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Clinical characteristics and short term outcomes of childhood immune complex membranoproliferative glomerulonephritis and C3 glomerulopathy: a single centre retrospective study

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Abstract

Background Membranoproliferative glomerulonephritis, with its immune complex variety and C3 glomerulopathy, is a rare glomerular disease in children. The objective of this study was to determine the clinical features and short-term outcomes in children.

Methods This retrospective cohort study was conducted at the Department of Pediatric Nephrology, Sindh Institute of Urology and Transplantation, Karachi, from January 2020, to June 2022. All the children with membranoproliferative lesions identified via light microscopy and less than 18 years were included.

Results A total of 35 children were diagnosed MPGN, 7 (20%) with C3 glomerulopathy and 28 (80%) idiopathic immune complex MPGN. In the IC-MPGN group, 14 patients (50%) had crescentic glomerulonephritis. Induction therapy consisted of cyclophosphamide and methylprednisolone followed by steroids, azathioprine was prescribed for maintenance phase. At the 18-month follow-up, 9 (64%) patients were in complete remission (CR), 3 (21%) were in partial remission (PR), and 2 (15%) progressed to chronic kidney disease. The remaining 14 (50%) had non-crescentic idiopathic IC-MPGN and were prescribed steroids only, cyclophosphamide with steroids and angiotensin converting enzyme inhibitors. The outcomes at 18 months were relatively poorer than those with the crescentic variety. Four (28%) patients achieved CR, 8 (56%) PR, and 2 (14%) did not respond. In the C3 glomerulopathy cohort, 3 (43%) had crescentic glomerulonephritis, one child was in CR, and two were in PR. The non-crescentic C3G were kept on ACEI 3 (43%) and Mycophenolate mofetil 1 (14%). One child treated with ACEIs achieved a PR, two were in CR, and one child treated with MMF did not respond.

Conclusions The outcome of MPGN (immune complex and C3G) is quite variable, and aggressive therapy for crescentic glomerulonephritis may show a favourable response. Considering the similar clinical presentations and patient outcomes, C3G and IC-MPGN might represent two facets of the same disease.

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Keywords Immune complex MPGN, C3 glomerulopathy, Outcome

Background

Glomerulonephritis (GN) is defined as glomerular injury of variable severity caused by different aetiologies [1]. For decades, it has been categorized by histopathological findings. The development of immunomodulatory drugs has improved our understanding of the role of immunopathogenesis in GN [2]. Membranoproliferative glomerulonephritis (MPGN), also known as mesocapillary glomerulonephritis, is a pattern of glomerular injury rather than a specific disease entity. MPGN has poor prognosis with almost 50% progress to end stage kidney disease over 10 years [3]. The traditional classification includes three types on the basis of the location of immune deposits on electron microscopy: types I, II, and III [4].

A consensus report published in 2013 proposed the classification of MPGN on the basis of immunofluorescence (IMF) findings into C3 glomerulopathy (C3G) and immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN). In the former variety there is significant immunoglobulin and complement deposition in the glomeruli, while in later complement C3 and absent or scarce immunoglobulin deposits are present. C3G can be further categorized on the basis of electron microscopic findings into dense deposit disease (DDD) containing intramembranous deposits and C3 glomerulonephritis (C3GN) with subepithelial, subendothelial and mesangial deposits [5, 6]. Complement dysregulation plays a crucial role in the development of MPGN. In IC-MPGN, activation of the classical pathway occurs via the antigen–antibody reaction, whereas C3G develops as a result of defects in the alternative complement pathway [7].

MPGN is uncommon in children, and the literature concerning the frequency and treatment outcomes of children suffering from these specific types of glomerular injuries according to the current classification is scarce. Therapeutic approaches for MPGN and C3G have yielded suboptimal results. Despite the use of various immunosuppression drugs over the years, none have demonstrated consistent outcomes [8]. This study aims to categorize children according to the updated classification system and evaluate their short-term outcomes. This would add to our existing knowledge and help us formulate better diagnostic and therapeutic interventions in the future.

