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Study of Systemic Hypertension in Children with Nephrotic Syndrome

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1. Introduction

Nephrotic syndrome is a common kidney disease worldwide and an important chronic kidney disease in children. Its incidence is reported to be 2 - 3/100000 children in Western countries, while it is slightly higher in children of South Asian origin (2 - 7/100000), with a prevalence of 12 - 16/100000 children.[1, 2, 3]

It is classically defined by proteinuria in the nephrotic range (≥40 mg/m^2/hour or urine protein/creatinine ratio ≥ 200 mg/Ml or 3 + protein in urine test), hypoalbuminemia (> 25 g/L), and edema.[4] NS may be congenital in infancy and occurs within the first three months of life. Apart from the congenital form of nephrotic syndrome, a wide variety of causes can precipitate nephrotic syndrome, including glomerular disorders, vasculitides, infections, toxins, malignancies, genetic mutations, and, most commonly, unknown causes.[5, 6]

Hypertension is one of the most common comorbidities of this disease. It has usually been attributed to sodium retention, which is a major clinical feature of the nephrotic syndrome. The mechanisms responsible for sodium retention in this context have been the subject of debate for many years. Several lines of evidence suggest that activation of the ENaC (endothelial sodium channel) by proteases filtered through damaged glomeruli contributes to urinary sodium retention in nephrotic syndrome.

NS in children is classified as a level II (moderate) cardiovascular risk factor by the American Heart Association. The etiology of HTN in nephrotic syndrome (NS) is multifactorial in origin; It includes multiple intrinsic and extrinsic/ environmental factors, both renal and non renal. Others are associated with chronic and persistent HTN, including renal fibrosis, decreased GFR, and progression of chronic kidney disease.[7]

Hypertension occurring in nephrotic syndrome (NS) is an event that causes poor prognosis in NS in both the steroid - resistant NS (SRNS) and steroid - sensitive NS (SSNS) groups.8 Hypertension occurring in children aged < 1 year and > 8 years in children with renal dysfunction causes a poor prognosis. Hypertension is more common in SRNS than in SSNS ($p > 0.05$), steroid therapy is associated with the occurrence of hypertension in a SN treatment regimen (< 0.01). Patients with SSNS have, on average, higher systolic and diastolic blood pressure than patients with SRNS, but the occurrence of hypertension is not significantly associated with SRNS and SSNS.[8]

Systemic hypertension is not usually a feature of MCD but may occur transiently during recurrence or during high - dose steroid therapy, with incidence varying from 14% to 95% in most studies.[9 - 13] Persistent hypertension in NS is usually associated with a significant renal lesion and may be an indication for renal biopsy. Regardless of the cause, hypertension can have both short - and long - term deleterious effects on various organ systems.[14, 15]

However, there are limited data on systemic hypertension in children NS. Therefore, we aimed to investigate systemic hypertension in children with nephrotic syndrome.

2. Aims & Objectives

- To study the systemic hypertension in children with nephrotic syndrome.
- To find prevalence of systemic hypertension in steroid sensitive nephrotic syndrome (SSNS)
- To observe prevalence of systemic hypertension in steroid resistant nephrotic syndrome (SRNS)

3. Material & Methods

Study population was 70 newly diagnosed and known cases of nephrotic syndrome in SRTR Government Medical College Ambajogai, Dist. Beed, Maharashtra, India during study duration. This was prospective observational study. Patients who were previously hypertensive due to any other cause other than nephrotic syndrome, all the cases of congenital nephrotic syndrome and patients/ relatives/care takers not willing and refused to give consent were excluded.

Relevant detailed history and examination including anthropometry (WHO growth standards) and biochemical investigations including lipid profile were done in 70 children. Blood pressure (BP) was recorded using a clinical sphygmomanometer (aneroid, dial type, Hiene, GammaG5) by auscultatory method with appropriate size cuff and charts from "The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents" was used to estimate 50th, 90th, 95th, and 99thpercentile BP for that age, sex and height [12].

Normal BP was defined as systolic blood pressure and diastolic blood pressure that is < 90th percentile for that gender, age and height. BP between the 90th and 95th percentile was prehypertension.

