Idiopathic collapsing glomerulopathy: A clinicopathologic analysis of 30 cases

A. Ahuja, R. Gupta, A. Sharma, A. Bagga[1], D. M. Bhowmik[2], S. K. Agarwal[2], A. K. Dinda

Departments of Pathology, [1]Paediatrics, and [2]Nephrology, All India Institute of Medical Sciences, New Delhi, India

ABSTRACT

Collapsing glomerulopathy (CG) is a distinct clinicopathologic entity associated with various infections, medications and acute ischemia. There have been few scattered reports of CG from India. This study aimed at evaluating the clinicopathologic features of idiopathic CG in Indian patients with comparison between adult-onset and childhood CG. This study included all cases of idiopathic CG diagnosed over a period of 4 years (2006-2009). Appropriate clinical details and laboratory findings were retrieved. Renal biopsies were reviewed and detailed pathologic features assessed. Statistical analysis was performed to compare various features between adult-onset and childhood CG. Over these 4 years, 30 cases of idiopathic CG were diagnosed. Of these, 11 were children. Childhood CG cases had longer duration of symptoms and lower serum urea and creatinine levels compared with adult patients. In renal histology, tubular atrophy and interstitial fibrosis was frequent in our cases. Pediatric cases of CG showed a higher proportion of segmental glomerulosclerosis. On clinical follow-up, nine of the 30 patients progressed to end-stage renal disease and these included two pediatric patients. Idiopathic CG is a significant cause of renal dysfunction in both pediatric and adult patients. Childhood and adult-onset CG differ in few clinicopathologic features. Early and accurate diagnosis of CG is imperative for appropriate management of these patients.

Key words: Collapsing, glomerulopathy, idiopathic, histology, prognosis

Introduction

Collapsing glomerulopathy (CG) was initially described in association with human immunodeficiency virus (HIV) infection and classified as a variant of focal and segmental glomerulosclerosis (FSGS). Recent studies have shown that CG is a distinct clinicopathologic entity with three variants: Idiopathic, genetic and reactive.[1] Idiopathic CG, with incidence of about 1%, has a dysregulated phenotype of podocytes with expression of proliferation marker, Ki-67.[2] Extensive search of the available indexed English literature yielded few scattered reports of CG from our country. However, a detailed analysis of idiopathic CG in Indian patients is lacking in the available literature.

CG has been shown to be an aggressive disease with relatively worse renal outcome.[3,4] A study also showed a correlation of renal outcome of CG with interstitial fibrosis, high serum creatinine and heavy proteinuria.[3] There have been no reports of a comparison of childhood and adult-onset CG with respect to the clinicopathologic features.

The present study describes the clinicopathologic features of 30 patients of idiopathic CG, the largest series from this subcontinent. In addition, an attempt is made to compare these features between childhood and adult-onset CG.

Materials and Methods

All native kidney biopsies diagnosed as idiopathic CG over 4 years (2006-2009) were retrieved. Detailed clinical and laboratory findings were reviewed. Over the duration of 4 years, 30 cases of CG were diagnosed as idiopathic among the 3314 renal biopsies evaluated in the department and were included in this study. The histologic criteria for diagnosis of CG was the demonstration of at least one glomerulus with segmental or global capillary tuft collapse, with hyperplasia and hypertrophy of the

Address for correspondence:
Dr. Amit K. Dinda, Department of Pathology,
All India Institute of Medical Sciences,
Ansari Nagar, New Delhi - 110 029, India.
E-mail: amit_dinda@yahoo.com

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overlying visceral epithelial cells (podocytes) exhibiting features of activation.

Detailed demographic and clinical data were recorded for all the cases, including clinical presentation, course of disease, therapeutic approach and renal outcome at the last follow-up. Results of laboratory investigations including viral serology (hepatitis B, C, HIV, parvovirus), tests for autoimmune diseases (antinuclear antibody, anti-dsDNA, antineutrophil cytoplasmic antibody) and renal function tests (serum creatinine, urea, 24-h urinary protein excretion, urinalysis etc.) were recorded.

The renal biopsy slides (stained with H and E, Periodic Acid Schiff, Jones silver methenamine and Masson's trichrome) were reviewed and the following information recorded: Total number of glomeruli; proportion of globally sclerosed glomeruli, glomeruli with CG, glomeruli showing FSGS without collapse; tubular atrophy and interstitial fibrosis, interstitial inflammation, presence of tubular dilatation, casts, necrosis or degeneration; and vascular changes. The results of direct immunofluorescence examination (in all cases) and ultrastructural studies (performed in a subset of patients) were reviewed.

