

The collapsing variant of focal segmental glomerulosclerosis in children

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SUMMARY

The collapsing variant of focal segmental glomerulosclerosis (FSGS) is a renal injury that may be idiopathic or associated with various factors; it is characterized by glomerular collapse, which leads to steroid-resistant nephrotic syndrome (NS) and progressive chronic renal failure. FSGS has not been well studied in children, in which most of the cases are idiopathic. We report six cases of the collapsing variant of FSGS in HIV-negative children who were resistant to immunosuppressive treatment. Three of the children died.

KEY WORDS

Chronic Renal Failure, Focal Segmental Glomerulosclerosis, Nephrotic Syndrome

RESUMEN

Variante colapsante de la glomeruloesclerosis focal y segmentaria en niños

La variedad colapsante de glomeruloesclerosis focal y segmentaria (GEFS) es una lesión renal que puede ser idiopática o estar asociada a diferentes factores; se caracteriza por colapso glomerular que lleva a un síndrome nefrótico corticorresistente y a falla renal crónica progresiva. Ha sido poco estudiada en niños y en ellos la mayoría de los casos son idiopáticos. Presentamos seis casos de esta variedad de GEFS en niños negativos para VIH, resistentes al tratamiento inmunosupresor; tres de ellos murieron.

PALABRAS CLAVE

Fallo Renal Crónico; Glomeruloesclerosis Focal y Segmentaria; Síndrome Nefrótico

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INTRODUCTION

The collapsing variant of focal segmental glomerulosclerosis (FSGS), also called collapsing glomerulopathy, is a well-defined glomerular disease. This variant of FSGS was first described by Weiss in 1986, who found these lesions in HIV-negative patients (1-3). This glomerulopathy is one of five variants of FSGS (2) proposed by a group at Columbia University in 2000 (4). Histologically, there is a global or segmental obliteration of the glomerular capillary lumen with basement membrane breakdown, hypertrophy and hyperplasia of podocytes (4), and the crowding of cells in Bowman's space, which results in the formation of pseudo-crescents (5-7). Clinically, the collapsing variant of FSGS is characterized by nephrotic syndrome (NS) with massive proteinuria, hematuria, and hypertension (HTN) (2). Patients with this variant have a poor response to empirical therapy and exhibit rapid deterioration of renal function (3,8,9).

Idiopathic cases exist; however, the collapsing variant of FSGS is often associated with secondary forms due to HIV and parvovirus infections (2,10); drugs, such as pamidronate (2); autoimmune diseases, such as lupus (11); malignant neoplasms (3), thrombotic microangiopathy, and mitochondrial diseases (3). There have been several reports on this disease in family groups, and mutations in the CoQ2 and ACTN4 genes were found to be responsible (2,5).

Pathogenesis of collapsing glomerulosclerosis is currently under investigation (11). Several authors suggest that this glomerulopathy is a model of proliferative parenchymal injury because, in contrast to other variants of FSGS in which podocytopenia and sclerosis are present, podocytes lose their differentiation markers and enter the cell cycle again in the collapsing variant (3,7), which leads to marked epithelial proliferation and hyperplasia (5,11).

Another proposed hypothesis for the collapsing variant of FSGS is aberrant repair with proinflammatory hyperplasia, which leads to fibrosis and atrophy of the injured parenchyma and impairs the glomerular capillary structure, thereby altering glomerular filtration (11). However, other authors propose the expression of viral proteins in renal parenchyma, which leads to the release of cytokines and glomerular growth factors (3). In HIV infection, there is an intracellular

expression of the viral genome or, indirectly, a release of inflammatory cytokines in the renal parenchyma (5).

To date, no adequate therapy is available to change the course of the disease. Initial treatment begins with steroids at a dose of 60 mg/m²/day, which is similar to treatment for patients with NS (11). However, remission rates are very low, ranging from 9.6%-15.2% (11). There have been few controlled trials with other immunosuppressive drugs, and their results are contradictory (9). Most patients require a combination of steroids with other immunosuppressive drugs, such as cyclophosphamide or cyclosporine, plus an inhibitor of the angiotensin-converting enzyme; however, the treatment remission rate was only 10%-15% in different series of children and adults (12).

