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STUDY ON RISK FACTORS FOR RELAPSE IN CHILDHOOD NEPHROTIC SYNDROME PRESENTING IN RIMS, RANCHI

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ABSTRACT

Background: Nephrotic syndrome (NS) is a disease characterised by heavy proteinuria, hypoalbuminemia (serum Albumin <2.5g/dl), hyperlipidemia (serum cholesterol >200mg/dl) & edema. Nephrotic range proteinuria is present if early morning urine protein is 3+/4+ (on dipstick or boiling test), urine albumin excretion >40 mg/m^2 per hr (on a timed-sample) or spot urine protein/creatinine ratio > 2.[1] The risk factors associated with frequent relapse of Nephrotic Syndrome are early age at onset, delayed time to achieve remission with steroid in 1st attack, presence of upper respiratory tract infection or any other associated infection during 1st episode or during relapse, more number of relapses in first six months after initial episode, shorter time interval between 1st episode and first relapse, inadequate/irregular initial therapy, history of hematuria, hypercholesterolemia and low serum albumin during initial diagnosis as shown in various studies.[2-5] In our country, inadequate health care facility, less organized referral system, lack of adequate knowledge about disease course among parents are great problems in early detection and treatment of relapse cases. Hence, prediction & prevention of risk factors is the key to successful management of childhood Nephrotic Syndrome. **Objective:** To evaluate different risk factors associated with the group of frequent relapsing Nephrotic Syndrome compared to the group of infrequent relapsers. To identify certain risk factors as predictors for frequently relapsing Nephrotic Syndrome, to address those risk factors and minimize frequency of relapses. **Method:** This hospital based cross-sectional observational study was conducted in the Department of Pediatrics, Rajendra Institute of Medical Sciences, Ranchi, Jharkhand, over a period of 1 year from June 2020-May 2021. A total of 100 children who met the inclusion criteria were enrolled into the study. **Results:** Mean age at onset was 6.5±3.374 years. Boys constituted 71% (71 out of 100 children) & girls 29% (29 out of 100) of total study population. Among 100 patients with SSNS, 39 patients were included in FRNS group, rest 61 patients were in IFRNS group. In this study, male to female ratio was 2.4:1. Mean age of onset in FRNS group in this study was lower in comparison to the IFRNS group but the difference was found to be statistically insignificant. Presence of infection during 1st episode played a statistically significant role for relapse ($p<0.05$). UTI was found to be the most common infection associated in FRNS. Massive edema was more in the FRNS group but the difference was found to be statistically insignificant. Time interval between remission in 1st attack & onset of 1st relapse was significantly lower in FRNS. Steroid free time interval between completion of treatment of 1st attack and onset of 1st relapse was also significantly lower in FRNS. H/o inadequate initial treatment was significantly more in FRNS. In FRNS group, remission occurred later than IFRNS group but there was no statistically significant association. Serum albumin concentration during disease onset was significantly less in FRNS. Serum cholesterol level was significantly higher in FRNS group. Hematuria, hypertension or presence of atopy at the onset of disease were not found as risk factor for increased relapse rate in this study. **Conclusion:** It was concluded that the following parameters were found to be associated with increased rate of relapse in children with SSNS and therefore may be considered as risk factor for relapse like Presence of infection during initial attack of NS, Presence of infection during 1st relapse of NS,Less time interval between remission in 1st episode of NS & onset of 1st relapse, Less steroid free time interval between completion of treatment of 1st attack & onset of 1st relapse, Inadequate period of treatment (duration in total <12 weeks i.e. daily doses @60mg/m^2/day for <6 weeks, alternate day doses @40mg/m^2/day for <6 weeks or irregular) of 1st episode of NS, Low serum albumin (with median value 1.6g/dl) and high serum cholesterol level (with median value 430mg/dl) at onset of disease. Finally, the hypothesis of the study was tested by chi-square test and found that the above mentioned risk factors for NS relapse were acceptable. But the result of this study may not be applicable for the total community as it was conducted in a single centre over a limited time period in small sample size. Further study with larger sample size in multicenter with longer follow up observations is required to evaluate the results of this study for universal acceptance.

