

Research Article

Childhood Steroid-sensitive Nephrotic Syndrome: Characteristics and Predictors of Relapses (A Study at a Single Center in Khartoum)

Eltigani M. A. Ali, Nahla Mohamed Elhadi, Mohamed B Abdelraheem, and Rashid A Ellidir

Pediatric Renal Unit, Soba University Hospital, Khartoum, Sudan

Abstract

Background: Childhood steroid-sensitive nephrotic syndrome (SSNS) usually has a favorable outcome in spite of its relapsing course. The objective of the authors was to study the demographic and clinical characteristics, outcome and risk factors for relapses in children with SSNS at a single center in Khartoum, Sudan. **Material and Methods:** In this cross-sectional, facility-based study, the authors retrospectively reviewed all the records of children with SSNS, followed at the Pediatric Renal Unit, Soba University Hospital, Khartoum between 2001 and 2014. SSRNS was defined as the remission of proteinuria within 4–6 weeks of corticosteroids. Relapse is the recurrence of proteinuria after remission; frequent if ≥ 2 within initial six months or ≥ 4 within one year, and steroid dependence if 2 during therapy or within 14 days after stopping it. **Results:** 330 children (males 220; 66.7%) with SSNS were studied with a mean age of 5.2 ± 3.5 years of whom 42.4% aged 1–5 years. At the presentation, hypertension was detected in 31.8% and hematuria in 19.1%. Serum cholesterol was elevated in all patients (mean 347.34 ± 117.87 mg/dl) and serum creatinine in 7.27% (mean 1.4 ± 0.35 mg/dl). Renal histology showed mesangioproliferative glomerulonephritis (MesPGN) in 57.5%, minimal change disease (MCD) in 35.5%, and focal segmental glomerulosclerosis (FSGS) and IgM nephropathy in 3.5% each. During the course of the illness, 10.3% achieved long-term remission, 89.7% relapsed—of whom 52.3% had frequent relapsing/steroid-dependent (FR/SD) course and 37.7% had infrequent relapses. Risk of frequent relapses were age of onset and low/moderate socioeconomic status ($P = 0.015$ and 0.019 , respectively). Infections were recorded in 71.8%, but not significantly associated with the risk of frequent relapses ($P > 0.05$). **Conclusions:** The majority children with SSNS at this single center in Khartoum had a relapsing course with the majority being FR or SD. Predictors of frequent relapses were young age at onset and low socioeconomic status.

Corresponding Author:
Eltigani M. A. Ali; email:
eltigani_ali@yahoo.com

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1. Introduction

The majority of children with nephrotic syndrome (NS) are steroid responsive referred to as steroid-sensitive nephrotic syndrome (SSNS) [1]. More than 90% of these SSNS patients have minimal change pathology and therefore have favorable long-term renal outcome [1]. In Africa, children have a different pattern of NS with a paucity of minimal change disease (MCD), with the majority being steroid resistant with a higher risk of progression to CKD [2]. About 80–90% of SSNS children experience one or more subsequent relapses that can be infrequent or frequent relapses (FR) or steroid dependence (SD) [3, 4]. The age of onset of the disease [5], time to respond to steroids [6], length of treatment [6, 7], infections [8, 9], rapid steroid tapering [10] were reported to be the predictors of the relapses and their frequency. Prolonged use of steroids increases the risk of steroid toxic effects and infections with subsequent high morbidity and mortality. Therefore, Alkylating agents, Levamisole, Calcineurin inhibitors, Mycophenolate mofetil and Rituximab have been used as steroid-sparing agents. Complications of SSNS, occurring with variable frequencies were infections [11] (bacterial or viral), thromboembolism [12] (arterial or venous), renal insufficiency [13], hypovolemia [13], and drugs-related side effects. There are limited data on the long-term outcome of SSNS, but multivariate analysis showed that renal function remains normal in adulthood and that long-term sequels are generally related to side effects of medications [14]. The aim of this study was to identify the demographic and clinical characteristics, and predictors of relapse and outcome of SSNS in children at a Single center in Khartoum.

