Childhood Nephrotic Syndrome, Frequent and Infrequent Relapses and Risk Factors for Relapses

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ABSTRACT:

BACKGROUND:

Most patients with steroid sensitive nephrotic syndrome (SSNS) have frequent relapses until disease resolve spontaneously toward the end of second decade of life and so the main problem in such disease is frequent relapses and their association with complications of disease or side effects of drugs used in each relapse.

OBJECTIVE:

In this study, we evaluate different factors which might be associating or leading to occurrence of frequent relapses.

PATIENTS AND METHODS:

A retrospective study was done in the Central Child Teaching Hospital from Feb. 2007 - Feb. 2008, during this period, 120 patients with nephrotic syndrome (NS) randomly selected who were diagnosed & or treated in this hospital. Out of 120 patients, 85 (70.8%) patients with steroid sensitive nephrotic syndrome (SSNS), 9 (7.5%) patients with steroid dependant nephrotic syndrome (SDNS) and 26 (21.7%) patients with steroid resistant nephrotic syndrome (SRNS). The steroid sensitive patients were divided into 24 (28.2%) patients as undetermined (UD) group, 35 (41.2%) patients with frequent relapses (FR) group and 26 (30.5%) patients with infrequent relapses (IFR) group. We compare between frequent and infrequent groups regarding to age, sex, type of presentation, biochemical finding, precipitating factors, family history of renal disease, the time needed to responsd to steroid therapy and duration of steroid therapy.

RESULTS:

The age ranged from 1-16 years, with peak incidence at age group from 1-5 years. There were 64 patients (53.3%) presented with this age group, most of them were steroid sensitive nephrotic syndrome 53 (82.5%) patients. There were 73 male and 47 female & M: F ratio 1.5: 1, most of them (70.8%) with steroid sensitive nephrotic syndrome & male to female ratio was 1.8: 1. The main type of presentation was preiorbital oedema; the main type of precipitating factor was respiratory tract infection. The family history of renal disease (P value = 0.0006) and the delay in response to steroid therapy, 2 weeks and more (P value = 0.0477 & 0.0486) were statistically significant correlation with frequent relapsers (FR) group in comparison to infrequent (IFR) group.

There were no statistically significant differences between frequent and infrequent groups regarding other factors.

CONCLUSION:

There were significant correlation between family history of renal disease & delay in response to steroid therapy with occurrence of frequent relapses supporting other studies but this study fails to confirm previous studies about other factors.

KEY WORDS: steroid sensitive nephrotic syndrome (SSNS), frequent relapses (FR), infrequent relapses (IFR).

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INTRODUCTION:

The term NS refers to tetrad of any condition with heavy proteinuria (> 40 mg/m^2/hr or protein: creatinine ratio > 200mg/mmol.) hypoalbuminemia, oedema and hyperlipidemia[1, 2]. Although relationship among these finding was recognized as early as the fifteenth century, the term nephrosis first achieved by volhard and fabr in early part of the 20th century. Later developments, notably the advent of percutaneous renal biopsy, facilitated further delineation of the

many forms of kidney disease that result in the nephrotic syndrome[2]. Nephrotic syndrome could be subdivided into: congenital, idiopathic (primary) and secondary to any overt disease, medications or others [2, 3]. In children most common variety is minimal changes disease (MCD) characterized by response (sensitive), to steroid therapy, few patients with (MCD) don't respond to steroid and few steroid responders have histology other than (MCD) [4]. There is a tendency for patients with MCD to run a relapsing-remitting course, approximately 30% of children experience only one attack and are definitively cured after single course of steroids. Persistent remission for 18-24 months after stopping treatment is likely to reflect definitive cure, and the risk of later relapse is low. Relapse occurs in more than two-thirds of children and nearly 50% relapse more than four times. Long-term remission can be expected in 75% of initial responders who do not relapse within 6 months. Less than 5% of children with MCD enter adulthood still having relapses, although the younger the onset of the first attack, the longer the child is likely to continue having relapses. In general, increasing time since last relapse reduces the risk of further relapses [5, 6].

