# Histopathological spectrum of childhood idiopathic steroid-resistant nephrotic syndrome in Tunisia

Tahar Gargah*, Aymen Labassi*, Rim Goucha-Louzir**, Fatma Ben Moussa***, Mohamed Rachid Lakhoua*

*Department of Pediatric Nephrology. Charles Nicolle hospital. Tunis. Tunisia.
**Department of Nephrology. Charles Nicolle hospital. Tunis. Tunisia.
***Deparment of Nephrology. La Rabta Hospital. Tunis. Tunisia.
Tunis El Manar University

*T. Gargah, A. Labassi, R. Goucha-Louzir, F. Ben Moussa, M. R. Lakhoua*

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## RÉSUMÉ

**Prérequis :** La biopsie rénale est un outil indispensable dans la prise en charge des enfants ayant un syndrome néphrotique idiopathique et cortico-résistant. Elle a un intérêt à la fois diagnostique, thérapeutique et pronostique.
**But :** Etudier le profil histologique des enfants ayant un syndrome néphrotique cortico-résistant et essayer d'établir une corrélation entre la lésion histologique sous-jacente et la réponse au protocole thérapeutique associant la cyclosporine et les corticostéroïdes.
**Méthodes :** Nous avons mené une étude rétrospective sur l'ensemble des enfants suivis et traités pour syndrome néphrotique cortico-résistant durant une période allant de 2002 à 2009.
**Résultats :** Trente patients ont été inclus dans notre étude. Les lésions histologiques sous jacentes sont : la hyalinose segmentaire et focale (n=16), les lésions glomérulaires minimes (n=8) et la prolifération mesangiale diffuse (n=6). Le protocole thérapeutique associant cyclosporine-prednisone a permis une rémission complète dans 50% des cas et partielle dans 30 % des cas. Six patients soit 20% des cas ont résisté au traitement. On n'a pas trouvé de relation statistiquement significative entre la réponse thérapeutique et le type histologique.
**Conclusion :** La hyalinose segmentaire et focale est la lésion histologique la plus fréquemment retrouvée au cours du syndrome néphrotique cortico-résistant. Le taux de rémission sous le protocole thérapeutique cyclosporine-prednisone est important et comparable à celui de la littérature. Cette réponse thérapeutique semble être indépendante du type histologique.

## Mots-clés

Enfant ; Syndrome néphrotique ; Cortico-résistance ; Biopsie rénale ; Hyalinose segmentaire et focale ; Cyclosporine

## SUMMARY

**Background:** In children, renal biopsy is routinely required in the management of idiopathic steroid-resistant nephrotic syndrome particularly prior to starting nephrotoxic immunosuppressive agents.
**Aim:** To investigate the correlations between the results of initial renal biopsy in Tunisian children with idiopathic steroid-resistant nephrotic syndrome and the subsequent response to cyclosporine-prednisolone combination.
**Methods:** We conducted a retrospective study of children with idiopathic steroid-resistant nephrotic syndrome over the period 2002-2009. Data on clinico-biological features, histological diagnosis and response to cyclosporine-prednisolone were collected.
**Results:** Thirty patients were enrolled, of whom 16 had focal segmental glomerulosclerosis, eight had minimal change disease and six had diffuse mesangial proliferation. Complete Remission was achieved in 15 patients (50%). Nine patients (30%) went into partial remission. Only six patients presented no response (20%). No statistically significant relationship between the different pathological types and the response to CsA-prednisone was found.
**Conclusion:** In our study, two important facts were noted: 1) the predominant histopathological subtype was the focal segmental glomerulosclerosis; 2) a high remission rate was achieved in our patients using a combined cyclosporine-prednisolone treatment regimen. This response is not dependent on the histological type.

## Key-words

Children; Nephrotic syndrome; Steroid-resistance; Renal biopsy Focal segmental glomerulosclerosis; Cyclosporine.

