Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2018;43(Suppl 1):194-198
DOI: 10.17826/cumj.441742

ARAŞTIRMA / RESEARCH

Incidence of post-infectious glomerulonephritis: single center results

Post-enfeksiyöz glomerülonefrit sıklığı: tek merkez bulguları

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Cukurova Medical Journal 2018;43(Suppl 1):194-198

Abstract

Purpose: The aim of this study was to retrospectively evaluate the incidence of post-infectious glomerulonephritis (PIGN) in department of Pediatric Nephrology at Cukurova University between November-December 2016.

Materials and Methods: The clinical and laboratory datas of 13 children with PIGN who were seen in our clinic between November-December 2016, and their follow-up results were evaluated retrospectively.

Results: Thirteen children who diagnosed PIGN were evaluated with the mean age of 9 (3-15) years. All of the patients had history of throat or gastrointestinal infections. Symptoms of the patients at admission were edema (100%), oliguria (38.5%), macroscopic hematuria (23%), hypertension (15.3%), dispnea (15.3%), respectively. Serum complement C3 was low in all patients while one patient had both low serum complement C3 and C4. The patient who had hypocomplementemia (both C3 and C4) also had severe proteinuria and acute kidney injury. Renal biopsy was performed to this patient and diagnosed diffuse proliferative glomerulonephritis after renal biopsy.

Conclusion: PIGN is observed with higher incidence in the developing countries in current era. We detected an increase in the number of PIGN patients in a short period and we aimed to draw attention of pediatricians about PIGN patients with different clinical presentations.

Key words: Children, post-infectious glomerulonephritis, proteinuria, hypocomplementemia

Öz

Amaç: Bu çalışmanın amacı Çukurova Üniversitesi Tıp Fakültesi Çocuk Nefroloji Bilim Dalında Kasım-Aralık 2016 aylarında başvuran hastalarda post-enfeksiyöz glomerülonefrit (PIGN) tanı sıklığını geriye dönük değerlendirmektir..

Gereç ve Yöntem: Bu tarihlerde kliniğimize başvuran 13 PIGN'li çocuk hastanın klinik, laboratuvar sonuçları ve takiplerinin sonuçları incelenmiştir.

Bulgular: Çalışamaya alınan 13 PIGN tanılı çocuğun ortalama yaşı 9 (3-15) idi. Tüm hastaların üst solunum yolu veya gastrointestinal enfeksiyon öyküsü vardı. Başvuru şikayetleri sıklık sırasına göre ödem (%70), oligüri (%38,5), makroskobik hematüri (%23), hipertansiyon (%15,3), nefes darlığı (%15,3) idi. Kompleman C3 tüm hastalarda düşük iken bir hastada C3 ve C4 düşüklüğü vardı. Aynı hastada nefrotik düzeyde proteinüri ile birlikte akut böbrek yetmezliği vardı. Bu hastaya böbrek biyopsisi yapılarak diffüz proliferatif glomerülonefrit tanısı konuldu.

Sonuç: Günümüzde PIGN gelişmekte olan ülkelerde daha yüksek oranda görülmektedir. Biz de kısa bir dönem içerisinde PIGN hasta sayısında artış tespit ettik ve bu çalışma ile farklı klinik başlangıcı ve seyri olan bu hastalar için genel pediatri hekimlerinin dikkatini çekmeyi amaçladık.

Anahtar kelimeler: Çocukluk çağı, post-enfeksiyöz glomerülonefrit, proteinüri, hipokomplemantemi

INTRODUCTION

Acute glomerulonephritis, one of the earliest clinical observations of nephrology, is known to last for more than 200 years with dark color and reduced urine after scarlet fever[1]. Post-infectious glomerulonephritis (PIGN) is the most common cause of acute glomerulonephritis in children[2]. PIGN term defines as an acute glomerulonephritis which develops as a result of following various infections[1]. The typical clinical symptom of PIGN is acute nephritic syndrome accompanied by macroscopic or microscopic hematuria, edema,

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Geliş tarihi/Received: 9.6.2018 Kabul tarihi/Accepted: 25.7.2018 Published online: 15.9.2018

hypertension and mild-moderate proteinuria. The other clinical presentations are nephrotic syndrome, rapidly progressive glomerulonephritis or subclinical course[3]. Post-streptococcal glomerulonephritis (PSGN) is the prototype and the most common form of PIGN and triggered by nephritogenic strains of group A beta hemolytic streptococcus (GAS) which is responsible for throat or skin infections. Different bacterial, viral, and fungal agents were reported as responsible factor in PIGN[2].