Statistical analysis

SPSS 17.0 software (SPSS Inc., Chicago, USA) was used for performing the statistical analysis. Categorical data was analyzed using Chi-square test and numerical data was compared using Student's *t*-test. Adult-onset and childhood cases (<14 years of age at diagnosis) of CG were compared for clinical and biochemical parameters. $P < 0.05$ was considered to be significant.

Results

Of the 3314 native kidney biopsies received during the study period, 30 cases were diagnosed as idiopathic CG (0.9%). The mean age of patients was 27.35 years (±16.5 years). Of the 30 patients, 11 were children (mean age 7 ± 4.7 years). There was a male predominance (M:F 5:1). The duration of symptoms at the time of clinical presentation varied from 10 days to 12 months (median duration 2 months). Hypertension at presentation was noted in 18 patients (60%) while 10 patients (33.3%) had a reduction in the urinary output [Table 1].

Urinalysis revealed microscopic hematuria in all 30 cases (100%) with active sediments in the form of red cell casts (RBC) and/or >30% dysmorphic RBCs in 12 cases (40%). Nephrotic-range proteinuria was noted in 16 patients (53.3%) and subnephrotic in the rest of the cases. The mean 24-h urinary protein excretion was 3.98 g (±1.57 g). Derangement of renal function tests was frequent in our patients. The mean serum urea was 95.3 mg/dl (±52.9 mg/dl) while serum creatinine was 4.86 mg/dl (±3.93 mg/dl).

The clinical and biochemical parameters were compared between childhood CG (11 cases) and adult-onset CG (19 cases). The duration of symptoms was marginally higher in pediatric patients with CG (6.5 ± 2.1 months) compared with 4.24 ± 2.1 months in adult patients ($P = 0.053$). The mean serum urea and creatinine were significantly different between pediatric and adult patients. Serum urea in children was 48.5 ± 6.39 mg/dl compared to 115.36 ± 13.5 mg/dl in adults ($P = 0.0057$) while serum creatinine was 1.88 ± 0.25 mg/dl in pediatric patients as against 6.12 ± 1.08 mg/dl in adult patients ($P = 0.022$). Quantitative 24-h urinary protein excretion was similar in both groups (3.45 ± 1.36 g/24 h in children and 4.29 ± 1.75 g/24 h in adults, $P = 0.31$) [Table 2].

Renal histology

Renal biopsy in all the included cases was adequate with a mean of 13.3 glomeruli (±1.66) per biopsy. The number of obsolescent glomeruli (globally sclerosed) in these cases was 2.9 ± 0.98. Glomerular collapse with hyperplasia/hypertrophy of the overlying podocytes [Figure 1a-d]

Table 1: Clinical features of patients with collapsing glomerulopathy

Parameter	No. of cases (%)
Hypertension	18 (60)
Microscopic hematuria	30 (100)
Urinary active sediments	12 (40)
Oliguria	10 (30)
Nephrotic range proteinuria	16 (53.3)

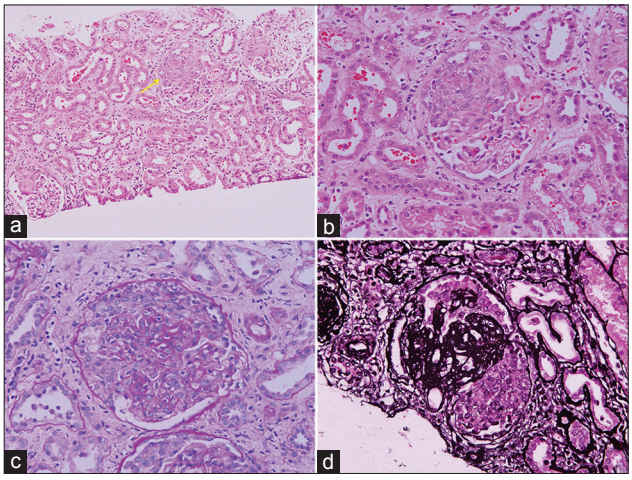

Figure 1: Panel of photomicrographs showing a glomerulus with collapse (arrow) of the tuft (a) H and E, ×100), better appreciated at higher magnification (b) H and E, ×400. Periodic acid schiff stain demonstrates the podocyte hypertrophy and collapse of tuft (c) PAS ×400. Silver methenamine stain highlights the collapsed tuft and marked podocyte hypertrophy (d) SM ×400

was seen to involve a mean of 4.1 ± 0.76 glomeruli in our study. In addition, 2.25 ± 0.46 glomeruli showed segmental sclerosis without features of collapse.

