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Idiopathic collapsing glomerulopathy in children

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Abstract Idiopathic collapsing glomerulopathy (ICG) is a clinically and pathologically distinct variant of focal segmental glomerulosclerosis, characterized clinically by rapid progression of renal insufficiency, a male and African-American racial predominance, and pathologically by segmental glomerular collapse, visceral epithelial cell hypertrophy and hyperplasia, and the absence of endothelial tubuloreticular inclusions. Pathologically similar lesions have been reported in adult and pediatric patients with human immunodeficiency virus (HIV) infection and/or intravenous (IV) drug abuse. Most patients with ICG who have been reported in the literature are adults. Six children with ICG were retrospectively identified (two from East Carolina University, four from University of North Carolina-Chapel Hill). Clinical data and renal biopsy findings were reviewed for all patients. All six patients were male; five African-American and one Hispanic. Ages ranged from 2 to 17 years (mean 12 years). Steroid-resistant nephrotic syndrome was the presenting clinical finding. Average 24-h urine protein excretion was 6.3 g (range 3.2–15 g). Five patients were serologically negative for HIV infection (one patient not tested) and none had a history of IV drug abuse or known HIV risk factors. Progression to end-stage renal insufficiency in two patients within 1 year of biopsy required renal transplantation, and within 1 month of biopsy one patient required dialysis. We report a series of pediatric patients with ICG, an aggressive variant of focal segmental glomerulosclerosis. ICG in children is similar clinically and pathologically to this disease in adult patients.

Key words Idiopathic collapsing glomerulopathy · Focal segmental glomerulosclerosis

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Introduction

Idiopathic collapsing glomerulopathy (ICG) is a clinically and pathologically distinct variant of focal segmental glomerulosclerosis (FSGS), characterized clinically by rapid progression of renal insufficiency, a male and African-American racial predominance, and pathologically by segmental to global glomerular collapse, visceral epithelial cell hypertrophy and hyperplasia, and severe tubulointerstitial disease [1–3]. Pathologically similar lesions have been reported in adult and pediatric patients with human immunodeficiency virus (HIV) infection and/or intravenous (IV) drug abuse [4, 5]. Lesions with the histological finding of "glomerular collapse" were first described by Weiss et al. [6] in 1986 who reported six adult patients with nephrotic syndrome, progressive irreversible renal failure, and pathological features of glomerular capillary collapse with prominent visceral epithelial cell hyperplasia. However, in their report, with the exception of one patient reported to have developed acquired immunodeficiency syndrome (AIDS), the HIV status of the patients was not addressed. This led to speculation that the patients described may have had occult HIV nephropathy, because of the similarity between the glomerular lesions in the patients of Weiss et al. [6] and those with HIV-associated nephropathy. In 1994, Detwiler et al. [3] published the first complete report of ICG in 16 adult patients without evidence of HIV infection or IV drug abuse. More recent-

ly, Valeri et al. [1] reported a series of 43 patients with ICG, of which 10 were in the pediatric age group (less than 18 years old), with 4 younger than 12 years.

Materials and methods

We retrospectively identified six pediatric patients with no clinical or serological evidence of HIV infection or IV drug abuse with pathological features of collapsing glomerulopathy similar to those recently described by Detwiler et al. [3] and Valeri et al. [1]. These six patients form the basis of our report. From a total of 7,009 consecutive nontransplant renal biopsies evaluated at the University of North Carolina and at East Carolina University between December 1987 and December 1996, 754 (11%) cases of FSGS were identified, of which 43 (5.7%) were in the pediatric age group. Of these, 6 cases (14% pediatric FSGS cases, 0.8% of total FSGS cases) with pathological features of collapsing glomerulopathy were identified. Primary morphological criteria for diagnosis, based upon criteria previously defined by Detwiler et al. [3], were demonstration of focal segmental or global collapse of glomerular capillaries, with wrinkling and folding of basement membranes and visceral epithelial cell hyperplasia and hypertrophy in any glomeruli. The degree of accompanying tubulointerstitial injury (tubular atrophy, dilatation and simplification, interstitial fibrosis, and inflammation) was evaluated using a semiquantitative index based upon the percentage of biopsy surface area affected (1+<25%, 2+25%–50%; 3+>50%). Exclusion criteria included any serological evidence for HIV infection or any evidence of HIV risk factors or IV drug abuse. Medical records were reviewed for clinical data at initial presentation, time of biopsy, treatment, and clinical course. End-stage renal disease (ESRD) was defined as the time dialysis or renal transplantation was instituted. Clinical remission was defined as trace or absence of proteinuria.

