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Clinicopathological Spectrum and Treatment Outcome of Clinically Suspected Rapidly Progressive Glomerulonephritis: An Analysis of 35 Cases in a Tertiary Care Center, Bangladesh

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Abstract

Background and Aim: Rapidly progressive glomerulonephritis (RPGN) is characterized by a rapid decline in the renal function and urinary abnormalities. There is limited information on epidemiological factors and clinical and histopathological patterns of RPGN from developing countries. Therefore, the objective of this study was to identify the etiology, clinical features, histopathological patterns, and treatment outcomes of patients with clinically suspected RPGN.

Methods: This retrospective study was conducted in the Pediatric Nephrology Department of Bangabandhu Sheikh Mujib Medical University from January 2014 to January 2019. Patients with clinically suspected RPGN that underwent renal biopsy were enrolled in this study.

Results: Thirty-five patients were recruited in this study. Macroscopic hematuria, edema, hypertension, uremia, and oliguria were common clinical presentations. Diffuse proliferative GN (28.5%) and crescentic GN (22.8%) were the most common histological diagnoses in this study. Immune mediated GN (62%) followed by idiopathic GN (25%) were found to be the most frequent cause of crescentic GN. Renal replacement therapy was required in 45% of the cases and 11.4% of the patients developed end-stage renal disease.

Conclusion: Renal histology is an integral part of the investigation of patients with suspected RPGN for both diagnostic and prognostic purposes. Diffuse proliferative GN was the most common histopathological diagnosis in patients with clinical RPGN in our population. Preservation of renal function depends on early intervention and detection of RPGN in pediatric patients.

Keywords: Nephritis; Glomerulonephritis; ESRD; End-Stage Kidney Disease; Child.

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Introduction

Rapidly Progressive Glomerulonephritis (RPGN) is a pathological condition characterized by rapid deterioration of the renal function within weeks to months (1). It usually manifests by features of glomerular disease in the urine and is morphologically characterized by extensive crescent formation (2, 3). It is a life-threatening condition that carries a risk of kidney failure requiring renal replacement therapy in up to 30% of the cases (4, 5).

It has been reported that crescentic glomerulonephritis (CSGN) comprises 2.1% to 4.5% of all kidney biopsies (6).

The severity of RPGN is in part related to the degree of crescent formation. Patients with circumferential crescents in >80% of the glomeruli tend to present with advanced renal failure, whereas patients with crescents in <50% of the glomeruli, particularly if the crescents are non- circumferential, typically follow a more indolent course (7).

Although it may look like a single entity, RPGN is a very heterogonous disease. Indeed, the diverse etiology results in injuries within the glomeruli through alteration in various inflammatory pathways (8). The primary diseases that subsequently lead to RPGN show regional variation (9). However, the processes initiating inflammation and destruction within the renal tissue underlie the same subsequent changes in glomeruli. Therefore, the tendency towards crescent formation and its distribution are likely to be more important for the evaluation and management of this disease (10, 11). Renal biopsy is of critical importance and the gold standard for establishing the diagnosis of RPGN (12). It is also associated with a higher diagnostic yield and a lower procedural risk (13). RPGN results in patterns that could be identified using a light microscope and further characterized using other histological techniques. Therefore, it is currently classified into three types according to the predominant immunological injury pattern: pauci-immune, immune complex, and anti-glomerular basement membrane antibody mediated (14, 15).

Since initial validation demonstrated that the sclerotic histological group had the worst treatment response and renal and patient survival chances, a question was raised whether RPGN patients are in need of an aggressive immunosuppression therapy (12). Totally immunosuppression especially in children is associated with an altered immune response and increased risk of infections as well as other complications leading to higher mortality rates (16-18). There is a paucity of data on epidemiological factors, clinical and histopathological patterns, and also the outcome of RPGN from developing countries.

The objective of this study was to identify the etiology, clinical features, histopathological patterns, and outcomes of patients with RPGN.

Methods

This retrospective observational study was conducted in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2014 to January 2019. All patients age <18 that were admitted to the Pediatric Nephrology Department with a clinical suspicion of RPGN and underwent a renal biopsy procedure for confirmation of histological diagnosis were enrolled. Patients with a solitary kidney, deranged coagulation profile, and inadequate data were excluded from this study. The medical records of the patients were reviewed to extract the following data for analysis: age at diagnosis, gender, and clinical features at the time of admission. The creatinine level was measured using the Jaffe method. The results of the following laboratory tests were also recorded: serum albumin level, microscopic hematuria, nephrotic and non-nephrotic proteinuria evaluated in the urine sample, estimated glomerular filtration rate (eGFR) using the Schwartz method.

