Scholars Academic Journal of Biosciences
Abbreviated Key Title: Sch Acad J Biosci
ISSN 2347-9515 (Print) | ISSN 2321-6883 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatric Nephrology

Etiology and Morphological Pattern in Rapidly Progressive Glomerulonephritis

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DOI: 10.36347/sajb.2021.v09i06.004 | **Received:** 11.05.2021 | **Accepted:** 19.06.2021 | **Published:** 26.06.2021

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Abstract **Original Research Article**

Introduction: Rapidly progressive glomerulonephritis (RPGN) is a type of GN disease of the kidney. It is clinically characterized by a rapid decrease in the glomerular filtration rate (GFR) of at least 50% over a short period, from a few days to 3 months. The main pathologic finding is extensive glomerular crescent formation. The present study was conducted to recognize the morphological pattern in RPGN, underlying causes, and the outcome of RPGN in children**.** ***Aim of the study:*** To assess the histopathology of Rapidly Progressive Glomerulonephritis (RPGN), as RPGN can cause rapid irreversible damage to renal glomeruli in the form of crescents. ***Methods:*** This study was done on 34 RPGN children at the department of pediatric Nephrology in Dhaka Shishu (Children) Hospital over the period of June 2017 to December 2019. ***Result:*** The etiology of RPGN in this study showed, HSP nephritis was the commonest (23.5%) followed by IgA nephropathy (21.9%) and postinfectious glomerulonephritis (17.64%). Hematuria, proteinuria, and edema were present in almost all cases. The proportion of glomeruli displaying cellular crescent was 21%, fibrous crescent 7.1%, and fibrocellular crescent was 35% respectively. In terms of outcome, 61.7% of patients exhibited total recovery of renal function, 14.7% of patients were lost during follow-up, 5.8% were dialysis dependant, 5.8% patients developed chronic kidney disease and 11.7% died during hospitalization. ***Conclusion:*** RPGN is one of the important causes of unexplained acute kidney injury (AKI). Rapid and irreversible loss of renal function and remarkable mortality consider the need for awareness and development of a specific registry for Pediatric RPGN in hospitals.

Keywords: RPGN, Children, Histopathology.

INTRODUCTION

Crescentic glomerulonephritis (GN) is clinically characterized by features of rapidly progressive glomerulonephritis (RPGN) and rapid loss of renal function. GN is not a singular disease but a group of glomerular diseases that are characterized by glomerular injury associated with inflammation. The primary histologic finding of this is the presence of extensive glomerular crescents (usually greater than 50%). Depending on the histopathological and clinical presentation, GN can be classified into different types. There are five different categories of GN, which are, (1) immune complex GN, (2) pauci-immune GN, (3) anti-glomerular basement membrane GN, (4) monoclonal Ig–associated GN, and (5) C3 glomerulopathy. Although GN is observed to occur worldwide with lower incidence in children, a higher incidence was reported in children from Asian and Middle Eastern regions. This is a rare and fatal condition in children [1]. It is usually manifested by hematuria, proteinuria, oliguria, edema, and hypertension [2]. It is a type of nephritic system that, if not treated promptly and intensely, can progress into acute renal failure or death within several weeks. Integration of clinical characteristics, renal biopsy findings, and immunological tests are required for a complete diagnosis of RPGN. The presence of large epithelial

crescents involving 50 percent or more glomeruli is a characteristic of Crescentic GN which present clinically as RPGN. Crescents is a histologic marker of severe glomerular injury, which may occur in systemic and renal vasculitis, IgA nephropathy, HSP, systemic lupus erythematosus (SLE) membranoproliferative, and postinfectious GN. Without crescents, Similar clinical presentation may occur in hemolytic uremic syndrome, diffuse proliferative GN, and acute interstitial nephritis [1]. RPGN is a diagnostic as well as therapeutic emergency [3]. There is significant diversity in the etiology and outcome of RPGN with limited data from Bangladesh. The aim of this study was to assess and evaluate the incidence, the underlying primary disease, the outcome in children with RPGN.

METHODS

This cross-sectional study was done on children with RPGN <18yrs at the department of Pediatric Nephrology, Dhaka Shishu (Children) Hospital from June 2017 to December 2019. The clinical and biochemical evaluation was done for these patients. Detailed clinical symptoms, age, gender, duration of follow-up, treatment regimen, and clinical outcome in view of renal function (serum creatinine) were evaluated. Biochemical follow-up, urine routine and microscopic examination, antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), and serum complement levels (C3, C4) were also recorded. Renal biopsy was performed in all the patients which was evaluated by pathologists. Renal tissue samples were fixed in 10% formaldehyde for light microscopy, embedded in paraffin, and cut into thin sections. Tissue processing was performed with hematoxylin-and-eosin, periodic acid Schiff, and silver methenamine stains. The histological proportion of glomeruli including sclerosis with crescents (cellular, fibrous and fibrocellular crescent), presence of tubular atrophy, and interstitial fibrosis were recorded [4]. Frozen sections of the renal biopsy were performed for immunofluorescent staining. IgA, IgG, IgM, C3, CIq, and fibrinogen deposition was observed. The results were obtained by chi-square test for qualitative variables and t-test for quantitative variables. A P-value of <0.05 was considered significant.

