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ORIGINAL ARTICLE

Pediatric C3 glomerulopathy: a 12-year single-center experience

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Abstract

Background Complement component 3 glomerulopathy (C3G) is a disease with limited data in children. We aimed to compare childhood C3G cases with adults. We also studied subgroups of pediatric C3G and predictors of poor outcome.

Methods This is a 12-year retrospective, single-center cohort, observational study. All cases of C3G were defined based on the 2013 consensus guidelines.

Results C3G was diagnosed in 162 patients (119 adults, 43 pediatric) predominantly affecting males. With varied light microscopic patterns, pediatric C3G cases were categorized as follows: 23 C3 glomerulonephritis (C3GN) and 11 dense deposit disease (DDD) on electron microscopy. The pediatric DDD patients were relatively younger with more severe disease at presentation (more crescents in biopsy) but with lesser chronicity in biopsy compared with pediatric C3GN patients; however, both had a similar outcome. On comparing pediatric and adult C3G cases, adults had lower median eGFR and a higher degree of chronicity in the biopsy. The prognosis of C3G was better in pediatric patients. Predictors of kidney failure in pediatric C3G were low eGFR (HR = 0.82, $p = 0.05$) and severe interstitial fibrosis/tubular atrophy (HR = 1.05, $p = 0.02$).

Conclusions Electron microscopy-based subgroups of pediatric C3G differ in clinical presentation and course of the disease but have similar prognosis and long-term outcomes. Pediatric C3G differs from adult C3G with respect to presentation, laboratory results, biopsy features, treatment, and outcome, and as such, it should be considered as a separate entity rather than a smaller version of adult C3G.

Keywords Pediatric C3G · C3 glomerulonephritis · Dense deposit disease · Outcome · Prognosis

Abbreviations

C3G	complement component 3 glomerulopathy
DDD	dense deposit disease
C3GN	C3 glomerulonephritis
PIGN	post-infectious glomerulonephritis
MPGN	membranoproliferative glomerulonephritis
DPGN	diffuse proliferative glomerulonephritis
MesPGN	mesangioproliferative glomerulonephritis
CrGN	crescentic glomerulonephritis
GFR	glomerular filtration rate
IFTA	interstitial fibrosis and tubular atrophy
ACEI	angiotensin-converting enzyme inhibitors
CR	complete remission
PR	partial remission
CKD	chronic kidney disease
HR	hazard ratio
UPCR	urinary proteinuria: creatinine ratio

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Introduction

Complement component 3 glomerulopathy (C3G) is a diagnosis based on the predominance of C3 immunostaining in glomeruli [1], which is caused by uncontrolled activation of the alternative complement pathway [2]. The alternative pathway dysfunction may be either due to genetic factors or acquired antibodies to factor H, factor B, or C3 convertase [3]. Determining etiopathogenesis may not be possible in every

case due to the unavailability of laboratory testing for alternative pathway dysregulation at many centers worldwide [4] and economic constraints in many low-income countries. Currently, C3G is broadly classified as dense deposit disease (DDD) and C3 glomerulonephritis (C3GN) on the basis of differences in the pattern of electron-dense deposits on electron microscopy. There is still limited data on the characteristics and behavior of this disease in children. Also, no major studies have been conducted describing the differences of C3G in pediatric and adult populations. This study aimed to investigate the clinicopathological characteristics of C3G in children with an emphasis on the differences between the two subgroups (C3GN and DDD), predictors of poor prognosis in pediatric C3G, and differences from the adult population.

Methods

Study design, setting, and participants

This is a 12-year retrospective, single-center cohort, observational study (June 2007 to June 2019) conducted at the Sanjay Gandhi Post-Graduate Institute of Medical Sciences, India. The database of the hospital was searched to identify all patients with C3 glomerulopathy in their native kidney biopsies, which was defined on the basis of the 2013 C3 glomerulopathy consensus guidelines [5]. Since C3G as a distinct entity was formally recognized in 2010, kidney biopsies performed prior to that were re-reviewed by two nephropathologists.

Exclusion criteria Those patients who had a suspicion of post-infectious glomerulonephritis (PIGN) were excluded on the basis of infective symptoms and typical clinical course of PIGN. Patients who had a full clinical and serologic recovery after the resolution of the infectious episode without further disease relapse were excluded [5]. Patients with positive hepatitis B, C, or HIV viral serologies were also excluded.