All renal biopsies were processed via standard techniques for light, immunofluorescence, and electron microscopy. Light microscopic sections were evaluated at multiple levels using standard paraffin section techniques in five cases and plastic sections in one case, with hematoxylin and eosin, periodic acid-Schiff (PAS), trichrome, and methenamine silver stains.

Results

Renal biopsy findings

An average of 11 glomeruli per level of section were seen. The characteristic morphological finding was the presence of focal segmental or global glomerular capillary collapse with overlying hyperplasia and hypertrophy of adjacent visceral epithelial cells. These changes were present in 6%–50% of glomeruli. These features were best seen on PAS- and methenamine silver-stained sections (Fig. 1). There was no predilection for perihilar or glomerular tip regions to be affected in segmentally involved glomeruli. Hypertrophied epithelial cells often contained hyaline droplets and in some cases resembled crescents (Fig. 2). However, unlike true crescents, the proliferation involved visceral epithelial cells rather than parietal epithelial cells and continuity with Bowman's capsule. None of the uninvolved glomeruli revealed classic FSGS with perihilar sclerosis. Varying degrees of interstitial fibrosis, tubular atrophy, tubular dilatation and simplification, and mononuclear inflammation were seen. Variable numbers of proximal tubular epithelial cells contained prominent resorption droplets. No sclerotic changes were seen in blood vessels.

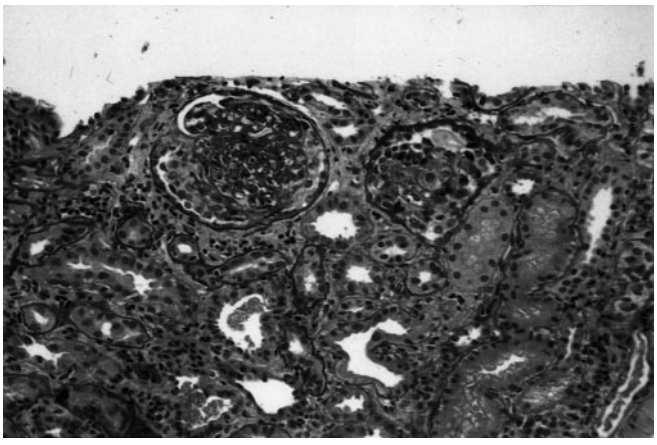

Fig. 1 Medium-power view of renal parenchyma with two glomeruli demonstrating characteristic morphological changes of focal segmental glomerular capillary collapse with overlying visceral hypertrophy and hyperplasia (periodic acid-Schiff stain, ×130)

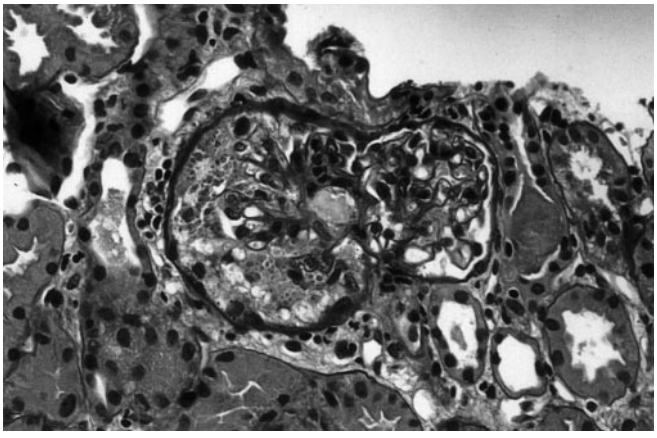

Fig. 2 High-power view of glomerulus with hypertrophied and hyperplastic visceral epithelial cells with cytoplasmic hyaline droplets (periodic acid-Schiff stain, ×260)

