

## Original Article

## Recurrence of nephrotic syndrome after transplantation in a mixed population of children and adults: course of glomerular lesions and value of the Columbia classification of histological variants of focal and segmental glomerulosclerosis (FSGS)

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### Abstract

**Introduction.** Recurrence of nephrotic-range proteinuria in patients with idiopathic nephrotic syndrome (INS) and focal and segmental glomerulosclerosis (FSGS) on native kidneys is associated with poor graft survival. Identification of risk factors for recurrence is therefore an important issue. In 2004, Columbia University introduced a histological classification of FSGS that identifies five mutually exclusive variants. In non-transplant patients, the Columbia classification appears to predict the outcome and response to treatment better than clinical characteristics alone. However, the predictive value of this classification to assess the risk of recurrence after transplantation has not been addressed.

**Methods.** We retrospectively studied 77 patients with INS and FSGS on native kidneys who underwent renal transplantation. Of these, 42 recipients experienced recurrence of nephrotic range proteinuria.

**Results.** At time of recurrence, minimal-change disease (MCD) was the main histological feature. On serial biopsies, the incidence of MCD decreased over time, while the incidence of FSGS variants increased. The variant type observed in the native kidneys was not predictive of either recurrence or type of FSGS seen on the allograft. Patients with complete and sustained remission did not develop FSGS.

**Conclusion.** In conclusion, the Columbia classification is of no help in predicting recurrence after renal transplantation or histological lesions in the case of recurrence of proteinuria.

**Keywords:** FSGS; histopathology; kidney transplantation; recurrence

### Introduction

Steroid-resistant idiopathic nephrotic syndrome (INS) in native kidneys is frequently associated with progression to end-stage renal disease (ESRD) [1–3]. In most patients, initial renal biopsy shows focal and segmental glomerulosclerosis (FSGS). However, in early stages, FSGS and minimal-change disease (MCD) are indistinguishable at the clinical level [4–6]. Serial renal biopsies indicate that some patients with minimal changes on initial renal biopsy develop FSGS during the course of the disease. This was observed in 60% of cases in a series of 48 patients with steroid-resistant minimal change [7]. After kidney transplantation, recurrence of nephrotic-range proteinuria is observed in 30% of cases and is associated with poor graft survival [8–14]. Identification of risk factors for recurrence is an important issue.

In 2004, Columbia University introduced a histological classification of FSGS that identifies five mutually exclusive variants: perihilar (PH), cellular (CELL), tip lesion (TIP), collapsing (COL) and not otherwise specified (NOS) [15]. Since then, several studies have correlated renal prognosis with histological features in native kidneys. In non-transplant patients, the Columbia variant seems to predict outcome and response to treatment better than clinical characteristics alone. TIP seems to be the most steroid-sensitive variant, with COL being the least favourable variant [16–20]. The impact of this classification to predict the FSGS variant in the transplant has been recently studied [21]. In one report, Ijpelaar *et al.* concluded that, in most cases, the FSGS variant observed in the transplant kidney was the same as in the native kidneys, suggesting that the histological variant of the native kidney could predict the variant observed in patients with recurrence. However, the predictive value of this classification to assess the risk of

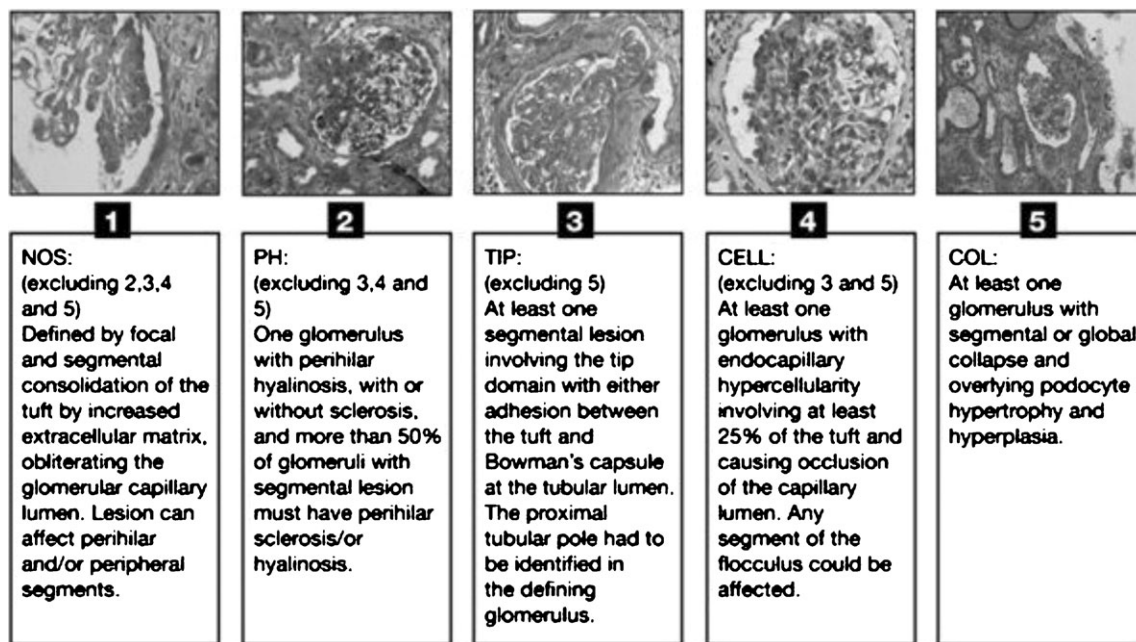


Fig. 1. FSGS variants in native kidneys (NOS,  $n = 38$ ; PH,  $n = 6$ ; TIP,  $n = 6$ ; CELL,  $n = 17$ ; COL,  $n = 10$ ).

recurrence after transplantation and graft outcome has never been addressed. We investigated in a large series whether the Columbia classification of FSGS variants provides a relevant indicator for the risk of proteinuria recurrence after renal transplantation and the type of variant in the case of recurrence.