Tubulointerstitial changes were frequent in our cases. Tubular atrophy (involving >25% of the cortical area) was noted in 12 cases (40%) with marked atrophy (>50% of cortical area) in two cases. Rest 18 cases showed minimal to mild tubular atrophy (<25% of cortical area). Tubular dilatation with the formation of intratubular casts [Figure 2a] was seen in nine biopsies (30%). Three cases each (10% each) showed features of acute tubular necrosis and regenerative features in tubular epithelial cells. Interstitial fibrosis of variable degree was noted in all cases. The fibrosis was mild (<25% of cortical area) in 18 cases (60%), moderate (26-50% of cortical area) in nine (30%) and marked in three biopsies (10%). Accompanying lymphocytic interstitial inflammation was seen in 26 cases (86.67%).

The histological features were compared between childhood and adult-onset CG. Renal biopsies of pediatric patients with CG showed significantly higher proportion of glomerular segmental sclerosis without collapse (26.75 ± 5.9% in childhood vs. 12.95 ± 3.6 in adult-onset CG, $P < 0.001$). Other features like proportion of glomeruli with collapse, tubulointerstitial fibrosis and interstitial inflammation were similar in both groups.

Table 2: Clinical and biochemical parameters between childhood and adult-onset CG

Parameter	Childhood CG	Adult-onset CG	*P* value
Duration of symptoms (months)	6.5±2.1	4.2±2.1	0.053
Serum urea (mg/dl)	48.5±6.3	115.3±13.5	0.0057
Serum creatinine (mg/dl)	1.88±0.25	6.12±1.08	0.022
24 h proteinuria (g/day)	3.45±1.36	4.29±1.75	0.31

CG: Collapsing glomerulopathy

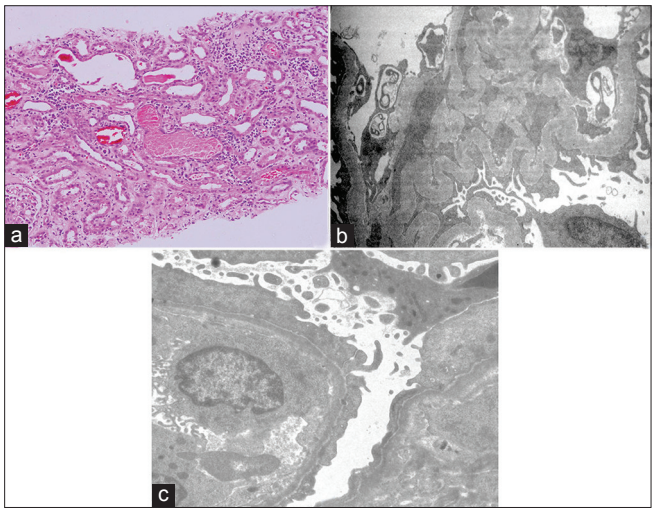

Figure 2: Photomicrograph demonstrating the tubulo-interstitial changes (a) H and E, ×100. Ultrastructural photomicrograph showing folded glomerular basement membrane with loss of foot processes of the overlying podocytes (b) uranyl acetate-lead citrate ×10,000). Higher magnification better demonstrates the loss of foot processes of podocytes and microvillus transformation (c) uranyl acetate-lead citrate ×16,000)

Immunofluorescence showed mesangial deposits of IgM and C3 in 27 cases. IgA and IgG were negative in all cases.

Electron microscopic examination could be performed in 12 cases. These cases showed endothelial swelling, marked effacement of podocyte foot processes, degenerative changes like cytoplasmic vacuolation and microvillous transformation of podocytes. In addition, wrinkling and collapse of glomerular capillary loops [Figure 2b and c] was seen in eight cases where the glomerulus involved by CG was included in the ultrathin section. None of the cases examined showed tubuloreticular inclusions on ultrastructural examination.

Follow-up

All the 30 patients received oral steroid therapy. In addition, 14 patients received calcineurin inhibitors (cyclosporine or tacrolimus). The mean duration of follow-up in our cases was 12.85 months (±2.3 months). Of the 30 patients, nine progressed to end-stage renal disease (ESRD) requiring dialysis. These nine patients included two pediatric cases. The time to ESRD from the onset of disease varied between 3 and 24 months (median 13.3 months). On statistical analysis, occurrence of ESRD was not correlated with age at presentation, gender, serum creatinine and urea at diagnosis, degree of proteinuria or various histological features.

