Focal segmental glomerulosclerosis in children

Hyalinose segmentaire et focale de l'enfant

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RÉSUMÉ

Introduction : La hyalinose segmentaire et focale est responsable de 20% des syndromes néphrotiques primitifs de l'enfant. Elle est caractérisée par sa diversité clinique et évolutive. Le but de cette étude était d'étudier les caractéristiques histologiques, thérapeuti+++ques et évolutives de la hyalinose segmentaire et focale de l'enfant

Méthodes : Il s'agissait d'une étude rétrospective s'étendant sur une période de 15 ans (1996-2010), menée dans le service de pédiatrie de l'hôpital de Charles Nicolle de Tunis, l'étude génétique n'était pratiquée chez aucun de ces patients.

Résultats : Il s'agissait de 30 enfants répartis en 16 garçons et 14 filles. L'âge moyen était de 7±4 ans. Ils présentaient à l'admission un syndrome néphrotique dans 26 cas, une hématurie dans 2 cas et une insuffisance rénale dans 2 cas. Le type histologique le plus fréquent était la variante classique. Vingt six patients ont reçu la prednisone. Seulement trois patients ont répondu aux corticoïdes. Le traitement par ciclosporine A était prescrite chez 21 patients avec un taux global de rémission de 81% dont de rémission complète et 24% de rémission partielle. Le cyclophosphamide était administré chez 6 patients avec un taux global de rémission de 50%. Chez les enfants traités par mycophénolate mophétil, on n'avait pas obtenu de rémission. Douze patients ont évolué vers l'insuffisance rénale chronique.

Conclusion : les résultats de notre étude ont montré que la majorité des enfants ont eu des taux élevés de rémission avec la ciclosporine A.

MOTS-CLÉS

enfant, hyalinose segmentaire et focale, insuffisance rénale, syndrome néphrotique.

SUMMARY

Background: Focal segmental glomerulosclerosis (FSGS) represents 20% of nephrotic syndrome in children. The clinical course and prognosis is heterogeneous in children. The aim of this study was to analyze treatment and outcome of children with FSGS.

Methods: This retrospective study was conducted in the Department of Pediatrics in Charles Nicolle Hospital during a 15-year period (1996-2010).

Results: There were 30 children, 16 boys and 14 girls. The mean age was 7 ± 4 years. Nephrotic syndrome was observed in 26 patients, hematuria was noticed in 2 patients and renal insufficiency was detected in 2 patients at presentation. FSGS, not otherwise specified, was the predominant variant. All patients with nephrotic syndrome were treated with steroids. Only three patients responded to it. Twenty one patients were treated with cisclosporin A and this resulted in a 57% complete remission and a 24% partial response. Cyclophosphamide was administered to 6 patients and engendered a 50% complete remission. Six patients were treated with mycophenolate mophetil and showed no response in all cases. Renal insufficiency has been developed in 12 children.

Conclusion: Results from this study showed that the majority of children with FSGS achieve a high sustained remission rate with ciclosporine A.

Key-words

Children, focal segmental glomerulosclerosis, renal insufficiency, nephrotic syndrome.

Focal and segmental glomerulosclerosis (FSGS) is not a disease entity, but rather an injury pattern with diverse clinical and morphological features and underlying pathogenesis. Focal segmental glomerulosclerosis is a podocyte disease, characterized by a segmental sclerosis involving glomeruli in a focal distribution [1, 2]. Various morphologic variants have been defined, and a classification has been proposed to better characterize the diversity of FSGS [3].

In children, FSGS is clinically characterized by nephrotic syndrome (NS) frequently associated with hematuria and hypertension at presentation [2]. FSGS accounts for 10%-20% of pediatric nephrotic syndrome cases [3]. FSGS carries a poor prognosis, and 50% of patients will develop advanced chronic kidney disease within 5-10 years of the diagnosis [4]. Focal segmental glomerulosclerosis (FSGS) is one of the leading causes of end-stage kidney disease (ESKD) [5]. Resistance to steroid therapy has been reported in 70% of patients diagnosed with primary FSGS. Although several therapies have been tried, no satisfactory treatment has been found for FSGS.

The aim of this study was to analyze clinical characteristics, course and resistance to steroid as well as other immunosuppressive medications and outcome of Tunisian children with primary FSGS referred to our center.

METHODS

This was a retrospective study of patients who were aged from 1 to 18 years at diagnosis, presented to the department of pediatrics, Charles Nicolle Hospital in a period lasting from January 1996 to December 2010, and underwent renal biopsy. Inclusion criteria were histologic diagnosis of primary FSGS as defined by Columbia FSGS classification system [6] and followed up for at least 1 year after the biopsy. The following patients were excluded from the study: patients with disease onset during the 1st year of life (exclusion of congenital and infantile nephrotic syndrome, those with reflux nephropathy, renal hypoplasia, focal sclerosis secondary to membranoproliferative glomerulonephritis and those with systemic disease such as systemic lupus erythematosus and IgA nephropathy).

