Post-Infectious Glomerulonephritis in Pediatric Patients over Two Decades: Severity-Associated Features

Rona Dagan BSc[1,3*†], Roxana Cleper MD[2,3*], Miriam Davidovits MD[1,3], Levana Sinai-Trieman MD[4] and Irit Krause MD[1,3]

[1]Institute of Pediatric Nephrology, Schneider Children's Medical Center of Israel, Petah Tikva, Israel
[2]Pediatric Nephrology Service, Dana-Dweq Children Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[4]Department of Pediatrics, Kaplan Medical Center, Rehovot, Israel

ABSTRACT: **Background:** The incidence of post-infectious glomerulonephritis (PIGN) has decreased over the last decades. As a result, recent epidemiological data from industrialized countries are scarce.

Objectives: To evaluate patterns of PIGN in children and detect possible predictors of disease severity.

Methods: We collected clinical and laboratory data of patients with PIGN admitted to Schneider Children's Medical Center during 1994–2011. Diagnostic criteria included presence of hematuria with/without other features of nephritic syndrome along with hypocomplementemia and/or microbiological/serological evidence of streptococcal infection. Patients with other diseases (systemic lupus erythematosus, vasculitis, etc.) were excluded from the study.

Results: A total of 125 patients with a mean age of 5.8 ± 3.3 years (range 1.5–17.6), of whom 16% were < 3 years, matched the study criteria. Presenting features included hypertension in 103 (82.4%) patients, azotemia in 87 (70.2%), fever in 49 (40%), and elevated C-reactive protein in 75 (81.5%). Isolated macrohematuria was found in 21 (16%). Full-blown nephritic syndrome was diagnosed in 51 patients (41.1%) and 28 (22.9%) had nephritic syndrome with nephrotic-range proteinuria. Depressed C3 complement levels were associated with the presence of nephritic syndrome (OR 0.73, 95%CI 0.60–0.88, P = 0.001) as well as older age (OR1.24, CI 1.08–1.43, P = 0.001). At last follow-up (mean 42 months) all examined patients (100 of 125) had normal renal function, 6 had hypertension, and 1 had proteinuria.

Conclusions: PIGN remains an important cause of glomerular disease in children and may affect very young patients. Nephrotic-range proteinuria with hypoalbuminemia seems to be more frequent than previously reported. Hypocomplementemia is associated with a more severe disease course, namely, azotemia and nephritic syndrome.

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KEY WORDS: post-infectious glomerulonephritis (PIGN), nephrotic-range proteinuria, nephritic syndrome, complement, C-reactive protein (CRP), streptococcal infection

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***The first two authors contributed equally to the study**

Post-infectious glomerulonephritis (PIGN) is the most common cause of acute glomerular disease in children worldwide. The estimated global incidence of the disease is 472,000 cases per year, of which 77% occur in developing countries [1]. The incidence has decreased over the last few decades [2,3], possibly due to widespread use of antibiotics, better health care delivery, and improved socioeconomic and nutritional conditions. Large population studies from developed countries in the last decade are scarce. A decline in the incidence and severity of PIGN over recent decades was reported in a single-center study from northern Florida [3]. A survey from Australia reported significant differences in the incidence of PIGN between rural and urban areas as well as a high rate of complications [4]. The disease primarily affects children aged 3–12 years. It is considered uncommon below age 3 [5,6]. The most common and the most studied form is post-streptococcal glomerulonephritis (PSGN), which is induced by nephritogenic strains of group A beta-hemolytic Streptococcus (GAS). Other viral, bacterial and fungal pathogens were reported in association with PIGN [7]. Since these cases are much less common, data regarding their epidemiology, pathogenesis and clinical course are insufficient. Affected individuals may be asymptomatic, and clinical presentation varies from microscopic hematuria to full-blown nephritic syndrome [8,9].