In the international literature, few reports document histopathological spectrum of childhood idiopathic steroid-resistant nephrotic syndrome (ISRNS). However, focal segmental glomerulosclerosis has been reported as the main leading cause indicating poor outcome and warranting more aggressive therapy [1, 2]. In this study, we are interested in histopathological subtypes in Tunisian children with idiopathic steroid-resistant nephrotic syndrome. We intend to establish a correlation between these histopathological subtypes and initial response to cyclosporine.

## PATIENTS AND METHODS

### Patients

This is a retrospective study involving all children with ISRNS who underwent renal needle biopsy under ultrasound, between 2002 and 2009. We analyzed and compared the clinical, therapeutic and pathological data of patients. Inclusion criteria were: (1) steroid resistance, either primary or secondary; (2) age at onset of nephrotic syndrome>1 year and <14 years; (3) glomerular filtration rate > 60ml/min/1,73m$^2$; (4) patients initially treated with cyclosporine-prednisone combination; (5) diagnosis of idiopathic nephrotic syndrome between January 2002 and December 2009. Exclusion criteria were: (1) nephrotic syndrome underlying secondary causes; (2) patients with family history of SRNS; (3) congenital or syndromic forms.

### Definitions

Nephrotic syndrome was defined as proteinuria more than 50 mg/kg per 24 hours or protein/creatinine > 3 mg/mg associated with hypoproteinemia < 60 g/l and hypoalbuminemia < 30 g/l.

The Steroid-resistance, either primary or secondary, was defined as a failure to achieve resolution of clinical and laboratory features of nephrotic syndrome after four consecutive weeks of treatment with prednisone at 60mg/m$^2$ body surface area per day followed by three intravenous pulses of methyl- prednisolone at a dose of 1g/1,73m$^2$.

The complete remission was defined as a proteinuria less than 10 mg/kg/day. The remission was considered as partial when proteinuria is between 10 and 50 mg/kg/day with a serum albumin greater than 30g/l.

### Histopathology

Renal biopsy was performed after a diagnosis of steroid resistance and before immunosuppressive treatment. All children underwent renal needle biopsy under ultrasound guidance with automated gun after obtaining appropriate informed consent. Two cores of native renal biopsy were routinely obtained for evaluation by light microscopy and Immunofluorescence. Biopsy specimens were processed using standard procedures that included hematoxylin-eosin, periodic acid-Schiff, and green Masson straining of formalin-included pieces; Immunofluorescence of frozen samples were carried out with a panel of antiserum protein antibodies against IgA, IgM, IgG, $C_3$ and $C_4$. The biopsy specimens were reviewed and interpreted by the same pathologists.

### Therapeutic Regimen

In our department, we adopted the protocol treatment established by the French Society of Pediatric Nephrology [3]. So, cyclosporin was given to all patients at an oral initial dose of 150-200mg/m$^2$ body surface area per day (not exceeding 200mg/m$^2$ per day) in two equal doses. The dosage was adjusted to obtain trough concentrations between 100 and 150 ng/ml as measured by the monoclonal antibody radioimmunoassay on whole blood before the morning taking. Prednisone was administered at a single dose of 30 mg/m$^2$ per day during the first month and on alternate days for 5 months.

The therapeutic response was assessed 4 months after starting treatment protocol. In patients who had not achieved complete or partial remission, the therapeutic regimen was stopped.

### Statistical analysis

The statistical analysis was made using the Stat View software 5.0. Categorical variables were compared using the unpaired student's T-test. Nominal variables were compared using chi square. A statistically significant difference was assumed when the p value was less than 0.05.

## RESULTS

The study included 30 children with idiopathic steroid-resistant nephrotic syndrome. Mean age at diagnosis of steroid-resistance was 7.16 ± 4.36 years with a range of 1,4–14 years. The male-to-female ratio was 1.7:1. Details regarding age and sex distribution are presented in Table 1. The most common presenting symptoms are facial and limb oedema (Table 2). Nineteen patients (63%) had an initial steroid-resistance, while eleven patients (37%) had a late steroid-resistance. Mean serum albumin was 20.1±5.14 (range 8.6-26g/l).

