Jornal Brasileiro de Patologia e Medicina Laboratorial
ISSN: 1676-2444
jbpml@sbpc.org.br,adagmar.andriolo@gmail.com
Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial

de Abreu Testagrossa, Leonardo; Avancini Costa Malheiros, Denise Maria

Study of the morphologic variants of focal segmental glomerulosclerosis: a Brazilian report
Jornal Brasileiro de Patologia e Medicina Laboratorial, vol. 48, núm. 3, junio, 2012, pp. 211-215
Sociedade Brasileira de Patologia Clínica/Medicina Laboratorial
Rio de Janeiro, Brasil

Available in: http://www.redalyc.org/articulo.oa?id=393541966009

Study of the morphologic variants of focal segmental glomerulosclerosis: a Brazilian report

Primeira submissão em 11/09/11
Última submissão em 13/02/12
Aceito para publicação em 12/03/12
Publicado em 20/06/12

Estudo brasileiro das variantes morfológicas da glomerulosclerose segmentar e focal

Leonardo de Abreu Testagrossa[1]; Denise Maria Avancini Costa Malheiros[2]

key words

Focal segmental glomerulosclerosis

Variants of FSGS

Collapsing FSGS

abstract

Introduction: Focal segmental glomerulosclerosis (FSGS) is the most frequent primary glomerulopathy in Brazil and its incidence is increasing worldwide. Pathogenesis is related to podocyte injury, which may be due to several factors including viruses, drugs, genetics and immunological factors. In 2004, the Columbia classification of FSGS identified five histological variants of the disease: collapsing (COL), usual (NOS), tip lesion (TIP), perihilar (PHI) and cellular variant (CEL). The objective of this study was to classify the FSGS biopsies in these morphological variants. **Methods:** One hundred thirty-one cases of renal biopsies with primary FSGS diagnosis, which had been performed at a Brazilian reference center from 1996 to 2006, were classified according to the Columbia criteria. **Results:** FSGS cases were distributed as follows: 38.2% NOS variant, 36.6% COL, 14.5% TIP, 6.9% PHI and 3.8% CEL. **Conclusion:** COL variant of FSGS seems to be more prevalent in Brazil in comparison with other centers worldwide, which may be related to environmental and socioeconomic factors..

unitermos

Glomerulosclerose segmentar e focal

Variantes da GESF

GESF colapsante

resumo

Introdução: *A glomerulosclerose segmentar e focal (GESF) é a glomerulopatia primária mais frequente no Brasil e sua incidência está aumentando em todo o mundo. Sua patogênese está relacionada com a lesão de podócitos, que pode ser devida a vários fatores, incluindo vírus, drogas, fatores genéticos e imunológicos. Em 2004, a classificação de Columbia GESF definiu cinco variantes histológicas da doença: colapsante (COL), usual (NOS), lesão apical (TIP), Peri-hilar (PHI) e variante celular (CEL). O objetivo deste estudo foi classificar as biópsias com diagnóstico de GESF nessas variantes morfológicas.* ***Métodos:*** *Cento e trinta e um casos de biópsias renais com diagnóstico de GESF primária em um centro brasileiro de referência em nefrologia, no período de 1996 a 2006, foram classificados de acordo com os critérios de Columbia.* ***Resultados:*** *Os casos se distribuíram da seguinte forma: 38,2% da variante de NOS; 36,6% de COL; 14,5% de TIP; 6,9% de PHI; 3,8% de CEL.* ***Conclusão:*** *A variante COL de GESF parece ser mais prevalente no Brasil do que em outros centros internacionais e isso pode ser reflexo de fatores socioeconômicos e ambientais.*

1. Doutor em Ciências; médico da Divisão de Anatomia Patológica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (DAP-HC-FMUSP).

