Primary focal segmental glomerulosclerosis in children: epidemiology, clinical presentation and prognosis

Hyalinose segmentaire et focale primitive de l'enfant : épidémiologie, clinique et facteurs pronostiques

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Abstract

Introduction: Focal segmental glomerulosclerosis is a histopathological entity.

Aim: To analyze the epidemiological, clinical and histological profile of primary focal segmental glomerulosclerosis in children, as well as their prognostic factors.

Methods: This was a retrospective cross-sectional study over a period of 20 years (2001-2020), conducted in the Department of Pediatrics at Charles Nicolle Hospital in Tunis, which included children followed for primary focal segmental glomerulosclerosis.

Results: There were 35 children, 19 boys and 16 girls. The median age was 4.5 years. Nephrotic syndrome was seen in 88% of patients. Macroscopic hematuria was found in 4 cases, hypertension in 8 cases and renal failure in 7 cases at presentation. The most common variant was the not otherwise specified variant (77.1%). Steroid-sensitive nephrotic syndrome was observed in 71% of cases, and steroid-resistance in 29% of cases. Treatment with cyclosporine was indicated in 23 patients with complete remission rate of 56.5%. 42,8% children had progressed to chronic kidney disease, including an end-stage renal disease in 11.5% of cases. Only the presence of a family history of kidney disease was found as a predictive factor of progression to chronic kidney disease and end-stage renal disease. Renal survival rates were estimated at 100% at 3 years, 85% at 5 years and 73% at 10 years.

Conclusion: Identification of patients at high risk for chronic kidney disease progression, such as those with a family history of kidney disease or those who have failed to respond to corticosteroids, would allow therapeutic adjustments.

Key words: Primary focal segmental glomerulosclerosis - Nephrotic syndrome – Child –Renal failure – Prognosis

Résumé

Introduction : La hyalinose segmentaire et focale représente environ 7-10% des syndromes néphrotiques de l'enfant.

Objectif : Etudier le profil épidémiologique, clinique et anatomopathologique des hyalinoses segmentaires et focales primitives de l'enfant, ainsi que leurs facteurs pronostiques.

Méthodes : Il s'agissait d'une étude transversale rétrospective sur 20 ans (2001-2020), menée au service de pédiatrie de l'hôpital de Charles Nicolle de Tunis ayant inclus les enfants suivis pour une hyalinose segmentaire et focale primitive.

Résultats : Il s'agissait de 35 enfants (19 garçons et 16 filles). L'âge médian était de 4,5 ans. Les circonstances de découverte étaient dominées par le syndrome néphrotique dans 88% des cas. Le type histologique le plus fréquent était la variante non spécifique (77,1%). Le syndrome néphrotique était corticosensible dans 71% des cas, et corticorésistant dans 29% des cas. Le traitement par ciclosporine était indiqué chez 23 patients avec un taux global de rémission de 56,5%. 42,8% des enfants ont évolué vers l'insuffisance rénale chronique dont une insuffisance rénale terminale dans 11,5% des cas. Seule la présence des antécédents familiaux de néphropathie est retenue comme facteur prédictif d'évolution vers l'insuffisance rénale chronique et l'insuffisance rénale chronique terminale. La survie rénale était de 100% à 3 ans, de 85% à 5 ans et de 73% à 10 ans.

Conclusion : L'identification de patients à haut risque d'évolution vers l'insuffisance rénale chronique comme ceux aux antécédents familiaux de néphropathie ou ceux n'ayant pas répondu aux corticoïdes permettrait d'adapter la prise en charge thérapeutique.

