Research Article

Comparison of Etiologies and Outcome of Children with Crescentic Glomerulonephritis – A Tertiary Care Experience

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Abstract

Background: Rapidly progressive glomerulonephritis (RPGN) is a condition characterized by clinical evidence of glomerulonephritis and rapid progressive decline in kidney function. The prognosis for most children with post-infectious crescentic glomerulonephritis is generally favorable. There is scarcity of data regarding outcome of RPGN in local pediatric population.

Objectives: To determine different etiologies and compare the outcome of crescentic glomerulonephritis in children.

Methods: This was Quantitative, prospective, cross-sectional study conducted in Department of Pediatric Nephrology, University of Child Health Sciences within duration n of one year. Thirty children with biopsy proven RPGN were enrolled. Causes of RPGN were evaluated. All children received treatment with intravenous methylprednisolone pulses for 3 days followed by oral prednisone. All subjects were followed-up for 6 months to assess response to treatment and to evaluate outcome. Data was analyzed in SPSS version 25.0.

Results: Mean age of children was 9.07 ± 2.82 years. There were 18 (60%) males and 12 (40%) females. Out of 30 children, 1 (3.3%) each had anti-GBM disease and ANCA associated vasculitis, 5 (16.7%) had Lupus nephritis, 11 (36.7%) had Pauci-immune glomerulonephritis, and 12 (40%) patients developed RPGN due to post-infectious glomerulonephritis. Complete response to treatment was noted in 1 (3.3%) patient after 1 month and in 16 (53.3%) children at 3 months of follow up. 18 (60%) cases achieved complete remission at 6 months, while 7 (23.3%) required hemodialysis for CKD. Rituximab was given to one patient after 6 months of treatment. Plasmapheresis was done in patient with anti-GBM disease.

Conclusion: Most common cause of rapidly progressive glomerulonephritis (RPGN) was post-infectious glomerulonephritis followed by pauci-immune and lupus glomerulonephritis. Clinical presentation and outcome varied depending on the underlying etiology and type and / or number of glomerular crescents found on renal pathology.

Keywords: Etiology, Outcome, rapidly progressive glomerulonephritis, Children.

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Introduction

Rapidly progressive glomerulonephritis (RPGN) represents a group of renal diseases characterized by clinical evidence of glomerulonephritis and a rapid progressive decline in kidney function.[1] The condition progresses swiftly over a period of days or weeks and is often characterized by presence of crescents in the glomeruli when examined histologically. When over 50% of the glomeruli are affected, it results in acute kidney injury which is evident in almost all patients at the time of diagnosis. The fraction of crescent-exhibiting glomeruli determines clinical severity. Patients with circumferential crescents affecting more than 80% of glomeruli develop renal failure, whereas those with less than 50% involvement have a slower and less severe disease progression.[2, 3] The prevalence of RPGN in children is still uncertain with seven cases per million reported in United States annually. Adult renal biopsies reveal an annual prevalence of 3.2%, 3.3% and 5.5% in Saudi Arabia, Romania and India respectively.[4] The various etiologies of this condition encompass diseases characterized by the presence of anti-glomerular basement membrane (GBM) antibodies, immune complex deposition, pauci-immune conditions associated with antineutrophil cytoplasmic antibodies (ANCA), instances following renal transplantation, and cases of rapidly progressive glomerulonephritis (RPGN) without crescents.[5]

