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ban@renal.org.ar

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Jerzak, Patryk; Konieczny, Andrzej; Sroka, Michał;
Lis, Łukasz; Witkiewicz, Wojciech; Hruby, Zbigniew

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Focal and Segmental Glomerulosclerosis in Adults: Early Clinical Course and Prognostic Factors for Short-Term Outcome

Glomeruloesclerosis Focal y Segmentaria en adultos: Evolución clínica temprana y factores pronósticos de resultados a corto plazo

Patryk Jerzak¹, Andrzej Konieczny², Michał Sroka¹, Łukasz Lis¹, Paweł Podgórski¹, Wojciech Witkiewicz¹, Zbigniew Hruby¹

ABSTRACT

Background: Primary focal and segmental glomerulosclerosis progresses to end-stage renal disease in every other patient, and therefore determinants of its long-term outcome have been extensively studied. Immediate response to treatment has been regarded as a positive prognostic predictor and short-term manifestation of the disease could affect its determinants. Therefore, we have sought to assess the early clinical course of primary adult focal and segmental glomerulosclerosis and analyze its prognostic factors.

Methods: We have retrospectively assessed clinical course of primary focal and segmental glomerulosclerosis ("not otherwise specified" histological variant) in 84 adults. Renal function was expressed as serum creatinine concentration and equilibrated glomerular filtration rate (MDRD equation). Proteinuria was expressed as protein to urinary creatinine ratio, assessed in the morning voiding sample. The evaluation of these parameters was performed every 3 months after diagnosis. Statistical analysis was achieved using package Statistica.

Results: As result of treatment, complete remission of proteinuria, was attained in 30 subjects (35.7%), partial remission in 37 persons (44%), whereas in 17 patients protein excretion rate remained unchanged (20.2%). The severity of glomerular injury, at initial presentation of the disease, correlated with its early (12 months) outcome: patients attaining early complete

remission have had the lowest initial proteinuria, higher serum albumin and total protein concentrations than those who have failed to achieve remission. Pharmacotherapy with prednisone, but not with calcineurin inhibitors or mycophenolate mofetil was demonstrated to significantly affect achievement of remission.

Conclusions: Early remission of proteinuria in response to treatment is feasible in 44% of patients with primary focal and segmental glomerulosclerosis, it is best achieved in subjects presenting with mild glomerular injury, and in patients treated with prednisone. Higher serum albumin and total protein concentrations predict better response to induction of remission.

KEYWORDS: focal and segmental glomerulosclerosis; prognosis factors; adults; renal function; remission

RESUMEN

Antecedentes: La glomeruloesclerosis focal y segmentaria se convierte en nefropatía terminal en uno de cada dos pacientes, por lo que los factores determinantes de sus desenlaces a largo plazo han sido objeto de muchos estudios. La respuesta inmediata al tratamiento se considera un factor pronóstico favorable, y las manifestaciones a corto plazo de la enfermedad pueden afectar los factores determinantes. Por todo ello, hemos buscado evaluar la evolución clínica temprana de la glomeruloesclerosis focal y segmentaria primaria, y analizar

1) Department of Nephrology, Voivodship Specialty Hospital, Center for Research and Development, Wrocław, Polonia

2) Department of Nephrology and Transplantation Medicine, Wrocław Medical University, Wrocław, Polonia

Correspondencia:

Dr. Łukasz Lis
ORCID: 0000-0002-4075-6924
lislukasz@gmail.com

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sus factores pronósticos. **Material y métodos:** Hemos realizado un estudio retrospectivo para evaluar la evolución clínica de la glomeruloesclerosis focal y segmentaria primaria (variante histológica “sin otra especificación”) en 84 pacientes adultos. Se evaluó la función renal a través de la creatinina sérica y filtrado glomerular equilibrado calculado mediante la ecuación MDRD. La proteinuria se expresó como relación proteína/creatinina urinaria, evaluada en la muestra miccional matutina. La evaluación de estos parámetros se realizó cada 3 meses después del diagnóstico. El análisis estadístico se logró utilizando el paquete Statistica.