In Colombia, no studies have been conducted on this variant of FSGS in children. The objective of our study was to assess the clinical presentation, the treatment, and the progress of a group of children with a clinical and histological diagnosis of the idiopathic collapsing variant of FSGS.

MATERIALS AND METHODS

In this retrospective descriptive study, we evaluated the clinical records of children who were diagnosed with NS and the collapsing variant of FSGS according to renal biopsies that were processed in the Department of Pathology at the University of Antioquia from January 2000 to December 2009. The minimum follow-up period was two years. All cases were classified as primary because there was no secondary cause of the NS. Tests for HIV, CMV, and the hepatitis B virus were negative, and none of the patients had a history of intravenous (IV) drug abuse.

Kidney tissue specimens were processed for conventional and immunofluorescence (IF) microscopy. For light microscopy, specimens were stained with hematoxylin and eosin, Masson's trichrome, periodic acid-Schiff (PAS), and methenamine silver. IF (for IgA, IgG, IgM, C3, C1q, κ, and λ) was performed to determine the presence of hyalinosis, capillary collapse, or immune complex deposits in the segments of glomerulosclerosis and rule out other causes of NS. All biopsies were reassessed, and the percentage of interstitial fibrosis was calculated using Masson's trichrome and methenamine silver staining.

The following demographic and laboratory data at the time of the renal biopsy and during the clinical course of patients were obtained from the medical records: sex, age, blood pressure, proteinuria, and serum creatinine levels. In addition, the percentage of patients with impaired kidney function was assessed according to the creatinine levels by age and the pharmacological treatment received. Remission was considered when proteinuria was below 4 mg/m²/hour.

Data obtained from the medical records were entered into a form previously designed in *Microsoft Excel*, which was exported to *SPSS*, version 17.0, software (*SPSS Inc., Chicago, IL, USA*) to perform statistical analyses. Due to the small sample size, quantitative variables were expressed as the medians and the interquartile ranges, and categorical variables, as absolute and relative values.

RESULTS

Out of a total of 321 biopsies from patients diagnosed with FSGS, we found 94 biopsies from children, of which six (6.4%) had the collapsing variant of FSGS as determined by histology. In every case, the indication for renal biopsy was steroid-resistant NS. The median follow-up period was 329 days (p25-75: 142.5-580 days). The ages at diagnosis ranged from 2-13 years, and the median age was 5.5 years (p25-75: 1.75-13 years). The gender distribution was three women and three men. Five patients were from Antioquia and one, from Chocó. In total, five patients were of mixed race and one was black.

Clinical signs and symptoms

HTN was observed in five of six patients; it was moderate in two, severe in two more, and mild in one. Hematuria was found in four patients. The median proteinuria level at diagnosis, which was determined in five patients, was 297 mg/m²/hour (p25-75: 10-398 mg/m²/hour) (table 1). Regarding the lipid profiles, data were obtained from four patients who had high cholesterol levels. No patient had positive HIV serology or a history of IV drug abuse.

The median follow-up period was 329 days (p25-75: 142.5-580 days). Creatinine values at diagnosis

ranged from 0.4-2.6 mg/dL, with a median of 0.7 mg/dL (p25-75: 0.55-1.55 mg/dL). At the end of the follow-up, the median creatinine level was 1.15 mg/dL (p25-75: 0.52-2.3 mg/dL). The median creatinine clearance level at diagnosis, as measured with the Schwartz formula, was 71 mL/min (p25-75: 27.5-106 mL/min). At follow-up, the median level was 42 mL/min (p25-75: 16.5-114 mL/min). At diagnosis, three of the six patients had impaired renal function.