Materials and methods

This retrospective cohort study was conducted at the Department of Pediatric Nephrology, Sindh Institute of Urology and Transplantation, Karachi, after the approval from the Institutional Ethical Review Committee. The records of patients from January 2020 to June 2022 were reviewed for eligibility. All children aged less than 18 years and diagnosed with MPGN via light microscopy and IMF consistent with immune complex or dominant C3 staining were included. Patients with inadequate biopsy samples (< 10 glomeruli), IC-MPGN secondary to infections (Hepatitis B, C, HIV), lupus nephritis, IgA nephritis, infection-related GN and those with a follow-up of less than one year were excluded. Medical records were reviewed, and a structured proforma was used for data collection, including demographic and clinical profiles.

The indications of kidney biopsies were, children with rapidly progressive glomerulonephritis, acute nephritic syndrome, nephrotic syndrome and atypical course of post infectious glomerulonephritis.

Kidney biopsy samples were processed via a standard technique, and routine stains were applied. IMF was performed on fresh tissue. All the biopsies were reviewed by a histopathologist (MM) with extensive experience in reporting renal histopathology.

MPGN was categorized on the basis of IMF findings into C3G and IC-MPGN according to the consensus report [6]. The further division of C3G into C3 glomerulonephritis and dense deposit disease could not be performed due to the lack of electron microscopy. The estimated glomerular filtration rate (eGFR) was calculated via the modified Schwartz equation [9]. Rapidly progressive glomerulonephritis (RPGN) was defined by acute nephritic illness accompanied by rapid loss of renal function (> 50% decrease in GFR) over days to weeks [10]. A complete response was defined as the absence of proteinuria (urinary dipstick trace or negative), a serum Albumin concentration > 3 g/dL and an eGFR > 90 mL/min/1.73 m^2. Partial response was defined as proteinuria (urinary dipstick + 1 - +3), serum albumin > 3 g/dL, and improved or stable eGFR (15 mL/min/1.73 m^2). No response was labelled on the basis of a lack of complete or partial remission after 6 months of therapy.

IC-MPGN and C3G patients with normal renal function and non-nephrotic range proteinuria were managed with angiotensin converting enzyme inhibitors (ACEIs) only. If these patients had RPGN and crescents on kidney biopsy, then pulse doses of intravenous cyclophosphamide (CYC) 500 mg/m^2 monthly for 3–6 months and methylprednisolone (MP) 20–25 mg/Kg daily 3–5 days were given. Later, maintenance therapy was continued with Azathioprine 2-2.5 mg/Kg daily and low-dose Prednisolone 0.25–0.5 mg/Kg alternate days. IC-MPGN patients with normal or near-normal renal function and

nephrotic range proteinuria were started on oral Prednisolone 2 mg/kg/day daily for 8 weeks; if no response was observed, Cyclosporine (CYS) 5 mg/Kg divided two doses every 12 hourly or Mycophenolate mofetil (MMF) 1200mg/m^2 every 8 to 12 hourly was started with low-dose steroids. Children diagnosed with C3G with normal renal function or renal failure with no crescents on kidney biopsy were treated with MMF 1200 mg/m^2 every 8 to 12 hourly and low-dose steroids. The levels of MMF could not be monitored at our institute. Eventual outcomes with respect to complete remission, partial remission or no response and progression to CKD or ESRD were documented at 18 months.

SPSS version 23 was used for the statistical analysis. The normality of the distributions of the quantitative variables was verified via the Shapiro–Wilk test. The results are presented as the means (standard deviations) and medians (interquartile ranges). The qualitative variables are expressed as percentages or ranges. T tests and chi-square tests were used for continuous and categorical variables, respectively. A P value < 0.05 was considered significant.

Results

A total of 37 children had MPGN lesion on kidney biopsy. One each had, less than 10 glomeruli and Hepatitis B, and both were excluded. Therefore, 35 children were included in the study, with a mean age of 10.4 ± 2.9 years. There was a male preponderance, with a male to female ratio of 1.7:1. The baseline demographics are presented in Table 1.