KEYWORDS: FRNS, IFRNS, SSNS, risk factors, proteinuria, nephrotic syndrome.

INTRODUCTION

Nephrotic syndrome (NS) is an important chronic disease in children characterised by heavy proteinuria, hypoalbuminemia (serum Albumin <2.5g/dl), hyperlipidemia (serum cholesterol >200mg/dl) & edema. If early morning urine dipstick protein is 3+/4+ and urinary albumin excretion is >40 mg/ m^2 per hr (on a timed-sample) or spot urine protein/creatinine ratio > 2^1 then the patient is having nephrotic range proteinuria. It is quite common clinical condition in our country, affecting usually the young children. Estimates on annual incidence range from 2-7 per 100,000children (peaking in 1-4 years old children) & prevalence ranges from 12-16 per 100,000 population.[3]

Approximately 90% of children with NS have idiopathic nephrotic syndrome(NS). Most frequent type(85%) of Idiopathic NS is minimal change disease(MCD) & more than 95% of MCD well respond to steroid therapy.[4] Although long term prognosis of steroid sensitive NS is believed to be good with the condition resolving in adolescence or early adult life in most children,80-90% of them experience one or more relapses.[5,6] Of those who relapse, approximately 40-50% of children relapse frequently or become steroid dependent and may suffer from a number of adverse effects related to disease and its treatment.[7] The course of illness may vary from a single episode to infrequent relapses to frequent relapses, and rarely the occurrence of late steroid resistance.[8,9]

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 month after diagnosis and treatments are likely to follow an infrequently relapsing course.[4] Various studies have shown that frequently relapsing NS is associated with an early age at onset, delayed time to achieve remission with steroid in 1st attack, presence of upper respiratory tract infection or any other associated infection during 1st episode or during relapse, more number of relapses in first six months after initial episode, shorter time interval between 1st episode and first relapse, inadequate/ irregular initial therapy, history of hematuria or atopy and low serum albumin during initial diagnosis.[4,8,9]

In our country, inadequate health care facility, less organized referral system, lack of adequate knowledge about disease course among parents are great problems in early detection and treatment of relapse cases. Hence, prediction & prevention of risk factors is the key to successful management of childhood nephrotic syndrome. An understanding of risk factors that determine the course, is useful in taking decisions regarding therapy and enables counselling. No recent study on risk factors for relapse in childhood NS in Eastern India is found in published literatures, therefore this study is being proposed which may contribute some important inputs in this field.

MATERIALS AND METHODS

This Hospital based cross sectional observational study was performed in the Department of Pediatrics and Neonatology, Rajendra Institute of Medical Sciences, Ranchi on 100 children aged 1-12years, over a period of 1 year from June 2020- May 2021. Inclusion criteria included Patients with steroid sensitive NS, age between 1 to 12 years and with history of onset of first episode atleast one year back having available adequate medical records supplemented with history from reliable source. The study excluded Congenital NS, age less than 1 yr or above 12 years, steroid resistant NS (SRNS), secondary NS, patient with inadequate medical records and parents not giving consent.

