

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 $\leq 1\%$ with UKI $< 60\%$ indicated primary sodium retention and with UKI $> 60\%$ suggested secondary sodium retention due to intravascular hypovolemia.

26 Results: Out of 20 nephrotic children, 16 showed urinary sodium
27 retention ($\text{FeNa} \leq 1\%$). Two out of these 16 children also had high UKI
28 ($>60\%$) indicative of secondary sodium retention. In the remaining 14
29 children out of 16, UKI was $<60\%$ indicative of primary sodium
30 retention. None of the subjects had IVCI in hypovolemic range. Three
31 subjects had IVC/Ao ratio in hypovolemic range and two of these had
32 urinary indices indicative of secondary sodium retention due to
33 hypovolemia.

34 Conclusion: Echocardiographic measurement of IVC/Ao ratio is useful
35 for assessment of intravascular volume status in children with nephrotic
36 syndrome with oedema and ascites. Sodium retention during
37 oedematous phase of NS in children is
38 mainly due to primary sodium retention and is not associated with
39 intravascular hypovolemia.

40 **Introduction**

41 Nephrotic syndrome (NS), a common renal disorder in children, is characterised by
42 hypoalbuminaemia (serum albumin $\leq 2.5\text{gm/dl}$), nephrotic range proteinuria
43 ($>40\text{mg/m}^2$ body surface area/hr) and oedema. Oedema is the symptom, most
44 commonly requiring intervention. After confirmation of diagnosis, these patients are
45 routinely managed with steroids and diuretics.

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

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

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

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

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

78 The echocardiographic assessment of Inferior Vena Cava (IVC) size, its variation
79 with phases of respiration measured as IVC collapsibility index (IVCI), ratio of
80 Inferior Vena Cava and Aorta (Ao) diameters (IVC/Ao index) have been used as
81 markers of intravascular volume status in dehydrated and critically ill children
82 [10,11].

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

91 **Methods**

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

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

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

$$118 \quad \text{FeNa(\%): } \frac{\text{Serum Creatinine X Urine Sodium}}{\text{Urine Creatinine X Serum Sodium}} \times 100$$

$$120 \quad \text{UKI(\%): } \frac{\text{Urine Potassium}}{\text{(Urine sodium + Urine Potassium)}} \times 100$$

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

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

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

134 IVC collapsibility index (IVCI) (%):

135
$$\frac{\text{IVC diameter during expiration} - \text{IVC diameter during inspiration}}{\text{IVC diameter during expiration}} \times 100$$

136

137 IVC/Aorta index (IVC/Ao):
$$\frac{\text{IVC diameter during expiration (maximum value)}}{\text{Aorta diameter (maximum value)}}$$

138

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

142 **Results**

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

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

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

153 Based on echo IVC collapsibility index, none of the subjects had hypovolemia.

154 Three subjects had IVC/Ao ratio in hypovolemic range (<0.8) (Table 3).

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

158

159 **Discussion and conclusions**

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

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

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

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

187 In nephrotic patients, Donckerwolcke et al. noticed sodium retention at the onset of
188 the proteinuria with urine indices revealing low average FeNa (0.2%) and UKI
189 (<60%) [6]. They reported that in patients with sodium retention (FeNa <0.5%), UKI
190 was often higher than 60% and there was better correlation between log
191 aldosterone and UKI than with other parameters measuring renal potassium
192 handling such as transtubular potassium gradient, fractional excretion of potassium.
193 In patients with renal sodium retention [(FeNa)% less than 0.5],
194 $\text{Urine(K+)}/\text{Urine(Na+)} + \text{Urine(K+)}$ ratio higher than 0.60 identified patients with
195 increased aldosterone levels indicating functional hypovolemia.

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

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

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

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

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

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

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

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

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

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333

334

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

Variable	Value
Age (Years) Median (range)	6 (2-12)
Sex (n)	
Female	08
Male	12
Nephrotic syndrome episode (n)	
First episode	05
Relapse	15
Weight (Kg) Mean±SD	23.3±6.4
Children with hypotension	
Systolic	Nil
Diastolic	Nil
Orthostatic	Nil
Signs of poor peripheral perfusion (n)	
Cold extremities	Nil
^a CFT > 3sec	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

336 ^aCFT- Capillary Filling Time

337

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

340

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

341 ^aFeNa-Fractional excretion of Sodium; ^bUKI-Urine Potassium Index

342

343

Table 3: Echocardiographic assessment of intravascular volume status

Parameter	Number of children (N=20)
^a IVCI, n <ul style="list-style-type: none"> • <20% (Hypervolemia) • 20-80%(Normovolemia) • >80% (Hypovolemia) 	8 12 0
^b IVC/Ao ratio, n <ul style="list-style-type: none"> • >1.2 (Hypervolemia) • 0.8-1.2 (Normovolemia) • <0.8 (Hypovolemia) 	2 16 3

344 ^aIVCI- Inferior Vena Cava Collapsibility Index; ^bIVC/Ao- Inferior vena cava/Aorta
 345
 346

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

347
 348 ^aFeNa- Fractional excretion of sodium; ^bUKI- Urine potassium index
 349
 350