The prognosis of crescentic glomerulonephritis depends

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on the underlying etiology, timeline of diagnosis and treatment. Therefore, it is imperative to initiate empirical therapy prior to establishing a clear diagnosis, particularly in situations where there is a delay in doing a kidney biopsy.[6] The therapy consists of two distinct phases: induction and maintenance. The conventional induction therapy is with high doses of steroids and cyclophosphamide. Additional therapy in the form of plasma exchange and / or Rituximab is provided for those with severe illness that poses a danger to their lives or organs. Cyclophosphamide, mycophenolate mofetil (MMF), and/or Rituximab are used during the maintenance phase. Azathioprine is the primary treatment utilized for long-term management in ANCA-associated vasculitis. Methotrexate is also an alternative option for maintenance treatment but contraindicated in people with moderate to severe renal impairment.[8] The prognosis for children with crescentic glomerulonephritis due to post infectious etiology is favorable as they often recover normal kidney function without requiring any particular therapy. In fact, over 90% of these cases restore complete renal function. However, it is noted that in underdeveloped countries, there is a risk of chronic kidney disease (CKD) in up to 31% of cases.[9] Immune complex mediated rapidly progressive glomerulonephritis (RPGN) and lupus nephritis are associated with the most severe renal outcomes, with end-stage kidney disease (ESKD) emerging in 54% and 29% of cases, respectively. The renal histology revealing the presence of more than 80% crescents together with tubular atrophy and interstitial fibrosis is associated with a risk of ESKD in more than 50%.[3] Pediatric ANCA associated vasculitis is linked with a high recurrence risk of disease, prolonged maintenance therapy and substantial organ damage.[1]

Our study aims to find out the etiological spectrum and outcome of treatment given to the pediatric population diagnosed with RPGN in our tertiary care center. As limited local data has been retrieved from literature, this study will help us to gain knowledge and devise new diagnostic, therapeutic and prognostic strategies in children with RPGN.

Methods

This quantitative, prospective, cross-sectional study was conducted in the Department of Pediatric Nephrology, University of Child Health Sciences, The Children's Hospital, Lahore. The duration of study was one year. All the children presenting during the study period and diagnosed as crescentic glomerulonephritis by renal biopsy were enrolled in the study by applying non-probability, consecutive sampling. Children of age 5-15 years of both genders with biopsy proven RPGN were selected. RPGN was defined as presence of nephritic / nephrotic syndrome with rapidly progressing renal failure characterized histologically by crescentic formation in more than 50% glomeruli.[2] Informed consent was taken from the parents. Demographics of patients (name, age, gender, weight, duration of symptoms) were noted and laboratory assessment included BUN, serum creatinine and urinalysis for proteinuria, hematuria, and casts. Causes of RPGN were evaluated from history, physical examination and serological investigations (serum complement levels, anti-double stranded DNA antibody, p-ANCA, c-ANCA and anti-GBM antibody). The parents were explained the procedure of renal biopsy which was performed under ultrasound guidance using sedation with Nalbuphine and Midazolam. The samples were preserved in formalin and normal saline filled containers for light and immunofluorescence microscopic examination, respectively. The latter was essential to determine the pattern of distribution of immunoglobulins and glomerular complement deposition. Sufficient (>5 glomeruli per two-micron section) material was obtained from all subjects and biopsies were considered positive for immunofluorescence when glomerular staining showed a trace or higher of the stained immunoglobulin or complement component on the scale of 0, trace, 1, 2, 3 and 4.

The children received targeted treatment for RPGN comprising induction with intravenous pulses of methylprednisolone at a dose of 15-20 mg/kg BW (maximum 1 g) per day for 3 consecutive days. This was followed by oral prednisone at a daily dose of 1.5-2 mg/kg for 4 weeks, with a gradual reduction of 0.5 mg/kg per day over a period of 3 months. Afterwards, the dosage was further tapered to every other day for 6-12 months. In addition to corticosteroids, intravenous cyclophosphamide was administered at a dose of 15 mg/kg every two weeks for three pulses, followed by four pulses at monthly intervals. The dosage of cyclophosphamide was modified in order to sustain a leukocyte count of 3000-4000 cells/mm3 two weeks after therapy.[11] In maintenance phase, MMF was added at a dose of 1000-1200 mg/m^2/day (in 2 divided doses) and continued for 12-18 months depending upon the underlying etiology. All subjects were followed-up in outpatient clinic at 1, 3 and 6 months. Blood and urine samples were taken at every visit for monitoring disease activity, to assess response to treatment and to evaluate the outcome regarding resolution of disease, development of chronic kidney disease and mortality. Complete response was achieved in terms of resolution of clinical symptoms, proteinuria, hematuria and reinstatement of normal kidney function. CKD was defined as kidney damage with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 for 3 months or more requiring kidney replacement therapy. eGFR was calculated by bedside Schwartz formula based on serum creatinine levels and height of child. The indications for plasma exchange and / or Rituximab were severity of renal disease and refractory cases, while peritoneal dialysis / hemodialysis was offered in patients with severe renal disease. All the data was entered in a specially designed Performa. Data was entered & analysed by using SPSS version 25.0. Quantitative variables like age, weight, duration of symptoms and laboratory parameters were calculated as mean and standard deviation. Qualitative variables like gender, need for dialysis, causes of