Table 1 Characteristics of the study participants ($n = 35$)

Parameters	Value (No. %, Mean with SD and Median with IQR)
Age (Years)	10.4 ± 2.90
Sex (Boys)	22 (63%)
BMI (kg/m^2)	16.7 ± 2.37
Serum creatinine (mg/dl)	0.60 (0.35–2.3)
Serum Albumin (Gram/L)	2.3 (1.7–2.7)
Presenting features	
Nephrotic syndrome	13 (37%)
Acute Glomerulonephritis/Nephritic syndrome	20 (57%)
Rapidly progressive glomerulonephritis	2 (6%)
Serum complements	
Low C3	26 (74%)
Low C4	6 (17%)
Both C3 and C4 low	3 (9%)
Blood pressure	
Normal	8 (23%)
Elevated	4 (11%)
Stage I	10 (29%)
Stage II	9 (26%)
More than Stage II	4 (11%)

SD Standard deviation, IQR Interquartile range, BMI Body mass index

IC-MPGN was observed in 28 (80%) patients, and the remaining 7 (20%) patients had C3G. The mean eGFR at presentation was 120.5 ± 80.4 ml/min/1.73 $m^{2,}$ and 15 (43%) patients had an eGFR less than 90 ml/min/1.73 m^2. Hypertension stage I and above was found in 23 (66%) children at presentation, with 14 (70%) having eGFRs above 90 ml/min/1.73 m^2. At the time of diagnosis, the complement level C3 was low in 26 (74%), C4 in 6 (17%) and both in 3 (9%) patients. The infectious profile for hepatitis B, C and HIV was negative, and none of the children had systemic autoimmune disease.

The biopsy results revealed a median number of glomeruli of 12 (9–17 per biopsy), and half of the study population had crescents of 18 (51%). The median percentage of cellular crescents was 35 (20–50%). Interstitial fibrosis was reported as mild or moderate in 15 (43%) and 2 (6%) patients, respectively. Endocapillary proliferation was rare in 4 patients (11%). IMF was performed on fresh tissue from all the samples, and C3 dominant deposits were described in 7 (20%), whereas the remaining 28 (80%) had findings consistent with IC-MPGN.

Among the 28 (80%) idiopathic IC-MPGN patients, 14 (50%) had crescentic glomerulonephritis. After induction treatment with MP and CYC and maintenance with Azathioprine, at the 18-month follow-up, 9 (64%) patients were in complete remission, 3 (22%) were in partial remission, and one each (14%) progressed to stage III chronic kidney disease and end-stage kidney disease. The remaining 14 (50%) children had non-crescentic idiopathic IC-MPGN. These children presented with nephrotic syndrome 8 (58%), renal failure with a variable degree of proteinuria 3 (21%) and non-nephrotic-range proteinuria and normal renal function 3 (21%). The treatment modalities prescribed were steroids only, cyclophosphamide with steroids and angiotensin converting enzyme inhibitors. The outcomes at 18 months were relatively poorer compared to those with the crescentic variety, though the difference was not statistically significant. Four patients (28%) achieved a complete response, 8 (56%) achieved a partial response, and 2 (14%) did not respond to the given therapy Table 2.

The C3 glomerulopathy cohort included 7 (20%) and 3 (43%) patients who presented with a histopathological diagnosis of crescentic glomerulonephritis and were treated similarly to patients with IC-MPGN with crescents. At the 18-month follow-up, one child was in complete remission, and two showed a partial response. The rest of the non-crescentic C3G were kept on ACEI 3 (43%) and Mycophenolate mofetil 1 (14%). One child treated with ACEIs achieved a partial response, two were in complete remission, and one child treated with MMF achieved no response. The outcomes of C3G and MPGN

Table 2 Comparison of the IC-MPGN and C3G

Parameters	ICMPGN (*n* = 28)	C3G (*n* = 07)	*P*-value
Age (years)	10.3 ± 2.9	11.1 ± 3	0.51
Sex (boys)	17 (61%)	5 (71%)	0.60
Presentation			
Acute GN	15(54%)	2 (29%)	0.77
RPGN	02 (7%)	4 (57%)	
Nephrotic syndrome	11 (39%)	1 (14%)	
Hypertension	20 (71%)	3 (43%)	0.15
eGFR less than 90 ml/min/1.73m^2)	11 (39%)	4(57%)	0.43
S. Albumin	2.6 ± 0.75	2.9 ± 0.73	0.31
Low C3 level	20 (71%)	7 (100%)	0.10
Low C4 level	5 (18%)	1 (14%)	0.82
Crescents on biopsy	14 (50%)	4 (57%)	0.73
Outcomes at 18 months			
Complete remission	13 (47%)	3 (43%)	0.77
Partial remission	11 (39%)	3 (43%)	
No response	2 (7%)	1 (14%)	
CKD/ESKD	2 (7%)	0	