Serology

ANA (anti-nuclear antibody) and anti-Ds DNA antibody were measured in all patient using the ELISA method. ANCA (anti-nuclear cytoplasmic antibody) was evaluated in 25 patients.

Serum complements

The reference ranges for C3 and C4 were 72 to 156 mg/dL and 20 to 50 mg/dL, respectively. An ASO titer >200 was considered positive.

Histopathology

All renal biopsy specimens were processed for light microscopy and immunofluorescence. Electron microscopy was not performed due to non-availability at the Department during the study period. For light microscopy, renal tissue samples were fixed in 10% formaldehyde, embedded in paraffin and cut into thin sections. The sections were stained with hematoxylin and eosin and periodic acid-Schiff. For immunofluorescence, renal tissue was fixed in normal saline.

All patients were treated with intravenous methylprednisolone (IV MP) at a dose of 15 mg/kg/dose for 3 to 6 doses followed by oral prednisolone. Of 35 patients, 30 received IV cyclophosphamide at a dose of 500 mg/m^2/dose along with IV MP for induction and one patient was given MMF (Mycophenolate mofetil) at a dose of 25 mg/kg/day followed by IV MP. The other 4 patients were treated with only IV MP due to a less severe disease course. They were followed up for at least 6 months. Clinical outcomes were classified as follows: complete or partial recovery, relapse, chronic kidney disease (CKD), and progression to ESRD. The need for dialysis, kidney transplant, and death were also included in the analysis of outcomes.

Definitions

Nephrotic range proteinuria was defined as proteinuria >1g/m^2/day with or without hypoalbuminemia (19).

Acute glomerulonephritis was defined by hypertension, hematuria, oliguria, and edema
Clinically suspected RPGN was defined by a severe acute nephritic syndrome with acute deterioration in the renal function manifested as a two-fold rise in serum creatinine or a decrease in creatinine clearance by 50%.
Crescentic GN was defined as the presence of the crescentic proliferation of Bowmen's capsular epithelial cells in >50% of the glomeruli.
Microscopic hematuria was defined as the presence of ≥5 red blood cells per high-powered field in a properly collected urine sample.
Remission was defined as normalization of eGFR(>90 ml/1.73m^2/min) and proteinuria of below 0.4 g/day (20).
Partial remission was defined as a 50% reduction in serum creatinine if its level was above 2.3mg/dL and a 50% reduction in proteinuria compared to the initial value. (20). Chronic kidney disease was defined as a GFR of less than 60 mL/1.73 m^2/min persisting for more than 3 months (21).
Relapse was defined as a rise in the creatinine concentration with nephritic sediment and other signs or symptoms of vasculitis. End-stage renal disease was defined as a GFR of less than 15 mL/1.73 m^2/min which requiring renal replacement therapy (21).

Data analysis

The data were encoded using the Microsoft Excel and analyzed using the SPSS Software version 16.0.

Results

Patient characteristics

Thirty-five patients were included in this study of whom 21 (60%) were male and 14 (40%) were female. The majority of the patients were 10-15 years old ranging from 7 to 17 years and presented with macroscopic hematuria, edema, hypertension, oliguria. Sixteen patients (45%) required renal replacement therapy (Table 1).
The laboratory results and immunological profile of the patients are shown in Table 2. Serum creatinine at presentation was >5mg/dL in 14 (40%) patients, >3 to 5mg/dL in 8 (22.8%) patients, and <3mg/dL in 13 (37.1%) patients.

Table 1. Clinical symptoms at admission and their frequency distribution

Clinical presentation	N	%
Edema	26	74%
Macroscopic hematuria	22	62.8%
Oliguria	22	62.8%
Hypertension	22	62.8%
Needed dialysis	16	45%
Nephrotic range proteinuria	15	42%
Vomiting	2	5.7%
Headache	2	5.7%
Encephalopathy	2	5.7%
Seizures	1	2.8%
Fever	1	2.8%
Rash	1	2.8%
Hepatomegaly	1	2.8%
Splenomegaly	1	2.8%

The percentage of histological diagnosis of clinically suspected RPGN is shown in Table 3. The most common finding was diffuse proliferative GN in 10 (28.5%) and crescentic GN in 8 patients (22.8%). Therefore, although 35 subjects were included as patients with clinically suspected RPGN, renal biopsy revealed that most of them did not have crescentic GN and diffuse proliferative GN was the most frequent cause. In our study group, other than crescentic GN, patients with diffuse proliferative GN, lupus nephritis, membrane proliferative GN (MPGN), IgA nephropathy, Mesangioproliferative GN (MesPGN) and acute tubular necrosis presented with RPGN like feature.

