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Evaluation of Post-Infectious Glomerulonephritis: Single Center Experience

Post-Enfeksiyöz Glomerülonefrit Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Aim: Post-infectious glomerulonephritis (PIGN) is an acute glomerulonephritis, often develops after infections with nephritogenic strains of group A beta hemolytic streptococcus. Patients may present with mild findings such as asymptomatic microscopic hematuria and non-nephrotic proteinuria or they may present with severe findings such as macroscopic hematuria, nephrotic range proteinuria, edema, hypertension, and acute kidney injury. In this paper, we aimed to present the laboratory and clinical findings of patients who applied to pediatric nephrology clinic in a short period of six months and were followed up with the diagnosis of PIGN.

Materials and Methods: The medical records of 30 patients who were followed up in Adana City Training and Research Hospital with the diagnosis of PIGN in a six-month period (between October 2022 and March 2023) were evaluated retrospectively. The clinical, laboratory and treatment data of the patients were recorded.

Results: Acute nephritic syndrome was the most common clinical presentation with 22 patients (73.3%) followed up with PIGN. Four (13.3%) of the patients presented with nephrotic syndrome, two (6.7%) with rapidly progressive glomerulonephritis, and two (%6.7) with hypertensive encephalopathy. Kidney biopsy was performed in 3 patients, two of whom presented with rapidly progressive glomerulonephritis and one whose complement 3 level remained low beyond 8 weeks. The pathological diagnosis of these patients was reported as diffuse proliferative glomerulonephritis.

Conclusion: Although PIGN usually occurs as a benign nephritis, it should be kept in mind that patients whose diagnosis is delayed and not treated appropriately may present with poor clinical

Keywords: Glomerulonephritis, post-streptococcus glomerulonephritis, children, nephrotic syndrome, acute nephritic syndrome

ÖZ

Amaç: Post-enfeksiyöz glomerülonefrit (PIGN), sıklıkla A grubu beta hemolitik streptokokların nefritojenik suşları ile enfeksiyonlardan sonra gelişen akut bir glomerülonefrittir. Hastalar asemptomatik mikroskobik hematüri ve nefrotik olmayan proteinüri gibi hafif bulgularla başvurabilecekleri gibi makroskopik hematüri, nefrotik düzeyde proteinüri, ödem, hipertansiyon ve akut böbrek hasarı gibi ciddi bulgularla da başvurabilirler. Bu yazıda altı ay gibi kısa bir sürede çocuk nefroloji kliniğine başvuran ve PIGN tanısıyla takip edilen hastaların laboratuvar ve klinik bulgularını sunmayı amaçladık.

Gereç ve Yöntem: Adana Şehir Eğitim ve Araştırma Hastanesi'nde PIGN tanısıyla altı aylık dönemde (Ekim 2022 ile Mart 2023 tarihleri arasında) takip edilen 30 hastanın tıbbi kayıtları retrospektif olarak değerlendirildi. Hastaların klinik, laboratuvar ve tedavi bilgileri kaydedildi.

Bulgular: Akut nefritik sendrom, enfeksiyon sonrası glomerülonefrit ile takip edilen 22 hasta (%73,3) ile en sık görülen klinik tabloydu. Hastaların 4'ü (%13,3) nefrotik sendrom, 2'si (%6,7) hızlı ilerleyen glomerülonefrit ve 2'si (%6,7) hipertansif ensefalopati ile başvurdu. İkisi hızlı ilerleyen glomerülonefrit ile başvuran ve kompleman 3 düzeyi 8 haftadan fazla düşük kalan bir hasta olmak üzere 3 hastaya böbrek biyopsisi yapıldı. Bu hastaların patolojik tanısı diffüz proliferatif glomerülonefrit olarak bildirildi.

Sonuç: PIGN genellikle benign nefrit şeklinde ortaya çıksa da tanısı geciken ve uygun şekilde tedavi edilmeyen hastaların kötü klinik tabloyla başvurabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Glomerülonefrit, post-streptokoksik glomerülonefrit, çocuk, nefrotik sendrom, akut nefritik sendrom

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INTRODUCTION

Post-infectious glomerulonephritis (PIGN) is an immune-mediated glomerular damage occurring as a result of the host response to an extrarenal infection[1]. The most prominent mechanism of glomerular damage in PIGN is the development of an autoimmune response against nephritogenic streptococcal antigens.

