Crescentic glomerulonephritis in children: a single centre experience

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Background: **Crescentic glomerulonephritis (CsGN) is characterized by crescents in 50% or more of glomeruli and clinically by a sudden and progressive decline in renal function.**

Methods: **We evaluated the etiology, clinical features, prognostic factors and long-term outcome of CsGN. Between January 2000 and December 2010, 45 children (26 girls, 19 boys) with biopsy-proven CsGN (>50% crescents) were investigated retrospectively.**

Results: **The mean age of the patients was 130.86±33.77 months. The mean duration of symptoms prior to diagnosis was 26±12 days (4-40 days). Most of the children had hypertension (62.2%), macroscopic hematuria (73.3%), oligoanuria (44.4%), edema (51.1%) and purpuric rash (40%) at presentation. The final clinical status of the patients was complete remission (*n*=21), partial remission (*n*=5) or chronic kidney disease (*n*=19). Adverse outcomes were significantly associated with a long duration between the onset of symptoms and treatment (*P*=0.038), the presence of oligoanuria (*P*=0.006), a severe decreased glomerular filtration rate (GFR <30 mL/min/1.73m²) and the need for dialysis (*P*=0.003) on admission, the ratio of crescents (>75%) (*P*=0.03), and the ratio of fibrous crescents (*P*=0.015).**

Conclusion: **The outcome of CsGN in children continues to be poor, and it should be treated as a renal emergency.**

World J Pediatr 2016;12(2):225-230

Key words: **glomerulonephritis; renal biopsy; renal failure**

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doi:10.1007/s12519-015-0036-0
Online First December 2015

Original article

Introduction

Crescentic glomerulonephritis (CsGN) is a rare entity in children. While the exact incidence is unknown,[1] this disease accounts for about 5% of the renal biopsies reported in different studies. CsGN is characterized clinically by a sudden and progressive decline in renal function and histopathologically by crescents in 50% or more of glomeruli. This disease can accompany most forms of primary glomerulonephritis, but it is also associated with various systemic diseases.[2]

The severity of the disease is related in part to the degree of crescent formation. Patients with crescents in more than 80% of glomeruli tend to present advanced renal failure that may not respond well to therapy. In contrast, patients with less than 50% of crescents typically follow a more indolent course.[3] Prognosis also depends on the type of crescents and the immunopathologic category. The best predictor of outcome for CsGN is the time of therapy initiation. Even several days' delay in diagnosis and treatment can have a major negative impact on the outcome. Thus, early diagnosis and prompt treatment are the key to the management of CsGN.[4]

In this retrospective study, we investigated the etiology, clinical features, prognostic factors and long-term outcomes of CsGN in childhood.

Methods

Forty-five children diagnosed with CsGN between January 2000 and December 2010 were included in the study. The mean follow-up period was 69.64±36.26 months (6-116 months).

Medical records of the patients were reviewed. The age, gender, history of infection, duration of symptoms before admission, findings on physical examination

and presence of hypertension and oliguria on admission were evaluated. Laboratory parameters including serum creatinine and albumin levels, urinalysis, 24-hour urinary protein levels, anti-nuclear antibodies, anti-neutrophilic cytoplasmic antibodies, anti-double stranded DNA, serum complement levels (C3, C4) and, when necessary, anti-glomerular basement membrane antibodies (anti-GBM) were recorded in addition to the renal biopsy, therapeutic regimens and the prognosis.

Crescentic glomerulonephritis was diagnosed when the patients had visceral and parietal epithelial cells filling Bowman's space in more than 50% of glomeruli on renal biopsies. Hypertension was diagnosed based on the Task Force recommendations.[5] Proteinuria was diagnosed when protein excretion greater than 4 mg/m^2 per hour (abnormal proteinuria: 4-40 mg/m^2 per hour; nephrotic range proteinuria: >40 mg/m^2 per hour);[6] patients got complete remission with improvement of renal function tests and urinalysis to normal levels; for partial remission: improvement of serum albumin and creatinine levels to normal values; glomerular filtration rate (GFR) is in normal limits but hematuria and/or proteinuria (not in nephrotic range) persist; chronic kidney disease (CKD) was diagnosed according to the criteria by Hogg et al;[7] end-stage renal disease means GFR decreased to <15 mL/min per 1.73 m^2 and the need for renal replacement therapy.

