

Original paper

The Incidence of Hypertension in Children with Nephrotic Syndrome in Comparison with Low & High-Risk Group & Associated Risk Factors.

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Abstract

Background: Hypertension is common among steroid resistant and steroid dependent nephrotic syndrome patients. hypertension is one of the most common sequelae of chronic kidney disease in pediatric age group.

Patients & methods: A cross sectional study which was carried out in Nephrology Department at Central Child Teaching hospital & Al-Karamah Teaching hospital with total of 255 patients included 102 patients with nephrotic syndrome & with measurement of blood pressure of 102 child with no history of any disease, this study also included measurement of blood pressure for 51 patients with chronic kidney disease.

Results: In this study, the total number of cases of nephrotic syndrome, chronic kidney disease, & normal children were 102, 51, 102 cases respectively, male to female ratio was 1.5:1 for both nephrotic syndrome & normal children while it was 1.8:1 for chronic kidney disease patients. hypertension was reported in 2 cases only of total 102 cases of normal population & in 33 cases of total 102 cases of nephrotic syndrome While it reported in 29 cases of total 51 cases of chronic kidney disease.

Conclusions: Nephrotic syndrome can be considered to be intermediate risk factor for development of hypertension between normal children & chronic kidney disease. Hypertension was found to be more in steroid resistant nephrotic syndrome and steroid dependent nephrotic syndrome group than in steroid sensitive nephrotic syndrome group. hypertension also was found to be more in frequent relapsing nephrotic syndrome. The incidence of hypertension was more in nephrotic patients with elevated blood urea and S.Creatinine than in patient with normal renal function.

Keywords: Hypertension, Nephrotic Syndrome, Chronic Kidney Disease.

Introduction

Nephrotic syndrome is a disease of the kidneys that results from increased permeability of the glomerular filtration barrier. It is characterized by four major clinical characteristics used in reaching the diagnosis: proteinuria, hypoalbuminemia, edema, and hyperlipidemia⁽¹⁾. The most common cause of nephrotic syndrome in children is idiopathic nephrotic syndrome, also called nephrosis⁽²⁾. Idiopathic nephrotic syndrome is the most common acquired glomerulopathy in children. Population-based epidemiological data are scarce, and the etiologic mechanisms of the disease remain largely unknown. Idiopathic nephrotic syndrome is likely a primary immune disorder, and viral infections—especially upper respiratory tract infections—have been reported as triggers of first manifestation and relapses⁽³⁾. Although nephrotic syndrome most often occurs as a primary disorder in children, it can also be secondary

to several systemic diseases in children. Secondary causes include the following, again in order of approximate frequency: Diabetes mellitus, Lupus erythematosus, Viral infections (e.g., hepatitis B, hepatitis C, human immunodeficiency virus [HIV]), Amyloidosis and paraproteinemias, Preeclampsia, Allo-antibodies from enzyme replacement therapy⁽⁴⁾. Overall, 16% of children with nephrotic syndrome have hypertension at presentation. The presence of marked hypertension should suggest the possibility of underlying glomerulonephritis⁽⁵⁾.

Hypertension in Nephrotic Syndrome:

Hypertension may be present; International Study of Kidney Disease in Children (ISKDC) studies demonstrated that approximately 30% of patients with minimal change nephrotic syndrome (MCNS) have both systolic and diastolic pressures above the 90th percentile for age. When systolic and diastolic blood pressure above the 98th percentile was used to denote

an abnormality, then approximately 20% had elevated systolic pressures, and about 13% of the diastolic pressures were aberrant. The percentage of children with nephrosis who exhibit hypertension is higher with other subsets, such as children with focal segmental glomerulosclerosis (FSGS) and, particularly so in patients with membranoproliferative glomerulonephritis (MPGN) in which hypertension may be severe⁽⁶⁾. hypertension in nephrotic syndrome occurs in 30–89% of adults and 14–21% of children⁽⁷⁾. hypertension prior to corticosteroid therapy is unusual in MCNS but is present in 50% of children with FSGS⁽⁸⁾.

Hypertension and Chronic Kidney Disease: Hypertension is one of the most common sequelae of chronic kidney disease (CKD) in children. Renal hypertension is the most common (approximately 85%) identifiable secondary hypertension in children. It is one of the earliest and most prevalent complications of pediatric chronic kidney disease (CKD)⁽⁹⁾. Over half of all children have hypertension, even in early CKD, increasing to 50-75% in CKD stage 5. At 6 months after dialysis was initiated, 67.9% of 3447 patients (65.7% on peritoneal dialysis and 34.3% on hemodialysis) had uncontrolled or untreated hypertension, and 57.8% were prescribed antihypertensive medications.

