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Original Research Article

A study to assess the prevalence of hypertension in children with nephrotic syndrome

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ABSTRACT

Background: Hypertension is been one of the most common co morbidity of this disease. It was mostly attributed to sodium retention, which is a major clinical feature of nephrotic syndrome. These mechanisms likely have a role in the development of hypertension in nephrotic syndrome, where hypertension may be difficult to control, and provide new therapeutic options for the management of blood pressure in the setting of nephrotic syndrome. Objective of study the prevalence of hypertension in children with NS and also the number of antihypertensive required to control it.
Method: A Retrospective study of the hospital records of 100 children diagnosed with nephrotic syndrome admitted to Pediatric and Nephrology Ward at YMCH was accessed.
Results: In our study 35 (35%) of them were Infrequent relapse nephrotic syndrome (IFNS) and 35(35%) were Frequent relapse nephrotic syndrome (FRNS) ,while 30 cases (30%) were First episode nephrotic syndrome (FENS). 65 cases were steroid sensitive, while 28 and 7 of them were steroid dependent and resistant respectively. Of the 100 study population 54 of them had hypertension while 46 of them did not develop it .Of the 54 hypertensive nephrotic syndrome children, 15 of them (28.%) required three anti hypertensives to control the pressure, while 19 (35%) and 20 (37%) required single and dual anti hypertensives respectively.
Conclusion: Prevalence of hypertension is increasing among the children with nephrotic syndrome. Its more prevalent among the male then female FRNS, SRNS and SDNS are more prone to develop hypertension and also they needed two or more antihypertensives to control the hypertension, whereas hypertension in SSNS could be managed with single drug.

Keywords: Epithelial sodium channel, Hypertension, Nephrotic Syndrome, Proteinuria, Steroid resistant nephrotic syndrome

INTRODUCTION

Nephrotic syndrome is the clinical manifestation of glomerular disease presenting with the triad of hypoalbuminemia(<2.5g/dl), edema, and hyperlipidemia (cholesterol >200mg/dl).[1] NS generally has a glomerular cause and is currently categorized into primary and secondary forms. Hypertension is been one of the most common co morbidity of this disease. It was mostly attributed to sodium retention, which is a major clinical feature of nephrotic syndrome. The mechanisms responsible for sodium retention in this setting have been a subject of debate for years. Several lines of evidence

suggest that activation of ENaC (endothelial sodium channel) by proteases aberrantly filtered through damaged glomeruli contributes to urinary sodium retention in nephrotic syndrome.[2,3]

Recent studies have provided new insights regarding mechanisms by which sodium transporters are activated by factors present in nephrotic urine. These mechanisms likely have a role in the development of hypertension in nephrotic syndrome, where hypertension may be difficult to control, and provide new therapeutic options for the management of blood pressure in the setting of nephrotic syndrome.[4]

Moreover, studies have shown a higher prevalence of initial and subsequent steroid resistance, a characteristics not consistent with typical minimal change NS with a benign prognosis. The results suggest that in the current era, NS in children may not be as benign as indicated by earlier studies. This changing trend of the disease as also increased the prevalence of hypertension in nephrotic syndrome[5]. Hence the present study is on prevalence of hypertension in children with NS and also the number of antihypertensive required to control it.

Objective of the study to estimate the incidence of hypertension and usage of Antihypertensives in children with nephrotic syndrome

METHODS

A Retrospective study was conducted at YMCH from 2016 to 2018. A total of 100 children who were diagnosed with Nephrotic Syndrome and admitted to Pediatric and Nephrology Ward at YMCH were included in the study. The patients record were obtained from the Medical Records Department and data such as relevant history, general status, number of relapses, use of regular antihypertensives, and blood pressure at admission and also the treatment given were taken.

Inclusion Criteria

1. The children admitted with Nephrotic Syndrome.

Exclusion Criteria

1. Patient with congenital Nephrotic Syndrome.
2. The children who were taking Antihypertensive treatment for any other cause of hypertension other than nephrotic syndrome.

Terminologies in nephrotic syndrome[1,6]

1ST episode

When a child is diagnosed with protienuria/nephrotic syndrome for the first time is called 1st episode.

Remission

When the early morning sample urine albumin is nil or trace (proteinuria <4 mg/m2/hr) for 3 consecutive days it is refered to as remission.

Relapse

Urine albumin 3+ or 4+ (or proteinuria >40mg/m2/hr) for 3 consecutive early morning specimens, after having been in remission.

Infrequent relapse

Patient who have three or less relapse a year.

Frequent relapses

Two or more relapses in initial 6 months or more than three relapses in any 12 months.

Steroid dependence

Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.

