



Predictors of Relapse in Steroid Sensitive Nephrotic Syndrome

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Abstract

Background: Nephrotic syndrome affects 1-3 per 100,000 children below 16 years. The majority of children have steroid sensitive nephrotic syndrome (SSNS) with a favorable prognosis, 10% do not respond and hence defined as steroid resistant. Even though SSNS has a favourable outcome, about half of them become frequent relapsers and or steroid dependent. Objectives of this study was to analyse the predictors of relapse in children with idiopathic steroid sensitive nephrotic syndrome.

Materials and Methods: A retrospective observational study was conducted in a medical college hospital in Mangalore in children aged 1-15 years who presented with first episode of nephrotic syndrome between Jan 2014 to September 2018. Data was extracted from the hospital records. Variables like children age of onset, gender, hypertension, hematuria, azotemia at onset and weeks to remission and presence of infection were collected.

Results: Out of 33 cases, 8 were non relapsers and 25 were relapsers, of whom 21 were males (63.6%) and 12 females (36.4%). Out of 21 males, 16 (76.2%) were relapsers and 5(23.8%) were non relapsers and among 12 females, 9 (75%) were relapsers and 3(25) were non relapsers. 60% had infrequent relapse and 40 % had frequent relapse. Of 25 patients who had relapse, 8 had hypertension at onset and 87.5% of them became frequent relapsers, this was statistically significant (p value – 0.002). Of 24 early responders, 66.7% developed relapse and 33.3% did not relapse. Out of 9 late responders, all had relapse and this result was statistically significant (p value-0.041).

Conclusion: Male gender, presence of hypertension at the onset and late response to steroids can predict future relapses in nephrotic syndrome.

Keywords: Nephrotic syndrome, predictors, relapse.

Introduction

Nephrotic syndrome is characterised by massive proteinuria (urinary total protein >1gm/m²/day or urinary spot creatinine ratio of >200mg/mmol), hypoalbuminemia (serum albumin <2.5gm/dl),

edema and hypercholesterolemia (serum cholesterol >250mg/dl).¹

The annual incidence of idiopathic nephrotic syndrome in children is 2-7 per 100,000 population in children <16 years.² In Asia, a higher incidence of 9-16 cases per 100000

children per year has been reported.³ The majority of children have minimal change disease which is steroid sensitive.⁴

The International Study of Kidney Disease in Children has analyzed the factors at presentation that can be correlated with future outcome and reported that the number of relapses occurring during the first 6 months were highly predictive of future relapses.⁵

Constantinescu et al reported that age, gender, race and hematuria, as independent variables, do not predict relapses in the first year. In this study, they found that the patients without hematuria and who achieved remission within the first week of therapy were more likely to be infrequent relapsers²

Noer et al reported that the time interval between steroid response and the first relapse, the number of relapses within the first 6 months and infection during the first relapse were significant predictors of relapse in his study subjects.⁶

Objective of the Study

The objective of this study was to analyse factors which predict the future relapses in steroid sensitive nephrotic syndrome.

Materials and Methods

This was a retrospective time bound observational chart based study conducted in Paediatric Outpatient and Inpatient department, Father Muller Medical College, Mangalore. Data extraction period was from January 2014 to September 2018.

Data was collected from the records of the patients aged 1-15 years who presented with first episode of nephrotic syndrome for whom at least one year follow up was completed. Children who were on previous treatment with steroids/ immunosuppressants, any systemic disease known to produce nephrotic syndrome, steroid resistance, incomplete treatment and follow up less than 12 months were excluded.

Variables like age of onset, gender, presence of hypertension, azotemia and hematuria (at least 5

RBC/microliter of urine) at onset and time to remission (in weeks) and relapses were recorded in a predesigned proforma

Statistical Analysis

Numerical variables were expressed as mean and standard deviation and categorical variables were expressed as frequency and percentages. To obtain the association of study variables with relapses, chi square test/ Fischers exact test were applied.

A p value of <0.05 was considered as significant.