Table 2. Laboratory parameters and immunological characteristics of patients at presentation

Laboratory parameters		Immunological characteristics	
Parameters	**Mean ± standard deviation**	**Parameters**	**No. of patients (percentage)**
Creatinine at presentation	5.6 ± 4.01mg/dL	ANA	7(20%)
Hemoglobin	8.8 ± 3.1g/dL	Anti-dsDNA	7(20%)
S albumin	2.5 ± 0.8g/dL	ANCA	
24 h urinary protein	2.59 ± 1.4g	MPO	2(5.7%)
		PR3	2(5.7%)
		C3 low	19(54.2%)
		C4 low	7(7%)

MPO: Myeloperoxidase, PR3: Proteinase3, ANCA: Antineutrophil cytoplasmic antibody, ds-DNA: Double-stranded deoxyribonucleic acid.

Table 3. Histological diagnosis of clinically suspected RPGN

Histological diagnosis	Number (percentage)
Diffuse proliferative glomerulonephritis	10(28.5%)
Crescentic GN	8(22.8%)
Membranoproliferative GN	4(11.4%)
Lupus nephritis	5(14.2%)
Mesangioproliferative GN	2(5.7%)
IgA nephropathy	4(11.4%)
ATN	2(5.7%)

GN- Glomerulonephritis, ATN- Acute tubular necrosis

Figure 1 shows the distribution of the histological patterns of RPGN according to sex. MPGN, IgA nephropathy, and proliferative GN were male-predominant whereas lupus nephritis was female-predominant.

The most frequent causes of crescentic GN are highlighted in Figure 2. Figure 3 shows the etiology of diffuse proliferative GN, indicating that post infectious GN comprised 80% of the cases with diffuse proliferative GN.

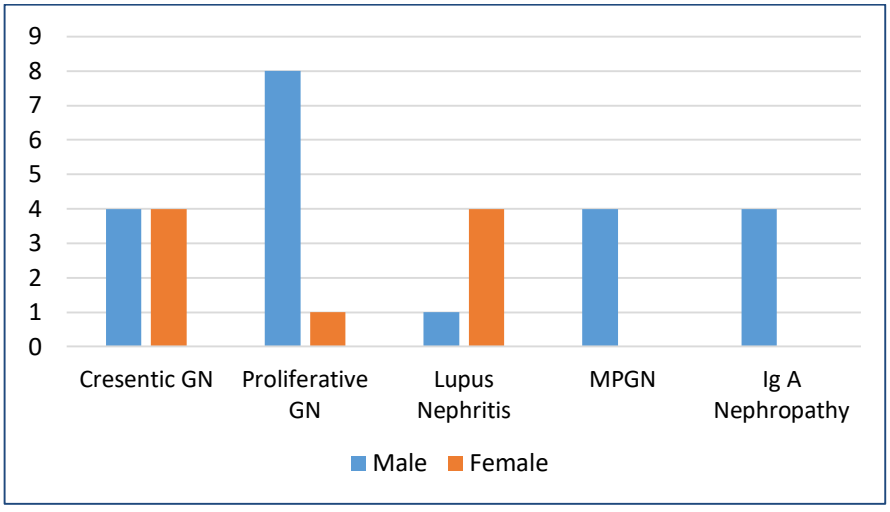

Figure 1. Histopathological patterns of RPGN in different males and females.

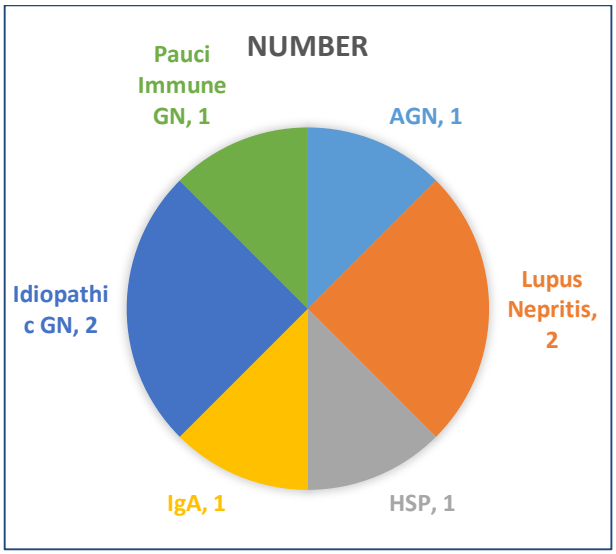

Figure 2. Etiology of crescentic GN (N=8).

