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ORIGINAL PAPER

Long-Term Study in Children with Steroid-Resistant Nephrotic Syndrome Progressing to End-Stage Renal Disease

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ABSTRACT

Introduction: *Steroid-resistant nephrotic syndrome (SRNS) in children is a glomerular disease who often fails to respond to immunosuppressive treatment and is a leading cause for progression to end-stage renal disease (ESRD) and dialysis. Some risk factors, that appear to be common in patients with SRNS and progression to ESRD, have been identified and reported: focal and segmental glomeruloslerosis on kidney biopsy, high range persistent proteinuria, microscopic hematuria, hypertension, episodes of acute kidney injury (AKI) and resistance to immunosuppressive agents. The challenge is to identify these risk factors and improve patients' management, because children with ESRD have many associated complications and a high rate of morbidity and mortality.*

Objective: *The aim of our study is to observe the incidence of SRNS in our patients and identify the presence of common risk factors in those progressing to ESRD with requirement for dialysis or kidney transplant.*

Materials and methods: *We studied a total number of 125 pacients who were diagnosed with nephrotic syndrome in the Department of Pediatric Nephrology of "M. S. Curie" Emergency Clinical Hospital for Children, Bucharest, Romania, from January 2013 to December 2020. Twenty six patients diagnosed with SRNS were included in our study; all of them underwent clinical examination and laboratory tests and were regularly monitored to assess the progression of kidney disease to ESRD.*

Discussion and results: *Steroid-resistant nephrotic syndrome is associated with an increased risk for developing ESRD with requirement for dialysis and transplant. Resistance to immunosuppressive agents was associated with ESRD in our patients. Focal segmental glomerulosclerosis (FSGS), the most common histopathologic lesion, had no value for progression to ESRD in our study. Hematuria, persistent high value proteinuria, hypertension and episodes of AKI were found in our patients with SRNS and progressed to ESRD.*

Keywords: corticosteroid nephrotic syndrome, renal failure, dialysis.

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INTRODUCTION

Nephrotic syndrome (NS) is the most common primary glomerular disease in children. It is characterized by heavy proteinuria (>50 mg/kg *per* day), hypoalbuminemia-serum albumin < 3 g/dL, hyperlipidemia and edema. Most of the children (80-90%) will respond to steroid therapy and achieve complete remission and that defines the steroid-sensitive NS with a favorable prognosis (1-3).

The remaining 10-20% of cases did not obtain complete remission with a minimum of four weeks of corticosteroid daily therapy (60 mg/m^2 *per* day) and they were considered SRNS with unfavorable prognosis (1). Kidney biopsy, genetic testing and measurement of kidney function, by determining the estimated glomerular filtration rate (eGFR) are recommended due to the high risk of progression to ESRD and dialysis.

On kidney biopsy, the majority of children with steroid resistant form will have FSGS carrying the worst prognosis, but also another histopathologic variant may be present, such as minimal change disease (MCD), membranous nephropathy (MN) or diffuse mesangial proliferation (DMP).

Genetic testing is not routinely recommended due to its variable availability and significant cost and also because there is no specific treatment based on genetic mutations. Genetic forms of SRNS have a poor response to immunosuppressive therapy and for these patients a positive result helps the clinician to decide stopping the immunosuppressive therapy in order to avoid patient's exposure to side effects of an ineffective medication.

The initial response to steroid treatment is an important indicator of disease progression. KIDGO recommends four weeks of daily corticosteroids treatment for children who do not achieve remission and may be continued for an additional 2-4 weeks, totaling 6-8 weeks to define SRNS and start a second line agent. After the diagnosis of steroid resistance, patients were treated with one or more of the following immunosuppressive drugs: Cyclophosphamide, Cyclosporine, Tacrolimus, Mycophenolate mofetil or Rituximab.

Other important risk factors are also associated with progression to ESRD, including hematuria, hypertension, older age at onset, AKI at presentation, serum creatinine and urea levels, and decreased kidney function by determining the eGFR.