## Material and methods

Kidney transplant recipients with INS and FSGS on native kidneys and progression to ESRD were eligible for inclusion. Patients with familial history of proteinuria or secondary forms of FSGS were excluded, i.e. ischaemia-related podocyte injury, sickle cell disease, renal hypoplasia, thrombotic microangiopathy, reflux nephropathy, human immunodeficiency virus and genetic disorders when a test was available. Patients with non-adequate biopsies were also excluded (i.e. the biopsy sample containing fewer than five glomeruli).

Our study population included children ( $n = 56$ ) and adults ( $n = 21$ ) (age > 16 years). There were 40 males and 37 females. The 77 patients included in the study received a sequential quadruple immunosuppression including induction therapy (thymoglobulin,  $n = 47$ ; basiliximab,  $n = 30$ ), corticosteroids, a calcineurin inhibitor (cyclosporine,  $n = 65$ ; tacrolimus,  $n = 12$ ), azathioprine ( $n = 53$ ) or mycophenolate mofetil ( $n = 24$ ). Seventy-one patients had received a first kidney transplant; 4 patients had received a second transplant and 2 a third one. Kidney allografts were obtained from a deceased donor in 69 cases and from a living-related donor in 8 cases. No patient received pre-emptive treatment for recurrence (i.e. cyclosporine A IV or pre-operative plasmapheresis).

Recurrence was defined by massive proteinuria in the nephrotic range (>3 g/day for adults or >50 mg/kg/day for children), with normal glomeruli and without evidence of acute or chronic rejection, glomerular deposits or allograft glomerulopathy on initial kidney biopsy. Cameron's classification was applied to define time of recurrence: immediate (<48 h), early (<3 months) and late recurrence (>3 months) [10].

Transplant biopsies were performed either when indicated by proteinuria and/or acute renal failure, or routinely as screening biopsies at 3 and 12 months post-transplant. Native and transplant kidney biopsies were processed following the international recommendations for light microscopy and immunofluorescence. The median number of glomeruli per biopsy was  $13.7 \pm 4.6$  (range 6–24). Histology slides were stained with haematoxylin

and eosin, periodic acid–Schiff, Masson trichrome and methenamine–silver. For each biopsy, FSGS variant was evaluated according to the Columbia classification [15]. The five FSGS variant definitions are summarized in Figure 1. All native and transplant biopsies were reviewed by three senior pathologists. As electron microscopy is not of current routine practice in France, we were able to describe foot process fusion in only one case. Nevertheless, patients with proteinuria in the nephrotic range and no features of FSGS variants on kidney biopsy were classified as having MCD.

## Results

From January 1984 to December 2007, 77 patients with INS and biopsy-proven FSGS on native kidneys received a renal transplant. Patients were classified in two categories according to whether proteinuria recurred in the nephrotic range (R group,  $n = 42$ ) or not (NR group,  $n = 35$ ). The demographic characteristics of the patients are summarized in Tables 1 and 2. The mean age at onset of nephrotic syndrome was  $10.4 \pm 10$  years and  $9.2 \pm 6.9$  years for patients in the NR group and in the R group, respectively ( $P = \text{NS}$ ). The delay between the onset of disease and ESRD was  $4.8 \pm 2.3$  years in the NR group and  $3.9 \pm 3.3$  years in the R group ( $P = \text{NS}$ ). There was no difference in the immunosuppressive regimen between the two groups. Four patients in each group received a kidney from a living donor. In the NR group, all patients were genotyped for *NPHS1* and *NPHS2*, and none of them had mutation. In the R group, 30/42 patients were genotyped for *NPHS1* and *NPHS2*. Two patients had a heterozygous variant, polymorphism (pA242V) [22].

On native kidney biopsies, MCD was initially observed in 10 (children exclusively) out of 77 cases, and repeat renal biopsies showed the development of FSGS in all these patients. All variants were present on native kidneys. The

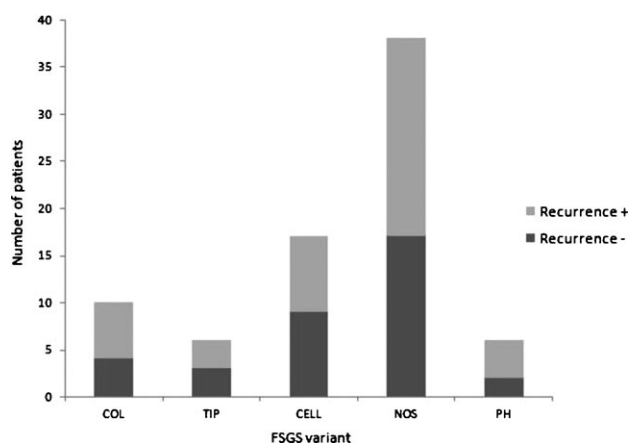
**Table 1.** Characteristics of patients in the NR group