Resultados: Como resultado del tratamiento, se obtuvo una remisión completa de la proteinuria en 30 sujetos (35,7%), una remisión parcial en 37 personas (44%), mientras que, en 17 pacientes, la tasa de excreción de proteínas se mantuvo sin cambios (20,2%). En la presentación inicial de la enfermedad, la gravedad de la lesión glomerular se correlacionó con su resultado temprano (12 meses): los pacientes que lograron una remisión completa temprana mostraron los niveles más bajos de proteinuria inicial, y concentraciones más altas de albúmina sérica y proteínas totales que aquellos que no alcanzaron la remisión. Se demostró que la farmacoterapia con prednisona –pero no con inhibidores de calcineurina o micofenolato de mofetilo– condiciona de forma significativa el logro de la remisión. **Conclusiones:** La remisión temprana de la proteinuria en respuesta al tratamiento es factible en el 44% de los pacientes con glomeruloesclerosis focal y segmentaria primaria; se obtienen mejores resultados en sujetos que presentan una lesión glomerular leve y en pacientes tratados con prednisona. Las concentraciones más altas de albúmina sérica y proteínas totales predicen una mejor respuesta para inducir la remisión.

PALABRAS CLAVE: glomeruloesclerosis focal y segmentaria; factores pronósticos; adultos; función renal; remisión

INTRODUCTION

Focal and segmental glomerulosclerosis (FSGS) accounts for nearly 40% of all cases of nephrotic syndrome (NS) in adults, and along with other glomerular diseases, is responsible for the second, after diabetic nephropathy, most frequent cause of end stage renal disease (ESRD).⁽¹⁾ Its pathogenesis

is highlighted by damage to glomerular podocytes, by unidentified factor, leading to foot process’ effacement, denudation of basement membrane with subsequent hyalinization and glomerular sclerosis, causing progressive loss of renal function.

⁽²⁾ The main histopathological feature of the disease is hyalinization of glomerular tufts, expansion of mesangial matrix and mononuclear cell infiltrate in the tubulointerstitium. Variable expression of these lesions in individual cases formed basis for identification of five histologic variants of the FSGS.⁽³⁾ These types present as distinct clinical entities, with different course and response to treatment, including glomerular tip lesion, collapsing glomerulopathy, peri-hilar and cellular types, along with poorly defined “not otherwise specified” (NOS) FSGS glomerulopathy. The latter is regarded as the most common variant, occurring in approximately 62% of cases.⁽⁴⁾ The main clinical manifestations of FSGS comprise proteinuria (including NS and its consequences), arterial hypertension and progressive loss of glomerular filtration. The principal purpose of treatment is remission of proteinuria, good hypertension control and halting progression of renal failure. The overall prognosis is unfavorable, since approximately 50% of patients reach ESRD at 10 years after diagnosis.⁽²⁾

Goal of the study

The main purpose of the study was to identify determinants of the short-term outcome of primary FSGS within the first year of diagnosis. In this regard we have tried to find out, whether the severity of disease at presentation influenced the patients’ outcome 12 months later.

MATERIAL AND METHODS

A retrospective analysis was performed on clinical data of patients, hospitalized in department of nephrology, in the years 2008-2016, due to NF, with biopsy proven FSGS, as part of standard diagnostic procedure. The histological assessment of percutaneous renal biopsy specimens was based on evaluation of light and immunofluorescence microscopic images. A possibility of secondary FSGS was ruled out on clinical and anamnestic grounds, by excluding subjects with evident exposure to toxins, infections and conditions characterized by glomerular hyperfiltration.⁽⁵⁾

In each patient renal function was assessed

by serum creatinine concentration (sCr) and equilibrated glomerular filtration rate (eGFR) value, the latter using abbreviated MDRD equation. Moreover, serum total protein and albumin concentrations were taken into account. Proteinuria was expressed as protein to urinary creatinine ratio (UPCR), assessed in the morning voiding sample. The subsequent evaluation of the above parameters was performed every 3 months after diagnosis.