2. Doutora em Ciências; professora da FMUSP.

Introduction

Focal segmental glomerulosclerosis (FSGS) is a clinical and pathological renal syndrome causing proteinuria, usually in the nephrotic range, and occurring predominantly in young individuals. According to several authors, the worldwide incidence of FSGS is on the rise annually, including in Brazilian statistics[1, 8, 9]. Data from the Paulista registry of glomerulopathies shows that FSGS is the most common primary glomerulopathy in 11 centers of São Paulo, accounting for 29.7% of cases, followed by membranous nephropathy (20.7%) and immunoglobulin A (IgA) nephropathy (17.8%)[12]. From an etiological standpoint, FSGS may be associated with a variety of conditions, including viral infections (human immunodeficiency virus [HIV], simian virus 40 [SV40] , parvovirus B19), several drugs (heroin, pamidronate, interferon), adaptive to hyperfiltration (as in hypertension, obesity, and sickle-cell anemia), and genetic disorders (familiar forms), and may be idiopathic[11]. Podocyte injury is the core pathophysiological event of FSGS and some studies have found anomalous expression of podocyte proteins in FSGS[2, 10, 16].

The Columbia classification for primary FSGS, first published by D'Agati *et al.*, in 2004, proposed five mutually exclusive morphological variants of the disease (histologic criteria shown in **Table** and **Figure**). Studies of these variants demonstrated correlation with distinct clinical characteristics and prognostic and therapeutic implications[4, 18].

Recognition of these variants through a combination of morphologic and molecular features might bring about a better understanding of the pathogenesis of FSGS and promote identification of new therapeutic targets. The present study aimed to classify cases of primary FSGS diagnosed at the Divisão de Anatomia Patológica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (DAP-HC-FMUSP) into the collapsing (COL), cellular (CEL), usual (NOS), tip lesion (TIP), and perihilar (PHI) morphologic variants.

Methods of case selection

We obtained 525 consecutive biopsies with FSGS diagnosis from the archives of the DAP-HC-FMUSP from 1996 to 2006, of which we selected 131 cases based in the following exclusion criteria:

• secondary FSGS due to known etiology (glomerular sclerosis scarring, chronic pyelonephritis, hypertension, reflux nephropathy);

- age below 18 and over 45 years- to guarantee, as good as possible, that we were working on primary FSGS, once we did not have access to the patient charts;
- less than five glomeruli in a sample to minimize the possibility of include focal segmental glomerulosclerosis secondary to diabetic glomerulopathy, chronic glomerulonephritis etc.;
- recurrence in kidney allografts;
- biopsies from HIV seropositive patients;
- advanced stage of histologic chronicity (more than 90% of sclerotic glomeruli);
- biopsies without or with unsatisfactory immunofluorescence;
- biopsies with positive immunofluorescence for IgA and/or IgG in glomeruli.

Slides and blocks of each case were separated and reviewed.

Table Classification of undiagnosed primary FSGS cases at the DAP-HC-FMUSP. Comparison with other published series

	HC-FMUSP (1996-2006)	North Carolina (1982-2001)	Deegens, J. K.[5] (1980-2003)
	n = 131 (%)	*n* = 197 (%)	*n* = 93 (%)
NOS	50 (38,2)	83 (42)	30 (32)
COL	48 (36,6)	22 (11)	5 (5)
CEL	5 (3,8)	6 (3)	0 (0)
TIP	19 (14,5)	34 (17)	34 (37)
PHI	9 (6,9)	52 (26)	24 (26)
PHI + NOS	59 (45,1)	135 (68)	54 (58)

DAP-HC-FMUSP: Divisão de Anatomia Patológica do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo; FSGS: Focal segmental glomerulosclerosis; NOS: usual; COL: collapsing; CEL: cellular; TIP: tip lesion; PHI: perihilar.

