Pathophysiology of Edema Formation in Children with Nephrotic Syndrome Not Due to Minimal Change Disease

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Abstract. It has been shown that children with nephrotic syndrome due to minimal change disease (MCD) can present with avid salt retention and stimulated vasoactive hormones, as well as with stable edema. The present study examines these conditions in children with nephrotic syndrome not due to MCD (non-MCD). In six children with hypovolemic symptoms (congenital nephrotic syndrome in four), strong sodium retention (fractional sodium excretion, FENa, 0.2 ± 0.2%) was found. Lithium clearance (FELi) and maximal water excretion (Vmax) were suppressed, suggesting avid sodium reabsorption throughout the nephron. Aldosterone, renin, and norepinephrine were elevated. Sixteen other children with non-MCD had stable edema. FENa was 1.8 ± 1.1%, whereas FELi, Vmax, and hormones were normal, and not different from data in 35 nonproteinuric children. In children with MCD, 12 presented with hypovolemic symptoms and strong sodium retention (FENa 0.3 ± 0.3%), whereas 15 were stable (FENa 1.1 ± 0.7%). Regarding tubular sodium handling and hormones, the same distinction could be made as for the children with non-MCD. However, hypoproteinemia differed. In the children with non-MCD lesions, plasma colloid osmotic pressure was significantly lower in the hypovolemic types (4.2 ± 0.4 mmHg) than in those with stable edema (13.0 ± 3.8 mmHg; P < 0.05); in MCD, no such difference existed (respectively, 8.1 ± 3.0 and 9.9 ± 2.2 mmHg). In summary, children with nephrotic syndrome may present with pathophysiologic pictures of decreased effective circulating volume or of stable edema, regardless of whether they have non-MCD or MCD. The pathogenesis of the hypovolemic picture seems to be different, since it is associated with extreme hypoproteinemia only in the children with non-MCD.

Discrimination between these two factors in sodium retention may be particularly relevant and instructive in children. Nephrotic children often display severe proteinuria, and thus are more prone to develop hypovolemia and secondary sodium retention. We have reported recently that children presenting with a relapse of MCD can be divided clinically into a group displaying symptoms of hypovolemia, increased vasoactive hormones, and an active edema-forming state, and a group showing a steady state, without hypovolemia or increased vasoactive hormones, and with normal sodium excretion (9,10). Interestingly, plasma COP was similarly decreased in these two groups. We suggested that extreme proteinuria occurring early in a relapse can deplete plasma albumin so quickly that a temporary disequilibrium between plasma and extravascular albumin stores develops. Thus, children relapsing into an episode of MCD may pass through a stage of (impending) hypovolemia, characterized by clinical symptoms, strongly stimulated sodium-retaining hormones, and avid sodium retention, before entering into a stage of stable edema but no active sodium retention (9–11).

Less is known about the mechanism of sodium retention in children with other, chronic forms of nephrotic syndrome. We will designate these children as having “non-MCD,” since pathogenesis and histologic changes (as opposed to minimal changes) are variable. These children may not form a uniform group. Some are clinically in steady state, similar to what has

Our understanding of the pathophysiology of sodium retention in the nephrotic syndrome has evolved over the past few decades. Although it was originally believed that sodium retention was purely the result of a decrease in circulating volume, related to the fall in plasma colloid pressure (COP) (1,2), evidence was found later for a primary renal disturbance in sodium handling (3–5). Indeed, in adults with the nephrotic syndrome has evolved over the past few decades. Although it was originally believed that sodium retention was purely the result of a decrease in circulating volume, related to the fall in plasma colloid pressure (COP) (1,2), evidence was found later for a primary renal disturbance in sodium handling (3–5). Indeed, in adults with the nephrotic syndrome may present with pathophysiologic pictures of decreased effective circulating volume or of stable edema, regardless of whether they have non-MCD or MCD. The pathogenesis of the hypovolemic picture seems to be different, since it is associated with extreme hypoproteinemia only in the children with non-MCD.

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been described for the established MCD, whereas others remain clinically hypovolemic, and depend on daily albumin infusions to assist their circulation (12,13). Thus, in children with chronic nephrotic syndrome, a similar division may be made in avid sodium reabsorption and stimulated hormones versus relatively normal intrarenal sodium handling and hormones. We hypothesize that, in contrast to the observations in patients with MCD, such different presentations correspond to differences in severity of hypoproteinemia, but this has not been investigated. We therefore studied intrarenal sodium handling in a group of patients with non-MCD. The results were compared with those found in children with MCD, in part published previously (9,10).