Immunofluorescence microscopy revealed irregular staining with antisera specific for IgM and C3 within collapsed glomerular segments in four cases. Resorption droplets in glomerular visceral and tubular epithelial cells often stained for immunoglobulin and complement. Electron-microscopic examination revealed wrinkling and collapse of glomerular basement membranes in affected segments along with variable visceral epithelial foot process effacement. No immune complex-type electron-dense deposits were seen. Ultrastructurally, none of the biopsies had endothelial cytoplasmic tubuloreticular inclusions.

Clinical findings

The mean age at diagnosis was 12 years (range 2–17 years) with two patients less than 12 years of age. All six patients were male. Five patients were African-American and one was Hispanic. All six patients presented with

nephrotic syndrome. Two patients manifested hypertension at the time of presentation. One patient had gross hematuria while one other had microscopic hematuria at presentation. The duration of symptoms prior to presentation was less than 3 months and the time from presentation to biopsy was less than 2 months. All six patients had received a trial of high-dose daily steroids (prednisone at 2 mg/kg per day) prior to renal biopsy and were steroid resistant.

The mean serum creatinine at presentation was 1.6 mg/dl (range 0.3–4.9 mg/dl). Average 24-h urine protein excretion was 6.3 g (range 3.2–15 g). The degree of proteinuria and serum creatinine level did not seem to be associated with ultimate renal outcome. In addition, the serum creatinine level at the time of presentation and/or biopsy did not correlate with the amount of glomerular collapse and/ or degree of tubulointerstitial damage present on biopsy.

All six had elevated serum cholesterol levels. One patient had a normocytic, normochromic anemia. None of the patients had liver transaminase elevation, hypocomplementemia, and serum electrolyte abnormalities. The four patients who were tested were all negative for hepatitis A, B, and C. It has been previously reported that IV drug abuse may be a cofactor in the development of HIV nephropathy. None of the six patients had a history of IV drug abuse. Five of the six patients had negative serological tests for HIV infection. The one patient not tested for HIV had neither risk factors for this virus at presentation nor has developed clinical evidence of HIV infection during follow-up.

Treatment and renal outcome

All patients in our series were treated with a trial of prednisone (2 mg/kg per day) at the time of presentation but were all steroid resistant. No remissions were achieved with steroid therapy alone. None of the patients received cytotoxic drugs (i.e., cyclophosphamide or chlorambucil). Two patients in our series were treated with cyclosporine (4–5 mg/kg per day for 6 months) after failure of prednisone to obtain a remission. Both patients treated with cyclosporine achieved remission.

Follow-up data were available on all six patients for an average of 36 months (range 24–72 months). In four of the six patients, progression to ESRD occurred within an average of 7 months from time of presentation, at which time two were on dialysis and two had received renal transplants. As stated previously, two of the six patients treated with cyclosporine had clinical remissions.

The two patients who underwent renal transplantation had normal serum creatinine values (0.8 mg/dl and 0.9 mg/dl) and no proteinuria at last follow-up (2 and 5 years post transplantation).

Discussion

FSGS represents a commonly occurring pattern of glomerular injury with a varied etiological, morphological, and clinical course [1, 2]. Distinction between primary and secondary forms of FSGS is critical with regard to both prognosis and therapy [2, 7–13]. In 1986, Weiss et al. [6] described six patients with nephrotic syndrome, progressive irreversible renal failure, and renal biopsy findings of glomerular capillary collapse and visceral epithelial cell swelling and hyperplasia, and suggested that this may represent a distinct clinicopathological entity. However, the HIV status of all but one patient, who developed AIDS, was not addressed, leading to speculation that these cases may have represented unrecognized HIV-associated nephropathy. In 1994, Detwiler et al. [3] published the first complete report of ICG. Valeri et al. [1] reported the largest series of ICG in which 43 patients were identified over a 20-year period. We have identified six pediatric patients with pathological findings identical to those in the series of Detwiler et al. [3] and Valeri et al. [1], and who have no serological and/or clinical evidence of HIV infection and IV drug abuse.

