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ORIGINAL ARTICLE

C3 Glomerulopathy and post-infectious glomerulonephritis define a disease spectrum

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Abstract
Background Post-infectious glomerulonephritis (PIGN) usually follows a benign course, but few children have an atypical, severe presentation, and these exceptional cases have been linked to the dysregulation of the complement alternative pathway (CAP). There is a considerable overlap in the histopathological features of PIGN and C3 glomerulopathy (C3G), which is also associated with CAP dysregulation but has a poorer outcome. We hypothesized that PIGN and C3G define a disease spectrum, and that in the past there may be some children with C3G who were misclassified with PIGN before C3G was described as a separate disease entity.

Methods Children with PIGN ($n = 33$) diagnosed between 1985 and 2010 who underwent a renal biopsy due to their unusual course were reviewed and of them, 8 were reclassified into C3G based on the current classification criteria. Outcome was based on the degree of proteinuria, C3 level, and renal function at follow-up.
Results Sixteen (72.7%) children with typical PIGN recovered completely as compared to only 2 (25%) with C3G. Of note, children with "typical" PIGN had a more severe disease course at onset; however, the outcome at last follow up was favorable.
Conclusions Our results support the hypothesis that PIGN and C3G form a disease spectrum and have different long-term clinical implications and management strategies.

Keywords Post-infectious glomerulonephritis · C3 glomerulopathy · C3 glomerulonephritis · Dense deposit disease · Complement alternative pathway · Eculizumab

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Introduction

Post-infectious glomerulonephritis (PIGN) is a common cause of acute glomerulonephritis in children. PIGN typically presents with edema, gross hematuria, hypertension, and low complement 3 (C3) levels. Triggered by a preceding infection (e.g., β-hemolytic streptococci), circulating immune complexes are formed and deposited in the kidney, causing leukocyte recruitment and activation of the complement alternative pathway (CAP) [1]. Patients with the disease typically recover within days to weeks and the overall prognosis is excellent. The kidney biopsy in classical PIGN is histologically characterized by an acute proliferative glomerulonephritis on light microscopy

(LM), C3 and immunoglobulin G (IgG) deposition on direct immunofluorescence microscopy (IF), and subepithelial hump-like deposits on electron microscopy (EM) [2, 3].

C3 glomerulopathy (C3G) is a recently introduced term that defines a spectrum of glomerular diseases with predominant C3 and scant immunoglobulin deposition [4]. C3G includes two entities, C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), which are defined by characteristic C3 distribution patterns on IF (C3GN) and deposition of electron-dense material in basement membrane (DDD), respectively [5]. Recent advances in the understanding of the pathogenesis of C3G suggest a pivotal role for uncontrolled activation of the CAP—in particular in the fluid phase—for disease pathogenesis. This new pathogenetic concept is supported by the identification of autoantibodies and mutations disturbing proper CAP control in C3G patients [6], thereby identifying the need for an in depth complement work-up and the potential for complement-targeting therapies in C3G patients, respectively [7, 8].

A subgroup of patients clinically diagnosed with PIGN follow an atypical course showing ongoing C3 consumption, persistent proteinuria beyond the expected period of recovery, and progressive decline of renal function [9]. Furthermore, renal biopsies in such patients can show C3 deposition without IgG deposition, suggesting persistent activation of the CAP. In support of this observation, a recent study identified genetic complement abnormalities in the majority of patients with clinically atypical PIGN [9]. Similar to PIGN, C3G also often presents after a preceding infection (including *Streptococcus pneumoniae*) and can show hump-like deposits on kidney biopsy, suggesting that PIGN and C3G may represent two opposite ends of a disease spectrum [5]. In keeping with this concept, the recent consensus report by Pickering et al. [5] emphasized that the presence of any atypical clinical or histological feature in a case of apparent PIGN (e.g., C3 deposits only, persistently low C3 levels, and progressive kidney disease) should raise the suspicion of C3G.