RPGN, treatment response, progression to chronic kidney disease, need for plasma exchange and mortality were calculated as frequency and percentage. Chi-square test was applied to compare groups for outcomes. The formula used to calculate chi-square is:

$$\chi^2 = \sum_i \frac{(O_i - E_i)^2}{E_i}$$

χ 2 = Chi-Square, Σi = Sum, Oi = Observed frequency, Ei = Expected frequency

Results

The mean age of 30 children was 9.07 ± 2.82 years at presentation with 18 (60%) males and 12 (40%) females. The mean duration of symptoms was 22.50 days and the median interval of time between onset of illness and kidney biopsy was 20.5 days. Out of 30 children, 1 (3.3%) each had anti-GBM disease and ANCA associated vasculitis as a cause of RPGN, 5 (16.7%) had Lupus nephritis, 11 (36.7%) had Pauci-immune glomerulonephritis, and 12 (40%) patients developed RPGN due to post-infectious glomerulonephritis (Figure 1). The details of the number and type of crescents on renal biopsy are shown in Table 1.

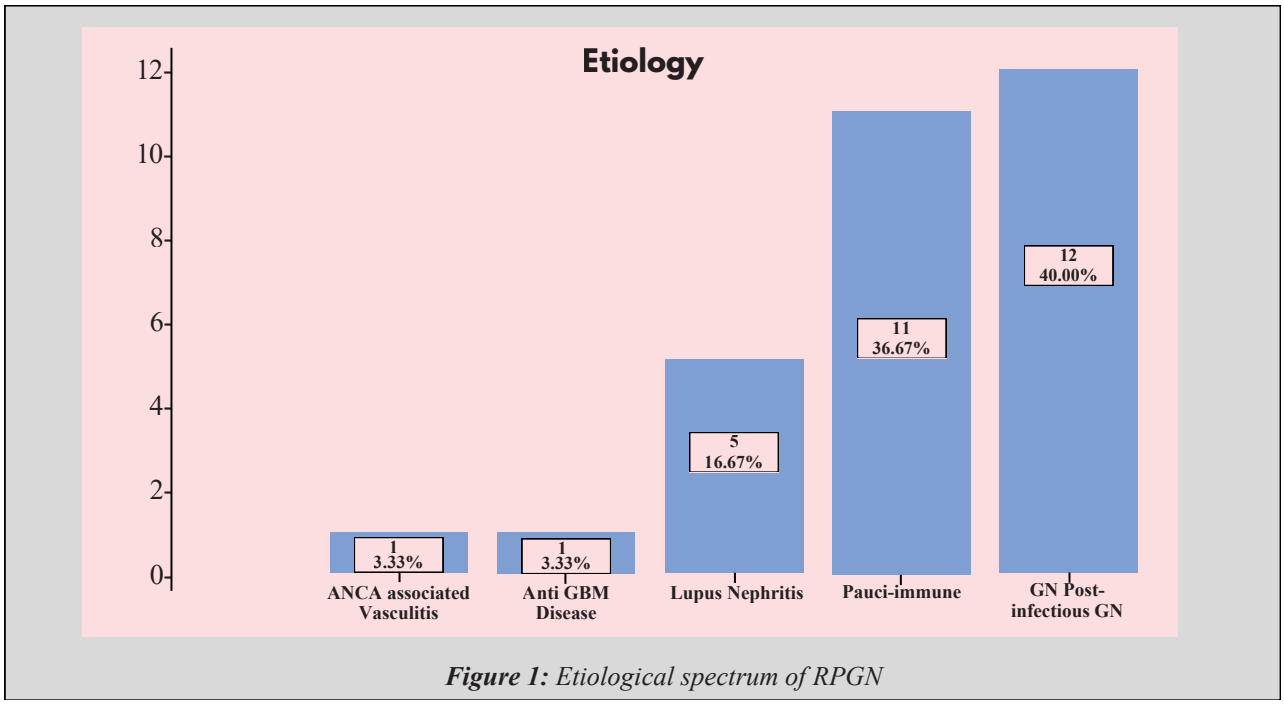

Figure 1: *Etiological spectrum of RPGN*

Table 1: *Renal biopsy findings of types of crescents*

Features	Mean
Glomeruli with crescents	17.77 ± 3.84
Percentage of crescents	14.60 ± 3.49
Percentage of Cellular crescents	82.25 ± 8.25
Percentage of Fibro-cellular crescents	50.83 ± 15.75
Percentage of Fibrous crescents	22.61 ± 8.74
Glomeruli with crescents	8.98 ± 7.48

Complete response to treatment was noted in only 1 (3.3%) patient after 1 month and in 16 (53.3%) patients at 3 months of follow up. 18 (60%) cases achieved complete remission at 6 months while 10 (33.3%) patients showed partial response, and 2 (6.7%) children died during the course of study. Hemodialysis was initiated in 27 (90%) subjects at the time of presentation and 8 (26.7%) patients were kept on maintenance dialysis therapy as they developed chronic kidney disease. 