Histological findings

The number of glomeruli that were assessed ranged from 5-23. The percentage of glomeruli with segmental or collapsing lesions ranged from 22%-100%, and the median percentage was 71.9% (p25-75: 37.6%-82.7%). Collapsing lesions were characterized by the loss of capillary lumens with wrinkled walls or walls that were folded together without an obvious increase in collagen and marked hypertrophy and hyperplasia of podocytes. Bowman's space was expanded, and several glomeruli had proteinaceous material in the lumen (figure 1). Only one biopsy revealed focal global glomerulosclerosis. Glomerular *tip lesions*, perihilar lesions, or endocapillary cellularity were not found in any patient. One case exhibited microcytic dilatation of tubules with hyaline casts in the lumen and hypertrophy of the epithelium. The median interstitial fibrosis percentage was 5% (p25-75: 0%-12.5%). None of the biopsies revealed hyaline arteriosclerosis. In two cases, there was mild tubulointerstitial inflammation. In three cases, there were scarce, focal, and segmental, nonspecific deposits of immunoglobulin M and C3. In the other cases, IF was negative for immunoglobulins or complement fractions.

Treatment and progress

In all patients, corticosteroids were the initial treatment; however, all of them became steroid-resistant. Five patients received a second immunosuppressive drug, either cyclophosphamide or cyclosporine, but none of them underwent complete remission of proteinuria. Three patients died due to infectious diseases: severe sepsis in two cases and *Listeria monocytogenes* meningitis in one.

Table 1. Demographic data and laboratory results

Patient	Sex	Age at diagnosis	Proteinuria mg/m ² /hour	Hematuria at diagnosis	Serum creatinine at diagnosis	HTN
1	Female	2	300.00	Yes	0.40	Yes
2	Male	2	No data	Yes	2.60	Yes
3	Female	13	497.00	No	0.80	Yes
4	Male	13	5.00	No data	0.60	No
5	Female	1	297.00	Yes	1.20	Yes
6	Male	9	15.00	Yes	0.60	Yes

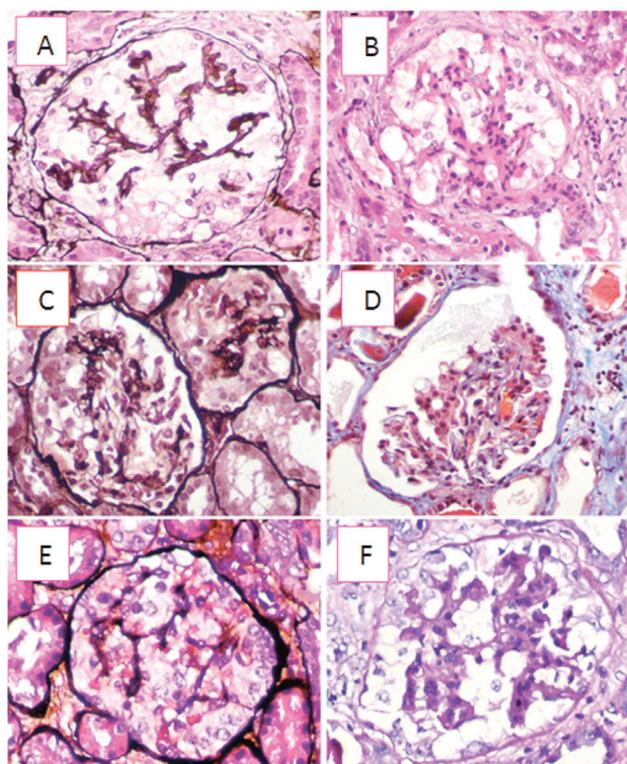


Figure 1. A and B. Glomeruli with complete collapse of the capillary tuft. Observe the large (hypertrophic) podocytes that are increased in number (hyperplasia) and partially occupy the enlarged Bowman's space. **C.** Two glomeruli are shown: The largest one has partial collapse in the upper portion, and the smallest has global collapse. There is hypertrophy and hyperplasia of podocytes in both glomeruli. **D.** Glomerular collapse has caused Bowman's space to become more evident, so that it appears mostly empty. Hypertrophy and hyperplasia of podocytes are evident only in one segment. **E.** The obvious podocyte hyperplasia completely fills Bowman's space, which suggests extracapillary proliferation (epithelial crescent). **F.** A glomerulus similar to that in images A and B with PAS staining. **A, C and E:** methenamine silver, **B:** hematoxylin-eosin, **D:** Masson's trichrome, and **F:** PAS staining. All images have an original magnification of 400X.