RESULTS

In our study mean age at onset was 6.5±3.374 years. Boys constituted 71% (71 out of 100 children) & girls 29% (29 out of 100) of total study population. Among 100 patients with SSNS, 39 patients were included in FRNS group, rest 61 patients were in IFRNS group. In this study, male to female ratio was 2.4:1. Mean age of onset in FRNS group in this study was lower in comparison to the IFRNS group but the difference was found to be statistically insignificant. Presence of infection during 1st episode played a statistically significant role for relapse (p value <0.05). UTI was found to be the most common infection associated in FRNS. Massive edema was more in the FRNS group but the difference was found to be statistically insignificant. Time interval between remission in 1st attack & onset of 1st relapse was significantly lower in FRNS (p value <0.0082). Steroid free time interval between completion of treatment of 1st attack and onset of 1st relapse was also significantly lower in FRNS (p value <0.0087). History of inadequate initial treatment was significantly more in FRNS (p value <0.0055). In FRNS group, remission occurred later than IFRNS group but there was no statistically significant association. Serum albumin concentration during disease onset was significantly less in FRNS. Serum cholesterol level was significantly higher in FRNS group. Hematuria, hypertension or presence of atopy at the onset of disease were not found as risk factor for increased relapse rate in this study.

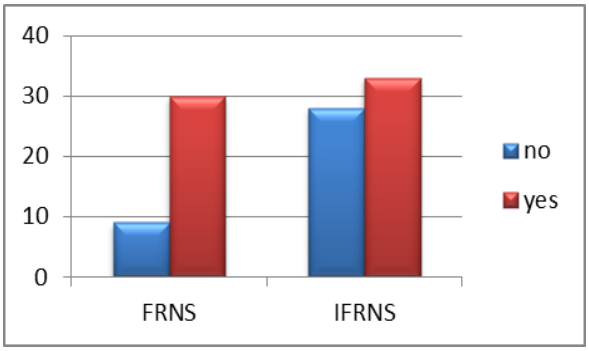

Figure 1: Distribution of Presence of any infections in 1st relapse in two groups.

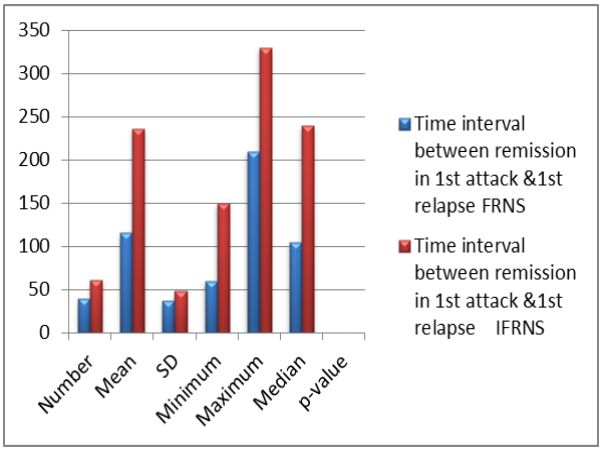

Figure 2: Time interval (in days) between remission in 1st attack & onset of 1st relapse.

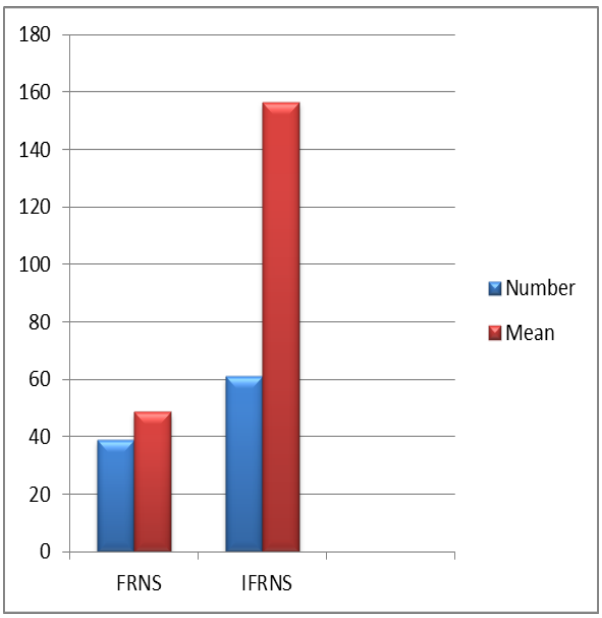

Figure 3: Steroid free time interval (in days) between completion of treatment of 1st attack & onset of 1st relapse in two groups.