The recently published data from Valeri et al. [1] on 43 patients with ICG included 10 pediatric-age patients, of which 4 were 12 years or younger. However, their results were not stratified according to age, making comparison with our data difficult. Nonetheless, comparison of our clinical and renal biopsy data with published data from both the series of Detwiler et al. [3] and Valeri et al. [1] is summarized in Table 1. The following similarities are noted: in both children and adults, ICG is characterized by African-American racial predominance, relatively short duration of symptoms prior to presentation, high levels of proteinuria, and rapid progression to ESRD [1, 3]. Although the mean serum creatinine and 24-h protein excretion in urine at the time of presentation appears to be lower in our series, these values are not adjusted for body mass and therefore may not represent a statistically significant difference in values. In our series, the duration of symptoms prior to presentation and to renal biopsy was shorter than in the other two series (Table 1).

In our series, neither the serum creatinine at presentation nor the degree of proteinuria correlated with the ultimate renal outcome. The serum creatinine at the time of presentation and/or biopsy did not correlate with the amount of glomerular collapse or the degree of tubulointerstitial damage. This is in contrast to the series of Valeri et al. [1], in which there was significant and independent correlation between these parameters. Indeed, previous studies have documented that patients with noncollapsing FSGS, HIV-associated nephropathy, and various immune-mediated glomerular diseases have a more-aggressive course, with the presence of nephrotic-range proteinuria and increasing degrees of tubulointerstitial damage [14, 15]. In our patients with ICG, it is possible that the rate of progression and decline in renal function

Table 1 Comparative clinical data – idiopathic collapsing glomerulopathy (*ICG*) in children versus published series in adults (*ESRD* end-stage renal disease)

	Children (*n*=6)	Adults	
		Valeri et al. [1] (*n*=43)	Detwiler et al. [3] (*n*=16)
African-American race	83% (mean)	61% (mean)	81% (mean)
Duration of symptoms prior to presentation and/or biopsy	<2 months	7.9 months	<6 months
Time from onset to ESRD	7 months	13 months	15 months
Serum creatinine at presentation	1.6 mg/dl[a]	4.1 mg/dl	3.5 mg/dl
24-h protein in urine at presentation	6.3 g/24 h[a]	10.2 g/24 h	13.2 g/24 h

[a] Value not corrected for lean body mass

Table 2 Comparative treatment and outcome data – ICG in children, published series in adults

	Children (*n*=6)	Adults	
		Valeri et al. [1] (*n*=43)	Detwiler et al. [3] (*n*=16)
Treatment			
Steroids – remissions	6/6 (100%) none	26/43 (60%) none	4/14 (28%) 1/4 (25%)
Cyclosporine – remissions	2/6 (33%) 2/2 (100%)	3/43 (7%) 2/3 (66%)	0/14 (0%) –
Cyclophosphamide – remissions	0/6 (0%) –	6/43 (14%) 1/6 (17%)	1/14 (7%) 0/1 (0%)

occurred at such an accelerated pace, thus not allowing significant correlation of both degree of proteinuria and tubulointerstitial damage with progression to ESRD.

The histopathological findings in our series were similar to those previously described [1, 3, 6]. Focal segmental to global glomerular collapse with overlying visceral epithelial hypertrophy and hyperplasia was the hallmark and occurred in 6%–50% of glomeruli. The previously reported series described involvement of 8%–92% of glomeruli, with features of glomerular collapse and visceral epithelial hyperplasia [1, 3, 6]. Other subgroups of FSGS, including the classic and cellular variants, can also have glomeruli with collapsing features, but are reported to generally affect less than 20% of glomeruli and do not have the associated marked epithelial changes that are so characteristic of ICG [1, 2]. Features of classic perihilar scarring have also been reported to variably co-exist with collapsing lesions [1, 3, 5]. None of our patients demonstrated classic perihilar scarring in any glomeruli.