Materials and Methods

Patients

The data presented in this report concern 22 children with non-MCD nephrosis (14 males, eight females; age: 6.2 ± 4.0 yr). Their data are compared with data collected in 27 patients with MCD (17 males, 10 females; age 8.0 ± 3.9 yr). Thirty-five children in remission from MCD were studied as a control population (24 males, 11 females; age 9.1 ± 4.4 yr). Some of the data collected in the patients with MCD (n = 21) and the patients in remission (n = 33) were published previously (9,10). Histologic diagnosis was obtained by renal biopsy in all cases. Children with overt renal failure (plasma creatinine >3.9 g/L), and pitting edema. In the youngest children, general malaise and diarrhea. In the very small children, urine collection periods were adapted to their spontaneous need to void.

Analytical Techniques

Sodium and potassium were measured by a standard flame photometry, and lithium by means of a Perkin Elmer 3030 atomic absorption spectrophotometer. Osmolality was measured with an advanced osmometer. Inulin was determined photometrically after hydrolyzation to fructose (15), and PAH was determined photometrically by a chromoaldehyde reaction (16). RIA were used to measure plasma concentrations of aldosterone, renin (17), and ANP (18). Norepinephrine was estimated by HPLC with fluorescence detection (19). COP was measured with a colloid osmometer built for 10-μl samples (20).

Statistical Analyses

Data are presented as means ± SD. Clearances and fractional excretions were calculated by standard formulas. GFR, RPF, and maximal water excretion (V_{max}) were normalized for 1.73 m². We also calculated the quotient of urine potassium and urine sodium + potassium, expressed as %: [(U_K)/(U_Na+K)] × 100%. This quotient may be taken as an indicator for sodium/potassium exchange in the distal nephron (21).

Differences between all groups were tested with the Kruskall–Wallis test for multiple groups. If the P value was <0.05, differences between groups were tested with the Mann–Whitney U test (with Bonferroni's protection for multiple comparisons). Correlations were assessed by Pearson correlations matrix.

Results

The average ages of the children studied in remission from MCD (9.1 ± 4.4 yr), and of the nephrotic groups with non-MCD (6.2 ± 4.0 yr) and with MCD (8.0 ± 3.9 yr) were not
significantly different, and in all groups the male/female ratio was about 2:1.

**Children with Non-MCD**

Six of the 22 children with non-MCD displayed symptoms compatible with hypovolemia. The remaining clinical and experimental data will be presented according to this division. The gender ratio in these two groups was similar, but the symptomatic children were much younger and smaller than all other groups (Table 1). It is also relevant that most of these symptomatic children had Finnish type nephrotic syndrome, whereas the children without hypovolemic symptoms mostly had acquired forms of glomerulonephritis (Table 2). The symptomatic patients with non-MCD had more severe proteinuria, and lower levels of plasma albumin and COP than the asymptomatic patients.

The children with non-MCD and without manifestations suggesting hypovolemia were indistinguishable from the control group with respect to RPF, and had a normal urine dilution capacity and maximal urine flow, and normal fractional lithium excretion and ([U_K]/[U_Na+K]) (Table 3). Their GFR was somewhat low, and fractional sodium excretion was high. Filtration fraction was decreased.

In the clinically unstable patients, GFR was normal. However, normal GFR may be difficult to judge in these children, given their low weight and chronic muscle wasting condition. This is not the case for filtration fraction, which was significantly decreased. The intrarenal sodium handling parameters in these children were markedly changed. Urine dilution capacity was decreased, and fractional excretions of sodium and lithium were very low. The quotient ([U_K]/[U_Na+K]) was elevated. Substantial variability was found for most parameters. To illustrate this, individual data for FE_{Na} and FE_{Li} are presented in Figure 1.

Hormone measurements were also indistinguishable from normal in the nonsymptomatic children (Table 4). However, the symptomatic children displayed elevated levels of renin, aldosterone, and norepinephrine. Plasma ANP was not abnormal. Individual data are given in Figure 2.