Kidney biopsy evaluation

Three core biopsies were taken under ultrasound guidance, one each for light microscopy, immunofluorescence, and electron microscopy. Standard processing techniques were followed for all biopsies. Recorded immunofluorescence findings included the strength of staining for IgG, IgM, IgA, C3, C1q, kappa, and lambda; graded on a 1 to 4 semiquantitative scale. Kidney biopsies were evaluated by either of the two nephropathologists. The light microscopy pattern of the kidney biopsies was noted and classified as membranoproliferative glomerulonephritis (MPGN), mesangioproliferative glomerulonephritis (MesPGN), diffuse proliferative glomerulonephritis (DPGN), or crescentic glomerulonephritis (CrGN). The percentage of glomeruli with crescent formation was reported as none, 1–50% or > 50%. Those glomeruli having > 50% crescents were defined as CrGN. The percentage of globally sclerosed glomeruli was noted and classified as none, 1–50% or > 50%. Interstitial fibrosis and tubular atrophy (IFTA) were classified as none, 0%; mild, < 25%; moderate − 25–50%; and severe, > 50%. Electron microscopy was used to divide the cases into two categories: C3 glomerulonephritis (C3GN) and dense deposit disease (DDD).

Data source and variables

Clinical data, laboratory data, and follow-up records of the patients were retrieved from the hospital information system. The treatment received by patients was noted from the treatment charts.

Definitions

C3 glomerulopathy was defined as C3c intensity 2 orders of magnitude more than any other immunoreactant on a scale of 1 to 4 [6]. Patients ≤ 18 years of age were regarded as children. Microscopic hematuria was defined as at least 5 red cells per high-power field on microscopic examination or positive blood by urine dipstick. Nephrotic syndrome was defined as nephrotic range proteinuria > 3.5 g per 24 h per 1.73 m^2 (in children, > 40 mg/m^2/h or PCR > 2000 mg/g (> 200 mg/mmol)) along with hypoalbuminemia and edema [7].

The nephritic syndrome was defined as the presence of hypertension, hematuria, and sub-nephrotic proteinuria with or without mild kidney dysfunction. Sub-nephrotic proteinuria was defined as proteinuria ranging from 4 to 40 mg/m^2/h [8]. The standard procedure for measurement of blood pressure was followed as per the American Academy of Paediatrics guideline published in 2017 [9].

Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome defined by the rapid loss (within days to weeks) of kidney function, accompanied by features of nephritic syndrome with proteinuria, glomerular hematuria, and often oliguria [10].

Advanced kidney failure was used for patients fulfilling any of these KDIGO AKI stage 3 criteria: increase in serum creatinine to > 4.0 mg/dl or the initiation of kidney replacement therapy or, in patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m^2 [11].

On the basis of the type of treatment received, patients were grouped into three treatment groups: (1) patients on conservative management (angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB)); (2) patients on immunosuppression in the form of steroids alone; (3) patients who were given low dose steroids with other immunosuppression.

Study outcomes

The follow-up period was considered as the time interval between kidney biopsy and the last outpatient visit, death, or

kidney failure, whichever happened earlier. Only those patients who had a minimum of 2 months of follow-up were included.

The primary outcome of interest was kidney failure, defined as a decrement in the patient's kidney function to a level at which either long-term dialysis or kidney transplantation is required to sustain life [12]. Secondary outcomes studied were complete remission, partial remission, chronic kidney disease (CKD), and death. Complete remission (CR) was defined as the return of serum creatinine to the previous baseline, plus the reduction in proteinuria to < 0.5 g/day or 0.5 g/g creatinine by urinary proteinuria: creatinine ratio (uPCR) [7]. Partial remission (PR) was defined as stable (± 25%) or improved serum creatinine, but not back to normal, plus ≥ 50% reduction in proteinuria to < 3 g/day (or 3 g/g uPCR) [7]. Chronic kidney disease was defined as kidney damage or glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for 3 months or more. eGFR was calculated using the updated Schwartz equation [13].

Statistical analysis

The statistical analysis was done using SPSS Version 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables expressed as numbers or percentages were compared using chi-square and Fisher's exact test (as applicable). Continuous variables reported as mean or median (depending on the normality of data) were compared using Wilcoxon rank-sum methods. With kidney failure as the primary outcome of interest, kidney survival was determined using the Kaplan–Meier method, and group comparisons for survival were performed using the log-rank test. Predictors of kidney failure were determined using Cox proportional hazards methods. Univariate survival comparisons were made using the log-rank test. A p value < 0.05 was considered statistically significant. Variables previously found to affect kidney survival in the univariate analysis were included in the multivariate Cox proportional hazards model.

