ORIGINAL ARTICLE

PREDICTORS OF RESISTANCE TO STEROIDS IN PEDIATRIC NEPHROTIC SYNDROME AT A TERTIARY HOSPITAL, ADDIS ABABA

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ABSTRACT

Background: *Nephrotic Syndrome is a major health problem worldwide and an important chronic renal disease in children. It is the second most common renal disease in pediatric practice in Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. No studies done that show prevalence and predictors of resistance to steroids in our setting.*

Objective: *The aim of this study was to determine prevalence and factors predictive of resistance to steroids in pediatric nephrotic syndrome*

Patients and Methods: *A cross-sectional retrospective review of medical documents of children 1-15 years of age with the diagnosis of nephrotic syndrome was done from September 2012 to January 2019 who were on follow up at Pediatric Renal Clinic of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.*

Result*: A total of 85 children with the diagnosis of nephrotic syndrome were identified and their mean age was 6.2 (+3 years). Males were 59/85 (69.4%) with a male to female ratio of 2.3:1. Sixty-nine of 85 (81.2%) children responded to steroids, but 16/85 (18.8%) were steroid resistant. Thirteen of 85 (15.3%) children were steroid dependent. Hematuria was detected in 42/85 (49.4%). Twenty-nine out of 85 (34.1%) and 13/85 (15.3%) children had microscopic and gross hematuria, respectively. On bivariate analysis children with gross hematuria, decreased urine output, hypertension and elevated creatinine were more likely to be steroid resistant ($p < 0.001$). On multivariate analysis gross hematuria and decreased urine output were independent risk factors for resistance to steroids.*

Conclusion*: Predictors of steroid resistance are comparable with other studies. These findings are important for early decision about the requirement for more aggressive immunosuppressive treatment.*

Keywords*: nephrotic syndrome, steroid resistance, relapse, children, Ethiopia*

INTRODUCTION

Nephrotic Syndrome (NS) is the commonest glomerular disease in children around the globe (1). It is diagnosed according to Kidney Disease Improving Global Outcomes (KDIGO) guideline (1,2): Heavy proteinuria (greater than 40mg/m2/hr. or spot urine protein to creatinine ratio greater than 2 or dipstick 3+/4+ proteinuria), hypoalbuminemia of less than 2.5gm/dl, edema and hypercholesterolemia of greater than 200 mg/dl (1, 2).

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The estimated annual incidence of nephrotic syndrome is 1-3 per 100,000 children and cumulative prevalence of 12-16 per 100,000 worldwide (2-3). Children with nephrotic syndrome are further classified based on their steroid responsiveness and this has a very important diagnostic and prognostic value for the treating physician. (1-7). Steroid responsiveness is one of the most important clinical parameters that differentiates idiopathic nephrotic syndrome (1). In a study done at Tikur Anbessa Specialized Hospital, Addis Ababa, , nephrotic syndrome accounted for 16.9% of the whole pediatric admissions making it the second most common renal disease (7). The characteristics of NS presenting in childhood varies according to geographic, genetic differences and also influenced by environmental factors and infection, which determines histological expression of disease (8, 9). Currently there is no evidence that steroid resistant nephrotic syndrome predominates in African children (1, 2, 9). The presence of hypertension, hematuria, anemia, persistent hypocomplementemia with persistent raised creatinine and high cholesterol and age (<2years and >8years) are considered as indicators of steroid resistance and bad prognostic indicators (1, 2).

NS usually manifests between two and six years of age, M:F ratio is 2:1, in which the gap reduces during adolescence (1). The major presenting symptom is sudden onset of edema often following upper respiratory tract infections (URTI) or allergic reaction like an insect bite. Edema becomes clinically detectable when fluid retention exceeds 3-5% body weight. Initially periorbital edema followed by leg edema, sacral, penile and labial edema. Some develop anasarca with pleural and pericardial effusion, which is followed by dyspnea (1). Nonspecific symptoms such as abdominal pain, malaise, fatigue, irritability and headache could also be present. Microscopic hematuria is found in 20% of nephrotic children, while few could have atypical presentations (10,11). Most children with steroid sensitive nephrotic syndrome (SSNS) have repeated relapsing course with good long-term prognosis. In contrast, without treatment NS is associated with high risk of death, particularly from bacterial infection (12).