In more recent years, dialysis initiation was associated with higher use of antihypertensive medication, and lower systolic BP and diastolic BP Z-scores measured over time from 6 months to 3 years after dialysis initiation. Other factors associated with higher BP included black race, glomerular disease, younger age, hemodialysis (systolic BP only), and antihypertensive use.

There were significant differences in BP control by dialysis modality and disease etiology, with patients on hemodialysis or those with glomerular diseases having the

highest percentage of uncontrolled hypertension⁽¹⁰⁾. In another cross-sectional study that included 624 pediatric patients on chronic hemodialysis, 79% of patients had hypertension⁽¹¹⁾.

The current study aimed to study the relative frequency of hypertension in children with nephrotic syndrome & the factors that increase the incidence of hypertension in these patients. Also, to compare the incidence of hypertension in patients with nephrotic syndrome, patients with chronic kidney disease, and

normal populations concerning low, medium, and high-risk groups.

Patients and methods

Study Subjects: The study was conducted as a cross-sectional study was carried out in the Nephrology Department at Central Child Teaching hospital & Al-Karamah Teaching hospital with a total of 255 patients, including 102 patients with nephrotic syndrome diagnosed and/ or treated and followed up in the pediatric nephrology consultation clinic & nephrology ward from the first of June 2016 to the thirty-first of August 2017 to study the relative frequency of hypertension in children with nephrotic syndrome & the correlated factors that increase the incidence of hypertension in these patients. This study also included the measurement of blood pressure of 102 children with no history of any disease of the same age & sex as nephrotic patients who visited the outpatient clinics in Central Child Teaching hospital over 8 months period from the first of January to the thirty-first of August 2017; also this study included measurement of blood pressure was done for 51 patients with chronic kidney disease who visited the Hemodialysis Centre in Central Child Teaching hospital from the first of June 2016 to the thirty-first of August 2017 to compare the incidence of hypertension in patients with nephrotic syndrome, patient with chronic kidney disease & normal population.

Study Sample & Inclusion Criteria:

Cases with nephrotic syndrome, a total number of 102 cases met the inclusion criteria for the primary nephrotic syndrome:

1- Clinical signs & Symptoms: Edema [generalized, puffy face, leg edema, ascites, oliguria (defined as a urine output less than 1 mL/kg/h in infants, less than 0.5 mL/kg/h in children).

2- Investigation: The urinalysis reveals 3+ or 4+ proteinuria; microscopic hematuria is present in 20% of children. A spot urine protein: creatinine ratio should be >2.0., The serum albumin level is <2.5 g/dL; serum cholesterol and triglyceride levels are increased, exceeding 220 mg/ dL, and there is no evidence of systemic disease. A renal biopsy is not routinely done if the patient fits the standard clinical picture of MCNS.

A percutaneous renal biopsy was done for patients with steroid-resistant nephrotic syndrome, those developing gross hematuria at the onset and prior to therapy with cyclosporine⁽¹²⁾.

Information about 62 cases were obtained from the history, clinical examination, investigations, and management of cases with nephrotic syndrome in the nephrology ward in Central Child Teaching hospital over 8 months period from the 1 of January to the 31 of August 2017, while the remaining 40 cases were obtained from the case files in pediatric nephrology consultation clinic in Al-Karamah Teaching hospital & Central Child Teaching hospital during 2016. The parameters documented were gender, age, weight, height, age of presentation, clinical presentation, family history, blood pressure, investigations {complete blood count (CBC), results of urinalysis, 24-hour urine protein estimation, Urine C/S, Blood Urea, S. Creatinine, S. Electrolytes}, type of nephrotic syndrome, type of treatment, response to the treatment, occurrence of relapse), the blood pressure for them was measured 3 times in both standing & sitting position in left & right arm. Patients who were hypertensive received either captopril 0.3-0.5 mg/kg/dose; titrated to a maximum 6 mg/kg/day divided q6-12hr or amlodipine 0.1-0.2 mg/kg/day (QD); titrate to a maximum 6 mg/kg/day up to 10mg/d or both.