Given this background, we postulated that in the past, before the concept of C3G gained broad acceptance, children with C3G may have been misdiagnosed as having PIGN. We therefore studied children who were originally diagnosed with PIGN and underwent a renal biopsy due to their unusual clinical presentation to determine: (1) the proportion of children with suspected PIGN who could be reclassified as C3G based on the new histopathological criteria, and (2) the difference between the clinical presentation and outcome of children with PIGN and C3G.

Methods

Study design and setting

This was a single-center, longitudinal cohort study conducted at The Hospital for Sick Children, Toronto, ON, Canada.

Participants

We included all children from 1985 to 2010 who had a clinical diagnosis of PIGN and underwent a renal biopsy due to their atypical presentation in form of rapidly progressive presentation ($n = 14$), persistent low C3 level ($n = 3$), persistent proteinuria ($n = 9$), and systemic involvement in the form of joint pain, rash etc. ($n = 6$). Relevant data on clinical history, biochemical parameters, biopsy indications, treatment modalities, and outcome were collected. Figure 1 shows the flow diagram of reclassification of patients as well as outcome variables. The hospital's Research Ethics Board approved the study.

Exposure assessment and classification

A single renal pathologist who was blinded to the study reviewed all kidney biopsies (Fig. 2). Thereafter, children were reclassified into two categories, namely, PIGN and C3G, based on IF and EM findings using the current classification criteria (Table 1). The PIGN group was further divided into two subgroups based on presence (Group A) or absence (Group B) of IgG deposits on IF. There were 16 children in Group A with both subepithelial hump-like deposits on EM and C3 deposition with IgG on IF. An additional nine children were placed in Group B based on the lack of IgG deposition on IF. The C3G group was also sub-divided into two groups primarily based on absence of subepithelial deposits (Group C) or presence (Group D) of intramembranous deposits. Group C included six children who showed absence of subepithelial humps by EM but deposits elsewhere, such as mesangial and subendothelial humps, and strong C3 staining with or without immunoglobulin deposition on IF. Group D included two children that showed C3 only by IF and intramembranous dense deposits on EM with no or only rare subepithelial humps.

Outcome assessment and classification

Data were collected until the last follow-up, and outcome was determined based on improvement in clinical and laboratory parameters and compared between the PIGN and C3G groups. Of note, two children in Group B were excluded from the study as they developed end-stage renal failure that was not a direct effect of their original glomerular disease (one case each of hereditary nephritis and tubulo-interstitial nephritis).