Management of steroid resistant nephrotic syndrome (SRNS) is challenging in our country, because of paucity of second line medications and expensive histologic diagnosis. The aim of this study was to identify the prevalence of steroid resistance and factors predictive of resistance to steroids in pediatric nephrotic syndrome. Identifying the magnitude of steroid resistance would be an evidence for policy makers to improve specific diagnostic and therapeutic services for these high-risk children.

PATIENTS AND METHODS

Study area

This study was conducted in Addis Ababa University, College of Health Science, Tikur Anbessa Specialized Hospital, Department of Pediatrics and Child Health. It is the largest medical school in the country with undergraduate, postgraduate and subspecialty trainings. It has around 850 beds and serves

nearly 350,000 patients as outpatients annually. Pediatric renal clinic is one of the follow up clinics working twice a week where renal patients are followed. The clinic is attended by pediatric nephrologist, residents and nurses with an estimated 25-30 patients seen per clinic day. The largest number of patients in the clinic is nephrotic patients.

Study design

Hospital based retrospective study with medical document review.

Inclusion criteria

All children with NS between the age of 1-15 years were included but children with incomplete data, family history of NS, secondary NS, age less than one year and greater than 15 years, follow up period less than eight weeks and children with comorbidity with other illness were excluded.

Data analysis

Data were collected using a pretested questionnaire and analyzed using Statistical Software for Social Sciences (SPSS) version 24 software. Analysis included univariate, bivariate and multivariate analysis done. Proportion, percentage, ratios, frequency of distribution, measure of central tendency and measure of dispersion was employed for univariate analysis. Bivariate regression analysis was used to examine association between dependent and independent variables. This was done using odds ratio and significance of statistical association was tested using 95% confidence interval. A P value <0.05 was considered statistically significant.

Operational definitions

- Remission: Urine albumin nil or trace (<4mg/m^2/hour for three consecutive early morning sample)
- Relapse: Urine albumin 3+/4+ (>40mg/m^2/hour) for three consecutive early morning specimens, having been in remission previously; frequent relapse: greater than or equal to two relapses in initial six months or greater than three relapses in any twelve months
- Steroid dependent: Two consecutives relapses on alternate day prednisolone or within 14 days of its discontinuation
- Steroid resistance: Absence of remission despite therapy with daily prednisolone at a dose 60mg/m^2/day for four weeks
- Hematuria: Presence of more than five red blood cells (RBC) per high power field (1,2).
- Modified Schwartz formula: Clearance of Cr ml/minute/1.73m2=K*height (cm)/ serum creatinine (mg/dl), (K =0.413) (11)
- Hypertension (HTN): Given in Table 1 below (12).

Table 1, Updated definition of hypertension, blood pressure categories and stages

For children aged 1 to 13years	For children aged >13years
Normal BP*:<90^{th} percentile	<120/<80mmHg
Elevated BP:≥90^{th} percentile to <95^{th} percentile	120/<80 to 129/<80mmHg
Stage 1 HTN**:≥95^{th} percentile to <95^{th} percentile +12mmHg	130/80 to 139/89 mmHg
Stage 2 HTN:>95^{th} percentile +12mmHg	>140/90 mmHg

BP: blood pressure, HTN: hypertension

- normal serum creatinine values: <2 years of age (0.4-0.5 mg/dl), 2-8 years (0.5-0.7 mg/dl, 9-18 years (0.6-0.9 mg/dl) (1).

Ethical Considerations: the study was ethically cleared by the research and publication committee of the department of pediatrics and child health.

RESULTS

Among 108 children with NS in the study period 23 were excluded based on the exclusion criteria. The study group comprised 85 children, 59/85 (69.4%) were males with male to female ratio of 2.3:1. The mean age of studied children was 6.2 (±3) years. Duration of symptoms ranges from one week to 76 months. Sixty-five children presented in less than five months of symptoms. The mean duration of symptoms at presentation was 5.5 (±1.5) months. The mean duration of follow up was 2.4 (±3.3) years, and 96.5% had follow up for three or more months. Sixty-nine children (81.2%) were steroid sensitive but 16/85 (18.8%) were resistant. Majority of children were less than 8 years of age 59/85 (69.4%). Table 2 shows the baseline characteristics of these children.

