RESEARCH PAPER

Etiology and Outcome of Crescentic Glomerulonephritis

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Objective: To determine the etiology, course and predictors of outcome in children with crescentic glomerulonephritis (GN).

Study design: Retrospective, descriptive study.

Setting: Pediatric Nephrology Clinic at a referral center in Northern India.

Methods: Clinic records of patients aged <18 year with crescentic GN diagnosed from 2001-2010 and followed at least 12-months were reviewed. Crescentic GN, defined as crescents in ≥50% glomeruli, was classified based on immunofluorescence findings and serology. Risk factors for renal loss (chronic kidney disease stage 4-5) were determined.

Results: Of 36 patients, (median age 10 yr) 17 had immune complex GN and 19 had pauci-immune crescentic GN. The etiologies of the former were lupus nephritis (*n*=4), postinfectious GN (3), and IgA nephropathy, Henoch Schonlein purpura and membranoproliferative GN type II (2 each). Three patients with pauci-immune GN showed antineutrophil cytoplasmic antibodies (ANCA). Rapidly progressive GN was present in 33 patients, and required dialysis in 12. At median 34 (19-72) months, 2 patients with immune complex GN and 8 with pauci-immune GN showed renal loss. Renal survival was 94.1% at 3 yr, and 75.3% at 8 yr in immune complex GN; in pauci-immune GN survival was 63.2% and 54.1%, respectively (*P*=0.054). Risk factors for renal loss were oliguria at presentation (hazards ratio, HR 10.50; P=0.037) and need for dialysis (HR 6.33; *P*=0.024); there was inverse association with proportion of normal glomeruli (HR 0.91; *P*=0.042).

Conclusions: Pauci-immune GN constitutes one-half of patients with crescentic GN at this center. Patients with pauci-immune GN, chiefly ANCA negative, show higher risk of disease progression. Renal loss is related to severity of initial presentation and extent of glomerular involvement.

Key words: *Antineutrophil cytoplasmic antibody, Rapidly progressive glomerulonephritis, Vasculitis.*

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Crescentic glomerulonephritis (GN), characterized by rapidly progressing renal failure, is relatively rare in childhood. Reports are limited to case series with scant information on long-term course [1-5]. Crescentic GN in children is commonly secondary to postinfectious GN, Henoch Schonlein purpura and IgA nephropathy [1,3,4]. While pauci-immune crescentic GN is common in adults [6,7], there are few reports of this condition in children [2,3].

In 1992, we described our experience on the clinical features and renal histology in 43 consecutive patients with crescentic GN [4]. Immunofluorescence examination showed immune complexes in 17 of 20 cases; testing for antineutrophil cytoplasmic antibodies (ANCA) was not available. Outcomes were unsatisfactory irrespective of etiology, with progressive renal impairment in 86% cases. During the last decade we have noticed a reduction in proportion of patients with postinfectious GN and increasing occurrence of pauci-immune crescentic GN. While recent reports are limited [1,8], prompt diagnosis and intensive therapy has resulted in better patient outcomes. The present report describes the etiological profile and clinical course among 36 patients with crescentic GN evaluated at this centre. The short-term course in nine patients has been reported elsewhere [9].

METHODS

Hospital records were reviewed to identify children (<18 years) diagnosed with crescentic GN between June 2001 and June 2010 and followed for at least 12-months. Records were reviewed for clinical and biochemical features, therapies received and course. Blood was examined for levels of creatinine, electrolytes, complement C3, antistreptolysin O and antinuclear antibodies. Prior to 2006, ANCA were screened by immunofluorescence; later enzyme immunoassay for myeloperoxidase and proteinase-3 were also performed [10]. Standard definitions were used for hematuria (>5

erythrocytes/high power field of centrifuged specimen), proteinuria (protein to creatinine ratio, Up/Uc ≥0.2 mg/mg), nephrotic syndrome (edema, proteinuria 3-4+ or Up/Uc >2.0, and serum albumin <2.5 g/dL) [11] and hypertension (blood pressure >95th percentile for age, gender and height) [12].