Ethics approval and consent This was not sought as it was a retrospective study and did not involve any active participation of the patients. The patients whose data was analyzed could also not be contacted further. Many patients were de-identified and the waiver of their consent did not adversely affect the rights and welfare of the participants. A local ethics committee ruled that no formal ethics approval was required in this particular case.

Results

A total of 6812 native kidney biopsies were studied, of which 856 were pediatric biopsies. One hundred sixty-two (2.37%) patients were diagnosed with C3 glomerulopathy, of which 43 were pediatric and 119 were adult cases. Electron microscopy was not available for 9 pediatric cases and these were excluded from the study.

Pediatric C3G was more common in males, with a male:female ratio of 1.6:1, and the mean age of presentation was 14.7 ± 3.7 years. Most of the patients presented with nephrotic syndrome (25 (73.5%)). Twenty-six (76.5%) patients had low C3 complement levels and low C4 levels were seen in 6 (17.6%) patients. On biopsy, MPGN pattern was seen in 22 (64.7%), DPGN in 8 (23.5%), CrGN in 2 (5.9%), and MesPGN in 1 (2.9%) patients. In one patient, no pattern could be elucidated as there was diffuse glomerulosclerosis. The demographic profile, laboratory, histopathological details, treatment, and outcome results of these patients are shown in Table 1.

On electron microscopy, there were 23 (67.6%) patients with C3GN and 11 (32.4%) cases of DDD. The patients with DDD were comparatively younger than those with C3GN (mean age 13 years vs. 15.5 years) with a male predominance in both groups. Although the nephrotic syndrome was the most common presentation, nephritic syndrome/nephrito-nephrotic picture was present in 4 (36.3%) patients with DDD as compared with only a single patient (4.3%) with C3GN. All six of the patients with low C4 complement levels in the study belonged to the C3GN group. The biopsy findings showed a predominant MPGN pattern in both groups. However, there were two patients with CrGN morphology and a single showing MesPGN pattern on biopsy, both of whom belonged to the DDD group. Patients with C3GN had a higher degree of glomerulosclerosis (mean 21.1% vs. 3.4%) as well as IFTA, when compared with DDD patients. The clinicopathological differences between C3GN and DDD patients are shown in Table 2.

There was a male predilection of the disease for both pediatric as well as adult populations. Thirty-one (26%) adult patients with C3G presented with advanced kidney failure; however, this presentation was not seen in any of our pediatric population. Low serum C3 complement levels were seen in 26 (76.5%) pediatric C3G patients and 63 (52.9%) of the adult C3G patients. eGFR was significantly lower in adults as compared with children (p < 0.01). MPGN was the predominant pattern in adult as well as pediatric C3G; however, other patterns, viz. MesPGN, DPGN, and CrGN, were more common in adults. The mean degree of glomerulosclerosis for adults was 28.2 ± 30.4% while it was 15.4 ± 20.7% in pediatric C3G patients. Also in adult biopsies, 56 (47.0%) patients had mild, 32 (26.9%) had moderate, and 6 (5.0%) had severe IFTA, whereas pediatric patients showed mild IFTA in 14 (41.1%), moderate in 7 (20.6%), and severe in 1 (2.9%) patients. The clinicopathological differences between pediatric and adult C3G patients are shown in Table 3.

Treatment and outcome

The follow-up duration of the pediatric population ranged from 2 to 206 months with a median duration of 10 months.

Table 1 Demographic profile, laboratory findings, and histopathological features of pediatric C3G patients ($n = 34$)