Histopathology

All patients underwent percutaneous renal needle biopsy; histopathological examinations were conducted by the same pathologist, who was an expert on renal pathology. Biopsy materials that included 10 or more glomeruli were deemed adequate for examination. The number of glomeruli with crescents, type of crescents and degree of tubulointerstitial fibrosis and atrophy were investigated. Crescents were classified as cellular, fibrocellular, or fibrous using the following definitions modified from the World Health Organization classification of renal disease from Churg et al:[8] 1) cellular crescents: presence of at least two layers of cells in addition to visceral and parietal epithelial cells with the involvement of at least 10% of the glomerular circumference; 2) fibrocellular crescents: crescents showing an admixture of collagen fibres and membrane proteins among the cells; and 3) fibrous crescents: a lesion in which Bowman's space is composed predominantly of fibrous tissue.

To investigate the factors affecting prognosis, the patients were divided into two groups based on the presence or absence of CKD. The groups were compared with respect to the presence of oliguria and hypertension and the GFR value on admission, together with renal biopsy findings, including the type and ratio of crescents, the degree of tubular atrophy and interstitial fibrosis, fibrinoid necrosis and capillary infiltration.

Statistical analysis

Data analysis was performed using SPSS 11.5 for Windows. If the distribution of continuous variables was close to normal, analysis was performed using the Shapiro-Wilk test. Descriptive statistics for continuous variables are presented as the mean±standard deviation or median (minimum-maximum), and categorical variables are presented as the number of cases and percentile. Significant differences in averages between the groups were analyzed using Student's *t* test, and significant differences in median values were analyzed using the Mann-Whitney *U* test. Categorical variables were examined using the Chi-square test or Fisher's exact test. For all possible risk factors that could affect the presence of CKD, the odds ratio and 95% confidence interval were calculated using univariate logistic regression analysis. $P<0.05$ was considered statistically significant. The best predictor(s) of CKD were determined using the multiple logistic regression analysis (Backward LR) procedure. Any variable for which the univariable test had $P<0.05$ was accepted as a candidate for the multivariable model along with all variables of known clinical importance. The odds ratio, 95% confidence interval and Wald statistics for each independent variable were also calculated.

Table 1. Clinical and laboratory features on admission (n=45)

Clinical findings	n (%)
Macroscopic hematuria	33 (73.3)
Hypertension	28 (62.2)
Edema	23 (51.1)
Rash	21 (46.7)
Oliguria	20 (44.4)
Gastrointestinal findings	15 (33.3)
Cardiac and pulmonary findings	8 (17.7)
Arthritis/arthralgia	5 (11.1)
Neurological findings	5 (11.1)
Positive throat culture	4 (8.9)
Positive viral serology	None
Low levels of C3	8 (17.7)
Positivity of ANA, anti DNA, ANCA	6 (13.3)
Serum creatinine level >1 mg/dL	38 (84.4)
GFR <90 mL/min/1.73m^2	38 (84.4)
Serum albümin <2.5 g/dL	28 (62.2)
Proteinuria <4 mg/m^2 per hour	5 (11.1)
Proteinuria between 4 mg/m^2 per hour and 40 mg/m^2 per hour	5 (11.1)
Proteinuria >40 mg/m^2 per hour	35 (77.8)

C3: complement 3; ANA: anti-nuclear antibodies; ANCA: anti-neutrophilic cytoplasmic antibodies; GFR: glomerular filtration rate.