Inclusion Criteria

- Children under 18 years of age
- Proper authorization taken from legal guardians

Exclusion Criteria

- Mentally ill.
- Unable to answer the criteria question.
- Exclude those affected with other chronic diseases etc.

RESULTS

There were a total of 34 cases that were divided into 2 groups (<50% crescents and >50% crescents). Demographic characteristics show that majority of patients were male (61.7%). The mean age of admission was 10.24 years (range 3.5-16 years). The majority of the patients reported symptoms started 2-3 weeks prior to admission. Duration of illness was 28 days in group I and 33 days in group II. Table I shows the etiology of rapidly progressive glomerulonephritis. HSP nephritis was the commonest pattern (23.5%) followed by IgA nephropathy (21.9%) and postinfectious glomerulonephritis (17.64%). Concerning the clinical characteristics hematuria, proteinuria, and edema present in almost all cases. Oliguria was present in around 76.4% of cases on admission. Hypertension was found in 80% of cases in group II (>50% crescent) and 73.3% of patients in group I (<50% crescent). Other clinical features were highlighted in Table II. Of the 34 children, 30 underwent renal biopsy. Among them, 15 children had <50% crescents and 10 had >50% crescents, 3 tubulointerstitial nephritis patients had no crescents. Renal biopsy was not performed in 4 HSP nephritis patients as parents refused to do the biopsy. The proportion of glomeruli displaying cellular crescent was 21%, fibrous crescent 7.1%, and fibrocellular crescent was 35% respectively. Interstitial fibrosis and tubular atrophy were noted in 3.5% and 32.1% of biopsies. 14 (41.1%) patients required dialysis at presentation. No patient received plasmapheresis. Induction therapy included IV methylprednisolone (100%) I/V cyclophosphamide (36%) and MMF (58.8%) depending upon the immunological category of RPGN. Maintenance immunosuppression included oral prednisolone and MMF. All of the patients received supportive care. Antihypertensive received 21(61.7%%) children. Most of the patients who received methylprednisolone commenced the treatment before renal biopsy. 21(61.7%) patients exhibited favorable outcomes with a total recovery of renal function. Among the remaining, 5(14.7%) patients were lost to follow-up. 2(5.8%) were dialysis dependant (both diagnosed as IgA nephropathy). 2(5.8%) patients developed chronic kidney disease (One IgA nephropathy and another postinfectious GN), 4(11.7%) died during hospitalization. They were diagnosed as mesangioproliferative, postinfectious, and idiopathic crescentic GN.

Table-I: Etiological distribution of the patients(n=34)

Etiology	Number	percentage
H-S Purpura glomerulonephritis	8	23.5
IgA Nephropathy	7	21.9
Post Infectious glomerulonephritis	6	17.64
MPGN	4	11.7
ATN	3	8.8
Diffuse proliferative GN	1	2.9
Infective endocarditis	1	2.9
C1q Glomerulopathy	1	2.9
C3 Glomerulopathy	1	2.9
Idiopathic	1	2.9
Lupus Nephritis	1	2.9

Table-II: Patient clinical characteristics at presentation(total:34,Group I: 15, group II: 10)

Characteristics	Total n(%)	Group I(<50%) n(%)	Group II(>50%) n(%)	P value
Age(years)	10.24±2.8	9.6±2.7	10.0±3.23	0.335
Sex(Female)	15(46.9)	7(46.7)	5(50)	0.381
Duration of Disease(days)	33.71±19.53	28.00±14.87	33±6.23	0.087
Proteinuria	31(96.9)	15(100)	10(100)	
Haematuria	30(93.8)	14(93.3)	10(100)	0.600
Oligouria	30(93.8)	14(93.3)	9(90)	0.650
HTN	25(78.1)	11(73.3)	8(80)	0.545
Fever	26(81.3)	13(86.7)	8(80)	0.532
Arthritis	1(3.1)	1(6.7)	0(00)	0.600
Abdominal Pain/Vomiting	15(46.9)	6(40.0)	4(40)	0.663
H/O of URTI/Skin Rash	8(25)	4(26.7)	3(30)	0.601
Ascites/Oedema	32(100)	15(100)	10(100)	
Respiratory discomfort	11(34.9)	3(20)	4(40)	0.261
Convulsion	8(25)	2(13.3)	3(30)	0.301
Rash	8(25)	5(33.3)	1(10)	0.198