2. Material and Methods

In this cross-sectional, facility-based study, the authors retrospectively reviewed the hospital records of all children (age > 1–18 years) with SSNS who had been followed-up in the pediatric nephrology unit, Soba University Hospital, Khartoum, between August 2001 and January 2012. The criteria for diagnosis of NS were serum albumin < 2.5 gm/dl) and urine albumin-creatinine ratio [UACR] \geq 200 mg/mmol [15]. The inclusion criteria were: response to steroids (prednisolone 60 mg/m²/day) within 4–6 weeks [16], onset > 1 year, and follow-up \geq 6 months. The exclusion criteria were: congenital or syndromic forms, family history of NS, NS with systemic disease and incomplete records. Data were abstracted from the records using standard data collection sheet. Demographic features, blood pressure, height and weight, and socioeconomic status

were recorded. Laboratory data—urinalysis and culture, UACR, blood urea, serum creatinine, electrolytes, albumin, cholesterol, and kidney biopsy histology—were recorded. Treatment protocols and responses, complications, and outcome were also recorded.

3. Definitions

Definitions of remission, relapse, frequent relapse and steroid dependence were as per the International Study of Kidney Disease in Children (ISKDC) [17]. Remission: proteinuria $< 4 \text{ mg/m}^2/\text{hr}$ or albumin negative or trace on urine dipsticks for three consecutive days. Sustained remission: no relapse for at least six months. Relapse: proteinuria $> 40 \text{ mg/m}^2/\text{hr}$ or albumin 3+ on urine dipsticks for three consecutive days after having been in remission. Infrequent relapse: less than two relapses in six months of response or less than four in twelve months. Frequent relapse (FR): two or more relapses within six months of response or more than three in any twelve months. Steroid dependence (SD): two consecutive relapses while on alternate-day steroids or within 14 days of its discontinuation. Long-term remission: no relapse for at least three years. Estimated glomerular filtration rate (e GFR) was calculated using the Schwartz formula [18]. CKD was defined as $\text{GFR} < 60 \text{ ml/min/1.73m}^2$ for ≥ 3 months and CKD5 requiring renal replacement therapy (RRT) as $\text{GFR} < 15 \text{ ml/min/1.73 m}^2$ [19]. Hypertension was defined as blood pressure above 95th percentile for age [20]. Hematuria was defined as > 3 RBCs/HPF in urine sediment [21].

4. Treatment Protocols

NS was treated with prednisolone $60 \text{ mg/m}^2/\text{day}$ divided doses for 4–6 weeks and then tapered to $40 \text{ mg/m}^2/\text{day}$ (single dose) on alternate days for 4–6 weeks [1]. In FR and SD NS, Cyclophosphamide (CPM), Levamisole, Cyclosporine (CSA), or Mycophenolate Mofetil (MMF) were used after induction of remission with prednisolone. Doses and treatment durations were as follows: CPM: 2.5 mg/kg/day for 8–12 weeks, oral CSA: $4\text{--}5 \text{ mg/kg/day}$ in two divided doses for twelve months, MMF: 600 mg/m^2 twice daily for 12 months and levamisole: 2 mg/kg/day for 12 months. Outcome measures were remission (sustained, long-term), relapses (infrequent, FR, SD), CKD.

5. Data Analysis

Data were organized into a master sheet using the Statistical Package for Social Sciences (SPSS), version 19. Data were presented using frequencies and percentages for categorical variables and means \pm standard deviation (SD) for numerical continuous variables. Variables were compared using independent *t*-test for independent variables. For all statistical analysis, *P*-value less than 0.05 was considered as statistically significant.