Mots clés : Hyalinose segmentaire et focale Primitive - Syndrome néphrotique – Enfant - Insuffisance rénale- Pronostic

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INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is an anatomopathological entity characterized by hyaline deposits, sclerosing glomerular lesions, and effacement of podocyte foot processes. These lesions have a segmental and focal nature, meaning they affect only a portion of the glomerulus and certain glomeruli [1,2]. They account for 20% of idiopathic nephrotic syndromes in adults [3] and approximately 20-25% in children in the United States and Canada, with a prevalence that has been steadily increasing in recent years [4,5]. FSGS is the third leading cause of progression to end-stage renal disease (ESRD) and the primary cause of glomerulopathies leading to ESRD in children, according to the NAPRTCS (the North American Pediatric Renal Transplant Cooperative Study) [6]. The frequency of FSGS increases with age: it is less than 10% in children under 6 years old and increases to 20-50% in adolescents [7]. In many cases, the lesions are secondary to viral infection, nephron reduction of adaptive origin, or a mutation in a gene encoding a podocyte protein. However, there are other idiopathic forms that are attributed to immune system dysfunction and classified as systemic diseases [8]. The initial clinical presentation can include typical nephrotic syndrome (NS), gross hematuria, hypertension, or renal insufficiency [9]. Treatment is based on corticosteroid therapy, although there is a high rate of corticosteroid resistance. The use of cyclosporine (CsA) has shown high rates of remission [10]. In Tunisia, a few studies have focused on primary FSGS in children, their epidemiological characteristics, and their response to treatment. However, to our knowledge, the prognostic factors of this condition have not been studied. The aim of our study was to investigate the epidemiological, clinical, and anatomopathological profile of primary FSGS in children, as well as their prognostic factors.

METHODS

This is a retrospective cross-sectional study conducted at the Pediatrics Department of Charles Nicolle Hospital in Tunis over a 20-year period, from January 1st, 2001, to December 31, 2020. We included 35 patients aged ≤ 18 years at the time of diagnosis who had renal biopsy showing FSGS lesions and those in whom the diagnosis of primary FSGS was established after ruling out all other potential causes of secondary FSGS [3]: reflux nephropathy, unilateral renal agenesis or dysplasia, sickle cell disease, morbid obesity, genetic mutation (NPHS1 and NPHS2 gene study), nephropathy secondary to infection or toxic causes, and Alport syndrome. Hypertension was defined as systolic and/or diastolic blood pressure above the 97.5th percentile for age, height, and gender, according to the French Society of Pediatric Nephrology [9]. Glomerular filtration rate (GFR), reflecting renal function, was estimated using the modified Schwartz formula [10]. Chronic kidney diseases (CKD) were classified according to the KDIGO (Kidney Disease: Improving Global Outcomes) classification based on GFR values [11]. ESRD was defined as a GFR <15 ml/min/1.73m2SBA. All included children underwent renal biopsy based on the following indications: signs suggestive of secondary NS (gross hematuria, organic renal insufficiency, or hypertension), association of extrarenal signs, age <1 year or >12 years at the first episode, or steroid-resistant nephrotic syndrome (SRNS). Two renal fragments were obtained, one for light microscopy and the other for immunofluorescence. FSGS lesions were classified into five subtypes according to the Columbia classification of 2004 [12]: NOS (not otherwise specified), perihilar, cellular, tip lesion, and collapsing. The therapeutic protocol for treating NS followed the guidelines proposed by the French Society of Pediatric Nephrology [13], which consisted of steroid therapy using prednisone at a dose of 60 mg/m²/day, with a maximum dose of 60 mg/day for four weeks. If NS persisted after four weeks of treatment, three boluses of methylprednisolone at a dose of 1g/1.73 m^2 SBA were administered at 48-hour intervals. Oral steroid therapy was continued at the same dose between the infusions and for eight days after methylprednisolone infusions. Complete remission was defined as urinary protein excretion less than 5 mg/kg/d and serum albumin > 30 g/L after four weeks of oral corticosteroid therapy or after methylprednisolone infusions. Partial remission was defined as a significant reduction in proteinuria compared to the initial level with serum albumin > 30 g/L after four weeks of oral steroid therapy or after methylprednisolone infusions. SRNS was defined as persistent proteinuria > 50 mg/kg/d associated with serum albumin < 30 g/L, eight days after methylprednisolone boluses following four weeks of oral steroid therapy. Steroid dependence (SDNS) was

defined as relapse occurring during corticosteroid tapering or within three months after their discontinuation. CsA was administered at a dose of 150-200 mg/m²/day for 6 months, or alternatively, cyclophosphamide was given at a dose of 2 mg/kg/day for 12 weeks or a monthly bolus of 500 mg/m² for 6 months. In cases of non-response to CsA or cyclophosphamide or steroid dependence, mycophenolate mofetil (MMF) was administered at a dose of 1200 mg/m²/d.

