

Assessment of the etiologies and renal outcomes of rapidly progressive glomerulonephritis in pediatric patients at King Abdulaziz University Hospital, Jeddah, Saudi Arabia

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ABSTRACT

الأهداف: تهدف هذه الدراسة إلى التحقق من الأسباب نتائج متلازمة التهاب كبيبات الكلى المتري السريخ خطيرة لدى المرضى من الأطفال حيث أن المسببات التي تؤدي إلى هذا الالتهاب تختلف على مستوى اقليمي بجانب التدخل بشكل مبكر إلى أن تتشابه اختلاف النتائج في جامعة الملك عبد العزيز في جدة، المملكة العربية السعودية.

الطريقة: أجريت هذه الدراسة الاستباقية على 19 من الأطفال المرضى الذين تم تشخيصهم بالتهاب كبيبات الكلى المتري بين عامي 2006م إلى 2016م في قسم طب الأطفال في جامعة الملك عبد العزيز. وتم التقييم الارتباطات بين المتغيرات باستخدام اختبارات مستقلة تحليل التباين أحادي الاتجاه (ANOVA) واختبارات مربع.

النتائج: معظم المرضى ذكور 13 (68.4%) في متوسط العمر 8.52 (3.15) سنة (الانحراف المعياري) عند التشخيص. وأهم المسببات الأساسية هي التهاب كبيبات الكلى المعدية (63.2%) و التهاب الكلى الذئبي (21.1%) عرض ثلاثة عشر من المرضى تشخيص سريري جيد (68.4%). وتم تشخيص 6 من المرضى وكانت حالتهم ميؤوس منها (31.6%) 4 منهم يعانون من داء الكلوي بالمرحلة الأخيرة. واحد يعاني من الانتكاس ومرض الكلى المزمن المتطور. يرتبط التهاب كبيبات الكلى المعدية بشكل عام مع أفضل النتائج السريرية. تم تنفيذ العلاج في وقت مبكر في معظم المرضى واستمر لمدة 3 أشهر. من بين 19 مريضاً، توفي اثنان وواحد خضع لعملية غسيل الكلى.

الخاتمة: المسببات الأكثر شيوعاً الالتهاب كبيبات الكلى المتري هو التهاب كبيبات الكلى بعد العدوى وبشكل عام تم تشخيص المرضى السريري بشكل جيد. المعرفة المبكرة والعلاج من كبيبات الكلى المتري مهم للحفاظ على وظائف الكلى وهو عامل أساسي لتشخيص جيد.

Objectives: To investigate the etiologies and outcomes of rapidly progressive glomerulonephritis (RPGN) in pediatric patients at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia.

Methods: A retrospective study was conducted in 19 pediatric patients who were diagnosed with RPGN between 2006 and 2016 at the Department of Pediatric Medicine at KAUH. Associations between variables were evaluated using independent t-test, one-way analysis of variance (ANOVA) and Chi-squared tests.

Results: Majority of patients were male, (68.4%), with a mean±SD age at diagnosis of 8.52±3.15 years. The most common underlying etiologies were post-infectious glomerulonephritis (PIGN) (63.2%) and lupus nephritis (21.1%). Thirteen patients exhibited a good clinical prognosis (68.4%), with 6 exhibiting a poor prognosis (31.6%), 4 of whom progressed to end-stage renal disease (ESRD), one experiencing a relapse and one developing chronic kidney disease. Post-infectious glomerulonephritis was associated with the best clinical outcome overall. Treatment was implemented early in most patients and continued for 3 months. Among the 19 patients, 2 died and one underwent hemodialysis.

Conclusion: Post-infectious glomerulonephritis was the most common etiology of RPGN, with these patients achieving a good clinical prognosis overall. Early identification and treatment of RPGN is important to preserve renal function, which is a key factor for achieving a good prognosis.

