RESEARCH STUDY

KCMJ 2014; 10(1): 71-77

Basil M. Hanoudi, C.A.B.P [a]
Rajaa Mohammed M.B, Ch.B [a]
Khalid Waleed Al-Kaissi, M.B, Ch.B [a]

Study of Factors Associated with Childhood Nephrotic Syndrome, Frequent Relapsing and Infrequent Relapsing Type

ARTICLE INFORMATION

Authors addresses:
[a] **Department of Paediatrics**
College of Medicine
Al-Mustansiriyah University

* Corresponding Author
E-mail address:

Article history:
Received: 10th May2013
Accepted: 15th June 2013

Keywords:
Nephrotic syndrome, steroid therapy, renal biopsy

ABSTRACT

Background: Most of the patients with nephrotic syndrome develop relapses. The main concern in this disease is the response to treatment, relapses and their association with complications of the disease or side effects of drugs used in each relapse.

Objectives: To study different factors which might be associated or leading to the occurrence of relapse in nephrotic syndrome

Methods: A retrospective study of seventy patients with nephrotic syndrome with age range of 1-14 years, who were diagnosed and treated in Child's Central Teaching Hospital over the period of 1st of January and 1st of July 2008. The patients were divided into three groups; frequent relapses group, infrequent relapses group and undetermined group. We compared between frequent relapses group and infrequent relapses group in regard to age, sex, type of presentation, biochemical findings which include; total serum protein, serum albumin and renal function test, precipitation factors, family history of renal disease, the time needed to respond to steroid therapy, duration of maintenance steroid therapy and type of renal biopsy.

Results: The peak incidence of nephrotic syndrome was at 1-5 years, and male to female ratio was 2.3:1. There was significant correlation of age and type of steroid response in nephrotic syndrome(P 0.042), and no significant correlation regarding sex(P 0.571). The relation of frequent relapsing and infrequent relapsing type with age and sex was not significant(P 0.864, 0.69 respectively), but hematuria had significant relation(P 0.036). Family history of nephrotic syndrome, early response to steroid therapy and the prolonged duration of maintenance steroid therapy were statistically significant in correlation with frequent relapses and infrequent relapses of nephrotic syndrome(P 0.05, 0.016, 0.024 respectively). There was significant difference in correlation of type of steroid response and type of relapse(P 0.001), and focal segmental glomerulosclerosis is prominent in frequent relapsing type(66.7%), while the minimal change type was prominent in infrequent relapsing nephrotic syndrome(40%).

Conclusions: There was significant correlation between family history of nephrotic syndrome, hematuria, response to steroid therapy, short duration of maintenance steroid therapy and type of steroid therapy response with occurrence of frequent relapses in nephrotic syndrome. There was increasing incidence of focal segmental glomerulosclerosis in frequent relapses.

Introduction: Nephrotic syndrome (NS) is pathognomonic of glomerular disease. It is primarily a pediatric disorder, with 75% of cases are under 6 years and peak incidence between 2-3 years of age. The incidence is 2-3/100,000 children per year. The majority of cases occur as sporadic form, with familial incidence of 3-5%. It is characterized by: heavy proteinuria (>3.5 g/24 hr in adult, 40mg/m^2/hr in children), hypoalbummemia <2.5g/dl, edema and hyperlipdemia[(1)].

The majority of affected children will have steroid sensitive minimal change disease. It is classified into two types: steroid sensitive nephrotic syndrome (SSNS) and steroid resistant nephrotic syndrome (SRNS). The majority of children with nephrotic syndrome would relapse within the first 6 months of initial therapy. Relapse means edema plus proteinuria (+3, +4). patients with steroid dependent and frequently relapsing NS often encounter relapses. Almost 50-60% of patients would have frequent relapses[3].

Methods:

This is a retrospective study of seventy patients with NS with age range of 1-14 years, who were diagnosed and treated in Child's Central Teaching Hospital. The study started on 1st of January and ended on 1st of July 2008.

Detailed information was obtained from patient's family, hospital records, including; full history of illness, age and sex, also data of frequent relapsing NS (FRNS) and infrequent relapsing NS (IFRNS) patients in regard to age and sex, type of steroid response to treatment, mode of presentation, family history of renal disease, time needed to respond to steroid therapy, type of response to steroid therapy, duration of maintenance steroid therapy, blood biochemistry (total serum protein, serum albumin, blood urea and serum creatinine), and the histological types of renal biopsy. The following definitions were adopted in the study; Remission; urinary excretion <40mg/m^2/hr, nil or trace albumin by dipstick for 3 consecutive days.