Histology: Light microscopy examination was considered adequate in presence of at least one core with ≥10 glomeruli. Crescents were defined as proliferation of parietal cells forming two or more cell layers in the Bowman space; crescentic GN was the presence of crescents in 50% or more glomeruli [6]. Specimens were examined for cellularity of crescents, sclerosis, neutrophil infiltration, fibrinoid or tuft necrosis, mesangial or endocapillary hypercellularity and tubulointerstitial changes. Immunofluorescence (IF) examination was done for pattern and intensity of staining for immunoglobulins, C3 and C1q. Based on staining of immune deposits and serology, histology was classified as immune-complex GN (granular deposits of immune complexes along capillary wall and mesangium), pauci-immune GN (scant or no deposits, with or without positive ANCA) and anti-glomerular basement membrane GN (linear antibody deposits). Standard criteria were used for systemic lupus erythematosus (SLE), Henoch Schonlein purpura and Wegener's granulomatosis [13,14].

Therapy

Management included maintenance of fluid and electrolyte balance, dialysis if indicated, and therapy of coexisting infections and hypertension.

Pauci-immune GN. Remission was induced with 3-6 pulses of IV methylprednisolone (15-20 mg/kg, maximum 1 g/day), followed by IV cyclophosphamide (500-750 mg/m^2) for 6 doses at 3-4 week intervals, and oral prednisone (1.5 mg/kg/day for 4 weeks, tapered to alternate-day). Patients who were dialysis dependent also received double-volume plasma exchange for 7 days. During the maintenance phase, patients received either azathioprine (2 mg/kg/day) or mycophenolate mofetil (500-750 mg/m^2/day) for two or more years. Additional therapies included IV immunoglobulin and rituximab in one patient with Wegener's granulomatosis.

Immune complex crescentic GN. Initial therapy with IV methylprednisolone was followed by tapering doses of oral steroids for 6 months. Patients with crescentic GN secondary to SLE, IgA nephropathy and HSP received IV cyclophosphamide for 6 months, followed by long-term therapy with azathioprine or mycophenolate mofetil. Patients with postinfectious GN also received oral cyclophosphamide (2 mg/kg/day) for 12 weeks.

Monitoring and Follow up: Patients were followed every 3-6 months. Outcome at last follow up was categorized as: (*i*) complete recovery (urine protein nil/trace; serum albumin >2.5 g/dL and estimated GFR >90 mL/min/1.73 m^2), (*ii*) partial recovery (abnormal urinalysis: microscopic hematuria, ≥1+ proteinuria; hypertension; or estimated GFR 60-90 mL/min/1.73 m^2), (*iii*) chronic kidney disease (CKD) stage 3 (GFR 30-60 mL/min/1.73 m^2) and (iv) renal loss: CKD stage 4 or 5 (GFR <30 mL/min/1.73 m^2).

Statistical analysis: Data were analyzed using STATA 11.0 (College Station, Texas). Summary statistics are presented as median (interquartile range, IQR). Clinical features were compared using chi square and ranksum tests; renal survival (free of renal loss) was compared using Kaplan Meier analyses. Factors impacting outcome were examined by Cox regression and reported as hazards ratios (HR) with 95% confidence intervals (CI).

RESULTS

Of 36 patients with crescentic GN, 21 were boys. The median (IQR) age at onset of disease was 10 (8-11.5) years; 15 (41.7%) children were younger than 10 years. The clinical and laboratory features are presented in ***Table* I**. Based on histopathology and IF examination, immune complex GN and pauci-immune crescentic GN were present in 17 and 19 patients, respectively. Fifteen (88.2%) patients with the former and 18 (94.7%) with the latter presented with rapidly progressive GN; 3 had puffiness and mildly impaired renal function. Six patients in each group had systemic symptoms at presentation, including one with Wegener's granulomatosis. Thirteen patients with pauci-immune GN had isolated renal involvement.

Histology: Adequate tissue for histopathology was available in 35 patients; renal biopsy in one showed only 4 glomeruli, 3 of which had crescents. The median (IQR) proportion of glomeruli showing crescents was 62% (50-89%) in patients with immune complex GN and 67% (50-96%) in pauci-immune crescentic GN; crescents involving >80% glomeruli were seen in 6 and 7 cases, respectively. In immune complex GN, crescents were cellular and fibrocellular in 8 patients each (47.1% each); one patient showed fibrous crescents. The proportion of sclerosed and normal glomeruli was 20% (0-41%) and 14.5% (0-29%), respectively. Tubular atrophy and interstitial fibrosis was noted in 10 biopsies, while 8 showed chronic inflammatory infiltrate.

