Predictive Risk Factors of Steroid Dependency in Nephrotic Syndrome in Children

Hassnaa Ahmed Kareem[*], *Azhar Ahmed Khazraji*[**], *Bushra Jalil Salih*[**]

ABSTRACT:

BACKGROUND:

Patients with idiopathic nephrotic syndrome are usually steroid sensitive, however about 50% of relapsed children who experienced frequent relapses, develop steroid-dependency and become vulnerable for complications of long-term use of steroid.

OBJECTIVE:

Early detection of risk factors in patients with a nephrotic syndrome that could make them more liable to have steroid dependency after initial response to treatment with steroid.

PATIENTS AND METHOD:

A hospital-based retrospective cross-sectional study of patients aged 1-16 years; Followed up for at least 6 months at the outpatient clinic of the pediatric nephrology unit in central child teaching hospital .The study group was divided into two groups, group A included 68 patients with infrequent relapses nephrotic syndrome and group B included 32 patients with steroid-dependent nephrotic syndrome. Data was collected from medical record of patients visiting our hospital from 1st. of January 2015 to 31st. of December 2017.

RESULTS:

A sample of 100 patients participated in the current study; it shows that the male gender represents 51%, whereas the dependents patients on steroid occurred in 32% versus 68% infrequently relapse patients. It also shows the history of atopy (17%), microscopic hematuria (24%), hypoalbuminemia (79%), hypercholesterolemia (57%) and positive history of upper respiratory tract infection in 33%. It reveals that there was statistically significant (P0.015) association of steroid response with gender with a higher proportion of dependent patient in males than females. Also there was statistically significant association between steroid dependency and microscopic hematuria (P0.030) and between steroid dependency and history of upper respiratory tract infection (P0.043).While there were neither significant relationship with history of atopy nor with serum albumin level. There was a highly statistically significant (0.004) association with days of remission, higher proportion in more than 20 days, and highly statistically significant association of steroid dependency with hypercholesterolemia (0.001). Also there were significant higher mean of days of remission in the dependent patient(P0.044), statistically significant higher mean of serum cholesterol (0.0005)and statistically significant higher mean of systolic and diastolic blood pressure(0.001 and 0.017 respectively). Finally there was a highly statistically significant difference in means according to the numbers of relapse with higher mean in dependent patients (0.002).

CONCLUSION:

Prolong duration of first remission, hypertension, male gender, increasing number of relapse, microscopic Hematuria and history of infection of the upper respiratory tract have a high predictive value to be steroid dependent in children with nephrotic syndrome.

KEYWORDS: Nephrotic syndrome, Steroid dependency, Predictive risk factors

INTRODUCTION:

Nephrotic syndrome (NS) is a group of symptoms due to glomerular diseases. The patients presented with protein in urine which is considered as protein in urine of more than $40mg/m^2$/hour or when ratio of protein to creatinine in urine is more than 2. The triad of clinical findings associated with nephrotic syndrome arising from the large urinary losses of protein is hypoalbuminemia (<2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL)[1,2].

* Al - Numan General Hospital, Baghdad, Iraq

** Central Teaching Hospital of Pediatric, Baghdad, Iraq.

Nephrotic syndrome results from alterations of the glomerular capillary wall selective permeability which becomes unable to restrict protein loss to less than 100 mg/m^2 body surface per day[3].

So the diagnosis of nephrotic syndrome requires the presence of edema, hypoalbuminemia (less than 2.5 g/dl) and protein in urine (more than 40 mg/m^2/hour)[4].

The histological changes in the glomeruli include minimal change, focal segmental glomerular sclerosis (FSGS), and diffuse mesangial proliferative changes[5].

After treating a patient with nephrotic syndrome either he will be in remission (which is the disappearance of oedema, serum albumin become more than 3.5g/dl and a reduction of protein in urine or even trace) or the patient becomes resistant to steroid treatment (SRNS), or becomes steroid dependent (SDNS) .

Steroid - Dependent Nephrotic syndrome (SDNS):

Is defined as steroid sensitive nephrotic syndrome (SSNS) with 2 or more consecutive relapses during tapering or within 14 days of stopping steroids.

The following parameters were studied as risk factors of steroid dependency: age at time of the study and diagnosis, gender, microscopic hematuria, history of atopy, history of upper respiratory tract infections (URTI), serum cholesterol level and days of remission with initial steroid therapy

The aim of the study is early identification of risk factors in patients with nephrotic syndrome that could make them liable to have steroid dependency after becoming initially responsive to steroid treatment.

PATIENTS AND METHODS:

This is a hospital-based retrospective cross-sectional study of patients aged 1-16 years; file review was performed on all patients with steroid-sensitive Nephrotic syndrome Followed up for at least 6 months at the outpatient clinic of the pediatric nephrology unit in central teaching hospital of Pediatrics.