Discussion

CG was initially described as a variant of FSGS, later shown to be associated with HIV infection and included as HIV-associated nephropathy.[5] Later studies reported the occurrence of CG in HIV-negative patients and this entity was renamed as collapsing FSGS.[6] However, more recent reports have suggested that CG is a distinct clinicopathologic entity, unrelated to FSGS.[1] A recently proposed taxonomy for podocytopathies recognized three variants of CG: Idiopathic, genetic or reactive.[1] Genetic or familial CG has been described in association with arthritis or neurologic disease and mutations in COQ2 have been detected in this variant of CG suggesting mitochondrial dysfunction in CG.[7] The list of etiologies of reactive CG, which started with HIV infection, is ever-expanding with other factors including infections, medications and acute ischemia being added.[5]

Idiopathic CG is characterized by a dysregulated phenotype, manifested by loss of maturity markers such

as synaptopodin, podocalyxin and re-expression of early podocyte markers (PAX2 and cytokeratin) along with proliferation marker, Ki-67.[2,8] In addition, Wilms' tumor gene-1 expression is lost indicating functional phenotypic changes.[8] The incidence of idiopathic CG in previous studies is approximately 1%.[3,4,6,9] In the present study, idiopathic CG constituted 0.9% of all native kidney biopsies performed over the duration of 4 years. Review of the available indexed literature revealed a few reports of idiopathic CG from the Indian subcontinent, including a report of 10 cases in adults from Pakistan and another description of six pediatric cases from India.[10,11] However, a detailed clinicopathologic analysis of idiopathic CG in Indian patients is still lacking in the literature. This study represents the first such large clinicopathological study of 30 patients with idiopathic CG from this subcontinent.

The clinical presentation of patients in our study is in consonance with the previous reports. We found a male predominance with a mean age at presentation of 27.35 years. A study by Laurinavicius *et al*. and Valeri *et al*., also showed male preponderance with similar mean age at diagnosis.[3,4] The mean time to biopsy in our patients was 4.9 months, which is in agreement with 2.3 months in the study by Laurinavicius *et al*. and 7.9 months reported by Valeri *et al*.[3,4] In the present study, 36.7% of the patients were children (11 out of 30) compared with 23.2% (10 of 43 patients) in the report by Valeri *et al*.[4]

In the present study, an attempt was made to compare the clinicopathologic features of adult-onset and childhood CG. Among clinical features, childhood CG had a longer duration of symptoms prior to biopsy with lower serum urea and creatinine at diagnosis. Statistical analysis of pathologic features showed that childhood CG had a higher proportion of segmentally sclerosed glomeruli not involved by collapse ($P < 0.001$). This is the first time that adult-onset and childhood CG has been compared with respect to clinical and pathologic features.

CG has been known as an aggressive disease with relatively worse clinical outcome. The median renal survival of idiopathic CG is reported to be less than 18 months.[3,4] In the study by Valeri *et al*., the patients were followed for a mean duration of 32 months during which 51% of patients progressed to ESRD.[4] In our series, the mean follow-up duration was 13 months and nine patients (30%) progressed to ESRD at the end of this period. This included two pediatric patients. On statistical analysis, the progression to ESRD was not related to age at presentation, gender, serum creatinine and urea at presentation, degree of urinary protein excretion or histological features such as percentage of glomeruli with collapse, global or segmental sclerosis. In contrast, the study by Laurinavicius *et al*., (including HIV and non-HIV CG) showed relation of extensive interstitial fibrosis, high serum creatinine and high proteinuria with renal death. Presence of extensive collapsing lesions (>20% of glomeruli) showed a positive effect on renal survival suggesting partial reversibility of acute lesions with appropriate/aggressive therapy.[3]

In summary, we describe the clinicopathologic features of a large series of patients with idiopathic CG. Children constituted about one-third of all patients with idiopathic CG, thus implying that timely performed renal biopsy and early recognition of this entity is imperative in this age group as well. Approximately, one-third of the patients progressed to ESRD in our study. Considering the rapidly progressive course, poor prognosis and increasing incidence in non-HIV patients, early and accurate diagnosis of CG by the renal pathologist may assist in improving the renal outcome of these patients.

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