Original Research Article

Sodium retention and intravascular volume status in childhood nephrotic syndrome

Title: Sodium retention and intravascular volume status in childhood Nephrotic Syndrome

Abstract:

Introduction: Overfill and underfill hypotheses have been posited to explain the development of sodium retention in children with nephrotic syndrome (NS). The clinical assessment of intravascular volume status during the oedematous phase of NS in children is challenging. We aimed to study the intravascular volume status in nephrotic children using urinary electrolyte indices and echocardiographic (echo) measurements of inferior vena cava (IVC) collapsibility and Aortic (Ao) diameter.

Methods: Prospective observational study. Twenty nephrotic children with oedema and ascites and not on any medications were enrolled. The intravascular volume status was assessed using urinary electrolyte indices [Fractional excretion of sodium (FeNa) and Urinary potassium index (UKI)] and echo IVC collapsibility index (IVCI) and ratio of IVC and Ao diameters (IVC/Ao). FeNa ≤1% with UKI <60% indicated primary sodium retention and with UKI >60% suggested secondary sodium retention due to intravascular hypovolemia.

Results: Out of 20 nephrotic children, 16 showed urinary sodium retention (FeNa ≤1%). Two out of these 16 children also had high UKI (>60%) indicative of secondary sodium retention. In the remaining 14 children out of 16, UKI was <60% indicative of primary sodium retention. None of the subjects had IVCI in hypovolemic range. Three subjects had IVC/Ao ratio in hypovolemic range and two of these had urinary indices indicative of secondary sodium retention due to hypovolemia.

Conclusion: Echocardiographic measurement of IVC/Ao ratio is useful for assessment of intravscaular volume status in children with nephrotic syndrome with oedema and ascites. Sodium retention during oedematous phase of NS in children is

mainly due to primary sodium retention and is not associated with intravascular hypovolemia.

Introduction

Nephrotic syndrome (NS), a common renal disorder in children, is characterised by hypoalbuminaemia (serum albumin ≤ 2.5gm/dl), nephrotic range proteinuria (>40mg/m^2 body surface area/hr) and oedema. Oedema is the symptom, most commonly requiring intervention. After confirmation of diagnosis, these patients are routinely managed with steroids and diuretics.

Two main hypotheses have been posited to explain the development of sodium retention in nephrotic syndrome. A common explanation is underfill theory which states that the hypoalbuminaemia reduces the plasma oncotic pressure and causes fluid shift, resulting in intravascular hypovolemia and activating the Renin Angiotensin Aldosterone System (RAAS). Activation of RAAS leads to increased

sodium and water retention (secondary sodium retention) [1]. The second possible mechanism suggested is overfill theory which states that the proteinuria leads to intrinsic activation of Na-K- ATPase in the cortical collecting ducts of the nephrotic kidneys leading to sodium retention (primary sodium retention) [2-6]. The sodium retention in turn causes intravascular volume expansion and transudation of fluid into interstitial spaces (overfill theory) and there is no role of RAAS activation. Based on these hypotheses, it is suggested that the oedema in nephrotic syndrome is associated with variable intravascular volume status i.e. hypovolemia or hypervolemia.

It is clinically difficult to assess the intravascular volume status during the oedematous phase of NS in children. This poses a therapeutic challenge when taking the decision about the use of diuretics or albumin infusion to control the oedema. If the child is in hypovolemic state, diuretic use may lead to further intravascular hypovolemia, shock and acute kidney injury and albumin infusion may lead to development of intravascular fluid overload and pulmonary oedema in these nephrotic children.

Nephrotic children with intravascular hypovolemia are expected to have higher renin, aldosterone, and anti-diuretic hormone (ADH) concentration as compared to normovolemic/hypervolemic group. However measurement of these hormones levels cannot be used for routine clinical decision making due to prohibitive cost and availability. Urinary electrolyte indices [Fractional excretion of Sodium (FeNa) and Urinary Potassium Index (UKI)] have been suggested as surrogate markers of intravascular volume status [7-9]. UKI is considered as a marker of aldosterone activity. In hypovolemic state, sodium excretion will be low while potassium excretion will be high due to secondary hyperaldosteronism while in primary sodium

retention, low urinary sodium excretion will not be associated with increased urinary potassium excretion.

The echocardiographic assessment of Inferior Vena Cava (IVC) size, its variation with phases of respiration measured as IVC collapsibility index (IVCI), ratio of Inferior Vena Cava and Aorta (Ao) diameters (IVC/Ao index) have been used as markers of intravascular volume status in dehydrated and critically ill children [10,11].