Biopsies in patients with pauci-immune crescentic GN showed cellular (*n*=11, 57.9%), fibrocellular (*n*=6, 31.6%) or fibrous (*n*=2, 10.5%) crescents. The median proportion of sclerosed and normal glomeruli was 8.5%

TABLE I PATIENT CHARACTERISTICS AT PRESENTATION

Characteristic	*Immune complex GN (n=17)*	*Pauci-immune crescentic GN (n=19)*	*P*
Boys	11 (64.7)	10 (52.6)	0.46
Age, y	11 (10-12)	9 (7-11)	0.09
Duration of symptoms, weeks	8 (3-21)	4 (3-16)	0.57
Oliguria	9 (52.9)	12 (57.9)	0.77
Gross hematuria	9 (52.9)	12 (63.2)	0.54
Fever	6 (35.9)	10 (52.6)	0.30
Seizures, encephalopathy	3 (17.7)*	1 (5.3)	0.24
Rash	6 (35.3)	4 (21.1)	0.46
Arthralgia	2 (11.8)	2 (10.5)	0.91
Hypertension	10 (58.8)	16 (84.2)	0.14
Creatinine, mg/dL	1.8 (1.2-4.8)	3.9 (1.7 - 5.3)	0.24
Nephrotic range proteinuria	13 (76.5)	15 (83.3)	0.69

*Categorical variables are shown as number (percentage) and continuous variables as median (interquartile range); *2 with hypertensive encephalopathy; 1 with systemic lupus erythematosus.*

(IQR 0-40%) and 5% (0-21%) respectively. Tubular atrophy and interstitial fibrosis were seen in 14 (73.7%) and 12 (63.2%) biopsies. Fibrin deposition was present in 12 (63.2%) cases and tuft necrosis in 4 biopsies. Faint deposits of C3 and IgM were seen in 3 and 1 patients, respectively.

Immune complex GN was secondary to SLE in 4 patients, and IgA nephropathy, Henoch Schonlein purpura and membranoproliferative GN type II in two cases each; GN was postinfectious in 3 cases and idiopathic in 5 patients. Three patients with pauci-immune crescentic GN were ANCA positive. Two patients had microscopic angiitis based on constitutional symptoms and specificity against myeloperoxidase and one with chest infiltrates and specificity against proteinase-3 was diagnosed as Wegener's granulomatosis. Serology for ANCA was negative in 16 patients with pauci-immune GN.

Twelve (33.3%) patients required dialysis at presentation. Eight patients, all with pauci-immune GN, underwent plasma exchanges. Therapy for induction included IV methylprednisolone (*n*=31; 86.1%), IV cyclophosphamide (27; 75%) and oral cyclophosphamide [4]. Maintenance immunosuppression included oral prednisolone (36; 100%), azathioprine (18; 50%) and mycophenolate mofetil (11; 30.6%).

The outcome at last follow up, at 34 (19-72) months, is shown in ***Table* II**. Seven (19.4%) patients had complete recovery, while 10 (30.6%) had CKD 4-5. The latter includes 3 patients who were followed for 53-121 months after renal transplantation. ***Fig.* 1** shows that renal survival was 94.1% at 1, 3 and 5-yr, and 75.3% at 8 and 10-yr in patients with immune complex crescentic GN. Renal survival in patients with pauci-immune GN was lower at 63.2% at 1 and 3-yr, and 54.1% at 5 and 8-yr (log rank test; *P*=0.054).

On univariate analysis, factors predicting renal loss were presentation with oliguria (HR 10.5; 95% CI 1.16-95.25; *P*=0.037), need for dialysis at presentation (HR 6.33; 1.27-31.57; *P*=0.024), and the proportion of glomeruli showing fibrous or fibrocellular crescents (HR 4.74; 0.99-22.52; *P*=0.050). Renal loss was inversely correlated to the proportion of normal glomeruli (HR 0.91, 0.83-0.99; *P*=0.042). There was no relation between renal loss and the presence of hypertension (*P*=0.22) at disease onset.