Mean age at diagnosis		14.7 ± 3.7
Sex	Males	21 (61.8%)
	Females	13 (38.2%)
Clinical presentation	Sub-nephrotic proteinuria	1 (2.9%)
	Nephritic syndrome	2 (5.9%)
	Nephrotic syndrome	25 (73.5%)
	Nephritic-nephrotic syndrome	3 (8.8%)
	RPGN	2 (5.9%)
	Hematuria	1 (2.9%)
Median eGFR (ml/min/1.73 m^2) (IQR)		66 (56)
Urinary protein	2+	4 (11.8%)
	3+	13 (38.2%)
	4+	17 (50%)
Urinary RBC*	0	5 (14.7%)
	1+	9 (26.5)
	2+	7 (20.6)
	3+	7 (20.6)
	4+	6 (17.6%)
Serum complement levels	Low C3 levels	26 (76.5%)
	Low C4 levels	6 (17.6%)
Light microscopic pattern**	MPGN	22 (64.7%)
	MesPGN	1 (2.9%)
	CrGN	2 (5.9%)
	DPGN	8 (23.5%)
	DGGS	1 (2.9%)
Crescents	None	27 (79.4%)
	1–25%	3 (8.8%)
	25–50%	2 (5.9%)
	> 50%	2 (5.9%)
Glomerulosclerosis	None	17 (50%)
	1–25%	7 (20.6%)
	25–50%	7 (20.6%)
	> 50%	3 (8.8%)
Interstitial fibrosis and tubular atrophy	None	13 (38.2%)
	Mild	13 (38.2%)
	Moderate	8 (23.5%)
	Severe	1 (2.9%)
Vascular changes	None	31 (91.2%)
	Hypertensive changes	3 (8.8%)
Immunofluorescence (location Of C3)	Along the glomerular basement membrane	11 (32.4%)
	Mesangial	3 (8.8%)
	Both	20 (58.8%)
Electron microscopy***	C3GN	23 (67.6%)
	DDD	11 (32.4%)
Follow-up time (months)		23.7 ± 39.3 (1–216)
Treatment	Conservative	8 (23.5%)
	Steroids only	21 (61.8%)
	Cyclophosphamide	1 (2.9%)
	MMF	4 (11.8%)

Table 1 (continued)

Outcome****	CR	9 (26.5%)
	PR	11 (32.4%)
	CKD	3 (8.8%)
	KF	4 (11.7%)
	Death	6 (17.6%)
	LTF	1 (2.9%)

*Urinary RBC (0 = < 3RBC/HPF, 1 = 3–5 RBC/HPF, 2 = 6–10 RBC/HPF, 3 = > 10 RBC/HPF, 4 = gross hematuria

***MPGN*, membranoproliferative glomerulonephritis; *MesPGN*, mesangioproliferative glomerulonephritis; *CrGN*, crescentic glomerulonephritis; *DPGN*, diffuse proliferative glomerulonephritis; *DGGS*, diffuse global glomerulosclerosis

****C3GN*, C3 glomerulonephritis; *DDD*, dense deposit disease

*****CR*, complete remission; *PR*, partial remission; *CKD*, chronic kidney disease; *KF*, kidney failure; *LTF*; lost to follow-up

All of these patients received ACEI/ARB. In addition, immunosuppression was given in 26 (76.4%) patients. Almost 62% of the patients responded to steroids alone and only 14% needed additional immunosuppression with mycophenolate mofetil (MMF) or cyclophosphamide (MMF in 4 (11.8%) patients and cyclophosphamide in 1 (2.9%)). One patient was lost to follow-up and 6 (17.6%) patients died. Complete remission was seen in 9 (26.5%) patients (7 (30.4%) in the C3GN group and 2 (18.1%) in the DDD group), whereas partial remission was noted in 11 (32.4%) patients (6 (26.08%) in the C3GN group and 5 (45.4%) in the DDD group). CKD was present in 3 (8.8%) patients (1 (4.3%) in the C3GN group and 2 (18.1%) in the DDD group) and 4 (11.7%) patients (3 (13.04%) in the C3GN group and 1 (9.09%) in the DDD group) progressed to kidney failure. In the adult population, in addition to ACEI/ARB, steroids were given in only 29 (24.3%) patients. Additional immunosuppression was needed in 23 (19.3%) patients: cyclophosphamide in 19 (15.9%), calcineurin inhibitors in 2 (1.6%), and MMF in 2 (1.6%) patients. Thirty-five patients were lost to