Normal children, A total number of 102 children with no history of any disease of the same age & sex as nephrotic patients who visit the outpatient clinics in Central Child Teaching hospital were included in this study & were divided into 3 age groups: (1-5 years), (6-10 years), (more than 10 years), their height & weight were measured, a detailed history & full examination were performed for them in outpatient clinics in Central Child Teaching hospital, their blood pressure was measured 3 times in both standing & sitting position, in left & right arm.

Cases with chronic kidney disease, a total number of Fifty-one patients with chronic kidney disease who visited the Hemodialysis Centre in Central Child Teaching hospital were included. Twenty-nine cases were collected over eight months from the 1st of January to the 1st of August 2017, while the remaining 22 cases were obtained from the case files of CKD patients who visited the Hemodialysis Centre in Central Child Teaching hospital in 2016. Blood pressure was measured 3 times in standing and sitting positions and in the left and right arms. The same procedure & technique for blood pressure measurement was done for all cases included in this study, which will be explained later.

Exclusion criteria: Patients with congenital nephrotic syndrome & Patients for whom there were incomplete data from the initial presentation in their case files, or patients who missed follow-up have been excluded from this study.

Data collection: Parameters about the patients with nephrotic syndrome were collected and recorded from the parents, and their files (after consent) include the following information: Gender & Age, weight & Height, and age at the time of presentation (the cases were divided into three groups: [(1-6 years), (more than 6-10 years), (more than 10 years)]. It also includes the family history of renal disease and hypertension (HT), type of Nephrotic syndrome according to response to steroids & relapse: sensitive, dependent + frequent, resistant, Blood pressure (BP): normal, HT during the initial attack, HT developed later, investigations such as renal function test, renal biopsy, and treatment type (steroid only, steroid + 2nd line of therapy).

Blood pressure measurement

Hypertension was defined as systolic and/or diastolic BP 95th percentile for age, sex, and height on three occasions⁽¹³⁾. The procedure for BP measurement via manual auscultation in sitting and standing positions was performed according to⁽¹³⁾.

Statistical analysis: The data has been analyzed with computer software SPSS version 24. Chi-square and Fisher's exact tests have been used to define the association between the categorical variable. A confidence level of 95% with a P value equal to or less than 0.05 was considered significant.

Results

The total number of nephrotic patients enrolled during the study period was 102. Males (61) (59.8% of total cases) outnumbered females (41) (40.2%) with male to female ratio of 1.5:1. Age range between 1-14 years. A total of 75 patients (73.5%) (Male and female) were in the age group 1-5 years, followed by 15 patients (14.7%) in the age group (6-10) and 12 patients (11.8%) in the age group >10 years. Positive family history of renal diseases was reported in 10 cases (9.8%), while a family history of hypertension was reported in 7 cases (6.9%), as shown in Table 1. The total number of normal children with no history of illnesses enrolled during the study period was 102 children, the same age & sex of nephrotic patients. Males (61) (59.8% of total cases) outnumbered females (41) (40.2%) with male to female ratio of

1.5:1. Age range between 1-14 years. A total of 75 patients (73.5%) (Male and female) were in the age group 1-5 years, followed by 15 patients (14.7%) in the age group (6-10) and 12 patients (11.8%) in the age group > 10 years, Positive family history of renal diseases was reported in 4 cases (3.9%) while family history of hypertension was reported in 5 cases (4.9%), Blood pressure was normal in 100 patients (98%), hypertension was reported in 2 cases only (2%) as shown in Table 2.

Table 1. Frequency distribution of the demographic variables in nephrotic patients (n 102)

Variables		Fre- quency	%
Gender	Male	61	59.8
	Females	41	40.2
Age at time of presentation	1-5 yr	75	73.5
	6-10 yr	15	14.7
	> 10 yr	12	11.8
Family history of renal disease	Positive	10	9.8
	Negative	92	90.2
Family history of Hypertension	Positive	7	6.9
	Negative	95	93.1
Blood pressure	Normal	69	67.7
	Elevated	33	32.3

Table 2. Frequency distribution of the demographic variables in normal population.

