

## Complement C3 Levels in Membranoproliferative and Post-infectious Glomerulonephritides

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### Abstract

**Objectives** – Post infectious glomerulonephritis (PIGN) is the most common type of nephritis in children. Presentation is variable, and most cases initially have low serum complement C3. Membranoproliferative glomerulonephritis (MPGN) is a chronic nephritis less frequently seen in children and is also associated with low serum C3. While management of PIGN is predominantly supportive, MPGN usually requires immunosuppressive therapy. Differentiating PIGN from MPGN at presentation is difficult. Early diagnosis can help inform evaluation and treatment decisions. **Materials and Methods** – This is a retrospective study of all children 1-21 years of age diagnosed with PIGN and MPGN, treated by nephrologists at Nationwide Children's Hospital between January 2014 and December 2019. Clinical data, results of kidney function, complement levels, urine testing and biopsy were collected. Children with other types of glomerulonephritis were excluded. **Results** – Fifty-seven children were included (43 with PIGN and 14 with MPGN). PIGN children were younger at presentation (median age: 7 vs 9.5 years,  $P=0.0159$ ) and more likely to have a C3 level  $<40$  mg/dl compared to MPGN children ( $P=0.0031$ ). Most children with PIGN (74.42%) had normal complement levels within 12 weeks after diagnosis compared to 35.71% of children with MPGN. More children with MPGN had evidence of chronic kidney disease as compared to PIGN children, who were more likely to have a full kidney recovery. **Conclusions** – Younger children with more significant hypocomplementemia at presentation were more likely to have PIGN than MPGN. We recommend earlier evaluation for MPGN in adolescents with milder degrees of hypocomplementemia ( $>40$  mg/dl).

**Key Words:** Complement C3 ■ Postinfectious glomerulonephritis ■ Membranoproliferative glomerulonephritis.

### Introduction

Glomerular diseases account for 15-29% of children with end stage kidney disease (ESKD) worldwide (1). Post infectious glomerulonephritis (PIGN) is the most common type of nephritis in the pediatric population, and usually presents with a combination of hypertension, hematuria, variable degrees of acute kidney injury (AKI) and / or proteinuria (2). PIGN can occur after different infections but is most commonly seen 1-4 weeks after an infection with specific serotypes of group A streptococci in

children (3). The annual incidence in children varies as it is estimated to be around 24.3 per 100.000 children in less developed countries and 6 per 100.000 children in developed regions (4).

Membranoproliferative glomerulonephritis (MPGN) is an umbrella term that comprises both C3 glomerulopathy and immune-complex MPGN. It can be caused by an abnormal complement system or occur secondary to certain infections, autoimmune conditions or malignancies. It is seen in children and young adults and has variable presentations, from mild nephritis to rapidly progressive

GN needing dialysis. The annual incidence is estimated to be 1-2 per million population (5). It is usually managed with immunosuppressive agents, depending on its severity A (6). As expected, the long-term outcome for children with GN is largely dependent on the etiology.

At presentation, identifying the cause of hypocomplementemic GN can be difficult on clinical grounds. Systemic lupus erythematosus (SLE) GN is usually associated with multiorgan involvement (rash, anemia, etc.), presence of lupus antibodies (such as anti DsDNA, anti-Smith) and suppression of both C4 and C3 serum levels. PIGN and MPGN, on the other hand, can have low complement levels, specifically low serum C3 level and both diseases can present after infections (6, 7, 8, 9).

The disease course for MPGN can differ significantly from PIGN. PIGN patients most commonly achieve spontaneous recovery while MPGN can lead to long-term kidney disease and sometimes kidney failure requiring transplantation (6,8). Most children with PIGN need supportive therapy, contrary to children with MPGN where long term immunosuppressive therapy is often required (7). For these reasons, it is important to distinguish MPGN from PIGN early in the course of disease.

C3 levels usually recover after 8-12 weeks in PIGN and remain chronically low in MPGN (7). Resolution of symptoms may happen before the full normalization of serum C3 level in PIGN (10). The need for kidney biopsy becomes an issue and is necessary for the diagnosis in children with persistently low C3 levels and prolonged symptoms. Biopsy is not typically performed in the early course of disease if PIGN is suspected. However, for patients with MPGN, this delay can lead to late diagnosis and delayed initiation of therapy. In a study by Xu et al, earlier diagnosis of MPGN was associated with more children achieving partial or full remission (7).