The striking similarities between the clinical and pathological findings in HIV-associated nephropathy and ICG have been well documented previously [1–6]. To rule out the possibility that our patients may actually represent unrecognized HIV-associated nephropathy, we documented seronegativity for HIV infection in five of the six patients. The one patient not tested serologically had no risk factors for developing HIV infection, including no history of IV drug abuse at the time of presentation. He has not developed clinical evidence of HIV infection during 2.5 years of follow-up. The absence of endothelial cytoplasmic tubuloreticular inclusions on renal biopsy is also evidence against HIV infection [5].

The etiological agent causing ICG remains unclear. The similarities with HIV-associated nephropathy have led to speculation that an infectious/viral agent common to patients with ICG and HIV-associated nephropathy may be involved. In a recent abstract, Moudgil et al. [16] reported, for the first time, the presence of parvovirus B19 DNA in 9 of 10 patients with ICG compared with 3 of 12 patients with FSGS and only 1 of 13 control patients [16]. The authors speculated that parvovirus B19 infection may be associated with the development of ICG.

Comparative treatment and outcome data are summarized in Table 2. All six patients in our series were treated with a trial of corticosteroids (2 mg/kg per day) at the time of presentation and all six were steroid resistant, achieving neither partial or complete remission. In the series of Detwiler et al. [3], 4 of 14 patients were treated with corticosteroids alone and only 1 achieved remission. In the series of Valeri et al. [1], of the 26 patients treated with corticosteroids, none achieved remission. No patients in our series received cytotoxic drugs (cyclophosphamide or chlorambucil). The 1 patient in the series of Detwiler et al. [3] treated with cyclophosphamide and corticosteroids did not achieve remission. In the series of Valeri et al. [1], of 6 patients treated with cyclophosphamide, 1 achieved partial remission (<1 g protein/day). Two patients in our series were treated with

Table 3 Comparative outcome data – ICG in children, published series in adults

	Children (*n*=6)	Adults	
		Valeri et al. [1] (*n*=43)	Detwiler et al. [3] (*n*=14)
Time from onset to ESRD	7 months	13 months	15 months
ESRD	4/6 (66%)	22/43 (51%)	8/14 (57%)
Dialysis	2/6 (33%)	15/43 (35%)	5/14 (36%)
Transplant	2/6 (33%)	7/43 (16%)	excluded from study
Remissions			
Treatment	2/6 (33%)	3/26 (11%)	0/14 (7%)
Spontaneous	0/6 (0%)	3/17 (18%)	9/14 (7%)

cyclosporine after failure of corticosteroids to achieve remission and both achieved complete remission. In the series of Valeri et al. [1], 2 of 3 patients (adults, personal communication) given cyclosporine achieved complete remission, with 1 patient having no proteinuria and the other with a urinary protein excretion of <1 gram protein/day. In a report of 15 children with HIV infection, 3 children with FSGS with collapsing features were treated with cyclosporine and all achieved clinical remission, whereas children treated with corticosteroids alone did not [13]. Investigators have previously reported a 40%–60% remission rate with cyclosporine therapy in noncollapsing variants of FSGS in children and 30% remission rate in adults [17–19]. Although the optimal treatment for ICG is not known, results from our series as well as the series of Valeri et al. indicate a potential role for cyclosporine; however, additional controlled trials are needed to make any firm recommendations.