DISCUSSION

Collapsing glomerulopathy is a histological variant that is prevalent in black patients (3,6); it is often associated with HIV infection, but can also be found in an idiopathic form. This study is the first in Colombia to assess the collapsing variant of FSGS in a group of children with NS and histological findings consistent with it. In this series, no secondary cause was found to explain the disease. All patients had negative serology for HIV, and no other associated infections or autoimmune diseases were found. Unfortunately, none of the patients was studied for parvovirus, which is another pathogen associated with the development of this glomerulopathy (12).

Of all the biopsies of children with FSGS, 6.4% were classified as the collapsing variant; this proportion is similar to that reported in the literature. El-Refay et al. conducted a study in Egypt of 72 children with FSGS from 1995-2008, and 6% of them were classified as having the collapsing variant (13). In addition, Gulati et al. found a frequency of 5.6% in a pediatric population in India (9).

Histological findings in our patients were similar to those reported in the literature: severe impairment of the glomerular filtration barrier, collapse and retraction of glomerular capillaries (2,11), prominence of visceral epithelial cells, and hyperplasia of podocytes in collapsed capillaries with the formation of pseudo-crescents (7). Additionally, microcytic and hypertrophic changes were found in the renal tubules (3). The diagnosis of collapsing glomerulopathy is based on conventional microscopic histology due to the marked hyperplasia of podocytes, which can be interpreted as a crescent. The main differential diagnosis of the collapsing variant is extracapillary proliferative glomerulonephritis (*crescentic*). Methenamine silver, PAS, and trichrome staining are useful for making the differential diagnosis. In cases with at least one collapsing lesion and one *tip lesion*, perihilar lesions, or endocapillary hypercellularity, the diagnosis is the collapsing variant according to the Columbia classification criteria (4). IF is useful to rule out other glomerular diseases mediated by immune complexes, and electron microscopy may provide additional information in these cases with the detection of tubuloreticular inclusions, which may suggest lupus nephritis or HIV infection (7).

Clinical manifestations in our patients were similar to those reported in the literature with difficult NS and resistance to corticosteroid therapy in all cases (3,9,10,14). These findings are consistent with those in previous studies. In a study by Valeri et al., 26 patients with the diagnosis of the collapsing variant of FSGS were treated with steroids; however, remission was not achieved in any of them. Silverstein et al. studied 11 patients 1-18 years of age who were diagnosed with the collapsing variant of FSGS and found that all of them were steroid-resistant (15).

In this study, five of the six patients required a second immunosuppressive drug, which included cyclophosphamide and cyclosporine; however, remission rate was low. This finding is consistent with those in other studies, such as Valeri et al., in which partial remission was achieved in only one out of six patients treated with cyclophosphamide (16). In our series, no other drugs, such as rituximab, or plasmapheresis were used, which are investigational treatments for this condition with inconclusive results to date (9). However, the mortality rate in this series was very high (50%), and all fatal cases were secondary to serious infectious processes possibly due to the immunosuppressive therapy. Therefore, before starting other immunosuppressive therapy, an appropriate balance must be established between the goal of achieving health improvement and the risk of the therapy used (17).

In conclusion, the collapsing variant of FSGS in children is a rare disease characterized mainly by NS with rapid deterioration of renal function (6) and frequent resistance to immunosuppressive therapy. In contrast to the adult population, the collapsing variant of FSGS is idiopathic in most children. Further studies are needed to fully clarify the pathophysiology of this variant. In addition, preventive strategies and more promising treatments need to be developed to improve the prognosis in the pediatric population.

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