Patients	Age at onset of proteinuria (years)	FSGS variant on native kidney	Number of glomeruli	Delay between onset and ESRD (years)
1	0.8	CELL	10	7
2	11	COL	14	1.6
3	3	MCD then NOS	16	2
4	5	TIP	11	8
5	2	NOS	23	5
6	10	MCD then CELL	16	2
7	3.3	NOS	12	8
8	2	COL	9	2.5
9	3	NOS	22	4
10	11	CELL	13	5
11	2	COL	14	7
12	0.3	MCD then NOS	8	1.8
13	2	NOS	25	6
14	3	CELL	17	7
15	0.5	NOS	11	7
16	5	CELL	19	2
17	1	NOS	29	4
18	6	TIP	25	4
19	2	NOS	14	2
20	4	CELL	16	6
21	1	NOS	11	9
22	6	NOS	10	9
23	18	MCD then PH	13	4
24	12	NOS	20	6
25	24	MCD then NOS	22	1
26	22	PH	18	8
27	31	TIP	9	7.2
28	14	CELL	9	2.4
29	17	CELL	7	4
30	29	COL	11	3.1
31	19	NOS	12	3.7
32	16	NOS	15	4
33	34	CELL	10	5.5
34	28	NOS	9	5
35	18	NOS	9	4.5
<i>Mean ± SD</i>	<i>10.4 ± 10</i>		<i>14 ± 5.6</i>	<i>4.8 ± 2.3</i>

FSGS variant observed on native kidney biopsies was NOS in 38 cases (49.3%), CELL in 17 cases (22.2%), COL in 10 cases (12.9%), PH in 6 cases (7.8%) and TIP in 6 cases (7.8%). There were no differences in FSGS variant representation between R and NR groups (Figure 2).

After kidney transplantation, recurrence of proteinuria occurred immediately in 32/42 cases (children  $n = 28$ , adults  $n = 4$ ), early in 9/42 cases (children  $n = 4$ , adults  $n = 5$ ) and late in 1/42 case (adult  $n = 1$ ). The treatment for recurrence consisted of intravenous (IV) cyclosporine A (CsA) +plasmapheresis (PP) in 10 cases, CsA IV+PP+ a high dose of steroids in 3 cases, CsA IV alone in 10 cases, oral CsA+ PP in 3 cases, oral CsA alone in 8 cases, oral CsA + PP+ rituximab in 1case, cyclophosphamide+ PP in 1 case, CsA IV+ PP+ rituximab in 4 cases, CsA IV+ enalapril in 1 case and immunoadsorption in 1 case (Table 2).

The distribution of glomerular lesions in transplanted kidneys with recurrence of INS (group R,  $n = 42$ ) is summarized in Table 2 and Figure 2. MCD was the main histological feature observed in 32 out of 33 biopsies performed early after recurrence, D6 to D60 days after transplantation. Only one patient had already developed and FSGS lesion (Table 2: patient 38, PH variant on Day 15). At Month 3, an

**Fig. 2.** Distribution of FSGS variants on a native kidney of patients with or without recurrence of proteinuria in the nephrotic range.

FSGS lesion was observed in 11 out of 39 cases. At Month 12, FSGS lesion was observed in 14 out of 37 cases. Seventeen of the 42 patients went into complete and persistent remission, and none of them developed FSGS (2 patients

**Table 2.** Course of FSGS variants on kidney biopsies performed in transplant recipients with recurrence of proteinuria in the nephrotic range