The aim of this study is to determine if there are notable differences in C3 levels at presentation- as well as other clinical, laboratory, or demographic characteristics- to help differentiate PIGN cases from MPGN early in the course. This could lead to an early diagnosis of MPGN and, thus, timely initiation of evaluation and treatment.

## Materials and Methods

This is a single center, retrospective study of all children diagnosed with PIGN and MPGN who were managed by nephrology practitioners at Nationwide Children's Hospital between January 2014 and December 2019. Inclusion criteria included children between 1 and 21 years of age with a clinical diagnosis of PIGN (nephritis, recent upper respiratory or skin infection, low C3 and supportive levels of ASO and / or kidney biopsy if available) or MPGN (kidney biopsy-based diagnosis in all these children). We included all children who had a complement level at presentation and at least 1 additional complement level within the following 6 months. Children with glomerulonephritis with normal complements (such as IgAN, IgA vasculitis), Lupus nephritis (diagnosed based on Lupus antibodies, Lupus criteria and confirming kidney biopsy of Lupus nephritis), or who did not have complement testing were excluded.

Clinical data, including demographics, clinical presentation, BUN, creatinine, complement levels, proteinuria, kidney biopsy results (if available), and treatments were collected. For children who did not have complement levels collected at the final follow-up visit, previously available complement level was collected for analysis (since C3 level was often not repeated once a normal C3 level was achieved). CKiD U25 equation was used to calculate creatinine-based eGFR. (11) Data collected included those from the time of the initial presentation, then at 1-3-, 6-, and 12-month mark and at the time of the last clinic visit. Hypertension (HTN) was defined as having SBP or DBP >95% for age, height and sex as per the 2017 AAP guidelines, > 130/80 for children 13 years of age and older, or when using antihypertensive medications for management of HTN. (12) AKI in this study was defined as having an eGFR less than 90 cc/min/1.73 m<sup>2</sup> at the time of presentation. Proteinuria was presented as protein to creatinine ratio (UP/C in mg/mg) and was considered negative if protein checked by urine dipstick was negative to trace.

**Statistical Analysis**

ANOVA or Kruskal-Wallis test was used for continuous variables, and Fisher Exact test or Chi-Square test was used for categorical variables to assess statistical difference in median (IQR) or frequencies (proportions) between PIGN and MPGN groups. A P-value equal to or less than 0.05 was considered statistically significant. The statistical analysis for this study was performed using Statistical Analysis System (SAS, version 9.4).

**Results**

The study included a total of 57 children (43 with PIGN, 14 with MPGN). A summary of the patients' demographics can be found in Table 1. Children

with PIGN were more likely to be younger at presentation compared to those with MPGN (median age of 7 vs 9.5 years, P=0.0159). There were no significant differences in race (reported per family / subjects) or sex and the majority were males and Caucasian. Most children did not have a recent ASO titer or throat culture at the time of diagnosis.

Twenty-eight children (65%) with PIGN and 10 children (71%) with MPGN had hypertension at presentation with no significant difference between the two groups (P= 0.7537) (Table 1). Two children with PIGN developed severe hypertension associated with seizures at presentation, with imaging consistent with posterior reversible leukoencephalopathy syndrome (PRES). None developed PRES in the MPGN group. Between the two groups, there were no statistically significant differences in