Table 2 Clinopathological differences between pediatric C3GN and DDD patients

Variable		C3GN ($n = 23$) n (%)	DDD ($n = 11$) n (%)	p value
Mean age at diagnosis (years)		15.5	13	0.05
M:F		1.3:1	2.6:1	0.3
Clinical presentation	Nephrotic syndrome	18 (78.2%)	7 (63.6%)	0.02
	Nephritic/nephrito-nephrotic syndrome	1 (4.3%)	4 (36.3%)	
Median eGFR (ml/min/1.73 m^2) (IQR)		68 (55)	64 (65)	0.9
Serum complement levels	Low C3 levels	17 (73.9%)	9 (81.8%)	0.6
	Low C4 levels	6 (26%)	0	0.06
Light microscopic pattern*	MPGN	18 (78.2%)	5 (45.4%)	0.04
	DPGN	5 (21.7%)	3 (27.2%)	
	CrGN	0	2 (18.1%)	
	MesPGN	0	1 (9.09%)	
Mean percentage of crescents		1.8%	18.4%	0.001
Mean percentage of sclerosed glomeruli		21.1%	3.4%	0.001
Interstitial fibrosis and tubular atrophy (> 25%)		10 (43.4%)	1 (9.09%)	0.04
Outcome**	CR	7 (30.4%)	2 (18.1%)	0.5
	PR	6 (26.08%)	5 (45.4%)	
	CKD	1 (4.3%)	2 (18.1%)	
	KF	3 (13.04%)	1 (9.09%)	
	Death	5 (21.7%)	1 (9.09%)	

**MPGN*, membranoproliferative glomerulonephritis; *MesPGN*, mesangioproliferative glomerulonephritis; *CrGN*, crescentic glomerulonephritis; *DPGN*, diffuse proliferative glomerulonephritis

***CR*, complete remission; *PR*, partial remission; *CKD*, chronic kidney disease; *KF*, kidney failure; *LTF*, lost to follow-up

Table 3 Clinicopathological difference between pediatric and adult C3 glomerulopathy patients

Variable		≤ 18 ($n = 34$) n (%)	> 18 ($n = 119$) n (%)	p value
Gender (males)		21 (61.7%)	86 (72.2%)	0.3
Mean age		14.6	37.8	0.00
Clinical presentation	Sub-nephrotic proteinuria	1 (2.9%)	5 (4.2%)	0.001
	Nephritic syndrome	2 (5.8%)	9 (7.5%)	
	Nephrotic syndrome	25 (73.5%)	46 (38.6%)	
	Nephrito-nephrotic syndrome	3 (8.8%)	3 (2.5%)	
	RPGN	2 (5.8%)	24 (20.1%)	
	Advanced kidney failure	0	31 (26.0%)	
	Hematuria	1 (2.9%)	1 (0.8%)	
Urinary protein	1+	0	16 (13.4%)	0.004
	2+	4 (11.8%)	32 (26.9%)	
	3+	13 (38.2%)	43 (36.1%)	
	4+	17 (50.0%)	28 (23.5%)	
Low C3		26 (76.5%)	63 (52.9%)	0.01
Median eGFR (ml/min/1.73 m^2) (IQR)		66 (56)	25 (44)	0.00
Light microscopy*	MPGN	22 (64.7%)	54 (45.4%)	0.04
	MesPGN	1 (2.9%)	16 (13.4%)	
	DPGN	8 (23.5%)	20 (16.8%)	
	CrGN	2 (5.9%)	16 (13.4%)	
	DGGS	1 (2.9%)	13 (10.9%)	
IFTA	None	13 (38.2%)	23 (19.3%)	0.04
	Mild	14 (41.1%)	56 (47.0%)	
	Moderate	7 (20.6%)	32 (26.9%)	
	Severe	1 (2.9%)	6 (5.0%)	
Mean percentage of crescents		7.2 ± 19.6	13.7 ± 26.2	0.02
Mean percentage of sclerosed glomeruli		15.4 ± 20.7	28.2 ± 30.4	0.006
Vascular hypertensive changes		3 (8.8%)	44 (36.9%)	0.001
Treatment	Conservative	8 (23.5%)	67 (56.3%)	0.00
	Steroids only	21 (61.8%)	29 (24.3%)	
	Cyclophosphamide	1 (2.9%)	19 (15.9%)	
	CNI	0	2 (1.6%)	
	MMF	4 (11.7%)	2 (1.6%)	
Outcome**	CR	9 (26.4%)	19 (15.9%)	0.00
	PR	11 (32.3%)	10 (8.4%)	
	KF	4 (11.7%)	28 (23.5%)	
	CKD	3 (8.8%)	12 (10%)	
	Death	6 (17.6%)	15 (12.6%)	
	LTF	1 (2.9%)	35 (29.4%)	