CKD, Chronic kidney disease; ESKD, End stage kidney disease; IQR, Interquartile Range; eGFR, Estimated glomerular filtration rate

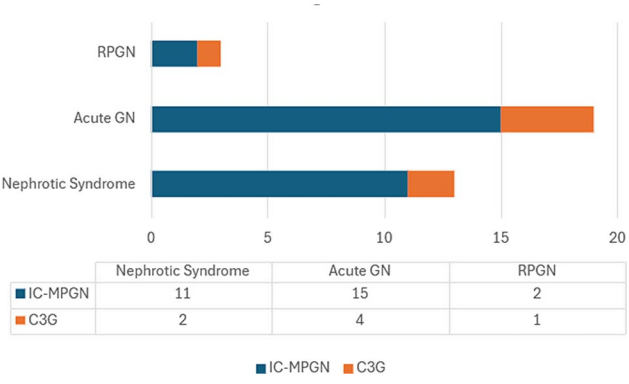

Fig. 1 IC-MPGN and C3G with respect to initial presentations. GN Glomerulonephritis, RPGN Rapidly progressive glomerulonephritis

patients with respect to clinical presentation are shown in Fig. 1.

A comparison between Crescentic GN and non Crescentic GN in the entire cohort ($n = 35$) revealed significantly higher proportion of children with eGRF less than 90 ml/min/1.73 m^2 in Crescentic GN [$n = 13$ (72%) versus $n = 2$ (11.7%); $p = 0.00$]. No differences were found in the gender distribution, serum albumin levels, or the presence of hypertension at presentation.

The analysis of baseline clinical characteristics was done with outcome groups including complete remission, partial remission, no response, CKD and ESKD. Children presenting with acute glomerulonephritis had higher rates of complete remission compared to those with nephrotic syndrome (60% [12/20] vs. 30% [4/13], $p = 0.008$). We did not find any significance of younger age (< 10 years), gender, estimated GFR at presentation and proteinuria.

Discussion

The last decade has provided a better understanding of the pathophysiology of MPGN. The updated classification has offered deeper insight into the disease mechanism and potential therapeutic advancements. We have previously published the short-term outcomes of 67 children with MPGN who were diagnosed and managed according to the older classification [11]. The management of our current cohort is mainly based on the management guidelines of KDIGO [12].

We found IC-MPGN in 28 (80%) children and C3G in 7 (20%) children. This contrasts with the findings of Amit et al., in which IC-MPGN and C3G were equally distributed [13]. Additionally, Priyanka et al. reported the predominant category of C3G and observed misclassification of a few cases to IC-MPGN on the IMF [14]. Similarly, the mean age and male preponderance are similar to those reported in the cohort by Kawasaki et al. These differences and similarities could be due to the different diagnostic techniques used in distinct cohorts. However, large scale, multicentre studies are needed to determine whether this represents a different geographic and genetic predisposition in our children.

Among the IC-MPGN patients, the chief presenting feature was acute GN and RPGN in 17 (61%), and the remaining 11 (39%) had nephrotic syndrome. Unlike our cohort, Priyanka et al. reported that 65.2% of patients presented with nephrotic syndrome and that 15.2% had acute GN [14]. This could be explained by the fact that our institute is a tertiary care referral centre, and acute GN and RPGN have dreaded complications, which compels primary care physicians for prompt referral. The presentation of IC-MPGN with nephrotic syndrome is considered a poor prognostic feature [15]. Similar findings were reported in our study, with 3 (27%) patients able to achieve complete remission. At the initial visit, 23 (66%) patients were hypertensive, and a slightly higher frequency of 78% was reported from Germany [16]. On the other hand the children with C3G had most common presentation of acute GN 4 (57%), nephrotic syndrome 2 (28%) and RPGN (15%).

The activation of the complement pathway is at the centre stage of the pathophysiology of MPGN. The level of C3 was low in 26 (74%), C4 in 6 (17%) and both C3 and C4 was low in 3 (9%). All the children in the C3G category had low C3 levels, and the mean C3 level was lower than that of the children in the IC-MPGN category (0.28 ± 0.15 versus 0.54 ± 0.34, p value 0.01). Slightly lower levels of C3 and C4 were observed by Ravindran et al. in C3GN patients, with percentages of 42% and 12%, respectively [17]. The variation in complement levels

might be explained by the imbalance between the consumption and production of complement proteins as well as the stage of disease during which the samples were tested [18].