The complete remission criteria were the following: a fall of the UPCR below 0.3, along with sCr within limits of normal and serum albumins above 3.5 g/dl. UPCR in the range of 0.3-3.5 with stable sCr (change in sCr of up to 25% of the initial value) was regarded as the partial remission criteria. Alternatively, UPCR of 0.3-3.5, provided that it resulted from reduction of proteinuria by at least 50% was also regarded as a partial remission.

Results obtained were presented as means and standard deviations. Statistical analysis was performed using statistical package Statistica (StatSoft, Tulsa, OK, USA). Numerical data were presented as mean values and standard deviations.

All these data were evaluated as to the normal distribution, utilizing Shapiro-Wilk W test. Data characterized by normal distribution and meeting the assumption of homogeneity of variances were assessed with t-student test when comparing 2 groups or with the analysis of variances (ANOVA) when comparing at least 3 groups. When with the ANOVA test a zero hypothesis on equality of the groups was discarded, further analysis was performed using post-hoc Bonferroni test. Data lacking normal distribution were assessed utilizing U Mann Whitney test, when comparing 2 groups and nonparametric Chi-square Pearson test for qualitative parameters. Level of statistical significance was set at $p < 0.05$.

RESULTS

84 patients (32 females and 52 males) were enrolled in the study, with histopathologically confirmed primary FSGS NOS histopathological type (Columbia University classification). Main laboratory data of persons enrolled have been presented in the **Table 1**.

Table 1. Main Laboratory Data

Parameter	Mean	Min	Max
Age	52.6	20	91
sCr (mg/dl)	1.3	0.6	6.6
eGFR (ml/min/1.73 m ²)	68.7	9.01	119.3
UPCR (g/24 h)	3.1	0.3	12.4
Plasma albumin concentration (g/dll)	3.4	1.4	4.8
Plasma total protein concentration (g/dll)	5.7	3.4	8.2

Management of glomerulopathy included supportive antihypertensive therapy with angiotensin converting enzyme inhibitor (ACEI) or angiotensin I receptor blocker (ARB) in 77 subjects (92% of the population enrolled) at a maximal tolerated dose, unless contraindicated. Subsequently, remission induction was undertaken with administration of oral prednisone, starting from 1 mg/kg body weight (up to 60 mg/day) in 65 patients (77% of the total group enrolled). This dosage was continued for 12 weeks, later on tapered to 0.5 mg/kg and carried on for further 12 weeks. In case of non-response to prednisone the therapy was supplemented by calcineurin

inhibitors: cyclosporine in 31 persons (37%) or tacrolimus in 3 individuals (6.3%). Intolerance to calcineurin inhibitor resulted in treatment with use of mycophenolate mofetil in 7 patients (8.3%).

As a result of treatment, complete remission of proteinuria, defined by the KDIGO Guidelines⁽⁶⁾ was attained in 30 subjects (35.7%), partial remission in 37 persons (44%), whereas in 17 patients protein excretion rate remained unchanged (20.2%). **Table 2** summarizes patients' data at completion of observation in the treated group.

