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Renal Sodium Handling in Children with Nephrotic Syndrome

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ABSTRACT

Background and Objectives: Neprhrotic Syndrome (NS) is a predictable complex with severe, prolonged increase in glomerular permeability for protein leading to hypo-albuminemia. Edema is the other major abnormality; but the underlying mechanism is incompletely resolved. Again during edema formation stage, some of these children express clinical symptoms of hypovolemia, while others do not. The purpose of the study was to identify the NS-children with hypovolemia by measuring the parameters of renal function in respect to their specificity and easy availability.

Methods: We studied renal function in 17 children with NS in full blown nephrosis who had come to the Nephrology-Follow up Clinic or the OPD in Dhaka Shishu (Children) Hospital (DSH) and got admitted into the hospital as nephrotic patients with relapses or 1st episodes. The period of study was July 2001 to December 2001 for total period of 6 months. Findings were related to presence or absence of symptoms suggestive of hypovolemia, and were compared to results of similar studies in the same children in remission.

Results: Nine children presented with hypovolemic symptoms, and 8 without such symptoms. Both groups displayed severe proteinuria, hypo-albuminemia and edema. Twelve (70.5%) children showed higher blood pressure values in comparision to those of remission. Symptomatic patients showed tendency for a low glomerular filtration rate (GFR), and significantly impaired urine dilution, lower urine-sodium (U_{Na}/U_{cr}), decreased fractional sodium excretion (FE_{Na}), and elevated sodium-potassium exchange quotient, $U_K/(U_K+U_{Na})$. In the non-symptomatic patients, these parameters were normal.

Conclusions: Among parameters of renal functions, $U_K/(U_K+U_{Na})$-sodium-potassium exchange quotient was found to be the most specific - higher values in hypovolemic patients and lower in patients with stable edema, and in remission too.

Key words: Nephrotic syndrome, hypovolemia, edema.

ORIGINAL ARTICLE

INTRODUCTION

Massive proteinuria, hypoalbumiema and volume retention or edema formation are the major abnormalities in nephrotic syndrome (NS), but underlying mechanism is incompletely resolved. Primary renal excretion disturbance and secondary sodium retention due to hypovolemia are two much debated mechanisms. Indeed, rather than these two mechanisms being considered mutually exclusive, it is likely that both are involved, although to different extents in an individual patient.[1-4]

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The reduction in serum albumin and serum oncotic pressure which accompany NS would be predicted to alter Starling forces in a direction favoring net flux of fluid across the capillary bed. Despite this alteration, however, fluid tends not to accumulate within the interstitium, because of the activation of a series of defense mechanisms which oppose fluid movement from intravascular space. These edema preventing factors include increased inerstitial hydrostatic pressure, increased interstitial protein mobilization through accelerated lymphatic flow, a parallel decline in plasma and interstitial oncotic pressure, and a decrease in capillary permeability to protein. However, in the setting of ongoing primary renal salt retention and /or continued massive proteinuria, these buffering mechanisms become exhausted and clinically apparent edema may become evident. This occurs because salt retention leads to increase in capillary hydrostatic pressure at the very time defense mechanisms normally employed to prevent edema have been maximized. In the hypoproteinemic patient without salt retention, edema-preventing factors may be sufficient to protect against the development of edema. Thus, edema formation in NS results from the combined effects of primary salt retention coupled with reduced defenses against edema.[5,6]

Clinical data suggest that there are different stages in NS. Patients retain sodium early following onset of proteinuria without significant alteration in plasma albumin and oncotic pressure (incipient NS). During edema formation stage, which is characterized by a progressive increase in body- wt, nephrotics retain sodium. Some of these patients express clinical symptoms suggestive of hypovolemia, while others do not. Eventually the majority of nephrotics reach a steady state proteinuric stage characterized by severe proteinuria, hypoalbuminemia, and no further increase in body wt. In these patients sodium excretion matches intake (sodium balance).[7,8,4,9]

