

Factors Associated With Hypertension and Cardiovascular Parameters in Children With Infrequently Relapsing Nephrotic Syndrome

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Objective: To assess the prevalence of hypertension in children with infrequently relapsing nephrotic syndrome (IRNS) and its association with dyslipidemia, and end organ damage including left ventricular hypertrophy (LVH), at relapse and after steroid induced remission.

Methods: Prospective observational study conducted in 83 children aged 1-12 years with IRNS, presenting in relapse. Blood pressure, fundus examination, blood and urine investigations were done at relapse and then at 4 weeks of therapy. Echocardiography at 4 weeks was performed for assessment of LVH and relative wall thickness (RWT) for concentric geometry (CG). **Results:** 27 patients (32.5%) developed hypertension, out of which 21 patients (25.3%) had stage I hypertension. Hypertension in first episode (63.0%, $P<0.01$) and in previous relapses (87.5%, $P<0.001$) was significantly associated with hypertension in the current episode. 12 patients had a positive family history of hypertension, of which 8 (66.7%) were classified under the hypertensive group ($P=0.016$). Concentric geometry (CG) was found in 28% of hypertensive and 5.5% of non-hypertensive children ($P=0.011$). On regression analysis, a lower Up:Uc at the time of relapse was found to have a protective role for development of hypertension. **Conclusion:** One third children with IRNS had hypertension at relapse and a high proportion of hypertensive patients had CG pattern on echocardiography.

Keywords: Blood pressure, Concentric geometry, Echocardiography, End-organ damage.

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Hypertension in children diagnosed with nephrotic syndrome is often multifactorial. It may be attributed to certain intrinsic causes (renal and non-renal) or extrinsic factors (environmental) or both [1]. While some of these contributing factors may cause acute episodic elevations in blood pressure due to fluid shifts, medications, other causes like renal fibrosis and decreased glomerular filtration rate result in a more chronic and sustained hypertension with further progression to chronic kidney disease (CKD) [2]. Childhood hypertension may eventually result in target end organ damage of which left ventricular hypertrophy (LVH) and concentric remodeling (CR) are important. However, the degree of blood pressure elevation that causes target end organ damage and increases cardiovascular risk has still not been established. Children with nephrotic syndrome also have a higher overall risk of an adverse cardiovascular outcome in adult life [3]. This may not only be due to the underlying prolonged hypertension, but also secondary to other

contributory risk factors like dyslipidemia and kidney disease related risk factors.

The primary objective of this study was to assess the prevalence of hypertension in children with infrequently relapsing nephrotic syndrome (IRNS). The secondary objective was to establish the association of hypertension with dyslipidemia, end organ damage including left ventricular hypertrophy at the time of relapse and after steroid induced remission.

Invited Commentary: Pages 435-36

METHODS

We conducted a prospective cohort study at the Pediatric Nephrology Division in a tertiary care public hospital from November, 2018 to April, 2020. Institutional ethical clearance was obtained prior to the study. After taking a written informed consent, children aged 1-12 years, diagnosed with IRNS (irrespective of disease duration)

and off steroids, taking antihypertensive medications for minimum of 3 months were included in the study at the time of relapse. Children with IRNS presenting in shock, secondary causes of nephrotic syndrome, congenital heart disease and secondary causes of hypertension were excluded. A detailed clinical assessment, classification, diagnosis and management of nephrotic syndrome was done as per the standard guidelines of the Indian Society of Pediatric Nephrology [4,5].

The sample size was calculated to be 73 with an estimated prevalence of hypertension in IRNS of 25%, alpha error of 5% and acceptable absolute precision of 10% and 95% confidence interval. Assuming 10% attrition, a total of 83 patients with IRNS were recruited in the study.