The relapse in NS; urinary protein excretion >40mg/m^2/hr, >3+ albumin by dipstick for 3 consecutive days having previously been in remission and appearance of edema.

Patients were categorized into three groups according to the following definitions:

- Steroid sensitive NS; remission achieved with steroid therapy alone.
- Steroid dependent NS; occurrence of 2 consecutive relapses during steroid therapy or within 2 weeks of its cessation.
- Steroid resistant NS; failure to achieve remission after 8 weeks of daily therapy with oral prednisolone at a dose of 2mg/kg/24hr.

Then patients were subdivided into three groups according to the following definitions:

- Frequent relapse NS(FRNS): Two or more relapses during the first six months of initial response or more than four relapses over twelve months periods.
- Infrequent relapse NS(IFRNS): Less than two relapses during the first six months of initial response or less than four relapses during any 12 months afterwards.
- Undetermined group: First time diagnosed and responded to steroid therapy, but still on alternative day steroid or completed therapy but not more than six months period, to determine to which one of the previous groups the patient belongs[1,4].

Patients of the undetermined group were excluded from the study group, only sixty two patients; frequent relapse NS(35) and infrequent relapse NS(27) were involved in the study.

The data of information was analyzed and results were expressed in numbers and percentages, the statistical analysis was done using t-test and Chi-square and P-value <0.05 was considered as significant and below 0.01 was considered highly significant.

Results:

Total numbers of patients included in this study were seventy patients, with age range of 1-14, forty nine patients were males and twenty one patients were females with males to females ratio (2.3:1). The following table shows the details;

Table 1: The age and sex distribution of patients with nephrotic syndrome

Age groups	No.	Percentage
1-5 years	44	62.9%
>5 - 10 years	19	27.1%
>10 years	7	10.0%
Sex		
Male	49	70.0%
Female	21	30.0%

The frequency of different types of NS concerning the response to steroid in relation to age (P = 0.042) was significantly different, and to sex (P = 0.571) was not significantly different as seen in the following table

Table 2: The type of steroid therapy response of seventy patients with nephrotic syndrome according to age and sex

Type of steroid response to treatment	Age groups (years)					
	1-5 year		>5-10 year		>10-14 year	
	No.	%	No.	%	No.	%
Steroid sensitive nephrotic syndrome	29	72.5 %	10	25.0%	1	2.5%
Steroid dependent nephrotic syndrome	10	62.5%	4	25.0%	2	12.5%
Steroid resistance nephrotic syndrome	5	35.7%	5	35.7%	4	28.6%
Type of steroid response to treatment	Sex					
	Male		Female			
	No.	%	No.	%		
Steroid sensitive nephrotic syndrome	30	75.0%	10	25.0%		
Steroid dependent nephrotic syndrome	10	62.5%	6	37.5%		
Steroid resistance nephrotic syndrome	9	64.3%	5	35.7%		

*P value 0.042 (significant) using Pearson Chi-square test
**P value 0.571 (not significant) using Pearson Chi-square test

Table 3: The type of relapses in patients of nephrotic syndrome by age, sex and mode of presentation

Type of steroid response to treatment	Age groups (years)					
	1-5 year		>5-10 year		>10-14 year	
	No.	%	No.	%	No.	%
Steroid sensitive nephrotic syndrome	29	72.5 %	10	25.0%	1	2.5%
Steroid dependent nephrotic syndrome	10	62.5%	4	25.0%	2	12.5 %
Steroid resistance nephrotic syndrome	5	35.7%	5	35.7%	4	28.6 %
Type of steroid response to treatment	Sex					
	Male				Female	
	No.		%		No.	%
Steroid sensitive nephrotic syndrome	30		75.0%		10	25.0 %
Steroid dependent nephrotic syndrome	10		62.5%		6	37.5 %
Steroid resistance nephrotic syndrome	9		64.3%		5	35.7 %

The number of relapsing NS patients were sixty two, and NS was divided into two subgroups;the frequent relapse group 35(56.45%) and the infrequent relapse group 27(43.54%). The comparison between frequent relapses and infrequent relapses in relation to age and sex was statistically not significant with P value (0.864) and (0.069) respectively. While the correlation between the mode of presentation and type of relapses revealed hematuria a significant mode of presentation (P 0.036) as shown in table 3

.