1 (3.3%) child with ANCA associated vasculitis received Rituximab at 6 months of follow up when he relapsed on cyclophosphamide treatment while the patient with RPGN due to anti-GBM disease underwent plasmapheresis sessions for two weeks along with immunosuppressive therapy (Table 2).

The correlation of the types of crescents with response to treatment is shown in Table 3.

Table 2: *Renal biopsy findings of types of crescents*

Follow-up	at 1 month	at 3 months	at 6 months
Complete Response	1 (3.3%)	16 (53.3%)	18 (60%)
Chronic kidney disease	Nil	8 (26.7%)	7 (23.3%)
Hemodialysis	27 (90%)	8 (26.7%)	7 (23.3%)
Expiries	Nil	1 (3.3%)	2 (6.7%)
Plasma exchange	1 (3.3%)	1 (3.3%)	1 (3.3%)
Need for Rituximab	Nil	Nil	1 (3.3%)

Table 3: *Correlation of types of crescents with response to treatment*

Type of crescent	Complete response	Partial response	None	p-value
n	18	10	2	
Total glomeruli	18.28 ± 2.89	18.60 ± 3.63	9.00 ± 1.41	0.001
Glomeruli with crescents	14.89 ± 2.99	15.60 ± 2.88	7.00 ± 0.00	0.002
Cellular	10.33 ± 2.66	7.70 ± 4.30	4.00 ± 0.00	0.018
Fibro-cellular	3.39 ± 1.14	5.30 ± 2.16	2.50 ± 0.71	0.008
Fibrosis	1.22 ± 0.88	2.60 ± 1.90	0.50 ± 0.71	0.022

Discussion

RPGN is a rare entity in pediatric age group and poses a significant challenge especially in settings with limited resources.[1]

RPGN following post-infectious glomerulonephritis generally has a favorable outcome in children showing spontaneous improvement with supportive management. No advantage has been seen for use immunosuppression over conservative management in majority of cases. On the other hand, crescentic GN due to immune-complex-mediated glomerulonephritis and lupus nephritis is linked to a bad prognosis, with over 50% and 30% progressing to end-stage kidney disease respectively.[1]