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Glomerulonephritis (GN) is a group of glomerular diseases characterized by glomerular injury associated with inflammation.¹ Glomerulonephritis is usually manifested by hematuria, proteinuria, edema, and hypertension.¹ Glomerulonephritis can be classified into different types depending on the histopathological and clinical presentation.² A 2010 systematic review estimated the worldwide incidence of primary GN to vary between 0.2 and 2.5/100,000 per year. The incidence was lower among children, except in the geographic regions of Arabia and Asia, where an incidence rate among children was 7.2-11.6/100,000 per year in Arabia and 6.2-15.6/100,000 per year in Asia was reported.³ Rapidly progressive glomerulonephritis (RPGN), also known as crescentic glomerulonephritis, is an uncommon but serious clinical syndrome in pediatric patients.⁴ Rapidly progressive glomerulonephritis is characterized by a rapid deterioration of renal function, which can progress to end stage renal disease (ESRD).⁵ Rapidly progressive glomerulonephritis is classified into 4 subtypes: anti-GBM antibody disease, immune complex, pauci-immune, and idiopathic.² The clinical manifestations of RPGN include a sudden onset of hematuria, proteinuria, oliguria, and edema.⁵ The diagnosis of RPGN is based on laboratory findings and kidney biopsy to identify characteristic crescentic formation in Bowman's capsule.⁵ An elevation in plasma creatinine at the time of diagnosis has also been reported in the majority of cases.⁵ Although the incidence rate of RPGN is estimated at 7 cases per one million per year in the United States, a 2010 study conducted in Saudi Arabia reported a 3.2% incidence of crescentic glomerulonephritis among 233 renal biopsies performed in patients 17 to 43 years old.^{6,7} Etiologies that could lead to RPGN differ regionally; along with early possible intervention, different outcomes are suspected.^{8,9} Considering regional differences in etiology, the severity of the disease and the likelihood of a poor prognosis, RPGN is deemed to be an important public health issue in pediatrics worldwide.¹⁰ As RPGN, despite being rare, is considered one of the renal emergencies as mentioned in the study carried out by Dewan et al.¹⁰ An epidemiological study of 36 children with RPGN in India reported complete recovery in 19.6% of these cases (7 patients), with 30.6% (10 patients)

progressing to chronic kidney disease (CKD).¹¹ A study of 37 children with RPGN in Saudi Arabia identified acute renal injury (AKI) in 68.2% of these patients, with 12.5% requiring dialysis at the time of biopsy.¹² Previous studies³ looked in history, clinical features and incidence, in addition to the pathomorphology and prognosis, as Maslauskiene et al⁹ mentioned in their study, the treatment of GN disease is still not well known and still empirical and risky.¹ A study on Kaunas University found that the percentage of patients who had renal dialysis was 56.5%, although they received treatment. And out of those, only 47.8% of patients had improved renal function.⁹ Unfortunately, there is insufficient evaluation regarding the renal outcomes of RPGN in pediatric patients in Saudi Arabia, especially in the western province. Therefore, the aim of our study was to investigate the etiologies and renal outcomes of RPGN in pediatric patients at King Abdulaziz University Hospital (KAUH) in Jeddah, Saudi Arabia.

Methods. The study was approved by the institutional review board (IRB) of KAUH and was carried out according to the principles of Helsinki Declaration.¹³ A retrospective study was conducted on 19 pediatric patients, diagnosed with RPGN at the Department of Pediatric Medicine at KAUH, between 2006 and 2016. King Abdulaziz University Hospital is a referral center for nephrology cases in the western region of the Kingdom and the number of RPGN cases is estimated to be 3 cases per years. The total number of pediatric cases is 1500-2000 cases per year. We included in this study patients <18 years old, and were diagnosed with RPGN based on clinical assessments, laboratory findings, and biopsy results which were positive for crescentic formations in $\geq 50\%$ of the glomeruli. The research method was also used to find prior related research.