| Variable                                 | Level            | PIGN (N=43)        | MPGN (N=14)          | Total (N=57)       | P value  |
|--|------------------|--------------------|----------------------|--------------------|----------|
| Age (Median, IQR, min, max)              | Year             | 7 [4, 10]; (2, 15) | 9.5 [8, 14]; (4, 18) | 8 [5, 11]; (2, 18) | 0.0159*  |
| Race: N (%)                              | African American | 3 (6.98)           | 1 (7.14)             | 4 (7.02)           | >0.9999† |
|  | Caucasian        | 35 (81.4)          | 12 (85.71)           | 47 (82.46)         |          |
|  | Hispanic         | 3 (6.98)           | 0 (0)                | 3 (5.26)           |          |
|  | Other            | 2 (4.65)           | 1 (7.14)             | 3 (5.26)           |          |
| Sex: N (%)                               | Female           | 11 (25.58)         | 5 (35.71)            | 16 (28.07)         | 0.4636‡  |
|  | Male             | 32 (74.42)         | 9 (64.29)            | 41 (71.93)         |          |
| HTN at presentation: N (%)               | No               | 15 (34.88)         | 4 (28.57)            | 19 (33.33)         | 0.7537†  |
|  | Yes              | 28 (65.12)         | 10 (71.43)           | 38 (66.67)         |          |
| Abnormal kidney Ultrasound: N (%)        | No               | 19 (44.19)         | 3 (21.43)            | 22 (38.6)          | <0.0001† |
|  | Yes              | 2 (4.65)           | 9 (64.29)            | 11 (19.3)          |          |
|  | N/A              | 22 (51.16)         | 2 (14.29)            | 24 (42.11)         |          |
| Chest X Ray: N (%)                       | Abnormal         | 8 (18.6)           | 3 (21.43)            | 11 (19.3)          | >0.9999† |
|  | Normal           | 3 (6.98)           | 1 (7.14)             | 4 (7.02)           |          |
|  | N/A              | 32 (74.42)         | 10 (71.43)           | 42 (73.68)         |          |
| Seizures activity at presentation: N (%) | No               | 41 (95.35)         | 14 (100)             | 55 (96.49)         | >0.9999† |
|  | Yes              | 2 (4.65)           | 0 (0)                | 2 (3.51)           |          |
| C3 at presentation in mg/dl: (N (%))     | 0-40             | 35 (81.4)          | 6 (42.86)            | 41 (71.93)         | 0.0031†  |
|  | 41-85            | 8 (18.6)           | 5 (35.71)            | 13 (22.81)         |          |
|  | 86+              | 0 (0)              | 3 (21.43)            | 3 (5.26)           |          |
| AKI at presentation: N (%)               | eGFR <90         | 30 (69.77)         | 10 (71.43)           | 40 (70.18)         | >0.9999† |
| Proteinuria at presentation ††: N (%)    | UP/C >0.2        | 32 (74.42)         | 14 (100)             | 46 (80.7)          | 0.0493‡  |

PIGN=Post infectious glomerulonephritis; MPGN=Membranoproliferative glomerulonephritis; AKI= Acute kidney injury; N/A=Not applicable; \*Kruskal-Wallis test; † Fisher Exact tests; ‡ Chi-square test. †† Five children with PIGN did not have quantitative proteinuria levels.

the frequency of PRES, abnormal chest X-ray findings (defined as the presence of pulmonary edema) or abnormal kidney ultrasound results.

AKI was seen in 30 children (69.77%) with PIGN and in 10 children (71.43%) with MPGN, with no significant difference between the two groups ( $P=>0.9999$ ). Most subjects in both groups had proteinuria (UP/C  $>0.2$  mg/mg), including 32 children (74.42%) with PIGN and 14 children (100%) with MPGN ( $P=0.0493$ ), as shown in Table 1 and Table 2. The average UP/C for children with PIGN was 1.86 vs 6.92 mg/mg in children with MPGN ( $P=0.005$ ). The average serum albumin level at presentation was lower for children with MPGN at 2.4 g/dl as compared to 3.4 g/dl for children with PIGN ( $P=0.0004$ ). Criteria for nephrotic syndrome were met in two children with PIGN (4.65%) and 3 children with MPGN (21.43%) (See table 2). All children with PIGN

and MPGN had either microscopic or gross hematuria at the time of presentation.

All children with PIGN had low C3 levels at presentation ( $<85$ mg/dl) and they were more likely to be severely suppressed (level  $<40$  mg/dl) compared to MPGN children (81.4 vs 42.8 %,  $P=0.0031$ ) (see Table 1). At presentation, three (21%) of the children with MPGN had normal C3 levels, while the rest had low C3 levels.

In 32 children with PIGN (74.42%), C3 returned to normal ( $>85$  mg/dl) by 12 weeks and 6 children (14%) did not have a C3 level rechecked within the first 12 weeks. Five children (35.71%) with MPGN had normal C3 levels when rechecked within the first 12 weeks after presentation. These data were constrained by a lack of consistency in the timing of repeat measurements of C3 levels. Results are summarized in Table 3.