Table 2. Treatment protocols according to the underlying etiology

HSN	24 patients; iv. pulse MPZ+oral prednisone+oral cyclophosphamide
MPGN	4 patients; iv. pulse MPZ for 6 mon (monthly)+oral prednisone+oral cyclophosphamide
APIGN	2 patients; iv. pulse MPZ+oral prednisone 1 patient; iv. pulse MPZ+oral prednisone+oral cyclophosphamide
SLE nephritis	2 patients; iv. pulse MPZ for 6 mon (monthly)+oral prednisone+oral cyclophosphamide followed by azathioprine
Pauci-immun GN	2 patients; iv. pulse MPZ for 6 mon (monthly)+oral prednisone+oral cyclophosphamide followed by azathioprine 1 patient; iv. pulse MPZ for 6 mon (monthly)+oral prednisone+iv cyclophosphamide+plasmapheresis
Idiopathic GN	6 patients; iv. pulse MPZ for 6 mon (monthly)+oral prednisolone+oral cyclophosphamide 3 patients; iv. pulse MPZ for 6 mon (monthly)+iv cyclophosphamide+plasmapheresis

HSN: Henoch-Schonlein purpura nephritis; MPGN: membranoproliferative glomerulonephritis; APIGN: acute post-infectious glomerulonephritis; SLE: systemic lupus erythematosus; GN: glomerulonephritis; iv.: intravenous; MPZ: methylprednisolone.

Table 3. Clinical and laboratory parameters and prognosis

Variables	CKD- (*n*=26)	CKD+ (*n*=19)	*P*
Age (mon)	128.3±28.0	134.4±41.0	0.549
Male, *n* (%)	12 (46.2)	7 (36.8)	-
Female, *n* (%)	14 (53.8)	12 (63.2)	0.532
Duration between onset of symptoms and treatment (d)	17.5 (4-20)	30.0 (7-40)	0.038
Oligoanuria at presentation, *n* (%)	7 (26.9)	13 (68.4)	0.006
Hypertension at presentation, *n* (%)	14 (53.8)	14 (73.7)	0.175
Proteinuria levels (mg/m^2 per hour)	136 (3-212)	78 (3-182)	0.034
Number of the patients with macroscopic hematuria, *n* (%)	23 (88.5)	10 (52.6)	0.007
Serum creatinin levels (mg/dL)	1.85 (0.27-8.30)	3.90 (0.90-11.0)	0.012
GFR (mL/min/1.73 m^2)	42 (4.8-125)	23 (5.1-91)	0.041
Serum albumin levels (g/dL)	2.35 (1.00-4.90)	2.54 (1.40-3.80)	0.939
Hemoglobin (g/dL), mean±SD	9.6±2.7	9.2±2.4	0.602
ESR (mm/h)	82 (10-150)	105 (35-148)	0.441
CRP (mg/dL)	28.1 (2-90)	9.4 (1.5-142.3)	0.964

GFR: glomerular filtration rate; ESR: eryhtrocyte sedimentation rate; CRP: C-reactive protein; CKD: chronic kidney disease; SD: standard deviation.

Results

During the study period, 844 renal biopsies in 45 patients (26 girls, 19 boys) were performed in our clinics; of these, 45 (8.3%) were CsGN. Diagnosis was based on the clinical features, laboratory parameters and histopathological findings.

The mean age of the patients was 10 years, 9 months (range: 5 years, 4 months to 16 years). The mean duration of symptoms before referral was 26±12 days (range: 4-40 days). The majority of patients presented with macroscopic hematuria, hypertension, decreased urine output and edema (Table 1). Purpuric rash was also common among our patients. Laboratory values were as follows: mean serum hemoglobin levels at the time of diagnosis, 9.43±2.52 g/dL (range: 2.6-14g/dL); erythrocyte sedimentation rate, 93.60±34.89 mm/hour (range: 10-150 mm/hour); and CRP levels, 31.51±34.87 mg/L (range: 1.5-142 mg/L). Urinary protein excretion over a 24-hour period ranged from 2 mg/m^2 per hour to 212 mg/m^2 per hour, with an average of 99.57±60.98 mg/m^2 per hour; the serum albumin level was 2.53±0.73 g/dL (1-4 g/dL). Serum creatinine levels at presentation ranged from 0.27 to 11 mg/dL (mean: 3.19±2.6 mg/dL). GFR was calculated using the Schwartz formula; the mean GFR was 40.55±30.11 mL/min per 1.73 m^2 (range: 4.85-125 mL/min per 1.73 m^2). Laboratory parameters of patients at admission are summarized in Table 1.