Blood pressure (BP) was measured in the right arm of the child placed at the level of the heart, 90 degrees supported, after 3-5 minutes of rest in a quiet room. The Heine Gamma BP apparatus was used and BP measurements were compared with the standard tables. The correct cuff size with the bladder length of 80-100% and a width of at least 40% of the arm circumference with cuff bladder to arm width circumference ratio of 0.45 to 0.55, as recommended was followed. Childhood hypertension was defined as per the updated American Academy of Pediatrics clinical guidelines [6]. An average of three BP readings taken at each visit at a gap of 5-10 minutes was used to classify hypertension. BP was measured during the office visit before starting steroids and then again at 2 weeks and 4 weeks of steroid therapy. Treatment included lifestyle modification and dietary changes for all cases. Pharmacological therapy including angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers (amlodipine) and rarely beta blockers (labetalol) was used depending upon individual cases. Diuretics were used for very few in-patients with resistant edema during albumin infusion and for a very short duration of time. As the patients enrolled were assessed at different time points to classify hypertension, effect of diuretics on the outcome was not included in the analysis. Hypertension was assessed in either one or both parents as per AHA, 2017 guidelines based on either use of antihypertensive drugs, self-reporting of hypertension or high office BP records measured after an average of three readings [7].

Dyslipidemia was diagnosed as any abnormalities in either one or more of the parameters in fasting lipid profile of both children and their parents as per the Indian Society of Pediatric Nephrology (ISPN) and American Association of Clinical Endocrinology (AACE), 2017 guidelines, respectively [8,9]. For dyslipidemia, only lifestyle modification was advised for patients as per the standard guidelines. No pharmacological therapy was initiated.

Investigations including a complete blood count, serum electrolytes, kidney function tests, total protein and albumin, complete lipid profile, urine dipstick and urinary protein to creatinine ratio (Up:Uc) were done at the time of relapse, before starting treatment and then repeated at 4 weeks of therapy. Patients were followed up during the course of treatment and blood pressure and fundus was assessed for any evidence of hypertensive changes at the onset and then at 4 weeks of drug induced remission.

For echocardiographic assessment, a specific procedure for determining the left ventricular mass and the definition of LVH by M-mode and Doppler echocardiography were performed using the Philips 11 HDXE at 4 weeks. LVH was defined as LV mass $>51 \text{ g/m}^{2.7}$ or LV mass $>115 \text{ g}$ per body surface area (BSA) for boys and LV mass $>95 \text{ g/BSA}$ for girls [6]. A LV relative wall thickness $>0.42 \text{ cm}$ indicated concentric geometry/concentric remodeling and LV wall thickness $>1.4 \text{ cm}$ indicated concentric hypertrophy. This study used linear method of LV mass estimation, which uses end-diastolic linear measurements of the interventricular septum (IVSd), LV inferolateral wall thickness and LV internal diameter derived from 2D-guided M-mode or direct 2D echocardiography. This method utilizes the Devereux and Reichek cube formula [11]. Relative wall thickness (RWT) was measured as $(2 \times \text{posterior wall thickness})/(\text{LV internal diameter at the end of diastole})$ [13].

The LV target organ injury measures include LV structure (LV mass and the relationship of LV wall thickness or mass to LV cavity volume). LV structure was stratified into four groups on the basis of LV mass (normal or hypertrophied) and relative LV wall thickness (normal or increased): *i*) Normal geometry: Normal LV mass and wall thickness; *ii*) Concentric geometry: Normal LV mass and increased LV wall thickness; *iii*) Eccentric LVH: Increased LV mass and normal LV wall thickness; and *iv*) Concentric LVH: Both increased LV mass and increased LV wall thickness.

Statistical analysis: Categorical variables are presented in number (%) and continuous variables are presented as mean (SD) and median (IQR). Chi-square test was used to compare qualitative variables and unpaired *t* test/ Mann-Whitney *U* test for quantitative variables. Logistic regression analysis was used to identify the association with hypertension. *AP* value <0.05 was considered significant.