In this prospective observational study, we used urinary electrolyte indices and echocardiographic measures to determine the intravascular volume status during oedematous phase of nephrotic syndrome in children. The aim of the study was to understand the pathophysiology of fluid retention and intravascular volume status during oedematous phase of childhood nephrotic syndrome using routinely available tests and measurements. The findings from the study will also help in bedside decision making regarding use of diuretics and/or albumin infusion for mangement of oedema in nephrotic children.

Methods

This prospective observational study was conducted in a tertiary care hospital on nephrotic children aged 2-12 years, who presented with oedema and ascites during first episode or in relapse. The standard criteria was used for diagnosing nephrotic syndrome (Nephrotic range proteinuria i.e. urine dipstix for proteins 3-4+ for 3 consecutive morning samples or spot urinary protein creatinine ratio >3, serum albumin cut off as <2.5gm/dl and oedema). The study subjects with following associated conditions, which can affect the intravascular volume or urinary electrolytes excretion, were excluded from the study:

a) Secondary nephrotic syndrome
b) Use of drugs like diuretics, antihypertensives, ACE inhibitors, steroids
c) Dehydration/dyselectrolytemia/shock due to causes like gastroenteritis, sepsis, subacute bacterial peritonitis.
d) Deranged renal function (BUN and serum creatinine levels abnormal as per age based cut offs).
e) Hypertension
f) Known endocrinal disorders affecting urine electrolyte levels.

The study protocol was approved by the institutional ethics committee. The informed written assent and consent were obtained from the study subjects and their parents respectively, prior to enrolment. All children presenting with first episode of nephrotic syndrome underwent detailed evaluation to rule out secondary nephrotic syndrome. All study subjects were evaluated for clinical markers of intravascular volume status by measuring their pulse rate, Blood pressure (supine and lying positions for orthostatic hypotension), pulse volume, capillary filling time (CFT). Blood and urine samples were collected at the time of admission and before starting any medications for estimation of Fractional excretion of sodium (FeNa) and Urine potassium index (UKI) which were calculated as below:

$$\text{FeNa}(\%) = \frac{\text{Serum Creatinine} \times \text{Urine Sodium}}{\text{Urine Creatinine} \times \text{Serum Sodium}} \times 100$$

$$\text{UKI}(\%) = \frac{\text{Urine Potassium}}{(\text{Urine sodium} + \text{Urine Potassium})} \times 100$$

Based on data from previous studies FeNa ≤1% and urine potassium index >60% was taken as the marker of secondary sodium retention due to intravascular

hypovolemia whereas FeNa ≤1% and Urine potassium index <60% was taken as a marker of primary sodium retention [7,9].

The echo assessment of intravascular volume was done on the same day of admission, before starting on medications and was done by the same pediatric cardiologist for each subject using Epiq 7 Philips echocardiography machine. Inferior vena cava (IVC) and aorta (Ao) diameters were measured at the level of diaphragm using M-Mode. IVC diameter was recorded during inspiratory and expiratory phases of respiration [11-13]. Three readings were taken of each measurement and maximum value out of the three readings was taken for calculation of following indices:

IVC collapsibility index (IVCI) (%):

$$\frac{\text{IVC diameter during expiration - IVC diameter during inspiration}}{\text{IVC diameter during expiration}} \times 100$$

IVC/Aorta index (IVC/Ao):

$$\frac{\text{IVC diameter during expiration (maximum value)}}{\text{Aorta diameter (maximum value)}}$$

IVCI >80% and IVC/Aorta index <0.8 were taken as markers of intravascular hypovolemia. IVCI <20% and IVC/Aorta index >1.2 were taken as markers of hypervolemia.

Results

Total 32 children were evaluated during the study period, out of which only 20 children meeting the inclusion and exclusion criteria were enrolled as study subjects. Baseline clinical profile of the study subjects is depicted in table 1. Five of these 20 subjects presented with first episode of NS while remaining 15 presented

with relapse. None of the study subjects had clinical features of hypovolemia at the time of enrolment into the study.

Sixteen children had FeNa <1% (Table 2). Two out of these 16 children with low FeNa also had UKI >60% indicative of secondary sodium retention. In the remaining 14 children out of 16 children with FeNa <1%, UKI was <60% suggestive of primary sodium retention by the renal tubules.

Based on echo IVC collapsibility index, none of the subjects had hypovolemia. Three subjects had IVC/Ao ratio in hypovolemic range (<0.8) (Table 3).

Out of the 03 subjects with IVC/Ao ratio in hypovolemic range, two had features of secondary sodium retention based on urinary indices (FeNa<1% and UKI>60%) (Table 4).