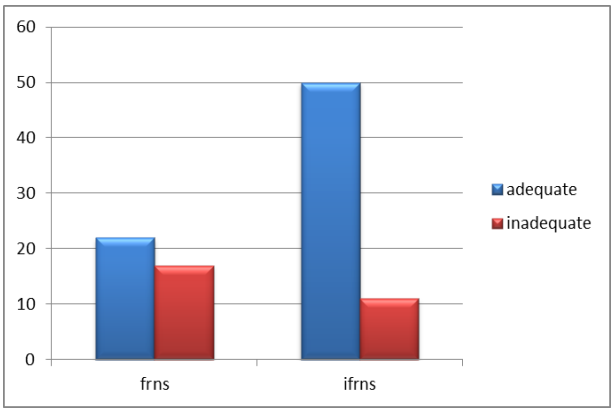

Figure 4: Distribution of Duration of treatment of 1st attack in two groups.

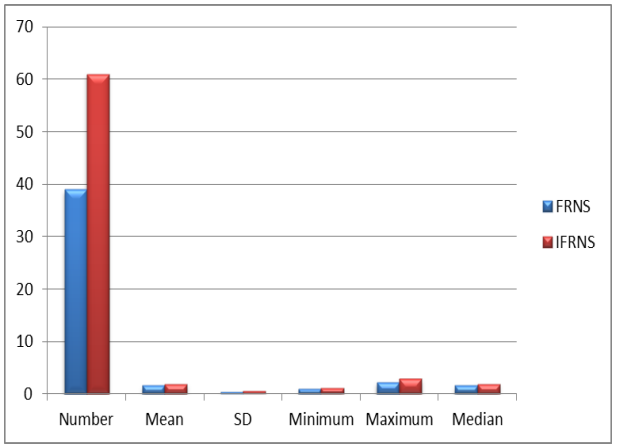

Figure 5: Distribution of serum albumin(g/dl) in two groups.

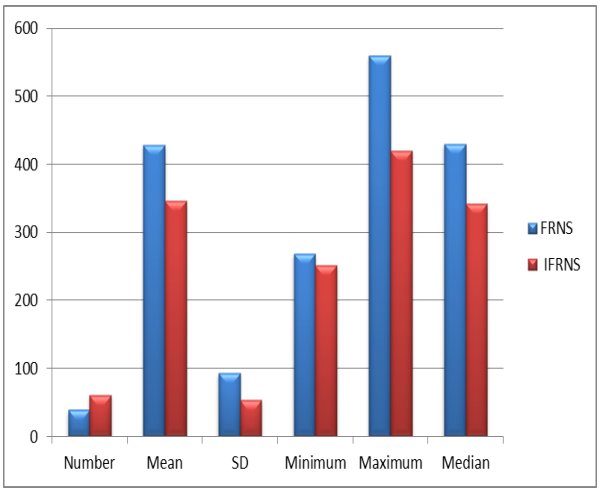

Figure 6: Distribution of serum Cholesterol(mg/dl) in two groups.

CONCLUSION

It was concluded that the following parameters were found to be associated with increased rate of relapse in children with SSNS and therefore may be considered as risk factor for relapse like Presence of infection during initial attack of NS, Presence of infection during 1st relapse of NS, Less time interval between remission in 1st episode of NS & onset of 1st relapse, Less steroid free time interval between completion of treatment of 1st attack & onset of 1st relapse, Inadequate period of treatment (duration in total <12 weeks i.e. daily doses @60mg/m^2/day for <6 weeks, alternate day doses @40mg/m^2/day for <6 weeks or irregular) of 1st episode of NS, Low serum albumin (with median value 1.6g/dl) and high serum cholesterol level (with median value 430mg/dl) at onset of disease.