PATIENTS AND METHODS:

A retrospective study was done in the Central Child Teaching Hospital from Feb. 2007 - Feb. 2008, during this period, 128 patients with nephrotic syndrome (NS) randomly selected who were diagnosed & or treated in this hospital, 8 patients excluded from study because they had congenital nephrotic syndrome and only 120 patients eligible in this study. The information which were obtained from clinic files and follow-up reports are **[**age, sex, date of diagnoses, type of presentation, precipitating factors, family history of renal disease, biochemical findings (blood urea, serum creatinine, total serum protean, serum albumin), number of relapse and the time of each relapse, time needed to responsd to steroid therapy (≤ 2 weeks, > 2 – 4 weeks, > 4 – 8 weeks), duration of steroid therapy as alternative day (≤ 2m., > 2 – 3 m., > 3 – 6 m.)].

From these information, our patients divided into 3 groups:

1- Steroid sensitive N.S. (SSNS)
2- Steroid dependence N.S. (SDNS)
3- Steroid resistance N.S. (SRNS).

The steroid sensitive were divided into subgroup according to useful definition:

1- Undetermined N.S.: first-time diagnosed and response to steroid therapy but they still on alternative day or complete therapy but not more than 6 month.
2- Frequent relapse N.S. (FRNS): two or more relapse per 6 months after remission from 1st attack. Or 4 or more relapse with any whole year.
3- In frequent relapse N.S. (IFRNS): less than 2 attacks of relapse with in 6 m. of 1st attack or less than 4 attacks of relapse per any year after.

The data performing from these information including comparing between different types of N.S. in regarding to age and sex, and data comparing between FR and IFR patient in regarding to age, sex type of presentation, type of precipitating factor, biochemistry finding including renal function (blood urea & serum creatinine) and total serum protein & serum albumin, Family history of renal disease, time needed to responsd to steroid therapy and duration of steroid therapy on alternative day.

Statistically Analysis:

Data collected were analyzed using available statistical soft ware package of SPSS variation 10:00 through computer.

The data results then presented as simple measures of number or percentage with use of Chi-square test (X^2) for testing significance of statistical difference between different parameter as number of percentage with use of probability value P. value (P. value ≤ 0.05) as the level of significance.

RESULTS:

There was a high percentage of patients with SSNS compared to other groups as shown by table (1). There were 85 patients (70.8%) with SSNS with male predominance and males: females ratio was 1.8: 1, followed by SRNS then SDNS. The distribution of different forms of NS in relation to sex showed male predominance, there were 73 males and 47 females & M: F ratio was 1.5: 1, most of them SSNS with M: F ratio 1.8: 1.

Table 1: The distribution of different forms of NS in relation to sex.

	Male	Female	M: F	Total	%
SSNS	55	30	1.8: 1	85	70.8
SDNS	5	4	1.2: 1	9	7.5
SRNS	13	13	1: 1	26	21.7
Total	73	47	1.5: 1	120	100

These 3 groups distributed according to age as shown by table (2). The patients divided into 3 age groups the list between 1 – 5 years, the other > 5 – 10 years and the last group > 10 – 16 years. The main age group was between 1 – 5 years and 64 patients (53.3%) presented with this age group & most of them were SSNS (53) patients.

Table 2 : The distribution of different forms of NS in relation to age.

	1 – 5 y	> 5 – 10 y	> 10 – 16 y	Total
SSNS	53	18	14	85
SDNS	3	4	2	9
SRNS	8	7	11	26
Total	64	29	27	120
%	53.3	24.2	22.5	100

The main studied group was SSNS and divided into UD (undetermined), FR (frequent relapses) and IFR (infrequent relapses) and these 3 subgroups distributed according to sex, age, type of presentation, biochemical finding, type of precipitated factors, family history of renal disease, the time needed to response to steroid therapy and duration of steroid therapy. As shown in table (3). which showed that only the family history of renal disease (P value = 0.0006) and the delay in respond to steroid therapy (2 weeks and more with the P values (0.0477 & 0.0486) were statistically significant factors, but other factors were not significant.

Table 3 : Correlation between clinical, biochemical findings and frequent relapses.