Nephrotic-range proteinuria is seen in up to 10% while nephrotic syndrome is considered rare (2–4%) [10]. The laboratory hallmark of PIGN is depressed C3 level at the onset of symptoms and is found in 90% of patients [11]. Low C3 levels were not reported to be associated with disease severity [4,10]. PIGN is considered a benign disease in children. In typical cases, proteinuria and edema decline rapidly (within 5–10 days). While microscopic hematuria may persist for months or even years, more than 95% of children recover completely with normalization of C3 levels within 6–8 weeks [10]. Adults have a poorer prognosis [12]. Data from industrialized countries regarding changes in clinical course of sporadic PIGN are scant and inconsistent. Therefore, in order to evaluate the clinical and laboratory patterns of the disease we retrospectively studied 125 pediatric patients with PIGN who were admitted to our hospital over 17 years.

PATIENTS AND METHODS

We retrospectively reviewed the medical records of all patients diagnosed with PIGN who were admitted to Schneider Children's Medical Center over 17 years (1994–2011). Diagnostic criteria included presence of hematuria with/without other features of nephritic syndrome, hypocomplementemia (with normalization of complement levels up to 8 weeks following disease onset), and/or microbiological/serological evidence of streptococcal infection: positive throat culture and/or elevated anti-streptolysin O (ASLO) titers > 200 IU/ml at admission. Patients with normocomplementemia were included if they fulfilled the other diagnostic criteria. Patients with clinical or laboratory evidence of underlying systemic conditions such as systemic lupus erythematosus (SLE) or vasculitis were excluded from the study. Data on demographics, presenting symptoms and signs, diseases that preceded glomerulonephritis, clinical course of the disease, and laboratory tests during hospital stay and at the last follow-up visit were collected.

Hypertension was diagnosed if blood pressure (BP) values were higher than the 95th percentage for age, gender and height. BP was measured at admission and during hospitalization at least two to three times daily or more if elevated values were obtained and according to existing guidelines for BP measurement [13]. Oliguria was defined as urine output < 0.5 ml/kg/hour during an observation period of at least 12 hours. Fever was defined as temperature > 38ºC. Pharyngitis was diagnosed if any of the following was present: pharyngeal erythema or exudates on the tonsils. Upper respiratory tract infection was diagnosed when cough and rhinitis were present. Hematuria was defined if ≥ 5 red blood cells/high power field were found in urine sediment. Nephrotic-range proteinuria was defined as urinary protein excretion of > 40/mg/m²/hr applying 24 hour urine collection, or protein > 300 mg/dl on a urine sample dipstick or if protein/creatinine ratio was > 2 in the urine sample. Hypoalbuminemia was defined as serum levels of albumin < 3 g/dl. Glomerular filtration rate (GFR) was calculated according to the Schwartz formula [14] using the appropriate coefficient for the type of creatinine assay. Azotemia was defined if GFR was < 90 ml/min/1.73 m² or if serum creatinine was above the normal age-adjusted range of values. Anemia was defined as hemoglobin (Hb) levels below the mean-2SD for age and gender. Nephritic syndrome was diagnosed if hematuria, hypertension or azotemia was present. Laboratory tests were performed in the Multidisciplinary Laboratory of Schneider Children's Medical Center. Azotemia, the presence of nephritic syndrome and/or nephrotic-range proteinuria with hypoalbuminemia were considered measures of disease severity.

All patients were treated with standard supportive therapy for acute glomerulonephritis according to each patient's needs, including fluid and electrolyte control, blood pressure control, correction of acidosis, and dialysis as required.

STATISTICAL ANALYSIS

Statistical analysis was performed using BMDP Statistical Software (Dixon WJ, 1993, University of California Press, Los Angeles, USA). Continuous variables were compared using analysis of variance (ANOVA). Discrete variables were compared using Pearson's chi-square test or Fisher's exact test, as applicable. Variables found to be significant on univariate analysis were entered into a stepwise logistic regression to determine the variables most significantly associated with severity of disease (presence of nephritic syndrome, nephrotic-range proteinuria with hypoalbuminemia, and/or renal failure). When comparing variables with non-Gaussian distributions, we used the non-parametric Mann-Whitney U-test. In order to compute the correlation between C3 and estimated GFR, we applied a log-transformation on C3, since C3 does not have a Gaussian distribution. A P value ≤ 0.05 was considered significant.