The development of the autoimmune response leads to immune complex formation and activation of the alternative complement pathway, causing glomerular inflammation and damage[2].

PIGN can be seen after viral, bacterial and fungal infections[3]. Group A beta hemolytic streptococcal (GAS) infections are the most common cause of acute nephritis. Of the estimated 470 000 new post-streptococcal glomerulonephritis (PSGN) cases annually, 97% occur in countries with poor socioeconomic status[4,5].

Patients usually have a history of previous skin or throat infection with GAS[6]. There is a latent period of 1-3 weeks following GAS pharyngitis and 3-6 weeks following GAS skin infection. Clinical presentation varies widely, from asymptomatic microscopic hematuria to acute kidney injury[2].

Approximately two-thirds of the patients have widespread edema and hypervolemia due to water and sodium retention. In severe cases, fluid overload can lead to pulmonary edema, causing respiratory distress. Macroscopic hematuria is present in approximately 30-50% of patients. Hypertension is present in 50-90% of patients, and hypertensive encephalopathy is a rare but serious complication[7,8]. Acute kidney injury develops in approximately 20% of the cases but rarely requires dialysis[9].

Complement 3 (C3) level is low in the first two weeks of the disease course and complement 4 (C4) level is generally normal in approximately 90% of the patients. However, in some patients, C4 and complement 2 (C2) levels may be low, suggesting the activation of both classical and alternative pathways. C3 level returns to normal within 4-8 weeks after the onset of the disease[2,10].

The presence of a previous history of GAS infection is important for the diagnosis of PSGN. Although throat culture or rapid antigen test shows GAS infection during acute infection, throat culture is positive in only 20-25% of patients when nephritic symptoms begin. Since the diagnosis of impetigo is made with clinical findings without taking a wound culture, culture results are not required for the diagnosis of PSGN. In the absence of a positive culture result, anti-streptolysin O (ASO) and anti-DNase B can be used. ASO increases 2-4 weeks following an upper respiratory tract infection, reaches its peak after 3-5 weeks and remains elevated for several months; DNase B increases 2 weeks after infection and reaches its peak in 6-8 weeks[5,11]. Therefore, an increase in ASO titer over time is diagnostic. Although high DNase B levels can also be seen in upper respiratory tract infections, unlike ASO, they are also increased in pyodermal infections[11]. In this paper, we aimed to present the laboratory and clinical findings of patients who applied to Adana City Training and Research Hospital pediatric nephrology clinic in a short period of six months and were followed up with the diagnosis of PIGN.

MATERIAL AND METHODS

Following the approval of the ethics committee with decision number 3233 at the 149th the approval was received from Adana City Training and Research Hospital Clinical Research Ethics Committee (decision no: E-60116787-020-476142, date: 15.01.2024). The medical records of 30 patients who were followed up in with the diagnosis of PIGN were evaluated retrospectively. The clinical, laboratory and treatment data of the patients were recorded. Patients who applied to the pediatric nephrology outpatient clinic in a six-month period (between October 2022 and March 2023) and had a minimum follow-up period of 3 months were included in the study. PIGN was diagnosed in the presence of proteinuria accompanying hematuria, low C3 that resolved within 2 months, a history of previous infection or evidence of streptococcal infection (ASO, anti-DNAse B elevation and/or throat culture positivity). ASO >200 IU/mL and anti-DNAse B >200 U/mL were defined as high ASO and anti-DNAse B levels, respectively. C3<0.79 g/L was defined as low C3 level. Non-nephrotic proteinuria was defined as protein/creatinine ratio 0f 0.2-2 mg creatinine in spot urine, and nephrotic range proteinuria as protein/creatinine ratio of >2 mg creatinine in spot urine. Serum creatinine above normal limits for age was defined as azotemia.