In children with resistant steroid form and increased risk of progression to ESRD, AKI is common during time periods with persistent high range proteinuria and severe hypoalbuminemia.

Children reaching ESRD have associated complications, such as impaired exocrine and metabolic function of the kidney, increased risk of cardiovascular disease, as well as a greatly reduced life expectancy. Dialysis or renal transplant are required. Following renal transplant, the risk of recurrence of SRNS is about 30% (5, 6).

Study objectives

The aim of the present study is to observe the incidence of SRNS in children as well as their response to immunosuppressive treatment and to identify the presence of some factors that may increase the risk for progression to chronic kidney disease (CKD) and ESRD with requirement for dialysis or kidney transplant. ❑

MATERIALS AND METHODS

This retrospective study has been performed on all patients diagnosed with NS in the Department of Pediatric Nephrology, of "M. S. Curie" Emergency Clinical Hospital for Children, Bucharest, Romania, from January 2013 to December 2020. Our goal was to evaluate patients with SRNS who would rapidly progress to ESRD and renal replacement therapy (RRT) requirement.

Twenty six patients diagnosed with SRNS were included in our research.

During the study, possible risk factors for rapid progression to ESRD were assessed.

Data collected from the medical records included age, gender, environment factors (socioeconomic and demomographic data), histopathologic and clinical features (hypertension, presence of hematuria, rapid increase in serum creatinine and ureea, high value of spot urine protein/creatinine ratio or persistent proteinuria >3 g/dL/24 hours, eGFR, and episodes of AKI throughout the course of the disease or due to medication.

Renal replacement therapy (hemodialysis, peritoneal dialysis) was chosen according to age and long- and short-term benefits.

Definition of steroid response, remission, relapse, steroid-resistant/dependent or sensitive nephrotic syndrome was based upon KIDGO 2012 guidelines.

Hypertension was defined as blood pressure >95th percentile for sex, height and age.

Decreased kidney function was defined as the glomerular filtration rate (GFR) below 90 mL/min/1.73 m^2. eGFR was calculated using the original bedside Schwartz formula (9, 10)

End-stage renal disease was defined as the requirement for RRT (hemodialysis, peritoneal dialysis and kidney transplant). ❑

RESULTS

The present study included a total number of 125 patients, of which 84 (67%) were males and 41 (33%) females. Most participants (80%) lived in rural areas of the country. They came from poor backgrounds and only 10-15% had a poor compliance to the treatment (corticotherapy or steroid-sparing immunosuppressive agents).

Patients' ages ranged from one year to 18 years. The mean age of those in whom SRNS progressed to ESRD and RRT was 10.1 years (3,7–14 years).

Socio-demographic factors, including economic status, child life quality, lack of treatment compliance and regular monitoring, were linked to a poor prognosis. Some of our patients were admitted to hospital with CKD stage 4 and rapid progresion to ESRD.

While monitoring patients by their response to steroid therapy, we encountered: 26 (21%) cases of steroid-resistant patients, 37 (30%) steroid-dependent subjects and 62 (49%) steroid-sensitive patients (Figure 1). Patients were monitored daily with 24-hour proteinuria or spot