**MPGN*, membranoproliferative glomerulonephritis; *MesPGN*, mesangioproliferative glomerulonephritis; *CrGN*, crescentic glomerulonephritis; *DPGN*, diffuse proliferative glomerulonephritis; *DGGS*, diffuse global glomerulosclerosis

***CR*, complete remission; *PR*, partial remission; *CKD*, chronic kidney disease; *KF*, kidney failure; *LTF*, lost to follow-up

follow-up and 15 (12.6%) of the adult patients died. Complete remission was seen in 19 (15.9%) patients and partial remission in 10 (8.4%) patients. CKD was present in 12 (10%) patients, whereas 28 (23.5%) progressed to kidney failure. The differences in the treatment and outcome of children and adult patients are given in Table 4. Figure 1a and b depict the Kaplan–Meier survival curves for C3G according to electron microscopic classification and age of patients, respectively.

On Univariate analysis, the predictors of kidney failure in the pediatric population were nephrito-nephrotic presentation (HR = 1.12, $p = 0.04$), low eGFR (HR = 0.94, $p = 0.03$), 4+

Table 4 Showing the prognostic parameters for kidney failure in pediatric C3G

Variable	Univariate analysis			Multivariate analysis		
	HR	CI (± 95%)	*p* value	HR	CI (± 95%)	*p* value
Age (years)	1.16	0.83–1.62	0.3	0.153	0.001–2039	0.83
Gender (male)	1.16	0.37–3.6	0.7	1.3	0.00–1953	0.9
Clinical presentation (nephrito-nephrotic syndrome)	1.12	1.01–1.37	0.04	0.01	0.00–5.2	0.6
Low eGFR (ml/min/1.73 m^2)	0.94	0.89–0.99	0.03	0.82	0.16–0.83	0.05
Urinary protein (nephrotic range)	47.3	0.01–2.8	0.9	2.6	0.00–1.0	0.7
Urinary RBC (4+)	1.1	1.03–3.45	0.04	1.6	0.00–5.9	0.8
Light microscopic pattern (crescentic glomerulonephritis)	0.3	0.06–1.64	0.1	31.1	0.00–9.6	0.9
Glomerulosclerosis (> 50%)	1.0	0.9–1.0	0.09	1.5	0.3–1.6	0.5
Percentage of crescents (> 50%)	0.9	0.85–1.1	0.6	1.07	0.103–11.2	0.9
IFTA (severe)	1.5	1.1–2.4	0.02	1.05	1.01–2.9	0.02
Electron microscopy (DDD)	1.3	0.44–4.3	0.5	21.7	0.00–5.3	0.8

HR, hazard ratio; *CI*, confidence interval; *eGFR*, estimated glomerular filtration rate; *RBC*, red blood cells; *IFTA*, interstitial fibrosis and tubular atrophy; *DDD*, dense deposit disease

hematuria (HR = 1.1, p = 0.04), and severe IFTA (HR = 1.5, $p = 0.02$). However, on multivariate analysis, only low eGFR (HR = 0.82, $p = 0.05$) and severe IFTA (HR = 1.05, $p = 0.02$) predicted poor outcome (Table 4).

Discussion

We present one of the largest cohorts of pediatric patients with C3 glomerulopathy subdivided into C3GN and DDD based on electron microscopy. Along with the clinicopathological characteristics and outcome, some important questions answered include whether the electron microscopic subdivision is necessary keeping in mind the limited number of centers where electron microscopic facilities are available, especially in countries like India, and also how adult C3G is different from pediatric C3G.

The incidence of C3G in pediatric patients was higher (5.02%) as compared with the overall population (2.3%). The reasoning for this higher incidence in children could be twofold. First is the manifestation of complement disorders early in life and second is the relatively limited conditions in which kidney biopsy is performed in children. A similar pattern of incidence is seen in other studies [14–16]. As described in previous studies [17], we also found a predominance of males. The clinical manifestations of the disease can be diverse [5]. The most common clinical presentation in our pediatric C3G patients was nephrotic syndrome occurring in 73.5% of the patients. Most of our patients (76.5%) also showed low serum C3 levels which is compatible with the ongoing dysfunction of the alternative complement pathway. The degree of hypocomplementemia reported in the literature varies from 49.4–75% [18–21]. Kidney biopsy showed a variable light microscopic picture with MPGN pattern being the dominant one followed by DPGN, CrGN, and MesPGN. A predominant MPGN pattern that has both acute and chronic components could be related to the disease process. Abnormal complement activation is an ongoing process that persists chronically until halted. Similar histological patterns have been described in other studies [17].