Patients	Age at onset of proteinuria (years)	FSGS variant on native kidney (number of glomeruli)	Delay between onset and ESRD (years)	Time of recurrence	Treatment	Response to treatment	Evolution after transplantation	Transplant biopsy at time of recurrence (number of glomeruli)	Transplant biopsy on Month 3 (number of glomeruli)	Transplant biopsy on Month 12 (number of glomeruli)	Other biopsy
1	8	NOS ( <i>n</i> = 12)	2	D0	CsA IV+PP	Partial	Transplantectomy M12	MCD M1 ( <i>n</i> = 22)	MCD ( <i>n</i> = 12)	MCD ( <i>n</i> = 14)	
2	2	NOS ( <i>n</i> = 12)	4	D0	CsA IV+PP	No remission	Transplantectomy M1	MCD M1 ( <i>n</i> = 16)	X	X	
3	6	MCD ( <i>n</i> = 14) then CELL ( <i>n</i> = 8)	7	D0	CsA IV	Partial	ESRD 9 years	MCD M1 ( <i>n</i> = 15)	MCD ( <i>n</i> = 9)	MCD ( <i>n</i> = 21)	COL M24, NOS M96
4	1.5	NOS ( <i>n</i> = 9)	1.5	D0	CsA oral	No remission	Transplantectomy M3	MCD M1 ( <i>n</i> = 18)	MCD ( <i>n</i> = 13)	X	
5	10	NOS ( <i>n</i> = 18)	2	D0	Immunoadsorption	Complete followed by relapse	Transplantectomy M48	MCD D15 ( <i>n</i> = 7)	MCD ( <i>n</i> = 15)	MCD ( <i>n</i> = 14)	Transplantectomy M48 COL
6	2	COL ( <i>n</i> = 17)	3	D0	CsA IV +PP	Complete and persistent		MCD D10 ( <i>n</i> = 12)	MCD ( <i>n</i> = 7)	MCD ( <i>n</i> = 18)	MCD M62
7	0.5	CELL ( <i>n</i> = 11)	2	D3	CsA IV	Complete followed by relapse at M36	Transplantectomy M60	MCD M1 ( <i>n</i> = 14)	CELL ( <i>n</i> = 8)	CELL ( <i>n</i> = 9)	CELL M36, Transplantectomy M60 NOS
8	2	MCD ( <i>n</i> = 20) then PH ( <i>n</i> = 6)	7	D0	CsA IV + PP	Complete and persistent			MCD ( <i>n</i> = 12)	MCD ( <i>n</i> = 21)	
9	1.3	NOS ( <i>n</i> = 8)	5	D0	CsA IV	Complete and persistent			MCD ( <i>n</i> = 24)	MCD ( <i>n</i> = 10)	MCD M108
10	1.5	NOS ( <i>n</i> = 10)	8	D0	CsA IV + PP + Rituximab	Complete and persistent		MCD D14 ( <i>n</i> = 12)	MCD ( <i>n</i> = 12)	MCD ( <i>n</i> = 18)	MCD M36
11	2	TIP ( <i>n</i> = 12)	12	D0	CsA IV	Complete and persistent		MCD D15 ( <i>n</i> = 19)	MCD ( <i>n</i> = 15)	MCD ( <i>n</i> = 9)	
12	8	MCD ( <i>n</i> = 14) then NOS ( <i>n</i> = 7)	3	M6	CsA oral	Partial	Died at M144	MCD M6 ( <i>n</i> = 12)		MCD ( <i>n</i> = 9)	MCD M36
13	3	NOS ( <i>n</i> = 8)	17	D0	CsA IV + PP	Complete and persistent		MCD M1 ( <i>n</i> = 22)	MCD ( <i>n</i> = 18)	MCD ( <i>n</i> = 8)	
14	6	CELL ( <i>n</i> = 20)	4	D0	CsA oral	Partial	Transplantectomy M36		MCD ( <i>n</i> = 11)	MCD ( <i>n</i> = 14)	Transplantectomy M36 NOS
15	2.1	NOS ( <i>n</i> = 15)	3.2	D1	CsA IV + enalapril	Complete and persistent			MCD ( <i>n</i> = 7)	MCD ( <i>n</i> = 11)	MCD M96
16	9	COL ( <i>n</i> = 7)	4	D20	CsA IV + PP	No remission	Transplantectomy M60	MCD D10 ( <i>n</i> = 24)	MCD ( <i>n</i> = 11)	NOS ( <i>n</i> = 6)	Transplantectomy M60 NOS
17	8	NOS ( <i>n</i> = 9)	7	D0	CsA oral	No remission	Transplantectomy M9	MCD M1 ( <i>n</i> = 21)	NOS ( <i>n</i> = 9)	X	Transplantectomy M9 NOS
18	7	NOS ( <i>n</i> = 11)	4	D1	CsA IV + PP	Complete followed by relapse at M48			MCD ( <i>n</i> = 18)	MCD ( <i>n</i> = 11)	MCD M48, MCD M96
19	10	MCD ( <i>n</i> = 11) then NOS ( <i>n</i> = 12)	0.4	D1	CsA IV	Complete followed by relapse at M9	ESRD M96	MCD D21 ( <i>n</i> = 20)	MCD ( <i>n</i> = 9)	COL ( <i>n</i> = 14)	COL M9
20	3	NOS ( <i>n</i> = 14)	9	D8	CsA IV + PP + rituximab	Complete and persistent		MCD M1 ( <i>n</i> = 12)	MCD ( <i>n</i> = 15)	MCD ( <i>n</i> = 9)	

