status, and hygiene (8). However, APSGN remains one of the important causes of acute kidney injury (AKI) among the pediatric populations and the leading cause of hospital admission in developing countries (9). However, the nature of the preceding infectious disease is not associated with the clinical course and severity of APSGN. Although the exact mechanisms of glomerular injury in APSGN have not yet been elucidated, they appear to be caused primarily by an autoimmune response to nephritogenic streptococcal antigens. This autoimmune response leads to the formation of immune complexes and activation of the alternative complement pathway, resulting in glomerular inflammation and damage. These antigens activate the alternative complement pathway which often leads to low levels of C3 (10).

The severity of complement activation is an important factor determining the severity of a possible APSGN clinic (11). There is no specific therapy to treat APSGN. Management is supportive and is focused upon treating the volume overload that causes the clinical complications of APSGN. These general measures include sodium and water restriction, and diuretic therapy, but according to the clinical findings immunosuppressive therapy and kidney replacement therapy may be required (4). Most patients, particularly children, have an excellent outcome (12,13). However, APSGN remains among the important causes of hospitalization and acute kidney failure in children (14).

In this study, we aimed to analyze APSGN cases diagnosed before and after the pandemic, with their demographic characteristics and clinical and laboratory findings.

MATERIALS and METHODS

Study population

This present study retrospectively analyzed pediatric patients diagnosed with APSGN between 2010-2022 years and September 2022 and March 2023 in a single-center, tertiary children's hospital. Patients were divided into two groups: group I (n=153, pre-pandemic) and group II (n=28, post-pandemic). Clinical, radiological and laboratory findings were compared between the two groups. The inclusion criteria for the study were 1-18 years of age and ≥ 1 year follow-up. Patients with kidney disease or clinically unproven diagnostic evidence of underlying kidney disease, including chronic kidney disease (CKD), were excluded from the study.

Definition

Evidence of prior streptococcal infection was determined based on the presence of a high ASO level. Patient data retrospectively obtained from medical records included the following: clinical and demographic data, age, sex, symptoms, physical examination findings; including blood pressure at presentation and at each follow-up visit, laboratory findings; including the serum creatinine and urea levels, estimated glomerular filtration rate (eGFR), albumin, potassium, anti-streptococcal antibodies (ASO), and complement factor 3 (C3) and C4 levels, urine microscopy findings and proteinuria values, abdominal ultrasonography (USG) findings, kidney biopsy findings, and treatment method. Renal biopsy was performed in cases with persistent hematuria or proteinuria and persistent azotemia (15).

According to the American Academy of Pediatrics 2017 HT Guidelines, the diagnosis of hypertension (HT) based on office blood pressure (BP) measurement is as follows: HT is defined as the average of three consecutive systolic and/or diastolic BP measurements above the ≥ 95th percentile for age, sex, and height using the auscultation method, or as BP >130/80 mm Hg in participants aged 13 years and older (16).

Oliguria was defined as 1 ml/kg/hr in infants or 0.5 ml/kg/hr or <500 ml/day in children. An estimated glomerular filtration rate (eGFR) was calculated according to the Schwartz formula (17). Protein excretion in urine was defined by non-nephrotic (spot urine protein/creatinine ratio > 0.2 or 24-hour urine protein excretion of -40 mg/m^2/hour) or nephrotic (spot urine protein/creatinine ratio >2 or 24-hour urine protein excretion >40 mg/m^2/hour) ranges (18).

Hematuria was defined as the presence of more than 5 erythrocytes in a microscopic field in the urine sediment. The values of C3 <0.76 g/L and C4<10 mg/dL were considered low. A low albumin level was defined as <2.5 g/dL. Evidence of prior streptococcal infection was determined based on the presence of a high ASO titer and ASO level >200 UI /mL were considered abnormally high. Magnetic resonance imagination (MRI) was performed in patients with central nervous system involvement. Treatment data included diuretics, antihypertensives, benzathine penicillin, fluid restriction, corticosteroids, and renal replacement therapies. The study was approved by the Clinical Research Ethics Committee No. 1 of Ankara Etlik City Hospital (2022-KAEK-141/123).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine the normality of the distribution of the study variables. Parametric variables are shown as mean and standart deviation, and nonparametric variables were shown as median (range). Categorical data presented as frequency and percentage. Student's t test was used to compare parametric variables and the Mann–Whitney U test was used to compare nonparametric variables. The χ^2 test or Fisher's exact test was used to compare categorical variables. The level of statistical significance was set at p<0.050.

RESULTS

The cases were defined as group I (pre-pandemic) and group II (post-pandemic), and the findings were evaluated together.