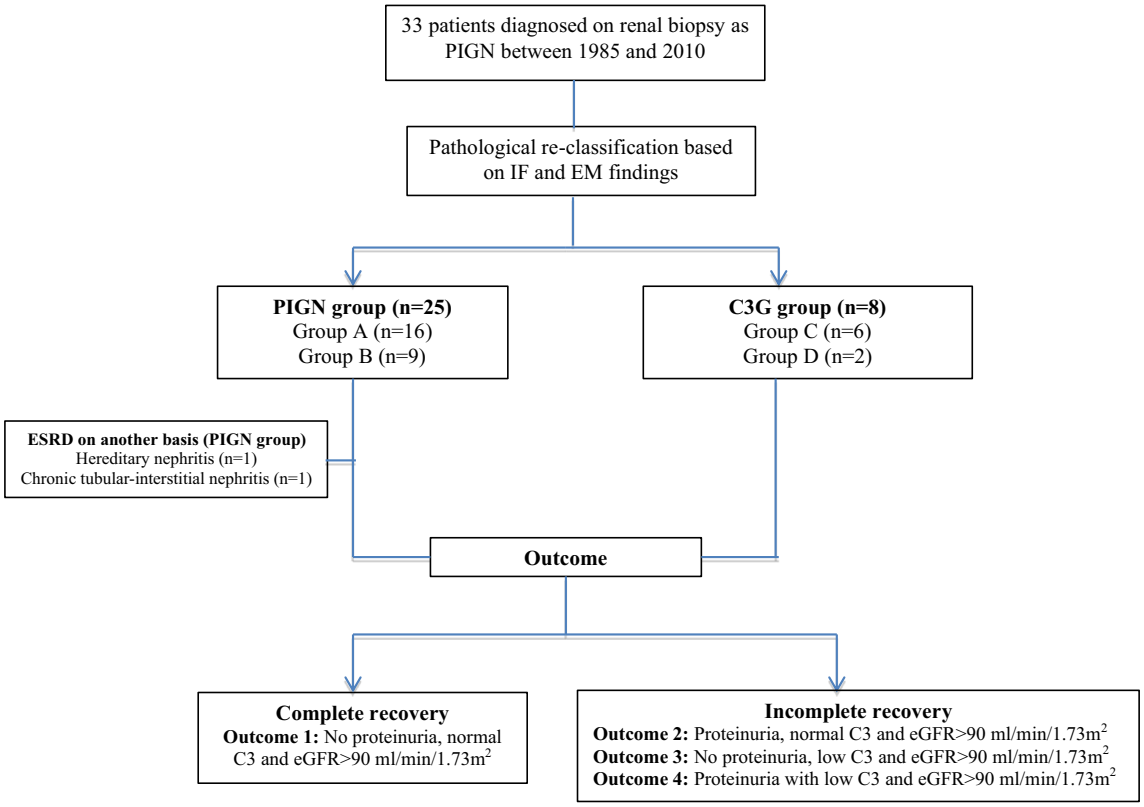

Fig. 1 Flow diagram of the study showing reclassification of patients into a group with post-infectious glomerulonephritis (*PIGN*) and complement 3 glomerulopathy (*C3G*) based on histological features of renal biopsy on electron microscopy (*EM*) and immunofluorescence microscopy (*IF*), and outcomes. *ESRD* End-stage renal disease, *C3* complement 3, *eGFR* estimated glomerular disease

Estimated glomerular filtration rates (eGFR) were calculated using the original Schwartz formula (until March 2008) [10], or the modified Schwartz formula (after March 2008 [11]. Children with an eGFR of <90 mL/min/1.73 m^2 were considered to have chronic kidney disease. Proteinuria was defined based on the absence (negative/trace or <0.3 g/L) or presence (≥0.3 g/L) of protein on dipstick, as urine protein-to-creatinine ratios were not available in children diagnosed before the year 2000. Hypertension was defined as blood pressure >95th percentile for age, sex, and height.

Complete recovery was defined as no proteinuria, a normal C3 level (range 0.77–1.43 g/L), and an eGFR of >90 mL/min/1.73 m^2 (Outcome 1). Incomplete recovery was classified into three categories: proteinuria only, with a normal C3 level and an eGFR of >90 mL/min/1.73 m^2 (Outcome 2); no proteinuria, with a low C3 level and an eGFR of >90 mL/min/1.73 m^2 (Outcome 3); proteinuria and a low C3 level and an eGFR of >90 mL/min/1.73 m^2 (Outcome 4).

Statistical analysis

Statistical analysis was performed using Stata 12 (StataCorp.2011—Stata Statistical Software: Release 12. StataCorp LP, College Station, TX) software. Categorical variables were reported as numbers and percentages, and continuous variables were reported as median and interquartile range as the distribution was skewed. A two-sided p value of <0.05 was considered to be significant. Clinical features and outcomes were compared using the chi-square test (or Fisher's exact test if the value of any cell was <5) and the Mann–Whitney U tests.

Results

Data on 33 children (19 boys, 57.6.%) with PIGN and renal biopsy were collected. After pathological reclassification, 25 children were diagnosed with PIGN, and the remaining eight (24.2%) were diagnosed with C3G. Cases of PIGN were further divided into Group A (16 children) and Group B (9 children), the latter showing typical subepithelial humps but lacking IgG deposition. Histopathological features prompting reclassification as C3G were lack of IgG deposition ($n=4$), lack of subepithelial humps ($n=8$), and presence of dense deposits ($n=2$) (Table 1).