6. Results

Out of 460 children admitted with idiopathic NS, 330 (71.7%) had steroid-sensitive NS (SSNS). Of them, 220 (66.7%) were males and 110 (33.3%) females, with a male to female ratio of 2:1. The mean age at presentation was 5.2 ± 3.5 (range 1.5–16) years. The age spectrum was variable with 42.4% of patients being in the age range of 1–5 years. The mean age of onset of the disease was 5.4 ± 3.57 years with 62.7% being in the age range of 1–5 years. Hypertension was detected in 105 patients (31.8%) and hematuria in 63 (19.1%). Serum cholesterol was elevated in all patients (100%) with mean serum levels of 347.34 ± 117.87 (range 224–687) mg/dl. Serum creatinine was elevated in 24 (7.3%) with a mean of 1.4 ± 0.35 (range 0.9–2) mg/dl, respectively. Serum albumin was less than 2 gm/dl in 264 patients (80%) with a mean level of 2.18 ± 0.68 (range 0.9–3.3 GM/dl). Renal biopsies were performed in 84 patients (25%), and indications were shift to CSA in 44 FR/SD cases (52.4%), macroscopic hematuria 11 (13.1%), late age at onset 8 (9.5%) and persistent elevated serum creatinine in 4 (4.7%). Types of histological lesions are shown in Table 1. Non-MCD lesions were the commonest types. During the follow-up period (mean 3.2 ± 2.6 , range 1.5–13 years), 34 patients (10.3%) achieved long-term remission, 123 (37.3%) had FR/SD, and 173 (52.4%) had infrequent relapses. Predictors of frequent relapses are shown in Table 2. Age of onset less than five years and low socioeconomic status were significantly associated with the risk of FR/SD course ($P = 0.015$ and 0.019 , respectively). Infections were recorded in 237 (71.8%) patients with SSNS and in 232 (78.4%) with relapsing NS; 49.3% respiratory, 28% UTI and 1.1% peritonitis. But infections were not significantly associated with frequency of relapses ($P > 0.005$). In about 87 (70.7%) patients with FR/SD nephrotic syndrome, steroid-sparing drugs were used, whereas in 36 (29.3%) small-dose alternate-day steroids were used. Types and frequency of use of these drugs are shown in Table 3. Non-infectious complications were recorded in 32 (9.7%)

patients with SSNS. Frequency and types of these complications are shown in Table 4. Lastly, follow-up visit after a mean follow-up period of 3.2 ± 2.6 years (range 1.5–13 years), 235 patients with SSNS (71.2%) were in remission, 68 (20.6%) in relapse, 3 (0.9%) developed CKD, and 24 (7.3%) were lost to follow-up; Table 5.

TABLE 1: Types of histopathology lesions in studied patients with SSNS underwent renal biopsy.

Histopathology lesion	Number	Percentage
Mesangial-proliferative glomerulonephritis	48	57.5%
Minimal Change Disease	30	35.5%
Focal segmental glomerulosclerosis	3	3.5%
IgM nephropathy	3	3.5%
Total	84	100.0%

TABLE 2: Risk factors for relapses in studied children with SSNS (frequent versus infrequent relapsing).

Risk factor	FR/SD (n = 123)	Infrequent relapsing (n = 173)	P-value
Gender			
Male	85 (69.1%)	115 (66.5%)	
Female	38 (30.9%)	58 (33.5%)	0.061
Age at onset			
< 5 years	104 (84.6%)	86 (52.5%)	
> 5 years	9 (15.4%)	58 (47.5%)	0.015*
Time to initial response			
< 2 weeks	53 (43.1%)	71 (41%)	
> 2 weeks	70 (46.9%)	102 (59%)	0.091
Socioeconomic status			
Low	89 (64.2%)	78 (45.1%)	
High	5 (4.1%)	9 (5.2%)	0.019*
Initial mean serum albumin	1.17 \pm 0.72	1.2 \pm 0.64	0.588
Infections			
Respiratory	70 (47.9%)	76 (52.1%)	0.281
UTI	40 (48.2%)	43 (51.8%)	0.211

* P-value is statistically significant.