Table 2. Difference between PIGN and MPGN for Albumin, UP/C, eGFR at Presentation and Nephrotic Syndrome

| Variable  | Level                   | PIGN (N=43)                               | MPGN (N=14)                                | Total (N=57)                              | P Value              |
|---|-------------------------|---|--|---|----------------------|
| Average serum Albumin at Presentation (mg/dL)*            | Median [IQR] (min, max) | 3.40<br>[3.00, 3.08]<br>(2.30, 4.70)      | 2.40<br>[2.10, 3.20]<br>(1.60, 4.10)       | 3.30<br>[2.90, 3.80]<br>(1.60, 4.70)      | 0.0004 <sup>†</sup>  |
| Average UP/C at Presentation (mg/mg)**                    | Median [IQR] (min, max) | 1.86<br>[0.50, 7.14]<br>(0.00, 34.90)     | 6.92<br>[4.14, 11.10]<br>(2.60, 19.02)     | 3.80<br>[0.86, 8.80]<br>(0.00, 34.90)     | 0.0050 <sup>††</sup> |
| Average eGFR at Presentation (cc/min/1.73m <sup>2</sup> ) | Median [IQR] (min, max) | 76.00<br>[46.00, 98.00]<br>(5.50, 128.00) | 61.50<br>[38.00, 99.00]<br>(17.00, 118.00) | 74.00<br>[44.50, 98.50]<br>(5.50, 128.00) | 0.5375 <sup>†</sup>  |
| Nephrotic Syndrome: N (%)                                 | Nephrotic syndrome      | 2 (4.65%)                                 | 3 (21.43%)                                 | 5 (8.77%)                                 | 0.0893 <sup>‡</sup>  |

PIGN=Post infectious glomerulonephritis; MPGN=Membranoproliferative glomerulonephritis; \*Five children with PIGN and one with MPGN did not have serum albumin checked at the time of presentation; <sup>†</sup>P values were from ANOVA test; <sup>††</sup>P value was from Kruskal-Wallis test; <sup>‡</sup>P values were from Fisher Exact tests; \*\* Five children with PIGN did not have quantitative proteinuria levels.

Table 3. Children with normal complement levels within 12 weeks of presentation and at last follow up.

| Variable                    | Level  | PIGN (N=43) | MPGN (N=14) | Total (N=57) | P value             |
|-----------------------------|--------|-------------|-------------|--------------|---------------------|
| C3 at 9-12 weeks: N (%)     | N/A    | 6 (13.95)   | 4 (28.57)   | 10 (17.54)   | 0.0266 <sup>*</sup> |
|                             | Low    | 5 (11.63)   | 5 (35.71)   | 10 (17.54)   |                     |
|                             | Normal | 32 (74.42)  | 5 (35.71)   | 37 (64.91)   |                     |
| C3 at last follow up: N (%) | N/A    | 2 (4.65)    | 0 (0)       | 2 (3.51)     | 0.0607 <sup>*</sup> |
|                             | Low    | 2 (4.65)    | 4 (28.57)   | 6 (10.53)    |                     |
|                             | Normal | 39 (90.7)   | 10 (71.43)  | 49 (85.96)   |                     |

PIGN=Post infectious glomerulonephritis; MPGN=Membranoproliferative glomerulonephritis; N/A=Not applicable \* P values were from Chi-Square tests.

Kidney biopsy in our cohort was performed in six children with PIGN and in all children with MPGN. Biopsy findings in the MPGN group were: Immune complex MPGN, C3 GN, Dense deposit disease in six, seven and one patient, respectively. Kidney biopsy was performed in PIGN if there was a delay in the resolution of proteinuria and/or hypocomplementemia for more than 8-12 weeks or when the diagnosis of PIGN was not clear at presentation either due to severe AKI or lack of previous infection and/or supportive timeline. Seven children with MPGN had active crescents, ranging from 5-30 % while two children with PIGN had active crescents ranging from 7-30%.

Children with PIGN received mostly supportive care with fluid restriction and low sodium diet. Furosemide and/or calcium channel blockers were the most common anti-hypertensive agents used for those with hypertension. At the time of the last visit, most children had full kidney recovery. Four children had reduced eGFR (51-89 cc/minute/1.73m<sup>2</sup>), of whom three met stage II CKD and one met stage III CKD criteria. One child had minimal proteinuria (UP/C 0.24 mg/mg).

Children with MPGN were treated with immunosuppressive agents. All children received a prolonged course of steroids, and two children additionally received mycophenolate mofetil (14%). All children were treated with ACE inhibitors or angiotensin receptor blockers to manage their proteinuria and/or hypertension. Treatment was effective in controlling the disease in most children with improvement in their kidney function. There was a 93% reduction in average UP/C at the time of the last follow up (8.15 mg/mg at presentation to 0.57 mg/mg) and a 26% improvement in average creatinine based eGFR (67 cc/minute/1.73 m<sup>2</sup> to 91 cc/minute/1.73 m<sup>2</sup>) after a mean follow-up period of 83 months. At the time of the last visit, five children (36%) had reduced eGFR (range 33-85 cc/minute/1.73m<sup>2</sup>) and ten (71%) had proteinuria (UP/C 0.22-2.8 mg/mg). Nine patients achieved full remission (UP/C <0.5 mg/mg with stable or improved eGFR) and three patients achieved partial remission (UP/C >0.5 - <2 mg/mg).

