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High plasma aldosterone is associated with a risk of reversible decreased eGFR in childhood idiopathic nephrotic syndrome

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Abstract

Background. Oedema formation in nephrotic syndrome (NS) may be associated with volume overload or volume contraction. The present study investigates if plasma aldosterone was related to a clinical course symptomatic of either volume expansion or hypovolaemia.

Methods. Twenty patients with NS were included. Blood and urine samples were collected before treatment of NS and at

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INTRODUCTION

Childhood idiopathic nephrotic syndrome (NS) is characterized by massive proteinuria, hypoalbuminaemia and formation of severe oedema. The pathophysiological mechanisms of oedema formation are incompletely understood with the ‘underfill’ hypothesis and the ‘overfill’ hypothesis as the suggested theories [1, 2]. The ability to distinguish between these two types of volume status has substantial therapeutic implications. Relief of severe oedemas using diuretics may increase the risk of circulatory collapse in the case of central blood volume ‘underfill’ [3]. On the contrary, albumin infusion can alleviate symptoms of hypovolaemia but may result in pulmonary oedemas in the case of central blood volume ‘overfill’ [4].

The majority of studies investigating the volume status during NS has been performed in adults or in animal models of NS, but results obtained in these settings cannot be critically extrapolated to the situation in children. Minimal change disease (MCD) is the cause of NS in ~80% of children characterized by massive proteinuria and severe hypoalbuminaemia [5], while MCD in adults is less frequent (~20%) [6]. Furthermore, most cases of primary NS in adults are characterized by irreversible renal affection and a more chronic nephrotic phase preventing the risk of functional hypovolaemia which is only occasionally reported [7]. Because of the clinical impact and the differences between childhood and adult nephrosis, several attempts have been made to characterize blood volume status in children with NS. The F-cell ratio and iodine-labelled albumin infusion has been used to determine total blood volume status. Studies using such techniques indicate that children with NS had a normal or slightly increased blood volume despite the occurrence of symptoms indicating hypovolaemia [8–10]. Other clinical parameters such as blood pressure almost uniformly indicated blood volume to be normal or increased [11, 12], while reports analysing the vasoactive hormones as indicators of effective central blood volume filling status showed a rather heterogeneous pattern. Indeed, these hormonal data have been conflicting and have contributed to the enigma of central blood volume filling in NS [13–15].

The aim of the present study was to examine if plasma aldosterone measured at admission was related to a subsequent clinical course symptomatic of either volume contraction or volume expansion. Our findings indicate that the determination of plasma aldosterone may be helpful in the clinical setting distinguishing between potential ‘underfill’ or ‘overfill’ situations.

RESULTS

Five patients were classified with stimulated aldosterone, mean 611 pg/mL [95% confidence interval (CI): 365–993], 12 with suppressed aldosterone, mean 13 pg/mL (95% CI: 6–26), and 3 with unchanged aldosterone, mean 117 pg/mL (95% CI: 101–135). Patients with high aldosterone were characterized by lower estimated glomerular filtration rate (eGFR) (87 ± 30 versus 142 ± 30, P < 0.01), and increased albuminuria (14 ± 11 versus 6 ± 4 g/L, P = 0.03) compared with the remaining patients. eGFR was normalized rapidly by volume expansion in four of these five patients.

CONCLUSIONS

Elevated plasma aldosterone during NS may be associated with a risk of temporary reduced eGFR. The normalization of eGFR by volume expansion supports the hypothesis of functional hypovolaemia in some patients. Our data suggest that acute measurement of aldosterone may have implications for the management of oedema.

MATERIALS AND METHODS

The patients were recruited consecutively from eight Pediatric Departments in Denmark from 2007 to 2009. Patients with the first episode of NS were admitted to the respective departments by the general practitioner (GP). When the diagnosis was justified, the patients and the relatives were asked to participate in the study. Patients with relapse called the Pediatric Departments directly when they suspected a relapse based on self-monitoring with urinary dipsticks. They were not informed about the present study before the diagnosis of NS was justified. Patients with debut or relapse of NS and aged 1–14 years were included. Patients with NS secondary to other medical conditions were excluded. The study was approved by the Central Denmark Region Committee on Biomedical Research Ethics. Patients were not included before written and oral informed consent was obtained from both parents.