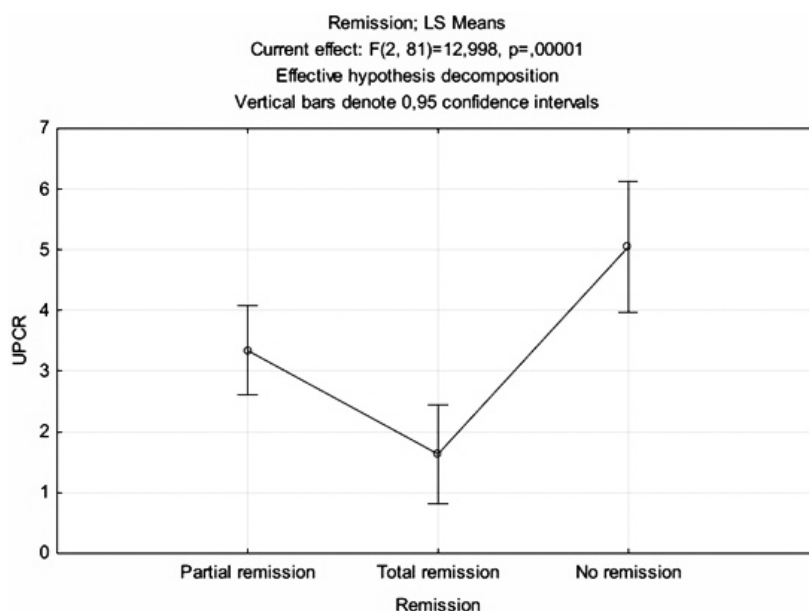
Table 2. Patients' data at completion

Parameter	Mean	Min	Max
sCR (mg/dl)	1.4	0.7	5.3
eGFR (ml/min/1.73 m ²)	65.6	9.8	139.1
UPCR	2.0	0.2	16.4
Serum albumin (g/dl)	3.7	1.5	4.8
Total serum protein (g/dl)	6.2	2.6	7.7

Statistical analysis revealed no significant differences in patients enrolled regarding reduction of proteinuria adjusted for patient's age, SCr, and eGFR between enrollment and termination of the study. The pace of achieving remission at the onset of treatment was not demonstrated to influence patient's outcome following one years' treatment/observation.

The severity of glomerular injury at initial

presentation of the disease appeared to influence it's early (12 months) outcome: patients attaining early complete remission have had the lowest initial UPCR (1.6), significantly lower than in the partial remitters (UPCR=3.3), as well as in those who have failed to achieve any remission at all (UPCR=5.05). Respective data have been presented in **Figure 1** and **Table 3**.

Figure 1. Relation between the magnitude of initial proteinuria and remission of the disease. (Significance of differences $p=0.00001$, vertical bars indicate confidence intervals at 0.95)**Table 3.** Results of Bonferroni test assessing significance of differences between groups achieving partial, complete and no remission of proteinuria at the onset of observation 3.3403 {1}, 1.6327 {2} and 5.0482 {3}. (UPCR by Bonferroni test. Probabilities of the post-hoc tests. Error: MS intergroup = 5.0471, df = 81.000)

	Bonferroni test; variable UPCR				
	Probabilities for Post Hoc Tests				
	Error: Between MS = 5.0471, df = 81.000				
Cell No.	Remission3.3403	{1}	{2}	{3}	
		1.6327	5.0482		
1	Partial remission		0.008136	0.033706	
2	Total remission	0.008136		0.000009	
3	No remission	0.033706	0.000009		

Statistical analysis has demonstrated that serum albumin concentration at diagnosis could be regarded as a predictor of early remission in response to treatment. It has been documented, employing Bonferroni's method, that in persons attaining complete remission of proteinuria,

albuminemia at the onset of disease (3.7 g/dl) was significantly higher, than in those with partial remission (3.5 g/dl), as well as in patients with no remission (2.7 g/dl). **Figure 2** and **Table 4** illustrate this finding.

Figure 2. Relation between achieving remission of proteinuria and initial serum albumins' concentration. (Significance of differences $p=0.00121$. Vertical bars indicate confidence intervals at 0.95)