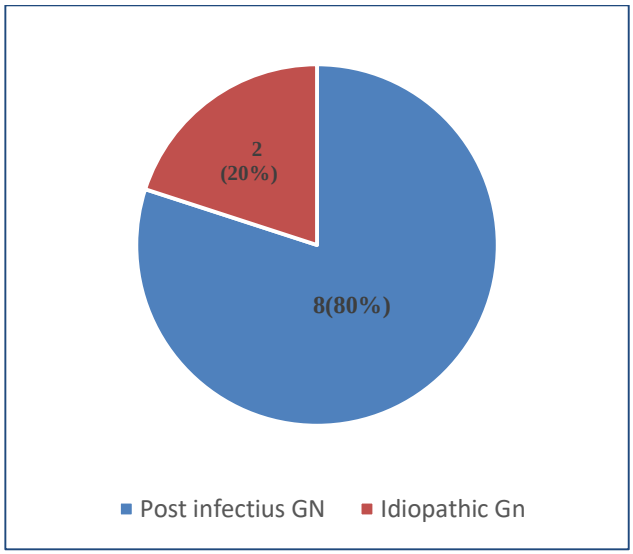

Figure 3. Eitiology of diffuse proliferative GN: of 10 patients, 8 had postinfectious GN.

Immune mediated GN (n=5/8, 62%) was the most frequent cause followed by idiopathic GN (n=2/8, 25%). Only one patient (12%) presented with pauci-immune GN, suggesting that childhood pauci-immune GN is a rare cause of RPGN. The causes of immune mediated GN included lupus nephritis, Ig A nephropathy, HSP nephritis, and acute post streptococcal GN.

Treatment given at presentation and the outcome of the patients are shown in Table 4.

Table 4. Treatment and outcome of patients

Outcome		Treatment of patients	
Parameters	**No. of patients (%)**	**Drugs**	**No. of patients (%)**
Complete recovery	19(54.2%)	Anti HTN drug	27 (77.1%)
Partial recovery	2(5.7%)	MP+CYC	30 (85.7%)
Relapse	4 (11.4%)	MP+MMF	1 (2.8%)
ESRD	4(11.4%)	MP	4 (11.4%)
Death	2(5.7%)	Hemodialysis	6 (17%)
Lost follow up	4(5.7%)(	Peritoneal dialysis	10 (28.5%)
		No dialysis	19 (54.2%)

ESRD: End-stage renal disease, MP: Methylprednisolone, MMF: Mycophenolate mofetil, CYC: Cyclophosphamide, HTN: Hypertension

Most of the patients (n=30/35, 85.7%) were treated with methylprednisolone (MP) and cyclophosphamide (CYP), four patients only received MP due to a less severe disease course. Sixteen patients required dialysis, of whom 10 underwent peritoneal dialysis and others received hemodialysis (HD).

Two patients that underwent HD eventually developed CKD and received maintenance HD. The patient with pauci-immune GN developed CKD and is currently on HD. Figure 4 shows the relationship between time of treatment (days of initiation of treatment) and outcome of the patients. No patient presented before 6th day. Five patients presented between 6 to 10 days and all of them went into complete remission. Twelve patients presented between 11 to 15days, 9 of them went into complete remission, 2 developed relapse and 1 developed ESRD.

Ten patients presented between 16 to 20 days and among them 6 underwent complete remission, one developed relapse, one had partial remission, one progressed to ESRD, one had death. Three patients presented after 20 days out of them 2 developed

ESRD, 1 died. Therefore, most of the patients who developed ESRD or patients with mortality presented after 15 days of onset of disease.