Immune complex glomerulonephritis was the most common etiology in patients, with Henoch–Schonlein purpura nephritis (HSN) in 24 patients, membranoproliferative glomerulonephritis (MPGN) in 4, acute post-infectious glomerulonephritis (APIGN) in 3 and systemic lupus erythematosus (SLE) nephritis in 2. Three patients had pauci-immune CsGN and 9 had idiopathic CsGN.

Except for the 2 patients with APIGN, all patients received intravenous pulses of methylprednisolone (30 mg/kg per day, maximum: 1 g for 3 consecutive days) followed by oral prednisone (in tapering doses), iv cyclophosphamide (500-750 mg/m^2 per dose, monthly) or oral cyclophosphamide (2-3 mg/kg per day, for 2-3 months) as induction therapy. Plasmapheresis was performed on 4 patients with pulmonary involvement. Details of therapy are given in Table 2. At the end of the follow-up period, 26 patients achieved remission (21 complete, 5 partial). Despite intensive immunosuppressive and supportive treatment, 19 patients (42.2%) developed CKD, and 14 of these patients progressed to end-stage renal disease (ESRD), requiring renal replacement therapy (7 peritoneal dialysis, 2 hemodialysis and 5 renal transplantation).

The clinical and laboratory risk factors affecting the prognosis are shown in Table 3. Neither sex nor age had a significant effect on prognosis. Adverse outcome was significantly associated with a long duration between the onset of symptoms and initiation of treatment (*P*=0.038), the presence of oliguria (*P*=0.006), macroscopic hematuria (*P*=0.007), severely decreased GFR (<30 mL/min per 1.73 m^2) (*P*=0.008),

Table 4. Relation between histopathological findings and prognosis

Variables	CKD- (*n*=26)	CKD+ (*n*=19)	*P*	Odds ratio (95 % CI)
Ratio of crescents, mean, % (range)	61 (50-100)	92 (50-100)	0.002	1.069 (1.024-1.116)
Ratio of cellular crescents, mean, % (range)	62 (0-100)	10 (0-100)	0.011	0.974 (0.954-0.994)
Ratio of fibrocellular crescents, mean, % (range)	36 (0-86)	42 (0-100)	0.684	1.004 (0.983-1.026)
Ratio of fibrous crescents, mean, % (range)	0 (0-61)	12 (0-90)	0.015	1.044 (1.009-1.081)
The number of the patients with crescent ratio ≥75%, *n* (%)	10 (38.5)	16 (84.2)	0.003	8.000 (1.839-34.793)
The number of the patients with fibrinoid necrosis, *n* (%)	11 (42.3)	5 (26.3)	0.192	0.420 (0.112-1.565)
The number of the patients with tubuler atrophy, *n* (%)	10 (38.5)	12 (63.2)	0.108	2.800 (0.784-9.994)
The number of the patients with interstitial fibrosis, *n* (%)	14 (53.8)	14 (73.7)	0.186	0.694 (0.168-2.864)
The number of the patients with tubular atrophy+interstitial fibrosis, *n* (%)	7 (26.9)	4 (21.0)	0.731	0.694 (0.168-2.864)

CKD: chronic kidney disease; CI: confidence interval.

Table 5. Factors affecting prognosis by multivariate logistic regression method

Variables	Odds ratio	95% confidence interval		Wald	*P*
		Lower limit	Upper limit		
Other causes of etiological diagnosis	1.000	-	-	-	-
HSN	0.002	0.00002	0.146	7.961	0.005
Idiopathic GN	0.439	0.026	7.294	0.329	0.566
Serum levels of creatinine	1.863	0.936	3.709	3.139	0.076
Duration between symptom onset and diagnosis	1.105	1.019	1.198	5.893	0.015

HSN: Henoch-Schonlein purpura nephritis; GN: glomerulonephritis. "-": other etiological factors were not included in this category of statistical methods because they were in a small number.

and the need for dialysis (*P*=0.003) on admission. Ten of 13 patients who required dialysis on admission developed CKD during the follow-up period. There was no significant prognostic relationship among age, gender, infection history, hypertension and massive proteinuria on admission with poor prognosis. Of the etiopathologies, HSN had the most favourable outcome.