Discussion and conclusions

In this study, we assessed the intravascular volume status during oedmatous phase of nephrotic syndrome in 20 children using urinary indices and echo measurements of IVC and aorta with an aim to understand the pathophysiology of oedema in nephrotic syndrome.

Sixteen out of these 20 nephrotic children showed features of sodium retention (FeNa<1%). Fourteen of these 16 children also had associated low UKI indicating primary sodium retention whereas remaining two had high UKI suggesting secondary sodium retention due to hypovolemia. On echo assessment, none of the children had hypovolemia based on IVCI while three had IVC/Ao ratio in hypovolemic range. Two out of these three children with IVC/Ao in hypovolemic range had urinary indices commensurate with hypovolemia (secondary sodium retention). These findings indicate that most of the nephrotic children in our study

were in normovolemic or hypervolemic state with urinary indices showing primary sodium retention and thus support primary sodium retention as the cause of oedema in nephrotic syndrome (overfill theory) rather than secondary sodium retention due to decrease in intravascular volume because of low oncotic pressure (underfill theory).

In a cross sectional study on 134 children with idiopathic nephrotic syndrome categorized into steroid responsive and steroid non responsive, Iyenger et al. found that the FeNa was significantly lower during relapse than in remission [14]. The values of FeNa and UKI were similar across various categories of nephrotic syndrome. Using a cut off of FeNa and UKI as 0.5 and 60%, respectively, they found that 50% of steroid responsive children and 36% of steroid non responders had primary sodium retention (UKI <60% along with low FeNa). The lower percentage of primary sodium retention in this study as compared to our study is likely to be due to use of lower cut off of FeNa (0.5%) to define urinary sodium retention.

In nephrotic patients, Donckerwolcke et al. noticed sodium retention at the onset of the proteinuria with urine indices revealing low average FeNa (0.2%) and UKI (<60%) [6]. They reported that in patients with sodium retention (FeNa <0.5%), UKI was often higher than 60% and there was better correlation between log aldosterone and UKI than with other parameters measuring renal potassium handling such as transtubular potassium gradient, fractional excretion of potassium. In patients with renal sodium retention [(FeNa)% less than 0.5], Urine(K+)/Urine(Na+) + Urine(K+) ratio higher than 0.60 identified patients with increased aldosterone levels indicating functional hypovolemia.

Vande Walle et al demonstrated that in majority of children in early relapse of NS, sodium retention was due to the intrarenal mechanism favouring primary sodium retention rather than due to hyperaldosteronism [8].

In a recent study, Werner Keenswijk et al prospectively studied the UKI as an indicator of hypovolemia in children with nephrotic syndrome [9]. They studied 44 nephrotic children and compared different parameters to a control group (36 children). They measured the renal perfusion, vaso-active hormones and urinary sodium and potassium. Subjects were grouped into low, normal, and high GFR groups. In the low GFR group, statistically significant lower renal plasma flow, higher UKI and non significant higher plasma renin activity and aldosterone were noted. The study concluded that nephrotic syndrome patients with decreased GFR, apparently related to hypovolemia can be detected by high UKI (>0.5–0.6) and these patients may benefit from albumin infusion.

Several experimental studies also support the intrinsic sodium absorption by renal tubules in nephrotic kidneys. Ichikawa et al. using unilateral puromycin aminonucleoside (PAN) infusion in rats created a nephrosis model such that one kidney was nephrotic and the other functioned normally [3]. They noticed that nephrotic kidney showed proteinuria and sodium retention, the contralateral normal kidney had no proteinuria and handled sodium normally as in control rats. An increased expression of epithelial sodium channel (ENaC) and Na/KATPase activity in cortical collecting duct of PAN model of nephrotic syndrome has been demonstrated in various studies [15-17].

Based on Echocardiographic measurements, none of our study subjects had hypovolemia as per IVC collapsibility index whereas 3 subjects had IVC/Ao index in

hypovolemic range. Two of these three children with IVC/Ao ratio in hypovolemic range also had urinary indices suggestive of hypovolemia. This indicates that in oedematous nephrotic children with ascites, IVC/Ao ratio is a better marker of intravascular volume status as compared to IVCI. Geers et al. estimated plasma volume in 88 adult patients with nephrotic syndrome using radioactive albumin and demonstrated that only 2% of the cohort had a low plasma volume [18]. There is no data on intravascular volume status assessment using echocardiographic indices in nephrotic children. Most of the studies on usefulness of echocardiographic indices to assess intravascular volume status have been done in critically ill children in ICU setting for assessment of dehydration or fluid replacement therapy [12,13]. Levine et al studied the role of IVCI and aorta/IVC ratio in assessment of degree of dehydration in children with diarrhea and vomiting. They reported IVC/Ao ratio better than IVCI for detecting severe dehydration with a sensitivity of 93% and specificity of 59% at its best cut off [13]. Y.Kim et al noted that IVC and aorta diameters differ with age, weight, height, body surface area and as the cut off values for these diameters for children are not yet established so IVC/Ao ratio was suggested as a novel parameter for volume assessment and was used in their study as an objective method of evaluating pediatric dehydration [19].