RESULTS

Our study included thirty-five children with a follow-up duration of 6.3 years (1-6.8 years). There were 19 boys (54%) and 16 girls (46%), with a sex ratio of 1.18. The median age of our patients was 4.5 years (ranging from 15 months to 17 years). Family history of nephropathy was observed in 8 cases. A CKD of undetermined etiology was observed in 6 cases, with progression to ESRD and the need for hemodialysis in 4 cases. Nephrotic syndrome was identified in 2 cases, with membranous nephropathy (MN) diagnosed in 1 case through renal biopsy. In 3 cases, the individuals were first cousins, while in 4 cases, they were distant cousins. One patient had an aunt who was being treated for MN. Parental consanguinity was found in only one patient who had a first cousin undergoing hemodialysis for a nephropathy of undetermined etiology. The most frequent reason for consultation was edema in 85.7% of cases. At the time of diagnosis, hypertension was present in 22.9% of cases, macroscopic hematuria in 11.4%, and renal insufficiency in 20% of cases (Table I). The diagnosis of NS was made in 31 patients (88%), while acute nephritic syndrome was diagnosed in only one patient. Non-nephrotic proteinuria was noted in 3 cases. NS was classified as pure in 57% of cases. Two patients presented with extra-renal signs upon admission: one had facial dysmorphism with a normal karyotype, and the other had sensorineural hearing loss.

The NS was steroid sensitive (SSNS) in 71% of cases, with 9.6% of those cases were SDNS. SRNS was found in 29% of cases. CsA was indicated in 23 patients with an initial dosage ranging from 121 to 222 mg/m²/d and a remission rate of 56.5%, including complete remission in 47.8% of cases. Cyclophosphamide was prescribed in only 4 cases with a remission rate of 50%. MMF was used in 16 cases (the second-line drug of choice after CsA in 12 patients). The outcome under MMF was favorable in 7 patients (43.8%).

Table 1. Patient's characteristics at the time of diagnosis

	n(%)	Median
Age (Years)		4,5
Arterial hypertension	8(22.9)	
Macroscopic hematuria	4(11,4)	
GFR < 90 ml/min/1,73m2SBA	7(20)	
Nephrotic syndrome	31(88)	
Serum total protein (g/l)		44.5
Serum albumin (g/l)		15
Daily proteinuria (mg/kg/d)		93
Creatinine clearance (ml/min/1,73m²SBA)		104

GFR: Glomerular filtration rate, SBA: Surface body area

Renal biopsy was performed at least once in all our patients. It was indicated in cases of SRNS in approximately 48% of cases (Figure 1). Histopathological analysis revealed 77.1% of NOS lesions, 17.1% of tip lesions, 2.9% of perihilar lesions, and 2.9% of collapsing lesions. No cellular lesions were observed. The NOS variant was the histological type that showed the best response to steroids (68.2%), CsA (50%), cyclophosphamide (84.6%), and MMF (57.2%). The progression was marked by the development of CKD with an estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m² in 15 children (42.8%), including ESRD in 4 cases (11.5%). Kidney transplantation was performed in a single case without recurrence on the graft.

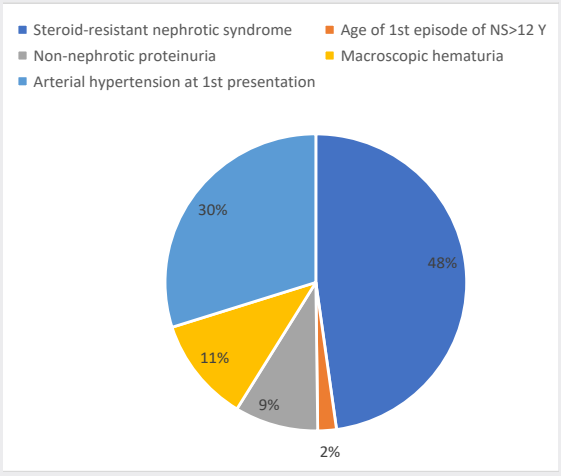

Figure 1. Indications for Kidney biopsy in our study

An increase in albumin levels on Day 8 following methylprednisolone bolus was a protective factor that decreased the risk of corticosteroid resistance by 79% (p=0.042; OR:0.79; CI95% [0,63-0,99].