In nephrotic patients with hypovolemia, absolute values of serum albumin (and /or COP) are not discriminative; renin and aldosterone levels -the best indices for such hypovolemia are not readily available in lab. A simple ratio of urinary potassium and sodium, $U_K/(U_K+U_{Na})$-quotient was the best correlation with aldosterone found in studies on NS-children by Van de Walle et al. It was high in children with NS with hypovolemia and low in without hypovolemia group.[3,4,8]

The identification of NS-children with features suggestive of hypovolemia is important in that without such discrimination patients may be administered with volume expanders like albumin etc that may cause hypervolemia and pulmonary edema in children with stable edema.

OBJECTIVES

a) To measure the parameters of renal function and find the pattern of renal sodium handling in nephrotic children in nephrosis and remission.

b) Identification of NS-patients with hypovolemia who retain sodium from those with stable edema with normal sodium handling, and determination of objective laboratory parameters of discrimination in such patients.

SUBJECTS & METHODS

a. Study Design:

A prospective comparative study of NS patients was performed in Dhaka Shishu (Children) Hospital (DSH). The selection of patients was purposive from among the children who had come to the Nephrology-follow up Clinic or the OPD and got admitted into the hospital as nephrotic patients with relapses or 1st episodes. The period of study was July 2001 to December 2001 for total period of 6 months.

The same children were again studied when they went into remission (Control).

b. Patients selection criteria:

1. Patients with urinary proteins 3+(in heat coagulation test/dipsticks test) for 3 consecutive days with edema, and plasma protein level less than 25g/L were included.

2. Urinary protein: creatinine (P/C)-ratio more than 3 were also considered as significant proteinuria.
3. Patients were not receiving diuretics nor steroids.
4. They were not on any salt or water restrictions and were instructed to continue the regular diet until the proposed tests were performed and samples were obtained.
5. Biopsy documentation for diagnosis or classification was not deemed necessary.
6. Patients with renal function impairment (serum creatinine more than 100 micromol/L) and/or clinically very sick patients were not included for study.
7. Informed consents of the parents were taken.

c. Protocol:

1. A standard clinical examination was performed on all the patients, considered nephrotic according to the selection criteria.
2. The patients were examined for presence or absence of "hypovolemic"-symptoms, the laterbeing defined as (any combination of) oliguria, abdominal pain, diarrhoea, vomiting, dizziness, tachycardia, cold limbs, and peripheral vasoconstriction.
3. Experiments described below were performed after hospital admission. Similar experiments were done in the same subjects during the remission and before their discharge.

Urine voided after admission and overnight recumbency was analysed for protein, and urea, creatinine and electrolytes and before the actual test, usually perfomed within 24 h of admission. Proteinura was corrected for creatinine excretion (mg/mg). A level of 3 corresponds with the accepted level for nephrotic proteinuria. Blood was sampled for urea, creatinine, electrolytes, total protein and albumin etc.

Subsequently a fully supervised "water diuresis-protocol" was followed and a water load was given (25 ml/kg) orally within 30 min. During the next hour urine collection was made- while a maximal urine dilution was maintained with an infusion of hypotonic saline (0.225% NaCl in 5% dextrose) at a rate of 20mL/min/1.73m^2. Blood samples were taken at the end of the test.[6] During the test procedure the patients were frequently assessed with monitoring of vital signs and auscultation of heart and lungs.

Blood and urine samples were analyzed for urea, creatinine, sodium, potassium, total protein and albumin.

GFR (mL/min/1.73m^2), urine osmolality (mosm/kg), U_{Na}/U_{creat}(mmol/mmol), FE_{Na}% and $U_K/(U_K+U_{Na})$-ratio were calculated.

d. Analytical technique:

Urea, creatinine, sodium and potassium were measured by auto-analyser in DSH lab. The GFR ((38xht in cm)/ plasma creatinine in micromole/l) and osmolality, (2(Na+K)+urea+ glucose in mmol/l) were calculated from standard formulae. Either Spot samples or urine collected over variable time were used.

e. Calculations and statistics:

Data were obtained as means±SD. Statistical analyses of variance between groups were assessed by means of Independent Sample t-Test for equality of means.

