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Blood Pressure Changes during Initial and Relapsing Episodes in Children with Nephrotic Syndrome: A Comparative Study

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Abstract: Hypertension is an important feature arising from altered homeostasis related to the disease process in nephrotic syndrome. It indicates the disease state and response to therapy as well as dictates the treatment plan.The present study aims to detect changes in diastolic and systolic blood pressure during the initial and relapsing episode of nephrotic syndrome and compare them for future guidance in therapy.This observational, cross-sectional study was conducted between October 2016 and January 2019 with patients attending the pediatric clinic with either initial episode or relapse of nephrotic syndrome. A total of 100 patients with 50 patients in each group were included. The blood pressure was recorded and blood, and urine samplesof each subject analyzed.The present study indicates that though the majority of the patients in both the groups have normal systolic and diastolic pressure, diastolic blood pressure was significantly high in the relapse group. There was alsoa significant reduction in serum albumin and spot protein creatinine ratio in the relapse group.Blood pressure measurement needs to be part of the routine examination of any child attending a nephrology consultation clinic or admitted to the hospital. Children who developed hypertension during treatment or relapse indicate that nephrotic syndrome should be followed up over a long duration. Altered blood pressure may necessitate encouragement for regular follow up in nephrology clinic for early recognition and treatment of long term complications.

Keywords: Nephrotic Syndrome, Blood Pressure, Initial episode, Relapse.

Introduction

Nephrotic syndrome in childhood presents with a variety of symptoms and signs due to altered physiology and complications. There is also alteration of various physiological parameters during disease and treatment. Hypertension is an important feature arising from altered homeostasis related to the disease. It indicates the control of the disease and dictates the treatment plan (Shatat IF *et al.,* 2019),(Koskimies O *et al.,* July 1982).

But there is limited data onalteration of blood pressure in various phases of the disease. The present study aims to detect changes in diastolic and systolic blood pressure during the initial and relapsing episode of nephrotic syndrome and compare them for future guidance in therapy.

Aims and Objectives

The main objective of the study was to observe and compare the diastolic (DBP) and systolic (SBP) blood pressure in patients with the initial and relapse phase of nephrotic syndrome. The study also aimed to find out if there were any significant changes in the other related physiologic parameters like Serum albumin, Creatinine, Urea, Total Cholesterol, Spot Protein creatinine ratio.

METHODOLOGY

This observational, cross-sectional study was conducted between October 2016 and January 2019 at a tertiary healthcare facility and medical college. The study was approved by the Institutional Ethical Board. All the children aged between 1 to 8 years and attending the pediatric clinic with either newly diagnosed or relapsing nephrotic syndrome have been included in this study. Total 100 cases with 50 patients of each group have been observed clinically. The patients were followed up for a period of one year.

The written informed consent was obtained for participation in the study and utilization of data for research from the legal guardian of each patient. Standard ethical guidelines were maintained throughout the study.

The following patients were excluded from the study:

- Cases with any other renal disease.
- Cases with hypertension due to any other pathology.
- Patient with underlying cardiac disease
- 4) Patient with hormonal abnormalities.
- Case suffering from tuberculosis.

Method of data collection:

Weight and height were measured for each child. Systolic and diastolic lood pressure was measured with the same Mercury Sphygmomanometer for all subjects.

The blood sample was collected from the cubital vein and the following parameters were recorded:

Serum albumin, Total protein, Cholesterol, Urea, Creatinine.

Urine was examined for routine and microscopy study (RE/ME), Culture and Sensitivity (C/S), urinary albumin (heat test), spot urine protein/ creatinine ratio (Pr:Cr), 24 hr urinary protein estimation.

Chest X-Ray (Postero-Anterior view) was done in all children.

Statistical Analysis

All data were tabulated and were analyzedwith Graph Pad Prism version 5 Software. Continuous data are expressed as with Mean ± Standard deviation (SD), and comparisons are made using the unpaired t-test. Nominal or ordinal variables were expressed as frequency and percentage (%), and compared using the *Chi*-square (χ^2) test. P-value < 0.05 was considered as significant.