Definitions

NS was defined as proteinuria (albumin/creatinine ratio > 200 mg/mmol, or proteinuria > 40 mg/m²/h), plasma albumin <25 g/L and oedema. Relapse was three consecutive days with plus two or more on urinary albumin dipstick. Remission was achieved when urinary dipstick was negative for protein for three consecutive days. Steroid-resistant NS was defined by the lack of response to steroid treatment (60 mg/m²/day, maximum 80 mg/day) within 4 weeks. Albumin infusion was given by a protocol of 20% albumin (1 g/kg) during a 3 h period supplemented by furosemide 1 mg/kg after 1.5 h and again after the albumin infusion was stopped.

Hypertension was defined as blood pressure of more than the 95th percentile for gender, age and height [16]. Glomerular filtration ratio was estimated using the revised Schwartz formula (k-value = 0.413) (eGFR) [17]. Tachycardia was defined as a heart rate above the upper heart rate limit adjusted for age.

Classification by plasma aldosterone

The patients were classified on the basis of alterations in plasma aldosterone levels comparing the concentration at debut/relapse with remission. The 95% confidence intervals (CIs) were calculated using the aldosterone concentrations at remission. Four patients received angiotensin-converting enzyme inhibitors (ACE-I) at remission and were excluded.
when the 95% CIs were determined. The aldosterone-stimulated group (‘ALDO stim’) was defined as a plasma concentration at debut/relapse above the upper 95% CI limit at remission. The aldosterone suppressed group (‘ALDO supp’) was defined as an aldosterone concentration at debut/relapse that was less than the lower 95% CI limit at remission. The aldosterone unchanged group (‘ALDO uc’) was formed by patients with aldosterone concentrations between the lower and upper 95% CI.

**Collection of samples and biochemical determinations**

Blood and urine samples together with clinical parameters were collected at debut/relapse of NS and at stable remission. Patients in remission were studied at least 30 days after inclusion but within 4 months after debut/relapse.

Blood samples were collected between 9 and 11 a.m. and urine samples at debut/relapse were collected during a 6-h period in hospital after the first morning voiding was discarded. Treatment with diuretics and steroids was withheld until blood sampling and the 6-h urine collection period was done. Also in patients with relapse, the steroid treatment with 60 mg/m²/day was withheld until the 6-h period was completed. A 24-h urine collection was performed at home at remission.

A total of 15 mL venous blood was collected in EDTA vacuum tubes to determine plasma hormones. Samples for aldosterone, angiotensin II (ANG II), atrial natriuretic peptide (ANP) and NT-pro-B-type natriuretic peptide (BNP) were immediately placed on ice and centrifuged at +4°C before storage. The blood sample for determination of renin was kept at room temperature until it was centrifuged and frozen. Plasma aldosterone was measured using a RIA assay (RIA ALDOSTERONE, Demidtec Diagnostic GmbH, Kiel-Welsee, Germany). The concentration of ANP was determined by a RIA assay from Euro-Diagnostica (Malmoe, Sweden). Plasma renin was measured in plasma using a RIA assay (RENIN III GENERATION, Cisbio, Bagnols-sur-Cèze Cedex, France). ANG II was analysed in plasma using a RIA assay previously described in detail [18]. NT-proBNP was measured as a standard procedure at the Department of Clinical Biochemistry, Aarhus University Hospital, Skejby, Denmark, using 6000 Cobas® analyzers series, Roche Professional Diagnostics.