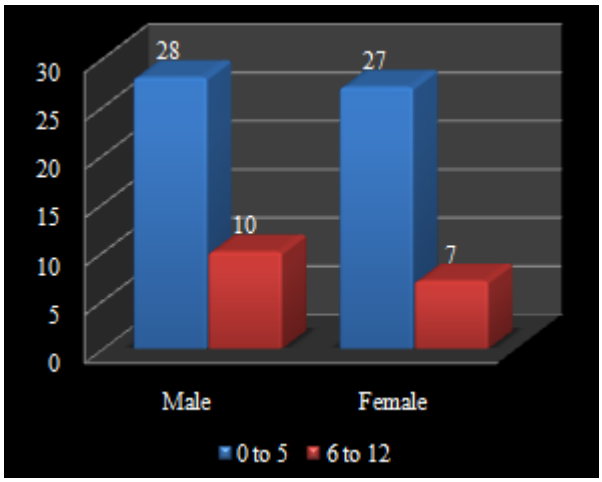
If BP > 90th percentile, BP was repeated twice in the same office and the average BP was used. Hypertension was defined as average SBP and/or DBP that is ≥ 95thpercentile for gender, age, and height on ≥ 3 occasions. In this study, BP was taken thrice on the same day at gap of5–10 min. Family history of hypertension was considered to be present on the basis of history of antihypertensive medication taken by any parents or grandparents.

Those with hypertension were further graded as stage I (95th percentile up to 99th percentile plus 5 mmHg) or stage II hypertension (> 99th percentile plus 5 mmHg). In all cases with hypertension, fundus examination for evidence of hypertensive retinopathy was done and classified [13]. Left ventricular mass indexed to body surface area was estimated by LV cavity dimension and wall thickness at end – diastole by 2 - D echocardiography was done to assess LV hypertrophy (LVH defined as LVMI ≥ 95th percentile compared to age and sex). Spot urine protein/ creatinine ratio was done to quantify proteinuria in hypertensive children

4. Results

Table 1: Distribution of study subjects according age and sex

Age	Male	Percentage (%)	Female	Percentage (%)	p value
0 to 5	28	40	25	36	0.7824
6 to 12	10	14	7	10	
Total	38	54	32	46	

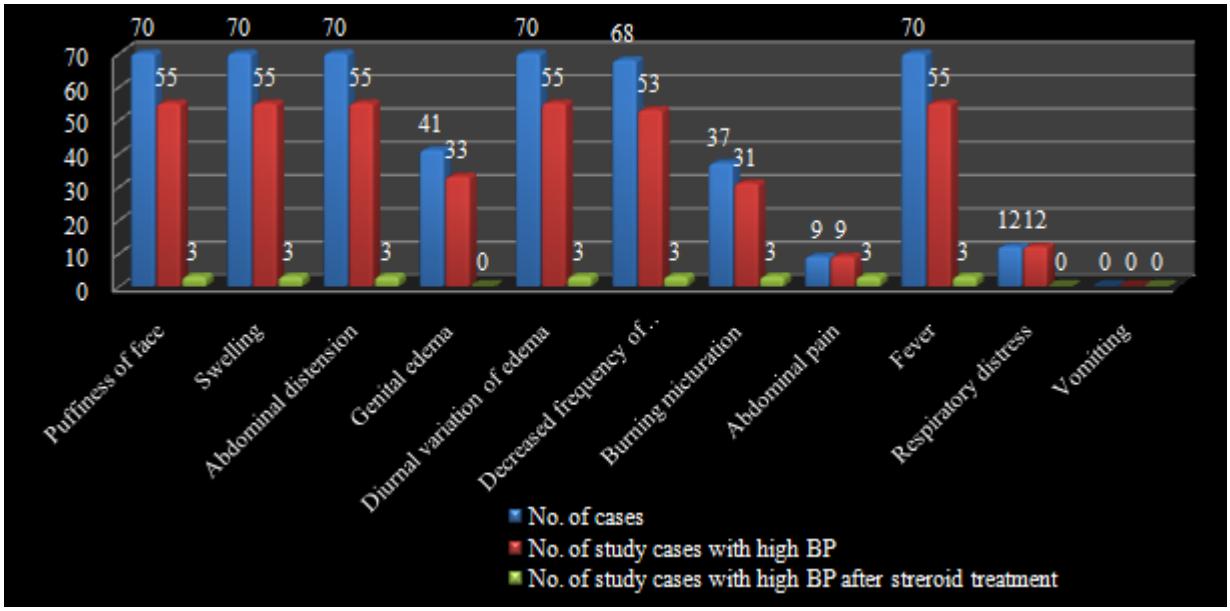


Graph 1: Distribution of study subjects according age and sex

There was no significant difference in age and sex although slight male preponderance is seen.