Variables		Fre- quency	%
Gender	Male	61	59.8
	Females	41	40.2
Age at time of presentation	1 - 5 yr.	75	73.5
	6 - 10 yr.	15	14.7
	> 10 yr.	12	11.8
Family history of renal disease	Positive	4	3.9
	Negative	98	96.1
Family history of Hypertension	Positive	5	4.9
	Negative	97	95.1
Blood pressure	Normal	100	98
	Elevated	2	2

The total number of children with CKD enrolled during the study period was 51 cases; males (33) (64.7% of total cases) outnumbered females (18) (35.1%) with male to female ratio of 1.8:1. Age range

between 1-14 years. A total of 18 patients (35.3%) (Male and female) were in the age group 1-5 years, followed by 24 patients (47.1%) in the age group (6-10) and 9 patients (17.6%) in the age group > 10 years, Positive family history of renal diseases was reported in 9 cases (17.6%) while family history of Hypertension was reported in 7 cases (13.7%), Blood pressure was normal in 22 patients (34.1%), Hypertension was reported in 29 cases (56.9%) as shown in Table 3.

In this study, HT was reported in 2 cases only out of the total (102 cases) of the normal population (2%) & in 33 cases out of a total of 102 cases of nephrotic syndrome (32.3%). In contrast, it was reported in 29 cases of a total of 51 cases of CKD (56.9%), so Nephrotic syndrome can be considered to be an intermediate risk factor for the development of HT, as shown in Table 4.

Table 3. Frequency distribution of the demographic variables in CKD patients.

Variables		Frequency	%
Gender	Male	33	64.7
	Females	18	35.1
Age at time of presentation	1 - 5 yr.	18	35.3
	6 - 10 yr.	24	47.1
	> 10 yr.	9	17.6
Family history of renal disease	Positive	9	17.6
	Negative	42	82.4
Family history of Hypertension	Positive	7	13.7
	Negative	44	86.3
Blood pressure	Normal	22	43.1
	Elevated	29	56.9

Table 4. Percentage of Hypertension in normal population, nephrotic syndrome & CKD patients

Variables	Total No. of children	No. Of Hypertensive patients	Percentage of HT %
Normal population	102	2	2 %
Nephrotic Syndrome	102	33	32.3 %
CKD	51	29	56.9 %

Blood pressure was normal in 69 nephrotic patients (67.7%), Hypertension in 33 cases of a total of 102 cases of nephrotic syndrome (32.3%), in 11 cases with an initial attack (10.8%) while it developed later in 22 cases (21.6%) as shown in Figure 1.

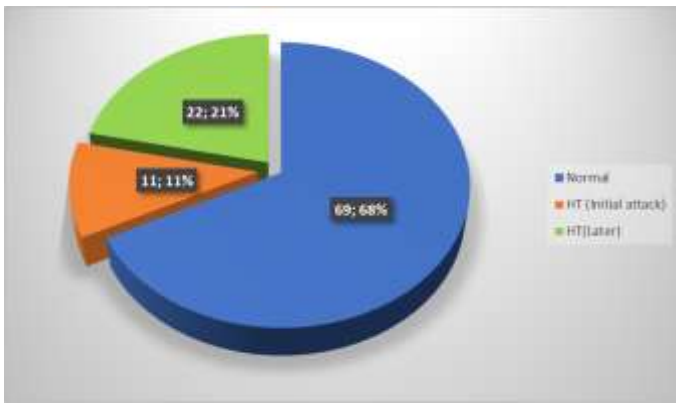


Figure 1. Frequency distribution of the blood pressure status within the sample.

Regarding *gender*, 16 male patients out of 61 male patients developed hypertension (26.2%), 7 cases at initial attack (11.4%) while 9 cases developed hypertension later (14.8%), in 41 female patients, 17 cases developed hypertension (41.5%), 4 cases initially (9.8%) & 13 cases later (31.7%). There was no significant association between gender & hypertension in nephrotic patients in this study (P value 0.124), as shown in Table 5.

Regarding age at the time of presentation, High blood pressure was reported in the age group (1-5) years in 26 cases among 75 cases (34.7%), initially, 7 cases (9.3%) and 19 cases (25.3%) developed HT later while in age group (6-10) years it reported in 4 cases among 15 cases (26.6%), only 2 cases (13.3%) initially and 2 cases (13.3%) later. In the age group

>10 years, it reported in 3 cases among 12 cases (25%), only 2 cases (16.7%) initially & 1 case (8.3%) presented later, with no significant association between Age at the time of presentation & hypertension in nephrotic patients was reported in this study (P value 0.594) as shown in table 5.

Regarding the family history of renal diseases, among 10 cases with a family history of renal problems out of 102 (9.8%), 4 cases developed hypertension (40%), 2 (20%) initially & 2 (20%) later, no significant relationship between family history of renal diseases & hypertension in nephrotic syndrome was reported in this study (P value 0.612) as shown in table no. 5.