The main reasons for a kidney biopsy were a rapidly progressive disease course (PIGN group), and persistent

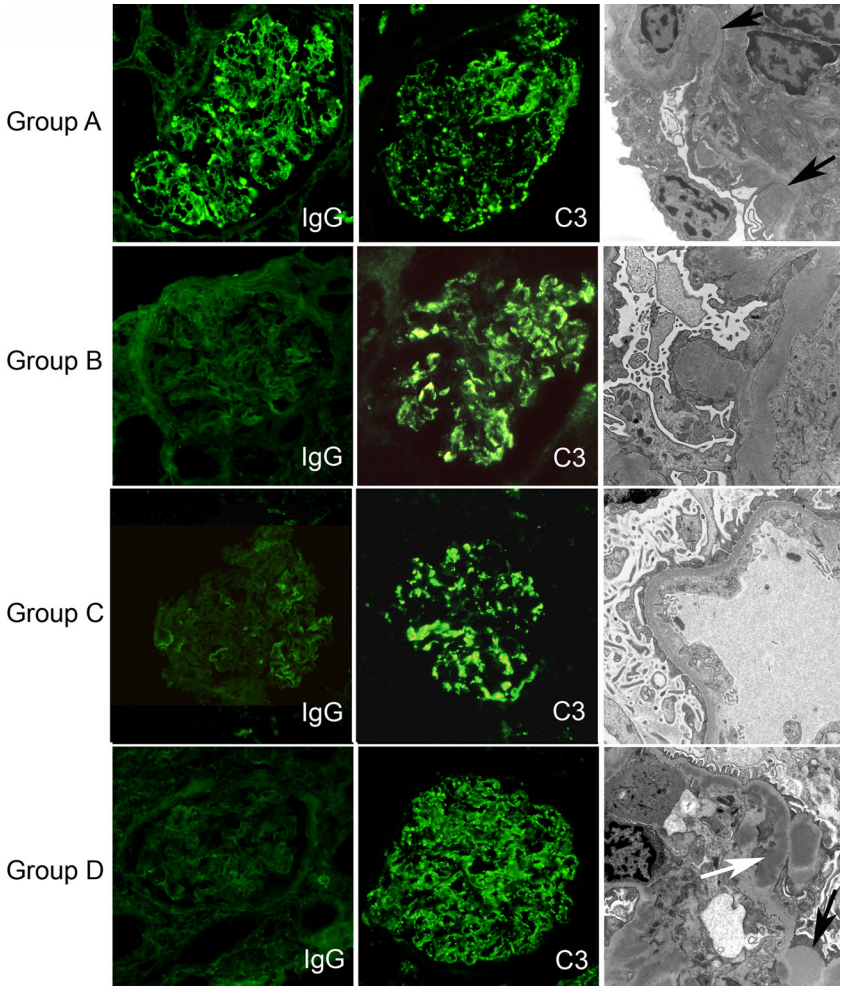

Fig. 2 Differentiating features of the patient subgroups categorized on the basis of pathological findings. Each row of 3 images is from the same case and includes a glomerulus stained for immunoglobulin G (*IgG*) (*left*) and C3 (*middle*) and an electron microscopy (*EM*) image of a capillary loop (*right*). Group A (*top row*) patients showed positive staining for IgG and C3 with electron-dense subepithelial deposits ('humps') along the capillary loops (*arrows*). Group B (*second row*) has positive staining for C3 and negative staining for IgG but subepithelial deposits ('humps') are still seen. Group C (*third row*) has positive positive staining for C3 and negative staining for IgG, but no electron dense deposits are seen. Group D (*bottom row*) has positive staining for C3 and negative for IgG, and by EM rare subepithelial deposits (*black arrow*) and a more electron-dense change in the capillary loop basement membranes (*white arrow*) and mesangial matrix are seen. Original magnification: all IF images ×400, all EM micrographs ×12,000. For more details on classification of the four subgroups, see Exposure assessment and classification section and Table 1

significant proteinuria with/without low C3 levels (C3G group). Biopsies were performed earlier in children of the PIGN group (91 % within 8 weeks of presentation) than in those of the C3G group (50 % within 8 weeks).