Our study was conducted to determine the etiological spectrum and outcome of crescentic GN in 30 children. We found the most common underlying etiology od RPGN to be post-infectious GN (40%) followed by Pauci-immune (36.7%). An analysis conducted by Meyer et al in 60 children with RPGN revealed that 75% had immune complex GN, 17% had ANCA-associated pauci-immune GN and 2% had anti-glomerular basement-membrane GN. [9] They identified crescentic GN in 7.5% of kidney biopsies. The finding of immune complex mediated glomerulonephritis as the most common cause of RPGN in children was comparable with other studies in the literature.[8, 10, 11] Gupta and Sinha et al observed a greater occurrence of pauci immune mediated rapidly progressive glomerulonephritis (RPGN) in comparison to immune complex mediated etiology (71.7% vs 28.3%). This finding raises the worry that pauci immune GN is also a significant contributing etiology of RPGN in youngsters.[12, 13] Kayki and co-workers, on the other hand identified IgA vasculitis (26.1%) to be the predominant cause of RPGN in a review of 88 renal biopsies.[18]

In our study, we noted that 60% of cases achieved complete remission at 6 months while 33.3% patients showed partial response, and 23.3% children developed chronic kidney disease as they remained on maintenance hemodialysis. A favorable outcome was observed in those with post-infectious GN who attained complete renal functional recovery. However, patients with Pauci-immune GN required chronic dialysis treatment due to progression to end stage kidney disease. A study from India documented development of ESKD in 19% children at one year of diagnosis [13] with almost similar results seen by Maliakkal [19] and Meyer et al.[9] ESKD at one year is a short-term outcome measure in patients with crescentic GN.

Rituximab has become a well-established choice for treating ANCA-associated vasculitis and provides a feasible alternative for individuals who cannot take cyclophosphamide due to contraindications.[15] For patients with RPGN due to ANCA-associated vasculitis, rituximab appears to be comparable to more commonly prescribed cyclophosphamide. It was well tolerated overall. Taking into consideration the significant costs associated with rituximab use and lack of clear evidence of clinical superiority, it is recommended reserving it for use in patients who fail to respond to initial treatment or who have intolerable side effects to it.[20] Out of the 30 patients we studied, only one needed the administration of Rituximab for relapse following a 6-month period of treatment. This patient kept showing state of remission on follow up visits during entire study period. However, two patients expired during the study period. Davies et al. performed an open-label investigation on 18 patients with RPGN due to Class III–V lupus nephritis and found that rituximab, low-dose intravenous cyclophosphamide, and intravenous glucocorticoids showed poor results. None of the four patients diagnosed with severe proliferative crescentic lupus nephritis, with an average crescent formation of 71% and an average creatinine level of 178 µmol/L, exhibited any response to treatment and had a fast progression to end-stage renal disease.[16]

The predictors of outcome of RPGN include the percentage and type of glomerular crescents. Our results concluded that the etiologies with predominantly cellular crescents had better outcome in response to treatment. Meyer et al, Morishita and colleagues also demonstrated that all patients who developed ESKD had crescents in more than 80% glomeruli.[9, 17] The relationship between the percentage of crescents and the outcome was consistent with the findings by Kayki et al showing similar results. They reported that children with less than 50% crescent achieved complete and partial remission.[18]The strength of our study was its Prospective study design, as the majority of the trials in literature are retrospective reviews of data and the results are generalizable to the local population. The limitation was a small sample size due to rarity of the entity of RPGN in children.

Conclusion

The study found that post-infectious glomerulonephritis was the predominant cause of rapidly progressive glomerulonephritis (RPGN) in children followed by pauci-immune and lupus glomerulonephritis. The majority (90%) of cases presented with acute kidney injury while 23.3% of children developed chronic kidney disease. Clinical presentation and outcome varied depending on the underlying etiology and type and / or number of glomerular crescents found on renal pathology.

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Authors Contribution:
RH, SP: Conceptualization, Methodology, Writing original draft.
RH, SP, AC, NA: Data collection, Formal analysis and interpretation.
RH, SP, AC, NA, ZT: Study design, Review critically and Editing.

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