The comparative outcome data are summarized in Table 3. Follow-up data for an average of 36 months were available on all six patients. The rapid rate of progression to ESRD was similar to the previously published series [1, 3, 6]. The time from onset to ESRD was shorter in our series at 7 months compared with 13 and 15 months in the series of Valeri et al. [1] and Detwiler et al. [3], respectively. Four of six patients in our series reached ESRD, of which two were placed on dialysis and two received renal transplants. As stated previously, the two patients treated with cyclosporine achieved clinical remissions. Both of the patients who underwent renal transplantation at last follow-up (2 and 5 years post transplantation) had normal serum creatinine levels and normal urinary protein excretion. In the series of Detwiler et al. [3], 8 of 14 patients (57%) with available follow-up progressed to ESRD and 5 of 14 (36%) required dialysis. Patients requiring transplantation were excluded from their study. In the series of Valeri et al. [1], 22 of 43 patients (51%) reached ESRD, 15 (35%) required dialysis, while 7 (16%) patients underwent renal transplantation. Of the 7 renal transplants, no recurrences have been reported [1]. Patients with noncollapsing FSGS have recurrence rates in renal allografts of 30%–40%. In a recent abstract, Detwiler et al. [20] reported ten renal transplant patients with ICG, three recurrent and seven de novo cases [20]. The clinical findings of rapid progression to ESRD, and African-American racial predominance were similar to ICG in nontransplant patients. The time from transplantation to diagnosis was also relatively short, with a mean of 11 months.

In conclusion, ICG in children is characterized clinically by African-American racial predominance, massive proteinuria, and rapid progression to ESRD. Pathological characteristics include focal segmental to global glomerular collapse, visceral epithelial cell hypertrophy/hyperplasia, varying degrees of tubulointerstitial injury, and lack of endothelial cytoplasmic tubuloreticular inclusions on renal biopsy ultrastructural examination. We found no distinguishing clinical or pathological features that correlated with ultimate renal outcome. ICG is clinically and pathologically similar to HIV-associated nephropathy in adults and children, except for the absence of endothelial tubuloreticular inclusions. Careful clinical history to exclude risk factors for HIV infection and serological testing can rule out this possibility. Although optimal treatment for ICG is not known, results from our series as well as the series of Valeri et al. [1] indicate a potential role for the use of cyclosporine in these patients. Further controlled clinical trials in larger patient groups are needed before firm recommendations can be made. It is important to distinguish ICG from other variants of FSGS, because of its worse response to conventional corticosteroid therapy and more-rapid progression to renal failure requiring dialysis and/or transplantation within less than a year of presentation. Accurate diagnosis of ICG in children will also provide proper stratification of patients into subgroups for further controlled clinical trials to evaluate more-intensive immunosuppressive drug regimens that may prevent deterioration of renal function and progression to ESRD.

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LITERATURE ABSTRACT

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Hypocomplementemia discloses genetic predisposition to hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: role of factor H abnormalities

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Familial hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) carry a very poor outcome and have been reported in association with decreased serum levels of the third complement component (C3). Uncontrolled consumption in the microcirculation, possibly related to genetically determined deficiency in factor H–a modulator of the alternative pathway of complement activation–may account for decreased C3 serum levels even during disease remission and may predispose to intravascular thrombosis. In a case-control study by multivariate analysis, we correlated putative predisposing conditions, including low C3 serum levels, with history of disease in 15 cases reporting one or more episodes of familial HUS and TTP, in 25 age- and gender-matched healthy controls and in 63 case-relatives and 56 control-relatives, respectively. The relationship between history of disease, low C3, and factor H abnormalities was investigated in all affected families and in 17 controls. Seventy-three percent of cases compared with 16% of controls ($P < 0.001$), and 24% of case-relatives compared with 5% of control-relatives ($P = 0.005$) had decreased C3 serum levels. At multivariate analysis, C3 serum level was the only parameter associated with the disease within affected families ($P = 0.02$) and in the overall study population ($P = 0.01$). Thus, subjects with decreased C3 serum levels had a relative risk of HUS or TTP of 16.56 (95% confidence interval [CI], 1.66 to 162.39) within families and of 27.77 (95% CI, 2.44 to 314.19) in the overall population, compared to subjects with normal serum levels. Factor H abnormalities were found in four of the cases, compared with three of the healthy family members ($P = 0.02$) and none of the controls ($P = 0.04$) and, within families, factor H abnormalities were correlated with C3 reduction ($P < 0.05$). Reduced C3 clusters in familial HUS and TTP is likely related to a genetically determined deficiency in factor H and may predispose to the disease. Its demonstration may help identify subjects at risk in affected families.