The difference in intravascular volume status assessment between the two echocardiographic parameters could be because of the effects of the intra abdominal pressure on the IVC due to ascites during the oedematous phase of nephrotic syndrome. Being a vein with thin walls, the variability in IVCI is decreased by raised intra abdominal pressure, however a small change in IVC size gets highlighted when it is compared with aorta which being a muscular walled structure with higher mean arterial pressure, is not much affected by raised intra abdominal

pressure. Study on assessment of CVP using USG in children admitted to PICU also found better sensitivity of IVC/Ao ratio in detecting low CVP as compared to IVCI [20].

Strengths of our study are that all the investigations and echocardiographic measurements were performed before the subjects were started on any medication. Echocardiographic measurements were performed by the same pediatric cardiologist and he was blinded to urinary indices values and clinical findings of intravascular volume status. This reduced the bias in echocardiographic measurements. Our study has few limitations. Firstly, the study was done on a small group of subjects. A larger sample size needs to be studied further to generate more robust evidence. Secondly, we didn't take into account the fluid and sodium intake of the subjects prior to measurements which could have affected the urine indices as the parents of the children with relapse of nephrotic syndrome might have restricted intake based on their prior experience or advice given to them. Thirdly, none of the study subjects had clinical features of hypovolemia so we could not substantiate the findings with clinical hypovolemia.

Based on the urinary indices and echocardiographic assessments in our study, majority of children with nephrotic syndrome had primary sodium retention and this was not associated with intravascular hypovolemia. The findings from our study support the overfill theory of oedema and ascites in nephrotic syndrome. Urinary indices and echocardiographic measure of IVC/Ao ratio can be used as markers of intravascular volume status before starting diuretic or albumin infusion for management of oedema in children with nephrotic syndrome.

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Table 1: Clinical profile of study subjects (n=20)

Variable	Value
Age (Years) Median (range)	6 (2-12)
Sex (n) Female Male	 08 12
Nephrotic syndrome episode (n) First episode Relapse	 05 15
Weight (Kg) Mean±SD	23.3±6.4
Children with hypotension Systolic Diastolic Orthostastic	 Nil Nil Nil
Signs of poor peripheral perfusion (n) Cold extremities [a]CFT > 3sec	 Nil Nil
Urine protein concentration (mg/dl) (mean±SD)	810±646
Serum Cholesterol (mg/dl) (mean±SD)	339±145
Serum Albumin (gm/dl) (mean±SD)	1.6±0.4

[a]CFT- Capillary Filling Time

Table 2: Urine indices in the study subjects during the oedematous phase of nephrotic syndrome

Parameters	Number (N=20)
[a]FeNa≤1%	16
Primary sodium retention (Low FeNa + Normal/Low [b]UKI)	14
Secondary sodium retention (Low FeNa + High UKI)	02

[a]FeNa-Fractional excretion of Sodium; [b]UKI-Urine Potassium Index

Table 3: Echocardiographic assessment of intravascular volume status

Parameter	Number of children (N=20)
[a]IVCI, n • <20% (Hypervolemia) • 20-80%(Normovolemia) • >80% (Hypovolemia)	 8 12 0
[b]IVC/Ao ratio, n • >1.2 (Hypervolemia) • 0.8-1.2 (Normovolemia) • <0.8 (Hypovolemia)	 2 16 3

[a]IVCI- Inferior Vena Cava Collapsibility Index; [b]IVC/Ao- Inferior vena cava/Aorta

Table 4: Urinary indices along with echocardiographic measures in children (n=16) with sodium retention (FeNa<1%)

Urinary indices	IVC Collapsibility index		IVC/Ao ratio	
	Normal or Hypervolemia	Hypovolemia	Normal or Hypervolemia	Hypovolemia
Primary sodium retention ([a]FeNa<1% & [b]UKI< 60%)	14	NIL	13	01
Secondary sodium retention (FeNa>1% &UKI>60%)	2	NIL	0	02

[a]FeNa- Fractional excretion of sodium; [b]UKI- Urine potassium index