

## Risk Factors for Relapses in Children with Steroid Sensitive Nephrotic Syndrome

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### Abstract

**Background Objective** Nephrotic syndrome (NS) is the most common glomerular disease seen in the pediatric age group. To study demographic, socioeconomic, disease related characteristics and the physical examination including height, weight and blood pressure correlation with frequency of relapses in children with steroid sensitive NS (SSNS).

**Methods** This is a cross sectional study that was conducted at Nephrology Consultation Clinic, in Al-Imamein Al-kadhimein (peace on them) Medical City, Baghdad, Iraq starting from 1<sup>st</sup> of January, 2020 to 31 July, 2021.

**Results** Total number of patients was 60 children with SSNS, 24 (40%) patients were frequent relapsers and 36 patients (60%) were infrequent relapsers. Most of the children at onset of the disease were less than 5 yr (76.7%) and males were more than females (78.3%). Fifty-three patients were responder to steroid in less than 2 weeks (88.3%). Ten patients with low body weight (16.7%) and 6 patients with low body height (10%), 25 patients presented with elevated blood pressure (41.7%). A significant correlation was found between future relapses and following characteristics; response to steroid in less than 2 weeks, urinary tract infection (UTI) and gross hematuria, low body weight, short stature and elevated blood pressure.

**Conclusion** Comparing frequent with infrequent relapsers, the following factors found to be statically significant: response to steroid less than 2 weeks, UTI, gross hematuria, low body weight, short stature and elevated blood pressure.

**Keywords** Relapse, steroid, nephrotic syndrome, frequency

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**List of abbreviations:** NS = Nephrotic syndrome, SRNS = Steroid resistant nephrotic syndrome, SSNS = Steroid sensitive nephrotic syndrome, URTI = Upper respiratory tract, UTI = Urinary tract infection

### Introduction

Nephrotic syndrome (NS) is the most common glomerular disease seen in the pediatric age group. NS is defined as proteinuria  $>40$  mg/h/m<sup>2</sup> or  $>50$  mg/kg/day or protein/creatinine ratio  $>0.2$  g/mmol ( $>2$

g/g) and hypoalbuminemia  $<25$  g/l with or without edema <sup>(1,2)</sup>.

NS in children is generally classified into steroid sensitive nephrotic syndrome (SSNS) and steroid resistant nephrotic syndrome (SRNS) based on the initial response to corticosteroid therapy at presentation <sup>(3)</sup>. NS incidence and prevalence varies between different geographical regions of the world and ethnicities <sup>(4)</sup>. About 80-90% of SSNS children experience one or more subsequent relapses that can be infrequent or frequent relapses or

steroid dependence. The age of onset of the disease, time to respond to steroids and length of treatment, rapid steroid tapering and infections were reported to be the predictors of the relapses and their frequency. Two-thirds of childhood NS present before the age of 6 years. The ratio of boys to girls is 2:1. By late adolescence, both sexes are equally affected<sup>(5)</sup>.

Most children with SSNS (89%) have repeated relapses. Although there is no proven way to predict an individual child's course, children who respond rapidly to steroids and those who have no relapses during the first 6 months after diagnosis are likely to follow an infrequently relapsing course. It is important to indicate to the family that the child with SSNS is unlikely to develop chronic kidney disease, that the disease is rarely hereditary, and that the child will remain fertile<sup>(6)</sup>.

This study aimed to identify risk factors for relapses in children with SSNS.

## Methods

This is a cross sectional study that was conducted at Nephrology Consultation Clinic, in Al-Imamein Al-kadhimein (peace on them) Medical City, Baghdad, Iraq, starting from 1<sup>st</sup> of January, 2020 to 31<sup>st</sup> of July, 2021. In this study, 60 patients were included and diagnosed as cases of SSNS. Well-formed questionnaire was designed by researchers including demographic and socioeconomic: residency, gender, age and economic condition, which classified according to family income: poor if less than 500,000 Iraqi Dinars (ID), middle if 500,000 – 1000,000 ID, upper if more than 1000,000 ID). Disease related data including age of onset of NS, response to steroid, types of NS (frequent or infrequent), atopy (asthma), gross hematuria, asthma and infections (upper respiratory tract (URTI) (within last 2 weeks) and urinary tract infection (UTI) (within last 2 weeks) in the last year. Physical examination was conducted for each patient including blood pressure, height, and weight and plotted on reference charts.