RESULTS

Table 1: Age and gender-wise comparison between the groups

Parameter		Initial episode	Relapse	p/ χ^2
Mean Age (SD)		4.91(1.77)	4.64(1.78)	p=0.458, χ^2=0.006 ,NS
Sex	Male	28	29	p=0.16,
	Female	22	21	χ^2=1.96, NS

NB. SD-Standard Deviation, S-Significant, NS-Not Significant

Both the groups were comparable according to age and gender-wise distribution of cases.

Table 2: Comparison of Blood pressure to episodes

Episode	Initial episode	Relapse	p/R^2(eta Squire)
DBP Mean(SD)	65.96(6.05)	69.28(9.85)	p=0.045,R^2=0.040(S)
SBP Mean(SD)	94.65(6.96)	95.8(10.44)	p=0.52,R2=0.004(NS)

NB. Systolic Blood Pressure-SBP, DBP-Diastolic Blood Pressure, SD-Standard Deviation, S-Significant, NS-Not Significant

In the present study 26.5% of the patient suffering from initial episode of nephrotic syndrome had high SBP (>110mmhg) whereas 26% of the patient with relapse episodes had high SBP. 83.8% of subjects including both groups had normal DBP. 10.2% of the patients from initial episode had high DBP, whereas 22% of the patient suffering from relapse had high DBP.

Though there was no significant difference in SBP between the groups, DBP was significantly higher in the relapse group.

Table 3: Comparison of various parameters after blood and urine sample analysis among the groups

Parameters Mean(SD)	Initial episode	Relapse	R^2 /p
Mean Serum albumin	2.20(0.34)	2.09(0.16)	p=0.041, R2=0.041, (S)
Mean Creatinine	0.37(0.18)	0.38(0.24)	p=0.81, R2=0.005, (NS)
Urea	13.15(1.90)	12.49(1.90)	p=0.085,R2=0.029, NS
Cholesterol	426.86(77.51)	190.3(40.50)	p=<0.0001,R2= 0.78, (S)
Number of Spot Pr:Cr +Ve	2.51(0.24)	1.77(0.34)	p=0.0001, R2=0.61(S)

There was a significant reduction in serum albumin and spot Pr:Cr in the relapse group. Mean spot Pr:Cr in initial episode was 0.24 whereas it was 0.34 in the relapse group.

Normal serum cholesterol levels was observed in 40.4% of test subjects. Statistically significant differences were observed between initial episode and relapse groups with respect to normal cholesterol levels, where no patient in the former group had elevated cholesterol but 80% of the patients with relapse had normal cholesterol levels of <200mg/dl.

59.6% of the study population were having a high (>2) urinary Pr:Cr ratio. 95.9% of the patients with initial episode nephritic syndrome were having a high urinary Pr:Cr ratio, whereas only 24%of the patients with relapse had the same.The difference was statistically significant.

DISCUSSION

Hypertension is present in 13% to 51% of children with nephrotic syndrome. Hypertension has been reported in upto 21% of children of 6 years and under with biopsy-confirmed minimal change nephrotic syndrome and maybe present in upto 50% of children with other histologic types(Nahla I. A l. Gabban *et al.,*2010).·The increased risk of hypertensionlasts many years after remission of the disease and discontinuation of therapy.

The central abnormality in all cases of nephrotic syndrome is the development of massive proteinuria. Due to hypoproteinemia, there is anaccumulation of fluid in the interstitial compartment. This in turn manifests as facial or generalized edema which is the cardinal symptom in children with nephrotic syndrome. (Bagga A *et al.,*2010). Although it is widely accepted that patients with nephrotic syndrome have an excess of total body sodium and water as a result of this compensatory mechanism, the status of their intravascular volume is somewhat controversial(Dias CB *er al.,* 2012).