RESULTS

A total of 83 children with IRNS including 53 (69%) males with mean (SD) age of 5.52 (2.27) years, were enrolled in the study and followed up for a period of 4 weeks (**Web Table I**). Forty-six children had the BMI *z* score between

-1SD to +1SD. Two patients were lost to follow up and four became late steroid resistant, one of whom died. Echo-cardiography was done for 80 patients after 4 weeks of steroid therapy by a single cardiologist.

Out of the 83 cases enrolled, 27 (32.5%) children reported hypertension during relapse with 21 (25%) in stage I and 6 (7%) in stage II hypertension. Of these, 8.6% children persisted to have hypertension at 4 weeks of follow-up. In children who developed hypertension, a retrospective analysis of records suggested significant presence of hypertension in the first episode (63.0%, $P<0.001$) and in previous relapses (87.5%, $P<0.001$) (**Table I**). This was significantly associated with hypertension in the current episode as compared to the normotensive group. A family history of hypertension in either/both parents was found in 12 IRNS patients at the time of enrolment with 66.7% ($n=8$) ($P=0.016$) belonging to the hypertensive group (**Table I**).

Echocardiographic evaluation showed two patients in hypertensive group and none in the non-hypertensive group having LVH (**Table II**). Concentric geometry on echocardiography was seen in 7 children with hypertension at relapse and 3 without hypertension ($P=0.011$). One among them turned out to be SRNS at 4 weeks (**Table II**). Subsequently we studied the association of concentric geometry with clinical and laboratory parameters (which were measured at relapse) in 77 IRNS patients and found significant association of hypertension ($P=0.014$) and low serum albumin ($P=0.045$) (**Web Table II**). About 11.1% of the hypertensive patients ($P=0.032$) had retinopathy at relapse (one each in stage 1, 2 and 3) with no new cases during the study period. Ten out of 83 children developed AKI at the time of relapse of which three children progressed to stage 3 AKI. Children in the hypertensive group also had higher risk of AKI at relapse ($P=0.010$) (**Table I**).

Table I Comparison of Characteristics of Children With Infrequently Relapsing Nephrotic Syndrome With and Without Hypertension at Relapse (N=83)

Characteristics	Hypertension		P value
	Present (n=27)	Absent (n=56)	
Age (y) ^a	5.39 (2.10)	5.59 (2.37)	0.770
Gender: Male	19	34	0.391
BMI (kg/m ²) ^a	15.83 (2.02)	16.16 (1.86)	0.333
BMI (SD)			
-3 to -2/-2 to -1/ -1 to median	2/6/5	0/9/14	0.419
Median to 1/1 to 2/ 2 to 3	7/4/3	20/7/6	
Hypertension in first episode	17	11	<0.001
Hypertension in previous relapse	14	17	<0.001
Hypertension in either/both parents	8	4	0.016
Dyslipidemia in either/both parents	6	9	0.549
Anasarca (at relapse)	20	8	<0.001
Systolic blood pressure	114 (7.21)	95.96 (6.57)	<0.001
Diastolic blood pressure	71.19 (7.99)	58.50 (5.48)	<0.001
Total protein (g/dL) ^a	3.34 (0.56)	3.87 (0.55)	<0.001
Serum albumin (g/dL) ^a	1.34 (0.30)	1.62 (0.29)	<0.001
Serum creatinine (mg/dL) ^a	0.38 (0.30)	0.28 (0.12)	0.510
Acute kidney injury	7	3	0.010
Urine protein/creatinine ratio ^a	7.18 (3.81)	4.01 (1.85)	<0.001
Total cholesterol (mg/dL) ^a	419.85 (146.75)	319.93 (90.75)	0.002
Triglycerides (mg/dL) ^a	274.89 (98.54)	211.62 (62.60)	0.002
Low density lipoprotein (mg/dL) ^a	250.93 (139.92)	167.93 (49.11)	0.001
High density lipoprotein (mg/dL) ^a	74.41 (26.70)	62.75 (17.68)	0.068
Hypertensive retinopathy	3	0	0.032

Data presented as numbers or ^amean (SD). IFRNS:infrequently relapsing nephrotic syndrome; TG: triglyceride.