Among the 7 (20%) patients who were diagnosed with C3G, 3 (43%) received intravenous cyclophosphamide due to crescentic GN, 2 (28%) received ACE inhibitors, and one each (14%) was managed with steroids alone and MMF with steroids. CYC therapy led to complete remission in 1 child and partial remission in 2 children, whereas therapy with MMF in one child did not improve the baseline clinical status. Ashwini et al. reported worse outcomes of crescentic GN in C3G, with all 18 (24%) children progressing to ESKD, and therapy with MMF was able to induce complete or partial remission in 7 (50%) [19]. The literature on the management of pediatric C3G is scarce, so therapeutic options depend on physician discretion. Various therapies targeting the alternate complement pathway are under investigation, and thus far, the role of eculuzumab in C3G has not been proven [20]. The suboptimal outcomes in C3G group could be attributed to uncertain proportion of DDD, which has poor overall treatment response.

Half of the IC-MPGN patients had crescentic GN on histopathology, and all of them received intravenous CYC and steroids. The remaining 14 (50%) patients with non-crescentic varieties of IC-MPGN were treated with 3 (21%) CYC, 8 (28%) steroids only and 3 (12%) were kept on conservative therapy. This immunosuppression led to a greater proportion of complete remission in crescentic IC-MPGN patients than in non-crescentic 9 (64%) patients versus 4 (28%) patients, with a p value of 0.08. Overall, 13 (46%) patients were in complete remission. In their study, Priyanka et al. treated children with IC-MPGN with MMF (11, 61%), CYC (4, 22%), steroids alone (2, 11%) and tacrolimus (1, 6%), with these immunosuppression regimens allowing the authors to achieve complete remission in 2 (11%) [14]. The frequent prescription of CYC in our cohort may have induced greater remission.

A comparison of C3G and IC-MPGN revealed indistinguishable rates of complete remission (43% and 46%, p value 0.92). However, two (7%) patients with IC-MPGN progressed to chronic kidney disease. The outcomes of C3G and IC-MPGN were similar in the Canadian cohort, as reported by Amit et al. [13]. They also reported that 5.7% of children had a GFR less than 15 ml/min/1.73 m^2. Differentiation of C3G from IC-MPGN remains a challenge, sequential biopsy from the same patient may demonstrate IC-MPGN to C3G or vice versa [21, 22]. Additionally, a potential shift from C3G to Hemolytic uremic syndrome has been reported, suggesting that some mutations in complement regulatory factors (e.g. CFH) may predispose to the development of both MPGN and aHUS [23].

Our study has certain limitations; it is a single centre study with a retrospective design and a small cohort of 35 children. We lacked the access to electron microscopy during the study duration, which is mandatory to distinguish between C3GN and DDD. The genetic analysis for complement factors and regulators has shown promising diagnostic potential recently, which we were unable to incorporate in our cohort.

In conclusion, we found a greater proportion of IC-MPGN and a relatively favourable response to aggressive therapy in crescentic GN patients. Considering the similar clinical presentations and patient outcomes, C3G and IC-MPGN might represent two facets of the same disease. Given the lack of consensus on therapeutic regimens for C3G, additional studies are necessary for further investigation.

Abbreviations

C3G	C3 glomerulopathy
MPGN	Membranoproliferative glomerulonephritis
GN	Glomerulonephritis
MMF	Mycophenolate Mofetil
CYC	Cyclophosphamide
AZA	Azathioprine

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Author contributions

IA and SK conceptualize the idea and wrote the study protocol, PK, IA and SH collected data, SH, SK and AL analysed the data, MM read the histopathology slides and contributed in writing, IA, SK and AL wrote the manuscript, PK and SK edited manuscript, SH and AL supervised the project.

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Data availability

The corresponding author will provide the data on request.

Declarations

Ethics approval and consent to participate

Ethical review committee of Sindh Institute of Urology and Transplantation approved the study with number SIUT-ERC-2023/A-458 and considering the retrospective review of charts, consent from the study participants was waived. The study followed ethical principles of declaration of Helsinki.

Consent for publication

Not applicable.

Trial register

Retrospective study design.

Competing interests

The authors declare no competing interests.

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