**Children with MCD**

Twelve of the 27 children with MCD displayed symptoms compatible with hypovolemia. In this group, the gender ratio was markedly shifted, in that significantly more males presented with hypovolemia (Table 1). The severity of proteinuria and hypoalbuminemia was similar for the symptomatic and asymptomatic children with MCD. In the asymptomatic children, renal hemodynamics, intrarenal sodium handling (Table 3), and hormones (Table 4) were not different from control findings. Instead, the symptomatic children displayed low GFR and filtration fraction, impaired dilution and maximal urine flow, and low fractional excretions of sodium and lithium. The quotient ([U_K]/[U_Na+K]) was elevated. Plasma norepinephrine, renin activity, and aldosterone were elevated, and ANP was low.

**Comparison between Children with Non-MCD and MCD, and Correlations**

In comparison to the children with non-MCD, asymptomatic and symptomatic children with MCD behaved comparably with respect to intrarenal sodium handling and hormones, except for plasma ANP, which was low only in the symptom-
atic children with MCD. There was, however, a marked difference, in that only the symptomatic children with non-MCD displayed extreme proteinuria and hypoalbuminemia and extremely low plasma COP, whereas in the symptomatic children with MCD these changes were similar to those in the asymptomatic patients with MCD or non-MCD.

We also studied relevant correlations. In the patients with non-MCD and with MCD (i.e., including both nonsymptomatic children as well as the symptomatic children), strong negative correlations were found between aldosterone on the one hand, and $\text{FENa, FE Li, and } [(U_K)/(U_{Na+K})]$ on the other (Table 5). There was a remarkable correspondence in these correlations between the two patient groups, illustrated by the coincidence of individual data points (Figure 3). However, an important difference appeared with respect to plasma COP: Whereas in the patients with non-MCD aldosterone was strongly correlated with plasma COP, no more than a tendency for such a correlation was found in the children with MCD (Figure 4). A similar pattern, but less conspicuous, was found for renin and norepinephrine. Plasma ANP was positively correlated with $\text{FENa, FE Li, and } [(U_K)/(U_{Na+K})]$ in MCD, whereas in the children with non-MCD it was only weakly correlated to $\text{FE Na}$.  

### Table 3. Renal function parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remission&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Non-MCD</th>
<th>MCD&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CS−</td>
<td>CS+</td>
<td>CS−</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>126 ± 29</td>
<td>102 ± 34&lt;sup&gt;c&lt;/sup&gt;</td>
<td>126 ± 36</td>
</tr>
<tr>
<td>RPF (ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>593 ± 155</td>
<td>605 ± 278</td>
<td>989 ± 441</td>
</tr>
<tr>
<td>FF (%)</td>
<td>22 ± 4</td>
<td>18 ± 7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>15 ± 5&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>U. osmol (mosmol/kg)</td>
<td>55 ± 17</td>
<td>69 ± 24</td>
<td>261 ± 112&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td>$V_{max}$ (ml/min per 1.73 m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>16.2 ± 5.3</td>
<td>13.4 ± 3.8</td>
<td>5.3 ± 4.1&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td>$\text{FE Na} (%)$</td>
<td>1.1 ± 0.7</td>
<td>1.8 ± 1.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.2 ± 0.2&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td>$\text{FE Li} (%)$</td>
<td>29.5 ± 7.9</td>
<td>30.7 ± 8.9</td>
<td>13.1 ± 1.1&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
<tr>
<td>$U_K/(U_{Na+K} (%)$</td>
<td>34 ± 16</td>
<td>28 ± 18</td>
<td>86 ± 14&lt;sup&gt;e,f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> RPF, renal plasma flow; FF, filtration fraction; U. osmol, urine osmolality; $V_{max}$, maximal urine flow; FE, fractional excretion. Other abbreviations as in Table 1.  
<sup>b</sup> Data in children in remission and with MCD were in part published previously (9,10).  
<sup>c</sup> $P<0.05$, compared with remission.  
<sup>d</sup> $P<0.05$, compared with nonsymptomatic group.  
<sup>e</sup> $P<0.01$, compared with remission.  
<sup>f</sup> $P<0.01$, compared with nonsymptomatic group.
Discussion

This study confirms our hypothesis that in children with chronic nephrotic syndrome, not associated with MCD, two basically different presentations can be discerned. Some are stable, with on average normal intrarenal sodium and water handling and sodium-retaining hormones. Others are clinically unstable, show symptoms of decreased effective circulating volume, and display strong tubular sodium reabsorption and stimulated hormones. Compared with stable children, the latter have massive proteinuria and extreme hypoproteinemia.