Table II Echocardiographic Parameters at Four Weeks in Children With Infrequently Relapsing Nephrotic Syndrome at Relapse (N=80)

Parameters	Hypertension (AAP, 2017)	
	Present (n=25)	Absent (n=55)
IVSD (mm)	6.28 (1.71)	5.70 (1.06)
LVEDD (mm)	31.58 (5.06)	32.35 (4.35)
PWd (mm)	6.00 (1.37)	5.58 (1.15)
Left ventricular mass (g)	46.76 (26.54)	42.49 (16.39)
LVMI (g/m ²)	62.40 (25.02)	57.47 (15.42)
LVH ^a	2 (8)	0
Relative wall thickness	0.37 (0.10)	0.35 (0.08)
Concentric geometry ^{a,b}	7 (28)	3 (5.4)

Values are mean (SD) or ^ano.(%). ^bP=0.01. IVSD: interventricular septum distance; LVEDD: left ventricular end diastolic diameter; PWd: posterior wall thickness; LVMI: left ventricular mass index; LVH: left ventricular hypertrophy. AAP: American Academy of Pediatrics [6].

Presence of persistent dyslipidemia at 4 weeks, seen in 31/77 (40.2%) children, was associated with a positive family history of dyslipidemia in either of the parents (32.3%, $P=0.009$). These children had significantly higher mean DBP (diastolic blood pressure), higher Up:Uc a lower serum albumin and higher prevalence of hypertension [15/31(48.4%)] which were measured at relapse (**Web Table III**). On regression analysis, a lower Up:Uc at the time of relapse was found to have a protective role towards development of hypertension ($P=0.017$) (**Table III**).

DISCUSSION

We found hypertension in about one-third of our patients with IRNS during relapse. Patients with nephrotic syndrome retain sodium even in a state of normovolemia with a normal plasma albumin indicating an intrinsic renal inability to excrete sodium [14]. In the study by Keshri, et

al, 23% of steroid sensitive nephrotic syndrome (SSNS) reported hypertension during remission and 73.68% had a family history of hypertension [15]. Kontchou, et al. [16] reported hypertension in 65% of SSNS in the first week and 34% after 4 weeks of steroid therapy with a higher overall prevalence (88%) of essential hypertension in family members of the hypertensive nephrotic syndrome cohort. In our study, a lower proportion but persistent hypertension during remission was noted. This difference could be because the earlier studies used lower threshold for defining hypertension (>90th centile) and had a higher prevalence of family history of hypertension. Studies conducted on patients with minimal change disease and focal segmental glomerulosclerosis have also shown higher incidence of hypertension compared to our findings [17]. High values are known to exist among patients with steroid dependent nephrotic syndrome and steroid resistant nephrotic syndrome [18], due to the chronicity of the underlying disease, use of nephrotoxic medications and prolonged use of corticosteroids in these children.

Single center studies from India, have reported incidence between 16-23.7% of AKI in children with nephrotic syndrome [19,22]. We also saw a significant higher overall serum creatinine values from baseline in the hypertensive group during relapse.

An interesting finding in our study was the presence of concentric remodeling (CR) even in the non-hypertensive group (5.5%). We believe this may be attributed to the masked hypertension. Though, studies have documented a high triglyceride to high density lipoprotein ratio as the main predictor of concentric geometry, we noted significantly low serum albumin and hypertension at relapse in our patients with CR as demonstrated by Xu, et al. [20] and Sarkar, et al. [21], in 39.5% and 16.2% among children with primary nephrotic syndrome and FRNS, respectively. Ambulatory blood pressure monitoring (ABPM) may

Table III Univariate and Multivariate Regression Analysis for Factors Associated With Hypertension in Children With Infrequently Relapsing Nephrotic Syndrome