The percentage of crescents ranged from 50% to 100% (mean: 77%±17.85%). The majority of children had cellular crescents (glomeruli with crescents: 43.31%±34.04%). The presence of cellular crescents was related to favourable prognosis (*P*=0.011). We evaluated the relationship between the histopathological findings and the outcome. The importance of the ratio and type of crescents and other histopathological findings is summarized in Table 4. Pathologic features associated with poor prognosis were the ratio of crescents (>75%; *P*=0.002) and the ratio of fibrous crescents (*P*=0.015). We also observed that the prognosis was worse in children who had crescents on biopsy specimens more than 75% (*P*=0.003)

The best predictors of CKD were determined by multivariate logistic regression analysis. The time between symptom onset and diagnosis was found to be the most important determinant of CKD. The development of CKD was significantly lower among patients with HSN (Table 5).

Discussion

While CsGN accounts for 5% of the reported fraction of renal biopsies,[1,2] 8.3% of the renal biopsies done over ten years at our centre were CsGN. This small difference may be related to the fact that our institute is a tertiary care hospital. Genetic and local factors may also affect the prevalence of the disease.

Unlike adult studies in which pauci-immune CsGN is the most common histopathological form, immune complex glomerulonephritis is the most common cause of CsGN in children. In concordance with the literature, 33 of our 45 patients were found to have immune-related CsGN, and HSN was the most common cause. Dewan et al[2] also reported that immune complex CsGN was the most common CsGN etiological entity, and APIGN was the most common cause. They concluded that APIGN was also the most common etiology in developing countries. Pauci-immune CsGN is less common, and anti-GBM glomerulonephritis is extremely rare in children. Williamson et al[9] showed that only 4 of the 2000 biopsies in 25 years were of anti-GBM glomerulonephritis. In our study, 9 patients (20%) were diagnosed with idiopathic CsGN, 3 patients (6.6%) with pauci-immune CsGN and none with anti-GBM glomerulonephritis. When we evaluated etiological factors, we found that the best prognosis was in patients in the immune complex group, especially

those with HSN. Consistent with our study, outcomes in patients with pauci-immune CsGN, MPGN and idiopathic CsGN are reported to be less favorable than those with HSN and SLE.[4,10,11]

Despite intensive immunosuppressive therapy, only 60%-70% of patients with CsGN have complete renal recovery.[1] Although 26 (57.8%) of 45 patients in our study achieved remission (21 complete and 5 partial), 19 (42.2%) developed CKD of varying stages. Among patients in the CKD group, 14 (73.7%) progressed to ESRD and required renal replacement therapy. These results are concordant with those of previous studies.

Early diagnosis is one of the most important factors predicting the long-term prognosis of CsGN.[4,10,11] Delay in diagnosis and treatment can have a major negative impact on the outcome owing to the rapidly progressive loss of renal function.[4] Therefore, early aggressive therapy is recommended.[10] Dewan et al[2] reported that the mean duration of symptoms before referral was 2.47 months and was related to delayed diagnosis. The majority of their patients were dialysis-dependent at presentation, and only 35% had normal serum creatinine levels at the last visit. They attributed this unfavorable outcome to the late referral of the patients.[2] In our study, the mean duration of symptoms before diagnosis was 26±12 days (4-40 days); as in the Dewan study,[2] development of CKD significantly increased with a delay in diagnosis.

Oliguria, anuria and hypertension are common in CsGN.[1] The presence and prolonged duration of oliguria may worsen the renal outcomes. Neild et al[12] demonstrated that oliguria was associated with a significantly poor outcome. Prolonged oliguria may be the cause of poor renal function on admission. In our study, 20 patients (44.4%) had oliguria anuria on admission, and oliguria significantly correlated with CKD (P=0.06). Hypertension is also a frequent feature of CsGN and was observed in 60%-80% of patients. In the report by El-Husseini,[13] hypertension was described as a significant risk factor affecting renal function. Of our patients, 28 (62.2%) were hypertensive at the beginning of the disease, but hypertension did not significantly affect the progression to CKD.