Table 1 Pathological reclassification of PIGN patients based on immunofluorescence and electron microscopy findings

Current classification criteria[a]	Post-infectious glomerulonephritis		C3 glomerulopathy	
	Group A (n = 16)	Group B (n = 9)	Group C (n = 6)	Group D (n = 2)
IgG (IF)	Present	Absent	Present or absent	Absent
C3 (IF)	Present	Present	Present	Present
Electron-dense deposits (EM)[2]	Frequent subepithelial	Frequent subepithelial	Absent subepithelial	Intra-membranous

IgG, Immunoglobulin; IF, immunofluorescence microscopy; C3, complement component 3; EM, electron microscopy

Baseline characteristics in both groups (Table 2) did not show significant differences. Surprisingly, a more severe disease course was noted in patients of the PIGN group. Of note, 17 (73.9%) children in the PIGN group had an eGFR of <90 mL/min/1.73 m^2, of whom 11 (64.7%) had an eGFR of <60 mL/min/1.73 m^2, and six children received renal replacement therapy (RRT) at disease onset. In contrast, only two (25%) children in the C3G group had an eGFR of <90 mL/min/1.73 m^2 at disease onset (one of whom had an eGFR of <60 mL/min/1.73 m^2 and required RRT).

A severe disease course in the PIGN group was also reflected by a more complex therapy, with eight (34.7%) of these children receiving treatment with steroids compared to only one child (12.5%) in the C3G group. Antihypertensive medications were given to 13 children (56.5%) in the PIGN group and to four (50%) in the C3G group. Four children (17.4%) in the PIGN group received angiotensin converting enzyme inhibitors for hypertension and proteinuria as compared to only one (12.5%) in the C3G group.

The main finding of our study was that the baseline C3 levels of children in the PIGN group (0.38 ± 0.25 g/L) were significantly lower than those in children of the C3G group (0.68 ± 0.37 g/L; $p = 0.02$; 95 % confidence interval −0.55 to −0.05). While data generated in our small patient cohort did not suffice to confirm these results at later time points (i.e., at 3 months and 1 year), we were able to demonstrate a trend indicating that the C3 levels normalized in both groups with time (Fig. 3).

Clinical parameters were assessed at last follow-up after a median duration of 16 and 20 months for children in the PIGN and C3G group, respectively (Table 2). Sixteen (72.7%) children recovered completely in the PIGN group as compared to only two children (25%) in the C3G group. Two children in each group had persistent proteinuria. Three children (37.5%) in the C3G group had both proteinuria and low C3 at last

Table 2 Clinical data at baseline and last follow-up in the post-infectious glomerulonephritis and C3 glomerulopathy groups

Clinical data at baseline and last follow-up	PIGN		C3G ($n = 8$)	p value
	Group A ($n = 16$)	Group B ($n = 7$)		
Clinical data at baseline				
Age at presentation (years)	10.0 (5.6–12.5)	6.1 (4.3–10.2)	13.1 (9.2–14.5)	0.2
Boys	10 (62.5 %)	5 (71.4 %)	4 (50 %)	0.8
Low C3[a]	14 (87.5 %)	6 (85.7 %)	5 (62.5 %)	0.4
Proteinuria	15 (93.7 %)	6 (85.7 %)	6 (75 %)	0.4
Hematuria				0.8
Gross	8 (50 %)	6 (85.7 %)	4 (50 %)	
Microscopic	8 (50 %)	1 (14.3 %)	3 (37.5 %)	
Absent	0	0	1 (12.5 %)	
eGFR <90 mL/min/1.73 m^2	13 (81.2 %)	4 (57.1 %)	2 (25 %)	0.2
Hypertension	10 (62.5 %)	3 (42.8 %)	4 (50 %)	0.6
Patients biopsied <8 weeks from onset	15 (93.7 %)	6 (85.7 %)	4 (50 %)	0.02
Clinical data at last follow-up (Outcome)[b]				
Duration of follow-up (months)	14.2 (5.5–18.0)	24.5 (4.1–37.6)	19.8 (5.5–40.3)	0.6
Hypertension	3	1	1	1.0
Complete recovery (Outcome 1)	10 (66.7 %)	6 (85.7 %)	2 (25 %)	0.07
Incomplete recovery				
Outcome 2	1 (6.7 %)	1 (14.3 %)	2 (25 %)	
Outcome 3	1 (6.7 %)	0	0	
Outcome 4	1 (6.7 %)	0	3 (37.5 %)	
No follow-up	2	0	1	