A total of 153 patients in the 1st group and 28 patients in the 2nd group were analyzed retrospectively. In both groups, two thirds (2/3) of cases were male [n=106 (69.3%), n=20 (71.4%) respectively]. There was no significant difference between the patient groups in terms of gender (p=0.800). As the mean age of group I was 7.36±2.92 years, the mean age of group II was 8.69±2.51 years and group II was significantly older (p=0.020). Upper respiratory tract infection (URTI) was reported at similar rates in both groups, n=138 (90.2%), n=27 (95.7%). There was no statistically significant difference between the patients in terms of history of pharengytis (p=0.438), pyoderma (p=0.086) and antibiotic use (p=0.740) between both of groups.

Clinical findings were analyzed in both groups. Macroscopic hematuria (p=0.010) was significantly more common in the 1st group, while hypertension (p=0.010) was significantly higher in the 2nd group. Macroscopic hematuria recovery time was significantly shorter in the 2nd group, which had a better clinical course (p<0.001). There was no significant difference between the groups in terms of microscopic hematuria (p=0.300), peripheral edema (p=0.300), and nephrotic proteinuria (p= 0.580). Oliguria was observed in 13 (46.4%) patients, however anuria was not reported. Hypertensive encephalopathy was observed in only one patient in the 2nd group and the patient was treated in the pediatric intensive care unit. Cerebral imagining (magnetic resonance imaging) was performed for hypertensive encephalopathy. In the 1st group, one fifth of the cases 19 (12.4%) progressed to RPGN, while in 2nd, one patient (3.5%) progressed to RPGN. There was no statistically significant difference in the patient groups in terms of RPGN prognosis (p=0.160).

The cases were analyzed in terms of laboratory findings. There was no significant difference between the groups in terms of serum creatinine levels (p=0.070), but glomerular filtration rate (GFR) was significantly high and GFR recovery time wassignificantly shorter in 2nd group (p=0.010). Complement levels were analyzed as C3 and C4, and C3 recovery time was significantly shorter in the 2nd group (p=0.001). The logistic regression analysis revealed that age and gender are not significant risk factors for the development of AKI (p=0.620, p=0.100, respectively). Initially, hypertension, nephrotic proteinuria, and macroscopic hematuria were not determined as significant risk factors (p=0.740, p=0.220, p=0.720, respectively). Complement 3 (C3) and albumin levels were also not determined as significant risk factors (p=0.900, p=0.170, respectively). Baseline characteristics of patients in pre and post-pandemic study were seen in Tablo I.

Antibiotic therapy was given to almost all cases in both groups (90.1%, 96.4% respectively). There was no statistically significant difference in the patient groups in terms of time of hospital stay (p=0.550).

Diuretic treatment was used in both groups [group I/group II; n=105 (68.6%), n=22, (78.6%)] approximately two-thirds (2/3) of the cases. Approximately one fourth (26.1%) of the patients in the 1st group and one third (28.6%) of the patients in the 2nd group required a second antihypertensive drug (nicardipine). Eighteen (11.8%) patients in the 1st group and only one patient in the 2nd group treated corticosteroids. In the 1st group, nine (5.9%) patients required renal replacement therapy (RRT) and hemodialysis was the preferred modality. None of the patients required RRT in 2nd group. Demographic and clinical features were given in Table II.

Tablo I: Baseline characteristics of patients in pre and post-pandemic study

Characteristic	Group I Pre-pandemic (n=153)	Group II Post-pandemic (n=28)	p‡
Gender male*	106 (69.3)	20 (71.4)	0.800
Patient age, years†	7.36±2.92	8.69±2.51	0.020*
Macroscobic hematuria*	116 (75.8)	18 (64.3)	0.010*
Microscobic hematuria*	37 (24.2)	10 (35.7)	0.300
Peripheral edema*	105 (68.6)	9 (32.1)	0.300
Hypertension*	66 (43.1)	24 (85.7)	0.010*
Nephrotic proteinuria*	54 (35.3)	18 (64.3)	0.580
Macroscobic hematuria, days†	10.81±7.38	4.57±3.70	0.000*
Hypoalbuminemia*	7 (4.6)	3 (10.7)	0.550
Hospitalization*	109 (71.2)	27 (96.4)	0.550
Serum creatinine, mg/dl†	1.15±1.08	0.78±0.31	0.070
C3 recovery time days†	63.68±69.29	38.04±24.21	0.001*
eGFR (ml/min/1.73 m²)†	65.13±28.94	80.29±25.32	0.010*
eGFR, recovery time days†	21.3±28.54	11.61±16.70	0.010*
Hospitalization, time days†	5.85±5.54	6.53±3.17	0.550
RPGN progression*	19 (12.4)	1 (4.3)	0.160