Factors	OR (univariable)	P value	OR (multivariable)	P value
Hypertension in parents	5.67	0.010	7.66	0.101
Total protein	0.14	0.001	0.08	0.003
Serum albumin	0.04	0.001	-	
Urine protein creatinine ratio	1.56	0.001	1.61	0.017
Total cholesterol	1.01	0.001	0.99	0.067
Triglyceride	1.01	0.002	1.02	0.019
Low density lipoprotein	1.01	0.003	1.01	0.112
Any infection	5.14	0.002	-	
Right wall thickness grading at 4wk	0.16	0.012	0.05	0.044

WHAT THIS STUDY ADDS?

- One third of children with infrequently relapsing nephrotic syndrome were hypertensive, 28% of whom had concentric geometry on echocardiography.

enable timely detection of masked hypertension to provide early treatment and avoid end organ damage. Even though no significant association between LVH and hypertension was found in our study, but the results demonstrate that hypertensive children had a greater mean LVMI and RWT as compared to normotensive children. Keshri, et al. [15] reported LVH in 10.5% patients with nephrotic syndrome despite the remission period emphasizing that organ damage in these patients is an ongoing process. As one tenth of the hypertensive children developed hypertensive retinopathy in our study, it emphasizes the role of regular ocular examinations.

Similar to the findings by Merouani, et al. [12,23], persistent dyslipidemia during remission at 4 weeks was also noted in our study in around 40% of patients with a positive family history of dyslipidemia noted in 31.5% of them. Hypertension at relapse, was significantly more seen these patients in compared to non-dyslipidemia group.

On multivariate analysis, Up: Uc ratio was found to have a significant correlation with hypertension at relapse. Previously studies have found family history of hypertension, LDL and total cholesterol to have a strong correlation with hypertension [15].

A lack of age- and sex-matched healthy control population for comparing the prevalence of hypertension, lack of association with total duration of nephrotic syndrome and a short follow up period, may limit the generalizability of findings. Moreover, the 2017 AAP classification [6] defines LV geometry using adult cut off values making it difficult to identify the expected association between left ventricular geometry and hypertension in the paediatric age group.

One third of the children with IRNS had hypertension during relapse, only one-fifth of whom had persistent hypertension after 4 weeks. A higher proportion of hypertensive patients were found to have concentric geometry pattern on echocardiography. Though, hypertension in most children with IRNS is transient, there is a need for early screening of hypertension in such children to identify those with CG.

Contributors: AS: conceptualized and designed the study, coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content; MF: acquisition of entire data, analysis and preparation of the

manuscript, follow up and clinical assessment of all patients; SC: analysis and editing of manuscript and preparation of final draft; AR, DB: performed echocardiography and offered expert cardiology opinion; MY: critically reviewed the manuscript and offered expert inputs while editing the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Note: Additional material related to this study is available with the online version at www.indianpediatrics.net

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Web Table I Baseline Characteristics and clinical parameters in Total Population at Relapse (N=83)

Baseline Characteristics	Mean [#] (SD)/frequency
Age (Years) [#]	5.52 (2.27)
Age (1-5)/ (5-9)/ (9-12) Y	40 /36/7
Gender (Males)	53
Weight (Kg) [#]	18.35 (5.27)
Height (cm) [#]	106.35 (15.16)
BMI (Kg/m2) [#]	16.05 (1.91)
BMI Z Score [#]	0.21 (1.23)
BMI Z Score (SD) -3 to -2 /-2 to -1/-1 to Median	2 / 15/ 19
eGFR (ml/min/1.73m2) [#]	176.54 (77.03)
AKI Absent / Stage 1/ Stage 2/ Stage 3	76 / 1/ 6/ 3
Urine Protein/Creatinine Ratio [#]	5.04 (3.02)
Total Cholesterol (mg/dL) [#]	352.43 (120.71)
Total Cholesterol (≥200 mg/dL)	83
Triglycerides (mg/dL) [#]	232.20 (81.22)
Triglycerides (≥200 mg/dL)	55
Hypertensive Retinopathy Absent/Stage 1/Stage 2/Stage 3	80 / 1 /1 /1

