Pathophysiological Role of Magnesium in Familial Bartter’s Syndrome

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We studied three siblings with Bartter’s syndrome associated with hypomagnesemia; two of them showing marked hypomagnesemia and the other mild hypomagnesemia. Urinary potassium, sodium and chloride excretions were determined and distal fractional chloride reabsorption and free water clearance on water loading test were compared before and after magnesium supplementation. Baseline urinary potassium and magnesium excretions were elevated in spite of the decreased plasma levels, whereas distal fractional chloride reabsorption and free water clearance were depressed in all patients. Magnesium repletion resulted in significant decrease in urinary potassium, sodium and chloride and subsequent increase in plasma potassium in all patients. However, neither distal fractional chloride reabsorption nor free water clearance was affected. Hypomagnesemia may contribute to urinary potassium wasting and aggravate urinary sodium and chloride wasting in familial Bartter’s syndrome by a mechanism independent of the defect in free-water formation by the active reabsorption of chloride in Henle’s loop.

(Internal Medicine 33: 1-5, 1994)

Key words: hypomagnesemia, hypokalemia, free water clearance

Introduction

Bartter’s syndrome, first reported in 1962, is characterized by hypokalemia, metabolic alkalosis, hyperreninemia, secondary aldosteronism, hyperplasia of juxtaglomerular cells and normal blood pressure (1). A defect in chloride and sodium reabsorption in the thick ascending limb of Henle’s loop provides a reasonable explanation for the serial events that characterize this syndrome (2, 3). Although hypomagnesemia has also been noted in some of the patients with this syndrome, little is known about its pathophysiological significance (4). Experimental magnesium depletion, on the other hand, causes hypokassemia which is due to an increased renal loss of potassium (5). Potassium depletion then might also affect chloride reabsorption in the loop of Henle (6, 7). Abnormal renal handling of magnesium could occur in the syndrome, in as much as the divalent cation is reabsorbed in the thick ascending limb of Henle’s loop (8-10). Thus hypomagnesemia in the syndrome may reflect a complex tubular disorder which also includes a defect of chloride reabsorption. However the role of hypomagnesemia in the syndrome has not yet been clearly elucidated (11). Moreover, the effects of magnesium repletion on hypokalemia, hyperreninemia and hyperaldosteronism have not been systematically studied in familial Bartter’s syndrome associated with hypomagnesemia.

The present study was undertaken to determine the effect of magnesium repletion on free water clearance, distal fractional chloride reabsorption, renin-angiotensin-aldosterone system and urinary sodium, potassium and chloride excretions in three siblings with familial Bartter’s syndrome and hypomagnesemia.

Case Reports

Case 1

A 24-year-old Japanese woman was admitted to our hospital because of tetany of greater than a ten-year duration. Tetany had become pronounced over the previous two months. She denied use of any diuretics, laxatives or any other medications and had not experienced vomiting or diarrhea.

On physical examination, the patient was well nourished, 160 cm tall and weighed 62 kg. Blood pressure was 112/60 mmHg without orthostatic change. Chvostek’s sign was negative, but Trousseau’s sign was positive. Carpopedal spasm readily appeared on slight hyperventilation. Physical and neurological examinations were otherwise non-contributory.

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Laboratory data on admission revealed serum sodium 142 mEq/l, potassium 2.2 mEq/l, chloride 96 mEq/l, bicarbonate 32.3 mEq/l, creatinine 0.7 mg/dl, blood urea nitrogen 9.0 mg/l,
dl and uric acid 4.6 mg/dl. Serum magnesium was 1.3 mg/dl (normal 1.7 to 2.1 mg/dl), calcium 9.5 mg/dl, phosphate 3.1 mg/dl. Total protein was 6.8 g/dl with albumin of 4.3 g/dl. Urinalysis revealed a pH of 7.3 and no protein, amino acid or glucose. The urinary sediment showed no abnormality. Endogenous creatinine clearance was 134 ml/min/1.73 m².

A percutaneous kidney biopsy specimen revealed hypertrophic and hyperplastic juxtaglomerular apparatus (Fig. 1).

Case 2

The younger sister of Case 1 aged 20 was referred to our hospital for evaluation of tetany. She had complained of carpopedal spasmus similar to her elder sister since the age of 10. She had spontaneous muscle spasmus during lengthy conversation. Physical examination revealed a well-nourished woman apparently in good health; she was 158 cm tall and weighed 50 kg. Blood pressure was 104/68 mmHg without orthostatic change. Chvostek’s sign was negative, but Trousseau’s sign was easily elicited by clamping a forearm for a few seconds. Other physical findings were within normal limits.