	Total SSNS n=85	UD n=24	FR n=35	IFR n=26	X^2	P value
Sex : Male	55	19	23	13	1.5230	0.4670
Female	30	5	12	13		
Age: 1-5 Y	53	19	19	15	0.070	0.9656
>5-10 Y	18	4	8	6	1.091	0.5796
>10-16 Y	14	1	8	5	0.11	0.9465
Type of presentation:						
- periorbital oedema	49	15	19	15	0.070	0.9656
- generalized odema	16	5	8	3	1.293	0.5239
- abdominal pain	14	2	7	5	0.005	0.9975
- decreased urine output	4	1	1	2	0.745	0.6890
- hematuria	2	1	0	1	1.368	0.5046
Biochemical findings:						
- renal impairment	19	2	10	7	0.020	0.9900
- total serum protein ≤ 4 g/dl	49	10	20	19	0.158	0.9240
- serum albumin ≤ 2 g/dl	40	16	19	15	0.070	0.9656
Types of precipitating factors:						
- upper respiratory tract infection	38	11	15	12	0.065	0.9680
- pneumonia	8	2	4	2	0.234	0.8896
Family history of renal disease	19	4	15	0	14.77	0.0006
Time to responsd to steroid:						
- < 2 week	10	2	5	3	0.098	0.9522
- 2-4 week	51	19	14	18	5.11	0.0477
- > 4 week	24	3	16	5	4.634	0.0486
Duration of treatment:						
- ≤ 2 months	27	12	7	8	0.933	0.6272
- > 2-3 months	40	10	20	10	2.083	0.3529
- > 3-6 months	18	2	8	8	0.482	0.7858

UD: undetermined nephrotic syndrome
FR: frequent relapse nephrotic syndrome
IFR: infrequent relapse nephrotic syndrome

DISCUSSION:

This study showed that the main type of NS is SSNS followed by SRNS then SDNS. These result similar to previous studies by Clark AG. et al [4] and Waston AR. et al [2]. The main age of presentation group for SSNS was between 1 – 5 years while in SRNS was > 10 – 16 years similar to previous studies [4, 2] and the studies done by Eltohami et al [7], Malag et al [8] and Gulati et al [9].

In SSNS the male: female ratio was approximately 1.8: 1 with main age group range between 1 – 5 years, this result is similar to the studies done by Zaki M. et al [10], Clark AG. et al [4] and Hoyer et al [11]. The variation or comparing between FR NS and IFR NS patients in regarding to age of presentation show in our result statistically not significant and so age is a poor predictive factors for outcome of NS patient, and these result differ from previous study done by Takeda A. et al [12] which mentioned that the early onset NS associated with frequent relapses.

The sex variation in FR & IFR was statistically not significant and so the sex is a poor predictor factor.

The type of presentation of SSNS was mainly periorbital oedema which was present in 49 patients (57.6%) and it was the main presenting feature for all the sub groups (FR and IFR). But all types of presentation were statistically not significant and this result is not similar to previous study done by Hirach et al [13].

The biochemical findings showed that renal impairment (increase blood urea and serum creatinine) and low serum protein or serum albumin were statistically insignificant as predictors for frequent relapses. This result is not similar to previous study which was done by Takeda A. et al [12] which showed that low serum protein or serum albumin work as significant predictors for frequent relapses in future.

The types of precipitating factors showed that the incidence of upper respiratory tract infection is high in SSNS (44.7%) but there was no statistically significant difference between (FR & IFR), so the types of precipitating factors are poor predictors of (FR) and this is similar to previous study which was done by Takeda A. et al [12] which showed that the precipitating factors are poor predictors of (FR).

The study showed that the family history of renal disease is a good predictor of FRNS and this result is similar to previous study which was done by White RH.R. et al [14], they conclude that familial nephrotic syndrome bread true both in respect of histopathology and steroid response.

Regarding the time needed to responsd to steroid therapy, most patients showed a delay in response to treatment, so 51(60%) patients with SSNS responded between 2 – 4 weeks and 24(28%) patients responded > 4 weeks, and with statistically difference between FR & IFR, this was similar to studies done by Wingen J. et al [15] and Hodson EM. et al [16] which concluded that there is evidence that the liability to subsequent relapse of SSNS is influenced by both the intensity and the duration of initial corticosteroid regimen.