Regarding the family history of hypertension, which was positive in 7 cases out of 102 (6.9%), HT was reported in 6 cases (85.7%), and one case (14.3%) developed hypertension initially. The other 5 cases (71.4%) developed it later. A highly significant association between a family history of hypertension & development of hypertension in nephrotic patients (P value 0.003) was demonstrated in this study, as shown in Table 5.

Regarding the type of Nephrotic syndrome, the patients were subdivided in this study into 4 groups, the induction group, which included 21 patients (20.6%), Responsive (sensitive) groups which included 34 cases (33.3%). In contrast, the frequent relapses + dependence group included 29 patients (28.2%) & resistance group included 18 cases (17.6%), as shown in Figure 2.

Table 5. Blood pressure association with the demographic variables.

Variables		Normal		HT (initial)		HT (Later)		P value
		No.	%	No.	%	No.	%	
Gender	Male	45	73.8	7	11.4	9	14.8	0.124 (NS)
	Female	24	58.5	4	9.8	13	31.7	
Age at time of presentation (Years)	1 – 5 yr	49	65.3	7	9.3	19	25.3	0.594 (NS)
	6–10yr	11	73.4	2	13.3	2	13.3	
	> 10 yr	9	75	2	16.7	1	8.3	
Family history of renal disease	No	63	68.5	9	9.8	20	21.7	0.612 (NS)
	Yes	6	60	2	20	2	20	
Family history of hypertension	No	68	71.6	10	10.5	17	17.9	0.003 (*)
	Yes	1	14.3	1	14.3	5	71.4	

(NS not significant) (* significant at alpha level of less than 0.05)

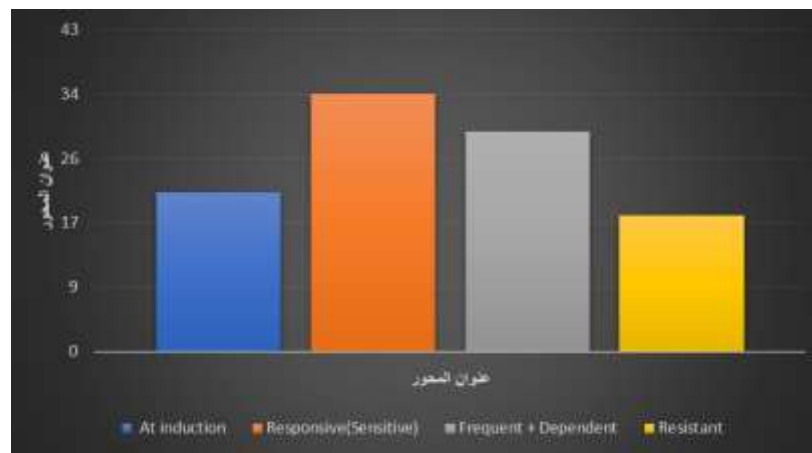


Figure 2. Frequency distribution of the sample according to the type of Nephrotic syndrome concerning response to steroid.

Only one patient among 21 patients (4.8%) in the induction group was hypertensive initially, while 5 patients among 34 patients (14.7%) in the Sensitive group were hypertensive, one patient (2.9%) was found to be hypertensive initially, and 4 patients in contrast, in resistance cases, hypertension was reported in 11 cases out of 18 cases (61.1%), 3 cases initially (16.7%) & 8 cases later (44.4%), which means that there is a strong association between the type of Nephrotic syndrome according to response to steroid & relapse with hypertension in nephrotic syndrome as shown in table (P value 0.0001), the more relapses & more resistant cases, the more chances to developed HT as shown in Table 7.

Regarding renal function tests, among 16 patients out of 102 patients (15.7%) with elevated blood urea, hypertension was reported in 10 patients (62.5%), 3 initially (18.75%) & 7 patients later (43.75%), while of 14 patients with elevated s.creatinine out of 102 patients (13.7%), hypertension developed in 9 patients (64.3%), 3 initially (21.4%) & later in 6 patients (42.9%), so this study shows a highly significant relationship between the development of hypertension & abnormal renal function test in nephrotic patients, in fact of decreased renal function may increase the probability of HT in nephrotic patients as found in this study as shown in Table 7.