Data collection was done by direct contact interview with patients and their parents, in addition to doctors involved in their management and the record files. A verbal consent from the parents was taken prior to enrollment in the study. Total no. of 60 children with NS were divided into 2 groups for comparison: frequent (24 patients - 40%) and infrequent (36 patients - 60%).

The following definitions were used: Relapsed NS is defined as proteinuria mg/h/m<sup>2</sup> or >50 mg/kg/day or Albustix +++ for 3 consecutive days after having been in remission. Frequent relapses (FR) are 2 or more relapses within 6 months of initial response or 4 or more relapses within a period of 1 year while infrequent relapses (IR) were less than 2 within 6 months or less than 4 for any year thereafter. SSNS is complete remission achieved with steroid therapy. SRNS defined as patients who fail to enter remission after 8 weeks of corticosteroid treatment<sup>(2,3,6)</sup>.

Gross hematuria: is referred as blood in the urine is visible to the naked eye<sup>(3)</sup>.

UTI: was considered positive when patient had symptoms and findings on urinalysis, confirmed by a urine culture<sup>(6)</sup>.

Hypertension: was defined as BP  $\geq$ 95<sup>th</sup> percentile for age, height, and sex<sup>(6)</sup>.

Low height or length for age; if below 3<sup>rd</sup> centile or less than 2 standard deviations for that specific age and sex<sup>(6)</sup>.

Low weight for age; if a child weight is below the 3<sup>th</sup> percentile or less than 2 standard deviations for that specific age<sup>(6)</sup>.

The data analyzed by the statistical package for social sciences (SPSS version 20) and Microsoft office Excel programs (2013) and Graph Pad Prism (6) for mean, standard deviation and p-value.

P value was calculated, statistically significant if it is <0.05 and highly significant if <0.001.

## Results

Total number of 60 patients with SSNS were enrolled in this study; FR were documented in 24 patients (40%), while IR was documented in 36 patients (60%).

The demographic characteristics of the study group came out with the following data: The age of the patients was ranging between 2.5-16 yr at the time of the study; 45 patients (75%) of them were older than 5 yr, while 46 (76.7%) were less than 5 yr age at time of onset of the disease. Males were 47 (78.3%) while females were 13 (21.6%) with a male:female ratio 3.6:1. Forty patients (66.7%) were residing in urban area, while 20 patients (33.3%) came from rural areas. Thirty patients (50%) lie in the middle socioeconomic status (29 patients with poor status and 1 patient from upper status). Considering the disease related characteristics, 53 patients (88.3%) responded to steroids in less than two weeks while 7 patients (11.7%) did not. Fifteen patients (25%) were reported to be asthmatics. Nineteen patients (31.7%) reported at least one episode of URTI in the last year, while 26 patients (43.3%) reported UTI in the last year. Episode(s) of gross hematuria was reported in 8 patients (13.3%).

Regarding the clinical characteristics of the disease, ten patients (16.7%) reported low body weight, six patients (10%) reported short stature, and hypertension was detected in 25 patients (41.7%).

Table (1) shows comparison of sociodemographic characteristics according to the frequency of relapse in the study group. Among this cohort group, the mean current age and age at onset were 8.0 yr and 4.5 yr for FR, while 7.9 yr and 4.2 yr for IR respectively. No statistical significance was noted among those parameters. Males were 22 (91.7%) in FR versus 25 (69.4%) in IR, while females represent 2 (8.3%) and 11 (30.6%) respectively, with no statistical significance. Fifteen patients (62.5%) of the FR were residing in urban area, while 25 patients (69.4%) of the IR do so. The comparison regarding the residency was not significant. Most of this cohort lie in the middle socioeconomic class 11 FR (45.8%) and 19 IR (52.8%) with a non-significant statistical comparison.