:** *n(%),* **†:** *mean ± SD,* **‡:** *Student's t test,x² sher' exact test,* ***C3: *complement 3,* ***eGFR:*** *mestimated glomerular filtration rate,* ***RPGN:*** *rapidly progressive glomerulonephritis.*

Table II: Demographic and clinical features of APSGN in children

	Group I Pre Pandemic	Group II Post-Pandemic	p†
Year of study	2010-2022	2022-2023	
Type of study	Retrospective	Retrospective	
Sample size, n	153	28	
F/M ratio	1:2.25	1:2.5	0.800
Hypertension*	66 (43.1)	24 (85.7)	0.010*
Ensephalopathy*	3 (3.9)	1 (4.3)	0.939
AKI*	68 (44)	18 (64.3)	0.057
Pyoderma releated*	15 (9.8)	1 (4.3)	0.009
Pharyngitis releated*	138 (90.2)	27 (95.7)	0.438

**: n(%),†: Student's t test, x^2 sher' exact test*

DISCUSSION

APSGN is the most common acute glomerulonephritis in children worldwide (19). There are over 470.000 cases of APSGN that occur annually leading to approximately 5000 deaths, with 97% of these cases in less developed countries (20). The annual incidence of APSGN is estimated to be 9.3 cases per 100.000 population in developing countries (21). In the Karakaya's single-centered study between 2010 and 2022, the frequency of APSGN was 1 case/month (22).

In our study, a very high number of newly diagnosed APSGN cases, such as an avarage of 4.6 cases per month, were observed. Although it is stated in the literature that there is a decrease in glomerulonephritis cases due to successful vaccination programs (23). However, we have reported a rapid increase in APSGN cases in our recent post-pandemic study. This can be explained stop to use of face mask after the Covid- 19 pandemics. However, it is possible that different streptococcal strains encountered after the pandemic may be the reason for the clinical difference in increasing APSGN cases. APSGN is common in the 5-12-year-old age group (1). In the study of Becguet et al. (23), the median age of APSGN cases was 6.7 and Gunasekaran et al. (24) was 6.8 years age (25). Although the mean age at diagnosis of the patients (8.69±2.51years) were older than in the literature, it was also significantly older than in 1st group (p=0.020). APSGN has a two-fold higher incidence in males in females (24,26,27). In our study, male gender was dominant in terms of gender ratios in both groups, like the literature (2.5/1). In the both groups in our studies the most frequently reported infection was URTI. Evidence that antibiotic therapy protects against the development of glomerulonephritis following streptococcal infection is conflicting (28-30). In both of our groups, antibiotic prophylaxis was given to almost all of the cases (90.1%/95.8%) for URTI. Although antibiotics are not routinely used in the treatment of APSGN, prophylactic treatment with an antibiotic covering the GAS spectrum is recommended to prevent the spread of nephritis-associated streptococcal infection (12). Hypertension is a very common complication in APSGN and often requires treatment. The prevalence of hypertension in various case series can range from 64%, to as high as 82.4%, to 92% (24,25,31). In our pre-pandemic study, macroscopic hematuria was the most common clinical finding, however in the post-pandemic study, hypertension (85.7%) was significantly the most common (p=0.010). Hypertension in APSGN is of the low renin type and is typically mild and biphasic, caused by water retention (32). Evidence of edema is particularly observed in cases before and after the pandemic. While there was no statistically significant difference between the patient groups, the increased frequency of hypertension supports a possible synergistic effect with potential pathophysiological mechanisms (33,34). In our study, approximately 63.4% of patients in the covid-19 center tested positive for covid-19 in the past six months, providing strong evidence for this hypothesis. Although we were not able to examine the strain of GAS in this study, the GAS strain, which is probably less virulent and better prognosis, caused the current APSGN clinical and laboratuary findings. Additionally, it is possible that the GAS strain may increase both the frequency of the disease and the risk of developing hypertension (35). In some series, cerebral complications related to hypertension have been reported in 30-35% of children with APSGN (9,31,36). In our study, one case was treated in the pediatric intensive care unit with generalized seizures and hypertensive encephalopathy. In the literature, nephrotic proteinuria has been reported in different series, ranging from 1.48%, 18%, 25% and 32% (24,25,31,36). As nephrotic proteinuria was seen in half of the cases in the pre-pandemic group, it was seen in 2/3 of the cases in the post-pandemic group. This condition more severe clinical course, but it regressed to non-nephrotic range within 2 weeks. However, APSGN is still one of the important causes of AKI and hospitalization in children (11). Studies have shown that AKI observed at rates ranging from 13.3% to 43.7% (12,37). In our study, AKI observed in two third (64.3%) of the cases, but none of the cases required dialysis. A study of adults determined both persistent hypertension and nephrotic proteinuria to be predictors of AKI (38). Gunasekaran et al. (25) found hematuria to be a predictor for AKI. However, in our post-pandemic study no correlation was found between the development of AKI and the presence of hematuria, hypertension or nephrotic proteinuria. Hematuria is seen in virtually all patients with APSGN. Individually evaluating the clinical findings showed that macroscopic hematuria is observed in 30–50% (12). In our study, macroscopic hematuria was observed as the second most common finding in approximately 64.3% (n=18) of the patients. Nephrotic proteinuria, hypertension, and macroscopic hematuria were seen at higher rates in this study compared to the literature and pre-pandemic studies. It may be a result of the immunological features of the releated GAS strain and rapidly developing but self-limiting complement activation (11,39).