**Echocardiography**

The central blood volume was estimated in the 10 patients admitted to the two centres housing paediatric cardiologists by measuring the cross-sectional diameter of the inferior vena cava (IVC) 1–2 cm under the diaphragm by two-dimensional colour Doppler echocardiography (IE33 Echocardiography System, Philips). The maximum and minimum IVC measurements were noted and the IVC index (IVCI) was calculated by dividing IVC with the body surface area. The patients were scanned during active NS and at remission.

**Formulas and statistical analyses**

Statistical analyses were performed using Stata Statistical Software: Release 10, College Station, TX, for Windows. P-values of <0.05 were considered statistically significant. Comparisons were performed using paired or unpaired t-tests. Logarithmic transformation was applied to hormonal data and FE$_{\text{Na+}}$. These data are presented as the geometric means with 95% CIs. The Wilcoxon rank-sum test or the Mann–Whitney U-test was used to test differences between data that are not normally distributed. The Kruskal–Wallis one-way analysis of variance test was done when more than two groups were analysed and the Bonferroni correction was done to adjust for multiple comparisons regarding hormonal data in Figure 1 (P < 0.005). Correlations were analysed by a linear regression analysis. Fractional excretion was estimated by $\text{FE}_\text{K+} = (U_{\text{K+}} \times P_{\text{creatinine}})/(P_{\text{K+}} \times U_{\text{creatinine}})$. The relationship between potassium/sodium exchange in the distal tubuli was estimated by $U_{\text{Na+}}/(U_{\text{K+}} + U_{\text{Na+}}) \times 100$ (%).

### RESULTS

**Subject characteristics**

A total of 20 patients with debut ($n=14$) or relapse ($n=6$) of NS were included in the study. Baseline characteristics are presented in Table 1. Hypotension was not observed in any of the patients. Three patients with the first episode of NS had a heart rate above the age-adjusted upper limit, but none exceeded a pulse of 120 beats/min. Two patients with relapse of NS were treated with ACE-I at inclusion and at remission. Further two patients with debut of NS received ACE-I at remission. Excluding these patients from the statistical analysis did not alter the reported differences between the groups concerning the hormonal data presented in Figure 1. None of the patients received diuretics at inclusions or at remission, but during the clinical course, a total of 10 patients received oral furosemide (2 mg/kg/day) to control oedema, including five patients in the ALDO stim group and five patients in the two other groups.

**Vasoactive hormones during NS**

Based on the criteria of alterations in aldosterone, five patients were defined as ALDO stim with increased aldosterone concentrations mean 611 (95% CI: 365–993) pg/mL at Day 1 compared with remission. All of these patients had debut of NS. A total of 12 patients had suppressed aldosterone concentration, mean 13 (95% CI: 6–26) pg/mL at Day 1 and were labelled ALDO supp. Three patients were classified as ALDO uc with unchanged aldosterone concentration, mean 117 (95% CI: 101–135) pg/mL comparing active disease with remission. Data on hormones are summarized in Figure 1. During NS plasma, ANG II and renin were significantly higher in the ALDO stim group compared with the ALDO supp group. In the ALDO supp group, both ANP and NT-proBNP were significantly increased at debut/relapse compared with remission. Surprisingly, a non-significant ($P = 0.07$) tendency towards higher NT-proBNP concentration during NS compared with remission was observed in the ALDO stim group.
A positive correlation was observed between plasma aldosterone and ANG II ($P < 0.001$, $r = 0.74$) and aldosterone and renin ($P < 0.001$, $r = 0.86$), whereas the positive correlation between plasma aldosterone and $U_{K_+}(U_{K_+} + U_{Na_+})$ was less strong ($P = 0.07$, $r = 0.24$). No negative correlation was observed between aldosterone and $FE_{Na_+}$. A correlation between ANP and NT-proBNP ($P < 0.001$, $r = 0.65$) was observed, but there was no association between $FE_{Na_+}$ and ANP or NT-proBNP.