The medical records of these patients were reviewed to extract the following information for analysis: age at diagnosis, gender, history of infection, duration of symptoms prior to admission, and clinical features at the time of admission. In addition to the classic symptoms of oliguria, edema and hypertension, the following symptoms were also considered: cardiopulmonary (chest pain, cyanosis, coughing, and hemoptysis), rheumatic (vasculitis, arthralgia, maculopapular, petechial, and purpuric skin rash), abdominal (hepatomegaly and splenomegaly), and neurological (seizures, encephalopathy, psychosis, and visual impairments). Creatinine levels were determined using the Jaffe method. This is an economical method but results can be influenced by chromogenic

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substances, like bilirubin. Outcomes of laboratory tests were also recorded: serum albumin level, microscopic hematuria, nephrotic and non-nephrotic proteinuria evaluated by urine sample; estimated glomerular filtration rate (eGFR) using the Schwartz estimate; and serological tests for anti-neutrophilic cytoplasmic antibodies (ANCA), complement levels (C3, C4, C1Q), anti-glomerular basement membrane antibodies (anti-GBM). All laboratory tests were obtained at admission and at the last follow up. Renal biopsy results (light microscopy, immunofluorescence and electron microscopy) were also reviewed. The report was carried out by a pathologist from our hospital who is specialized in pediatric nephrology.

Treatment methods were reviewed to identify the type of medication used, as well as the time of starting them, the dosage and duration. Clinical outcomes were classified as follows: complete or partial recovery, relapse, chronic kidney disease (CKD) or progression into ESRD. The need for dialysis, kidney transplant and death were also included in our analysis of outcomes.

Rapidly progressive glomerulonephritis was defined by the presence of crescentic cells in the Bowman's capsule in $\geq 50\%$ of glomeruli. Rapidly progressive glomerulonephritis was classified into 4 types: anti-GBM antibody disease, immune complex, pauci-immune, and idiopathic.⁵ Hypertension was classified according to the standards of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents; which adjusts values for age, gender, and height. Patients eGFR was measured through the bedside.¹⁴ Microscopic hematuria was defined by presence of ≥ 3 red blood cells per high-powered field in a properly collected urine sample.¹⁵ Nephrotic range proteinuria was defined by a cutoff level of 1 gm/m²/day. And nephritic syndrome was defined as hematuria, proteinuria (protein excretion, 3.5 g/d), hypertension, and edema, with eGFR < 60 mL/min/1.73 m². Complete recovery was defined by Normalized of GFR (> 90 ml/1.73 m²/min) and negative for protein and normalization of urinalysis parameters. Partial recovery was defined by Normalized of GFR (> 90 ml/1.73 m²/min) reduction of proteinuria more than 50% and serum albumin > 30 gm/l.

Acute renal injury was defined by the pRIFLE criteria (Pediatric Risk, Injury, Failure, Loss, and End Stage Renal Disease).¹⁶ Chronic kidney disease was defined by the Ronald J. Hogg's criteria as GFR < 60 ml/1.73 m²/min or no reduction of proteinuria more than 50% for 3 months.¹⁷ Relapse was defined as a rise in creatinine concentration, with nephritic sediment and other signs or symptoms of vasculitis.¹⁸ End stage

renal disease was defined by a GFR of < 15 mL/min per 1.73 m² and the need for renal replacement therapy.¹⁷ Early treatment was defined as starting the medications within the first 48 hours of presentation and late treatment was defined as starting the treatment after the 48 hours.

Data analysis. Data analysis was performed using the Statistical Package for the Social Science (SPSS) version 21 (IBM Corp., Armonk, NY, USA). Qualitative variables, expressed as a percentile value, were evaluated using a chi squared test and quantitative data using independent t-tests. The correlation between early diagnosis of RPGN and outcomes was evaluated, with one-way analysis of variance (ANOVA) used to evaluate the specific association between serum creatinine levels at admission and clinical outcomes.

Results. Demographic characteristics of the study group shows the majority of patients were male, (68.4%), with a mean (standard deviation) age at diagnosis of 8.52 (3.15) years, while females represent 31.58% with a mean (standard deviation) age at diagnosis of 6.16 (2.48).

The distribution of RPGN etiology shows that post-infectious GN (63.2%) and lupus nephritis (21.1%) being the most common etiologies in our study group, followed by immune complex, pauci-immune glomerulonephritis, SRNS with an equal percentage of (5.3%) for each.

Eleven of the 19 patients (57.9%) reported symptoms beginning in the 2 weeks prior to admission, with 4 patients (21.1%) reporting symptoms for > 2 weeks prior to admission. The majority of patients presented with macroscopic hematuria, edema, hypertension, and vomiting (Table 1). Out of the 17 patients testing positive for macroscopic hematuria at admission, post-infectious GN was diagnosed in 12 (63.2%; $p=0.026$). There was a significant lowering in serum creatinine levels from admission to the last follow-up (one-way ANOVA, $p=0.019$) (Table 2). Results of other laboratory tests at admission and at the last follow-up are reported in Tables 3 & 4.