Complement 3 level is a very important blood biomarker with nephritic-associated clinical features and activation of the alternative complement pathway in APSGN. The serum C3 level was low in 90% of the cases (11). In the pre-pandemic study, it was determined that disease severity and prognosis were positively correlated with the severity of complement activation. However, in the literature, C3 level Information on the relationship between and RPGN is variable. It is reported that the level of complement C3 fraction is lower in patients with a severe clinical course (12). However, another study reported that there was no relationship

between C3 fraction and the clinical course of RPGN (40). In our recently published pre-pandemic study, which reported the relationship between severe clinical features of APSGN (progress to RPGN), we found that especially low C3 and albumin levels and high CRP, PLR, CRP/albumin ratio and ESR, as well as nephrotic level proteinuria, are associated with APSGN (22). They have been found to be determinants of poor prognosis in children and have been identified as predictive factors in the progression of APSGN to RPGN (22). The significantly shorter post-pandemic C3 level recovery time compared to the first group is associated with a better clinical course. The APSGN prognosis was better in our post-pandemic study. We could not analyzed the type of GAS in our study, but it suggested the hypothesis that a possible more less virulent GAS strain or the strong immunity of the host causes a more benign clinical course. A recent study reported in South Korea reported that the degree of decrease in serum C3 level was milder in children with APSGN in recent years and that was associated with a decreased rate of acute nephritic features (11). This finding strongly supported our possible hypothesis.

Treatment of APSGN is completely symptomatic and comprise monitoring of fluid balance, blood pressure, body weight and the serum creatinine and electrolytes (9,41). Loop diuretics can be used if volume increase and loading findings are detected. Calcium channel antagonists can be used to treat HT (41). Antibiotics are not routinely used in APSGN, but prophylactic treatment with antibiotics is recommended for patients with signs of streptecoccal infection. Antibiotic therapy does not change the course of the disease, but from an epidemiological point of view it is very important to prevent the spread of nephritis (12). Long term antibiotic prophylaxis is not justified since recurrence of APSGN are very rare (42). In this study diuretic therapy (furosemide) was prescribed in three fourth of cases (75%) and a second anti-hypertensive drug (nicardipine) was given to 37.5% (n=6) of children, as in earlier studies (27,37,42). Only 8.3% patient treated three or more antihypertensives. Antibiotics are not routinely used in the treatment of APSGN, but prophylactic treatment with an antibiotic covering the GAS spectrum is recommended to obstruct the spread of nephritis-associated streptococcal infection. Additionally, in both groups the present study almost all of the cases (>90%) were treated antibiotics. Medical treatment of RPGN consists of corticosteroids and renal replacement therapies. In the literature, it has been reported that adult RPGN patients treated with corticosteroids have an excellent result, but the time of treatment is variable (43). We treated with corticosteroids our cases that progressed to RPGN in both groups, and with early diagnosis and treatment, chronic kidney damage (CKD) was not observed in any case.

In conclusion, APSGN continues to be a significant health problem in developing countries. Compliance with mask-wearing and hygiene recommendations emerges as the main factor in APSGN prevention. This study aimed to highlight the increased number of cases and different clinical presentations by comparing APSGN cases before and after the Covid-19 pandemic. The mean age of our patients was older. Hypertension was the most remarkable finding in the present study. Additionally, it is noteworthy that a significant portion of the cases (64.3%) had recently experienced a Covid-19 infection, which may have an impact on the clinical findings.

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