**FIGURE 1:** Vasoactive hormones at debut/relapse of idiopathic NS and at remission (REM). Patients were classified regarding the alterations in aldosterone concentration at debut and remission (see text for details). *$P < 0.005$, stim NS versus supp NS; †$P < 0.005$, stim NS versus UC NS; ‡ $P < 0.005$, stim NS versus stim REM; †† $P < 0.005$, supp NS versus stim REM.
Estimation of central blood volume by echocardiography

Echocardiography was performed in three patients classified as ALDO stim and seven in the ALDO supp/ALDO uc group. Both IVClmin and IVClmax tended to be lower in the ALDO stim group compared with the ALDO uc/supp group during active disease (Table 2).

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics of the patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Debut (n = 14)</td>
</tr>
<tr>
<td>Age, years (range)</td>
</tr>
<tr>
<td>Gender (female)</td>
</tr>
<tr>
<td>Weight gain (% of dry weight)a</td>
</tr>
<tr>
<td>Blood pressureb</td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Increased heart ratec</td>
</tr>
<tr>
<td>Immunosuppressiond</td>
</tr>
</tbody>
</table>

aInformation of dry weight was obtained from the parents.
bDefined by the 5th and 95th percentile for gender, age and height.
cNumber of patients with a heart rate above the upper heart rate limit adjusted for age.
dPatients were treated with CyA or Tac and a low dose of alternative day prednisolone.

<table>
<thead>
<tr>
<th>Table 2. Estimation of IVCI by echocardiography in 10 patients with NS and at remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDO stim (n = 3)</td>
</tr>
<tr>
<td>NS</td>
</tr>
<tr>
<td>IVClmax(mm/m²)</td>
</tr>
<tr>
<td>IVClmin(mm/m²)</td>
</tr>
<tr>
<td>Remission</td>
</tr>
<tr>
<td>IVClmax(mm/m²)</td>
</tr>
<tr>
<td>IVClmin(mm/m²)</td>
</tr>
</tbody>
</table>

Data are expressed as median with range.

Disease (Figure 3). This phenomenon was not observed in any of the other patients. Infusion with albumin in three of the patients and 0.9% saline in the fourth restored normal creatinine rapidly.

Three of the five patients in the ALDO stim group were steroid-resistant, but remission was achieved within 2 weeks with supplementary treatment with cyclosporin A (CyA) or Tacrolimus (Tac). Interestingly, relapses were observed in two of these patients since the debut of NS and both episodes were steroid-sensitive within 1 week. No complicating events occurred during these episodes.

DISCUSSION

The present paper illustrates that a subset of patients with idiopathic NS have very high plasma aldosterone concentrations and low eGFR during active NS. These patients experienced their first episode of NS and were identified with a plasma aldosterone above 365 pg/mL. With the possibility to make acute measurements of plasma aldosterone using commercially available ELISA kits, aldosterone may contribute to the initial evaluation of the volume status of patients with NS.

The association of high plasma aldosterone and temporary decreased GFR has previously been reported in groups of patients with NS and symptoms of hypovolaemia [9, 19]. Our data confirm these findings and the plasma aldosterone concentration reported in the two latter studies of 724 ± 353 and 694 ± 318 pg/mL is comparable with the data in the present study (Table 4). Contrary to these studies by the Vande Walle group [8, 9, 19] where patients were classified by the presence of symptoms of hypovolaemia, we decided to classify the patients by alterations in plasma aldosterone concentrations based on the 95% CI at remission. This strategy was chosen because some symptoms of hypovolaemia are rather subjective and objective indicators of hypovolaemia such as low blood pressure or tachycardia are a very infrequently observation in children with NS [8, 11, 12] which is also illustrated in Table 1.
A limited number of studies reported aldosterone to be consistently elevated or decreased in the studied populations of children with NS [13–15]. However, none of these studies provided information on how patients were included and in which situation the measurements were done. The conflicting data on aldosterone and the other vasoactive hormones truly illustrate the task of selecting a homogeneous group of patients with NS as the intravascular volume and clinical picture may change depending on the sodium load, plasma albumin concentration and treatment with diuretics even in a few hours within the same patient [20].