Steroid resistance

Absence of remission despite therapy with daily prednisolone at a dose of 2mg/kg/day for 4 weeks.

Initial steroid resistance

Lack of remission at first episode of nephrotic syndrome.

Late steroid resistance

Initially steroid sensitive, but later show steroid resistance.

The data was analyses using SPSS v 21. Chi-square test was used to evaluate the statistically significant relationship between variables.

RESULTS

The total number of patients enrolled during the study period was 100.

In our study the Males (68) outnumbered females (32) with male to female ratio 2.1:1 and age range between 1-18 years. A total of 26 patients (26%) were in the age group <5 years, followed by 40 (40%) in the age group (5-10) and 34(34%) in age group > 10 years. In our study 35 (35%) of them were Infrequent relapse nephrotic syndrome (IFNS) and 35(35%) were Frequent relapse nephrotic syndrome (FRNS), while 30 cases (30%) were First episode nephrotic syndrome (FENS).65 cases were

steroid sensitive, while 28 and 7 of them were steroid dependent and resistant respectively (Table 1).

Of the 100 study population 54 of them had hypertension while 46 of them did not develop it. Among the hypertensive patients 41(75.9%) were male and 13(24.1%) were female (Figure 1).

Table 1: Social profile of the children.

Social Profile		Frequency	Percentage
Age	<5 Years	26	26
	5-10 Years	40	40
	>10 Years	34	34
Gender	Male	68	68
	Female	32	32
Nephrotic Syndrome	Infrequent relapse nephrotic Syndrome (IFNS)	35	35
	Frequent relapse nephrotic Syndrome (FRNS)	35	30
	First Episode of Nephrotic Syndrome (FENS)	30	35
Response of Steroid on Nephrotic Syndrome	Steroid Sensitive	65	65
	Steroid Resistance	7	7
	Steroid Dependent	28	28

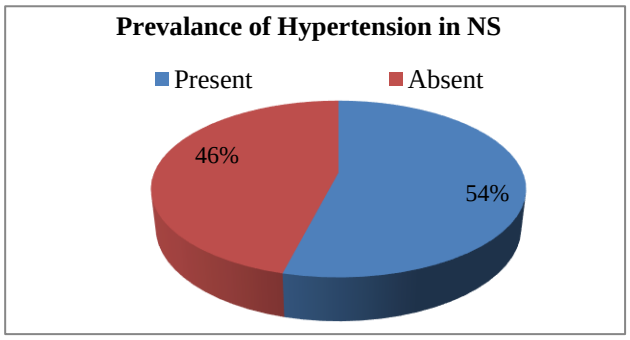

Figure 1: Prevalence of Hypertension in Nephrotic syndrome.

Out of 44.4% (24) of the hypertensive children belonged to frequent relapsers while 31.6% (17 cases) and 24% (13 cases) were IRNS and FENS respectively. (Table 2)

Of the steroid sensitive 65 cases, 30.7% (20 cases) developed hypertension, while 96.4% (27) and 100% (7) of steroid dependent and steroid resistant group respectively developed hypertension. p value is <0.001and r value is 0.05both of which are significant. (Table 3)

Table 2: Prevalence of Hypertension within the Subgroup.

Episodes of nephrotic Syndrome	Hypertensive		Normotensive	
	Frequency	Percentage	Frequency	Percentage
FENS	13	24%	17	37%
IFNS	17	31.6%	18	39%
FRNS	24	44.4%	11	24%

Table 3: Prevalence of Hypertension depending on Steroid Sensitivity of the disease.

Steroid Sensitivity	Hypertensive		Normotensive	
	Frequency	Percentage	Frequency	Percentage
SSNS	20	37%	45	98%
SDNS	27	50%	1	2%
SRNS	7	13%	0	0

p value <0.001, r value = 0.05

Of the 54 hypertensive nephrotic syndrome children, 15 of them (28.%) required three antihypertensives to control the pressure, while 19 (35%) and 20 (37%) required single and dual antihypertensives respectively. Within the subgroups of nephrotic syndrome 12(50%) of the hypertensive FRNS required triple antihypertensives while majority of the FENS (53.8%) responded well with single drug.

Hypertension in children with IRNS could be controlled with single (52.9%) or dual (47.1%) drugs. r value is 0.098 and on chi square test p value is <0.001 which is significant. (Table 4)

Majority of the hypertensive SDNS (37%) and SRNS (71.4%) required three antihypertensive, while 70% (14) of the hypertensive SSNS responded well to single therapy. 44.4% (12) of the hypertensive SDNS required dual drugs to control hypertension. both p and r value, <0.001 and 0.035 are reported respectively, which is significant. (Table 5)

Table 4: No. of Antihypertensive requirement within the subgroup.