RESULTS

A total of 17 patients were studied; 10 of them were boys (59%) and 7 were girls (41%). Their mean age was 5.8±3.0 yrs (range 2.8-12). Body wt. during nephrosis was 18.6±7.1 kg and estimated edema averaged 3.2±1.4 kg. All displayed heavy proteinuria (P/C ratio ranged 3-18.5), and hypoalbuminemia with a mean of 11.1±1.4 g/L. Twelve of the patients had multiple relapses.

Again 9 patients showed features of hypovolemia and 8 patients presented with no symptomatic hypovolemia; 10 patients presented with accumulating edema that is they showed increment of their weight after admission, and 7

patients were with stable edema that is they did not gain weight further and after a variable period lost it in remission.

Twelve (70.5%) patients showed higher blood pressure values either systolic or diastolic or both in nephrosis when compared to those of remission (Table I).

TABLE I. Values of BP's (mm Hg) of patients

Patient Nos	1*	2*	3*	4	5	6*	7*	8*	9
Nephrosis Group	90/60	90/70	120/90	95/60	110/70	100/70	100/75	100/60	100/60
Remission Group	90/67	100/80	95/70	100/75	100/70	95/65	100/70	110/80	110/70

Patient Nos	10	11	12*	13	14*	15*	16	17
Nephrosis Group	130/70	90/70	100/70	100/75	95/65	95/65	110/70	110/80
Remission Group	110/60	90/60	90/60	100/70	90/60	90/60	100/70	100/70

**symptomatic hypovolemia*

The background characteristics are shown in Table II.

TABLE II. Baseline characteristics of the study Patients

Variables	Hypovolemia (n=9) (mean±SD)	No hypovolemia (n=8) (mean±SD)
Age (yrs)	5.7±2.8	5.6±3.4
Male/Female	4/5	6/2
Nephrotic Wt (kg)	18.1±6.3	19.1±7.9
Remission Wt (kg)	14.2±5.3	16.2±6.9
Edema fluid (kg)	3.6±1.4	2.8±1.3
P/C ratio	7.5±5.0	8.1±5.0
Plasma albumin(g/L)	11.3±1.4	11.0±1.5

(a) Patients with hypovolemic symptoms during nephrosis: The study data are presented in Table IIIa below:

TABLE IIIa. Renal sodium handling in NS children with Hypovolemia during nephrosis and remission

Variables	Nephrosis	Remission	p-values
^1GFR	54.0±10.1	73.8±21.1	0.019
^2GFR	66.8±12.2	77.7±24.7	0.25
$^1U_{OSM}$	407.3±298.8	256.48±2.3	0.25
$^2U_{OSM}$	149.0+ 88.3	128.7±31.7	0.44
$^1U_{Na}/U_{cr}$	6.31±0.6	43.2±28.8	0.00
$^2U_{Na}/U_{cr}$	5.1±4.0	38.91±5.3	0.00
$^1FE_{Na}$	0.2±0.2	1.7±1.1	0.08
$^2FE_{Na}$	0.3±0.3	2.0±0.6	0.00
$^1U_k/U_k+U_{Na}$	0.6±0.1	0.1±0.1	0.00
$^2U_k/U_k+U_{Na}$	0.5±0.1	0.1±0.1	0.00

Note: *^{1}before water load; ^{2}after water load. GFR-glomerular filtration rate (ml/min/1.73m^2), U_{OSM}-urinary osmolality in mOsm/kg, FE_{Na}-fractional excretion of sodium %; abbreviations are used in table III a, b & c.*

(b) Patients without hypovolemic symptoms during nephrosis: The study data are in table IIIb below:

TABLE IIIb. Renal sodium handling in NS children without Hypovolemia during nephrosis and remission

Variables	Nephrosis	Remission	p-values
^1GFR	56.91±1.8	62.01±1.9	0.40
^2GFR	72.81±7.2	65.81±1.4	0.35
$^1U_{OSM}$	272.2±95.7	250.3±78.6	0.62
$^2U_{OSM}$	124.29±5.7	129.9±33.5	0.62
$^1U_{Na}/U_{cr}$	20.3±20.3	37.82±1.5	0.11
$^2U_{Na}/U_{cr}$	27.8±30.2	32.5±12.6	0.68
$^1FE_{Na}$	1.1±1.2	1.7±0.8	0.29
$^2FE_{Na}$	1.1±1.2	1.5±0.5	0.41
$^1U_k/U_k+U_{Na}$	0.3±0.2	0.2±0.1	0.25
$^2U_k/U_k+U_{Na}$	0.3±0.2	0.2±0.1	0.48

(c) NS Patients, with and without hypovolemic symptoms: The study data are in table IIIc below:

TABLE IIIc. Renal sodium handling in NS children with or without Hypovolemia during nephrosis

Variables	Nephrosis w hypovolemia	hypovolemia Nephrosis w-out hypovolemia	p-values
^1GFR	54.0±10.1	56.9±11.8	0.58
^2GFR	66.8±12.2	72.8±17.2	0.41
$^1U\text{-}_{OSM}$	407.3±298.8	272.2±95.7	0.24
$^2U\text{-}_{OSM}$	149.0±88.3	124.2±95.7	0.45
$^1U_{Na}/U_{cr}$	6.3±10.6	20.3±20.3	0.09
$^2U_{Na}/U_{cr}$	5.1±4.0	27.8±30.2	0.04
$^1FE_{Na}$	0.2+0.2	1.1±1.2	0.04
$^2FE_{Na}$	0.3±0.3	1.1±1.2	0.06
$^1U_k/U_k+U_{Na}$	0.6±0.1	0.3±0.2	0.01
$^2U_k/U_k+U_{Na}$	0.5±0.1	0.3±0.2	0.06

DISCUSSION

In NS, not only there is glomerular disorder but also there is tubular dysfunction.[4] Probably both mechanisms operate simultaneously to a variable extent, but it is hard to discriminate within individuals that sodium retention is due to hypovolemia, or primary renal sodium retention.[1,2,3,4,8,9] Water diuresis caused a theoretical body fluid dilution of about 6% in 1 h with minimal NaCl-expansion.[8] In our study, all the children were steroid responsive NS (SRNS); without biopsy documentation and differentiation. For unclear reasons there was a predilection for girls to present with hypovolemic symptoms. Age, severity of proteinuria and hypoalbuminemia and edema were not different (Table-II).

Remarkable distinction could be made between the children presenting with symptoms suggestive of hypovlemia and those without. Only the former group showed avid sodium retention, low GFR and distal tubular increased Na-K exchange. Importantly these differences were largely confirmed by paired comparison with data obtained in remission (Table-IIIa & IIIb). Our findings are consistent with those with Van de Walle et al[4,8] and Bohlin and Berg.[10] GFR during water diuresis showed clear difference in hypovolemic group, but failed to reach the level of significance. Probable reasons of difference in this respect may be-sampling on cases soon after remission rather than after 1-4 month in remission in other studies.[4,8] Again, we calculated GFR from formulae based on anthropometry, rather than with inulin clearance or endogenous creatinine clearance.

Besides, we found changes in osmolality relatively higher in nephrosis with hypovolemia-group than in remission. Similar changes were seen within nephrosis group (Table-IIIc). But no such difference was seen in nephrosis without hypovolemia and remission. The values before water loading is obviously higher than after load samples, showing concentrating and diluting capability of kidneys intact. Limitation of our study was that we did not use an osmometer for measuring osmolality, instead we calculated out the value from the formula: Osmolality in mOsm/kg=2x(Na+K)+ urea+glucose in mmol/L.