In agreement with our findings, Vande Walle et al. [8, 10] reported aldosterone and renin to be increased in some patients with NS and normal in others, despite the same degree of hypoalbuminaemia. These data were based on patients with relapse of NS. Contrary, none of our patients with relapse were classified with increased aldosterone. The relapse patients in our study had a mean plasma albumin of

### Table 3. Plasma and urinary parameters at debut/relapse in 20 children with NS

<table>
<thead>
<tr>
<th></th>
<th>Patients with debut</th>
<th>Patients with relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Remission</td>
</tr>
<tr>
<td>U-albumin (g/L)</td>
<td>7 (1–36)*</td>
<td>0.036*</td>
</tr>
<tr>
<td>P-albumin (g/L)</td>
<td>17 (11–22)*</td>
<td>44 (41–50)</td>
</tr>
<tr>
<td>P-Na⁺</td>
<td>134 ± 4*</td>
<td>139 ± 2</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)*</td>
<td>163 ± 53</td>
<td>156 ± 27</td>
</tr>
<tr>
<td>Diuresis (mL/h/kg)</td>
<td>1.2 ± 0.8</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>FeNa⁺ (%)</td>
<td>0.21 ± 0.32*</td>
<td>0.36 ± 0.14</td>
</tr>
<tr>
<td>Uₖ⁺/(Uₖ⁺ + Uₙ⁺) (%)</td>
<td>69 (27–99)*</td>
<td>37 (22–50)</td>
</tr>
</tbody>
</table>

Data are reported as mean ± SD or as median with range.  
*P < 0.05. Patients with debut, Day 1 compared with remission.  
§P < 0.05. Patients with relapse, Day 1 compared with remission.  
¤P < 0.05. Day 1, patients with debut compared with those with relapse.

### Table 4. Clinical and biochemical parameters in patients with debut of NS

<table>
<thead>
<tr>
<th></th>
<th>ALDO stim (n = 5)</th>
<th>ALDO uc/supp (n = 9)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-aldosterone (pg/mL)</td>
<td>611 (365–993)</td>
<td>14 (5–43)</td>
<td>0.001*</td>
</tr>
<tr>
<td>P-albumin (g/L)</td>
<td>16 ± 5</td>
<td>18 ± 2</td>
<td>0.59</td>
</tr>
<tr>
<td>P-Na⁺ (mmol/L)</td>
<td>131 ± 4</td>
<td>136 ± 3</td>
<td>0.03*</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>87 ± 30</td>
<td>141 ± 30</td>
<td>0.006*</td>
</tr>
<tr>
<td>U-albumin (g/L)</td>
<td>14 ± 11</td>
<td>6 ± 4</td>
<td>0.03*</td>
</tr>
<tr>
<td>Uₖ⁺/(Uₖ⁺ + Uₙ⁺) (%)</td>
<td>0.96 (0.62–0.99)</td>
<td>0.62 (0.27–0.93)</td>
<td>0.08</td>
</tr>
<tr>
<td>FEₙ⁺ (%)</td>
<td>0.03 (0.005–0.15)</td>
<td>0.11 (0.04–0.32)</td>
<td>0.22</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78 (65–100)</td>
<td>77 (65–119)</td>
<td>0.87</td>
</tr>
<tr>
<td>Blood pressure, systolic (mmHg)</td>
<td>111 ± 18</td>
<td>109 ± 15</td>
<td>0.79</td>
</tr>
<tr>
<td>Steroid-resistant patientsa</td>
<td>3/5</td>
<td>0/9</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Patients were group according to the concentration of aldosterone at inclusion (see text for details). Data are presented as mean ± SD, median (range) or the geometric mean with 95% CI.  
*P < 0.05 was considered significant. eGFR, glomerular filtration ratio estimated by the Schwartz formula. FEₙ⁺, fractional sodium excretion.  
aDefined by lack of response to steroids within 4 weeks of treatment (60 mg/m²/day, max 80 mg/day). Biopsies demonstrated MCD in all three patients.
29 g/L (Table 3) compared with a plasma albumin of 16 and 18 g/L in the population studied by the Vande Walle group, despite the same degree of proteinuria. The difference might reflect that all of our relapse patients were on immunosuppressive therapy during the relapse preventing the development of full-blown nephrosis.