DISCUSSION

The present report describes the etiology and outcome of disease in children with crescentic GN evaluated at a single center over nine years. A similar proportion of patients had pauci-immune and immune complex GN. These findings are in contrast to previous case series in children (***Web Table* I**) showing that immune complex GN constitutes the majority of cases with crescentic GN. The causes for immune complex GN are varied and include post-infectious GN, systemic lupus erythematosus, IgA nephropathy, Henoch Schonlein syndrome and membranoproliferative GN [1-5, 8, 15]. Pauci-immune crescentic GN, characterized by absence of significant glomerular immune deposits, is a severe illness that represents an important cause of crescentic GN in adults [6,7,16,17]. Data on pauci-immune crescentic GN is limited in children, with most previous reports suggesting that these account for 4.6-20% of all cases [1-3,5,8]. Therefore our finding, that pauci-immune GN constitutes more than one-half of all cases with

TABLE II OUTCOME AT LAST FOLLOW UP

	Immune complex GN (n=17)	*Pauci-immune crescentic GN (n=19)*
Normal renal function and urinalysis	4 (23.5)	3 (15.8)
Abnormal urinalysis or hypertension	7 (41.2)	5 (26.3)
Chronic kidney disease stage 2-3	4 (23.5)	3 (15.8)
Chronic kidney disease stage 4-5	2 (11.8)	8 (42.1)

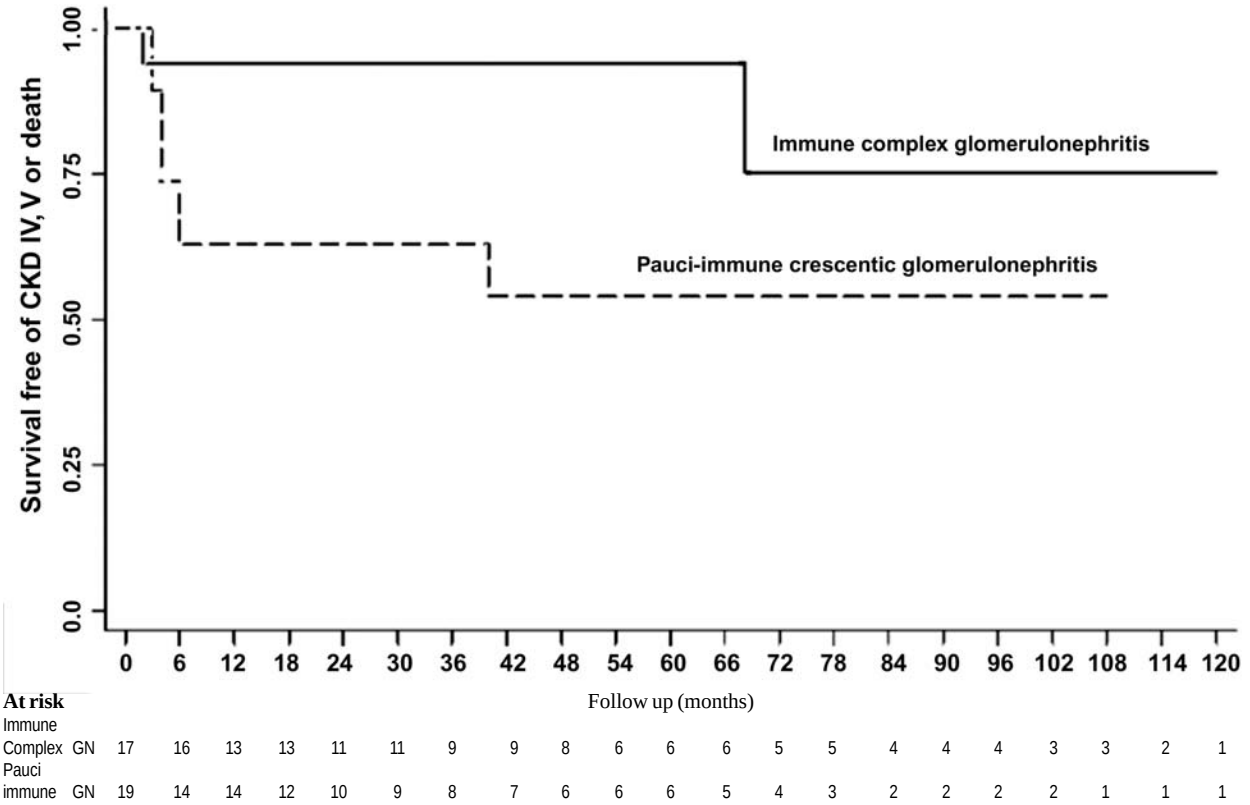

FIG. 1 *Kaplan Meier survival estimates for proportion of patients with renal loss (chronic kidney disease stage 4 and 5) or death in patients with immune complex (solid line) and pauci-immune crescentic glomerulonephritis (interrupted line) (log rank test P=0.054).*