All patients showing the following indications were biopsied: steroid dependency prior to cytotoxic therapy, no response to a 4-week course of prednisone therapy 60 mg/m²/day plus three doses of methyl prednisolone (1 g/1.73 m²) and atypical presentation (the presence of hypertension or gross haematuria or renal impairment). Columbia classification of primary FSGS was defined and prioritized within a hierarchy of five distinct pathologic variants: (*1*) Collapsing, (*2*) tip lesion, (*3*) cellular, (*4*) hilar and (*5*) not otherwise specified (NOS) [6].

The following data were analyzed: History and clinical examination at presentation, laboratory variables, renal histopathology, immunosupressive treatment and long-term outcome.

For all patients, the initial treatment of NS was an administration of 60 mg/m²/day oral prednisone (maximum 60 mg/day) for 4 weeks, followed by three intravenous pulses of methylprednisolone at a 1g/1.73m² dose unless there is a response to prednisone, followed by a single morning dose of a 60 mg/m² prednisolone, on alternate days, for 8 additional weeks and eventually the medication was gradually tapered through decreasing the dose by 15 mg/m² every 2 weeks. Complete remission occurred when the proteinuria level was less than 10 mg/kg per day. Remission was considered as partial when proteinuria was between 10 and 50 mg/kg per day, with a serum albumin greater than 30 g/L [7]. Steroid-resistance was defined as a failure to achieve resolution of clinical and laboratory features of nephrotic syndrome after four weeks of daily prednisone therapy (60 mg/m²) followed by three intravenous pulses of methylprednisolone at a 1g/1.73m² dose. A nephrotic syndrome relapse in patients who achieved complete or partial remission was defined as proteinuria reappearance of more than 50 mg/kg per day. Steroid dependency was defined as at least two relapses during alternate-day treatment with prednisone or within 14 days after stopping this treatment.

As far as the 21 non-responders to steroids are concerned, we started a cyclosporine A (CsA) protocol, after which we shifted to mycophenolate mofetil (MMF) unless there was a response. CsA was given to all patients at an initial oral dose of 150–200 mg/m^2 body surface area per day (not exceeding 200 mg/m^2 per day), divided into two equal doses. The dosage was adjusted between 100 and 150 ng/mL to obtain trough concentrations. Prednisone was administered at a 30 mg/m^2 single dose per day during the first month and then at the same dose, but on alternate days, for five months [8] and eventually ceased. MMF was given at an initial starting dose of 1200mg/m²/day divided into two doses (5 patients). Cyclophosphamide was given to 6 patients: 3 had no response to cyclosporine, 2 had ciclo toxicity, and one had steroid dependency.

All data were analyzed using SPSS program. We used X2 or Ficher's exact test to compare two proportions from independent groups. The student t test was used to compare means. We compared two groups: the first who had normal renal function and the second who had renal failure. $P<0.05$ was considered statistically significant. Univariate analyse analyses were used
to predict the risk factors.

RESULTS

Thirty patients were included in the study: 14 (47%) females and 16 (5%) males. The mean age of disease onset was 7.3±4.6 years (1.3-14 years). First-degree or

second-degree consanguineous marriage was present in 13 patients and familial history of NS was observed in 11 patients (36%). Patients presenting main clinical and laboratory characteristics are summarized in Table1. Two patients presented with gross haematuria at initial presentation, 12 (40%) presented with blood pressure levels above the 95th percentile for age and gender and 8 (26%) patients had renal failure.

Table 1: Patient's Characteristics at presentation

	n (%)	Mean ± SD
Hypertension	12(40)	
Microscopic haematuria	19(63.3)	
eGFR<90 ml/min/1.73 m²	8 (26.6)	
24-h urine protein (mg/kg)		113±87
Serum albumin (g/l)		17±9.5
eGFR (ml/min/1.73 m²)		110.5±46
Serum cholesterol (mmol/l)		

The mean total number of glomeruli per sections was 32±15. Interstitial and tubular atrophy changes were, respectively noticed in 57% and 43% respectively. Pathologic variants were as follows. Cellular: 8 patients (26%); collapsing: 3 patients (10%); not otherwise specified (NOS): 14 patients (47%); perihilar: 1 patient (3%) and Tip lesion: 4 patients (13%). As shown in Table 2, at presentation, high blood was significantly higher in patients with collapsing variant *versus* others variants. Renal failure was significantly associated with the collapsing variant (p=0.05).

Table 2 : Baseline clinical characteristics of various pathological variants among patients with focal and segmental glomerulosclerosis.