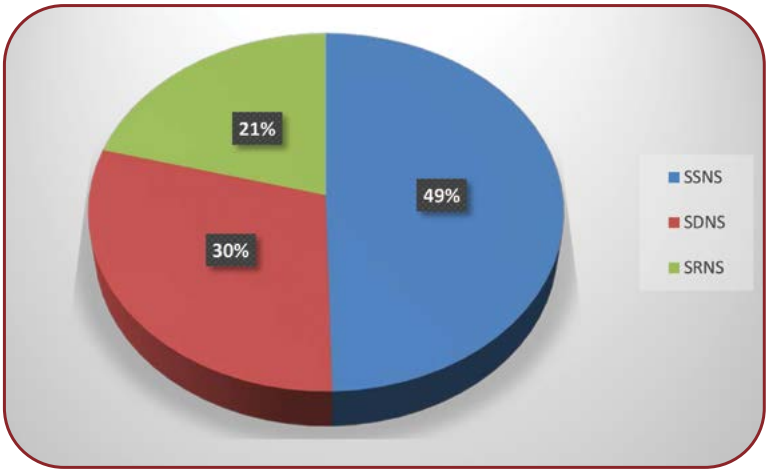

FIGURE 1. Nephrotic syndrome defined by the response to steroid therapy in steroid-sensitive nephrotic syndrome (SSNS), steroid-dependent nephrotic syndrome (SDNS) and steroid-resistant nephrotic syndrome (SRNS)

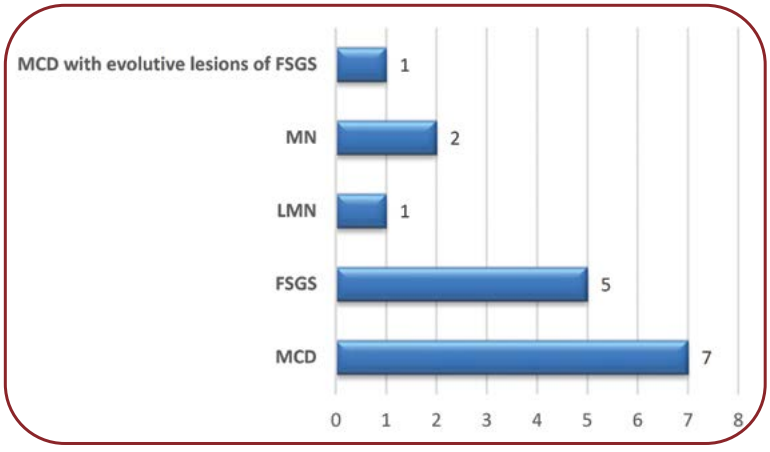

FIGURE 2. Renal histopathologic features in nephrotic syndrome: minimal changes disease (MCD); focal and segmental glomerulosclerosis (FSGS); membranous nephropathy (MN); lupus membranous nephropathy (LMN)