The duration of treatment doesn't show any statistically significant difference between FR & IFR and this is not similar to previous study done by Tarshish P. et al [17] and Ya, Ping Wang et al [18] and this may be due to irregular follow up of patients and inadequate adherent to medication by patients or their parents.

CONCLUSION:

We concluded that there were significant correlation between family history of renal disease & delay in response to steroid therapy with occurrence of frequent relapses supporting other studies but this study fails to agree with previous studies about other factors.

So we must encourage & enforce the patient for regular medication taken, regular & long term follow up. And patient with family history of NS and had late response to steroid must be treated for long period to decrease the incidence frequent relapses.

REFERENCES:

1. Ellis D. Avner, William E. Harmon, Patrick Niaudet; Steroid – sensitive idiopathic nephrotic syndrome in children. In Pediatric nephrology, fifth. Edition, 2004 ,543 – 556.
2. Watson AR Idiopathic nephrotic syndrome. Forfar and Arneils text book of pediatrics AGM Compell, Melntosh MD .15 ed. 1998, 968 – 972.
3. Appel GB. Glomerular disorders. In Cecil text book of Medicine Lee Goldman, Gland Bennet, J, WB Sunders Company Philadelphia 21st ed. 2000, 587 – 589.
4. Clark AG, Barratt TM, Avner ED, Harmon WE. Steroid responsive nephrotic syndrome. Pediatric nephrology text book, 4th ed. 1999, 731 – 147.
5. Richard. J. Johnson, John Feehally. Minimal change disease. Comprehensive clinical nephrology, 2nd ed. Section 5, chapter 20, 2003, 276.
6. Narchi H: Nephrotic syndrome relapse: need for better evidence based definition, Arch Dis. Child, 2004, 395.

7. Eltohami EA, Aki-KF. Primary nephrotic syndrome in Qatar. Arabian Gulf Pediatric nephrology, 1989; 3, 222 – 224.
8. Malaga – Guerrero – S – Sanchez – Jacob M. nephrotic syndrome; clinical, therapeutic and follow up characteristic in 100 cases. An – Espain – pediatric 1991; 34 , 220 – 4.
9. Gulati S, Kher V. Sharma RK. Steroid response pattern in Indian children with Nephrotic syndrome. Acta – Paediatr. 1994; 83,530-3.
10. Zaki M. helin I. mananoher DS. Primary nephrotic syndrome in Arab children in Kuwait. Pediatric nephrology. 1989; 3, 218 – 20.
11. Hoyer J. R. Idiopathic NS with minimal Glomerular change in BM Brenner and J.H. Stein (eds) Contemporary Issues in Nephrology. Nephrotic syndrome, New York Churchill Livingstone, 1982, 145.
12. Takeda A, Makoutani – II, Nimura F. Risk factors for relapse in childhood NS. Pediatric Nephrology; 1996; 10, 740.
13. Hirach – M, Takeda – N, Tsukahara H: Farorab L. Course of steroid responsive nephrotic children with mild initial attack. Kidney – Int. 1995; 47, 1392 – 3.
14. White RH. R The familial NS. LA European Survey clinical nephrology 1993, 215 – 219.
15. Wingen – AM, Muller – Wiefel DE. Comparison of different regimens of prednisone therapy in frequently relapsing NS. Acta – Pediatric – Scand. 1990; 79, 305 – 10.
16. Hodson EM, Knight JF, Willis NS, Craig JC; corticosteroid therapy for nephrotic syndrome in children. Update of Cochrane Database of Syst. Rev. CD 001533, 2005.
17. Tarshish. P., Tobin JN. Prognostic significance of the early course of minimal change nephrotic syndrome. J. Am.Soc. Nephrol. 1997; 8, 769-76.
18. Ya – Ping Wang, Ai –Min Liu: The treatment of relapsing nephrotic syndrome in children, Journal of Zhejiang University science 2005,1631.