Table 2: Correlation between clinical features and hypertension in study subjects having nephrotic syndrome.

Clinical features	No. of cases	No. of study cases with high BP	No. of study cases with high BP after steroid treatment	p value
Puffiness of face	70	55	3	0.0001
Swelling	70	55	3	0.0001
Abdominal distension	70	55	3	0.0001
Genital edema	41	33	0	0.0001
Diurnal variation of edema	70	55	3	0.0001
Decreased frequency of micturition	68	53	3	0.0001
Burning micturition	37	31	3	0.0001
Abdominal pain	9	9	3	0.009
Fever	70	55	3	0.0001
Respiratory distress	12	12	0	-
Vomiting	0	0	0	-

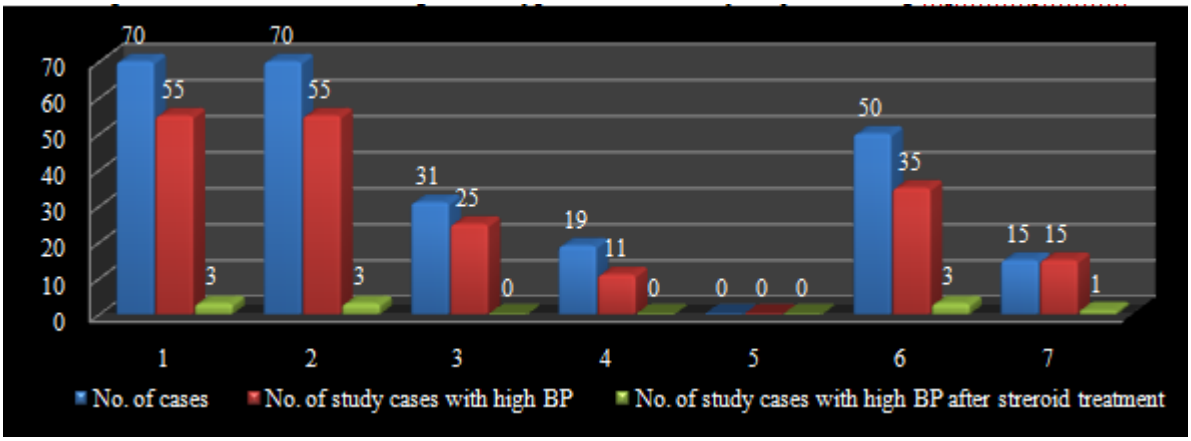


Graph 2: Correlation between clinical features and hypertension in study subjects having nephrotic syndrome.

Most of the clinical features had significant positive association with hypertension (p value 0.0001).

Table 3: Correlation between signs and hypertension in study subjects having nephrotic syndrome

Signs	No. of cases	No. of study cases with high BP	No. of study cases with high BP after steroid treatment	p value
Pitting edema	70	55	3	0.0001
Ascites	70	55	3	0.0001
Hepatomegaly	31	25	0	0.0001
Pallor	19	11	0	0.0001
Hematuria	0	0	0	-
Pyuria	50	35	3	0.0001
Convulsions	15	15	1	0.0001