Statistical Analysis

All statistical analyses were performed by SPSS version 21 software package. Normal distribution of numeric variables was tested with the Kolmogorov-Smirnov test. Continuous data were defined by means of mean ± SD under the parametric conditions and median under the non-parametric conditions. Independent sample t-test was used for the comparison of normally distributed numeric variables. P values less than 0.05 were considered to be statistically significant.

RESULTS

Of the patients, 20 were male and 10 were female. The mean age of the patients was 6.8±1.8 years. The mean ages of boy and girl patients were statistically similar (p>0.05). All of the patients mentioned a previous medical history of infection, including upper respiratory tract infection in 25 patients, skin infection (scabies) in 4 patients, and acute gastroenteritis in 1 patient (Table 1). Acute nephritic syndrome was the most common clinical presentation with 22 patients (73.3%). Four (13.3%) of the patients presented with nephrotic syndrome, two (6.7%) with rapidly progressive glomerulonephritis, and two (6.7%) with hypertensive encephalopathy Table 2. The patients who applied with the diagnosis of hypertensive encephalopathy were those whose applications to the health

institution were delayed due to the earthquake disaster in our country. They had a history of macroscopic hematuria.

Macroscopic hematuria was the most common presenting symptom in 25 of the patients. At admission, 19 patients had edema, 14 patients had hypertension, six patients had oliguria, two patients had respiratory distress, and two patients had convulsion (Table 2). Twenty-one of the patients were hospitalized and nine were treated as outpatients. The mean length of stay for the patients was 8.1±3.6 days. Fluid-sodium restriction and loop diuretics (furosemide) were used for the treatment of hypervolemia. Amlodipine was added as antihypertensive treatment in seven (23.3%) patients.

The median urea and creatinine levels of the patients at the time of diagnosis were 38 mg/dL and 0.52 mg/dL, respectively. The laboratory parameters of the patients at the time of admission are shown in Table 3. Kidney biopsy was performed in three patients, two with rapidly progressive glomerulonephritis (RPGN), and one with persistent hypocomplementemia beyond 8 weeks. The pathological diagnosis of these patients was reported as diffuse proliferative glomerulonephritis. These patients were commenced on corticosteroid immunosuppressive therapy. The C3 levels of the patients returned to normal in a mean of 35±32 days. Macroscopic hematuria resolved in a mean of 7±5 days, and microscopic hematuria resolved in mean of 68±34 days. At the end of the study, 12 patients still had microscopic hematuria. Follow-up data of the patients are shown in Table 4.

Table 1. Previous infections before PSGN

	n (%)
Upper respiratory tract infection	25 (83.3)
Skin infection	4 (13.3)
Gastroenteritis	1 (3.33)

PSGN: Post-streptococcal glomerulonephritis

Table 2. The clinical and laboratory features of the patients at admission

Clinical presentation	**n (%)**
Acute nephritic syndrome	22 (73.3)
Nephrotic syndrome	4 (13.3)
Rapidly progressive glomerulonephritis	2 (6.7)
Hypertensive encephalopathy	2 (6.7)
Clinical and laboratory features	**n (%)**
Macroscopic hematuria	24 (83.3)
Edema	19 (63.3)
Hypertension	14 (46.7)
Oliguria	7 (23.3)
Respiratory distress	2 (6.7)
Convulsion	2 (6.7)
Azotemia	7 (23.3)
Proteinuria Nephrotic range Non-nephrotic range	28 (93.4) 17 (56.7) 11 (36.7)
Hypoalbuminemia (<3.5 g/L) <2.5 g/L ≥2.5 g/L	18 (60.0) 3 (10.0) 15 (50.0)
Hypocomplementemia (low C3 level)	30 (100.0)
Increased ASO (>200 IU/mL)	25 (83.3)
Increased anti-DNAse B (>200 U/mL)	8 (26.7)

ASO: Anti-streptolysin O, C3: Complement 3

DISCUSSION

Acute glomerulonephritis is the pathological process characterized by inflammation and/or cellular proliferation of the glomeruli, in which the kidneys are not directly infected but are damaged as a result of autoimmune inflammation[11].