Values in table are presented as the number/number with percentage in parenthesis for categorical variables and as the median and interquartile range (IQR) for continuous variables

PIGN, post-infectious glomerulonephritis; C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate

[a] Normal range for C3: 0.77-1.43 g/L

[b] Outcome 1: complete recovery—no proteinuria, a normal C3 level (range 0.77–1.43 g/L), and an eGFR of >90 mL/min/1.73 m^2. Outcomes 2, 3, 4: incomplete recovery, with Outcome 2 characterized by proteinuria only, a normal C3 level, and an eGFR of >90 mL/min/1.73 m^2; Outcome 2 characterized by no proteinuria, a low C3 level, and an eGFR of >90 mL/min/1.73 m^2; Outcome 3 characterized by proteinuria, a low C3 level, and an eGFR of >90 mL/min/1.73 m^2

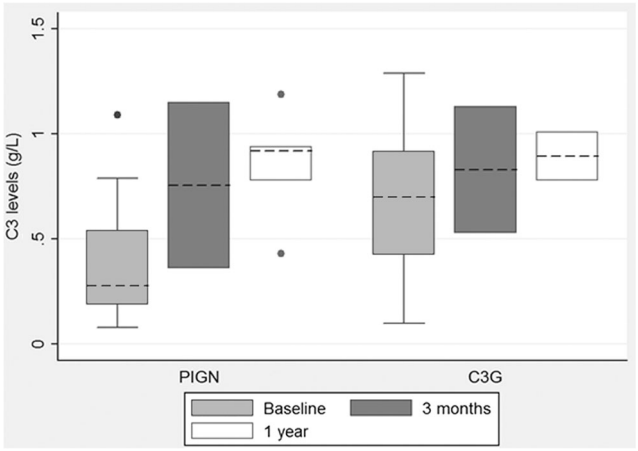

Fig. 3 Box plots demonstrating C3 levels at disease onset, 3 months, and 1 year in the post-infectious glomerulonephritis (*PIGN*) and C3 glomerulopathy (C3G) groups. The difference in C3 levels between the C3G and PIGN groups at baseline was significant at $p = 0.02$. Normal range for C3: 0.77–1.43 g/L. *Box* Interquartile range, *broken horizontal line* median, *whiskers* maximum and minimum values, *filled circles* outliers

follow-up as compared to only one patient (4.5%) in the PIGN group. Of the six children in the PIGN group who received RRT, four recovered completely, and one had persistent proteinuria at last follow-up. Follow-up data on the remaining children was not available. Interestingly, all but one child in the entire cohort had an eGFR of >90 mL/min/1.73 m^2 at the last follow-up. This child had baseline chronic kidney disease due to small kidneys (eGFR 62 mL/min/1.73 m^2). He had a normal C3 level and no proteinuria at follow-up but was excluded from the final analysis.

The clinical features of the two PIGN subgroups are also compared in Table 2. It is evident that the two PIGN subgroups were more similar to each other than to the C3G group in terms of clinical presentation and outcome. The patients in both PIGN subgroups had a higher incidence of hypocomplementemia and proteinuria at disease onset than those in the C3G group. Although the proportion of cases with an eGFR of <90 mL/min/1.73 m^2 at disease onset was higher in Group A (81.2 %) than in Group B (57.1 %), the difference was not statistically significant ($p = 0.32$). Similarly, the outcome in the two subgroups was quite similar and favorable; however, Group B cases demonstrated a trend toward a better outcome as a higher proportion of Group B patients (85.7%) showed complete recovery as compared to Group A patients (66.7%); however, this difference did not reach statistical significance ($p = 1.0$). The individual details of the clinical presentation and outcome of eight children in the C3G group are shown in Table 3.

In summary, children with PIGN features on renal biopsy showed more severe renal impairment and lower C3 levels at disease onset. However, the outcome at follow-up was favorable with complete recovery in 73 % of these children. To the contrary, children with C3G had mild and progressive disease, and five of them (62.5%) continued to have proteinuria and/or low C3 at last follow-up.