7. Discussion

In developed countries, over 80% of children with idiopathic NS are steroid-sensitive [1]. In this series, children with steroid-sensitive NS (SSNS) constituted 71.7% of all children with idiopathic NS who were followed in the center. In contrast, in developing

TABLE 3: Types of treatment used in studied children with relapsing NS.

Treatment	Number	Percentage
Cyclophosphamide (CPM)	42	34.2%
Alternate-day steroids	36	29.3%
Cyclosporine A (CSA)	18	14.6%
CPM followed by CSA	14	11.4%
Mycophenolate Mofetil (MMF)	7	5.7%
Levamisole	6	4.8%

TABLE 4: Frequency and types of complications in studied children with SSNS.

Complication	Number	Percentage
Cushingoid features	12	37.5%
Hypertension	8	25.0%
Glucosuria	5	15.6%
Short stature	4	12.50%
CKD	3	9.40%
Total	32	100.00%

TABLE 5: Outcome of studied children with SSNS on last follow-up.

Outcome	Number	Percentage
Sustained remission	57	17.30%
Non-sustained remission	178	53.90%
Relapse	68	20.60%
CKD	4	0.90%
Lost to follow-up	24	7.30%
Total	32	100.00%

countries, especially in Africa, the majority tend to have steroid-resistant disease [2, 22], which could be related to the predominance of non-MGD lesions among these populations. In this study, males were predominantly affected, which is consistent with the finding reported by the ISKDC [23]. The mean age of presentation of children in this study was 5.2 years with 42.4% being in the age group 1–5 years. Hypertension, hematuria, and elevated serum creatinine were recorded at presentation in 31.8%, 19.1% and 7.3% of them, respectively. Similar finding was reported in other studies [24]. Earlier and recent studies showed that about 80–90% of SSNS children experience one or more subsequent relapses that can be infrequent or frequent relapses or steroid-dependent [3, 4]. Among them, 35 to 50% relapse frequently [4, 26]. Our series showed similar finding, as only 10.3% achieved sustained remission in the first 12 months, whereas the majority (89.7%) experienced relapses; among them 37.3% had

frequent relapses. However, other studies reported lower rate of infrequent and frequent relapses; Om P. Mishra et al. reported that 59.3% had relapses (52% infrequent, 7.3% frequent, and 0.6% steroid-dependent) [25]. Noer reported 63.6% had relapsing NS, including 50.5% infrequent and 13.3% frequent relapses [26]. These variations in the frequency of relapses have been related to many factors. Younger age at the onset of the disease was reported to be correlated with the frequency of relapse, with more frequent relapses in children younger than 4 years [27, 28]. The authors found that children in the age group 1–5 years had significantly more relapses in comparison to other age groups ($P = 0.015$). About 50–70% of relapses in NS are precipitated by a viral upper respiratory tract infection [29–31]. This is likely due to non-specific host response to infection rather than to viral antigen or antibody response [30]. Therefore, other infections such as UTI, peritonitis, and skin infections have also been reported as triggers of relapses [29, 32]. We found that the majority (71.8%) of relapses followed infections; upper respiratory (45.7%), UTI (25.1%), and peritonitis (1%), and this association was statistically significant ($P < 0.05$). However, there was no statistically significant difference between patients with frequent and those with infrequent relapses regarding the frequency of infections ($P = 0.211$). Low socioeconomic status was another risk factor for frequent relapses in this series ($P = 0.019$). This could be related to the fact that such children are vulnerable to infection and hence more likely to relapse. In this study, potential risk factors for relapse such as gender, time to initial response to steroids, and initial serum albumin, were not significantly associated with frequency of relapses ($P = 0.061$, 0.091 and 0.588 , respectively) as reported in other studies.

In conclusion, in a population of Sudanese children, SSNS is characterized by a relapsing course in the majority of patients. Predictors of relapse were young at onset and had low socioeconomic status. Although infections were documented in the majority of relapsing patients, they did not predict the frequency of relapses. High rate of relapse and non-sustained remission on last follow-up despite the use of a wide spectrum of steroid-sparing drugs reflects the need for effective therapy to prevent morbidity and mortality.