The study was approved by the Ethics Institutional Review Board of Rabin Medical Center, Petah Tikva, Israel.

RESULTS

A total of 125 patients matched the inclusion criteria: 93 boys (74.4%) and 32 girls (25.6%) with a mean age of 5.8 ± 3.3 (range 1.5–17.6). Twenty patients (16%) were 1.5–3 years old. The incidence of PIGN was highest (53.4%) during the winter months (December to February). The most common infectious disease preceding PIGN was pharyngitis in 56 patients (44.8%). Streptococcal infection was established by elevated ASLO titers in 109 (85%), while throat culture was positive in 39 (31.2%). Upper respiratory tract infection was reported in 32 (25.6%), gastroenteritis in 14 (11.2%), skin infection in 7 (5.6%), and pneumonia in 4 (3.2%). In 20 patients (16.1%) no recent infection was reported. Seven of nine patients with gastroenteritis as a preceding infection had elevated levels of ASLO. The main clinical features are presented in Table 1. One patient needed a short hemodialysis course (three sessions for pulmonary congestion). One patient had hypertensive encephalopathy-induced seizures. Laboratory findings are presented in Table 2.

Full-blown nephritic syndrome was diagnosed in 51 patients (41.1%). In 28 (22.9%) of them, combined nephritic-nephrotic features were present. Renal biopsies were performed in seven

Table 1. Clinical features at presentation

Clinical features	No. of patients (%) (n=125)
Isolated macrohematuria	21 (16.8%)
Oliguria	42 (33.6%)
Hypertension	103 (82.4%)
Fever	49 (40.2%)
Edema	74 (59.2%)

Table 2. Laboratory findings at presentation

Laboratory findings	No. of patients (%) (n=125)
Azotemia	87 (70.16%)
Proteinuria/nephrotic range	116 (92.8%)/40 (32.5%)
Hypoalbuminemia (‹ 3 g/dl)	27 (22.0%)
Elevated CRP (› 0.5 mg/dl)	75 (81.5%)
Low C3 level (‹ 90 mg/dl)	110 (89.0%)
Low C4 level (‹ 10 mg/dl)	29 (23.8%)
Anemia	98 (79.0%)
Hyperkalemia (› 5.5 mEq/L)	36 (28.8%)

Table 3. C3 levels according to clinical findings

Clinical findings	No. of patients (%) (n=125)	Mean C3 level (mg/dl ± SD)	Median C3 level (mg/dl ± SD)
Nephritic syndrome	51 (41.1%)	25.1 ± 16	20 (5.9–85)
Nephritic syndrome with nephrotic features*	28 (22.9%)	26 ± 16	22 (5.9–49)
Without nephritic syndrome or nephrotic features*	64 (51.6%)	50.4 ± 45.6	34.5 (4.2–168)

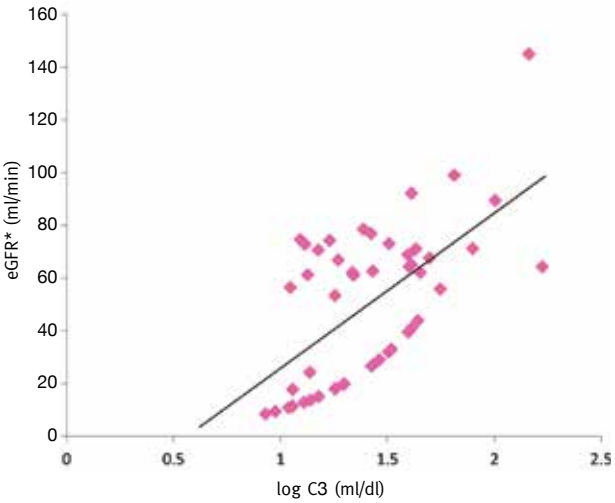
*Nephrotic features include nephrotic-range proteinuria with hypoalbuminemia