Relapses by age, sex and mode of presentation		Relapses				P value
		Frequent relapses		Infrequent relapses		
		No.	%	No.	%	
Age groups	1-5 years	21	53.8%	18	46.2%	0.864
	>5 - 10 year	11	61.1%	7	38.9%	
	>10 years	3	60.0%	2	40.0%	
Sex	Male	21	48.8%	22	51.2%	0.069
	Female	14	73.7%	5	26.3%	
Mode of presentation	Generalized edema	22	55.0%	18	45.0%	0.756
		13	59.1%	9	40.9%	
	Buffiness of face	12	57.1%	9	42.9%	0.937
		23	56.1%	18	43.9%	
	Abdominal pain	23	100%	-	-	0.207
		33	55.0%	27	45.0%	
	Decrease urine output	8	72.7%	3	27.3%	0.230
		27	52.9%	24	47.1%	
	Hematuria	10	83.3%	2	16.7%	0.036*
		25	50.0%	25	50.0%	

*The Pearson Chi-square statistic is significant at the 0.05 level.

The main precipitating factor of relapse was respiratory tract infection with percentage of FRNS and IFRNS (65.9%) and (34.1%) respectively (P value 0.037) which was statistically significant. There was high incidence of FR relapse in patients with positive family history of NS and was statistically significant (P value 0.058) as shown in table (4).

Table 4:

The type of relapses in patients with nephrotic syndrome by precipitating factor and family history of renal diseases.

Precipitating factor of relapse		Relapses				P value
		Frequent relapses		Infrequent relapses		
		No.	%	No.	%	
Respiratory tract infection	Yes	27	65.9%	14	34.1%	0.037*
	No	8	38.1%	13	61.9%	
Other infections	Yes	7	63.6%	4	36.4%	0.596
	No	28	54.9%	23	45.1%	
Irregular drug treatment	Yes	6	66.7%	3	33.3%	0.504
	No	29	54.7%	24	45.3%	
Family history of renal diseases						

Nephrotic syndrome	Yes	7	87.5%	1	12.5%	0.058*
	No	28	51.9%	26	48.1%	
Other renal diseases	Yes	2	50.0%	2	50.0%	0.788
	No	33	56.9%	25	43.1%	

The Pearson Chi-square statistic is significant at the 0.05 level.

The time needed to respond to steroid therapy and duration of steroid maintenance therapy were significantly different in FRNS and IFRNS groups (P value 0.016 and 0.024 respectively), as shown in table 5

Table 5: The relapses in patients with nephrotic syndrome by time needed to respond to steroid therapy and duration of maintenance steroid therapy.

Time needed to respond to steroid therapy and duration of maintenance steroid therapy	Relapses				P Value
	Frequent relapses		Infrequent relapses		
	No.	%	No.	%	
Time needed to respond to steroid therapy ≤2 weeks	9	39.1%	14	60.9%	0.016*
>2 - 4 weeks	11	50.0%	11	50.0%	
> 4 - 8 weeks	5	83.3%	1	16.7%	
Non responsive	10	90.9%	1	9.1%	
Duration of maintenance steroid therapy ≤2 weeks	7	77.8%	2	22.2%	0.024*
>2 - 4 weeks	11	64.7%	6	35.3%	
> 4 - 8 weeks	8	32.0%	17	68.0%	

* The Pearson Chi-square statistic is significant at the 0.05 level.

There was no statistical significant difference between FRNS and IFRNS in regard to biochemical findings. The steroid sensitive NS type was more in IFRNS 21(77.7%), while the steroid dependent and resistant type were more in FRNS 13(37.1%)
and 11(31.4%) respectively with a significant difference(P 0.001) as shown in table 6.

Table 6: The relapses in patients with nephrotic syndrome by laboratory findings and type of response to steroid therapy.

Biochemical findings and type of steroid response to treatment		Relapses				P Value
		Frequent relapses		Infrequent relapses		
		No.	%	No.	%	
Total serum protein	<6.0-5.0gr/dl	15	55.6%	12	44.4%	0.700
	4.9 - 4.0gr/dl	18	60.0%	12	40.0%	
	<4.0-2.0gr/dl	2	40.0%	3	60.0%	
Serum albumin	< 2.5 gr/dl	10	50.0%	10	50.0%	0.502
	≤ 2.0 -1.5 gr/dl	23	62.2%	14	37.8%	
	< 1.5-1 gr/dl	2	40.0%	3	60.0%	
Blood urea	≤ 40 mg/dl	32	56.1%	25	43.9%	0.867
	> 40 mg/dl	3	60.0%	2	40.0%	
Serum creatinine	≤ 0.9 mg/dl	32	54.2%	27	45.8%	0.119
	>0.9mg/dl	3	100.%	-	-	
Type of steroid response to	Steroid sensitive NS	11	34.4%	21	65.6%	0.001*
	Steroid dependent NS	13	18.8%	3	81.3%	

treatment	Steroid resistant NS	11	78.6%	3	21.4%

*The Pearson Chi-square statistic is significant at the 0.05 level.