U_{Na}/U_{Cr}-ratio and FE_{Na}% values were also significantly lower in NS with hypovlemia group-both before and during water diuresis in comparison to those in remission. There were no significant changes observed in NS without hypovolemia group. These values are lower in NS with hypovolemia group in comparison to no-hypovolemia group, but were just short of significance.

Those patients with symptoms of hypovolemia also showed stimulated distal tubule Na-K exchange, indicated by $U_K/(U_K+U_{Na})$-ratio.[4,8] A higher $U_K/(U_K+U_{Na})$-quotient was associated with symptoms of hypovolemia and a significantly lower value was found in chronic stable edema and in remission of NS. This quotient was significantly discriminative in basal state within nephrosis-group (but just lost it after water load) (Table-IIIc).

Van de Walle, et al. found suppressed fractional excretion of lithium (FELi) and fractional excretion of water (FEH_2O)-both considered qualitative markers of proximal tubule sodium reabsorption and suggested increased sodium reabsrption in the sodium retaining patients was not limited to a single nephron segment, but rather a generalized activity.[8]

Clinically BP was not low in these patients. In line with parameters of renal function suggestive of avid sodium retention it can be concluded that homeostatic drive to maintain circulating volume was very strong. The findings by Van de Walle, et al. of increased sodium reabsorption in different nephron levels and, of elevated plasma levels of renin and aldosterone support the notion of decreased circulating volume.[4,8] But Tulassay and Rascher found positive relation between plasma atrial natriuretic peptide (ANP) and sodium excretion in children with nephrosis[1,2] and Bohlin and Berg did not find such a relation of aldosterone in edema forming children in their study and suggested to some intrarenal mechanism.[10]

Then, we can explain the edema of NS in chronic stable condition without an evidence of active sodium retention by a primary renal sodium excretion defect. Van de Walle et al found a filtration impairment of persistent low filtration fraction. Other studies found impaired response to ANP[8] and high atrial vasopressin (AVP) etc.[1,2]

We also found $U_K/(U_K+U_{Na})$-ratio of either the pre load and post load samples discriminatory (Tables-III a, b & c).

CONCLUSION AND IMPLICATION

Identification of nephrotic children with hypovolemia from those without hypovolemia is important. Absolute values of serum albumin (and so of COP) are not discriminative. Protein excretion was not different, too. Cameron suggested this condition as a hyperacute condition resulting in a temporary disequilibrium in intravascular and interstitial protein pools.[1] Renin and aldosterone, the best indices of such hypovolemia, are not readily available in lab. That of all parameters the best correlation with aldosterone was found for simple $U_K/(U_K+U_{Na})$-ratio, an indicator of aldosterone stimulated distal Na-K exchange. It was high in hypovolemia, and low in stable edema. Other parameters of renal sodium handling e.g. GFR, U_{Na}/U_{cr}, FE_{Na}% etc may be helpful, but rarely available.[3,4,8]

Therefore 1) $U_K/(U_K+U_{Na})$-quotient could be used as discriminatory of hypovolemia in nephrotic relapse along with careful clinical assessment. Thus the use of volume expanders like albumin or edema fluid remover like diuretics could be rationalized without risks of extra hazards for development of hypervolemia or hypovolemia in NS patients.[3,4,8,9,11] 2) Albumin or plasma perfusion in chronic stable edema of NS with a low $U_K/(U_K+U_{Na})$-ratio can be hazardous and should be avoided. In fact they are candidates for use of diuretics, ACE-inhibitors, PG-inhibitors and even Cyclosporine-A.[3] 3) Cost of salt poor injectable 20% Human albumin 50 ml vial prepared in a European country is about $30 in the market of Dhaka. So if infusion of albumin can be rationalized, cost of management of a nephrotic relapse will definitely come down. This interesting issue should be evaluated in still larger number of nephrotic children.

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