In the unstable, symptomatic patients, lithium excretion, considered an indicator for proximal tubular sodium reabsorption (22,23), was decreased. Distal sodium potassium exchange, indicated by the term \( U_K/(U_K + U_N) \), was stimulated. Together, these changes suggest that the avid tubular sodium reabsorption in these patients was not limited to a single nephron segment, but a generalized tubular activity. Such a change can be expected if a decreased effective circulating volume rather than a specific tubular abnormality is the drive for the increased sodium reabsorption (24). The dilution impairment is also in agreement with this explanation. In stable patients, fractional sodium excretion was normal, as were the indices of intrarenal sodium handling and urine dilution. Apparently, renal sodium handling in these subjects was normal except for the inability to correct the fluid excess.

That the difference between these presentations is indeed based on the differences in effective circulating volume is indicated by the profound stimulation of renin, aldosterone, and norepinephrine in the symptomatic patients. The only finding not in agreement is the normal level of plasma ANP. Impaired cardiac function, as is often present in children with congenital nephrotic syndrome, may explain this discrepancy (25).

We assume that the difference between these two presentations relates to the severity of the hypoproteinemia. Hypoproteinemia causes a redistribution of albumin from interstitium to the blood (26). This restores the plasma-to-interstitial difference in COP, and thus prevents hypovolemia. However, the

Table 4. Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Remission⁵</th>
<th>Non-MCD</th>
<th>MCD⁶</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CS−</td>
<td>CS+</td>
<td>CS−</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>76 ± 31</td>
<td>79 ± 57</td>
<td>90 ± 50</td>
</tr>
<tr>
<td>NOR (pg/ml)</td>
<td>251 ± 141</td>
<td>361 ± 193</td>
<td>231 ± 178</td>
</tr>
<tr>
<td>PRA (µU/ml)</td>
<td>35 ± 34</td>
<td>151 ± 179</td>
<td>560 ± 281c,d</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>66 ± 51</td>
<td>97 ± 98</td>
<td>2126 ± 956c,d</td>
</tr>
</tbody>
</table>

a ANP, atrial natriuretic peptide; NOR, norepinephrine; PRA, plasma renin activity. Other abbreviations as in Table 1.

b Data in children in remission and with MCD were in part published previously (9,10).

c \( P<0.01 \), compared with nonsymptomatic group.
d \( P<0.01 \), compared with remission.

Figure 2. Individual values of plasma renin activity (PRA) and plasma aldosterone for children in remission (Rem), for children with minimal lesions and no clinical symptoms suggestive of hypovolemia (MCD−) and with symptoms (MCD+), and for children with nephrosis not due to MCD without (non-MCD−) and with (non-MCD+) such symptoms. Averages are indicated by horizontal bars. Data in children with MCD and in remission were in part published previously (9,10).
range of this compensation is limited, due to the limited amount of interstitial albumin. On the basis of data in humans (26,27) and animals (28,29), we suggested that blood volume can be maintained if plasma COP does not pass the critical minimum of approximately 8 mmHg. The avidly sodium-retaining patients with non-MCD had massive proteinuria and a plasma COP of only approximately 4 mmHg, clearly below this margin, in contrast to plasma COP of approximately 13 mmHg in the stable subjects. At such a low plasma COP, even complete mobilization of interstitial albumin to the blood cannot restore the plasma-to-tissue fluid COP gradient, and thus cannot restore the circulating volume (28). Consequently, although this is a chronic condition, the circulation cannot become stable at a level that restores sodium excretion. Most of the children with this picture had a congenital nephrotic syndrome. The extraordinary proteinuria and circulatory instability in this syndrome are well known, and necessitate daily albumin infusions (12,13) and often even nephrectomy at an early age (30). In adults, such extreme proteinuria is rare, but has been described in particular conditions such as amyloidosis (31) and in posttransplant kidneys (32).