crescentic GN, suggests a changing etiologic profile of the illness in children. However, the change in proportions might reflect a decline in rates of post-infectious GN [18]. Alternatively, it may represent a referral bias, with more cases with severe presentation, and therefore, a higher proportion of patients with pauci-immune crescentic GN, being referred to a tertiary care center.

A large proportion of patients with pauci-immune crescentic GN have circulating ANCA. Since early 1990s, the application of immunofluorescence and ELISA to detect ANCA and define its specificities, has allowed diagnosis of ANCA-associated vasculitis, including microscopic polyangiitis, Wegener's granulomatosis and renal limited vasculitis [6, 10, 14]. However, a recent review suggests that 10-30% patients with pauci-immune GN are negative for ANCA [19]. Compared to those who are ANCA positive, patients with negative serology are younger, show less constitutional and extrarenal symptoms, have higher proteinuria and severe lesions on histology, and an unsatisfactory renal survival [19, 20]. A recent report from northern India showed that 21 of 48 adults with pauci-immune rapidly progressive GN were negative for ANCA [21]. The diagnosis of ANCA negative serology is chiefly based on negative results on immunofluorescence [19-22]. Based on this examination, and confirmed in most by specific ELISA, 84.2% of the present patients with pauci-immune GN were negative for ANCA. While the outcome of patients with ANCA negative pauci-immune crescentic GN is considered unsatisfactory, we did not demonstrate differences in view of small patient numbers.

Outcomes in crescentic GN are generally unsatisfactory and progressive renal failure has been seen in 18.9-86% (***Web Table* I**) [1-5,8,15]. One-third of the present patients, followed for median duration of three years, progressed to CKD 4-5. Compared to our previous experience [4], the improved outcomes may reflect intensive immunosuppressive therapy and early institution of dialysis and/or plasmapheresis. We also found that outcome of patients with pauci-immune GN was less satisfactory compared to immune complex GN.

WHAT IS ALREADY KNOWN?

- Rapidly progressing glomerulonephritis, characterized pathologically by crescentic glomerulonephritis, is an important cause of acute kidney injury in childhood.
- The commonest cause of crescentic glomerulonephritis in childhood is post-infectious glomerulonephritis, associated with deposition of immune complexes.

WHAT THIS STUDY ADDS?

- Pauci-immune crescentic glomerulonephritis is an important cause of crescentic glomerulonephritis in children.
- A large proportion of patient with pauci-immune crescentic glomerulonephritis may be negative for antineutrophil cytoplasmic antibodies.
- The outcome of patients with pauci-immune crescentic glomerulonephritis is unsatisfactory compared to those with immune complex crescentic glomerulonephritis.

Of 19 patients with the former, 8 progressed to CKD stage 4-5, compared to only 2 of 17 with the latter. The findings are similar to that in adult patients, where pauci-immune GN has inferior outcome compared to immune complex GN [6]. While the cellularity of crescents is a marker of outcome [1-3], the proportion of fibrous and fibrocellular crescents was similar in pauci-immune and immune complex GN (42.1% *versu*s 53%) and was unlikely to account for difference in outcomes. Other predictors of prognosis in the present cases were similar to those reported previously, including dialysis dependence at onset [2, 4, 6] and proportion of normal glomeruli [23].

The current report highlights the change in etiological profile of crescentic GN in children that mirrors trends in adult onset disease. The distinction between subtypes based on immunofluorescence and serological findings has important implications for therapy and outcome. Patients with pauci-immune GN show a higher risk of progressive kidney disease. Further studies are necessary to characterize the natural history of disease in children with ANCA-negative pauci-immune crescentic GN.

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