Serum sodium was 142 mEq/l, potassium 2.4 mEq/l, chloride 99 mEq/l, and bicarbonate 30.3 mEq/l. Serum magnesium was 1.1 mg/dl and creatinine 0.7 mg/dl. Total protein was 7.1 g/dl with an albumin of 4.5 g/dl. Urinalysis revealed a pH of 7.2 and negative protein, amino acid and glucose. The urinary sediments showed no abnormalities. Endogenous creatinine clearance was 123 ml/min/1.73 m². Plasma angiotensin II was 75 pg/ml (normal <60 pg/ml). Intravenous infusion of 30 ng/kg/min angiotensin II did not cause blood pressure elevation, however 50 ng/kg/min angiotensin II increased systolic and diastolic blood pressure by 20 mmHg, suggesting a decreased vascular pressor sensitivity to angiotensin II.

Case 3

The 17-year-old younger brother of Cases 1 and 2 was admitted for the evaluation of hypokalemia. He had not experienced tetany, muscle weakness, spasmus, or other symptoms. He was 172 cm tall and weighed 60 kg. Blood pressure was 110/70 mmHg without orthostatic change. Physical examination did not reveal any abnormalities.

Laboratory data on admission revealed the following: serum sodium 139 mEq/l, potassium 2.6 mEq/l, chloride 97 mEq/l, bicarbonate 29.6 mEq/l, magnesium 1.6 mg/dl, calcium 9.3 mg/dl, phosphate 4.3 mg/dl, uric acid 6.7 mg/dl, blood urea nitrogen 20.9 mg/dl and creatinine 1.0 mg/dl. During the observation period, he showed mild hypomagnesemia ranging from 1.5 to 1.8 mg/dl. Endogenous creatinine clearance was 99 ml/min/1.73 m². Urinalysis revealed constant alkali urine and no protein or glucose. The urinary sediment showed no abnormalities.

Plasma angiotensin II was 75 pg/ml (normal <60 pg/ml). Intravenous infusion of 30 ng/kg/min angiotensin II did not cause blood pressure elevation, however 50 ng/kg/min angiotensin II increased systolic and diastolic blood pressure by 20 mmHg, suggesting a decreased vascular pressor sensitivity to angiotensin II.

Other family members including their parents and grandmothers were healthy and showed a normal serum potassium and magnesium level.

Methods

The three siblings were admitted to the metabolic ward during the studies. The following protocol had been approved by the ethical committee of Tokyo Medical and Dental University. They were placed on a diet containing 120 mEq sodium, 80 mEq potassium, and 250 mg magnesium daily throughout the study. Three days after admission, the study was initiated. After a baseline observation period of seven days, magnesium sulphate, containing 400 mg of magnesium, was infused daily for seven days. The duration of Mg infusion was five hours at a speed of 80/h. Urine was collected for 24-hour periods except during half-saline infusion tests. The endogenous creatinine clearance was used to estimate the glomerular filtration rate (12). The mean±standard error of urinary and serum electrolytes for seven days before and during magnesium infusion periods was considered as the average value of urinary and serum electrolytes.

Free water clearance (\( \Delta H_2O \)) studies, to estimate the index of chloride reabsorption in the ascending limb of the loop of Henle (13, 14), were performed on the morning after seven-day baseline and Mg infusion periods.

To suppress endogenous vasopressin, each patient was first given a bolus of 0.45% saline solution intravenously over a 40 minutes (20 ml/kg body weight), then the infusion rate was 5 ml/min, and was subsequently adjusted to exceed urinary flow by 5 ml/min. Blood and urine samples were obtained every 30 minutes after completing an initial load of intravenous half saline to measure creatinine, osmolality, sodium, potassium, chloride and magnesium concentrations. To confirm endogenous vasopressin suppression, plasma arginine vasopressin concentrations were determined both at the end of initial half-

Fig. 1. Malpighian body of biopsy specimen of Case 1 showed hyperplasia of juxtaglomerular apparatus of afferent arteriole. This section was stained with periodic-acid Schiff (PAS) reagent (×400).
saline load and at the end of each infusion. Free water clearance was calculated by the formula: $C_{H_2O} = V - (U_{osm} V / S_{osm})$, where $V = $ urine flow, $U_{osm} = $ urine osmolality and $S_{osm} = $ serum osmolality. Chloride clearance ($C_{Cl}$) was calculated by the formula: $C_{Cl} = U_{Cl} V / S_{Cl}$, where $U_{Cl} = $ urinary chloride concentration and $S_{Cl} = $ serum chloride concentration. Distal fractional chloride reabsorption was calculated as $C_{H_2O} / (C_{H_2O} + C_{Cl})$.