**Table 1 :** Age and sex distribution of the patients

| Age (years) | Male | Female | Total | Percentage |
|---|---|---|---|---|
| 1- ≤5 | 9 | 5 | 14 | 47 |
| >5- ≤10 | 3 | 4 | 7 | 23 |
| >10 | 7 | 2 | 9 | 30 |

**Table 2 :** Signs and symptoms revealing ISRNS

| Symptoms | Number | Percentage |
|---|---|---|
| Facial oedema | 25 | 83 |
| Limb oedema | 30 | 100 |
| Scrotal oedema | 5 | 17 |
| Ascitis | 13 | 43 |
| Pleurisy | 5 | 17 |
| Anasarca | 3 | 10 |
| Microscopic hematuria | 12 | 40 |
| Gross hematuria | 5 | 16 |
| Hypertension | 10 | 33 |
| Oliguria | 4 | 13 |

All patients underwent a renal biopsy which was studied by light microscopy and Immunofluorescence. The mean number of glomeruli studied was 24 (range 8–49). Focal and segmental glomerulosclerosis (FSGS) was the most common histopathological subtype, occurring in 16 of 30 children (53%). Minimal change disease (MCD) was the second histological pattern which was found in 8 patients (27%). Diffuse mesangial proliferation (DMP) was encountered in only 6 patients (20%). In children aged more than 5 years, FSGS was the most common histopathological subtype (10 patients among 16). In children aged less than 5 years, FSGS and MCD had the same proportion (6 patients for each subgroup). Among 10 patients with hypertension, 6 had a FSGS. Gross hematuria was observed only in patients with FSGS and DMP. In the MCD subgroup, no patient had hematuria; only one patient had hypertension. In 3 patients with FSGS, mild interstitial fibrosis was observed. The therapeutic response to cyclosporine-prednisone combination was assessed 4 months after starting the treatment protocol. Six patients (20%) showed no response to the therapy. Fifteen patients (50%) achieved complete remission. Partial remission was achieved in nine patients (30%). So, the overall response (complete or partial remission) regardless of pathological types is 80%. The remission was achieved: during the first month of treatment in 25% (6/24) of patients, during the second month in 33,33% of patients (8/24), during the third month in 33,33% (8/24) and during the forth month in 8,4% (2/24). Also, the response to treatment was analysed according to pathological type. We did not find a statistically significant relationship between the different pathological types and the response to CsA-prednisone. In contrast, we found a statistically significant correlation between serum albumin at presentation and the response to cyclosporine. Indeed, patients with remission (including complete remission and partial remission) have a significantly higher rate of serum albumin: 21,85±3,7 vs 13,33 ± 4,3 g/l ($p<0.0001$).

There is no significant correlation between the response to cyclosporine and age, sex, and glomerular filtration rate. Moreover, the rate of remission is the same in patients with initial or late steroid-resistance (table 3).

**Table 3 :** Therapeutic response to cyclosporine according to age, clinical presentation, sex and histological types

| | | Response to CyA | | P |
|---|---|---|---|---|
| | | Responders (n=24) | Non- responders (n=6) | |
| **Age (months)** | | 86 (17-168) | 86,5 (41-168) | 0,981 |
| **Sex** | M | 16 (84%) | 3 (16%) | 0,641 |
| | F | 8 (73%) | 3(27%) | |
| **Steroid-resistance** | | | | 0,372 |
| | Initiallly | 14 (74%) | 5 (26%) | |
| | Secondary | 10 (91%) | 1 (9%) | |
| **Histopathology** | | | | 0,966 |
| | MCD | 7 (78%) | 2 (22%) | |
| | FSGS | 12 (80%) | 3 (20%) | |
| | PMD | 5 (83%) | 1 (17%) | |