Hypertension in Nephrotic syndrome: Pathophysiology

There aretwo hypotheses regarding sodium handling and regulation in blood pressure in nephroticsyndrome.In the underfiil hypothesis, hypovolemia secondary to low oncotic pressure and third spacing leads to activation of the renin-angiotensin-aldosterone system (RAAS) and sodium retention.In the overfill hypothesis, RAAS is suppressed and it is believed that the sodium retention is related to an intrinsic renal defect in sodium handling (Ray EC *et al.,*2015),(Haruhara K *et al.,* 2017).

Multiple investigators have examined the role of sodium epithelial channel (ENaC) activation in sodium and water retention in nephrotic syndrome.Activation of ENaC not only enhances the development of edemabut also has implications on blood pressure regulation (Du ZD *et al.,* 2004), (Kontchou LM *et al.,*2009).

Management of hypertension

Treatment of hypertension needs to address the underlying disease pathophysiology and include lifestyle modifications. Blood pressure generally improves with remission of the disease and reduction in proteinuria. When antihypertensive therapy is indicated angiotensin converting enzyme inhibitors (ACE I) or angiotensin II receptor blockers (ARB) remain the first-line agents.

To control the blood pressure to less than 90th percentile of normal low salt diet, exercise and weight reduction in obese patients are recommended. For chronic hypertension, ACEI or ARB are prescribed (Patnaik SK *et al.,*2018), (Kontchou LM *et al.,.,*2009).

Hypertension in Nephrotic syndrome: Implications

Blood pressure should be carefully monitored in nephrotic syndrome children.It can be either low due to intravascular volume depletion or elevated due to neurohumoral response to hypovolemia, intrinsic renal causes, or occasionally renal vein thrombosis. A study by Haas *et al.,* supported the existence of a feed-forward loop between albuminuria and blood pressure. Genetically elevated albuminuria was strongly associated withanincreased risk of hypertension (Haas ME *et al.,* 2018). Kontchou *et al.,* reported improved blood pressure profile in children with minimal change nephrotic syndrome after 4 wks of steroid therapy (Kontchou LM *et al.,* 2009).

Hypertension is common in children with frequently relapsing nephrotic syndrome, particularly those receiving prolonged therapy with corticosteroids and calcineurin inhibitors. Steroids which are first-line treatment for children with MCNS, cause hypertension

utilizing multiple mechanisms such ashyperstimulation of the nonselective receptor for mineral corticoids,an increase in reabsorption of sodium and water, expansion of the blood volume, and then hypertension (Sarkar S, *et al.,* 2017). Careful examination of the abdomen should also be performed to exclude abdominal tenderness or guarding that may be signs of bacterial peritonitis.Extremities should be examined to exclude warmth, tenderness,or pain that may suggest venous thrombosis. Evaluation of a patient with suspected nephrotic syndrome includes history and physical examination,with attention to etiology,prior therapies,edema, blood pressure, anthropometry, and evidence of infections.

The present study indicates that the majority of the patients in both groups have normal systolic and diastolic pressure. An only a small number of patients, 28% and 28.5% population of initial episode and relapse respectively had hypertension (SBP>110mm Hg).The difference in SBP among the groups was not statistically significant. Though a small percentage of the patients, 29% and 28% in initial episode and relapse respectively had high DBP (>70mmhg), statistically significant higher BP was noted in the relapse group. Similarly statistically significantly higher serum cholesterol was noted in the initial episode group. There is a significant reduction in serum albumin and spot Pr: Cr in the relapse group.

CONCLUSIONS

Blood pressure measurement needs to be part of the routine examination of any child attending a nephrology consultation clinic or admitted to the hospital. Children who developed hypertension during treatment or relapse indicate that nephrotic syndrome should be followed up over a long duration. Altered blood pressure may necessitate encouragement and enforcement of patients for regular follow-up in nephrology clinic for early recognition and treatment of long-term complications. A balance between therapeutic effectiveness and avoiding undesirable medical consequences is difficult but needs to be maintained.

Conflict of Interest: None
Financial disclosure: None

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