Acute post-streptococcal glomerulonephritis (APSGN) is seen between the ages of 4 and 14 years, and is extremely rare under the age of two years. The male to female ratio has been reported as 2:1[1,12]. In our patient population, male gender was predominant with a percent of 67%, similar to the literature, and the mean age of the patients was 7 years.

Table 3. The laboratory parameters of the patients at the time of admission

	Median (IQR)
Urea (mg/dL)	38 (22)
Creatinine (mg/dL)	0.52 (0.20)
Sodium (mmol/L)	139 (12)
White blood count (×10³/µL)	10.3 (4.3)
Platelet (×10³/µL)	375 (166)
	Mean ± SD
Uric acid (mg/dL)	5.3±1.7
Hemoglobin (g/dL)	10.8±1.0
Potassium (mmol/L)	4.6±0.5
Calcium (mg/dL)	9.0±0.6
Phosphate (mg/dL)	4.9±0.7
Total protein (g/dL)	6.5±0.7
Albumin (g/dL)	3.3±0.6

Table 4. Follow-up data of the patients

Follow-up data	Mean ± SD (days)
Follow-up time	165±51
Macroscopic hematuria resolving time	7±5
Hypoalbuminemia resolving time	17±9
Hypocomplementemia (C3) resolving time	35±32
Proteinuria resolving time	48±32
Microscopic hematuria resolving time	68±34

C3: Complement 3

Nephritis often occurs after skin and upper respiratory tract infections, but it is also seen after infections affecting different organ systems[1,3]. In a study conducted in Armenia on 474 patients with acute post-infections glomerulonephritis over a 5-year period, 51% of the patients had a previous history of upper respiratory tract infection, 23% had a history of scarlet fever, 13% had impetigo, and 5% had a history of cervical adenitis[5]. Atmış et al.[3] reported that 84.6% of the patients had a history of upper respiratory tract infection and 15.4% had gastroenteritis. In our study, the majority of our patients, 83.3%, had a history of upper respiratory tract infection, 13.3% had a history of skin infection, and 3.3% had a history of acute gastroenteritis. The fact that the majority of our patient population had a history of upper respiratory tract infection and the low frequency of acute gastroenteritis was thought to be related to the seasonal characteristics of the period in which the study was conducted.

The clinical spectrum of PSGN is quite broad. Patients classically present as acute nephritic syndrome with hematuria, proteinuria, and volume overload. However, it can also occur as a disease characterized by nephrotic syndrome (severe proteinuria, hypoalbuminemia and edema) or particularly rapidly progressive glomerulonephritis[5,11]. In our study, consistent with the literature, the majority of patients (73.3%) presented with acute nephritic syndrome.

In the acute phase of the disease, congestive heart failure and pulmonary edema may occur as a complication of hypervolemia, as well as severe encephalopathy due to hypertension[13]. Hypertension-related seizures with documented posterior reversible encephalopathy syndrome may occur in children with PSGN. In the early stages of the patients with PSGN, it is particularly important to continue to have blood pressure assessed at regular intervals, even in children who are normotensive at presentation and are being monitored as outpatients[5]. In our study, although patients presenting with hypertensive encephalopathy and convulsion had a history of macroscopic hematuria, it was observed that their admission to the hospital was delayed due to the earthquake disaster in our country. This shows that patients who are not followed-up and treated appropriately and whose diagnosis is delayed may present with worse clinical presentations.

Considering the presenting findings of the patients, macroscopic hematuria is reported with a frequency of 17-93%, edema with a frequency of 59-72%, hypertension with a frequency of 64-82% and oliguria with a frequency of 18-51%[5,7,14-18]. The frequencies of macroscopic hematuria, edema and oliguria in our study were similar to those in the literature. Although the frequency of hypertension with 47% is lower than previously reported, we think that it can be explained by our low oliguria frequency of 23% in this study. Patients with PSGN often present with non-nephrotic proteinuria, and nephrotic proteinuria is relatively rare and has been reported with a frequency of up to 35%. In fact, there are publications reporting nephrotic range proteinuria with a frequency as low as 1%[5,7,14-18]. In this study, nephrotic level proteinuria was present in 56.7% of our patients, which was significantly higher than the rate in the literature. Although we think that the re-encounter of patients with viral and bacterial infections, from which they are largely protected due to quarantine, after the COVID-19 pandemic, causes a stronger immunological stimulation, we do not have sufficient supporting evidence on this issue. However, the limited number of our patients may be one of the factors affecting these results. Multicenter and prospective immunological studies involving more patients are needed in this field.