21	5	NOS ( <i>n</i> = 16)	5	D0	CsA IV	Complete and persistent		MCD ( <i>n</i> = 20)	MCD ( <i>n</i> = 12)	MCD 5 years	
22	0.5	NOS ( <i>n</i> = 10)	2	D3	CsA IV	Complete and persistent	MCD D22 ( <i>n</i> = 11)	MCD ( <i>n</i> = 7)	MCD ( <i>n</i> = 14)		
23	5	COL ( <i>n</i> = 9)	8	D1	CsA IV	Complete and persistent	MCD D10 ( <i>n</i> = 9)	MCD ( <i>n</i> = 24)	MCD ( <i>n</i> = 11)		
24	5	CELL ( <i>n</i> = 10)	5	D0	CsA IV	Complete followed by relapse on M24	MCD M1 ( <i>n</i> = 13)	CELL ( <i>n</i> = 12)	CELL ( <i>n</i> = 9)	CELL M24	
25	12	COL ( <i>n</i> = 11)	1	D0	CsA + PP	Complete and persistent		MCD ( <i>n</i> = 14)	MCD ( <i>n</i> = 10)		
26	5	NOS ( <i>n</i> = 18)	2	D0	CsA IV + PP	No remission	MCD M1 ( <i>n</i> = 19)	COL ( <i>n</i> = 6)	COL ( <i>n</i> = 9)	COL M24	
27	27	CELL ( <i>n</i> = 20)	5	D0	CsA IV + PP	Complete and persistent	MCD D8 ( <i>n</i> = 11)	MCD ( <i>n</i> = 9)	MCD ( <i>n</i> = 19)		
28	21	NOS ( <i>n</i> = 16)	2	D3	CsA IV + PP	Complete and persistent	MCD D6 ( <i>n</i> = 23)	MCD ( <i>n</i> = 14)	MCD ( <i>n</i> = 15)		
29	19	CELL ( <i>n</i> = 12)	5	D0	CsA oral	No remission	MCD D10 ( <i>n</i> = 18)	MCD ( <i>n</i> = 16)	NOS ( <i>n</i> = 18)		
30	14	COL ( <i>n</i> = 11)	3	D0	CsA IV + PP + high dose steroids	Complete and persistent	MCD D8 ( <i>n</i> = 14)	MCD ( <i>n</i> = 20)	MCD ( <i>n</i> = 11)		
31	19	CELL ( <i>n</i> = 9)	1.5	D4	CsA oral + PP	Partial remission	MCD D17 ( <i>n</i> = 18)	TIP ( <i>n</i> = 13)	PH ( <i>n</i> = 12)		
32	12	PH ( <i>n</i> = 7)	2	D0	CsA oral	No remission	Transplantectomy M6	MCD D12 ( <i>n</i> = 16)	COL ( <i>n</i> = 17)	X	Transplantectomy M6 COL
33	20	TIP ( <i>n</i> = 9)	2	D2	CsA oral	Partial remission		MCD D10 ( <i>n</i> = 11)	MCD ( <i>n</i> = 16)	NOS ( <i>n</i> = 14)	
34	12	COL ( <i>n</i> = 11)	1.6	D0	CsA IV + PP + high dose steroids	Complete and persistent		MCD ( <i>n</i> = 20)	MCD ( <i>n</i> = 22)		
35	16	CELL ( <i>n</i> = 13)	0.3	D4	CsA IV + PP + rituximab	No remission	Transplantectomy M36	MCD D60 ( <i>n</i> = 10)	MCD ( <i>n</i> = 19)	NOS ( <i>n</i> = 12)	Transplantectomy M36 COL
36	8	MCD ( <i>n</i> = 11) then NOS ( <i>n</i> = 16)	1	D0	CsA oral + PP + rituximab	No remission			PH ( <i>n</i> = 14)	PH ( <i>n</i> = 16)	
37	17	PH ( <i>n</i> = 9)	3	D0	CsA oral	No remission			CELL ( <i>n</i> = 11)	CELL ( <i>n</i> = 20)	
38	12	NOS ( <i>n</i> = 21)	1	D1	CsA oral + PP	Partial	PH D15 ( <i>n</i> = 17)	PH ( <i>n</i> = 14)	PH ( <i>n</i> = 9)		
39	18	TIP ( <i>n</i> = 15)	3	D8	CsA IV + PP + high dose steroids	Complete and persistent		MCD D10 ( <i>n</i> = 19)	MCD ( <i>n</i> = 17)	MCD ( <i>n</i> = 14)	
40	16	PH ( <i>n</i> = 14)	1.5	D1	CsA IV	No remission	Transplantectomy M6	MCD D11 ( <i>n</i> = 21)	COL ( <i>n</i> = 10)	X	Transplantectomy M6 COL
41	22	NOS ( <i>n</i> = 17)	4	D10	CsA oral + PP	No remission		MCD D12 ( <i>n</i> = 18)	COL ( <i>n</i> = 11)	COL ( <i>n</i> = 9)	
42	8	NOS ( <i>n</i> = 16)	1.2	D0	Cyclophosphamide + PP	No remission	Transplantectomy M24	MCD D10 ( <i>n</i> = 16)	MCD ( <i>n</i> = 20)	CELL ( <i>n</i> = 12)	Transplantectomy M24 CELL
<i>Mean ± SD</i>	<i>9.2 ± 6.9</i>		<i>3.9 ± 3.3</i>					<i>19.5 ± 11.6</i>			

D, day; M, month; CsA, cyclosporine; IV, intravenous; PP, plasmapheresis; CELL, cellular; COL, collapsing; NOS, not otherwise specified; TIP, tip lesion, PH, perihilar; MCD, minimal change disease; X, return in dialysis.

**Table 3.** Course of FSGS variants on kidney biopsies performed in transplant recipients with recurrence of proteinuria on successive kidney transplant

Patients	Native kidney	First allograft	Second allograft			Third allograft		
			Biopsy at time of recurrence (number of glomeruli)	Month 3 Biopsy (number of glomeruli)	Month 12 biopsy (number of glomeruli)	Biopsy at time of recurrence (number of glomeruli)	Month 3 (number of glomeruli)	Month 12 biopsy (number of glomeruli)
3	CELL	COL	MCD ( <i>n</i> = 12)	NOS ( <i>n</i> = 10)	NOS ( <i>n</i> = 7)	MCD ( <i>n</i> = 9)	MCD ( <i>n</i> = 18)	MCD ( <i>n</i> = 16)
7	CELL	NOS	MCD ( <i>n</i> = 23)	MCD ( <i>n</i> = 14)	X			
19	NOS	COL	MCD ( <i>n</i> = 16)	MCD ( <i>n</i> = 15)	NOS ( <i>n</i> = 8)			
32	PH	COL	MCD ( <i>n</i> = 15)	MCD ( <i>n</i> = 12)	TIP ( <i>n</i> = 12)			
36	NOS	PH	MCD ( <i>n</i> = 9)	MCD ( <i>n</i> = 20)	MCD ( <i>n</i> = 14)			
42	NOS	CELL	MCD ( <i>n</i> = 7)	MCD ( <i>n</i> = 18)	MCD ( <i>n</i> = 20)	MCD ( <i>n</i> = 17)	MCD ( <i>n</i> = 12)	MCD ( <i>n</i> = 9)