Post-infectious glomerulonephritis usually appears at the age of 4-15 years[1]. It is uncommon under 3 years of age. PIGN is seen more in boys than girls. PIGN occurs as a result of antigen-antibody reactivity. Nephritogenic immune complexes develop in the glomerular basement membrane (GBM) during circulation, causes local activation of complement system and coagulation cascade[1].

The incidence of PIGN has been gradually decreased together with the improved life standarts and prevalent use of antibiotics in western countries. Therefore, the studies which are involving a large number of children with PIGN, and reported from these countries are decreasing. It is known that PSGN due to pharyngitis is most prevalent between December and April, while PSGN due to skin infection, is most prevalent in rainy seasons. In addition to this, there is a certain increase in the number of patients with PIGN in department of Pediatric Nephrology at Cukurova University during November-December 2016 which was not seen previously. We aimed to investigate the reasons of this increment by retrospective evaluation of the patients' clinical and laboratory characteristics.

MATERIALS AND METHODS

The clinical and laboratory datas of 13 children with PIGN who were seen in our clinic at this period, and their follow-up results were evaluated retrospectively. The patients have been diagnosed with PIGN due to hematuria, presence of proteinuria, evidence of streptococcus infection (throat culture, rapid streptococcal antigen testing or increased antistreptolysin O levels for pharyngitis) or history of any infection, low serum complement C3 level and reach normal levels within 8 weeks. Hypertension was defined as average systolic blood pressure or diastolic blood pressure that is ≥95th percentile for gender, age, and height on three or more measurements according to Fourth report from the National High Blood Pressure Education Program Working Group on Children and Adolescents[4].

Blood pressure measurements of patients were done at admission and during the hospitalization at least 8 times/day. Oliguria was defined as urine output less than 0.5 ml/kg per hour during an investigation and follow-up period of at least 12 hours. Antistreptolysin O (ASO) level >200 IU/ml was defined as increased and serum complement C3 level <90 mg/dl, serum complement C4 level<10 mg/dl were defined decreased. Glomerular filtration rate (GFR) was calculated according to the Schwartz formula[5].

Azotemia was defined as estimated GFR was less than 90 ml/min/1.73 m^2 or serum creatinine was above the normal range of values. Nephrotic proteinuria was defined as urinary protein excretion of more than 40mg/m^2 per hour in 24 hour urine collection or urine protein creatinine ratio more than 2 mg/mg in spot urine. Non nephrotic proteinuria was defined as 4-40mg/m^2 per hour in 24 hour or urine protein creatinine ratio 0.2- 2 mg/mg in spot urine. Serum antinuclear antibody were tested for excluding systemic lupus erythematosus (SLE). The study was approved by ethical committee of Cukurova University Medical Faculty (06.07.2018-79/65).

Statistical analysis

Descriptive analysis of demographic features and laboratory findings of cases have been provided.