Monoclonality was not found in any of the patients. As no light chain restriction was seen on immunofluorescence, we presume monoclonality as the cause in none of our cases. The monoclonality as a cause of C3G occurs in limits and according to guidelines evaluation for monoclonality should be done for individuals > 50 years of age [22].

As previously reported for adult series [17], our pediatric cohort followed the same pattern, with DDD patients being younger than C3GN and a male predominance in both groups. Although the most common presentation in both these groups was a nephrotic syndrome, patients with DDD had a significantly higher nephritic/nephritic-nephrotic presentation as compared with C3G. The higher frequency of nephrotic syndrome in C3GN has also been observed in other studies [6], but the higher rates of nephritic/nephritic-nephrotic presentation in DDD have not been previously noted. All patients with low C4 levels belonged to the DDD group in our study and this group also had a higher percentage of C3 hypocomplementemia in their serum. Servais et al. also noted a higher frequency of low C3 levels for the DDD group. They had only a single patient with low C4 levels, who belonged to the DDD group [23]. Similar to other studies [3], we also did not find a statistically significant difference in the eGFR of patients with C3GN and DDD. There were differences in the histopathological picture of both the groups—C3GN and DDD—in our study. While severe disease, manifested as the formation of crescents, was more commonly

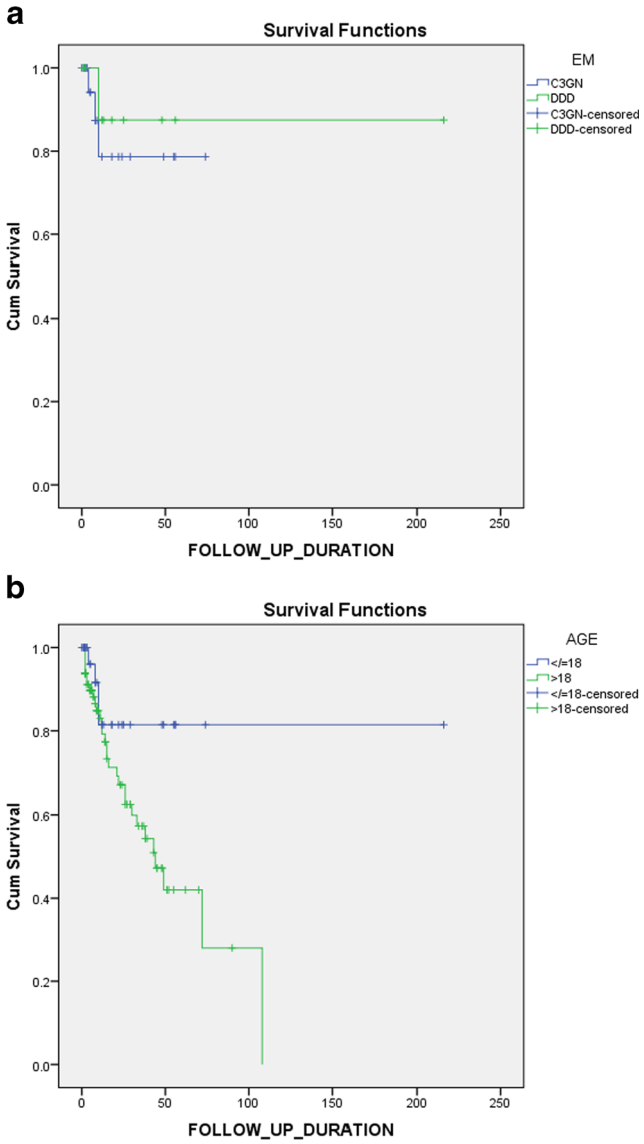

Fig. 1 **a** Showing similar kidney survival for C3GN and DDD ($p = 0.52$). **b** Showing better kidney survival for pediatric C3G patients as compared with adult C3G patients ($p = 0.03$)

seen in DDD, chronic changes in the form of glomerulosclerosis and IFTA were significantly higher in the C3GN group. Such observations have not been made previously. Although studies have noted a higher chronicity score for C3GN [6], no difference in the activity score was seen. However, the difference could be due to the fact that the previous study cohort included both children as well as adults, whereas our study compared the features in the pediatric population only [6].