CELL, cellular; COL, collapsing; NOS, not otherwise specified; TIP, tip lesion; PH, perihilar; MCD, minimal change disease; X, return in dialysis.

are on long-term permanent therapy with PP). Conversely, patients who never achieved complete and sustained remission developed FSGS lesions. Histological findings on native kidneys were not predictive of either recurrence or category of FSGS variant on 3-month or 12-month biopsies, and only 3 patients (Table 2: patients 7, 16 and 24) had the same variants on native kidney biopsies and on 12-month transplant biopsies. In four cases (Table 2: patients 3, 7, 31 and 35), the FSGS variant changed during the post-transplant course.

Six patients experienced a recurrence on a second allograft and two on a third one. Histological findings were different from native kidney on the first, second or even the third allograft (Table 3).

In the recurrence group, 6/42 patients lost their graft during the first year and 12/42 patients during the first 5 years. The five-year graft survival in this group was 71.5%. In the group exempt of recurrence, the 5-year graft survival was 85.5%.

Only one patient had an electron microscopy study (Table 2: patient 6) at the time of nephrotic-range proteinuria recurrence with the observation of foot process effacement.

## Discussion

An early transplant biopsy in patients with recurrence of nephrotic-range proteinuria without signs of rejection shows normal glomeruli by light microscopy and no deposit by immunofluorescence. Electron microscopy, when performed, shows widespread foot process effacement. Lesions of FSGS develop only after several weeks as a consequence of persistent proteinuria. Therefore, the term of FSGS recurrence is confusing, and in this paper the recurrence was considered when massive proteinuria occurs soon after transplantation even if renal biopsies did not show histological lesion of FSGS. In the absence of glomerular immune deposits and in the absence of histological sign of rejection, the diagnosis of recurrence is almost certain. Moreover, those patients with recurrence of massive proteinuria who respond to therapy with complete and sustained remission of proteinuria do not develop FSGS as it was the case in 17/42 patients in our series.

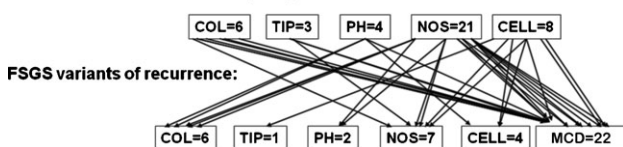
In native kidney, we found a distribution of FSGS variants different from the adult American population, but sim-

ilar to the only paediatric report available [23–25]. NOS and CELL were the most frequent variants observed, with a greater representation of NOS, supporting the idea that it is the commonest variant even in a paediatric population. Interestingly, we observed TIP (7.8%) and PH (7.8%) variants in children. The fact that all FSGS variants were present in the native kidney, even the TIP lesions that are often steroid sensitive and have a more favourable outcome [15], demonstrates that all FSGS variants can lead to ESRD. Interestingly, perihilar variant, usually observed in the secondary form [26], was present in native kidneys of four patients who experienced recurrence. Furthermore, after transplantation, two patients suffering from recurrence had a perihilar variant.

At the time of proteinuria recurrence, MCD was the most frequently histological pattern. Only one patient (patient 38) had already developed FSGS (PH variant) on Day 15, on the transplant kidney. One might hypothesize that this lesion was present in the donor kidney. But, this donor had no past history of proteinuria, and pre-transplant biopsy did not show any glomerular abnormality. Furthermore, the following course of this recipient was concordant with recurrence. Thus, we interpreted this as the result of a probably uncontrolled and more aggressive disease leading to the rapid constitution of FSGS. Interestingly, early FSGS was also observed in two patients in a recent study (COL on Day 7 and NOS on Day 10) [21].

At Month 3 and subsequently, the incidence of MCD decreased progressively while FSGS was increasingly observed in those patients with persistent proteinuria. Conversely, at 1 year, there was a strong association between sustained remission and the absence of FSGS. So, on serial biopsies, the incidence of MCD decreased over time and the incidence of FSGS variants increased. As we previously observed, patients who achieved complete remission under intensive and prolonged treatment of recurrence did not develop FSGS lesion [27]. These serial biopsies indicated a correlation between the clinical status and histological findings.

During this period (1984–2007), many treatments were used to treat INS recurrence with good efficiency (5-year graft survival is 71.5% in our study population). Concordant studies had demonstrated the relative efficiency of the association of intravenous cyclosporine with plasma exchanges to obtain and sustain complete remission [27,28].

**FSGS variants on native kidneys of patients affected with recurrence:**

**Fig. 3.** Summary of the different patterns of FSGS variant observed on a native kidney of patients with recurrence of proteinuria in the nephrotic range, and variant observed on a transplant kidney.

This series confirmed that rituximab did not dramatically change the course of recurrence, and did not consistently reach remission [29,30].