Conflict of Interests

Authors declare no conflict of interests.

Ethical Clearance

The authors declare that the research protocol has been approved by the Sudan Medical Specialization Board Research Committee and Soba Hospital Research Committees, and that an informed consent was then obtained. They also declare that the results of this study have not been published before, except for the abstracts.

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Author Contributions

The authors declare that they all had significant contributions to the study and that they all agree with the content of the study.

References

- [1] International Study of Kidney Disease in Children. (1981). The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisolone: A report of the International Study of Kidney Disease in Children. *The Journal of Pediatrics*, vol. 98, pp. 561-564.
- [2] Bhimma, R., Coovadia, H. M., and Adhikari, M. (1997). Nephrotic syndrome in South African children: Changing perspectives over 20 years. *Pediatric Nephrology*, vol. 11, pp. 429-434.
- [3] Tarshish, P., Tobin, J. N., Bernstein, J., et al. (1997). Prognostic significance of the early course of minimal change nephrotic syndrome: Report of International Study of Kidney Disease in Children. *Journal of the American Society of Nephrology*, vol. 8, pp. 769-776.
- [4] Hodson, E. M., Willis, N. S., and Craig, J. C. (2008). Non-corticosteroid treatment for nephrotic syndrome in children. *Cochrane Database Syst. Rev*, vol. 1, CD002290. DOI:10.1002/14651858. CD002290. pub 3'.

- [5] Kabuki, N., Okugawa, T., Hayakawa, H., et al. (1998). Influence of age of onset on the outcome of steroid sensitive nephrotic syndrome. *Pediatric Nephrology*, vol. 12, pp. 467-470.
- [6] Vivarelli, M., Moscaritolo, E., Tsalkidis, A., et al. (2010). Time to initial response to steroids is a major prognostic factor in idiopathic nephrotic syndrome. *The Journal of Pediatrics*, vol. 156, pp. 965-971.
- [7] Arbeitsgemeinschaft für Pädiatrische Nephrologie. (1988). Short versus standard prednisolone therapy for initial treatment of idiopathic nephrotic syndrome in children. *Lancet*, vol. 1, pp. 380-383.
- [8] Abeyagunawardena, A. S. and Trompeter, R. S. (2008). Increasing the dose of prednisolone during viral infections reduces the risk of relapse in nephrotic syndrome: a randomized controlled trial. *Archives of Disease in Childhood*, vol. 93, pp. 226-228.
- [9] Gulati, A., Sinha, A., Sreenivas, V., et al. (2011). Daily corticosteroids reduce infection-associated relapses in frequently relapsing nephrotic syndrome: A randomized controlled trial. *Clinical Journal of the American Society of Nephrology*, vol. 6, pp. 163-171.
- [10] Hiraoka, M., Tsukahara, H., Matsubara, K., et al. (2003). A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. *American Journal of Kidney Diseases*, vol. 41, p. 1155.
- [11] Alwadhi, R. K., Mathew, J. L., and Rath, B. (2004). Clinical profile of children with nephrotic syndrome not on glucocorticoid therapy, but presenting with infections. *Journal of Pediatrics and Child Health*, vol. 40, pp. 28-32.
- [12] Kerlin, B. A., Blatt, N. B., Fuh, B., et al. (2009). Epidemiology and risk factors for thrombo-embolic complications of childhood nephrotic syndrome: A Midwest Pediatric Nephrology Consortium (MWPNC) study. *The Journal of Pediatrics*, vol. 155, pp. 105-110.
- [13] Vande Walle, J. G., Donckerwolcke, R. A., Van Isselt, J. W., et al. (1995). Volume depletion in children with early relapse of minimal change nephrosis with or without hypovolaemic symptoms. *Lancet*, vol. 346, p. 148.
- [14] Fakhouri, F., Bocquet, N., Taupin, P., et al. (2003). Steroid sensitive nephrotic syndrome: From childhood to adulthood. *American Journal of Kidney Diseases*, vol. 41, pp. 550-557.
- [15] Report of Workshop by the British Association for Pediatric Nephrology and Research Unit, Royal College of Physicians. (1994). Consensus statement on