Values are expressed as mean±standard error unless otherwise stated. Significance of data was determined by Student’s t test.

Results

(1) Baseline data before magnesium infusion

The three patients strictly followed our dietary regimen during the study period. Average 24-hour urinary excretions of potassium, sodium, chloride and magnesium for seven days were 65±5.1 mEq, 134±8 mEq, 135±8 mEq and 115±22 mg, respectively (mean of three cases). Potassium and magnesium excretions were markedly elevated in spite of decreased serum levels at 2.3±0.2 mEq/l and 1.4±0.2 mg/dl, respectively. Plasma renin activity (PRA, normal: 0.8–4.4 ng Ang I/ml/hr) and plasma aldosterone concentration (PAC, normal: 2–13 ng/dl) were elevated in all patients (PRA: 19.1, 10.4, 13.4; PAC: 35.2, 15.4, 14.8 in cases 1, 2 and 3, respectively).

(2) Changes during magnesium infusion

After magnesium sulphate infusion (400 mg/day), the average urinary potassium excretion decreased significantly from 68±3 to 28±3 mEq/day in Case 1 (p<0.01), from 72±3 to 25±2 mEq/day in Case 2 (p<0.01) and from 55±2 to 22±2 mEq/day in Case 3 (p<0.01). Moreover, the average sodium and chloride excretions decreased significantly in Case 1 (Na: 120±13 vs. 66±10 mEq/day, p<0.01; Cl: 122±13 vs. 76±13 mEq/day, p<0.05) and Case 2 (Na: 135±15 vs. 72±11 mEq/day, p<0.01; Cl: 133±12 vs. 70±10 mEq/day, p<0.01), but the decreases did not reach statistical significance in Case 3 (Na: 148±5 vs. 137±6 mEq/day; Cl: 151±11 vs. 138±7 mEq/day).

Average serum potassium concentration for seven days increased from 2.2±0.1 to 2.7±0.1 mEq/l in Case 1 (p<0.01), from 2.1±0.1 to 2.6±0.2 mEq/l in Case 2 (p<0.01) and from 2.6±0.1 to 3.2±0.1 mEq/l in Case 3 (p<0.01). Serum magnesium also increased from 1.2±0.1 to 1.8±0.1 mg/dl in Case 1 (p<0.01), from 1.1±0.1 to 1.7±0.1 mg/dl in Case 2 (p<0.01) and from 1.6±0.2 to 2.0±0.1 mg/dl in Case 3 (p<0.01). Serum sodium and chloride did not change significantly in all three cases. Representative changes of serum and urine electrolytes in Case 1 are shown in Fig. 2.

PRA and PAC decreased from 19.1 to 6.6 ng/ml/hr and from 35.2 to 13.0 ng/dl, respectively in Case 1 after magnesium infusion. In Case 2, they also decreased from 10.4 and 15.4 to 5.0 ng/ml/hr and 12.1 ng/dl, respectively. However they were unchanged in Case 3 (PRA: from 13.4 to 15.4 ng/ml/hr, PAC: from 14.8 to 14.0 ng/dl). Serum bicarbonate and daily urine volume did not change significantly during magnesium infusion in all three cases.

Fig. 2. Representative changes of serum and urinary potassium, sodium, chloride and magnesium before, during and after magnesium sulphate infusion in Case 1. Dotted line represents total intake.
Table 1. Results from Maximal Free Water Clearance Study During Hypotonic Saline Diuresis Before and After Magnesium Infusion