The aims of this study were to determine if the Columbia classification of FSGS (1) could predict the risk of recurrence of INS, and (2) the type of FSGS variant after transplantation. Here, we showed that all FSGS variants, even the PH variant, were present in the native kidney of patients with idiopathic NS progressing to ESRD, and that no difference in their distribution was observed between recurrent and non-recurrent patients. In other words, recurrence of proteinuria/NS may be observed whatever the type of FSGS variant and conversely patients with an FSGS variant (COLL, CELL) were usually associated with a severe clinical course. On the other hand, all types of FSGS variants were observed in the transplant kidney and we did not find any correlation between the variant present in the native kidney and those occurring in transplanted kidney (Figure 3). It should be stressed that only 3/21 had the same FSGS variant in native and transplanted kidneys. Interestingly, all FSGS variants were observed in transplanted kidneys with recurrence.

The discrepancy between variant native and transplant kidneys may have several explanations. Several factors may play a role in the development of FSGS in nephrotic patients. First of all, the probable immunological course of the disorders may lead to the production of the pathogenic circulating factor. This factor is the same before and after transplantation, and its consequences could be modified by the immunosuppressive regimen. The long-term use of immunosuppressive drugs, especially calcineurin inhibitors, promotes obliterative vascular lesions and ischaemic territories that can lead to the development of FSGS. The form associated with ischaemia is usually the collapsing variant [31,32]. Secondly, the genetic background of the transplanted kidney, different from the recipient, may be also in question. Supporting this hypothesis, recent data have highlighted that multiple *MYH9* SNPs and haplotypes were recessively associated with FSGS [33]. In addition, the haemodynamic condition associated with a solitary kidney could favour the development of FSGS, or more specifically, the PH variant. Two other variables render it difficult to classify the variant: firstly biopsy sampling, and secondly the delay between onset of proteinuria and biopsy. In this series, biopsy specimens were serially studied and a mean of 13.7 glomeruli per biopsy was examined allowing a precise evaluation of FSGS variants. Indeed, late biopsies after the beginning of the disease are more difficult to interpret because all FSGS variants found at early stages of the disease might progress towards NOS variant [15].

Following transplantation, the rate of recurrence of proteinuria varies between 30% and 50% and is associated with a poor graft outcome [8–14]. Several risk factors for recurrence have been identified including older age at onset on disease, rapid progression to ESRD and recurrence on a previous graft but none of them can clearly distinguish between patients who will and those who will not be affected by recurrence [34]. On native kidneys, the recent Columbia University classification is interesting since it combines epidemiological data on native kidneys with information on the prognosis and response to treatment. The two main variants are NOS and CELL. The COL variant is associated with the worse prognosis i.e. poor or no response to treatment. In contrast, patients with the TIP variant often respond to corticosteroids and rarely progress to ESRD. NOS, PH and CELL variants are associated with an intermediate prognosis [23,25,35]. The aim of our study was to evaluate the potential value of the Columbia classification of FSGS to predict risk and the type of recurrence, questions that had never been addressed. Ijpeelaar *et al.* recently identified in 21 cases three distinct patterns of recurrence of FSGS in renal transplant: firstly, recurrence of the same variant of FSGS; secondly, recurrence of the same variant of FSGS after an intermediate state of MCD and a third pattern of recurrence with a different FSGS variant in the allograft [21]. The authors found a high rate of concordance of FSGS variant between native and transplanted kidneys. The discrepancy with our results may be explained by several differences. On the native kidney, diagnosis of FSGS and the type of variant in our series were all performed on renal biopsies with a mean of  $13.7 \pm 4.6$  (range 6–24) glomeruli, whereas it was performed on the nephrectomy specimen in 6/19 native kidney in the Ijpeelaar study. Indeed, the predominant pattern of NOS variant observed in their study is certainly explained by the course of disease progression as it was suggested in the Columbia Classification [15]. In the same way, after kidney transplantation, in the Ijpeelaar study, transplant biopsies were performed late, at a mean of 783.4 days (range 10–2555), suggesting that most biopsies at the time of recurrence, which occurred classically early after transplantation, were not available. In our series, renal biopsies were performed within the first 3 months of recurrence, an explanation for the diverse type of FSGS lesion observed.

In conclusion, our series is the first to report serial biopsy data in kidney transplant recipients with recurrent nephrotic syndrome. Our results suggest that the Columbia classification of FSGS is not helpful in predicting neither recurrence nor the histological variant of FSGS when recurrence develops.

*Conflict of interest statement.* None declared.

## References

1. Barisoni L, Schnaper HW, Kopp JB. A proposed taxonomy for the podocytopathies: a reassessment of the primary nephrotic diseases. *Clin J Am Soc Nephrol* 2007; 2: 529–542
2. Habib R, Levy M, Gubler MC. Clinicopathologic correlations in the nephrotic syndrome. *Paediatrician* 1979; 8: 325–348