All parameters are represented as number except # which are represented as mean(SD)

Web Table II Association Between RWT Grading (4 Weeks) and Clinical and Laboratory Parameters at relapse in Children With IRNS (n=77)

Parameters	RWT Grading (4 Weeks) Mean [#] (SD) /frequency			P value
	Concentric (n = 9)	Geometry	Normal (n = 68)	
Age (Years)	4.30 (2.00)		5.63 (2.30)	0.063
Male [#]	6		44	1.000
BMI (Kg/m2)	15.44 (2.57)		16.06 (1.77)	0.170
BMI Z Score (SD) [#] (-3 to -2) / (-2 to -1) (-1 to Median)	1 / 2/ 2 [#]		0 / 12/ 17 [#]	0.122
Median to 1 / (1 to 2)/ (2 to 3)	1 / 2/ 1		25 / 7/ 7	
S. Albumin (g/dL)	1.36 (0.30)		1.58 (0.31)	0.045
S. Creatinine (mg/dL)	0.33 (0.23)		0.29 (0.14)	0.994
Urine Protein/Creatinine Ratio	5.89 (3.75)		4.62 (2.67)	0.441
Total Cholesterol (mg/dL)	402.22 (108.69)		333.49 (114.77)	0.060
Triglycerides (mg/dL)	226.89 (69.40)		230.24(83.57)	0.787
LDL (mg/dL)	168.78 (44.31)		191.28 (101.66)	0.800
HDL (mg/dL)	58.78 (10.13)		66.43 (23.03)	0.475
SBP (mmHg)	109.33 (14.90)		99.94 (9.28)	0.072
DBP (mmHg)	67.11 (10.73)		61.29 (7.94)	0.152
Hypertension [#]	6		16	0.014
BP Grading (cenile) [#] (50th-90th) / (90th-95 th) / (>95 th) / (>95 th +12)	2 /1/4/2		48 /4/14/2	0.008

[RWT, relative wall thickness] Significant at p<0.05, 1 are represented as mean (SD), except which are represented as number (%). Among 80 patients whose echo was done at 4 weeks, 3 patients turned out to be SRNS at 4 weeks, hence association of clinical parameters with RWT grading was done in 77 IRNS patients.

Web Table III Association between Persistent Dyslipidemia (4 Weeks) and Laboratory Parameters at relapse in IRNS (n=77)

Parameters (n=77)	Persistent Dyslipidemia (4 Weeks) Mean [#] (SD) /frequency		P value
	Present (n = 31)	Absent (n = 46)	
Total Protein (g/dL)	3.63 (0.64)	3.82 (0.55)	0.138
S. Albumin (g/dL)	1.42 (0.31)	1.64 (0.28)	0.004
S. Creatinine (mg/dL) mean	0.33(0.17)	0.27 (0.13)	0.110
Dyslipidemia in Parent	10	4	0.009
Urine protein/creatinine ratio	6.34(3.67)	3.71 (1.25)	<0.001
Total Cholesterol (mg/dL)	438.74 (114.14)	276.00 (54.44)	<0.001
Triglycerides (mg/dL) mean	285.39 (83.89)	192.41 (54.84)	<0.001
LDL (mg/dL) mean	240.23 (130.15)	153.89 (38.26)	<0.001
HDL (mg/dL)	67.87 (24.61)	63.96 (20.21)	0.633
SBP (mmHg)	103.87 (12.50)	99.13 (8.35)	0.119
DBP (mmHg)	64.77 (10.08)	60.09 (6.60)	0.036
Hypertension	15	7	0.002

. All parameters are represented as mean (SD) except which are represented as number (%).