Histological types of renal biopsy in FRNS and IFRNS were; the focal segmental glomerulosclerosis is prominent in FRNS then the minimal change nephrotic syndrome, were 66.7% and 60.0% respectively. In the IFRNS the focal segmental glomerulosclerosis was 33.3% and the minimal change nephrotic syndrome was 40.0% as shown in table 7

Table 7: The relapses in patients with NS by type of renal biopsy.

Types of renal biopsy	Relapses			
	Frequent relapses		Infrequent relapses	
	No.	%	No.	%
Focal segmental glomerulosclerosis(FSGS) (6)	4	66.7%	2	33.3%
Minimal change nephrotic syndrome(MCNS) (5)	3	60.0%	2	40.0%
Membranous glomerular disease (2)	2	100%	-	-
Membranoproliferative glomerulosclerosis (3)	3	100%	-	-
Mesengial proliferative glomerulosclerosis(MPGS) (2)	2	100%	-	-
Not done (44)	21	47.7%	23	52.3%

Discussion

Regarding seventy patients with NS; Male to female ratio of (2.3:1), is similar to Reshi AR. et al[4] and Beth A et al [1]. With mean age at diagnosis (1-5) years, this result is similar to the studies done by Anochie I. et al[5] and Elzouki AY. et al[6].

In our study, regarding sixty two patients with FRNS and IFRNS; thirty five (56.4%) of patients were presented with FRNS and 27(43.5%) of patients were presented with IFRNS, this result was similar to the study done by Elzouki AY. et al[6], Mitwalli AH et al[7] and Constantinescu AR. et al[8].

Comparing between FR and IFR nephrotic syndrome patients in regard to age of sex, findings showed; no statistical significant difference (P 0.864, 0.069 respectively). So age and sex are poor predictive factors for outcome of patients with FRNS an IFRNS. This result was similar to study done by , Constantinescu AR. et al[8], Shaker IK et al[9] and Se Jin Parket al[10]. However Watson et al[2], found the risk of relapse is greater in children younger than 5 years at onset of disease and in males, this finding may be attributed to small study group or compliance of patients to the treatment[3].

Regarding the mode of presentation; hematuria was statistically significant(P 0.036). This result was similar to the study done by Constantinescu AR. et al[8] and Se Jin Park. et al[10] who reported that the rapid response to initial steroid therapy with the presence of hematuria could predicted future relapses and should be well documented.

The precipitating factors of relapse in patients with NS had high percentage of respiratory tract infections (65.9%), and was statistically significant (P value 0.037), so respiratory tract infections is a good predictor of FRSN and this result was similar to the study done by Toyabe S. et al[11]. Other study done by Davutoqhu M. et al [8] who reported that the number of relapse was proportional with number of infections (P value 0.05).

We found a positive family history of NS is a good predictor of relapse in NS (P value 0.05). The disease tends to develop in siblings at the same age with the same renal histology and same outcome, Maddalena Gigante [13].

In our study, the time to respond to steroid was statistically significant between FR and IFR (P value 0.016). This result was similar to the study done by Elzouki AY. et al[6], Constantinescu AR et al[8], and Kumar J et al[14].

The duration of maintenance steroid therapy in correlation with the rate of relapses decreased the frequency of relapses with elongation of the duration. This result was similar to the study done by, Elzouki AY. et al[6], dissimilar to the study done by Gulati S et al[15], and Abeyagunawardena AS. et al[16].

We found that renal function impairment regarding; total serum protein, serum albumin, blood urea and serum creatinine were significantly not different in FR and IFR nephrotic syndrome(P value 0.700, 0.502, 0.867 and 0.119 respectively) and were considered independent risk factors for relapses in childhood NS. This result was similar to the study of Se Jin Park. et al [10].

The type of response to steroid therapy in correlation with the rate of relapse was statistically significant between FR and IFR (P 0.001), this result was similar to the study done by Davutoqhu M. et al[13].

