MAGNESIUM IN PEDIATRIC NEPHROTIC SYNDROME

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MAGNESIUM IN PEDIATRIC NEPHROTIC SYNDROME (Abstract) Aim: In the present study, we aimed to evaluate serum Mg concentration in children with nephrotic syndrome and highlight the relationship between Mg concentration and acute nephropathy. Material and methods: We conducted a clinical study in 27 patients, aged 2 to 17 years, admitted to the Nephrology clinic of the Iaşi “Sf. Maria” Children's Hospital between 2011-2015, with the diagnosis of idiopathic nephrotic syndrome (NS), first episode or relapse. In each patient, we investigated serum urea and creatinine, total cholesterol, total serum proteins, serum magnesium, urinary proteins, creatinine clearance and renal histopathology. We also used a control group of 14 children with normal renal function. Results: 12 patients had NS in the acute phase, 6 steroid responsive and 6 steroid resistant. The remaining 15 patients were in the remission phase of NS, 7 steroid responsive and 8 steroid resistant. Significantly decreased serum Mg levels were found in NS active group compared to control group. Renal histopathological analysis in steroid responsive patients revealed the following pathological aspects: optically normal glomeruli (1 case), minimal mesangial changes (5 cases), IgM nephropathy (4 cases), mesangioproliferative glomerulonephritis (4 cases). Conclusions: The variations of serum and urinary Mg levels in children with acute nephropathy may be useful for early diagnosis and improving therapy. Keywords: MAGNESIUM, NEPHROTIC SYNDROME, CHILDREN.

Nephrotic syndrome (NS) is one of the most frequently encountered glomerulopathy in children, being characterized by altered permeability of the glomerular capillaries and the inability to control urinary protein loss, leading to hypoproteinemia, hyperlipidemia and edema (1). Of all NS cases, about 90% are idiopathic, with favorable response to corticosteroids, and good prognosis. Ten percent of cases are steroid resistant, with little or no response to usual corticosteroid treatment (2, 3).

In terms of histopathology, NS can have the following aspects: minimal change disease (76.4%), mesangioproliferative glomerulonephritis (2.3%), membranoproliferative glomerulonephritis (7.5%), focal segmental glomerulosclerosis (6.9%), and membranous nephropathy (1.5%). Of the patients with minimal change disease, 95% respond favorably to corticoids (4). In NS, impaired glomerular function causes tubulointerstitial alterations through different mechanisms: glomerular hemodynamic and
selectivity disturbances, immunologic mechanisms, inflammatory mediators, leukocyte migration. All these lead to destruction of the glomeruli and renal tubules, and finally to tubulointerstitial lesions (5). About one third of steroid-resistant cases evolve towards end stage renal disease within 5 years of disease onset. Histopathology with minimal glomerular damage and mild mesangiproliferative glomerulonephritis has a benign clinical and pathological course without major tubulointerstitial lesions. Instead, focal segmental glomerulosclerosis and diffuse mesangiproliferative glomerulonephritis associate significant tubulointerstitial alterations and an increased risk of developing chronic kidney disease (6). Thus, early recognition of the histopathologic type and of the degree of the tubulointerstitial damage could be useful in establishing a targeted and effective therapy.

In the present study, we aimed to evaluate serum Mg concentration in children with nephrotic syndrome and highlight the relationship between Mg concentration and acute nephropathy.

MATERIAL AND METHODS

We conducted a retrospective study of 27 patients, aged 2 to 17 years, admitted to the Nephrology clinic of the Iasi "Sf. Maria" Children's Hospital between 2011-2015 with the diagnosis of idiopathic nephrotic syndrome, first episode or relapse. Also, included in the study were patients diagnosed before the year 2011, but who during the study interval had at least one hospitalization for treatment and reassessment. Of the 27 patients, 12 had acute nephrotic syndrome, 6 steroid-responsive and 6 steroid-resistant. The remaining 15 patients were in the remission phase of NS, 7 favorably responding to corticosteroid therapy and 8 being steroid-resistant.

Inclusion criteria were: age 0 - 18 years; diagnosis of idiopathic nephrotic syndrome. Exclusion criteria were: diagnosis of congenital nephrotic syndrome or secondary nephrotic syndrome; simultaneous presence of other diseases such as systemic lupus erythematosus, Henoch-Schonlein purpura, conditions that could cause magnesium loss (gastrointestinal illnesses, burns), administration of nephrotoxic substances (loop diuretics, gentamicin, contrast agents).