On comparing our pediatric cohort with adults, a higher number of pediatric patients presented with nephrotic syndrome (73.5% vs. 38.6%). This was also reflected in their proteinuria. Nar et al. [24], on the other hand, found no significant differences in proteinuria and nephrotic syndrome presentation in pediatric and adult DDD patients. Their study however pertained exclusively to DDD patients, whereas our study involved all C3G patients. We found a higher frequency of adults presenting with advanced kidney failure. Also, eGFR was significantly lower in adults as compared with children, signifying a severe disease at presentation in adults. The degree of hypocomplementemia was higher in children as compared with adults (76.5% vs. 52.9%). This may be due to a difference in the levels of alternate pathway complement activation and possibly a different pathophysiological mechanism in adults and children, as also opined previously [24]. There were also significant differences in the biopsy findings of pediatric C3G and adult C3G patients in our study. While children had predominantly MPGN and DPGN patterns on biopsy (the less frequent morphologies being CrGN and MesPGN), adults had an almost equitable distribution of DPGN, MesPGN, and CrGN patterns. The mean percentage of crescents was also higher in adults as compared with children. Markers of chronicity, viz. glomerulosclerosis and IFTA, were significantly higher in adults as compared with children. Although chronicity indices (glomerulosclerosis and IFTA) have been noted to be higher in adults in previous studies [17, 24], they did not find any differences in light microscopic pictures of adults and children. We postulate that in adults, a higher number of cases showing a MesPGN pattern, which presents as an indolent disease along with frequent comorbidities (hypertension and diabetes), may be related to increased chronicity rates in them. The reason for the greater incidence of MesPGN in adults is not known. The poor prognosis of MesPGN due to any etiology when associated with IFTA has been reported previously [25].

All of the patients received ACEI. In addition, immunosuppression was given in 76.4% of pediatric patients. Almost 62% of the patients responded to steroids alone and only 14% needed additional immunosuppression with MMF or cyclophosphamide. In contrast, only 24.3% of the adults were treated with steroids alone. So C3G in children can be thought of as a relatively steroid-sensitive disease. On Kaplan–Meier analysis, cumulative 1-year kidney survival was 88.8%. This is higher than another study from the southern part of India where the kidney survival was 60.2% [3]. The prognosis of C3G is better in children than in adults, with the overall remission rate for children being 58.8% compared with 24.3% in adults. There was no significant difference in the outcome of patients with C3GN and DDD. Similar results have been described in other studies [26]. On multivariate analysis, the predictors of progression to kidney failure were low eGFR and the severity of IFTA. These markers have also been described previously [6]. However, on Cox regression analysis of C3G patients (adults as well as children), in addition to low eGFR and IFTA, urinary protein levels also predicted poor kidney outcomes.

We suggest that investigation of C3G should focus less on electron microscopy, and more on light microscopic patterns, with treatment modified accordingly: more intense

immunosuppression for patients with CrGN pattern and less for MesPGN pattern, where more chronicity is expected. Also, adults would require more aggressive immunosuppression than children.

Conclusions

Pediatric C3G has a higher incidence than in adults and usually presents as nephrotic syndrome. The electron microscopic groups of pediatric C3G—C3GN and DDD—can be considered as two faces of the same coin which differ in their clinical presentation and course of the disease but have similar prognosis and long-term outcomes. Pediatric C3G differs from adult C3G concerning presentation (higher frequency of nephrotic syndrome in children), laboratory results (more hypocomplementemia in children), and biopsy features (more MesPGN and CrGN in adults), as well as treatment and outcome (pediatric patients show a good response to steroids and have the better outcome). So, pediatric C3G should be considered as a different entity rather than merely a smaller version of adult C3G.

Strengths

The major strength is the sample size, which is the largest to date for pediatric C3G patients. Also, electron microscopy was done for all the included pediatric patients. Data of adult C3G cases was also analyzed which allowed comparison with pediatric C3G.

Limitations

The major limitation was the non-availability of genetic and serological testing for alternative pathway abnormalities. This is a retrospective study that dates back to 2013 before C3G was even defined, so limited data on etiology was available. Treatment was not standardized and none of our patients received eculizumab.

Availability of data and material The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' contributions All the authors contributed to study conception, design, editing, reviewing, and final approval of the article. Z.Z. and A.S.W. contributed to data acquisition, analysis, interpretation, and writing of the article.

Compliance with ethical standards

Ethics approval and consent to participate Not applicable.

Consent for publication Permitted.

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

Code availability NA.

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