Conclusions

- Family history of NS alerts the occurrence of frequent relapsing type of NS.
- Respiratory tract infection is the commonest significant precipitating factor of relapse in NS.
- There is no significant difference between frequent relapsing NS and infrequent relapsing NS in regard to

age, sex, renal functions, serum albumin and total serum protein.

- Hematuria is the most significant presentation in patients with FRNS
- Early response to steroid therapy and long duration of maintenance steroid therapy have significant role in decreasing rate of relapse.
- There was increased frequency of focal segmental glomerulosclerosis as a histological type of renal biopsy.

Recommendations

- We insist on proper documentation of information, especially in the first attack.
- In patients with family history of renal disease, meticulous history of close affected relatives must be taken, as such patients may show similar course and outcome.
- Encouraging patients for proper regular intake of medication, long term follow up and use of prolonged maintenance course of steroid therapy to reduce the relapse rate of the disease.
- Renal biopsy can predict the outcome of renal disease.

References

1. Beth A. Vogt and Ellis D. Avner. Conditions particularly associated with proteinuria. In Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Text Book of Pediatrics. 18th ed. Philadelphia, Saunders; 2007: 523-527: 2188-95.
2. Watson AR, Tayler CM, Graw MM. Disorders of Urinary System. In Mctntosh N, Helms PJ, Smyth RL, ed. Farfar and Arneil's Text Book of Pediatric. 16th ed. Philadelphia, Churchill Livingston; 2003: 16: 633-634.
3. McEnery PT, Strife CF. Nephrotic syndrome in childhood. Management and treatment in patients with minimal change disease, mesangial proliferation, or focal glomerulosclerosis. Pediatr Clin North Am. 1982 Aug;29(4):875-94.
4.Reshi AR, Bhat MA, Najar MS, Banday KA, et al. Etiological profile of nephrotic syndrome in Kashmir. Indian J Nephrol. 2008 Jan;18(1):9-12
5. Anochie I, Eke F, Okpere A. Childhood nephrotic syndrome: change in pattern and response to steroids. J Natl Med Assoc. 2006 Dec;98(12):1977-81.
6. Elzouki AY, Amin F, Jaiswal OP. Primary nephrotic syndrome in Arab children. Arch Dis Child. 1984 Mar;59(3):253-5.
7. Mitwalli AH, Al Wakeel JS, Al Mohaya SS, Malik HG, et al. Pattern of glomerular disease in Saudi Arabia. Am J Kidney Dis. 1996 Jun;27(6):797-802.
8. Constantinescu AR, Shah HB, Foote EF, Weiss LS. Predicting first-year relapses in children with nephrotic syndrome. Pediatrics. 2000 Mar;105(3 Pt 1):492-5.
9. Shaker IK, Al-Saedi AJ, Al-Salam S, Saleem MS, Al-Shamma IA. Spectrum of glomerular disease in iraqi patients from a single center. Saudi J Kidney Dis Transpl. 2002 October-December;13(4):515-9.
10. Se Jin Park, Jae Il Shin. Complications of nephrotic syndrome. Korean J Pediatr. 2011 August; 54(8): 322-328. Published online 2011 August 31.
11. Toyabe S, Nakamizo M, Uchiyama M, Akazawa K. Circannual variation in the onset and relapse of steroid-sensitive nephrotic syndrome. Pediatr Nephrol. 2005 Apr;20(4):470-3.
12. Davutoglu M, Ece A, Bilici M, Dagli A. Steroid responsiveness of children with idiopathic nephrotic syndrome in southeastern region of Turkey. Ren Fail. 2007;29(7):855-9.
13. Maddalena Gigante, Matteo Piemontese, Loreto Gesualdo, Achille Iolascon, Filippo Aucella. Molecular and Genetic Basis of Inherited Nephrotic Syndrome. Int J Nephrol. 2011; 2011: 792195. Published online 2011 September 6.
14. Kumar J, Gulati S, Sharma AP, Sharma RK, Gupta RK. Histopathological spectrum of childhood nephrotic syndrome in Indian children. Pediatr Nephrol. 2003 Jul;18(7):657-60. Epub 2003 May 13.
15. Gulati S, Kher V, Sharma RK, Gupta A. Steroid response pattern in Indian children with nephrotic syndrome. Acta Paediatr. 1994 May;83(5):530-3.
16. Abeyagunawardena AS, Hindmarsh P, Trompeter RS. Adrenocortical suppression increases the risk of relapse in nephrotic syndrome. Arch Dis Child. 2007 Jul;92(7):585-8. Epub 2007 Feb 6.