Regarding renal biopsy, which was done for 14 cases only who had failed to respond to steroid therapy (some parents refused to do it), nine of them was MCNS (64.3%), & 5 cases of them developed HT later (55.6%) & all 3 cases with FSGN out of 14

(11.8%) later on. In the frequent relapses & dependence group, hypertension was reported in 16 patients among 29 patients (55.2%) with frequent relapses, 6 patients initially (20.7%) & 10 patients (34.5%) developed HT later on.

cases (21.4%) developed HT initially (100%), while both 2 cases with MPGN out of 14 (14.3%) developed hypertension (100%), one case (50%) developed HT initially & one case (50%) developed it later. A highly significant relationship between the development of hypertension & type of nephrotic syndrome was demonstrated in this study (P value 0.016), Table 7.

Regarding the type of treatment, steroids and 2nd line of therapy (calcineurin inhibitors {cyclosporine, tacrolimus}) were used for treating patients with nephrotic syndrome. The steroid was used for 82 patients out of 102 (80.4%), while steroid and 2nd line of therapy was used in 20 patients (19.6%), as shown in Table 6.

HT was found in 21 patients among 82 patients who were treated with steroids only (25.6%), initially in 6 patients (7.3%) & later in 15 patients (18.3%). In comparison, HT was found in 13 patients among 20 patients who received steroids & 2nd line of therapy (65%), initially in 6 patients (30%) and seven patients later (35%). A highly significant relationship between the development of hypertension and the type of treatment was reported in this study (P value 0.008). The failure to respond to steroids and the 2nd line of therapy, including calcineurin inhibitors, may cause HT in nephrotic patients, as shown in Table 7.

Table 6. Frequency distribution of the clinical variables (n 102).

Variables		Frequency	%
Type of nephrotic syndrome	At Induction	21	20.6
	Sensitive (Responsive)	34	33.3
	Frequent + Dependent	29	28.2
	Resistant	18	17.6
Blood pressure	Normal	69	67.6
	HT during initial attack	11	10.8
	HT later	22	21.6
Blood urea	Normal	86	84.3
	Abnormal	16	15.7
S. creatinine	Normal	88	86.3
	Abnormal	14	13.7
Renal biopsy	Not done	88	86.3
	MCD	9	8.8
	FSGN	3	2.9
	MPGN	2	2
Management	Steroids	82	80.4
	Steroids with 2nd line of therapy	20	19.6

Table 7. Blood pressure association with the clinical variables & management (n 102).

Variables		Normal		HT (initial)		HT (Later)		P value
		No	%	No	%	No	%	
Type of nephrotic according to response to steroid	At induction	20	95.2	1	4.8	0	0	0.0001 (**)
	Responsive (Sensitive)	29	85.3	1	2.9	4	11.8	
	Frequent+ dependent	13	44.8	6	20.7	10	34.5	
	Resistant	7	38.9	3	16.7	8	44.4	
Blood urea	Normal	63	73.3	8	9.3	15	17.4	0.018 (*)
	Abnormal	6	37.5	3	18.75	7	43.75	
S. creatinine	Normal	64	72.7	8	9.1	16	18.2	0.035 (*)
	Abnormal	5	35.7	3	21.4	6	42.9	
Renal biopsy (n 14)	MCD	4	44.4	0	0	5	55.6	0.016 (*)
	FSGN	0	0	3	100	0	0	
	MPGN	0	0	1	50	1	50	
Type of treatment	Steroids	61	74.4	6	7.3	15	18.3	0.008 (*)
	Steroids with 2nd line of therapy	7	35	6	30	7	35	

(NS not significant) (* significant at alpha level of less than 0.05)

Discussion

Regarding the percentage of nephrotic patients with hypertension, this study shows that 33 patients among a total of 102 patients (32.3%) were hypertensive, which is slightly lower than what was found in Nahla Al-Ghabban et al.'s study⁽¹⁴⁾ and lower than what was reported in a previous Iraqi study⁽¹⁵⁾ and Ibadin et al. study⁽¹⁶⁾ and higher than that found in the Iranian study⁽¹⁷⁾, and the Jordanian study⁽¹⁸⁾.