The studied group was divided into two groups, group A was composed of 68 patients with steroid response with infrequent relapses (IR) NS and group B was composed of 32 patients who were steroid dependent patients with NS (SDNS). Data collected from medical records of patients visiting our hospital from the 1st of January 2015 to the 31st of December 2017 was; age at onset of disease, age at time of the study, sex, duration for first remission, serum albumin,

serum cholesterol, microscopic hematuria, blood pressure, follow up period duration, number of relapses during follow up, history of upper respiratory tract infection and family history of atopic disease (atopy is the tendency to produce an exaggerated immunoglobulin (IgE) immune response to harmless substances in the environment). Microscopic hematuria is considered when 5 or more erythrocytes per high power field are seen on microscopically examination of a centrifuged urine sample[6]. Hypertension is considered when average clinically measured Systolic and /or Diastolic blood pressure equal or more than 95 th percentile[7]. Exclusion criteria includes; congenital nephrotic, infantile type nephrotic syndrome, steroid resistant nephrotic syndrome and secondary type that occur following systemic illnesses, also children who were lost during follow up or not completed 6 months after starting treatment.

Relapse:

Is the recurrence of massive proteinuria (more tan 40mg/m^2 per hr).

Positive urine dipstick (≥ 3 for 3days or positive for 7 days) $\pm$Edema.

Steroid- Sensitive Nephrotic syndrome (SSNS):

Is the response to prednisolone 60mg/m^2 per day within 4-6wk$\pm$ methylprenisolone boluses.

Analysis plan used in the study:

Data has been managed and analyzed with computer software SPSS version 21,

Frequency distribution table, Chi-square test was used to show the relation between the categorical variable. A t-test sample has been used to define the mean of the continuous variables difference among the categorical variables and a confidence level of 95% with a P-value equal to or less than 0.05 was considered to be significant statistically.

RESULTS:

Frequency distribution

A sample of 100 patients participated in the current study, male to female ratio 1.04:1. Table 1 shows the frequency distribution of the categorical variables within the sample, it shows that the male gender represents 51%, whereas the dependents patients on steroid occurred in 32% versus 68% infrequently relapse patients. It also shows the history of atopy (17%), microscopic hematuria (24%) and positive history of upper respiratory tract infection in 33%.

Table 1: Frequency distribution of the categorical variables (n100).

Variable		Frequency	%
Gender	Male	51	51
	Female	49	49
Response to Steroid	Dependent	32	32
	IR	68	68
History of atop	Positive	17	17
	Negative	83	83
Microscopic hematuria	Positive	24	24
	Negative	76	76
S. albumina(g/dl)	Low	79	79
	Normal	21	21
S.cholesterol(mmol/L)	High	57	57
	Normal	43	43
History of URTI	Positive	33	33
	Negative	67	67

Table 2 shows the distribution of the continuous variables within the sample according to the standard deviation and the mean of the whole sample.

Table 2: Descriptive statics of the continuous variables (n 100).

Variable	Minimum	Maximum	Mean	± SD
Age ate onset	1	15	5,85	3.17
Age at study	3	16	7.12	3.34
days for Remission	5	29	17.42	12.78
S.Albumine(g/dl)	1	2.5	1.95	0.74
S.Cholesterol(mmol/L)	1.36	15.70	8.66	3.56
SBP(mmHg)	80	150	111.53	13.75
DBP(mmHg)	50	90	72.34	10.85
Follow up (months)	5	20	8.82	2.97
Number of relapses	0	5	1.20	1.29

Table 3 shows the distribution of the steroid response within the categorical variables using Chi-square test, it reveals that there was a statistically significant (P 0.015) association of steroid dependency with male gender. There was highly statistically significant association (0.004) of steroid dependency with the days for remission, higher proportion between 10-20 days, while there was no significant relationship with the history of atopy .The test also shows a significant association between steroid dependency and microscopic hematuria (P 0.030). A positive history of upper respiratory tract infection has a significant relationship with steroid dependency (P 0.043).

Table 3:The relationship between steroid response and the categorical variables(n100).

Variable		Dependent		Infrequent relapse		Statics
		No.	%	No.	%	
Gender	Male	22	43.1	29	56.9	X^2= 5.93 P= 0.015(*)
	Female	10	20.4	39	79.6	
Days for Remission	<10 days	2	7.4	25	92.6	X^2= 10.85 P=0.004(**)
	10-20 days	20	38.5	32	61.5	
	>20 days	10	47.6	11	52.4	
History of atopy	Positive	5	29.4	12	70.6	X^2= 0.036 P= 0.802(NS)
	Negative	27	32.5	56	67.5	
Microscopic Hematuria	Positive	12	50	12	50	X^2= 4.702 P= 0.030(*)
	Negative	20	26.3	56	73.7	
S.albumin(g/dl)	Low	26	32.9	53	67.1	X^2= 0.144 P= 0.705(NS)
	Normal	6	28.6	15	71.4	
S.Cholestrol(mmol/L)	High	26	45.6	31	54.4	X^2= 11.291 P= 0.001(**)
	Normal	6	14	37	68	
History of URTI	Positive	15	45.5	18	54.5	X^2= 4.097 P= 0.043(*)
	Negative	17	25.4	50	74.6	

Table 4:Steriod response distribution within the continuous variables (n100).