The following data were collected from each patient: socio-demographic characteristics, biochemical parameters: urea, creatinine, total cholesterol, total serum proteins, serum magnesium, urinary proteins, creatinine clearance, and renal histopathologic appearance. Measurement of all investigated parameters was performed using the standard methods of biochemistry and histopathology laboratories of the "Sf. Maria" Children's Hospital. Creatinine clearance was calculated using the formula: Cl Creat (ml/min/1.73m²) = ((0.035 x Age (years)) + 0.236) x 100) / serum creatinine (mg/dL) (7) and renal histopathological analysis.

We used a control group of 14 children, aged 2-17 years, with normal renal function, hospitalized in the General Pediatrics Clinic with functional abdominal pain syndrome, in which we followed-up the serum Mg levels for comparing them with the levels reported in the study group. The study was conducted with the approval of the Ethics Committee of the institution for the use of medical data and informed consent was obtained from all patients. Statistical analysis was performed using unpaired t-test and Fisher's test. The results were expressed as mean ± standard devia-
tion. Coefficient p values <0.05 were considered statistically significant.

RESULTS
The study was conducted on a sample of 27 patients (16 males and 11 females), aged 2 to 17 years, diagnosed with idiopathic nephrotic syndrome, which had at least one hospitalization in the Nephrology Clinic in the interval 2011-2015. The diagnosis of nephrotic syndrome was based on the presence of the following biological changes: hypoproteinemia, hypercholesterolemia, proteinuria. For NS in remission phase, the values of these parameters were within normal ranges.

In the study group, 12 patients had acute NS and 15 patients NS in remission phase. Depending on the response to treatment, steroid resistance was detected in 6 patients with active SN and 8 patients in remission (fig. 1).

![Fig. 1. Distribution of nephrotic syndrome in the study group](image)

The mean age was 6.58 ± 4.14 years for active NS group, and 9.66 ± 4.65 years for remission NS group.

### TABLE I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>active NS (n=12)</th>
<th>NS remission (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total serum proteins (g/l)</td>
<td>44.62 ± 7.18*</td>
<td>68.21 ± 5.40</td>
</tr>
<tr>
<td>total cholesterol (mg/dl)</td>
<td>381.16 ± 134*</td>
<td>169.06 ± 31.49</td>
</tr>
<tr>
<td>urinary proteins (mg/dl)</td>
<td>300 ± 0*</td>
<td>0</td>
</tr>
<tr>
<td>urea (mg/dl)</td>
<td>32.91 ± 11.62</td>
<td>27.33 ± 6.14</td>
</tr>
<tr>
<td>creatinine (mg/dl)</td>
<td>0.71 ± 0.58</td>
<td>0.59 ± 0.12</td>
</tr>
<tr>
<td>creatinine clearance (ml/min/1.73m²)</td>
<td>82.23 ± 31.38</td>
<td>96.90 ± 23.63</td>
</tr>
<tr>
<td>Serum Mg (mg/dl)</td>
<td>1.96 ± 0.30*</td>
<td>2.31 ± 0.77</td>
</tr>
</tbody>
</table>

*p<0.0001

The investigated parameters, namely total serum proteins, total cholesterol and urinary proteins, showed mean levels significantly different in patients with active NS compared to children with NS in remission. Thus, in the active NS group compared to remission NS group, serum proteins levels were low (p<0.0001), serum
total cholesterol levels were higher (p<0.0001) and proteinuria was present in all children with active NS, while patients in remission showed no urinary protein loss (p<0.0001) (tab. I). All these data confirmed the acute nature of the disease in the active NS group, and the favorable response to treatment with occurrence of remission and normalization of parameters that are typically affected in acute nephropathy for the group with NS in remission. Regarding renal function parameters, serum urea and creatinine, one case of azotemia was reported in active NS group (serum creatinine 2.47 mg/dl), while in NS remission group there was no case of nitrogen retention. Also, creatinine clearance values did not vary significantly between acute NS patients and NS remission group (tab. I).

Renal histopathological analysis of steroid-resistant patients in the 2 groups revealed the following pathological aspects: active NS group: optically normal glomeruli (1 case), minimal mesangial changes (2 cases), IgM nephropathy (3 cases); remission NS group: minimal mesangial changes (3 cases), mesangiproliferative glomerulonephritis (4 cases), IgM nephropathy (1 cases). The most common histological aspect was minimal mesangial changes (36%), followed by the mesangiproliferative aspects (29%) and IgM deposits (28%).