**Table 1. Comparison of sociodemographic characteristics according to the frequency of relapse in children with nephrotic syndrome**

Characteristic		Frequent relapse	Infrequent relapse	P value
		N=24 Mean±SD	N=36 Mean±SD	
Age at time of study (yr)		8.06±3.58	7.98±3.11	0.924*
Age at onset of NS (yr)		4.55±2.98	4.26±1.63	0.659*
		N (%)	N (%)	
Gender	Female	2 (8.3)	11 (30.6)	0.056**
	Male	22 (91.7)	25 (69.4)	
Residency	Rural	9 (37.5)	11 (30.6)	0.590**
	Urban	15 (62.5)	25 (69.4)	
Socioeconomic status	Poor	12 (50)	17 (47.2)	0.962***
	Middle	11 (45.8)	19 (52.8)	
	Upper	1 (4.2)	0 (0.0)	

NS: Nephrotic syndrome, \* p value by unpaired ttest, \*\* p value by Fisher exact test, \*\*\* p value by Yates chi square test

Table (2) shows comparison of disease-related characteristics according to the frequency of relapse in the study group. Out of the FR, 18 patients (75%) responded to steroids in less

than two weeks while 6 in more than two weeks (25%), 15 patients (62.5%) reported history of episode(s) of UTI in the past year, and 7 patients (29.2%) reported episode(s) of

gross hematuria. Out of the infrequent relapses, 35 patients (97.2%) responded to steroids in less than two weeks while 1 in more than two weeks (2.8%), 11 patients (30.6%) reported episode(s) of UTI in the past year, and 1 patient (2.8%) reported episode(s) of gross hematuria. The difference was significant in response to steroid among type of relapsers

(frequent versus infrequent) with a p value of 0.013, significant in regard to UTI among both groups (P value 0.018, and also significant in regard to gross hematuria among both groups, p value 0.005). It is not Significant among both groups in regard to asthma history and URTI among both groups (p values 0.3 and 0.7 respectively).

**Table 2. Comparison of disease-related characteristics according to the frequency of relapse in children with nephrotic syndrome**

Characteristic		Frequent relapse N=24 N (%)	Infrequent relapse N=36 N (%)	P value*
Response to steroids	≤2 wk	18 (75.0)	35 (97.2)	0.013
	>2 wk	6 (25.0)	1 (2.8)	
Asthma	Negative	20 (83.3)	25 (69.4)	0.362
	Positive	4 (16.7)	11 (30.6)	
URTI	Negative	17 (70.8)	24 (66.7)	0.784
	Positive	7 (29.2)	12 (33.3)	
UTI	Negative	9 (37.5)	25 (69.4)	0.018
	Positive	15 (62.5)	11 (30.6)	
Gross hematuria	Negative	17 (70.8)	35 (97.2)	0.005
	Positive	7 (29.2)	1 (2.8)	

URTI: Upper respiratory tract infection, UTI: Urinary tract infection, \* p value by Fisher exact test

Table (3) shows comparison of clinical characteristics according to the frequency of relapse in the study group. Among the FR cases, 16 patients (66.7%) had normal body weight while 8 patients (33.3%) showed low body weight, 18 patients (75%) showed normal height range while 6 patients (25%) were short in stature, and 15 patients (62.5%) reported high blood pressure reading. Among the IR

cases, 2 patients (5.6%) showed low body weight, no patients were reported to have short stature, and lastly 10 patients (27.8%) showed high blood pressure. All comparisons among both groups were statistically significant (p values 0.01 for body weight, 0.003 for height, and 0.015 for blood pressure reading).

**Table 3. Comparison of clinical characteristics according to the frequency of relapse in children with nephrotic syndrome**

Characteristic		Frequent relapse N=24 N (%)	Infrequent relapse N=36 N (%)	P value*
Body weight	Low	8 (33.3)	2 (5.6)	0.010
	Normal	16 (66.7)	34 (94.4)	
Body height	Low	6 (25.0)	0 (0.0)	0.003
	Normal	18 (75.0)	36 (100)	
Blood pressure	High	15 (62.5)	10 (27.8)	0.015
	Normal	9 (37.5)	26 (72.2)	

\* p value by Fisher exact test

### Discussion

Nephrotic syndrome is a chronic relapsing kidney disease with higher incidence compared to other kidney diseases. Frequency of relapses is highly variable and there are different risk factors associated with frequency of relapses. This study was done to compare the risk factors for relapses.