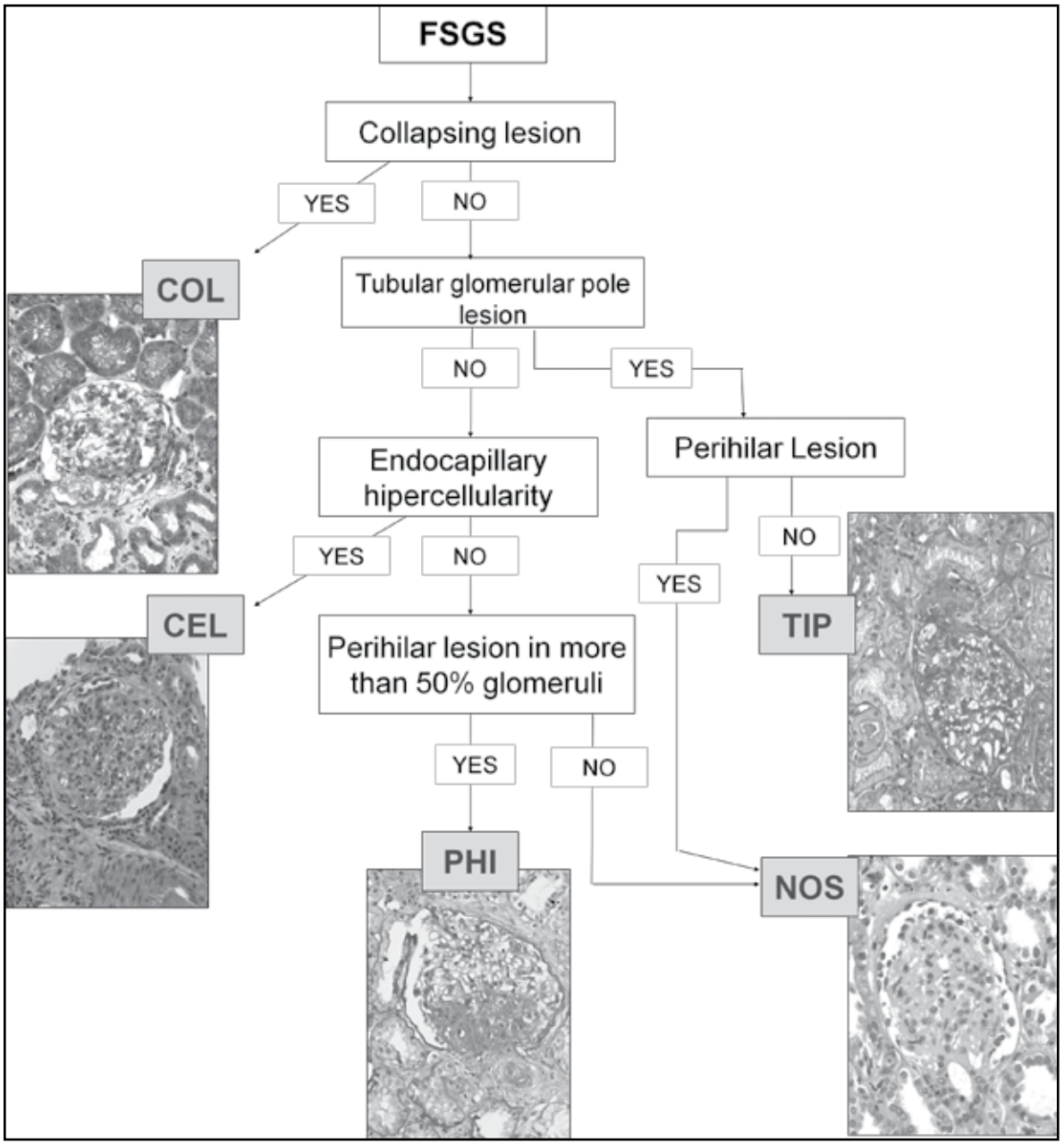

Figure – *Working algorithm to FSGS classification*
FSGS: focal segmental glomerulosclerosis; COL: collapsing; CEL: cellular; PHI: perihilar; TIP: tip lesion; NOS: usual.

Morphological analysis

Kidney biopsies slides of each case, stained by hematoxylin-eosin (HE), periodic acid Schiff (PAS), Masson trichrome and methenamine silver (PS Jones), were blindly reviewed by two nephropathologists (authors), on which were applied the morphologic criteria of Columbia for classification of FSGS in the variants: TIP, COL, CEL, PHI and NOS. Discordant results were analyzed together by the two pathologists to reach consensus.

Results

After application of the exclusion criteria, a total of 131 eligible cases remained and were assessed according to the histologic criteria proposed by the FSGS classification, which revealed 50 cases of NOS; 48, COL; five, CEL; 19, TIP; and nine, PHI (Table and Figure). The most prevalent discrepancy between the authors regarding the Columbia classification of FSGS was related to the CEL and COL variants, since there were cases previously classified as COL that were reclassified as NOS or CEL variant.