More than half of the patients received a combination therapy of corticosteroids and immunosuppressive therapy (52.6%), with other patients receiving corticosteroids only. Thirteen patients exhibited a good clinical prognosis (68.4%), which includes 5 (26.3%) with complete recovery, of whom 4 had a diagnosis of post-infectious GN, and 8 (42.1%) with partial recovery; all of them were diagnosed as post-infectious GN. Six patients exhibiting a poor prognosis (31.6%), 4 of whom progressed to ESRD, one experiencing a

Table 1 - Clinical symptoms at admission and their frequency distribution.

Clinical presentation	n	(%)
Macroscopic hematuria	17	(89.5)
Edema	17	(89.5)
Hypertension	11	(57.9)
Vomiting	10	(52.6)
Headache	7	(36.8)
Ascites	6	(31.6)
Seizures	5	(26.3)
Need for dialysis at presentation	5	(26.3)
Oliguria	4	(21.1)
Shortness of breath	4	(21.1)
Cough	3	(15.8)
Encephalopathy	3	(15.8)
Fever	3	(15.8)
Rash	2	(10.5)
Vision problem	2	(10.5)
Upper respiratory tract infection	2	(10.5)
Flank pain	2	(10.5)
Hepatomegaly	1	(5.3)
Splenomegaly	1	(5.3)
Dysuria	1	(5.3)
Systolic murmur	1	(5.3)
Pleural effusion	1	(5.3)

Table 2 - Serum creatinine levels (µmol/L) at the last follow-up.

Variables	N	Mean	SD	SE	Mean GFR at presentation	Mean GFR at last follow up
Complete recovery	5	47.60	11.65	5.21	29.66	102.86
Partial recovery	8	54.75	17.32	6.12	21.97	108.32
Relapse	1	374	-	-	-	-
CKD	1	545	-	-	-	-
ESRD	3	774.33	725.53	418.88	5.16	32.86
Total	18	217.66	381.45	89.90	18.93	81.34

SD - standard deviation, SE - standard error, CKD - chronic kidney disease, ESRD - end-stage renal disease, GFR - glomerular filtration rate

relapse and one developing chronic kidney disease.

All patients underwent renal biopsy examination using light microscopy, immunofluorescence and electron microscopy. Crescentic formation in the glomeruli was identified in 11 biopsy specimens, with 6 showing isolated crescents and 5 multiple types of crescentic formation, including crescents, cellular crescents and fibrocellular crescents. Acute tubular necrosis (ATN) was identified in 4 patients. Details of the biopsy results for the remaining 8 patients

Table 3 - Laboratory findings at presentation.

Test	Min	Max	Mean	SD
Microscopic hematuria	2	3318	360.44	825.83
Proteinuria g/dL	0	4	1.78	1
Serum Cr µmol/L	52	990	327.15	307.91
GFR mL/min1.73/m ²	8	57	23	21.40
Serum albumin g/dL	9	36	21.57	7.79
Hemoglobin g/dL	6	15	9.78	2.09
ESR mm/h	15	117	71.66	35.13
CRP mg/L	3	69	28.08	23.70
ASO titer IU/mL	43	2300	479.61	639.89
DNAase B titer IU/mL	78	1240	462.40	450.80
C3 g/L	0.20	1.31	0.99	0.35
C4 g/L	0.04	0.55	0.23	0.15

GFR - glomerular filtration rate, ESR - erythrocyte sedimentation rate, CRP - C-reactive protein, ASO - antistreptolysin O, C3 - complement 3, C4 - complement 4

Table 4 - Laboratory findings at the last follow up.