Two groups of patients were identified based on the creatinine clearance at the last consultation: a group of patients with a creatinine clearance < 60 ml/min/1.73 m² (CKD+): n=7 (20%), and a second group of patients with a creatinine clearance ≥ 60 ml/min/1.73 m² (CKD-): n=28 (80%), which was considered as the control group (Table II). Factors favoring progression to ESRD were a family history of nephropathy (p=0.030), extrarenal signs (p=0.010), initial response to corticosteroids (p=0.004), and response to CsA at 3 months (p=0.024). The presence of a family history of nephropathy was an independent risk factor for progression to ESRD (p=0.028). This risk was 15.6 times higher.

Table 2. Predictive factors of progression to chronic kidney disease

Variables	CKD-	CKD+	p
Age (median) Years	4	10	0.264
Gender			
Females	14(50%)	5(26.3%)	0.415
Males	14(50%)	2(12.5%)	
Family history of kidney disease	4(50%)	4(50%)	0.016
Extrarenal manifestations	0	2(100%)	0.035
Arterial hypertension	8(88.9%)	1(11.1%)	0.435
FSGS variants			
NOS	21(77.8%)	6(22.2%)	0.171
Perihilar	1(100%)	0	
Tip	6(100%)	0	
Collapsing	0	1(100%)	
Initial response to CS	20(90.9%)	2(9.1%)	0.043
Response to CsA at 3 months	12(92.3%)	1(7.7%)	0.127
GFR < 90 ml/min/1,73m2SBA	4(57.1%)	3(42.9%)	0.592
Daily proteinuria (mg/kg/d)	96.5	46	0.711
Interstitial fibrosis	17(77.3%)	5(22.7%)	0.618

FSGS: Focal segmental glomerulosclerosis, NOS: Not otherwise specified, CS: Corticosteroid, CsA: Cyclosporin; GFR: Glomerular filtration rate, SBA: Surface body area

Patients with the histological subtype tip lesion had the best 5-year renal survival (100%), followed by those with the NOS type (80%). The 5-year renal survival rate was 82% for CsA, 83% for MMF, and 75% for cyclophosphamide. There was no statistically significant difference between renal survival and the use or non-use of the various immunosuppressive treatments employed. Renal survival is illustrated by figure 2.

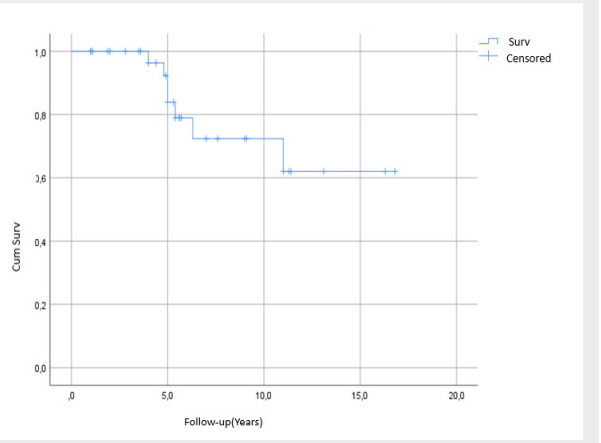

Figure 2. Kaplan-Meier renal survival curve

DISCUSSION

FSGS is an anatomopathological entity representing the third leading cause of progression ESRD in children, following malformative uropathies and renal dysplasia [14]. It accounts for 20% of idiopathic nephrotic syndromes in adults [15] and approximately 7-10% in children, with a prevalence that has been steadily increasing in recent years [3-5]. The cause of this increase is not known, although hypotheses suggest a relationship between genetic, environmental, and especially immune factors due to improved vaccination leading to the production of cytokines and T lymphocytes that can target the kidneys [5].