Discussion

Post-infectious glomerulonephritis is a common cause of glomerulonephritis in children and usually presents with nephritic syndrome and low C3 [12]. The prognosis of PIGN is typically good, and a renal biopsy is not warranted. However, a few PIGN cases present with atypical features, such as persistent proteinuria, low C3 and, sometimes, a decline in renal function. A defect in the regulation of the CAP has been detected in these patients [9, 13, 14]. Renal biopsies of this patient group reveal features of C3G, a glomerulonephritis arising from CAP dysregulation [5]. This overlap of clinical and histopathological symptoms may indicate that PIGN and C3G are situated at two ends of a spectrum of a glomerular disease with either primary or secondary complement activation triggered by infection.

In our cohort, around 25 % of the children had to be reclassified as C3G based on the new consensus guidelines [5]. Surprisingly, clinical symptoms such as proteinuria and renal dysfunction at initial manifestation were worse in children with biopsy features of PIGN. This finding may reflect a selection bias in our study as we only included PIGN patients who had undergone a kidney biopsy, and these patients would be those with more severe disease. Furthermore, more children in the PIGN group than in the C3G group had lower C3 levels at disease onset. However, the C3 levels became comparable in both groups during the course of the disease, suggesting that level of C3 at disease onset is not predictive of outcome. However, our study was not powered to test this possibility. The main characteristics of patients of the C3G group were persistently low C3 levels and ongoing proteinuria during follow-up. The literature in the adult and pediatric population is scarce. To the best of our knowledge, our study is the first to apply the new diagnostic criteria for C3G to a pediatric patient cohort historically diagnosed with PIGN. Based on these diagnostic criteria, of the 33 children enrolled in our study who were originally diagnosed with PIGN, eight (24.2 %) were reclassified as having C3G.

We were also able to demonstrate another clinically relevant point in our study based on the division of the PIGN cases into two subgroups, Group A and B, depending on the presence or absence of IgG deposits on IF, respectively. Children in Group B showed more similarity in terms of clinical features and outcome to the Group A children than to the children in the C3G group. This finding provides evidence for the relatively greater importance of finding frequent subepithelial hump-like basement membrane deposits on EM compared to the presence of C3 or IgG deposits on IF

Table 3 Clinical data at baseline and last follow-up of eight patients in the C3 glomerulopathy group

Disease category	Age at onset (years)	Sex	C3	Proteinuria (g/L)	Hematuria	Hypertension	eGFR at onset (mL/min/1.73m^2)	Therapy	Outcome
Group C	11.1	Female	Normal	>3	Microscopic	None	147	ACEI	2
Group C	13.5	Male	Low	0.3	None	None	126	None	2
Group C	16.5	Male	Normal	0.3	Gross	Yes	15	RRT	No data
Group C	1.3	Female	Normal	None	Gross	Yes	90.8	Anti-HTN; ACEI	1
Group C	12.5	Female	Low	>3	Gross	Yes	86.8	Anti-HTN	4
Group C	14.7	Male	Low	>3	Microscopic	None	163	NA	4
Group D	13.9	Male	Low	>3	Gross	Yes	140	Anti-HTN	1
Group D	7.2	Female	Low	None	Microscopic	None	154	None	4

eGFR, Estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitors; RRT, renal replacement therapy; anti-HTN, antihypertensive medications

in terms of making a pathological diagnosis of PIGN cases and defining the future outcome of these patients.

A diagnosis of C3G should prompt in-depth investigations of the CAP in general and, more specifically, testing for CAP specific autoantibodies [e.g., C3 nephritic factor (C3NeF); complement factor H (CFH); CFB] and mutations in CAP regulators (e.g., CFH), and a functional assessment of CAP activation (e.g., C3, C3d, sC5b-9). Moreover, a detailed