Type of Nephrotic Syndrome	Number of anti-hypertensive drugs							
	0		One		Two		Three	
FENS	17	37%	7	37%	3	15%	3	20%
IFNS	18	39%	9	47%	8	40%	0	0
FRNS	11	24%	3	16%	9	45%	12	80%

p value <0.001, r value = 0.098

Table 5: Antihypertensive requirement depending on the steroid sensitivity.

Type of Nephrotic Syndrome	Number of Anti-Hypertensive Drugs							
	0		One		Two		Three	
SSNS	45	98%	14	73.6%	6	30%	0	0
SDNS	1	2%	5	29.4%	12	60%	10	67%
SRNS	0	0	0	0	2	10%	5	33%

p value <0.001, r value = 0.035

DISCUSSION

Nephrotic syndrome remains a major cause of referral to paediatric nephrologists because of the chronicity of the disorder and the complexity of its evaluation.[7] In this study 100 patients aged (1-18) years with NS were studied, where male: female ratio was found to be 2.1:1 which is in accordance with the findings of previous authors Trompeter et al, Mishra et al, and Constantinescu AR et al.[8-10] Hypertension was found in patients with relapse and long-time treatment with steroid. In this study 54 patients (54%) were hypertensive a figure higher than that found in Mishra et al, (2013, 2014) Tarhish et al, (1997) where incidence of hypertension was noted as 10%, 10% and 12% respectively. Iranian and Jordanian study, which reported (15.6%)and (14.28%) hypertensive patients respectively, while the Ibadin MO et al, (1998), study showed 41.4%prevalence of hypertension in patients with NS. [9,11-15]

Among the hypertensive patients 41(75.9%) were male and 13(24.1%) were female. Of the 54 hypertensive patients 24 (44.4%) were FRNS, and 13(24%) and 17 (31.6%) were FENS and IRNS respectively. 43.3% of the FENS (13cases) developed hypertension which favours the hypothesis that, even at low levels, proteases filtered by leaky glomeruli may contribute to hypertension[12] as put forth by Buhl et al[16] in his study on diabetic patients with resistant hypertension, where microalbuminuria was associated with sufficient plasmin to activate ENaC (epithelial sodium cells) in cultured cells to precipitate hypertension.

Steroid therapy being the main stay therapy of nephrotic syndrome was received by all the patients with initial attack and relapses. Steroid sensitive NS was found in 65cases (65%), SDNS and SRNS were found in 28 (28%) and 7 cases (7%) respectively. High prevalence of SSNS also found in Port Harcourt contrasts with earlier reports from other parts of Nigeria where poor response to steroid therapy was common.[17,18] Steroid and alkylating agents were used for 7 patients who had no response to steroid alone. All seven (100%) of them developed hypertension. This result is higher than Saudi Arabia study which recorded that cyclosporine causes HT in only (20%).[19] The frequency of hypertension was observed in 20 cases (30.7%) of SSNS, 27 cases (96.4%) with SDNS and 7 cases (100%) in SRNS patients(p value o.ooo1 highly significant) ,these figures are higher than that of previous Iraqi study (2000) by AL-Mewashi H.H et al, which reported (11.2%), (6.1%), (10.2%) of SSNS, SDNS, SRNS respectively, and (2005) Gabban et al, study, where 7%. 19.7% and 12.7% were reported as SSNS, SDNS and SRNS respectively.[20,21]

In this study 50% (12 cases) of hypertensive FRNS required three antihypertensives with a significant p value of <0.001 and also of the 34 patients with SDNS and SRNS, 44.1% (15 cases) required triple drug therapy, while 70% (14) of the SSNS could be, managed with monotherapy. Significant p<0.001 and r<0.05 was noted.

In this study as described earlier higher incidence of hypertension is noted among SDNS and SRNS group and it required multiple antihypertensive to control it. This is similar to Kim JS et al, study which reported higher prevalence of hypertension and decreased kidney function is higher in steroid resistant nephrotic syndrome.

CONCLUSION

Prevalence of hypertension is increasing among the children with nephrotic syndrome. Hypertension is more prevalent among the male then female. Hypertension in NS is more prevalent among frequent relapsers and among steroid dependent and steroid resistant cases. Two or more drugs are needed to control hypertension among SDNS, SRNS and also FRNS, while hypertension in SSNS can be managed with single drug.

Recommendation

Further studies are needed to enumerate the exact cause of increasing prevalence of hypertension in nephrotic syndrome and also its possible correlation with increasing incidence of steroid resistance. Blood pressure has to be routinely monitored among the children with NS, as to not miss multidrug resistant hypertension and its associated complications.

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