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Original Article

Risk Factors for Frequent Relapse Nephrotic Syndrome in Children — A Case-Control Study

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ABSTRACT

Introduction: *Nephrotic syndrome (NS) is a renal disorder primarily affecting children and characterized by significant proteinuria, low levels of albumin, edema, and high levels of serum cholesterol. Relapses are often triggered by infections, immunizations, and other factors that activate T-cells and increase cytokine production.* ***Methods and materials:*** *This case-control study was conducted at the Department of Pediatrics of Sylhet M.A.G. Osmani Medical College Hospital, Sylhet, for a duration of six months from June 2012 to December 2012. The study included a total of 80 pediatric patients, divided into two groups: the case group and the control group. The collected data were analyzed using Statistical Package for Social Sciences (SPSS), software, version-23.0.* ***Results:*** *In this study children in the FRNS group had a significantly lower mean age (4.05 ± 2.147 years) compared to the control group (5.175 ± 2.435 years) (p=0.0314). Early onset of nephrotic syndrome (age 1-5 years) was more common in the FRNS group (65%) than the control group (47.5%) (p<0.049). Frequent relapse was more prevalent in rural children (75%) than in urban children (55%) (p<0.05). The FRNS group had a significantly higher incidence of UTI and RTI (72%) compared to the control group (38%) (p<0.001). Serum albumin levels were*

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significantly lower in the FRNS group (1.6 ± 0.2 gm/dl) than in the control group (2 ± 0.3 gm/dl) (p<0.001). ***Conclusion****: Several risk factors are significantly associated with frequent relapse nephrotic syndrome (FRNS). These include poor socioeconomic status, rural residency, early age of onset, and low serum albumin at the time of the initial attack and infection.*

Keywords: *Risk factors Nephrotic, Syndrome, Frequent Relapse, Children*

INTRODUCTION

Nephrotic syndrome (NS) is a clinical condition characterized by significant proteinuria (>40 mg/m2/hour or >1 g/m2/day), low levels of albumin (<2.5 g/dL), edema, and hyperlipidemia (serum cholesterol >250 mg/dL) [1, 2]. NS is a common renal disorder in children and occurs 15 times more frequently in children than in adults [3, 4]. The general incidence of NS is 2-3 cases per 100,000 children per year [1]. In Asian children, the annual incidence is higher, ranging from 9 to 16 cases per 100,000 [5]. Although there is no precise data available for Bangladesh, it is believed that the incidence of NS in Bangladesh may be higher than in Western countries. NS can be classified as primary nephrotic syndrome (90%) and secondary nephrotic syndrome (10%). Primary nephrotic syndrome is idiopathic, meaning the cause is unknown. The common types of idiopathic nephrotic syndrome are minimal change disease (85%), focal segmental glomerulosclerosis (10%), and mesangial proliferation (5%). Secondary nephrotic syndrome is caused by systemic disorders such as systemic lupus erythematosus, Henoch-Schonlein purpura, amyloidosis, infections like hepatitis B and C, malaria, syphilis, drugs like penicillamine, gold, mercury, heroin, lithium, non-steroidal anti-inflammatory drugs, immunologic factors such as bee stings, and malignancies like lymphoma and leukemia, among others [1, 2]. The most common type of idiopathic nephrotic syndrome is minimal change nephrotic syndrome, and over 90% of cases respond well to steroid therapy [6, 7]. Approximately 80% of children with steroid-sensitive nephrotic syndrome will experience one or more relapses. Among them, 50% will have frequent relapses or become steroid-dependent [8]. Frequent relapse is defined as two or more relapses within 6 months of the initial response or four or more relapses within 12 months [9]. Infrequent relapse is defined as three or fewer relapses within one year [2]. The underlying abnormality in NS is increased permeability of the glomerular capillary wall, leading to massive proteinuria and hypoalbuminemia. The cause of increased permeability is not well understood. In minimal change disease, it is suggested that T-cell activation leads to the production of one or more cytokines, such as IL, which causes the loss of negatively charged glycoprotein within the glomerular capillary wall [2, 4, 13]. This, in turn, increases glomerular permeability to proteins, primarily albumin [1, 9]. Relapses are often triggered by infections, immunizations, contact dermatitis, and bee stings, which activate T-cells and increase cytokine production [10-13]. Numerous studies have been conducted to identify risk factors for relapse of NS in children, but limited data are available regarding risk factors for frequent relapse of NS