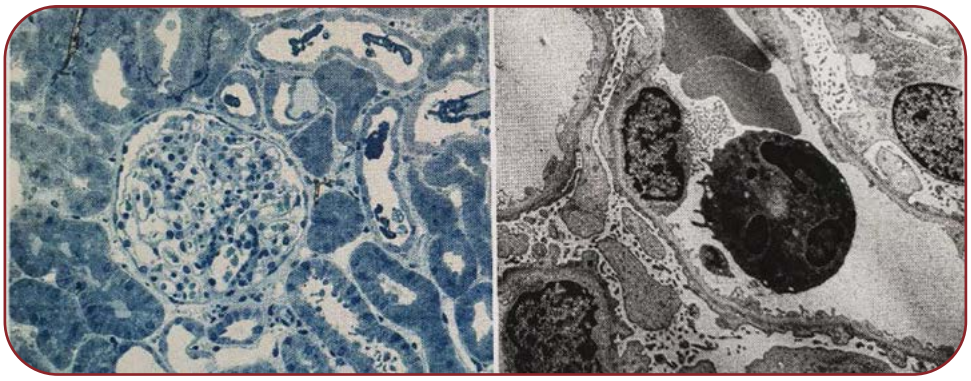

FIGURE 3. Minimal changes disease: A. optical microscopy; B. electron microscopy

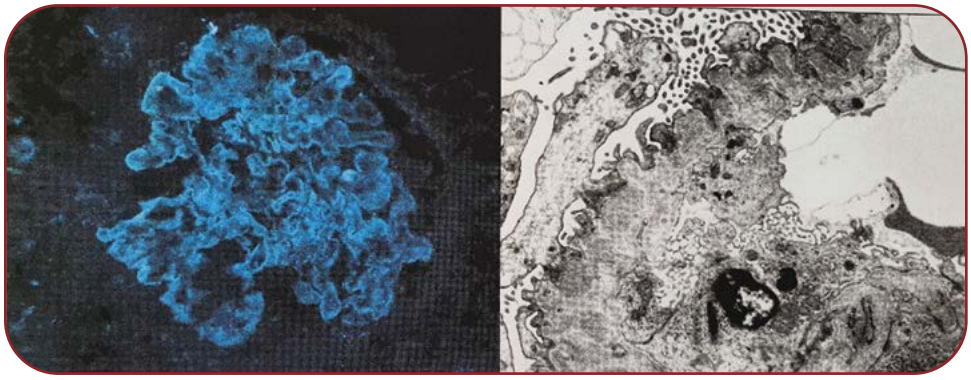

FIGURE 4. Membranous nephropathy: A. immunofluorescence (Ig G); B. electron microscopy

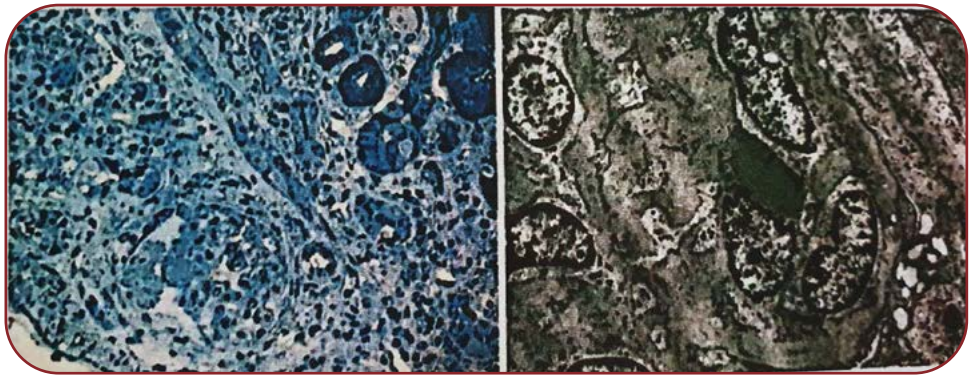

FIGURE 5. Focal and segmental glomerulosclerosis: A. optical microscopy; B: electron microscopy

urine protein to creatinine ratio, weight and 24-hour urine output.

After the diagnosis of steroid-resistance, patients required a second line with a steroid-sparing immunosuppressive agent. In our study, 26 patients received Cyclophosphamide (CP), 13 Cyclosporine (CsA), 10 Mycophenolate mofetil (MMF) and one patient received Rituximab.

Nine patients diagnosed with SRNS were identified from the first presentation in the hospital with some clinical features considered negative prognostic factors and also high-risk factors for progression to ESRD, including persistent high range nephrotic proteinuria > 3 g/dL, persistent microscopic hematuria, and elevated blood pressure.

According to our study, 15 out of the 26 patients with SRNS underwent renal biopsy. According to previous studies FSGS is the most prevalent histological pattern in SRNS and associated high risk for ESRD.

Our patients' histopathologic findings were different from what we expected. After analysing participants' results, we came to the following conclusions (Figure 2): seven cases with minimal changes disease (MCD) (Figure 3); five cases with focal and segmental glomerulosclerosis (FSGS)

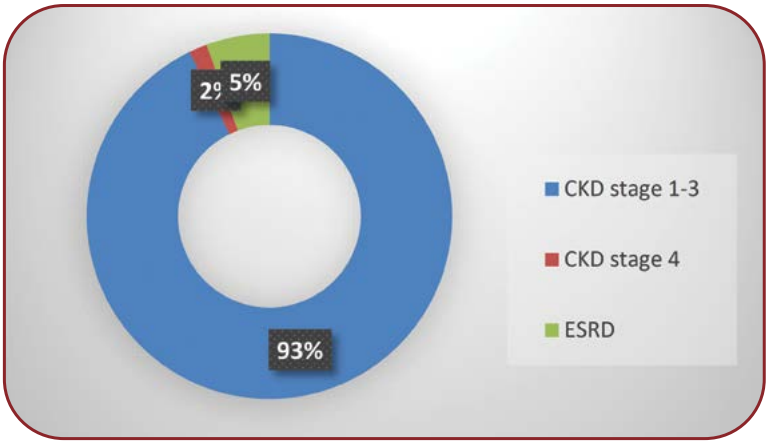

FIGURE 6. Patients' distribution according to their glomerular filtration rate (eGFR)