3. Cameron JS. The enigma of focal segmental glomerulosclerosis. *Kidney Int Suppl* 1996; 57: S119–S131
4. Howie AJ. Segmental sclerosing glomerular lesions. *Pediatr Nephrol* 1993; 7: 370–374
5. Kashgarian M, Hayslett JP, Siegel NJ. Lipoid nephrosis and focal sclerosis distinct entities or spectrum of disease. *Nephron* 1974; 13: 105–108
6. Cho MH, Hong EH, Lee TH *et al.* Pathophysiology of minimal change nephrotic syndrome and focal segmental glomerulosclerosis. *Nephrology (Carlton)* 2007; 12 (Suppl 3): S11–S14
7. Tejani A. Morphological transition in minimal change nephrotic syndrome. *Nephron* 1985; 39: 157–159
8. Ingulli E, Tejani A. Incidence, treatment, and outcome of recurrent focal segmental glomerulosclerosis posttransplantation in 42 allografts in children—a single-center experience. *Transplantation* 1991; 51: 401–405
9. Pardon A *et al.* Risk factors and outcome of focal and segmental glomerulosclerosis recurrence in adult renal transplant recipients. *Nephrol Dial Transplant* 2006; 21: 1053–1059
10. Cameron JS, Senguttuvan P, Hartley B *et al.* Focal segmental glomerulosclerosis in fifty-nine renal allografts from a single centre; analysis of risk factors for recurrence. *Transplant Proc* 1989; 21(Pt 2): 2117–2118
11. Dantal J, Baatard R, Hourmant M *et al.* Recurrent nephrotic syndrome following renal transplantation in patients with focal glomerulosclerosis. A one-center study of plasma exchange effects. *Transplantation* 1991; 52: 827–831
12. Dantal J, Souillou JP. Relapse of focal segmental glomerulosclerosis after kidney transplantation. *Adv Nephrol Necker Hosp* 1996; 25: 91–106
13. Tejani A, Stablein DH. Recurrence of focal segmental glomerulosclerosis posttransplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study. *J Am Soc Nephrol* 1992; 2(Suppl 12): S258–S263
14. Artero M *et al.* Recurrent focal glomerulosclerosis: natural history and response to therapy. *Am J Med* 1992; 92: 375–383
15. D'Agati VD, Fogo AB, Bruijn JA *et al.* Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004; 43: 368–382
16. Howie AJ, Pankhurst T, Sarioglu S *et al.* Evolution of nephrotic-associated focal segmental glomerulosclerosis and relation to the glomerular tip lesion. *Kidney Int* 2005; 67: 987–1001
17. Beaman M, Howie AJ, Hardwicke J *et al.* The glomerular tip lesion: a steroid responsive nephrotic syndrome. *Clin Nephrol* 1987; 27: 217–221
18. Detwiler RK, Falk RJ, Hogan SL *et al.* Collapsing glomerulopathy: a clinically and pathologically distinct variant of focal segmental glomerulosclerosis. *Kidney Int* 1994; 45: 1416–1424
19. Schwartz MM, Lewis EJ. Focal segmental glomerular sclerosis: the cellular lesion. *Kidney Int* 1985; 28: 968–974
20. Fuiano G *et al.* Serial morphometric analysis of sclerotic lesions in primary 'focal' segmental glomerulosclerosis. *J Am Soc Nephrol* 1996; 7: 49–55
21. Ijpeelaar DH *et al.* Fidelity and evolution of recurrent FSGS in renal allografts. *J Am Soc Nephrol* 2008
22. Tonna SJ *et al.* NPHS2 variation in focal and segmental glomerulosclerosis. *BMC Nephrol* 2008; 9: 13
23. Thomas DB, Franceschini N, Hogan SL *et al.* Clinical and pathologic characteristics of focal segmental glomerulosclerosis pathologic variants. *Kidney Int* 2006; 69: 920–926
24. Stokes MB, Valeri AM, Markowitz GS *et al.* Cellular focal segmental glomerulosclerosis: clinical and pathologic features. *Kidney Int* 2006; 70: 1783–1792
25. Silverstein DM, Craver R. Presenting features and short-term outcome according to pathologic variant in childhood primary focal segmental glomerulosclerosis. *Clin J Am Soc Nephrol* 2007; 2: 700–707
26. D'Agati V. Pathologic classification of focal segmental glomerulosclerosis. *Semin Nephrol* 2003; 23: 117–134
27. Canaud G, Zuber J, Sberro R *et al.* Intensive and prolonged treatment of focal and segmental glomerulosclerosis recurrence in adult kidney transplant recipients: a pilot study. *Am J Transplant* 2009; 9: 1081–1086
28. Salomon R, Gagnadoux MF, Niaudet P. Intravenous cyclosporine therapy in recurrent nephrotic syndrome after renal transplantation in children. *Transplantation* 2003; 75: 810–814
29. Yabu JM, Ho B, Scandling JD *et al.* Rituximab failed to improve nephrotic syndrome in renal transplant patients with recurrent focal segmental glomerulosclerosis. *Am J Transplant* 2008; 8: 222–227
30. Kamar N, Faguer S, Esposito L *et al.* Treatment of focal segmental glomerular sclerosis with rituximab: 2 case reports. *Clin Nephrol* 2007; 67: 250–254
31. Nadasdy T, Allen C, Zand MS. Zonal distribution of glomerular collapse in renal allografts: possible role of vascular changes. *Hum Pathol* 2002; 33: 437–441
32. Goes NB, Colvin RB. Case records of the Massachusetts General Hospital. Case 12–2007. A 56-year-old woman with renal failure after heart-lung transplantation. *N Engl J Med* 2007; 356: 1657–1665
33. Kopp JB, Smith MW, Nelson GW *et al.* MYH9 is a major-effect risk gene for focal segmental glomerulosclerosis. *Nat Genet* 2008; 40: 1175–1184
34. Fine RN. Recurrence of nephrotic syndrome/focal segmental glomerulosclerosis following renal transplantation in children. *Pediatr Nephrol* 2007; 22: 496–502
35. Stokes MB, Markowitz GS, Lin J *et al.* Glomerular tip lesion: a distinct entity within the minimal change disease/focal segmental glomerulosclerosis spectrum. *Kidney Int* 2004; 65: 1690–1702

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