Table 2: Baseline characteristics of children with nephrotic syndrome followed up at a tertiary hospital, Addis Ababa

Characteristics		N	%
Sex	Female	26	30.6%
	Male	59	69.4%
Age	≤3yrs	21	24.7%
	3-6yrs	17	20.0%
	6-8yrs	21	24.7%
	>8yrs	26	30.6%
Duration of symptom	≤1mo	43	50.6%
	1-5mo	22	25.9%
	>5mo	20	23.5%

Periorbital and leg edema were detected in all children. Hematuria was detected in 42 (49.4%) children. Thirteen (15.3%) had gross hematuria and 29 (34.1%) had microscopic hematuria. Hypertension was detected in 21/85 (24.7%) and Serum creatinine was elevated in 26/85 (30.5%) children. Table 3 shows clinical features and the laboratory values of these children.

A total of 69/85 (81.2%) children responded to standard steroid therapy but 16/85 (18.8%) were steroid resistant, and 13 (15.3%) were steroid dependent. This is shown in table 4.

Table 3. Clinical features and laboratory values of children with nephrotic syndrome followed up at a tertiary hospital, Addis Ababa

Characteristics		**Number**	**%**
Decreased UOP*	Yes	13	15.3%
	No	72	84.7%
Gross hematuria	Yes	13	15.3%
	No	72	84.7%
Blood pressure	Normal	45	52.9%
	Elevated	19	22.4%
	Stage 1	15	17.6%
	Stage 2	6	7.1%
Periorbital edema	Yes	85	100.0%
	No	0	0.0%
Decreased air entry on chest exam	Yes	37	43.5%
	No	47	55.3%
Abdominal fluid collection	Yes	45	52.9%
	No	40	47.1%
Leg edema	Yes	85	100.0%
	No	0	0.0%
Microscopic hematuria	Yes	29	34.1%
	No	56	65.9%
Creatinine	normal	59	69.4%
	elevated	26	30.5%
GFR**	≥90	33	38.8%
	60-89	37	43.5%
	30-59	13	15.3%
	15-29	1	1.2%
	<15	1	1.2%

**GFR: glomerular filtration rate in ml/minute/1.73m^2, *UOP: urine output

Children with microscopic or macroscopic hematuria, decreased urine output, elevated creatinine, decreased GFR, and the presence of hypertension were more likely to be steroid resistant ($p< 0.001$) (Table 5). Males were likely to be steroid resistant than females, but this was not statistically significant ($p=0.08$).

Table 4: Steroid response pattern of children with nephrotic syndrome followed-up at a tertiary hospital, Addis Ababa

Response		**N**	**%**
Sensitive		69	81.2%
	Dependent	13	18.8%
	Frequent relapse	10	14.5%
	Infrequent relapse	23	33.3%
	Remission	23	33.3%
Resistance		16	18.8%
	Primary	13	81.3%
	Secondary	3	18.8%

On multivariate analysis, decreased urine output (measured over 6-12 hours) and macroscopic hematuria were the variables that became independently associated with poor steroid response. (Table 6).

Table 5 bivariate regression of factors predictive of resistance to steroid treatment in children with nephrotic syndrome in a tertiary hospital, Addis Ababa

		Steroid response				**P**
		Sensitive		Resistance		
		N	%	N	%	
Sex	Female	24	92.3%	2	7.7%	0.081
	Male	45	76.3%	14	23.7%	
Age	<6	39	86.7%	6	13.3%	0.176
	>/6	30	75%	10	25%	
Decreased urine out put	yes	2	15.4%	11	84.6%	0.000
	no	67	93.1%	5	6.9%	
Gross hematuria	yes	2	15.4%	11	84.6%	0.000
	no	67	93.1%	5	6.9%	
Blood pressure	Normal	43	95.6%	2	4.4%	0.001
	elevated	13	68.4%	6	31.6%	
	HTN	13	62.0%	8	38.0%	
Microscopic hematuria	yes	17	58.6%	12	41.4%	0.000
	no	52	92.9%	4	7.1%	
Creatinine	normal	55	93.2%	4	6.8%	0.000
	elevated	14	53.8%	12	46.2%	
GFR*	Stage 1	33	100%	-	-	0.000
	Stage 2	32	86.5%	5	13.5%	
	≥Stage 3	4	26.7%	11	73.3%	

*GFR: glomerular filtration rate

Table 5: bivariate regression of factors predictive of resistance to steroid treatment in children with nephrotic syndrome in a tertiary hospital, Addis Ababa