Finally, the hypothesis of the study was tested by chi-square test and found that the above mentioned risk factors for NS relapse were acceptable. But the result of this study may not be applicable for the total community as it was conducted in a single centre over a limited time period in small sample size. Further study with larger sample size in multicenter with longer follow up

observations is required to evaluate the results of this study for universal acceptance.

DISCUSSION

Nephrotic syndrome is an important chronic disease in children. It has high propensity for relapse. Approximately, 80-90% of SSNS patients experience one or more relapses[5,6] during their lifetime. The main problem in such disease is frequent relapses and their association with complications of disease or side effects of drugs (mostly steroid) used in each relapse. So, it is very important to find out those risk factors in development of frequent relapses to anticipate the likely course of the disease. This study was conducted as a hospital based cross sectional observational study, in the Department of Pediatrics, at Rajendra Institute of Medical Sciences, Ranchi, over a period of 1 year from June 2020- May 2021. In this study 100 children (1-12 years of age) with steroid sensitive NS, were included. The mean age (mean ± s.d.) of patients was 6.5±3.37 years. Minimum age was 2 years and maximum age was12 years and the median age was 6 years. The mean age (mean ± s.d.) of patients was 6.1026 ± 2.8589 years with range 2 -12 years and the median age was 5 years in FRNS. In IFRNS, the mean age (mean± s.d.) of patients was 7.9590 ± 2.4871 years with range 2 -12 years and the median age was 8 years.

Boys constituted 71% (71 out of 100 children) & girls constituted 29% (29 out of 100). Among 100 patients with NS, 39 were in FRNS group and the rest 61 patients were in IFRNS group.

In this present study, the mean age at onset was lesser (40.51 ± 18.63 months) in FRNS group than IFRNS group (51.65 ± 25.71 months). Similar result was observed in several studies.

Andersen RF et al(2010)[12] concluded that low age at debut was associated with high risk of FRNS/SDNS.

Desman Situmorang et al(2010-2014)[17] also stated that age at diagnosis of NS ≤5 years was a risk factor of frequent relapse in NS patients.

The observed result in our study showed no statistically significant value (p>0.999) probably due to the small sample size of this study.

In the present study, male to female ratio was 2.4:1, and male to female ratio for frequent relapser and infrequent relapser were 3.3:1, 2.1:1 respectively. In group FRNS, 9(23.08%) patients were female and 30(76.92%) patients were male. In group of IFRNS, 20(37.79%) patients were female and 41(67.27%) patients were male.

It was also found in a study conducted by *Andersen RF et al(2010)*[12] that male gender was associated with high risk of FRNS/SDNS.

In this study, it was seen that presence of infection played a statistically significant role for relapse (p=0.0047). In the group of FRNS, 2 patients had no infection and 37 patients had infection during 1st attack of NS, i.e., 94.8% of FRNS, h/o infection is present during 1st attack. In the group of IFRNS, 17 patients had no infection and 44 patients had infection, i.e in 72.1% of cases, h/o infection was present during 1st episode. This is comparable with the findings found in the study done by *Khemchand N Moorani et al(2007-2008).*[14] According to them, infection is an important cause of frequent relapse.

In the present study, among 100 patients, 81 patients of SSNS presented with infections during 1st episode of NS. Urinary tract infection (UTI) was found to be the most common infection in our study. In FRNS/SDNS group, UTI was present in 48.7 % of cases & in the other group it is present only in 41.0% of cases.

Khemchand N Moorani et al(2007-08)[14] also concluded that ARI & UTI were the most common infections found in SSNS.

In our study, association between presence or absence of edema in two groups was statistically not significant (**p=0. 4216**). In the group of FRNS, none had no edema but in 39 patients edema was present. In group IFRNS 1 patient had no edema and 60 patients had edema.

However, no such studies have been found to show any association of edema in FRNS.

In my study, In the group of FRNS, 36(92.3%) patients had no hematuria in first attack and only 3(7.7%) patients had hematuria in first attack. In group IFRNS no patients had hematuria in first attack.