(FRNS) in children. The identified risk factors for FRNS include early age of onset, low serum albumin level during the initial attack, infections, atopic conditions, presence of hematuria during the initial attack, repeated intravenous albumin infusion, living in rural areas, and poor socioeconomic background [10, 11, 14-17]. In a study by Kabuki et al., factors predicting frequent relapse included onset at an age younger than three years, delayed time to remission

METHODS & MATERIALS

The case-control study was conducted at the Department of Pediatrics of Sylhet M.A.G. Osmani Medical College Hospital, Sylhet, for a duration of six months from June 2012 to December 2012. The study included a total of 80 pediatric patients, divided into two groups: the case group and the control group. The case group consisted of pediatric patients (aged 1-10 years) with frequent relapses of nephrotic syndrome, while the control group comprised pediatric patients (aged 1-10 years) with infrequent relapses of nephrotic syndrome, admitted to the same department. The study participants were selected using purposive sampling. Data collection utilized a semi-structured data sheet, which recorded information such as age at the initial attack, sex, serum albumin level during the first attack, socioeconomic status, and residence status. Additional data, including laboratory test results and diagnostic investigations, were gathered from patient records. The collected data were analyzed using Statistical Package for Social Sciences (SPSS), software, version-23.0. Unpaired t tests and Chi-square tests were performed to compare the study variables, where $p<0.05$ considered the level of significance with 95%CI. The ethical clearance of this study was obtained from the institutional Ethics Committee of Sylhet M.A.G. Osmani Medical College Hospital, Sylhet, Bangladesh.

Inclusion Criteria:

- Age: 1 -10 years.
- Nephrotic syndrome patients have two or more relapses within 6 months of initial response or four or more relapses within any 12 months.

Exclusion Criteria:

- Age <1 year and >10 years.
- Steroid-dependent nephrotic syndrome
- Steroid-resistant nephrotic syndrome.
- Frequent relapse nephrotic syndrome who has incomplete data from the initial presentation.

RESULTS

Table I: Distribution of the children by their age(N=80).

Age	Case (n=40) (Percent)	Control(n=40) (Percent)	p-value
1-4 years	24(60%)	16(40%)	0.0314
4-7 years	12(30%)	14(35%)	
> 7 years	4(10%)	10(25%)	

Total	40(100.0%)	40(100.0%)	
Mean ± SD	4.05 ± 2.147	5.175 ± 2.435	

In both groups most of the respondents were in the 1-4 years age group; 60.0% of the case group and 40.0% of the control group were in the age group. The mean ± SD of age was calculated to be, (4.05 ± 2.147) for the case group and control group (5.175 ± 2.435). The p-value was 0.0314 which means that there was a statistically significant difference in age distribution between the groups (p<0.05).

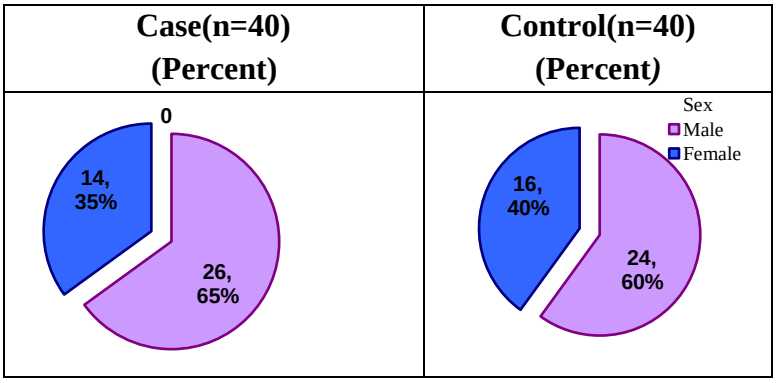

Figure 1: Distribution of the participants by their gender(N=80)