Discussion of results

Increases in the number of patients with chronic kidney disease (CKD) have led to growing interest in a better understanding of the renal conditions involved in CKD, including FSGS. Improved knowledge of pathogenic mechanisms would allow development of individualized and more efficient therapeutic actions. The recognition of histologic variants can be the first step in this direction in the case of primary FSGS, this has translated into recent definition of the five variant forms of the disease, namely, usual (NOS), collapsing (COL), cellular (CEL), perihilar (PHI), and tip lesion (TIP) variants. It is now known that certain histologic features in FSGS are associated with poor clinical progression, including rapid deterioration of renal function and marked proteinuria[3, 14, 18]. The present series included 131 cases of primary FSGS diagnosed between 1996 and 2006, which were classified according to the Columbia classification criteria[4] as 50 NOS (38.2%), 48 COL (36.6%), 19 TIP (14.5%), nine PHI (6.9%), and five CEL (3.8%) (Table). Thomas *et al.*[7] published a series of 197 cases recorded at the University of North Carolina between 1982 and 2001 and reported that 42% of cases were of the NOS variant, 17% were TIP, 13% were COL, 26% were PHI, and 3% were CEL[18] (Table). However, we think the authors were less strict in selecting cases of primary FSGS than us. Degeens *et al.*[5] observed 32% of NOS, 37% of TIP, 26% of PHI, 5% of COL and no CEL variant in an adult Dutch population[5]. Our data revealed a higher prevalence of the COL variant, diverging from the above cited case series. These data raise the vision of a possible environmental or infectious factor. Given that it is well known the bigger incidence in black race and close resemblance to HIV-associated nephropathy, a search for possible viral etiology and socioeconomic influences appears justified. Merlet-Bénichou *et al*. has found reduced numbers of glomeruli and larger glomerular volumes in newborn rats exposed to toxins in utero and in infants born with small placentas and low birth weights; these observations suggest that socioeconomic differences, such as poor nutrition or exposure to toxins during gestation, might affect the developing kidney and result in a reduced glomerular population with larger glomerular volume[6, 13].

In the present study, lesions were most easily classified into the TIP, NOS, or COL variants using the Columbia histological criteria; there was substantial overlap of criteria for the NOS and PHI variants, as well as with COL and CEL variants. Some authors question the existence of a separate CEL variant, and claim it is merely a form of the COL variant[17]. Others agree that both variants are very difficult to distinguish histologically and common pathophysiological pathways affecting cell cycle regulatory proteins have been established[3, 14, 15]. In our sample, there was also overlap of histologic findings for both variants.

In cases classified as COL, we found the coexistence of marked tubulointerstitial injury, sometimes with microcystic tubular dilatation, however similar findings were also present in other variants, particularly in advanced chronic disease, although these changes were more marked in COL variant. Therefore, these findings should not be considered specific to COL variant FSGS.

The distinction between the NOS and PHI variants also seemed unclear when using the current criteria. We believe the criterion of > 50% perihilar involvement varies according to the level of histological section. According to the proposed criteria, the diagnosis of PHI variant FSGS should only be considered when over 50% of sclerotic glomeruli show perihilar lesions, which may vary from one histologic section to another of a single biopsy. Several cases classified as NOS exhibited perihilar sclerosis and hyalinosis in additional sections which highlights the importance of having a representative sample in order to distinguish between the NOS and PHI variants. Stokes *et al.* did not include cases of the PHI variant in their series, as they believed this variant often refers to secondary FSGS, however, they found evidence of perihilar lesions in other variants mostly in NOS[17]. Maybe they found the same difficulty in the PHI *versus* NOS distinction.

In our sample, the TIP variant was particularly difficult to diagnose when the apical lesion was represented marginally, with no apparent relation to the origin of the proximal convoluted tubule, and, in some cases, coexisted with morphologic aspects similar to those of COL FSGS. These lesions sometimes presenting confluence of hypertrophic podocytes, parietal cells, and tubular epithelial cells, deformed the glomerular tuft, giving it an aspect alike to a collapsing injury. A search for classical lesions in contact with the origin of the tubule in additional histologic sections and the absence of podocyte proliferation can assist in differential diagnosis[7].