Test	Min	Max	Mean	SD
Microscopic hematuria	1	195	43.78	66.84
Proteinuria	0	3	1.29	1
Serum Cr µmol/L	33	1504	217.66	381.4
GFR mL/min 1.73/m ²	5	159	100.83	53.15
Serum albumin g/dL	9	41	32.40	8.67
Hemoglobin g/dL	8	15	11.18	2.07
ESR mm/hour	7	111	39.62	38.04
CRP mg/L	3	22	8.22	7.46
ASO titer IU/mL	161	935	489.00	326.93
DNAase B titer IU/mL	184	1070	664.33	447.6
C3 g/L	0	2	1.06	0.39
C4 g/L	0	0	0.21	0.10

Serum Cr - serum creatinine, GFR - glomerular filtration rate, ESR - erythrocyte sedimentation rate, CRP - C-reactive protein, ASO - antistreptolysin O, C3 - complement 3, C4 - complement 4

were not available. Immunofluorescence examination for immunoglobulin (IgG) protein was positive in most patients, with the following distribution of IgG subtypes. Testing for IgA was negative in 7 patients (36.8%), 6 of whom had a diagnosis of post-infectious GN ($p=0.118$), and negative for IgM in 8 patients (42.1%), all of whom had a diagnosis of post-infectious GN ($p=0.01$). Thirteen patients (68.4%) tested positive for complement component-3 (C3), 8 of whom had a diagnosis of post-infectious GN. Twelve patients tested negative for C4 and 8 for C1Q (42.1%), of whom 7 had a diagnosis of post-infectious GN. We found that a serum creatinine level >400 µmol/L at presentation was associated with a worse clinical prognosis. Out of the 4

patients who presented with such high serum creatinine levels, 2 progressed to ESRD and 2 underwent hemodialysis. In our study, we also found that macroscopic hematuria was the most common clinical finding (89.5%). All patients with post-infectious GN had macroscopic hematuria as their main complaint following an upper respiratory tract infection ($p=0.026$). Early treatment was started in 8 patients (42.1%) and late was found in 11 patient (57.9%), all received at least one corticosteroid treatment, with 10 patients (52.6%) receiving adjuvant immunosuppressive therapy. In our study, we found that the mean age at RPGN diagnosis was 8.5 years, an age when children are commonly susceptible to upper respiratory tract infection and, therefore, at risk for developing post-infectious GN.¹⁹ The majority of patients in our study group achieved a good clinical prognosis (68.4%), with the post-infectious GN group achieving the best overall prognosis, with the majority of children in this group recovering without undergoing hemodialysis. Thirteen patients exhibited a good clinical prognosis (68.4%), which includes 5 (26.3%) with complete recovery, of whom 4 had a diagnosis of post-infectious GN, and 8 (42.1%) with partial recovery all of them diagnosed as post-infectious GN. Six patients exhibiting a poor prognosis (31.6%), 4 of whom progressed to ESRD, one experiencing a relapse and one developing chronic kidney disease.

A Chi-square test between the presence of IgM in renal histopathology examination and the renal outcomes showed that IgM was negative in 8 (42.1%) patients who exhibited a good clinical prognosis, and was found positive in 4 (21.1%) patients who exhibiting a poor prognosis ($p=0.042$). A Chi-square test between the time of starting the medications and the prognosis of the patients showed that early intervention was not a contributing factor to the prognosis of the patients ($p=1.867$).

Discussion. Rapidly progressive glomerulonephritis is an uncommon and yet serious disease in pediatrics. The etiology, presentation, diagnosis, treatment, and clinical outcomes of RPGN have only been addressed in a few studies, with little specific information available for the Middle East and Saudi Arabia. This is why we conducted this retrospective study to provide clinical data regarding pediatrics, specifically in Saudi Arabia, at KAUH. One of the most important findings of our study was the identification of post-infectious GN and lupus nephritis as principal underlying etiologies of RPGN, accounting for 63.1% of post-infectious GN cases and 21% of lupus nephritis cases. Dewan et al¹⁰