RESULTS

Thirteen children who diagnosed PIGN were evaluated with the mean age of 9 (3-15) years. Five of patients (38.5%) were male. All patients were diagnosed PIGN with the presence of macro/microscopic hematuria, proteinuria, evidence of recent streptococcal infection, low serum complement C3 levels with normalization within 8 weeks. All of patients had history of previous infections such as pharyngitis or gastroenteritis. Eleven patient (84.6%) had high ASO titer, and also two of them had throat culture positivity for GAS. Two patients with history of gastroenteritis had negative stool culture and normal ASO titer. Although there was no serological evidence of

infection, gastroenteritis was considered as a preceding infection for PIGN in these two patients because of absence of any underlying disease. Symptoms of patients were edema (100%), oliguria (38.5%), macroscopic hematuria (23.1%), hypertension (15.3%), dispnea (15.3%), respectively. All patients had edema while two of patients (15.3%) had severe edema with systolic dysfunction and pulmoner edema. All patients had microscopic hematuria and three of them (23.1%) had macroscopic hematuria as well. Seven of patients (53.8%) had hypertension. Non-nephrotic proteinuria was detected in eleven of the patients (84.6%). Serum complement C3 was low in all patients while one patient had both low serum complement C3 and C4. All patients had normal complement C3 and C4 level within 8 weeks of onset of disease. Antinuclear antibody was negative in all patients. The patient who had hypocomplementemia (both C3 and C4) also had severe proteinuria and acute kidney injury. Renal biopsy was performed to this patient and diagnosed diffuse proliferative glomerulonephritis after renal biopsy. SLE was excluded in this patient with absence of other findings in new criteria of SLE[6]. Clinical characteristics of patients at admission time were shown in Table 1. Laboratory findings of patients at admission time were shown in Table 2.

Table 1. Clinical characteristics of patients at admission time

Clinical features	**n (%)**
History of infection	13 (100)
Upper respiratory tract infection	11 (84.6)
Gastroenteritis	2 (15.4)
Edema	13 (100)
Hypertension	7 (53.8)
Oliguria	5 (38.5)
Macroscopic hematuria	3 (23.1)
Congestive heart failure	2 (15.4)

Table 2. Laboratory findings of the patients

Laboratory findings	**n(%)**
Hypocomplementemia	13 (100)
Low C3 level	13 (100)
Low C3+C4 level	1 (7.7)
Microscopic hematuria	13 (100)
High ASO titer	11 (84.6)
Non-nephrotic proteinuria	11 (84.6)
Azotemia	4 (30.7)
Nephrotic proteinuria	2 (15.4)

ASO: Antistreptolysin O; Low C3 level<90 mg/dl (normal range: 90-180mg/dl), Low C4 level<10 mg/dl (normal range: 10-40 mg/dl); High ASO titer: >200 UI/ml

We started to furosemide treatment to all patients with sodium and fluid restriction. Four (30.7%) of the patients required antihypertensive treatment in addition to furosemide for blood pressure control. Enalapril was used in addition to furosemide treatment in two of patients, while enalapril and amlodipine were used in the other two patients. No patients required any antihypertensive treatment at the end of first year.

Two patients (15.4%) had congestive heart failure with systolic dysfunction, reduced ejection fraction (≤%50). One of them presented with macroscopic hematuria, dyspnea, systemic and pulmoner edema, while the other one had macroscopic hematuria, hepatomegaly, pleural effusion. These patients treated with oxygen therapy, furosemide infusion, sodium and fluid restriction. In addition, one patient required a short hemodialysis course due to the lack of adequate treatment with furosemide.

All patients had good clinical response with aforementioned therapy except one patient who required renal biopsy. This patient received methylprednisolone treatment. Proteinuria improved after four weeks of treatment and methylprednisolone was tapered and stopped after twenty-four weeks. At the last clinical visit, all patients had normal renal function and blood

pressure, while two patient (15.4%) had microscopic hematuria.

DISCUSSION

Prevelance of PIGN is decreased over the last decades. Furthermore, PIGN is rarely seen in developed countries where as it can be seen in adults in comorbid situations such as HIV or alcoholism[7]. The reduction in incidence of PSGN is attributed to a variety of factors, including easier and earlier medical treatment of streptococcal infections. PIGN frequency has been decreasing in worldwide but it is observed at a higher rate (9.3/100.000) in newly developing countries[1]. Dagan et al reported that 125 pediatric patients over the 17 years and they found the incidence of PIGN was highest (53.4%) during the winter months[8]. In accordance with this, we determined an increase in the number of patients diagnosed with PIGN between November-December 2016. We believed that, the major reasons for this increase were immigration to our city from other regions, and Syrian refugees who had low social economic level and poor hygienic conditions. Although it is known that increase in the incidence of PIGN is associated with an increase in the frequency of GAS infection in winter, there are no any studies which reported similar increases of PIGN in November-December 2016.