Conclusion

In conclusion, the 131 cases of primary FSGS resulted in 38.2% NOS variant, 36.6% COL, 14.5% TIP, 6.9% PHI and 3.8% CEL, according to Columbia classification, which points to a bigger prevalence of the COL variant than in other international centers. Additional studies to better explain the socioeconomic role on these prevalences might be of value on this field.

References

1. BAHIENSE-OLIVEIRA, M. *et al*. Primary glomerular diseases in Brazil (1979-1999): is the frequency of focal and segmental glomerulosclerosis increasing? *Clin Nephrol*, v. 61, n. 2, p. 90-7, 2004.
2. BARISONI, L.; SCHNAPER, H. W.; KOPP, J. B. A proposed taxonomy for the podocytopathies: a reassessment of the primary nephrotic diseases. *Clin J Am Soc Nephrol*, v. 2, n. 3, p. 529-42, 2007.
3. CHUN, M. J. *et al*. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. *J Am Soc Nephrol*, v. 15, n. 8, p. 2169, 2004.
4. D'AGATI, V. Pathologic classification of focal segmental glomerulosclerosis. *Semin Nephrol*, v. 23, p. 117-34, 2003.
5. DEEGENS, J. K. *et al*. Pathological variants of focal segmental glomerulosclerosis in an adult Dutch population – epidemiology and outcome. *Nephrol Dial Transplant*, v. 23, n. 1, p. 186-92, 2008.
6. GILBERT, T.; LELIEVRE-PEGORIER, M.; ME LET-BENICHOU, C. Longterm effects of mild oligonephronia induced in utero by gentamicin in the rat. *Pediatr Res*, v. 30, p. 450-6, 1991.
7. HAAS, M. The glomerular tip lesion: what does it really mean? *Kidney Int*, v. 67, n. 3, p. 1188-9, 2005.
8. HAAS, M. *et al*. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. *Am J Kidney Dis*, v. 30, p. 621-31, 1997.
9. HAAS, M.; SPARGO, B. H.; COVENTRY, S. Increasing incidence of focal-segmental glomerulosclerosis among adult nephropathies: a 20-year renal biopsy study. *Am J Kidney Dis*, v. 26, n. 5, p. 740-50, 1995.
10. KOOP, K. *et al*. Expression of podocyte-associated molecules in acquired human kidney diseases. *J Am Soc Nephrol*, v. 14, p. 2063-71, 2003.
11. KORBET, S. M. Primary focal segmental glomerulosclerosis. *J Am Soc Nephrol*, v. 9, p. 1333-40, 1998.
12. MALAFRONTE, P. *et al*. Paulista registry of glomerulonephritis: year data report. *Nephrol Dial Transplant*, v. 21, n. 11, p. 3098-105, 2006.
13. MERLET-BÉNICHOU, C. *et al*. Retard de croissance intra-utérin et déficit en néphrons. *Médecine/Sciences*, v. 9, p. 777-80, 1993.
14. MEYRIER, A. Y. Collapsing glomerulopathy: expanding interest in a shrinking tuft. *Am J Kidney Dis*, v. 33, n. 4, p. 801-3, 1999.
15. SHANKLAND, S. J. Cell cycle regulatory proteins in glomerular disease. *Kidney Int*, v. 56, n. 4, p. 1208-15, 1999.
16. SHARMA, M. *et al*. The focal segmental glomerulosclerosis permeability factor: biochemical characteristics and biological effects. *Exp Biol Med (Maywood)*, v. 229, n. 1, p. 85- 98, 2004.
17. STOKES, M. B. *et al*. Cellular focal segmental glomerulosclerosis: clinical and pathological features. *Kidney Int*, v. 70, n. 10, p. 1783-92, 2006.
18. THOMAS, D. B. *et al*. Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int*, v. 69, p. 920-6, 2006.

Mailing address

Leonardo de Abreu Testagrossa
Prédio dos Ambulatórios do HC-FMUSP
Divisão de Anatomia Patológica – 10º andar
Av. Dr. Enéas de Carvalho Aguiar, 255
Cerqueira César
CEP: 05403-000 – São Paulo-SP