Furthermore, the higher plasma albumin concentrations in our relapse patients may also reflect an earlier admission of the relapse patients both compared with the patients studied by the Vande Walle group [8] and with the patients in our study with the first episode of NS. Typically, the patients with the first episode of NS have been seen at least once by the GP and the admission to the hospital and initiating of treatment often has been delayed for several days contributing to the risk of a clinical picture more severe than seen in the relapse patients where the awareness of even discreet symptoms of NS is high. Indeed, the de novo NS patients presented with significantly lower plasma albumin and a higher urinary protein loss compared with the relapse patients (Table 3). If the loss of protein in urine is more pronounced in debut patients, it might contribute to a disruption of the compensatory mechanisms of transcapillary redistribution of albumin and the recirculation of albumin between plasma and the interstitial compartment, normally preventing hypovolaemia and hence stimulated renin–angiotensin–aldosterone system (RAAS) [21]. To limit the influence of the above-mentioned factors comparing de novo patients with relapse patients, a separated analysis was performed in the patients with debut of NS (Table 4).

A decreased GFR has, besides the association with high aldosterone, also been observed in correlation with excessive sodium retention during NS [15, 19] and it was suggested that patients with decreased FE\textsubscript{Na}\textsuperscript{+} and increased U\textsubscript{K}/(U\textsubscript{K} + U\textsubscript{Na}) ratio may be treated with volume expansion if clinically relevant [22]. A recent study in 134 patients with relapse reported an FE\textsubscript{Na}\textsuperscript{+} of 0.24% compared with 0.45% at remission [23] which is comparable to the overall results presented in Table 3. However, in the later study, patients with evidence of volume contraction were excluded, which may explain the quite high values of FE\textsubscript{Na}\textsuperscript{+} compared with the data in Table 4. Recently, Kapur et al. [24] reported urinary FE\textsubscript{Na}\textsuperscript{+} to be significantly lower in patients with evidence of volume contraction and concluded that diuretics alone were safe in patients with an FE\textsubscript{Na}\textsuperscript{+} exceeding 0.2%. In patients with debut, we observed a strong tendency towards decreased FE\textsubscript{Na}\textsuperscript{+} and increased U\textsubscript{K}/(U\textsubscript{K} + U\textsubscript{Na}) ratio in the ALDO stim group compared with ALDO uc/ALDO supp patients (Table 4). The median FE\textsubscript{Na}\textsuperscript{+} in our patients with high aldosterone was 0.03%, much similar to the 0.02% reported by Kapur et al. in his patient group defined as volume contracted. However, some patients in the ALDO uc/ALDO supp group had FE\textsubscript{Na}\textsuperscript{+} < 0.2%, indicating the urinary sodium excretion cannot be the isolated marker of volume status. One limitation of the present study was that the sodium intake could not be standardized in these patients studied just at debut or relapse. This may contribute the substantial variation on urinary sodium excretion. Furthermore, the number of patients was limited but comparable to the number of

![Figure 2: The linear correlation between plasma aldosterone and eGFR at the first episode of NS illustrating that eGFR significantly decreases with higher plasma aldosterone (n = 14, y = 144–0.087x, r\textsuperscript{2} = 0.54, P = 0.003).](image)

![Figure 3: The clinical course of four patients from the aldosterone-stimulated group with early-onset increase in plasma creatinine (b) and two patients with late-onset increase in plasma creatinine (a). Three of the patients were treated with one albumin infusion (dark arrow) normalizing plasma creatinine, whether one patient recovered after infusion with 0.9% saline (grey arrow). None of the patients achieved remission immediately after volume expansion and the degree of proteinuria was not decreased in the next following days. All patients were treated with furosemide and no alterations in doses were done in relation to the observed changes in plasma creatinine.