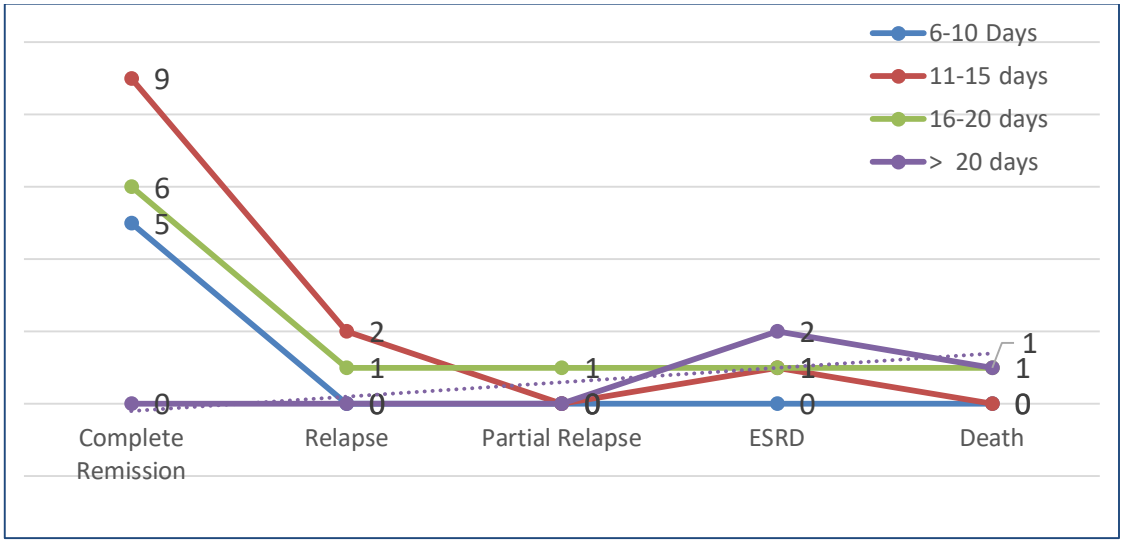

Figure 4. Relationship between days of initiation of treatment and clinical outcome.

Discussion

Rapidly progressive glomerulonephritis is an uncommon yet serious disease in the pediatric population. The etiology, presentation, diagnosis, treatment, and clinical outcomes of RPGN have only been addressed in a few studies, and little specific information is available from Bangladesh. This study was conducted to take a deeper look into the histological diagnosis of clinically suspected RPGN, which is very important for management purposes. Of 35 patients with RPGN, the most common age at presentation was 10-15 years with a male predilection. Gupta et al (22) also found a younger age at presentation of RPGN in India (17.1 years). In our study, the higher incidence of RPGN in males (60%) versus females (40%) was similar to a study conducted in India reporting an RPGN incidence rate of 64.7% in males and 35.3% in females (23). By contrast, a previous study conducted in Saudi Arabia reported a higher incidence rate in females (57.5%) compared to males (42.5%) (25).

In our study, most of the patients (74%) presented with edema while a study from India showed that hypertension was the most common presentation (87.5%) (26).

One of the most important findings of our study was that diffuse proliferative GN (28.5%) was the principal underlying etiology of RPGN followed by crescentic GN (22.8%). Dewan et al. (27) found that post-infectious GN was the most common cause of RPGN in pediatric patients, which is in contrast to a previous report from Saudi Arabia that identified lupus nephritis as the underlying etiology of RPGN in the majority of cases (54.1%), with post-infectious GN in only 16.2% of the cases [28]. Moreover, a recent study from India found that pauci-immune GN was the primary etiology of RPGN in about half of the cases, with lupus nephritis identified in 11.1% and post-infectious GN in 8.3% of the cases (29). Another study conducted in Japan concluded that pauci-immune GN was the most frequent etiology of RPGN (42%) (27)

While considering the etiology of crescentic GN, our study revealed that idiopathic GN (2 patient), lupus nephritis (2 patient), acute GN (1 patient), HSP (Henoch Schonlein Purpura) (1 patient), IgA nephropathy (1 patient), and pauci-immune GN (1 patient) were the most common etiologic factors for RPGN. In this study, ANA was positive in 7 patients, anti-ds DNA was positive in 7 patients, and the level of C3 was low in 19 patients. Biochemical parameters revealed high levels of serum creatinine in all patients at initial presentation. Prompt treatment after a clinical suspicion of RPGN with or

without dialysis showed favorable results. Nineteen patients achieved complete recovery, 4 developed ESRD, and 2 died. Patients with RPGN had an insidious onset of the disease and a slowly progressive course that led to a late presentation. These patients are often diagnosed too late when irreversible histopathological changes have already occurred and potential immunosuppressive therapy remains questionable. The poor economic status and lack of awareness of our patients could be other contributory factors. Early immunosuppressive therapy can prevent the inflammatory process, halt the transformation of cellular crescents to fibrous crescents, and thus prevent progression to CKD. Therefore, immunosuppressive therapy should start promptly even before the histopathology report is available. Our recommendation is to perform an early biopsy along with an accurate histopathology report to confirm the diagnosis and predict the prognosis.

Limitations of the Study

It was a retrospective single-center study and the sample size was small.

Conclusion

Clinically suspected RPGN patients show variations in histopathological patterns; therefore, renal histology is an integral part of the investigation of such patients for diagnostic and prognostic purposes. Diffuse proliferative glomerulonephritis was the most common histopathological diagnosis in patients with clinical RPGN in our population. Preservation of the renal function depends on early intervention and detection of RPGN in pediatric patients.

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Conflict of Interest

The authors declare no conflicts of interest.

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