We found it instructive to compare the present data with those in children with MCD. These data, in part published earlier (9,10), were therefore included in this report. It appears that children with nephrosis, whether associated with non-MCD or MCD, can present with symptoms of hypovolemia,

Table 5. Correlations of hormones, COP, and renal sodium handling

<table>
<thead>
<tr>
<th>Group</th>
<th>COP</th>
<th>FE_{Na}</th>
<th>FE_{Li}</th>
<th>U_k/(U_k + Na)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>P</td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Non-MCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aldosterone</td>
<td>&lt;0.001</td>
<td>-0.721</td>
<td>0.004</td>
<td>-0.588</td>
</tr>
<tr>
<td>PRA</td>
<td>&lt;0.001</td>
<td>-0.871</td>
<td>0.081</td>
<td>-0.380</td>
</tr>
<tr>
<td>norepinephrine</td>
<td>&lt;0.001</td>
<td>-0.775</td>
<td>0.065</td>
<td>-0.401</td>
</tr>
<tr>
<td>ANP</td>
<td>0.496</td>
<td>0.153</td>
<td>0.034</td>
<td>0.455</td>
</tr>
<tr>
<td>MCD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aldosterone</td>
<td>0.076</td>
<td>-0.348</td>
<td>0.002</td>
<td>-0.569</td>
</tr>
<tr>
<td>PRA</td>
<td>0.047</td>
<td>-0.386</td>
<td>0.018</td>
<td>-0.453</td>
</tr>
<tr>
<td>norepinephrine</td>
<td>0.014</td>
<td>-0.465</td>
<td>0.012</td>
<td>-0.477</td>
</tr>
<tr>
<td>ANP</td>
<td>0.139</td>
<td>0.292</td>
<td>&lt;0.001</td>
<td>0.650</td>
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</tbody>
</table>

*Correlations in children with MCD were partly published previously (10). Abbreviations as in Tables 1, 3, and 4.

Figure 3. Relationship between plasma aldosterone and fractional sodium excretion (FE_{Na}) and the quotient of urine sodium and potassium excretion U_k/(U_k + Na): MCD− and MCD+: children with minimal change disease without and with clinical symptoms suggestive of hypovolemia. non-MCD− and non-MCD+: children with nephrosis not due to minimal change disease without and with symptoms. Data in children with MCD were in part published previously (10).
avid sodium retention, and stimulated hormones, or with stable edema, sodium balance, and normal hormones. The similarity in means and ranges of renal sodium handling indices and hormones (Figures 1 and 2) indicates that there was no fundamental difference in this respect between children with non-MCD or MCD. This is underscored by the relation between plasma aldosterone and sodium handling indices (Figure 3). This relationship not only supports the importance of aldosterone for the sodium reabsorption activity, but also the marked similarity between patients with non-MCD and MCD, suggesting comparable impact of aldosterone on tubular sodium handling in these two syndromes. Somewhat surprisingly, previous studies showed no correlation between plasma aldosterone and sodium excretion in children with MCD (11,33). Other data for children with non-MCD are not available. In adults, we found previously that the negative correlation between plasma aldosterone and urine sodium in patients with MCD also existed in patients with non-MCD (8).

The most consistent change apparent from the renal hemodynamic studies was a low filtration fraction. This is known for children with MCD (11), but has not been published for children with non-MCD nephrosis. The modest decrease in GFR in the stable children with non-MCD cannot explain why they retain volume. Thus, as discussed previously for MCD (9,10), this must be due to some tubular defect, but our data do not indicate the responsible nephron segment. In rats with puromycin nephrosis, a model for human MCD, filtration fraction is low, and tubular sodium reabsorption high (37). In nephrotic models associated with histologic lesions, such as Heymann nephritis, filtration fraction is also low, and tubular sodium reabsorption high, in the absence of signs of a decreased effective circulating volume (38,39). In both cases, the increased reabsorption has been ascribed to impaired sensitivity of the inner medullary collecting tubules to ANP (40,41). The pathogenesis of the increased tubular reabsorption in humans is incompletely resolved; however, the present data in nephrotic children do not suggest a fundamental difference between patients with MCD and with nephrosis associated with non-MCD.

Children with non-MCD nephrosis constitute a quite heterogeneous group with regard to pathogenesis, glomerular pa-
thology, severity of proteinuria, and clinical course. Indeed, in accordance with the literature (12,13), proteinuria was particularly severe in the very young children with congenital nephrotic syndrome. Therefore, making comparisons as we did is not without hazard. On the other hand, it is this wide range in proteinuria that makes investigation of this group so instructive. Indeed, we believe that the present unique data are valuable for our understanding of the pathogenetic spectrum of nephrotic edema.

References

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