A slight male predominance was observed in our study with a sex ratio of 1.18. This finding is consistent with several other studies [5,16,17].

NS is the most common initial presentation in various studies: 88% in our series, 100% in the series by Abrantes [17], 92.4% in the series by Paik [18], and 89% in the series by Besbas [19]. Asymptomatic proteinuria was noted in 11.4% of cases in our series and found in 7.6% of cases in the series by Paik [18].

The diagnosis of FSGS is histological, based on the Columbia classification, which allows for a standardized approach to FSGS lesions for rigorous pathogenic, prognostic, and therapeutic evaluation. NOS was the most common form in our series (77.1%). This form was the most common in Shakeel's series in 89.1% of cases [20], El-Refaey's series in 85% of cases [21], and in 70%,

43.9%, and 40% of cases, respectively, in the series by Sozeri [22], Silverstein [23], and Tizki [24].

The treatment of FSGS is based on steroid therapy, with a steroid sensitivity rate of 71% in our series. The rate of steroid-sensitive FSGS is likely underestimated since the majority of childhood nephrotic syndromes are not biopsied. Over the past three decades, there has been an increase in the rate of steroid resistance, ranging from 43% to 63% and then to 86% [5]. In our series, the indication for CsA treatment was predominantly driven by corticosteroid resistance (21 out of 23 patients), with an overall remission rate of 56.5%.

Cattran et al. [25] demonstrated in their randomized trial involving 49 patients with SRNS a benefit of using CsA, with a response rate of 70% (complete or partial remission). CsA is the only medication whose efficacy has been documented in controlled clinical trials for corticosteroid-resistant FSGS in both adults and children [25-27].

In our study, progression to CKD was found in 42.8% of cases. Studies have shown that FSGS progresses to CKD in 25% to 62% of cases (28,29). Progression to CKD was noted in 15.3% of cases in El-Refaey's series [21] and in 21.8% of cases in Abrantes' series [17]. Abrantes reported that progression to CKD occurred after a median delay of 85 months (15-212 months) after the onset of NS, and predictive factors for progression to CKD were age >6.5 years (p=0.007), creatinine level >88 µmol/l (p=0.056), and lack of response to steroids (p<0.001).

Our study showed a progression rate to ESRD of 11.5%. Tizki et al. [24] reported in their series that 35% of children progressed to ESRD, while in El-Refaey's series [21], only 9.7% of patients reached the end-stage. According to the NAPRTCS, 60% of children with FSGS progress to ESRD within 24 months [28]. Analysis of several studies has highlighted that corticosteroid resistance is a risk factor for ESRD [18,30]. Cattran et al. [25] demonstrated in their study that CsA treatment significantly improved renal prognosis, with a 50% reduction in creatinine clearance over 4 years. This decline in estimated GFR was more common in the placebo group compared to the CsA group (p<0.05). Our study did not find a statistically significant difference between histological subtypes regarding progression to ESRD. D'Agati et al. [31] reported that the collapsing variant had a poor prognosis (47% progressed to ESRD) compared to other variants.

Several series have investigated renal survival in FSGS. According to Abrantes [32], renal survival is 92% at 5 years and 87% at 10 years. Paik [18] reported renal survival rates of 84% at 5 years and 64% at 10 years. D'Agati et al. [12] demonstrated that the collapsing variant had a poorer renal survival at 3 years (43%), followed by the NOS variant (85%), and then the tip lesion variant (94%).

CONCLUSIONS

FSGS is a heterogeneous entity. It is associated with a worse renal prognosis, with a more frequent progression to CKD and ESRD than other histological types. Careful investigation of family history of nephropathy, clinical signs, laboratory, and/or immunological findings that may indicate a renal biopsy would likely allow for early diagnosis of pediatric primary segmental and focal hyalinosis and, thus, enable the implementation of an appropriate therapeutic protocol to improve the renal and overall prognosis of these children.

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