M: male F: female MCD: minimal change disease FSGS: focal segmental glomerular sclerosis PMD: diffuse mesangiale proliferation

## DISCUSSION

Idiopathic nephrotic syndrome is one of the commonly glomerular diseases in children. Most patients are steroid sensitive and respond to the therapy with remission of proteinuria [4]. Approximately 10% of children with nephrotic syndrome, who do not respond to corticosteroids, are qualified as steroid resistant [5, 6]. Despite the absence of evidence based recommendations regarding the role of renal biopsy in these patients, this procedure provides important information on renal histology and outcome [7]. Otherwise, a renal biopsy is necessary before initiating treatment with potentially nephrotoxic agents, especially cyclosporine [8].

Most patients with steroid sensitive nephrotic syndrome (90%) show minimal change disease on renal histology [9]. The renal histology in ISRNS is different, with 30-40% patients each showing minimal change disease and FSGS, and a smaller group with diffuse mesangial proliferation [10]. In study from India, Gulta et al [11] reported FSGS in 50%, the same as our finding. In Saudi Arabia, a country comparable to our, the incidence of FSGS is more important than MCD [12]. Two studies, respectively, from Japan [13] and France [14], reported a significantly higher incidence of MCD compared to FSGS. The reasons for disparities in the prevalence of MCD and FSGS are not entirely clear. They are probably explained by racial, genetic and environmental factors [12-14]. Difficulties in interpretation of renal histology seem to have an important part in explaining these differences. So, distinction between different histological types is not always absolute. In early stages, FSGS might be difficult to distinguish from minimal change nephrotic syndrome, depending on the adequacy of biopsy. Furthermore, examination of renal histology in FSGS reveals a variety of histological subtypes, with variable response to therapy and outcome [15]. Repeat biopsies might show morphological transition between minimal change nephrotic syndrome, mesangial proliferation and FSGS. Thus, these histological conditions may be found alone or in combination on sequential biopsies in the same patient. Several studies document patients with SRNS whose initial kidney biopsy specimens demonstrated MCD and subsequently had a follow-up biopsy specimen that showed FSGS. This has led to the conclusion that MCNS and FSGS may represent a continuum of the same process [7].

The treatment of children with steroid-resistant nephrotic syndrome (SRNS) remains unsatisfactory. Children who fail to respond to oral steroids must be treated with immunosuppressive agents in addition to steroids [16]. Treatment with a combination of oral prednisolone and oral cyclosporine may lead to remission in a significant proportion of children [17]. The response to this therapy protocol was initially correlated by renal histology; patients with minimal change nephrotic syndrome show satisfactory response to the therapy, while presence of FSGS or chronic tubulointerstitial changes is associated with unsatisfactory outcomes [18]. However, in recent studies, this correlation is not always established. It seems that the response rate is similar whatever

the histological subtype [13, 16]. This has been well demonstrated in our study although the subgroups are incomparable in terms of statistics. Hymes [19] found that the overall response to CsA is very similar in the 3 histological types. However, the rate of complete remission is frequently observed during the MCD. The partial remission is more frequent in the FSGS and DMP. On the other side, Niaudet [3] obtained a poorer response in patients with FSGS compared with those with MCD (51.5% vs 40%). To maximize the rate of remission in patients with FSGS, Hamasaki et al [13] and associates have administered methylprednisolone pulse, in addition to CsA and prednisone. Therefore, the remission rate obtained was 85.7%.

In conclusion, this study shows that the response to cyclosporine is not correlated with the underlying pathological lesion. However, renal biopsy remains necessary to establish a long-term prognosis since the evolution towards ESRD is seen especially with FSGS [20]. A renal biopsy is also necessary before initiating treatment with potentially nephrotoxic agents.