In the case group, 26 (65.0%) were male and in the control group, 24 (60.0%) were male. In both groups, the male-female ratio was about 1.9:1 and 1.5:1. Males were proportionately higher in both groups, however, there was no statistically significant difference in male-female distribution between the groups (p-value = 0.4653).

Table II: Distribution of the children by the socioeconomic status of their family(N=80)

Socio-economic status	Case (n=40)	Control (n=40)	p-value
Higher class	2 (5%)	2 (5%)	0. 026
Middle class	9 (22.5%)	16 (40%)	
Lower class	29 (72.5%)	22 (55%)	
Total	40(100.0%)	40(100.0%)	

In both groups, relapses were higher in the lower socio-economic class (72% in the case group and 55% in the control group, p= 0.026). This was statistically significant (p<0.05).

Table III: Distribution of the patients by their age of onset of the first attack of NS (N=80).

Age	Case (n=40)	Control (n=40)	p-value
1-4 years	24(60%)	16(40%)	0.0314
4-7 years	12(30%)	14(35%)	
> 7 years	4(10%)	10(25%)	
Total	40(100.0%)	40(100.0%)	
Mean ± SD	4.05 ± 2.147	5.175 ± 2.435	

In the FRNS group, age 1-5 years had 65% and >5 years had 35% and IRNS group age 1-5 years had 47.5% and >5 years had 52.5%. The difference was statistically significant ($p<0.049$). So, the incidence of frequent relapse was higher in children with early-onset of disease.

Table IV: Distribution of the patients by residence (N=80).

Residence	Case(n=40)	Control(n=40)	p-value
Rural	30(75%)	22(55%)	0.048
Urban	9(22.5%)	17(42.5%)	
Urban slum	1(2.5%)	1 (2.5%)	

A significantly higher incidence of frequent relapse nephrotic syndrome was found in rural children (75%) than that in urban children (55%) ($p< 0.05$).

Table V: Association between infection and type of relapse (N=80).

Infection	Case (n=40)	Control (n=40)	p-value
UTI	17(44%)	10(25%)	0.035
RTI	9 (20.5%)	3(8%)	0.001
CSOM	3(7.5%)	2 (5%)	0.500
Total	29 (72%)	15(38%)	0.001

The FRNS group had a significantly higher incidence of UTI and RTI compared to the IFRNS group. The total frequency of infection was observed to be almost double in the former group (72%) than that in the latter group (38%) ($p<0.001$). The distribution of chronic suppurative otitis media (CSOM) was almost identical between the two groups.

Table VI: Relation of serum albumin level in initial attack with frequent and infrequent relapse (N=80).

Mean serum albumin level	Case (n=40) (gm/dl)	Control(n=40) (gm/dl)	p-value
	1.6 ± 0.2	2 ± 0.3	<0.001

The mean serum albumin level was significantly lower in the FRNS group (1.6 ±0.2 gm/dl) than in the IFRNS group (2 ± 0.3 gm/dl) (p<0.001).