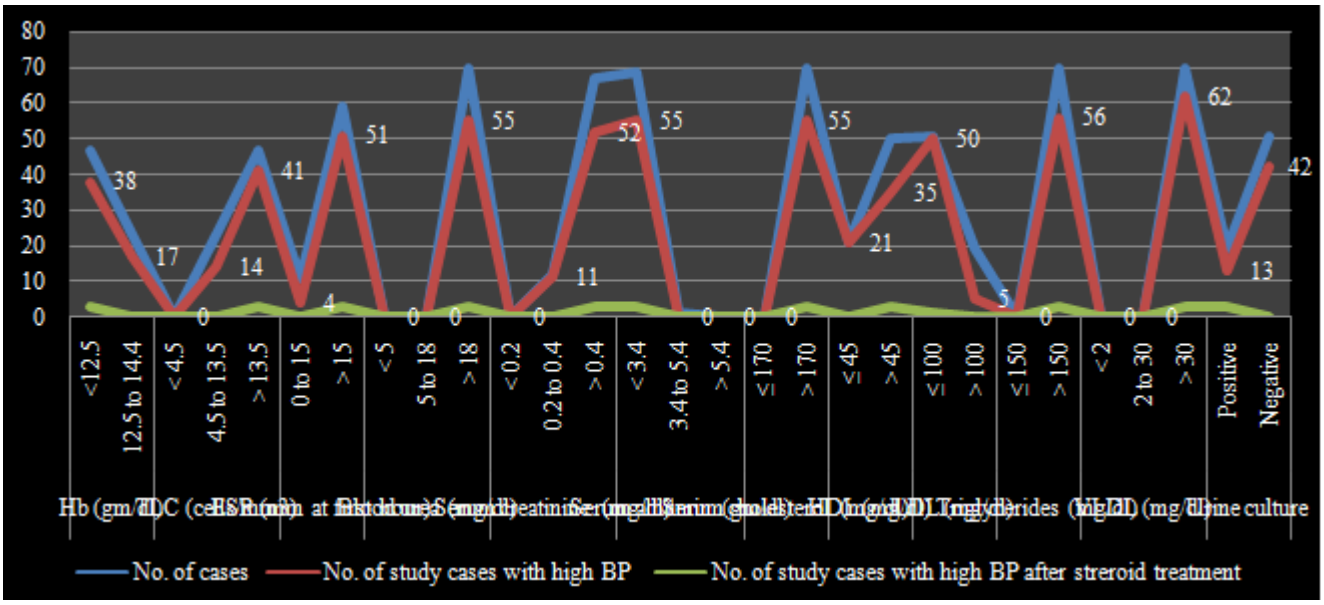
Graph 3: Correlation between signs and hypertension in study subjects having nephroticsyndrome

Signs and symptoms were observed to be more severe in pts with hypertension.

Table 6: Correlation between investigations and hypertension in study subjects having nephrotic syndrome.

Investigations	Investigations	No. of cases	No. of study cases with high BP	No. of study cases with high BP after steroid treatment	p value
Hb (gm/dl)	<12.5	47	38	3	0.1338
	12.5 to 14.4	23	17	0	
TLC (cells/mm3)	< 4.5	0	0	0	0.0001
	4.5 to 13.5	23	14	0	
	> 13.5	47	41	3	
ESR (mm at first hour)	0 to 15	11	4	0	0.0001
	> 15	59	51	3	
Blood urea (mg/dl)	< 5	0	0	0	-
	5 to 18	0	0	0	

	> 18	70	55	3	
Serum creatinine (mg/dl)	< 0.2	0	0	0	0.0001
	0.2 to 0.4	12	11	0	
	> 0.4	67	52	3	
Serum albumin (gm/dl)	< 3.4	69	55	3	-
	3.4 to 5.4	1	0	0	
	> 5.4	0	0	0	
Serum cholesterol (mg/dl)	≤ 170	0	0	0	-
	> 170	70	55	3	-
HDL (mg/dl)	≤ 45	21	21	0	0.0001
	> 45	50	35	3	
LDL (mg/dl)	≤ 100	51	50	1	0.0001
	> 100	19	5	0	
Triglycerides (mg/dl)	≤ 150	0	0	0	-
	> 150	70	56	3	
VLDL (mg/dl)	< 2	0	0	0	-
	2 to 30	0	0	0	
	> 30	70	62	3	
Urine culture	Positive	19	13	3	0.0181
	Negative	51	42	0	