Study Definitions:⁷

Steroid Sensitive Nephrotic Syndrome (SSNS) was defined as responding to steroid therapy within 4 weeks after initiation of therapy

Infrequently Relapsing Nephrotic Syndrome (IFRNS): Less than 2 relapses within first 6 months or less than 4 relapses within a year after initial responsive episodes.

Frequently Relapsing Nephrotic Syndrome (FRNS): More than 2 relapses within first 6 months or more than 4 relapses within a year after initial responsive episodes.

Relapse: Proteinuria (urine albumin 3+ or more) for 3 consecutive days after responsive episode

Early Responder: Remission attained within 2 weeks of steroid therapy

Late Responder: Remission attained after 4 weeks of steroid therapy

Treatment was according to the protocol of the Indian paediatric nephrology group.⁸

Results

A total of 42 children were initially screened, 33 were selected. 9 were excluded (4 were steroid resistant, 4 had poor compliance and 1 had SLE). Out of 33 cases, 25 were relapsers and 8 were non relapsers.

Gender Distribution: In this study there were 21 males (63.6%) and 12 females (36.4%). Out of 21 males, 16 (76.2%) were relapsers and 5 (23.8%) were non relapsers and among 12 females, 9 (75%) were relapsers and 3 (25%) were non relapsers.

Among 16 males who were relapsers, 10 (62.5%) were IFRNS and 6(37.5%) were FRNS and among 9 females, 5 (55.6%) were IFRNS and 4(44.4%) were FRNS.

Mean age among the study population was 5.63 years with a standard deviation of 3.31.

Age of onset was <6 years in 23 children and >6 years in 10 children. In the age group of <6 years , 19 (82.6%) were relapsers and in age group > 6 years, only 6 developed relapse. Among 19 relapsers in the age group <6 years, 11(57.9%) were IFRNS and 8(42.1%) were FRNS and among age group >6 years, 4(66.7%) were IFRNS and 2(33.3%) were FRNS

Hypertension: Out of 33, 11 had hypertension at the onset and 8 (72.7) among them were relapsers

and 3(27.3%) were non relapsers. Out of 8 Children who developed relapse, 7(87.5%) were FRNS and 1(12.5%) IFRNS. This result was statistically significant with a P value of 0.002. Hematuria and Azotemia: Only 3 children had hematuria at the onset, all developed relapse and out of this 2(66.7%) were FRNS and 1 (33.3%) IFRNS. 3 children with altered renal functional test during the first episode subsequently developed FRNS.

Response to Steroids: Out of 33 cases, 24 were early responders and 9 were late responders. Out of 24 early responders, 16 developed relapse and 8 did not develop relapse. Out of 9 late responders, all 9 became relapsers. This result was statistically significant with a p value - 0.047.

Table 1 Predictors of relapse included in the study.

Parameters	Classification	Infrequent Relapsers		Frequent Relapsers		χ^2 Value	p Value
		n	%	n	%		
Gender	Male (16)	10	62.5	6	37.5	0.116	1.000
	Female (9)	5	55.6	4	44.4		
Age of Onset	≤ 6 (19)	11	57.9	8	42.1	0.146	1.000
	> 6 (6)	4	66.7	2	33.3		
Hematuria	Present (3)	1	33.3	2	66.7	1.010	0.543
	Absent (22)	14	63.6	8	36.4		
Hypertension	Present (8)	1	12.5	7	87.5	11.060	0.002*
	Absent (17)	14	82.4	3	17.6		
Azotemia	Present (3)	3	100.0	0	0.0	2.273	0.250
	Absent (22)	12	54.5	10	45.5		
Response to steroids	Early responder (16)	12	75.0	4	25.0	4.167	0.041*
	Late responder (9)	3	33.3	6	66.7		

Discussion

Purpose of our study was to analyse the factors which predict future relapses in SSNS. In our study, total of 33 children were included, out of which 25 (75.8%) children had relapse. A majority of 15 (45.5%) had IFRNS and 10 (30.3%) had FRNS.