We also evaluated the effects of laboratory parameters [CRP, erythrocyte sedimentation rate (ESR) and hemoglobin levels] on the outcomes. In the adult study of Koyama et al,[14] CRP was found to be an important prognostic factor. Alexopoulos et al[15] reported that elevated levels of CRP negatively affected the response to treatment in idiopathic CsGN. In contrast to these reports, serum levels of CRP did not significantly impact the prognosis in our study (P=0.964). Correspondingly, hemoglobin levels and ESR were not important to the prognosis. Proteinuria, especially nephrotic range proteinuria, was related to shorter renal survival in the studies of El Husseini and Heilman.[13,16] Contrary to our expectations, proteinuria did not impact renal or patient outcomes significantly in our study. This finding can be attributed to inadequate collection of urine at the beginning of the disease owing to oliguria.

A strong predictor of the outcome for all types of CsGN is the severity of renal insufficiency at the beginning of treatment.[17-20] In a recent study, Ünal et al[21] reported that the initial serum urea and creatinine levels of patients who were nonresponsive to the treatment were significantly higher than those of patients who were responsive to treatment. Andrassay et al[22] reported decreased renal improvement despite aggressive immunosuppressive therapy when serum creatinine levels were more than 6 mg/dL upon admission. Dewan et al[2] showed that advanced renal failure requiring dialysis correlated with a high frequency of chronicity changes on renal biopsy, as evidenced by the presence of fibrocellular crescents. We observed a significant difference between patients who were responsive or nonresponsive to treatment with respect to mean serum creatinine levels (1.85 mg/dL *vs*. 3.9 mg/dL, respectively) and mean GFR (42 mL/min/1.73 m^2 *vs*. 23 mL/min/1.73 m^2, respectively). On admission, 13 of our patients required dialysis treatment, and 10 of them developed ESRD. Our study is consistent with other reports indicating that the degree of renal function impairment at presentation inversely correlates with the response to treatment and subsequent renal outcome.

In addition to demographic, clinical and laboratory variables, we examined the histopathological data on renal biopsies and their relationship to kidney function and prognosis. As reported in previous studies,[13,23] we found that the range and type of crescents correlated significantly with prognosis. In a study by the Southwest Pediatric Study Group,[23] the authors confirmed that the incidence of ESRD increased when the ratio of crescents reached 50% or more. Jennette et al[4] demonstrated that patient and renal recovery decreased with an increase in the ratio of crescents. Neild et al[12] reviewed 11 published CsGN series and confirmed that the extent of crescent formation negatively affected the recovery of renal function. Our findings were consistent with these studies. We also demonstrated that the ratio of fibrous and/or fibrocellular crescents inversely correlated with the response to treatment and development of ESRD. This finding is similar to that of the Southwest Pediatric Nephrology Study Group. They also observed that the incidence of CKD increased with the ratio of fibrous or fibrocellular crescents.[23] In addition to the crescent ratio and type, fibrinoid necrosis, tubular atrophy and interstitial fibrosis were reported to be important risk

factors for renal prognosis.[3,15,23] Although tubular atrophy was observed in 22 of 45 patients in our study, only 12 patients developed CKD; in contrast to the literature, this finding was not significant (P=0.108). Neither fibrinoid necrosis nor interstitial fibrosis affected the renal outcome in our patients. The patients who did not develop CKD had a smaller fraction of tubular atrophy and interstitial fibrosis on renal biopsy specimens.

In conclusion, CsGN continues to be a renal emergency, and the outcome in children remains poor. Prognosis mostly depends on early diagnosis and treatment, the degree of initial renal failure, renal histopathology and underlying disease. Recognizing the disease as soon as possible and applying prompt treatment are crucial. Renal recovery may be unfavorable despite intensive immunosuppressive treatment.

Funding: None.

Ethical approval: This research is performed according to *Declaration of Helsinki*. Local ethical committee of Dr Sami Ulus Childrens and Maternity Hospital indicated that this study does not need ethical approval.

Competing interest: None declared.

Contributors: Özlü SG wrote the body of the article under supervision of Aydoğ Ö and Demircin G. Çaltik A collected and analyzed data and Çakıcı E collected data. Bülbül M, Arda N and Öner A provided advices on medical aspects. All authors contributed to the design and interpretation of the study and to further drafts.

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Received June 22, 2014
Accepted after revision December 11, 2014