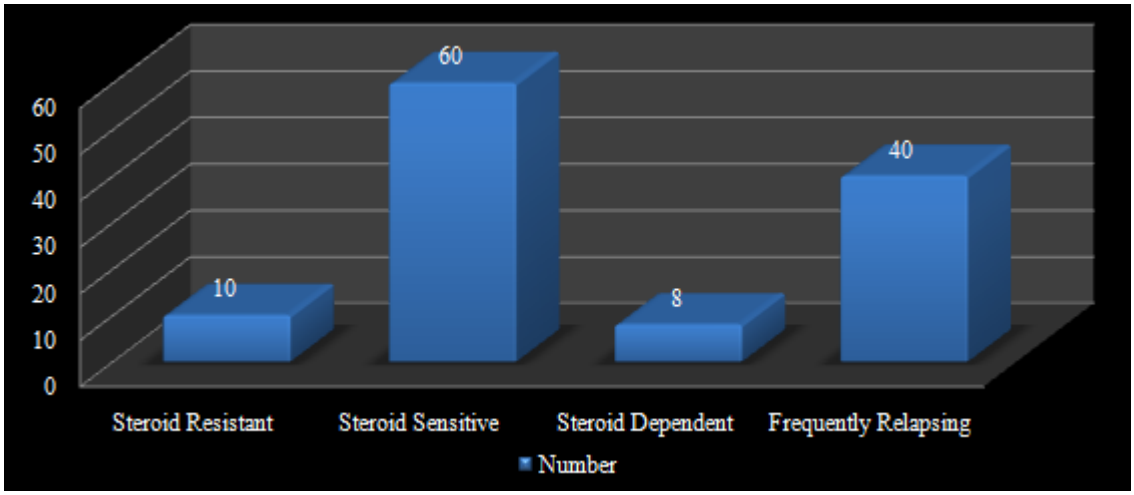


Graph 6: Correlation between investigations and hypertension in study subjects having nephrotic syndrome

Investigations like renal parameters lipid profile were seen to be significantly deranged in cases who presented with hypertension.

Table 9: Distribution of study subjects according to steroid response

Steroid response	Number	Percentage (%)
Steroid Resistant	10	14
Steroid Sensitive	60	75
Steroid Dependent	8	11
Frequently Relapsing	40	57

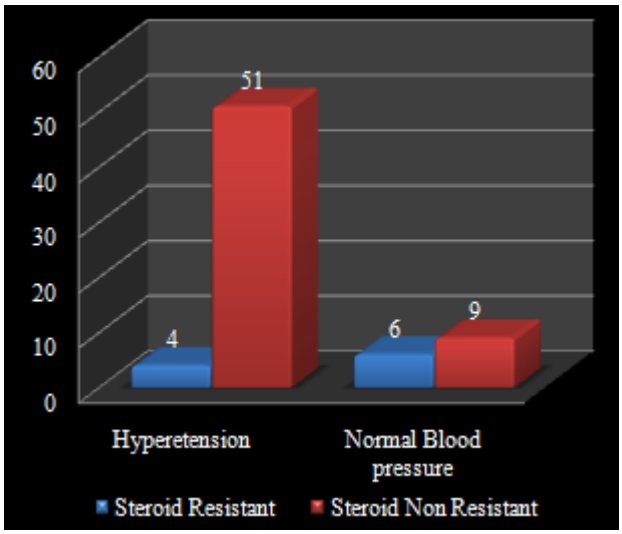


Graph 9: Distribution of study subjects according to steroid response.

Of all cases 75% (60) were steroid sensitive, 10% steroid resistant while 11% (8) were steroid dependent and frequently relapsing 40 (57%).

Table 12: Distribution of study subjects according tostatus of hypertension in steroid resistantpatients.

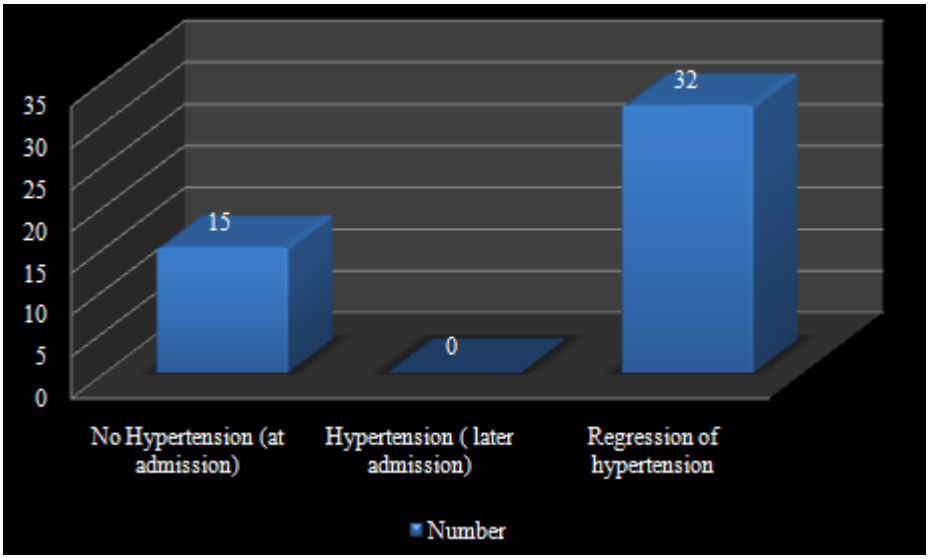
Variables	Hypertension	Normal Blood pressure	p value
Steroid Resistant	4	6	0.0048
Steroid sensitive	51	9	
Total	55	15	



Graph 12: Distribution of study subjects according tostatus of hypertension in steroid resistantpatients.