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patients in the majority of studies in this field of paediatric nephrology.

The finding of high aldosterone, decreased eGFR and the normalization of eGFR by volume expansion might be evidence of functional hypovolaemia in a subgroup of patients. Furthermore, there is a risk that a potential hypovolaemic situation has been further impaired because of treatment with diuretics in the five patients with ALDO stim, while no signs of volume contraction were observed in the remaining five patients treated with diuretics. An objective measure of volume status, like plasma aldosterone, might be able to guide treatment in these situations. The hypothesis of hypovolaemia was further supported by increased renin and angiotensin II in the ALDO stim group and by the observation that in three of the cases, albumin infusion together with furosemide was safe and reestablished normal plasma creatinine levels rapidly. In the last patient, volume expansion with 0.9% saline was chosen by the clinician with the same beneficial effect on eGFR (Figure 3). Contrary to our finding, one study reported no beneficial effect on GFR using albumin infusion in NS patients with acute renal failure [25]. However, in that paper, 6 of 11 patients were treated with CyA, which may be a major contributing factor to the impaired renal function rather than the NS itself [26]. In the ALDO supp group, higher concentration of ANP and NT-proBNP was observed during NS compared with remission, suggesting a situation with possible overfill blood volume. However, with the lack of a golden standard to determine blood volume status in this patient group, it is not possible with the present paper to contribute with hard evidence to the ongoing discussion upon ‘underfill’ or ‘overfill’ mechanisms of sodium retention during NS. The aim of the study was to provide the clinician with useful information on which patients may benefit from volume expansion to normalize eGFR during NS. Besides aldosterone, we investigated if NT-proBNP could contribute substantially to indicate the volume status. NT-proBNP is the N-terminal part of the precursor hormone cleaved in a 1:1 ratio of active BNP and NT-proBNP and was an indirect estimation of BNP concentration [27]. Surprisingly, NT-proBNP was high in the ALDO stim group during disease (Figure 1). However, NT-proBNP clearance is dependent on renal function which was temporary decreased in 80% of patients in the ALDO stim group, so the high levels of NT-proBNP may reflect decreased clearance rather than stretch of the heart musculature [28].

Previously, echocardiography has been performed in patients with NS to estimate the central volume status [29]. In the latter study, we observed no difference between the groups, but a tendency towards a decreased IVCI was seen in the ALDO stim group compared with the ALDO uc/supp group. The use of IVCI as an indicator of central blood volume filling should be investigated in a larger patient group and the method is of course limited by the risk of inter- and intra-observer variability.

It still remains unknown why minorities of NS patients have stimulated sodium-retaining hormones. It has been hypothesized that a rapidly developing episode of NS may lead to exhaustion of the protective mechanism against a severe drop in transcapillary oncotic pressure, resulting in reduced blood volume [22].

Interestingly, three of the five patients with stimulated RAAS hormones were defined as steroid-resistant, whereas relapses in two of these patients subsequently were steroid-sensitive. If there is pathological association between decreased central blood volume and insensitivity to steroids, for example as a consequence of reduced bioavailability of steroids caused by reduced blood flow to the intestine has yet to be investigated.

In conclusion, our study shows that also in patients with their first episode with NS, it is possible to identify a subset of patients with increased plasma aldosterone and a high risk of developing temporary decreased eGFR suggesting hypovolaemia. These patients were characterized by a plasma aldosterone above 365 pg/mL. We suggest that acute measurement of aldosterone may contribute to the identification of patients in whom volume expansion may acutely improve eGFR and to avoid further volume contraction using diuretics. Additional prospective studies are needed to elucidate if acutely determined plasma aldosterone in children with debut or relapse of NS is helpful to decide if treatment of oedema should be volume expansion with albumin infusion or volume elimination with diuretics.

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CONFLICT OF INTEREST STATEMENT

None declared.

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