Type histologique		NOS*	Perihilar	Tip lesion	Collapsing nephropathy	Collapsing nephropathy
Age (years)	7,3±4,6	6,6±4,6	11	11,7±2,5	3,8±1,2	3,8±1,2
Sex	53,3	42,8	100			
male(%)				75	33,3	33,3
néphrotic	86,6	92,8	100			
Syndrome (%)	40	14,2	0	75	66,6	66,6
hypertension (%)	40	21,4	0	50	66,6	66,6
Renal failure (%)				75	100	100
Serum Albumin	16,8±9,5	14,4±7,3	28			
g/l				17,6±9	20,9±10	20,9±10
24-h urine protein	113±87,5	91±36	61			
(mg/kg)				98,5±12	127±84,5	127±84,5
complete	52,4	66,6	100			
Remission (%)				66,6	0	0

*NOS : not otherwise specified

Initial response to the treatment showed that 18 (60%) patients had achieved a complete remission; 6 other patients achieved partial remission (20%) while 6 patients (20%) were resistant to all lines of treatment. The clinical status at the last patient clinical visit showed that 12 patients had renal failure (40%), 8 (26%) had end stage renal disease. Three patients received renal transplantation without recurrence. Chronic renal failure was significantly associated with non-response to cyclosporin A (p = 0.021). We noticed that the renal function is also correlated with consanguinity (p = 0.04) (Table 3).

Table 3 : Risk factors for chronic renal failure

		Normal renal function	Renal failure	P
Age (months)		83 ± 58	96± 52	0,44
Sex	Male	11 (61%)	5 (41,6%)	0,50
	female	7 (38,9%)	7(58,4%)	
Consanguinity		4 (30,8%)	9(69,2%)	0,04
Histologic Type				
	NOS	11 (78,6%)	3 (21,4%)	0,055
	Perihilar	1(100%)		
	Cellular	5 (62,5%)	3(37,5%)	
	« Tip lesion »	1(25%)	3(75%)	
	« Collapsing nephropathy »		3(100%)	
Hypertension		5/18(27,7%)	7/12(58%)	0,13
24-h urine protein (mg/kg)		109±86,7	119±92	0,51
cyclosporin A	**Remission**	12(70,6%)	5(29,4)	0,021

*NOS : not otherwise specified

DISCUSSION

In this study, we examined clinical, histological characteristics and outcome of children with primary FSGS. The clinical features of studied patients at presentation are not different from those of other cohorts. The cellular type is most frequently found; 12 patients had renal failure.

There has been a rising incidence of FSGS in children and adults in the past two decades [9,10]. In Tunisia, there are no studies describing the incidence of HSF. In a pediatric study of 30 children, Gargah et al [11] reported that FSGS was mostly and frequently occurring in the steroid-resistant nephrotic syndrome lesion (53%).

The mean age of 7.3 years at presentation in this study is similar to that of the previously reported studies from developed countries [12, 13]. Most studies reported a mean age of 6–7 years at baseline [14]. Male predominance reported by most of the series was not found in our study [15, 16]. The clinical characteristics of our patients are comparable with those reported in the literature. In the current study, 63% of patients presented haematuria and 40% presented hypertension. El-Refaey et al. [14] showed that haematuria was present in 24% of cases and 21% patients presented hypertension. Abrantes et al. showed haematuria in 38.2% and hypertension in 50% of patients [17].

All authors found the classical variant predominance: classical variant rate in children has been reported respectively in 72% of cases by Paik [18], 44% by Douglas [19] and 47% in our series. The cellular type is most frequently found in our series (27%) compared to Thomas study (3%) that included 192 adults. The difference between children and adults was already reported by Douglas. The type «collapsing nephropathy» was observed in 24% of cases and only by Douglas in 16% of cases by Abrantes [17, 19]. The collapsing variant rate was lower in our series (10%).

Previous studies have evaluated calcineurin inhibitors in FSGS and suggest solutions. The response to cyclosporine varies, but is generally satisfactory. Several studies in children with HSF showed a remission rate under satisfactory cyclosporine with a better response observed in steroid-sensitive patients [20, 21]. Lieberman et al [22] in their prospective randomized double-blind study, observed a significant decrease in proteinuria in all patients receiving cisclosporin A, as opposed to only 2 out of 12 patients receiving placebo. In our series, complete remission was observed in 52% patients who received cyclosporine A.

FSGS outcome is variable. Data from previous FSGS cohort studies conducted on children have shown that the progression to renal insufficiency occurs in 25% [23] to 62% [9]. We found that 12 patients had renal failure (40%) and 8 of them (27%) had end stage renal disease.

In other different types of studies, the relationship between some prognostic factors and outcome were determined. The overall kidney survival seems to be more favorable in younger patients, white patients, and patients with initial response to corticosteroid [24]. Our analysis to evaluate factors affecting kidney survival showed that consanguinity and non-response to treatment with cyclosporine were significantly associated with a poor outcome.

It has been reported that the remission rate after treatment is similar among patients with histological variants, and that response to therapy cannot be predicted on histological basis. In our study, poor prognosis was associated with the variant «collapsing nephropathy» [25]. However several authors reported a poor prognosis variant «collapsing nephropathy» [2, 17, 18].

We are aware of limitations associated with the retrospective. Another limitation consisted in the absence of genetic testing in our study. However, to the best of our knowledge, this is the first study conducted on Tunisian children with FSGS.

CONCLUSION

FSGS is one of the major causes of chronic renal diseases in pediatric patients. Treatment with cyclosporine appears to be efficacious.

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