The classical pathway of complement activation is partially blocked by immunoglobulin binding proteins on the streptococcal surface, and the alternative complement pathway is often activated. Therefore, C3 is usually low in blood tests, but classical pathway activation and decreased C1 and C4 can be seen in 15-30% of patients. However, despite significant complement activation, normal complement levels may also be observed in 10% of cases[13].

Therefore, the most useful confirmatory test for PSGN is usually a low C3 level, which classically returns to normal levels within 6-8 weeks. Although there are some reports that it takes longer for C3 levels to return to normal, if recovery exceeds 3 months, an alternative diagnosis such as membranoproliferative glomerulonephritis should be considered. Evidence of a previously diagnosed streptococcal infection (such as ASO and DNase B) may facilitate diagnosis in patients with PSGN[5].

Most children with a clear diagnosis of APSGN do not require an initial diagnostic kidney biopsy. In atypical cases or progressive loss of kidney function, biopsy helps make a definitive diagnosis and can rule out another cause that may require special treatment for recovery[5]. C3 levels were initially low in all of our patients; two presented with RPGN, and one with the low C3 level that lasted for more than two months and required kidney biopsy. Biopsy results were evaluated as diffuse proliferative glomerulonephritis.

Edematous or hypertensive patients should also be recommended a sodium-restricted diet and fluid restriction may be required. Since the presumed cause for hypertension is volume excess resulting from sodium and water retention, diuretics or the combination of a diuretic and a vasodilator such as a calcium channel blocker are often sufficient. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be avoided in the acute phase as they may exacerbate any reduction in glomerular perfusion resulting from glomerulonephritis itself[5]. In our study, all of our patients were placed on a liquid and sodium restricted diet; amlodipine was added to the treatment of hypertensive patients and blood pressure was controlled in all patients.

Most clinical signs and symptoms resolve spontaneously within a few weeks, but microscopic hematuria may persist for up to 2 years[5]. During an average follow-up period of 165 days, the macroscopic hematuria of our patients resolved in an average of 7 days. In 40% of the patients, microscopic hematuria continued during this period.

Finally, while Atmış et al.[3] evaluated 13 patients in nine months, Demircioglu Kılıc et al.[13] evaluated 75 patients in two years, and in our study, we evaluated 30 patients in six months. Being the only pediatric reference center in the region was effective in evaluating so many patients in short time. In addition, the earthquake disaster we experienced caused the hospital applications of patients to be delayed and caused patients to come with more serious clinics.

Study Limitations

The most important limitation of our study is its retrospective design. Although the small number of patients is another limitation, the fact that these patients presented within a short period of 6 months is one of our reasons for reporting this article.

CONCLUSION

PIGN usually occurs as benign nephritis, but it should be kept in mind that patients who are not treated appropriately and whose diagnosis is delayed may present with poor clinical pictures, like hypertensive encephalopathy. In addition, the higher frequency of serious clinical conditions such as nephrotic proteinuria in this study is a striking difference compared to previous studies. Multicenter and prospective immunological studies involving more patients are needed to understand the reason for this difference and stronger immunological stimulation.

Ethics

Ethics Committee Approval: The approval was received from Adana City Training and Research Hospital Clinical Research Ethics Committee. (decision no: E-60116787-020-476142, date: 15.01.2024).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: G.A.Y., S.T., Concept: G.A.Y., S.T., Design: G.A.Y., S.T., Data Collection or Processing: G.A.Y., S.T., Analysis or Interpretation: G.A.Y., S.T., Literature Search: G.A.Y., S.T., Writing: G.A.Y., S.T.

Conflict of Interest: No conflict of interest was declared by the authors.

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