In a study for sociodemographic characteristics by Moorani et al. <sup>(7)</sup>, the mean age at time of the study and onset of the disease was  $7.99 \pm 3.1$  and  $5.4 \pm 2.7$  yr respectively, which is nearly similar to current results, demonstrating a gap between the age of study and age of onset of NS in both FR and IR. Also, these results are in agreement with previous studies performed by Constantinescu et al. <sup>(8)</sup>, Fujinaga et al. <sup>(9)</sup> and Takeda et al. <sup>(10)</sup>, we did not find any correlation between age at time of study, nor age at onset of disease with future relapses among patients with FR and IR NS, but this was inconsistent with 2 other studies by Sarker MN. et al. and Situmorang et al. <sup>(11,12)</sup>.

This study showed predominance of male patients over female patients and the result was similar to elsewhere <sup>(6,13,14)</sup>. Like this study, statically nonsignificant correlation between gender and frequency of relapse was reported in Rahi et al. study <sup>(15)</sup>.

Most of the patients in this study came from urban area surrounding the hospital, however non-significant correlation between residency

and frequency of relapse and was detected. The same result was noticed previously by previous Iraqi study <sup>(13)</sup>. Yet, this finding is in contrast to Sarker et al. <sup>(11)</sup> who reported a significantly higher incidence of frequent relapse in rural children than in urban children and their explanation for this observation was the delay in the initiation of specific treatment in rural areas.

No statistical significance regarding socioeconomic status and relapse was present in both study groups and this because of the percentages in both frequent and infrequent relapsers were roughly the same. Sarker et al. <sup>(11)</sup> and Ali et al. <sup>(16)</sup> detected low socioeconomic status was another risk factor for frequent relapses and their explanation was that such children are vulnerable to infection and hence more likely to relapse.

Regarding disease related characteristics; apropos of response to steroid, interesting finding in this study was a statistically significant association between early response to steroid therapy and increased incidence of IR. The same was noticed by Fujinaga et al. <sup>(9)</sup> and Ali et al. <sup>(13)</sup>; who reported that patients who responded within early days of initial steroid therapy showed a favorable clinical course and less frequency of future relapses.

For asthma and URTI; asthma is common problem and mostly asthmatic attack is aggravated with respiratory infections, which

might underestimate the asthma itself as a trigger factor. The correlation between relapse and asthma in this study was statically nonsignificant and this was consistent with study done by Riar et al. <sup>(17)</sup> and Ali et al. <sup>(18)</sup>.

Whilst URTI is also statistically nonsignificant in this study ( $p$  value = 0.784), which is similar with Rahi et al. <sup>(15)</sup>, but URTI was important significant factor with relapses in Mantan et al. study <sup>(19)</sup>. This may be explained that different viruses implicated in exacerbations suggest that a host response to viral infection, rather than specific viral antibodies, may be the triggering factor for relapse following URTI <sup>(20)</sup>.

UTI is another significant factor of frequent relapse in this study and same result was present with Sarker et al. <sup>(11)</sup> and Balaji et al. <sup>(21)</sup>.

Regarding gross hematuria; there was highly significant difference between both groups and was evident by previous Iraqi study <sup>(13)</sup>.

In regard to clinical characteristics; low body weight and height in both groups was shown to have statistical significance. This result may be interpreted by poorly nourished patients, more liable to infections with more steroids using, which affect height due to more frequency of relapses in these patients. Relating to hypertension, the positive statistical significance was similar to what was mentioned by Balaji et al. <sup>(21)</sup>, and disagrees with Noer et al. <sup>(14)</sup> and these variable results may be explained by different pathophysiological contributing factors including renal factors (like albuminuria, Sodium retention, or decreased glomerular filtration rate) and extra-renal factors (like medication side effects, genetic predisposition, life style and diet or cardiovascular risk factors <sup>(22)</sup>).

In conclusions, comparing frequent with infrequent relapsers, the following factors found to be statically significant: response to steroid less than 2 weeks, UTI, gross hematuria, low body weight, short stature and elevated blood pressure.

The authors recommend involvement of a larger sample is mandatory to confirm the results. Urine examination routinely with each relapse to detect UTI. Involvement of dieticians for proper nutritional education of children

with NS. The blood pressure is important to be measure in each patient.

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### Author contribution

All authors have participated sufficiently in the intellectual content, conception and design of this work or the analysis and interpretation of the data, as well as the writing of the manuscript.

### Conflict of interest

The authors declare there is no conflict of interest.

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