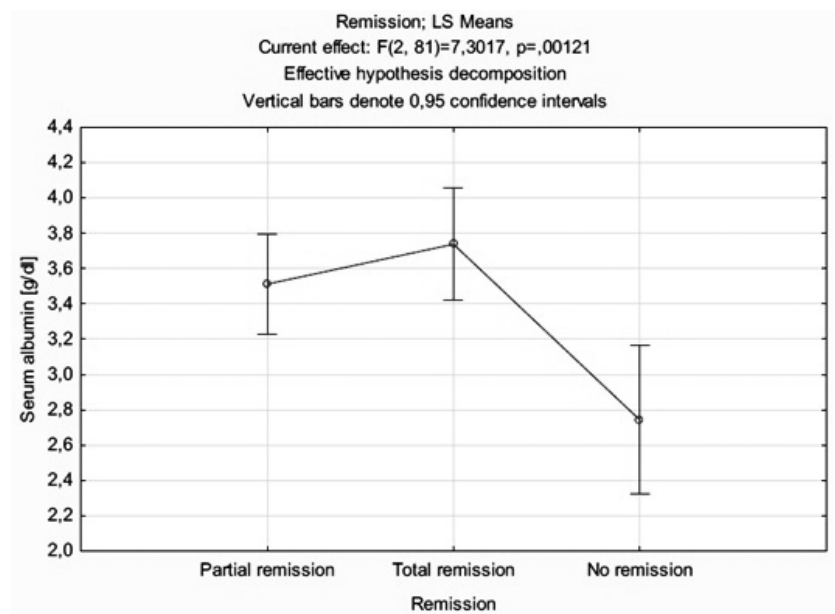


Table 4. Analysis of significance of differences (Bonferroni method) between groups attaining complete, partial or no remission in relation to the serum albumins' concentration of 3.5122 g/dl {1}, 3.7380 g/dl {2} or 2.7429 g/dl {3} at the onset of observation. Serum albumins by Bonferroni test. Probabilities of the post-hoc tests. Error: MS intergroup = 0.76121, df = 81.000

	Bonferroni test; variable Serum albumin [g/dl]			
	Probabilities for Post Hoc Tests			
	Error: Between MS = 0.76121, df = 81.000			
Cell No.	Remission 3.5122	{1}	{2}	{3}
		3.7380	2.7429	
1	Partial remission		0.885619	0.010476
2	Total remission	0.885619		0.000969
3	No remission	0.010476	0.000969	

Similarly, the serum albumin concentration at the onset of observation, also serum total protein concentration was observed to display statistically significant differences. Patients with complete and partial remission of proteinuria have had significantly higher total serum protein concentrations (respectively, complete remission 6.1 g/dl, partial remission 5.8 g/dl) than those in whom remission was not achieved (4.9 g/dl). These results have been illustrated in **Figure 3** and **Table 5**.

As far as the influence of pharmacotherapy on achieving remission is concerned, correlation between remission and medication employed was noted exclusively regarding prednisone. Among patients treated with this drug (N=65), 24 (37%) reached complete remission also 24 (37%) - partial remission, whereas 17 patients (26%) have failed to achieve any remission of proteinuria ($P=0.01501$). Comparable regularities were not observed for cyclosporine, tacrolimus or mycophenolate mofetil.

Figure 3. Relation between remission of proteinuria and initial total serum protein concentration (Significance of differences $p=0.00337$, vertical bars indicate confidence intervals at 0.95)