- management and audit potential for steroid responsive nephrotic syndrome. *Archives of Disease in Childhood*, vol. 70, pp. 151–157.
- [16] Kher, K. K., Schnaper, H. W., and Makker, S. P. (2007). *Clinical Pediatric Nephrology* (second edition). UK: Informa; Health care.
- [17] International Study of Kidney Disease in Children. (1978). Nephrotic syndrome in children. Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the international study of kidney disease in children. *Kidney International*, vol. 13, pp. 159–165.
- [18] Schwartz, G. J., Muñoz, A., Schneider, M. F., et al. (2009). New equations to estimate GFR in children with CKD. *Journal of the American Society of Nephrology*, vol. 20, pp. 629–637.
- [19] National Kidney Foundation. (2008). K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *American Journal of Kidney Diseases*, vol. 39, S1.
- [20] U.S. Department of Health and Human Services. National Institutes of Health National Heart, Lung and Blood Institute. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. *NIH Publication* No. 05-5267 (originally printed on September 1996, Revised May 2005).
- [21] Grossfeld, G. D. and Carroll, P. R. (1998). Evaluation of asymptomatic microscopic hematuria. *Urologic Clinics of North America*, vol. 25, pp. 661–676.
- [22] Olowu, W. A., Adelusola, K. A., and Adefehinti, O. (2010). Childhood idiopathic steroid resistant nephrotic syndrome in Southwestern Nigeria. *Saudi Journal of Kidney Disease and Transplantation*, vol. 21, pp. 979–990.
- [23] International Study of Kidney Disease in Children. (1997). Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. *Kidney International*, vol. 13, pp. 159–165.
- [24] Mishra, O. P., Abhinay, A., Mishra, R. N., et al. (2013). Can we predict relapses in children with idiopathic steroid-sensitive nephrotic syndrome? *Journal of Tropical Pediatrics*, vol. 59, pp. 343–349.
- [25] Koskimies, O., Vilska, J., Rapola, J., et al. (1982). Long term outcome of primary nephrotic syndrome. *Archives of Disease in Childhood*, vol. 57, pp. 544–548.
- [26] Noer, M. S. (2000). Predictors of relapse in steroid-sensitive nephrotic syndrome. *The Southeast Asian Journal of Tropical Medicine and Public Health*, vol. 36, pp. 1313–1320.
- [27] Lewis, M. A., Davis, N., Baildom, E. M., et al. (1989). Nephrotic syndrome: From toddlers to twenties. *Lancet*, vol. 86, pp. 255–259.

- [28] Kabuki, N., Okugawa, T., Hayakawa, H., et al. (1998). Influence of age at onset on the outcome of steroid-responsive nephrotic syndrome. *Pediatric Nephrology*, vol. 12, pp. 467-470.
- [29] Moorani, K. N. (2011). Infections are common a cause of relapse in children with Nephrotic syndrome. *Pakistan Pediatric Journal*, vol. 35, pp. 213-219.
- [30] MacDonald, N., Wolfish, N., Mclaine, P., et al. (1986). Role of respiratory viruses in exacerbations of primary nephrotic syndrome. *Journal of Pediatrics*, vol. 108, pp. 378-382.
- [31] Takahashi, S., Wada, N., Murakami, H., et al. (2007). Triggers of relapse in steroid-dependent and frequently relapsing nephrotic syndrome. *Pediatric Nephrology*, vol. 22, pp. 232-236.
- [32] Afroz, S., Khan Hossain, M. A., Roy, K. D., et al. (2010). Urinary Tract Infection (UTI) is associated with higher rate of relapse in children with nephrotic syndrome. *DS (Child) H J*, vol. 26, p. 826.