## References


1. Borges FF, Shiraichi L, Da Silva MP, Nishimoto EI, Nougueira PC. Is focal segmental glomerulosclrrosis increasing in patients with nephrotic syndrome? Pediatr Nephrol 2007;22:1309-13.
2. Kirpekar R, Yorgin PD, Tune BM, Kim MK, Sibley RK. Clinicopathologic correlates predict the outcome in children with steroid-resistant idiopathic nephrotic syndrome treated with pulse methylprednisolone therapy. Am J Kidney Dis 2002; 39:1143-52.
3. Niaudet P. Treatment of childhood steroid-resistant idiopathic nephrosis with a combination of cyclosporine and prednisone. J Pediatr 1994;126: 981-6.
4. Tarshish P, Tobin JN, Bernstein J, Edelmann CM. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney. J Am Soc Nephrol 1997;8: 769-76.
5. Kim JS, Bellew CA, Silverstein DM, Aviles DH, Boineau FG, Vehaskri VM. High incidence of initial and late resistance in childhood nephrotic syndrome. Kidney Int 2005;68: 1275-81.
6. Bagga A, Mantan M. Nephrotic syndrome in children. Indian J Med Res 2005;122:13-28.
7. Indian Society of Pediatric nephrology. Management of steroid resistant nephrotic syndrome. Indian Pediatr 2009;17:35-47.
8. Fujinaga S, Kaneko K, Muto T, Ohtomo H, Murakami H, Yamashiro Y. Independent risk factors for chronic cyclosporine induced nephropathy in children with nephrotic syndrome. Arch Dis Child 2006; 91: 666-70.
9. Brodehl J. The treatment of minimal change nephrotic syndrome: lessons learned from multicentre co-operative studies. Eur J Pediatr 1991; 150:380-7.
10. Nammalwar BR, Vijayakumar M, Prahlad N. Experience of renal biopsy in children with nephrotic syndrome. Pediatr Nephrol 2006;21: 286-8.
11. Gulati S, Sengupta D, Sharma RK, Sharma A, Gupta RK, Singh U, Gupta A. Steroid resistant nephrotic syndrome: role of histopathology. Indian Pediatr 2006;43:55-60.
12. Kari J A, Halawani M, Mokhtar G, Jalalah SM, Anshasi W. Histopathology of steroid-resistant nephrotic syndrome in children living in the Kingdom of Saudi Arabia. Pediatr Nephrol 2009;24:1429-30.
13. Hamasaki Y, Yoshikawa N, Hattori S, Sasaki S, Iijima K, Nakanishi K, et al. Cyclosporine and steroid therapy in children with steroid-resistant nephrotic syndrome. Pediatr Nephrol 2009;24:2177-85.
14. Mekahli D, Liutkus A, Ranchin B, et al. Long-term outcome of idiopathic steroid-resistant nephrotic syndrome: a multicenter study. Pediatr Nephrol 2009; 24:1525–32.
15. Thomas DB, Franceschini N, Hogan SL, et al. Clinical and pathological characteristics of focal segmental glomerulosclerosis pathologic variants. Kidney Int 2006; 69: 920-26.
16. Habashy D, Hodson EM, Craig JC. Interventions for steroid-resistant nephrotic syndrome: a systematic review. Pediatr Nephrol 2003; 18:906-12.
17. Cattran DC, Alexopoulos E, Heering P, et al. Cyclosporin in idiopathic glomerular disease associated with the nephrotic syndrome: workshop recommendations. Kidney Int 2007;72:1429-47.
18. International Study of Kidney Disease in Children. Primary nephrotic syndrome in children: clinical significance of histopathologic variants of minimal change and of diffuse mesangial hypercellularity. Kidney Int 1981; 20: 765-71.
19. Hymes LC. Steroid-resistant, cyclosporine-responsive, relapsing nephrotic syndrome. Pediatr Nephrol 1995;9:137-9.
20. Fuentes GM, Mesequer CG, carrion AP, Garcia-Pose A, Torres MN. Long-term outcome of focal segmental glomerulosclerosis after pediatric renal transplantation. Pediatr Nephrol 2010;25:529-34.