patients for rapidly progressive azotemia and/or prolonged macroscopic hematuria (> 1 month) or prolonged proteinuria (> 2 months). Histopathological findings in five specimens were compatible with PIGN: diffuse proliferation of glomerular cells, deposits of immunoglobulin G and C3 along with sub-epithelial dense deposits (hump-like) on electron microscopy (EM). Two specimens showed typical findings on light microscopy without hump-like deposits on EM. Mean length of hospitalization was 6.4 days (median 6 days, range 1–46 days).

Anemia was significantly associated with azotemia (76%, $P = 0.014$). Complement C3 levels were significantly lower in 84 patients with azotemia (31.9 ± 28.6 mg/dl) compared with 36 patients with normal renal function (53.2 ± 46 mg/dl), $P = 0.01$. Patients with nephritic syndrome had significantly lower C3 levels (25.1 ± 16 mg/dl, median 20 mg/dl) as compared to patients without nephritic syndrome (49.4 ± 44.8 mg/dl, median 33 mg/dl) [Table 3]. Moreover, a significant correlation was found between C3 levels and estimated GFR [Figure 1].

Nephritic syndrome was more common in children above the age of 3 years: 46.7% compared to 10.5% in the younger group. Variables that were associated with nephritic syndrome calculated by stepwise logistic regression were depressed C3: odds ratio (OR) 0.73, 95% confidence interval (95%CI) 0.60–0.88 ($P = 0.001$), and older age: OR 1.24, 95%CI 1.08–1.43 ($P = 0.001$).

Figure 1. Correlation between C3 levels and estimated GFR



*Estimated GFR (according to Schwartz formula) in 50 patients

The total number of patients hospitalized with PIGN each year did not change significantly during the study period, yet the incidence of admissions for PIGN (out of the annual number of hospitalizations due to all causes) declined from 0.12% to 0.062%. Patient demographics (age, gender) as well as incidence of azotemia, nephritic syndrome or nephrotic-range proteinuria did not change over the study period.

Follow-up data were available in 116 patients (92.8%). Mean duration of follow-up was 42 months (median 13). At the last visit all patients had normal renal function, microscopic hematuria was present in 29 (30%), and 1 had non-nephrotic proteinuria. Blood pressure measurements were available in 100 patients, 6 of whom (6%) had elevated levels. No significant difference in clinical and laboratory findings during the acute phase of the disease was noted between patients with high blood pressure and patients without hypertension. Complement levels were normal at the end of the follow-up.

DISCUSSION

The incidence of PIGN has decreased significantly during the last decades, mostly in industrialized countries, yet it remains a major cause of acute glomerular disease in children around the world. In contrast to previous reports, the demographic and clinical characteristics of our patients did not change during the study period. Since our hospital is a tertiary medical center, the spectrum of cases reviewed might represent a selected, possibly more severely affected, population. This might explain the relatively high rates of azotemia, and nephritic and nephritic-nephrotic features.

Selection bias might also apply to the surprisingly high (16%) rate of very young patients (1.5–3 years old) diagnosed with PIGN, as these subjects may require special observation during the acute phase of the disease. Another explanation for the relatively high rate of toddlers in our cohort may be the increasing incidence of streptococcal infection or possibly other infectious triggers in this population. In accordance with previous surveys, we found male predominance, albeit higher than reported (3:1), and seasonality (a higher incidence during the winter).

Most sporadic cases of PIGN occur following throat infection with streptococci rather than skin infection [15]. As in other studies, most of our patients had at least one laboratory finding supporting streptococcal infection presenting as pharyngitis. Yet, in a few patients, infection other than *Streptococcus* was probably the trigger of PIGN. No association was found between the nature of preceding infectious disease and the clinical course of glomerulonephritis. Of note, despite the relatively warm climate in our country, skin infections were rarely the trigger of PIGN. Many children in the study had signs of active infection at presentation – elevated CRP or fever; however, whether the cause was an ongoing infection that had also possibly triggered the glomerulonephritis process, or reflects the inflammatory process in the kidney, cannot be determined.