		Steroid response				P
		Sensitive		Resistance		
		N	%	N	%	
Sex	Female	24	92.3%	2	7.7%	0.081
	Male	45	76.3%	14	23.7%	
Age	<6	39	86.7%	6	13.3%	0.176
	>/6	30	75%	10	25%	
Decreased urine out put	yes	2	15.4%	11	84.6%	0.000
	no	67	93.1%	5	6.9%	
Gross hematuria	yes	2	15.4%	11	84.6%	0.000
	no	67	93.1%	5	6.9%	
Blood pressure	Normal	43	95.6%	2	4.4%	0.001
	elevated	13	68.4%	6	31.6%	
	HTN	13	62.0%	8	38.0%	
Microscopic hematuria	yes	17	58.6%	12	41.4%	0.000
	no	52	92.9%	4	7.1%	
Creatinine	normal	55	93.2%	4	6.8%	0.000
	elevated	14	53.8%	12	46.2%	
GFR*	Stage 1	33	100%	-	-	0.000
	Stage 2	32	86.5%	5	13.5%	
	≥Stage 3	4	26.7%	11	73.3%	

*GFR: glomerular filtration rate

Table 6: Multivariate logistic regression of factors affecting steroid response in children with nephrotic syndrome in a tertiary hospital, Addis Ababa

Characteristics		Number	Percent	COR	AOR	95% CI	
						Lower	Upper
Decreased UOP	Yes	13	15.3	0.025	26.911	1.51	479.28
	No	72	84.7		1.00		
Macroscopic hematuria	Yes	13	15.3	0.015	41.171	2.07	817.42
	No	72	84.7		1.00		
Adherence to medications	Yes	60	70.6	0.091	0.167	.02	1.33
	No	25	29.4		1.00		
Hypertension	Yes	21	18.7	0.157	6.696	0.48	93.04
	No	64	85.3		1.00		
Microscopic hematuria	Yes	29	34.1	0.495	0.435	0.04	4.75
	No	56	65.9		1.00		
Elevated Cr	Yes	26	29.8	0.140	0.280	0.02	1.70
	No	59	70.2		1.00		

DISCUSSION

In our study the affected children were with a mean age of 6.2 +3 years. This is comparable with studies done in India (5 years), Nigeria (5.9 years), Sudan (5.2 +3.5 years), Iran (4.98+2.6 years) (13-16). Males were predominantly affected in our study with a M: F ratio of 2.3:1. This is in agreement with studies done in Nigeria (1.7:1), Sudan (2:1), Iran (2:1) and Indonesia (2.4:1), (14-17). In our children blood pressure and creatinine were elevated in 24.7% and 30.5% respectively and hematuria was detected in 42 (49.4%). This is in agreement with the Indonesian study where blood pressure and creatinine were elevated in 33.3% and hematuria was present in 38.5% of their cases (17).

The proportion of steroid responsiveness in our study was 81.2% and this is in the range of the estimated steroid response rate in children with nephrotic syndrome. The reports of many other studies are quite comparable with our finding. A study from Indonesia showed response rate of 83.7%, from Nigeria (82.8%), Iran (75.2%), and Ethiopia (76.3%), (4, 14, 16, 17).

Studies have reported factors that can predict the likely hood of steroid resistance in children with nephrotic syndrome. In our study, the relative proportion of resistance was higher in those having hypertension, decreased urine output, gross hematuria, microscopic hematuria, increased creatinine and age older than 6 years. This result is similar to studies done in Indonesia, Nigeria, Iran and India (13, 14, 16, 17).

In our study the proportion of steroid resistance was higher among males compared to females but the difference was not statistically significant (p=0.081). A study done in Dhaka, Bangladesh and India also showed higher male resistance (18-20). In a study done in North western Iran, the frequency of steroid resistance was higher in females (16). This apparent difference in resistance pattern could be because of a small sample size or because of geographic differences in the pattern of steroid resistance.

Children with steroid resistance had higher frequency of macroscopic hematuria and, decreased urine output ($p < 0.05$); this is similar to findings in India and Northwestern Iran (16, 20,).

Decreased urine output, macroscopic or microscopic hematuria, hypertension and elevated creatinine were significantly associated with steroid resistance. on bivariate analysis; this is similar with other studies (14-20), but on multivariate analysis decreased urine output and macroscopic hematuria remained significantly associated with steroid resistance in our study; this could be because of low sample size.

Conclusion: Decreased urine output, macroscopic or microscopic hematuria, hypertension, and elevated creatinine were significantly associated with steroid resistance and this is comparable with other reports. These findings are important for early decision about the requirement for more aggressive immunosuppressive treatment.

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Conflict of interest:

We declare that there is no conflict of interest.

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