DISCUSSION

The study identified numerous risk factors. The majority of respondents belonged to the 1-4 years age group, with 60% in the FRNS group and 40% in the IFRNS group. The mean age was 4.05 ± 2.147 years for the FRNS group and 5.175 ± 2.435 years for the IFRNS group, which was statistically significant (p=0.0314). Another study reported a mean age of 2.8±1.1 years for the FRNS group and 4.2±1.5 years for the IFRNS group (p<0.001) [18]. Additionally, a study found that 67% of relapsed patients were between 2-6 years old, with a mean age of 5.3±2.1 years [19]. In the FRNS group, 68% of patients were <5 years old, while in the IFRNS group, 46% were <5 years old (P=0.019). Another study found that being <4 years old increased the likelihood of frequent relapse [20]. Similarly, in another study, 56% of patients in the FRNS group were younger (mean age 3.5 years) compared to those in the IFRNS group (mean age 8.5 years) (P<0.002) [18]. Approximately two-thirds (65%) of the patients in the FRNS group and 60% in the IFRNS group were male. The male-female ratio was 1.9:1 in the FRNS group and 1.5:1 in the IFRNS group. A similar finding was reported in a study, which showed a male-female ratio of 2:1 in the FRNS group and 1:1.5 in the IFRNS group[21]. Another study found that relapse was more common in males (75%) than females (25%) [20]. Furthermore, another study found that males were overrepresented in the FRNS group (69%) compared to the IFRNS group (39%) (p=0.03) [18]. These findings align with the present study. In the present study, 75% of participants in the FRNS group and 55% in the IFRNS group came from a poor socioeconomic class, which is statistically significant. Another study reported similar findings (72% in the FRNS group and 48% in the IFRNS group coming from a poor socioeconomic class) [21]. The study revealed that 75% of the patients in the FRNS group and 55% in the IFRNS group came from rural areas. A statistically significant number of FRNS cases were found in rural children compared to urban children. These findings are consistent with other findings, which showed that 72% of subjects in the FRNS group and 48% in the IFRNS group came from rural areas [21]. The present study found that the FRNS group had a significantly higher incidence of urinary tract infections (UTIs) (44%) and respiratory tract infections (RTIs) (35%) compared to the IFRNS group (25% and 17%, respectively). The total frequency of infection was almost double (72%) in the former group compared to the latter group (38%), which

is statistically significant. Another study reported similar findings. They found that 76% of patients in the FRNS group and 46% of patients in the IFRNS group had infections (RTI, gastrointestinal infections) [21]. Similarly, another study found that 72% of the FRNS group had infections including UTIs, RTIs, and chronic suppurative otitis media, while 38% of patients in the IFRNS group had similar infections (UTIs, RTIs, and chronic suppurative otitis media) (P=0.001) [19]. Specifically, urinary tract infection was observed in 44% of patients in the FRNS group and 24% in the IFRNS group (p=0.033), while RTI was observed in 34% of patients in the FRNS group and 16% in the IFRNS group (P=0.038). These findings from other studies align with the present study. Regarding the mean serum albumin level during the initial attack, the FRNS group had a significantly lower level at 1.6±0.2 mg/dl compared to the IFRNS group with a level of 2±0.3 mg/dl, demonstrating statistical significance. A similar study also reported that low serum albumin levels (<1.5 g/dl) at the onset of the disease were associated with frequent relapse [18]. Additionally, another study found that the serum albumin level during the initial attack was 1.5±0.2 g/dl in the FRNS group and 1.9±0.3 g/dl in the IFRNS group (P<0.001) [19]. These findings are consistent with the present study.

LIMITATIONS OF THE STUDY

The current study was conducted among only 80 patients. So, this is not a large study to draw a definite conclusion.

CONCLUSION

Poor socioeconomic status, rural residency, early age of onset, low serum albumin at the time of the initial attack, and infection are significantly associated with frequent relapse nephrotic syndrome. These risk factors should be addressed to prevent FRNS as far as possible which may reduce the suffering of these children and their families to some extent.

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Conflict of interest: None declared

Approval: The study was approved by the Institutional Ethics Committee

RECOMMENDATIONS

This was a small-scale study done at a single center over a brief duration. A large-scale, multi-center prospective type of study with proper follow-up and record-keeping over a long duration will give an elaborate picture of the risk factors of frequent relapse nephrotic syndrome.