The most common presenting features in our study were similar to those previously reported [11]: hematuria, azotemia, hypertension, and peripheral edema. Isolated macrohematuria was the presenting symptom in less than a quarter of all patients. This finding may be due to selection bias since we studied children who were admitted to the inpatient care facility. The clinical diversity of PIGN might also reflect geographic and ethnic variations [9,12,16].

In contrast to other studies [4], we found a previously unreported association between the severity of the acute-phase PIGN as reflected by the degree of azotemia and/or presence of full-blown nephritic syndrome and the extent of C3 depression. Complement activation mostly via an alternative pathway is recognized as playing an important role in the pathogenesis of PIGN, as evident by C3 glomerular sub-epithelial deposits and depressed serum C3 levels in 90% of the patients [11,17-19]. An explanation for the difference between our findings and others might be the timing of testing serum complement levels as they may vary during the course of the disease, or genetic diversity in the extent of complement activation. The long-term impact of the severity of C3 depression could not be assessed since the follow-up period of our cohort was not long enough.

Another parameter associated with nephritic syndrome in our study was older age. Adults with PIGN, especially elderly patients and those with pre-existing morbidity, may suffer from severe disease during the acute phase and have a worse prognosis than young patients [20]. Yet, no correlation between age and severity of glomerular disease within the pediatric patient group has been reported previously.

Anemia is one of the most commonly reported laboratory findings in patients with PIGN, as also found in 79% of our patients, and is attributed mainly to dilution due to intravascular fluid overload, although other factors such as inflammatory state, suppressed erythropoietin secretion and hemolysis may be involved [8]. Expectedly, the severity of anemia correlated with the degree of azotemia and the eventual full recovery.

Less than 1% of children with PIGN progress to end-stage renal failure; however, up to 20% may have persistent abnormal urinary findings (hematuria and proteinuria) and 3–6% have long-standing hypertension [21]. There are significant differences in the reported PIGN outcome in association with genetic and prenatally determined conditions (such as low birth weight) which influence the long-term PIGN outcome [21]. PIGN may contribute to progression of kidney damage as supported by the presence of reduced renal functional reserve found in otherwise healthy subjects who recovered from the disease [22]. Hypertension was found in 6% of our patients at the last follow-up visit. In a recent cohort study in young healthy adults in Israel a significant association was found between resolved childhood glomerular diseases (PIGN and steroid-responsive nephrotic syndrome) and a subsequent risk of hypertension [23], which was similar to our findings during the relatively short follow-up. These findings are worrisome and warrant long-term follow-up in apparently asymptomatic patients who recovered from PIGN during childhood. Prognostic factors for later deterioration of renal function following recovery from pediatric PIGN have still to be elucidated.

This study has several limitations. Due to its retrospective nature a complete clinical and laboratory data retrieval was not possible. Population selection bias derives from inclusion of only those children who were hospitalized. Nevertheless, the large sample and long time span provide important observations regarding clinical and laboratory characteristics of PIGN and insight into possible associations between various parameters and the course of the disease.

CONCLUSIONS

PIGN is still a major cause of acute glomerular disease in children and toddlers. Nephrotic features in the course of PIGN may be more common than previously reported but usually resolve spontaneously with careful surveillance. Lower C3 serum levels and older age are significantly associated with acute-phase azotemia and nephritic syndrome. Long-term follow-up is required since hypertension may persist. Further studies are needed to track changes in the epidemiology, clinical course and long-term prognosis of PIGN and to identify possible prognostic factors.

Correspondence
Dr. I. Krause
Institute of Pediatric Nephrology, Schneider Children's Medical Center of Israel, Petah Tikva 49100, Israel
Phone: (972-3) 925-3692
Fax: (972-3) 925-3511
email: ikrause@post.tau.ac.il

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