In this study, hypertension developed later in nephrotic patients more than it developed at initial presentation (may be due to disease complications or

treatment side effects). Hypertension occurred initially in 11 cases out of 33 cases (33.3%), which is as twice as what was reported in Nahla Al-Ghabban et al., which showed HT was found in 5 cases out of 28 (17.9%), with initial attacks⁽¹⁴⁾ & also as twice as El-zouki et al. (16.0%)⁽¹⁹⁾. In comparison, hypertension was developed later in 22 cases out of 33 cases (66.7%) in this study, which is lower than what was reported in Nahla Al-Ghabban et al., in which HT was developed in 23 cases out of 28 (82.1%) later⁽¹⁴⁾; these differences may be due to different study samples. BP in nephrotic syndrome can be either low (due to intravascular volume depletion) or high (due

to neurohumoral responses to hypovolemia, intrinsic renal causes, or occasionally renal vein thrombosis or due to side effects of treatment (steroid & calcineurin inhibitors {cyclosporine, tacrolimus})⁽²⁰⁾.

Regarding gender, this study shows no significant association between gender & development of hypertension in nephrotic patients, which agrees with Nahla Al-Ghabban et al.⁽¹⁴⁾. However, in contrast with a previous Iraqi study (2008) in which H was found to be more in males than in females, especially in patients with relapse and prolonged treatment with steroids⁽¹⁵⁾, this can be explained by the fact that a different selection of the patient was made for this study (102 cases in this study with male to female ratio 1.5:1, Vs.—50 cases in the previous Iraqi study with male to female ratio of 1.9:1).

Regarding age at the time of presentation, this study shows no significant correlation between age at the time of presentation & development of hypertension in nephrotic patients, which agrees with Nahla Al-Ghabban et al.⁽¹⁴⁾.

Regarding the family history of renal diseases, no significant relationship between family history of renal diseases & hypertension in nephrotic syndrome was reported in this study. The same finding was reported by Nahla Al-Ghabban et al.⁽¹⁴⁾. This can be explained by the difficulty of obtaining accurate information from the patient's family about the family history of renal disease that cannot be reliable to estimate if there is a correlation between family history of renal diseases with development of hypertension in nephrotic syndrome in this study.

Regarding the family history of hypertension, there is a significant association between family history of hypertension & development of hypertension in nephrotic patients (P value 0.003), which agrees with the finding reported by Monthe Kontchou L et al., which reveals the influence of the familial history of essential hypertension in the oedematous phase of the nephrotic syndrome in children.⁽²¹⁾ While Nahla Al-Ghabban et al. showed no association between the family history of hypertension & development of HT in nephrotic patients⁽¹⁴⁾.

Regarding the type of nephrotic syndrome, only one patient out of 21 patients (4.8%) in the induction group was hypertensive initially, while 5 patients out of 34 patients (14.7%) in the Sensitive group were hypertensive. In the frequent relapses & dependence group, hypertension was reported in 16 patients

among 29 patients (55.2%) with frequent relapses. In contrast, in resistance cases, hypertension was reported in 11 cases out of 18 cases (61.1%), which means there is a strong association between the type of Nephrotic syndrome according to response to steroids & relapse with hypertension in nephrotic syndrome (P value 0.0001). Similar results were found by Nahla Al-Ghabban et al., which showed that hypertension was observed in 5 cases out of 33 SSNS cases (15.2%), in 14 cases out of 28 SDNS cases (50%) & in 9 cases out of 10 SRNS cases (90%) (p-value 0.0001)⁽¹⁴⁾, these results are higher than what was found in a previous Iraqi study by AL-Mewashi H.H. reported (11.2%), (6.1%), (and 10.2%) SSNS, SDNS, and SRNS, respectively⁽²²⁾. The difference in study samples can explain this.

Hypertension occurs in cases receiving steroids for long periods & in large amounts & use of 2nd line of treatment. SRNS & SDNS is associated with an increased risk of complications due to persistent proteinuria and therapeutic drug side effects. Bacterial infections, malnutrition, hyperlipidemia, hypertension, thromboembolic phenomena, and progression to ESRD usually occur during the course of SRNS & SDNS.⁽²³⁾

Regarding Renal function tests, this study shows a highly significant relationship between the development of hypertension & abnormal renal function test in nephrotic patients. Among 16 patients with elevated blood urea, hypertension was reported in 10 patients (62.5%), while of 14 patients with elevated S. Creatinine, hypertension developed in 9 patients (64.3%), Ishikura et al. found that there is a correlation between renal insufficiency and hypertension⁽²⁴⁾. In contrast to Nahla Al-Ghabban et al. Which reported that abnormal renal function was presented in 8 patients out of 71 patients (11.26%) cases, and only two of them developed hypertension (25%)⁽¹⁴⁾.