REFERENCES

1. *Vogt BA, Avner ED. Nephrotic Syndrome. In: Kliegman RM, Jenson HB, Behrman RE, Stanton BF,editors. Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders; 2007. p 2190-2195.*
2. *Bagga A, Srivastava RN. Nephrotic Syndrome. In: Srivastava RN, Bagga A, editors. Pediatric Nephrology. 5th ed. New delhi: Jaypee; 2011. p195-231.*
3. *Uddin GM. Management of Steroid Sensitive Idiopathic Nephrotic Syndrome in Children. Journal of BCPS 2007;25:38-42.*
4. *Ruley EJ. Hoekelman RA, editors. Primary pediatric care. St louis : Mosby ;1987*
5. *Sharper PM, Pollution J, White RPR. Steroid responsive nephrotic syndrome is more common in Asians. Arch Dis Child 1985; 60:1014-1017.*

6. *Chang J, Habib R, White RHR. A report for international study of kidney disease in children, Pathology of nephrotic syndrome in children. Lancet 1970; 1:1299-1302. .*
7. *Biswas BK. ISKDC regimen – Prednisolone therapy in nephrotic syndrome in children- a follow up study. BJCH 1997; 21:59-62.*
8. *Tarshist P, Tobin JN, Bernstein J, Edelmann CMJ. Prognostic significance of the early course of minimal change disease in children. J AM soc Nephrol 1997; 8: 769- 776.*
9. *Consensus statement on management and audit potential for steroid responsive nephrotic syndrome . Report of a workshop by the British Association for Pediatric Nephrology and Research Unit, Royal College of Physicians. Arch Dis Child 1994;70:151-157.*
10. *MacDonald N, Wolfish N, Maclaine P,etai. Role of respiratory viruses in exacerbation of primary nephrotic syndrome. J Pediatr 1986;108:378-382.*
11. *Matoo TK, Mahamoud MA. Increased maintenance corticosteroids during upper respiratory infection decreased the risk relapse in children nephrotic syndrome. Nepron 2000; 85: 343-345.*
12. *Abeyagunawardena A, Goldbatt D, Andrews N et al. Risk of relapse after meningococcal c conjugate vaccine in nephrotic syndrome. Lancet 2003;362 :449-450.*
13. *Coughi D, Venturi P, Cheli E. Bee sting and relapse of nephrotic syndrome. Child nephrol1988;9:82-83.*
14. *Ishikura K, Yoshikawa N, Hattori et al. Treatment with micro emulsified cyclosporine in children with frequently relapsing nephrotic syndrome. Nephrol Dial Transplant 2010;25:3956-3962.*
15. *Rahman H, Karim A, Begum A et al.Risk Factor for Relapse in Childhood Nephrotic Syndrome. B J C 2002;26: 61-62*
16. *Takeda A, Sadimo M ,Takimoto H et al. Prediction of Subsequent Relapse in Children with Steroid Sensitive Nephrotic Syndrome . J P Nephrology2001;16:888-889.*
17. *Ataei N, Madani A, Falakolaflaki B. Evaluation of Clinical Course, Risk Factors For Relapse And Long –Term Outcome of Children with Primary Nephrotic Syndrome. TUMJ 2003;61:308-319.*
18. *Andersen RF, Thrane N, Noergaard K, Jespersen B, Rittig S. Early Age at Debut is a Predictor of Steroid- Dependent and Frequent Relapsing Nephrotic Syndrome. Pediatr Nephrol 2010; 25:1299-1304.*
19. *Sarker MN, Islam MMSU, Saad T, et al. Risk Factor for Relapse in Childhood Nephrotic syndrome.Faridpur Med coll.J. 2012;7:18-22*
20. *Kabuki N, Okugawa T, Hayakawa H et al. Influence of age at onset on the outcome of steroid sensitive nephrotic syndrome. Pediatr Nephrol 1998;12: 467-470.*
21. *Rahi K, AL-Badri AAS, Salih BJ, Hasan FO. Frequent and Infrequent Relapses and Risk Factors for Relapses. The Iraqi Med J 2009;8:41-42.*