similarly reported post-infectious GN to be the most common cause of RPGN in pediatrics. This 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 cases.¹² Moreover, a recent study in India identified pauci-immune GN as the primary etiology of RPGN in about half of the cases, with lupus nephritis identified in 11.1% and post-infectious GN identified in 8.3% of cases.⁹ Another study conducted in Japan concluded that pauci-immune GN is the most frequent etiology (42%) of RPGN.¹⁹ In our study we found that the mean age at RPGN diagnosis was 8.5 years, an age when children are commonly susceptible to upper respiratory tract infection and, therefore, at risk for developing post-infectious GN.¹⁹ The majority of patients in our study group achieved a good clinical prognosis (68.4%), with the post-infectious GN group achieving the best overall prognosis, with the majority of children in this group recovering without undergoing hemodialysis. Our outcomes are comparable to those reported by Hogg²⁰ who concluded RPGN to generally be a self-limiting disease process with an excellent outcome expected. In contrast, other studies in the United States, India, France, the United Kingdom, and Turkey reported mostly poor clinical outcomes in pediatric patients with RPGN.^{10,20-24} Interestingly, another study conducted in the central region of Saudi Arabia also reported better outcomes for their patients with RPGN than in other studies.¹² We believe that the favorable prognosis in our study reflected the early diagnosis in our hospital and the treatment methods that are used at the KAUH.

One of the unexpected findings in our study was the absence of IgM antibodies on immunofluorescence examination in the majority of patients ($p=0.01$). When present, IgM was predictive of a poor prognosis ($p=0.042$). With the exception of one study from India, reporting faint deposits of IgM in only one patient in their cohort group, our results are clearly different from previously published data in reporting absence of IgM in the majority of our patients with post-infectious GN.¹¹ Another unexpected finding of our study was the higher incidence of RPGN in males (68.4%) than in females (31.6%). This finding is similar to a report from India indicating an incidence rate of RPGN of 64.7% in males and 35.3% in females.¹¹ A previous study from Saudi Arabia reported a higher incidence rate in females (57.5%) than in males (42.5%). This difference in gender-specific incidence rate, compared to our study, may reflect the higher proportion of lupus etiologies in their cohort, compared to post-infection GN in our

cohort, with lupus being more common in females.^{12,25} We found that a serum creatinine level >400 µmol/L at presentation was associated with a worse clinical prognosis. Out of the 4 patients who presented with such high serum creatinine levels, 2 progressed to ESRD and 2 underwent hemodialysis. These results are similar to those from a previously published study in Turkey reporting that 19 patients presenting with a mean serum creatinine level of 344 µmol/L progressed to CKD.²⁴ In our study, we also found that macroscopic hematuria was the most common clinical finding (89.5%). All patients with post-infectious GN had macroscopic hematuria as their main complaint following an upper respiratory tract infection ($p=0.026$; Table 2).

All patients in our study group started treatment early and received at least one corticosteroid treatment, with 10 patients (52.6%) receiving adjuvant immunosuppressive therapy. The same therapeutic regimen was used in 2 previous studies from Turkey and India.^{24,11} It has been reported that early intervention and detection of RPGN is critical to achieve a better prognosis.^{9,26}

In our study, no association were found between early treatment and prognosis. Eight patients had received early treatment and 6 (75%) of them achieved good prognosis. Eleven patients who started late ($n=7$; [63.6%]) achieved good prognosis ($p=1.867$). These findings might be related to the etiologies in our sample; Grøndahl et al¹⁹, has concluded that the PSGN has an excellent outcome and prognosis over other types of GN. Other studies have recommended the early recognition, diagnosis and treatment are crucial to prevent the irreversible loss of renal function.²³

The main limitation of our study was missing or non-reported histopathological findings. In addition, height was not reported for most patients, which may have correlated with many of our findings. Another limitation was the small sample size, which reflects the rarity of RPGN.

Based on our outcomes, we recommend the development of a specific registry for pediatric RPGN, which will support the development of evidence-based diagnosis and interventions for this unique clinical population. Early intervention and detection of RPGN is of paramount importance and, therefore, we recommend initiation of treatment in suspected cases of RPGN awaiting diagnostic confirmation. Moreover, we recommend having an early biopsy procedure, along with an adequate histopathology report, to confirm the diagnosis and predict prognosis. Hospitals may also need to raise awareness of GN and promote the value of early identification before progression to achieve favorable outcomes.²⁷

In conclusion, in our study, post-infectious GN was the most common etiology of RPGN with the best outcome over all other etiologies. Early intervention and detection of RPGN is important to preserve renal function.

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