Table 14: Distribution of study subjects according to non - hypertensive patients on admission developed hypertension later

Parameter	Number	Percentage (%)
No Hypertension (at admission)	15	21
Hypertension (later admission)	5	7
Regression of hypertension	32	58



Graph 14: Distribution of study subjects according tonon - hypertensive patients on admission developed hypertension later

Out of 15 cases that did not have hypertension 5 cases developed HTN and of 55 cases that had hypertension 32 of them regressed to no hypertension at the end.

5. Discussion

In the present study the association between age and gender was not significant as p value was 0.7824. Nahla IA et al[16] in their study observed that they included 46 males and 25 females with male to female ratio 1.8: 1. Age ranges between 1 - 18 years. A total of 50 patients (70%) (Male and female) were in the age group 1 - 5 years, followed by 17 (23.9%) in the age group (6 - 10) and 4 (5.6%) in age group > 10 years. Kesari s et al[17] in their study mentioned that slightly male predominance (male: female ratio of 1.3: 1). The mean age of patients at the time of study was 5.57 + 2.11 years, the median being 5 years.

The association between signs &symptoms in cases with high BP and the cases remain persistent high BP even after steroid treatment was significant as p value 0.0001. In the similar study Sahana KS et al[3] stated that all patients presented with puffiness of face and swelling of limbs with diurnal variation noted in 76% of cases.76.6% patients presented with abdominal distension while as 31% of cases complained of genital swelling. History of decreased frequency and volume of micturition was obtained in 53.9% while as burning micturition was noted in 4.26% of cases. Other symptoms include abdominal distension, fever, vomiting and respiratory distress. Pallor was noted in 42% of cases. In a study done by Safaei et al[18] edema involving genital area was found to be 54.5%. Only one patient presented with respiratory distress due to massive edema (pleural effusion and massive).

Sahana KS et al[3] in their study found that on investigation 74% of cases had anemia with peripheral smear showing normocytic hypochromic in 26 cases and microcytic hypochromic in 9 cases. Total leukocyte range was between 6200 - 13, 200 with mean leukocyte count of 7890/mm3. ESR was elevated in all cases with mean ESR of 71mm at first hour. On biochemical investigation blood urea was between the ranges of 14 - 43 mg/dl with mean value of 25 mg/dl. Serum creatinine was in the range of 0.3 - 1.3mg/dl with mean value of 0.63mg/dl. Serum albumin was between 1.3 - 2.4mg/dl with mean value of 1.9 mg/dl indicative of hypoalbuminemia. Serum cholesterol range was in between 206 - 388 mg/dl with mean level of 294mg/dl suggestive of hypercholesterolemia Hypoalbuminemia and hypercholesterolemia was present in all cases. Mahmud KM et al[19] in their study mentioned that among 51 culture positive cases with UTI.

In the present study urine protein to urine creatinine ratio ≥ 0.5 was seen in 70 cases among these 56 were with high BP. In 3 cases BP remain high even after steroid treatment. Kesari S et al[17] in their study found that urine protein to urine creatinine ratio ≥ 0.2 in 6 cases of stage I hypertension and > 0.2 in 12 cases of stage I hypertension.

In the present study 10 (14%) were steroid resistant; 60 (75%) were steroid sensitive; 8 (11%) were steroid dependent 40 (57%) were FRNS. Nahla IA et al[16] in the similar study found that Hypertension was found in 5 patients (7%) with steroid sensitive nephrotic syndrome at late presentation, while 2 patients (2.8%) with steroid resistant nephrotic syndrome and 3 patients (4.2%) with steroid dependent nephrotic syndrome developed HT at initial attacks and 7 (9.8%) of steroid resistant, 11 patients (15.5%) of steroid dependent developed HT later on respectively (p value 0.0001 highly significant).

At the time of admission hypertension was present in 55 (79%) cases. Among them 51 was steroid sensitive and 4 were steroid resistant. In 15 (21%) cases hypertension was not seen at the time of admission, among them 5 had hypertension in later stage and regression of hypertension in previously hypertensive was seen in 32 (58%).

6. Conclusion

Hypertension can be considered a typical finding in SSNS, although it is more common in SRNS and FRNS. Therefore, all nephrotic patients who are in remission should be routinely monitored for blood pressure, and antihypertensive treatment should be started early to avoid complications.

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