The results were obtained by chi-square test for qualitative variables and t-test for quantitative variables. P-value was considered as significant at<0.05

DISCUSSION

We observed in the present study that immunocomplex GN (ICGN) constitutes the majority of cases of crescentic GN, similar to previous studies on crescentic GN. The most frequent etiology of ICGN in the current study were HSP nephritis (23.5%) followed by IgA nephropathy (21.9%) and postinfectious glomerulonephritis (17.64%). One Indian study also reported IgA nephropathy as their frequent etiology followed by lupus nephritis and postinfectious GN [5]. In contrast lupus Nephritis was the most common type of crescentic GN in China followed by pauci-immune and IgA nephropathy [6]. Two study from SaudiArab [7] and Subsaharan [4] study also found lupus as their first cause followed by PIGN. The high incidence of lupus in those areas could be due to racial and ethnic factors. One interesting observation from our study, HSP nephritis was one of the commonest etiology. PIGN is prevalent in the developing world and rural areas despite its reduced incidence worldwide [8]. Pauci-immune GN is the commonest variety of RPGN in an adult but in children, it is less common [9]. But a study result from India found a similar proportion of patients of pauci-immune and immunocomplex GN [10]. Most RPGN patients were treated initially in local health centers or by traditional healers before visiting the nephrology unit. So delayed diagnosis and delayed referral is a notable feature in our study. There is a higher incidence of RPGN in males compared to females in the present study. This finding correlates well with a report from India indicating an incidence rate of RPGN in males(64.7%) and (35.3%) in females [2]. In contrast a previous study from Saudi Arab reported a higher incidence rate in females (57.5%) than in males(42.5%) [2]. This difference compared to our study may reveal the increased proportion of lupus etiology. In the present study, almost all patients had severe disease at presentation. Renal impairment was found in 100% of patients which is close to the value of 90% in the series published by Arrayhani [11]. Proteinuria and hematuria were present in almost all patients, which is also similar to the study reported by Brown [12]. Hypertension was found in 80% cases in group I and 73.3% cases in group II. Sridevi [13] reported in their astudy, oedema, hematuria and hypertension in 75%,60% and 40% patients. The current study revealed fibro cellular crescent (46%) was the predominant crescent, which was similar to the finding reported by T.A.Chowdhury [14]. Histologically

cellular crescent was found in 21% of patients, this was close to Hussein's result [15]. However, Arrayhani [11] found that 61.7% had cellular crescent in his series. Crescents were fibrous in 25% of cases in the present study, but it was 11.7% in Hussein's study [15]. No significant differences in the proportion of glomeruli having crescent, sclerotic glomeruli, interstitial fibrosis, and tubular atrophy between the two groups in the current study which was consistent with the previous studies [11, 16]. All patients received standard protocol-based management according to etiology.14(56%) patients took dialysis at the time of presentation.Nagaraju [18], Gaurav Sharma [19], Gupta [4] and Rampelli SK [5] et al. had reported hemodialysis requirement in 75.9%, 65.3%,52.4% and 48.6% of patients respectively in their study. Most patient's received at least corticosteroid treatment with 88% received adjuvant immunosuppressive therapy, 58.8% MMF, and 36% patients received cyclophosphamide. Although 61.7% of patients in our study group achieved remission, overall prognosis was not satisfactory. Our outcome was comparable to other studies in the US, India, France, UK, and Turkey. They reported mostly poor clinical outcomes in pediatric patients with RPGN than in other studies. In spite of early institution of immunosuppressive therapy and dialysis, the renal survival remained poor. This was most probably due to delayed referral and higher serum creatinine concentration at presentation. Studies have shown that the severity of renal insufficiency before initiation of treatment is a strong predictor of renal survival [4].

Limitations of The Study

The study was conducted in a single hospital with small sample size. So, the results may not represent the whole community**.**

CONCLUSION

In conclusion, RPGN is one of the important causes of unexplained acute kidney injury(AKI). In our study immunocomplex GN was the most frequent etiology, among them HSP nephritis followed by IgA nephropathy and postinfectious glomerulonephritis were predominant. Rapid and irreversible loss of renal function and remarkable mortality consider the need for awareness. Moreover having an early biopsy procedure confirms the diagnosis and predict the prognosis. Further research is needed to formulate more aggressive and early institution of immunosuppressive policies following biopsy to ensure renal survival as well as long-term patient survival.

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