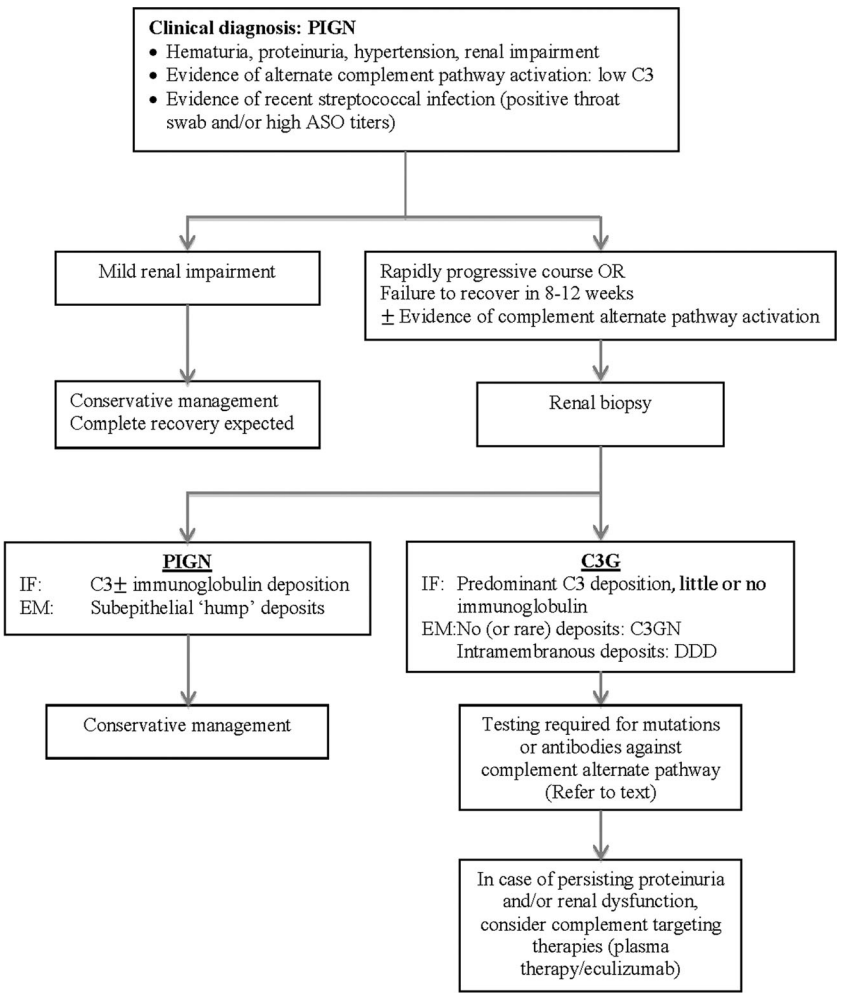

Fig. 4 Approach to a case clinically diagnosed as post-infectious glomerulonephritis (*PIGN*)

complement workup might help to discriminate patients with PIGN and C3G at a much earlier time point. Sethi et al. [9] recently published a series on 11 atypical PIGN patients and demonstrated an underlying defect in CAP in ten of these, with seven patients being positive for C3NeF, three having mutations in CFH, and one having a mutation in CFHR5.

The small number of children is the main limitation of our study. Due to its retrospective nature, follow-up data on C3 levels were not available in all children; furthermore, detailed complement testing could not be performed. Also, proteinuria was classified by the dipstick method rather than on the urine protein to creatinine ratio.

However, we were able to emphasize the importance of re-evaluating children with PIGN having atypical clinical features. Furthermore, we recommend an in-depth complement work-up, including testing for autoantibodies and genetic testing of complement factors in cases with atypical presentation or biopsy findings not consistent with typical PIGN. Patients with documented CAP defects and renal dysfunction and/or proteinuria may benefit from complement targeting treatment, such as plasma infusion [15] or eculizumab [8, 16]. A suggested algorithm to approach children with PIGN is shown in Fig. 4.

In summary, PIGN and C3G may represent opposite ends of a glomerular disease spectrum involving dysregulation of the CAP. In this regard, patients with atypical clinical or histological features may have been diagnosed as PIGN in the past but should now be reclassified as C3G as treatment modalities and prognosis are quite different. Larger prospective studies, including in-depth biochemical and genetics testing of the complement system, are required to further validate this new disease concept of PIGN/C3G.

Compliance with ethical standards

Conflict of interest None

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