Male preponderance in our study which was similar to studies by Constantinescu et al² and Bhatta et al.⁹ Age of onset was <6 years in majority of the children which was similar to studies done by Sarker et al where majority (67%) were between the age of 2-6 years.¹⁰

Hypertension at onset was a significant predictor of relapse. Among 25 relapsers, 8 had

hypertension and 7(87.5%) subsequently became FRNS this finding was similar to Prasun B et al.¹¹ Another important finding was time to respond to steroids and occurrence of relapses. In our study of total 33 children, 24 were early responders and 9 were late responders. Among 24 early responders, 16 developed IFRNS and 8 did not develop relapse. Out of 9 late responders, all became FRNS. This was significant and was similar to studies done by Constantinescu² where they observed that earliest predictor of relapse was the number of days the patient need to enter remission after initiating prednisolone therapy. The longer the time to remission, the greater was the possibility of becoming a frequent relapser.²

Conclusion

We identified male gender, age of onset <6 years, presence of hypertension during the first episode and late response to steroids as the predictors of relapse. Male gender and age of onset were not Statistically significant.

Identification of these factors will help the treating paediatricians to formulate better treatment plans for this children especially parent counselling regarding the disease pattern, need for regular follow up and treatment.

Acknowledgements

I extend my sincere gratitude to Dr. Sudheer Prabhu and Dr. Unnikrishnan who helped with the statistical analysis and I am grateful to my fellow postgraduates for their encouragement and words of wisdom.

Declaration

Funding: None

Conflict of interest: None declared

Ethical approval: Obtained from the Ethics committee, Father Muller Medical College Hospital

References

1. ISKDC (International Study of Kidney Disease in Children), Nephrotic Syndrome in Children: Prediction on histopathology from clinical and laboratory characteristics at the time of diagnosis. *Kidney Int.* 1978; 13:159-165
2. Constantinescu AR, Shah HE, Foote EF, et al. Predicting first- year relapses in children with nephrotic syndrome. *Pediatrics* 2000;105:492-5.
3. Sharples PM, Poulton J, White RH. Steroid-responsive nephrotic syndrome is more common in Asians. *Arch Dis Child* 1995;60:1014-5.
4. Pais P, Avner ED. Nephrotic Syndrome. In: Kliegman RM, Behrman RE, Stanton BF, St Geme JW, et al. *Nelson's text Book of Pediatrics*. Vol. 2.20thedn. Philadelphia: Saunders/Elsevier 2015; 2521-2527
5. The International Study of Kidney Disease in Children (ISKDC). Early identification of frequent relapsers among children with minimal change nephrotic syndrome. *J paediatr* 1982; 101: 514-18
6. Noer MS. Predictors of relapse in steroid-sensitive nephrotic syndrome. *Southeast Asian J Trop Med Public Health* 2000;36:1313-20.
7. Srivastava RN, Bagga A. Nephrotic Syndrome. In Srivastava RN, Bagga A.edn. *Paediatric nephrology*,5thed, New Delhi: Jaypee Brothers, Medical Publishers(P) Ltd, 2011; 195-234
8. Bagga A. Revised guidelines for management of steroid-sensitive nephrotic syndrome. *Indian Journal of Nephrology*. 2008;18(1):31.
9. Bhatta M, Shah G, Mishra O. Analysis of Predictors of Relapse in Children with Steroid Sensitive Nephrotic Syndrome. *Journal of Nepal Paediatric Society*. 2017;37(1):1.
10. Sarker M, Islam M, Saad T, Shoma F, Sharmin L, Khan H et al. Risk Factor for Relapse in Childhood Nephrotic Syndrome - A Hospital Based Retrospective Study. *Faridpur Medical College Journal*. 2012;7(1).
11. Prasun B, Payas J, Sujaya M. Prediction of relapses in children with idiopathic steroid sensitive nephrotic syndrome: a retrospective study. *Int J Contemp Pediatr*2017;4:57-61.
12. Dakshayani B, Lakshmana M, Premalatha R. Predictors of frequent relapsing and steroid-dependent nephrotic syndrome in children. *Türk Pediatri Arşivi*. 2018;53(1):24-30.