Post-infectious glomerulonephritis is usually seen in children at the age of 4-14 years and it is uncommon below the 3 years of age[1,9]. The mean age of our patients was 9 (3-15) years in accordance to the literature. While PIGN is seen more frequently in males than in females (M/F:2), only 38.5% of our patients were male. Demircioglu Kilic et al. showed that male predominance in PSGN within two years period in their study[10]. Furthermore, Dagan et al. showed that male predominance in PIGN within 17 years period in their study[8]. It is thought that female predominance in our study is caused by inclusion of patients who admitted within only two months.

Post-infectious glomerulonephritis is a result of various infections. Dagan et al reported that previous infections of PIGN were upper respiratory tract infection in 32 (25.6%) children, gastroenteritis in 14 (11.2%) children, skin infection in 7 (5.6%) children, and pneumonia in 4 (3.2%) children[8]. In our study 11 (84.6%) children had history of recent upper respiratory tract infection and 2 (15.4%) children had history of recent gastroenteritis.

The most common presenting feature of PIGN patients in our study was nephritic syndrome (hematuria, edema, hypertension, azotemia and proteinuria) similar to those previously reported[8,10]. The tea-colored or cola-colored urine occurs in approximately 25–60% of patients[7]. In our study only 3 (23.1%) of patients had macroscopic hematuria. Proteinuria is also present, but nephrotic-range proteinuria is seen in approximately 10% while nephrotic syndrome is noted rare (2-4%)[1]. All patients in this study had proteinuria but only two of them had nephrotic range proteinuria. It has been shown that 34-44% of proteinuria was the nephrotic range at the beginning of disease[11]. Proteinuria in one of patients who had nephrotic range proteinuria resolved within few days spontaneously, the other patient had persistent nephrotic range proteinuria, required renal biopsy and resolved after methylprednisolone treatment. We did not evaluate the relationship among proteinuria and severity of PIGN, but some studies reported that nephrotic range proteinuria was not found related to severity of PIGN [10,12,13].

A recent study showed that cardiac failure occurred as a presentation in 14% of their study group[12]. Wong et al. showed 8 (5%) of 176 patients with PSGN had congestive heart failure[13]. In our cohort 2 of 13 children (15.4%) had congestive heart failure at admission time. Although, there was no significant relationship between the presence of congestive heart failure and severity of PIGN, these patients require prompt and appropriate treatment as in our study.

The activation of complement system via alternative complement pathway, reduced C3, normal C1 and C4 levels are usually seen in patients with PIGN[1,3]. On the other hand, classical complement pathway activation with reduced C4 level is occasionally seen in patients with PIGN, but there is no evidence effects of low C4 to clinical course in these patients. In our cohort, one of our patients had low C4 level with decreased GFR and nephrotic range proteinuria, while two of patients with severe onset PIGN and congestive heart failure had normal C4 levels. It is thought that studies involving a larger number of patients are needed to clarify the effect of low C4 on the clinical course.

There are some limitations to this study. This was a retrospective study from a single center in a short term period and there were lack of datas PIGN patients in long term period. We did not able to

evaluate relationship clinical findings and long term outcomes of patients, but all of our patients good renal outcomes at the end of one year. The prognosis of PIGN is usually good in short term, nevertheless 3-6% have chronic hypertension and less than 1% of children with PIGN have azotemia in long term period[8,14]. We planned to close follow-up our patients for complications in long term period.

Post-infectious glomerulonephritis is observed with higher incidence in the developing countries in current era. We have detected an increase in the number of PIGN patients in a short period and we aimed to draw attention of pediatricians about PIGN patients with different clinical presentations.

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