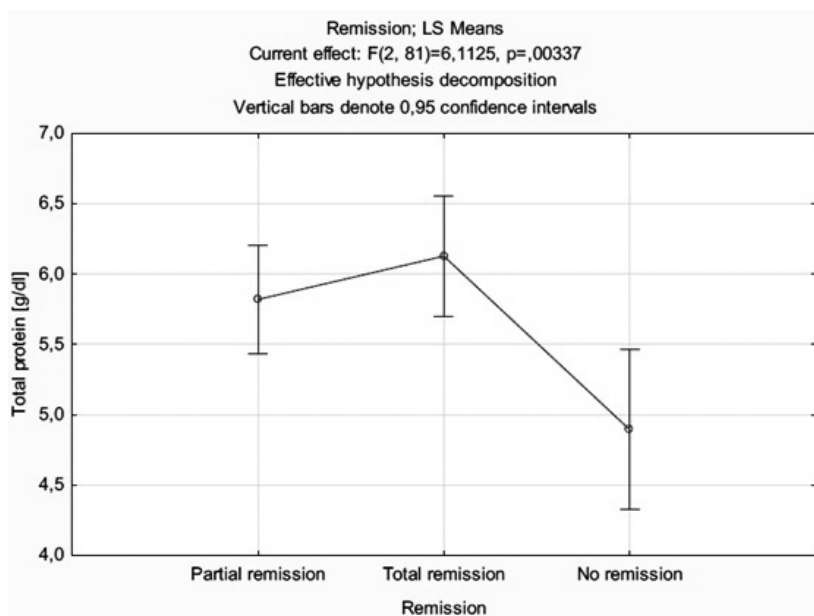


Table 5. Results of Bonferroni test illustrating differences between groups with regard to total serum protein concentration at the onset of observation

		{1}	{2}	{3}
		6.1277	4.8935	
			0.872423	0.026173
		0.872423		0.002637
		0.026173	0.002637	

Total serum protein [g/dl] by Bonferroni test. Probabilities of post-hoc tests. Error: MS intergroup = 1.3846, df = 81.000

DISCUSSION

Early complete remission of NS confers a very good prognosis for the long-term clinical course of primary FSGS.⁽²⁾ Histological variants of the disease include cellular, collapsing and NOS, the last one being most frequent, usually seen in over 40% of biopsies of the FSGS cases.⁽⁷⁾ Indeed, all the patients presented in this report were classified as the NOS subtype of primary FSGS. Nevertheless, with the exception of the collapsing type, histological variant hasn't been demonstrated to significantly impact upon the severity of the disease, or its prognosis.⁽⁸⁾ As demonstrated by investigators from the Toronto Glomerulonephritis Registry, also partial response to treatment could be regarded as a significant prognostic factor, heralding beneficial outcome of primary FSGS.⁽⁹⁾

This positive influence of partial remission on the rate of kidney function decline was seen regardless of the type of histopathological changes and mode of treatment of glomerular injury. In our

study, comparable results were obtained concerning fraction of patients reaching remission, although the observation time was too short to draw reliable prognostic conclusions.

Our analysis has demonstrated that the severity of glomerular injury at initial presentation of FSGS impacted upon its clinical course and response to treatment. Conceivably, those patients who have had lower proteinuria and higher serum albumins concentration were more likely to attain complete remission of glomerular injury in response to immunomodulatory treatment with glucocorticoids and/or calcineurin inhibitors. These therapeutic agents are still regarded as a mainstay of drugs inducing remission of FSGS.⁽¹⁰⁾

Our results have also pointed at prednisone as the most effective drug in management of glomerular injury caused by primary FSGS, contrary to other immunomodulatory agents used in our study.

Unfortunately, we have not been able to define any early predictors of clinical course in patients

with primary FSGS. Nonetheless, it appears from our results that the patients more severely affected by glomerular injury at presentation of the disease are less likely to respond to treatment. Both degree of proteinuria and hypoalbuminemia/hypoproteinemia predicted response to induction of remission. Hypoalbuminemia has been recently identified, by Chinese researchers, as a negative prognostic factor for renal outcome in diabetic nephropathy.⁽¹¹⁾

The weakness of our study is undoubtedly short time of the follow-up, although we have aimed at identifying characteristics and predictive factors of early clinical course in primary FSGS. At this point, it is worth to note that this disease is not a single entity of uniform prognosis, but rather should be regarded as a specific type of clinicopathological presentation of glomerular injury. With this respect, Dutch investigators have identified a subgroup of patients with primary FSGS, of short duration and normal GFR, who regardless of degree of nephrotic presentation were not subjected to immunomodulatory treatment.⁽¹²⁾

These patients were characterized by high spontaneous remission rate and favorable long-term prognosis: 65% of them were free of proteinuria after 9.4 years follow-up. The authors concluded that in early course FSGS of subjects with normal renal function, the wait-and-see strategy may spare the patients of unnecessary and potentially harmful immunosuppression.

This observation further adds to the complexity of management of FSGS and underlines the necessity of careful and frequent observation of our patients.

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