Variables	Dependent Mean±SD	Infrequent relapse Mean±SD	t-test	P value
Age at onset	6.28±3.09	5.65±3.21	0.920	0.360(NS)
Age at study	7.68±3.36	6.86±3.32	1.155	0.827(NS)
days for Remission	21.16±10.79	15.66±13.32	2.037	0.044(*)
S. Albumin (g/dl)	2.07±0.81	1.90±0.71	1.036	0.303(NS)
S. Cholesterol(mmol/L)	10.70±3.45	7.70±3.21	4.246	0.0005(**)
SBP(mmHg)	118.82±15.59	108.35±11.6	3.560	0.001(**)
DBP(mmHg)	76.09±12.68	70.57±9.47	2.431	0.017(*)
Follow up (months)	9.44±3.80	8.53±2.47	1.431	0.156(NS)
Number of relapses	2.31±0.68	1.14±0.99	7.278	0.0001(**)

Notes: - **(NS)** this mean it is not significant.
- (*) this mean it is significant at the alpha level of less than 0.05.
- (**) this mean it is highly significant at the alpha level of less than 0.01.

Table (4) shows the distribution of the steroid response within the continuous variables using independent sample t-test, it shows no significant means difference in the age at onset, age at study, serum albumin level and follow up months, whereas there were significantly higher mean of remission days in the dependent patient (P 0.044), statistically significant higher mean of serum cholesterol (P0.0005), statistically significant higher means of systolic and diastolic blood pressure (P0.001 and 0.017 respectively), and finally there was highly statistically significant difference in means according to the number of relapse with higher mean in dependent patients (P 0.002).

DISCUSSION:

One of the complicated problems during managing children with idiopathic nephrotic syndrome (INS) is that they become steroid dependent. These children will possibly have complications of long term steroid treatment and more likely to need asteroid sparing agents as a second line therapy. It appears significant to recognize these children as early as possible to adjust their treatment.

In this study, the mean age at onset of disease was 5.85 year which is approximate the result by Beatrice Letavernier(8), but Constantinescu AR et al found the mean age was 3.25 year (9).Current study shows steroid-dependent patients have no significant association with age at the beginning of nephrotic syndrome this is in agreement with a result by shuichiro fujinaga[10]. A study in Denmark done by Anderson et al[11] reported that young ages were associated with risk of steroid dependency. These different results might be due to racial variation between Asian and Caucasians in the study population. The finding of male predominance in steroid-dependent patient 43% compared to 20% in a female patient by this study is also found by Anderson et al[11] this is due to the predominance of a male patient with nephrotic syndrome. Another study done by Constantinescu et al[9] reported that there was no difference between both genders in the risk of steroid dependency. There was a highly significant association between steroid dependency and days of remission, a higher proportion in more than 20 days this result noticed also by marina vivarelli MD[12] and by Beatrice letavernier[8] and against the result by Lesa Dawman[13] which reported a time less than 10 days has a high predictive value, this difference might be related to following another steroid regime for treatment. The finding of a significant association between steroid dependency and microscopic hematuria in this study also shown by Yap H.[14], while in another study by Sanjeev Gulati[15] mentioned that there is no association between the hematuria and steroid Dependency, this difference might be related to longer follow up period (6-30 month) compared with our study. Idiopathic nephrotic syndrome has been thought to be an immune illness related to the seasonal episode in the atopic person, history of atopy have no significant association with steroid dependency in this study as the result found by Yap H.[14] This does not go with result by Rebien W.[16] which found an association between atopy and

the risk of steroid dependency, this discrepancy might be related to that only 40% of atopic children have a positive family history.

In another retrospective study of 84 children by Mehmet Davutoglu[17] in turkey showed no significant association between hypoalbuminemia and steroid dependency, this agreed with the result of this study. We find a high statistically significant association of steroid dependency and hypercholesterolemia which is also reported by Roy RR[18], while in another study by Maher Ahmed[19] reported the opposite result may be due to a small number (52 patient) of study samples in relation to our study. A positive history of upper respiratory tract infection has a significant relationship with steroid dependency (p 0.043) which is also noticed by Samuel N[10]. It's well known that relapse may be trigger by an episode of upper respiratory tract infection due to inadequate response to steroid therapy and recurrences among patients who were in remission state.

In this study, hypertension was significantly associated with risk of steroid dependency which is in agreement with Sanjeev Gulati[15], hypertension at the time of presentation may indicate non-minimal change disease so have a high rate of relapse, this finding is not in agreement with finding of Maher Ahmed[19] this may be because the current study was done in tertiary center and most patients referred from another hospital in advance stage.

The steroid-dependent patient will have a high relapse rate compared to infrequently relapsed patient in this study with a consequent risk of steroid toxicity and complications. The majority of these patients will develop steroid dependency which is similar to the result by Lesa Dawman[13].

CONCLUSION:

Prolong duration of first remission, hypertension, male gender, increasing number of relapse, microscopic Hematuria and history of infection of the upper respiratory tract have a high predictive value to be steroid dependent in children with nephrotic syndrome.

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