## Discussion

In this retrospective cohort study, we found that children with PIGN were more likely to be younger at diagnosis and to have significantly suppressed C3 complement levels (below 40 mg/dl), when compared to children with MPGN. Those with MPGN were also more likely to have severe hypoalbuminemia and higher grades of proteinuria. In our study, the median age at presentation for MPGN was 9.5 years. Similarly, the mean age of diagnosis of MPGN was between 8.7 and 10 years in previous pediatric studies (7, 13, 14). In contrast, the median age for PIGN presentation was 7 years which was similar to other pediatric PIGN studies (15, 16). Our results are in line with previous research suggesting that PIGN tends to manifest at a younger age compared to MPGN.

Complement C3 levels tended to be lower at presentation in the PIGN group with 81% of patients having C3 below 40 mg/dl compared to 42% of the MPGN group. In our study, most children with PIGN recovered normal complement levels within the first 12 weeks of follow-up unlike those with MPGN (72 % vs 35%). This concurs with previous research and supports the notion that persistently low C3 levels through 12 weeks may suggest MPGN. Complement levels during the follow-up period were not checked at uniform time points and this made it difficult to assess whether there were differences in the recovery rate of C3 levels between the two disease processes. Measuring complement levels at set time points after presentation would be helpful to determine if there are significant variations in the rate of complement recovery that could help distinguish PIGN from MPGN.

We found a propensity for higher proteinuria and lower serum albumin level at presentation in the MPGN group compared to the PIGN group (6.82 vs 1.86 and 2.4 vs 3.4, respectively). Previous research in pediatric PIGN showed lower frequency of hypoalbuminemia. In another large cohort of children with PIGN, initial serum albumin was below 3.5 g/dl in 37% with only 12% <2.5 (15). The finding of significant hypoalbuminemia among



children with MPGN is corroborated in other studies where the mean serum albumin was 1.9-2.4 g/dl in a group of 92 patients in one study and 12/17 had nephrotic syndrome in another (13, 7).

As expected, children with PIGN are more likely to achieve full kidney recovery while those with MPGN often have persistent kidney dysfunction. One study of children with PIGN over a 20-year span found that 100% of children had normal kidney function, 6 had hypertension, and 1 had proteinuria at the last follow-up, which was a median of 42 months after presentation (16). Conversely, a study done by Kahndelwal et al found that out of 92 children in their cohort, five-year kidney survival for MPGN children was between 62 and 88% (13). In another study of 80 children with MPGN, analyzing data from the National Registry of Rare Kidney Disease (RaDaR), 14% progressed to kidney failure and 10% required kidney transplantation (18). These differences in outcomes highlight the need for more research to identify biomarkers and other factors at presentation that can help distinguish one group from the other.

Hypertension and seizure activity at the time of diagnosis were not specifically associated with either diagnosis. A study done by Cameron et al. found that children with MPGN were less likely to present with hypertension in general than adults (19). Further research involving a data set consisting of a high number of critically ill children at presentation may help identify an association.

### *Limitations of the Study*

Our study is limited by its small sample size, single center status and the retrospective design. The relatively low number of MPGN cases in our study is reflective of the incidence of these diseases in the general population (4, 5). This made it difficult to assess differences in severe symptoms such as seizures/PRES between the two groups. In addition, for most patients ASO titer was not checked at the time of presentation. Future research involving multicenter retrospective and prospective data is needed to evaluate the association between the

degree of hypocomplementemia and final diagnosis of PIGN vs MPGN.

### **Conclusion**

Children with significantly low complement C3 levels < 40 mg/dl and younger age at the time of presentation are likely to have PIGN rather than MPGN. Those who are older with less severe hypocomplementemia and/or more severe hypoalbuminemia should be considered for earlier kidney biopsy, complement pathway and serological testing. Timely diagnosis can help initiate earlier treatment for children with MPGN and ultimately improve outcomes for this group of children.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Authors' Contributions:** Conception and design: MK, JDM and AW; Acquisition, analysis and interpretation of data: MK, AZ, MN, JDM and AW; Drafting the article: AW;

**Revising the article critically for intellectual content:** MK, AZ, MN, JDM and AW; Approved final version of the manuscript: MK, AZ, MN, JDM and AW.

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