**TABLE II.**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>Standard Error</th>
<th>Min</th>
<th>Max</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active NS</td>
<td>12</td>
<td>1.96</td>
<td>0.30</td>
<td>0.08</td>
<td>1.53</td>
<td>2.30</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>Remission NS</td>
<td>15</td>
<td>2.31</td>
<td>0.77</td>
<td>0.19</td>
<td>1.61</td>
<td>4.81</td>
<td>0.71</td>
</tr>
<tr>
<td>Control</td>
<td>14</td>
<td>2.23</td>
<td>0.10</td>
<td>0.02</td>
<td>2.10</td>
<td>2.43</td>
<td></td>
</tr>
</tbody>
</table>

*vs. control

The results showed decreased serum Mg levels in active NS group (1.96 ± 0.30 mg/dl) compared to control group (2.23 ± 0.10 mg/dl), the difference being statistically significant (p<0.05) (tab. II). However, although serum Mg was significantly lower in patients with acute nephropathy compared to controls (p<0.05), divalent cation concentration showed no significant variation between active and remission groups.

**DISCUSSION**

Literature data (8, 9) have suggested a link between serum and urinary Mg and tubulointerstitial function, given that both reabsorption of filtered Mg and retention of serum Mg occur in renal tubules. Any structural or functional alteration of the renal epithelium interferes with the tubular loss and reabsorption of Mg, leading to increased Mg urinary excretion. Hypomagnesemia is a common electrolyte disorder which occurs in approximately 12% of hospitalized patients. This incidence may increase to 60-65% in patients in Intensive Care Units due to nutritional deficiencies, hypoalbuminemia, hypotension, sepsis, use of such medications as diuretics or amino-
glycosides (10).

The results of our study show that serum Mg levels were significantly lower in patients with active nephropathy compared to those in remission (p<0.5). Since Mg is a divalent cation and its homeostasis depends on kidney filtration, low Mg levels in children with active NS reflect an alteration of renal excretion and reabsorption of Mg (11, 12).

In the literature, there are few studies regarding the implications of Mg deficiency on renal function after an episode of acute kidney injury (AKI). Santos et al. (13) showed that hypomagnesemia is a risk factor for irreversible renal function recovery in patients with AIDS (acquired immunodeficiency syndrome) and AKI. Similarly, Alves et al. (14) investigated Mg variation in a group of 232 patients admitted in the Intensive Care Unit and who experienced impaired renal function. It has been demonstrated that the prevalence of hypomagnesemia was 63% in the study group, the patients who showed no recovery of renal function having a significantly higher prevalence of hypomagnesemia (70%) compared with those with recovered renal function (31%).

Cheungpasitporn et al. (15) investigated the link between Mg variation and the occurrence of renal impairment in a group of 9241 patients, of which 124 developed AKI. Their results showed that the lowest incidence of AKI was in patients with serum Mg levels within the normal range, between 1.7 and 2.1 mg/dl. Instead, both hypomagnesemia (< 1.5 mg/dl) and hypermagnesemia (≥ 2.3 mg/dl) were associated with a higher incidence of developing kidney damage.

There are several theories that may explain the association between magnesium deficiency and renal impairment in AKI. Mg competes with calcium (Ca) transport in the cell membranes, leading to decreased intracellular calcium concentration, and secondary to smooth muscle relaxation (16). Administration of Mg produces peripheral vasodilatation, predominantly arteriolar, not only by stimulating the production of nitric oxide, but also by its ability to antagonize directly with Ca (17).

In addition to vasodilatory effects, Mg is associated with effects on microcirculation, such as: increased deformability of red blood cells, reduced platelet aggregation, anti-inflammatory effects, maintaining the endothelial integrity (18). Other similar studies (8, 19) which have investigated the homeostasis of Mg in nephrotic syndrome, showed the existence of increased Mg urinary excretion, in focal and segmental glomerulosclerosis and mesangioproliferative glomerulonephritis. Also, Gheissari et al. (20) revealed elevated renal Mg excretion, suggesting the possible use of Mg concentration as an early marker for detecting the tubular malfunction and as an indicator of residual tubular lesions.

Our results showed, in patients with steroid resistant NS, histopathological lesions which are consistent with literature data, indicating the presence of minimal change glomerulonephritis in steroid resistant NS in proportions ranging from 25% (21) to 45.5% (4).

CONCLUSIONS
The present clinical trial is particularly useful in medical practice, suggesting the importance of investigating the variations of serum and urinary Mg in pediatric acute nephropathy, along with standard measures of other ions such as Na, K, Cl, with the possible early detection of patients with unfavorable response to therapy.
REFERENCES