Very few studies showed hematuria as a predictor for relapse -
Constantinescu AR et al(2000)[10] demonstrated that presence of hematuria could predict future relapses.

My study showed that in the group of FRNS 36 (92.3%) patients had no atopy and 3(7.9%) patients had atopy. In the group of IFRNS 59 (96.7%) patients had no atopy and only 2(6.3%) patients had a history of atopy.

Shivraj et al[19] showed no association of asthma and allergies with frequently relapsing nephrotic syndrome, or with higher relapse rates.

In this study, in the group of FRNS, 36 (92.3%) patients had no hypertension in first attack and 3(7.7%) patients had hypertension in first attack. In the group of IFRNS 60(98.4%) patients had no hypertension in first attack and only 1(1.6%) patients had hypertension in first attack.

In study conducted by *Ataei N et al*[13], it was observed that, presence of hypertension fairly predict relapses.

In this study, very few patients presented with hematuria, hypertension & atopy during the first episode of the disease. That's why no statistical significance was drawn in these parameters.

Association between presence of any infections in 1st relapse in two groups was statistically significant (p=0.0211). In the group of FRNS 30 (76.9%) patients had infections in 1st relapse, whereas 9 (23.1%) patients had no h/o infection at that time. In the group of IFRNS, 33 (54.1%) patients had infection during 1st relapse but 28 (45.9%) patients had no infection.

Mohammad Sjaifullah Noer[20] demonstrated significant role of infection during first relapse as a predictor for frequent relapse.

Time interval between remission in 1st attack & onset of 1st relapse was significantly lower in FRNS (median value 105 days) than IFRNS (median value 240 days). Association between time interval between remission in 1st attack & 1st relapse in two groups was statistically significant (p<0.0082).

Desman Situmorang et al(2010-2014)[17] concluded that period of remission ≤6 month was risk factor for frequent relapse.

Steroid free time interval between completion of treatment of 1st attack &onset of 1st relapse was significantly lower in FRNS than IFRNS. Association between steroid free time interval between completion of treatment of 1st attack & onset of 1st relapse is statistically significant (p=0.0087).

However, no study has been found to show this association.

In this study, it was observed that among 100 children with SSNS, 28 patients received inadequate treatment of 1st attack, i.e. total treatment duration was <12weeks (daily steroid<6 weeks @60mg/m^2/day, alternate day steroid @ 40mg/m^2/days <6 weeks) or irregular treatment. 17 of them developed FRNS after 1 year of follow up. This result was statistically significant (p<0.005).

This result was comparable with the findings of the study done by *Shatha Hussain Ali et al(2012-2013)*[18], showing inadequate initial treatment as risk factor for relapse.

In my study, in FRNS group, remission occurred later (14.05 ± 3.63 days with range 9-22 days and the median value was 13 days) than IFRNS group (9.62 ± 2.50 with range 6-16 and the median value was 10 days) but there was no statistical significant association between delayed remission & frequent relapses (p=0.8886), probably due to the small sample size of this study.

Study done by *Letavernier B et al (2008)*[11] showed that risk factors for steroid dependence was high remission achieved after 20 days of initiation of steroid.

In the present study the mean serum albumin (1.67 ±0.40 g/dl vs 1.88 ± 0.52 g/dl) was significantly less in the FRNS group than those in the IFRNS group (p=0.008).

Jahan I et al(2006)[16] demonstrated low serum albumin level at the time of initial attack were independent risk factors for FRNS.

In the present study, serum cholesterol level was significantly higher in FRNS group than the other group. The mean cholesterol (mg/dl) (mean± s.d.) value was (428± 93.36)mg/dl and the median value was 430mg/dl in FRNS. In IFRNS, the mean value (mean± s.d.) was (346±53.68mg/dl) and the median value was 342mg/dl.

This findings was consistent with the findings of the study done *Mahmud S et al(2005-2006).*[15] They considered high serum cholesterol as predictor for relapse.

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