(Figure 5); two cases with membranous nephropathy (MN) (Figure 4); and one case of lupus membranous nephropathy (LMN).

The decline in renal function was assessed by determining the eGFR. For our patients with NS, we noticed that most of them were included in CKD stage 1-3 (93%), stage 4 (2%) and ESRD (5%) at the end of the present study (Figure 6).

We found four patients with SRNS and episodes of AKI in their evolution, with or without dialysis requirement, and observed that three of them had progressed to ESRD and one patient was able to preserve normal renal function at the end of follow-up.

Renal replacement therapy for children with SRNS and ESRD was chosen based on the need for emergency care, patient's characteristics (age, clinical status, comorbidities) and the possibilities of the clinic. Our patients received chronic hemodialysis or chronic peritoneal dialysis, and two patients received kidney transplant. One of these patients had posttransplant recurrence of FSGS on the graft and needed to resume dialysis. ❑

DISCUSSION

Steroid-resistant nephrotic syndrome is associated with an increased risk of developing ESRD, with requirement for dialysis and transplant. In our study, the prevalence of ESRD among children with SRNS was 34%.

All patients received a second line treatment with an immunosuppressive agent. The resistance to immunosuppressive agent was associated with ESRD in our patients.

We were unable to proceed genetic tests for any of the patients included in this study due to limited resources.

Focal segmental glomerulosclerosis is the most prevalent histological pattern in SRNS and a major cause of ESRD in previous studies. In our research, the initial histological lesion has no value for progression to ESKD, most of our patients have MCD. FSGS lesions are suspected when there is no response to corticosteroid therapy (6). In a European study involving children with SRNS, the initial histological pattern was not found as a predictor for ESRD (7). In another study, Niaudet P found that patients with MCD on initial biopsy who progressed to ESRD always developed FSGS (8).

In many studies, advanced age at presentation was associated with increased incidence of steroid resistance. In our study, patients with SRNS and progression to ESRD were aged between one year and 14 years, without a certain weight of age. So, the age was not found to be a predictor factor for ESRD in this study.

Hematuria, persistent high value of proteinuria, hypertension and episodes of AKI were found in our patients with SRNS and progression to ESRD.

At the end of the study, we concluded that from the 125 participants 93% are with CKD stage 1-3, 2% CKD stage 4 (2%) and 5% with ESRD with dialysis or renal transplant. ❑

CONCLUSIONS

Patients with SRNS represent a small percentage of those with nephrotic syndrome who are very difficult to treat, resistant to immunosuppressive therapy and at high risk to progress to ESRD. Our study underlines the importance of the response to an immunosupressive agent as a those indicator of disease progression.

Also, this study reflects the high incidence of other important risk factor for disease progresion such as hematuria, persistent high value proteinuria, hypertension (34%) and episodes of AKI (14%) with or without dialysis requirement, which is consistent with previously published data. The major histologycal pattern in SRNS-FSGS was not found to be dominant in our patients and these initial results proved to represent a signifiant predictor factor to ESRD. In our study, the majority of patients had MCD, resistance to treatment and progressed to ESRD. At the end of the current study, 34% of participants with SRNS progressed to ESRD with either dialysis or renal transplant requirement. Further studies should consider all these factors and genetic tests are necessary to improve the long term outcome for these children. ❑

Conflicts of interest: none declared.

Financial support: none declared.

Informed consent was obtained from all patients included in the study.

All procedures and experiments of this study are in accordance with both the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), and the national law.

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