In Anochie (Nigeria) study 4 patients from 28 developed HT and renal failure (14.3%)⁽²⁵⁾. Hypertension (HTN) is ubiquitous in renal failure. Renal disease has long been thought to interfere with salt excretion, leading to volume overload and consequent HTN. This theory gives prominence to the kidney in the long-term regulation of BP. Excess salt and water retention are assumed to increase the blood flow to the tissues, which sets the phenomenon of autoregulation in motion. The tissue arterioles vasoconstricts to decrease the excessive blood flow. The resulting

vasoconstriction raises peripheral vascular resistance, the cardinal most consistent finding in hypertension (whether essential or renal) ⁽²⁶⁾.

Regarding Renal biopsy, this study shows a highly significant relationship between the development of hypertension & type of nephrotic syndrome (P value 0.016). Renal biopsy was done for 14 cases only; in 9 cases with MCNS, 5 cases developed HT later (55.6%) & all 3 cases with FSGN developed HT initially (100%), while both 2 cases with MPGN developed hypertension (100%), in Nahla Al-Ghabban et al. renal biopsy was also done for 14 patients only; MCNS was presented in 5 patients, all of them developed HT later on (100%), FSGN was presented in 7 cases, five of them developed hypertension (71.4%) while MPGN was presented in 2 patients, both of them developed HT (100%)(14). These results are higher than reported in the ISKDC study in which hypertension has been reported in up to 21% of children six years and under with biopsy confirmed MCNS and may be present in up to 50% of children with other histologic types ⁽²⁷⁾. These differences may be due to the small numbers of patients who underwent renal biopsy in this study & Nahla Al-Ghabban et al. (only 14 cases in both studies & vs. 512 cases in the ISKDC study).

Regarding the type of treatment, there is a highly significant relationship between the development of hypertension & type of treatment in this study (P value 0.008). HT was found in 21 patients among 82 patients who were treated with steroids only (25.6%), while HT was found in 13 patients among 20 patients who received steroids and 2nd line of therapy (65%); these results are approximately close to the results reported by Nahla Al-Ghabban et al., in which 13 patients out of 58 patients (22.4%) who were treated with steroid alone developed HT later on and 10 cases out of 13 (76.9%) cases who received steroid and calcineurin inhibitors who had no response to steroid alone developed HT (p-value 0.001 significant)(14). Cyclosporine, tacrolimus & steroid may cause hypertension in nephrotic patients treated with these agents. (1) These results were higher than what was reported in the Saudi Arabia study, which recorded that cyclosporine causes HT in only 2 out of 10 patients (20%) ⁽²⁸⁾. These differences may be due to different study samples & numbers in these studies. In Saudi Arabia studies, only 10 cases of SDNS have enrolled the study, while in this study, a total of

102 were enrolled, with a different type of response to steroids, not only the dependent one; the same was applied in Nahla Al-Ghabban et al. study (total no. 71 cases).

In Comparison with the Low & High-Risk Group, HT was reported in 29 cases of a total of 51 cases of CKD (56.9%) in this study, which is nearly similar to what was reported in other literature; HTN in children is rare, with a prevalence of 3%–9%; however, in children with CKD, the prevalence rises to 50% ^(29,30).

In this study, HT was reported in 2 cases only of 102 cases of the normal population (2%) & in 33 cases of a total of 102 cases of nephrotic syndrome (32.3%), so Nephrotic syndrome can be considered be an intermediate risk factor for the development of HT.

Conclusions

Nephrotic syndrome can be considered an intermediate risk factor for the development of HT between normal children & CKD. the incidence of hypertension in CKD in this study is more than 50%, which agrees with lots of literature. In this study, hypertension developed later in nephrotic patients more than it developed at initial presentation. There is no significant correlation between gender, Age at the time of presentation, and family history of renal diseases with development of hypertension in nephrotic patients in this study. Hypertension was reported more in nephrotic patients with a positive family history of hypertension. There was a strong association between the type of Nephrotic syndrome according to response to steroids and relapse with hypertension in nephrotic syndrome. The more relapses and resistant cases, the more chances to develop HT. Hypertension was more prevalent in SRNS and SDNS groups than in the SSNS group. Hypertension also was found to be more in FRNS. The incidence of hypertension was higher in nephrotic patients with elevated blood urea and S. Creatinine than in patients with normal renal function. Hypertension was found to be more in nephrotic patients not responding to steroids only and treated with 2nd line of therapy, including steroid and calcineurin inhibitors.

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