<table>
<thead>
<tr>
<th></th>
<th>Case 1 Before</th>
<th>Case 1 After</th>
<th>Case 2 Before</th>
<th>Case 2 After</th>
<th>Case 3 Before</th>
<th>Case 3 After</th>
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<tr>
<td>V (ml/min)</td>
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<td>12.6</td>
<td>10.23</td>
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<td>Posm (mOsm/Kg H2O)</td>
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<td>251</td>
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<td>273</td>
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<td>Uosm (mOsm/Kg H2O)</td>
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<td>132</td>
<td>128</td>
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<td>120</td>
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<td>Cosm (ml/min)</td>
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<td>3.55</td>
<td>4.61</td>
<td>4.02</td>
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<td>CH2O (ml/min)</td>
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<td>CH2O+CCI (ml/min)</td>
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<td>6.35</td>
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<td>0.62</td>
<td>0.59</td>
<td>0.63</td>
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<td>GFR (ml/min)</td>
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<td>115</td>
<td>110</td>
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<td>1.5</td>
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<td>SCI (mEq/l)</td>
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(3) Half-saline diuresis studies before and after magnesium infusion (Table 1)

In all three patients, plasma arginine vasopressin was less than the detection limit through half-saline infusion studies. Before magnesium infusion, free water clearance (CH2O) was depressed remarkably to approximately half of the normal value (4) in Cases 1 and 2, whereas the impairment in Case 3 was slight (Table 1). Fractional distal chloride reabsorption (normal: >80%, ref. 3) was impaired in all three cases; 64, 62, 63% in Cases 1, 2, and 3, respectively (Table 1).

Free water clearance (CH2O) after 7-day magnesium infusion did not improve at all. Neither did distal fractional chloride reabsorption improve at all after magnesium infusion in two patients. However, it was slightly improved in Case 3, although still much lower than the normal value (Table 1). Plasma and urinary osmolality and urinary volume did not change appreciably after magnesium infusion.

Discussion

The diagnosis of familial Bartter’s syndrome was confirmed in the present three sibling patients, with hypokalemic alkalosis, high plasma renin activities, normal blood pressure, resistant to angiotensin II [Case 2, 3] and the hyperplasia of juxtaglomerular apparatus [Case 1]. Bartter’s syndrome is sometimes genetically transmitted in an autosomal recessive manner. In few instances the defect in distal fractional chloride reabsorption was described for all affected siblings (15). In our study, all affected siblings showed decreased distal fractional chloride reabsorption, which was originally proposed as the proximate cause of this syndrome by Gill and Bartter (3).

Hypomagnesemia has also been found in the syndrome in some of the patients. It was marked in Cases 1 and 2, and mild in Case 3. Since magnesium divalent ion is predominantly reabsorbed in the thick ascending limb of the loop of Henle by active chloride reabsorption as the major driving force, namely the site where most of distal chloride reabsorption takes place, impairment of renal magnesium conservation might also coexist in the syndrome (7, 8, 10).

Baehler et al (4) found that infusions of magnesium chloride (875 mg magnesium/day) restored the plasma magnesium level to normal, and corrected a defect in renal potassium wasting, remarkably improved plasma potassium, but failed to normalize PRA and PAC in a sporadic case of Bartter’s syndrome with hypomagnesemia. However, in familial Bartter’s syndrome such studies have yet to be done. Moreover, since they used a chloride compound to supplement magnesium, the changes in urinary chloride excretion were not assessed (4). A large amount of chloride ion might also affect the reabsorption of sodium and potassium in the renal tubule. Therefore the correction of renal potassium wasting might not be solely due to magnesium supplementation.

We have clearly demonstrated that in all three siblings with familial Bartter’s syndrome, infusion of magnesium sulphate (400 mg magnesium/day) normalized plasma magnesium and induced decreases in urinary potassium, sodium and chloride excretions and subsequent elevation in plasma potassium. Since sulphate is one of non-reabsorbable anion in renal tubule, it may aggravate hypokalemia by distracting the proton in the lumen. Therefore the correction of potassium is not due to the effect of sulphate. Magnesium supplementation decreased PRA and PAC in Cases 1 and 2. The decrease in PRA and PAC after magnesium infusion may be due to a correction of hypovolemia mediated by improved sodium and chloride reabsorption. In Case 3, corrections of urinary loss of chloride and sodium by magnesium infusion were small, therefore PRA and PAC were not decreased appreciably. The smaller degree of correction in serum electrolytes may be due to milder hypokalemia and hypomagnesemia of Case 3, before loading magnesium sulphate compared to the other two cases.

A possible role for magnesium as a modulator of the renin-aldosterone system is suggested by results of magnesium administration in several cases of hypomagnesemia. Plasma aldosterone concentration has been reported to increase in
response to magnesium deprivation (16). Hyperaldosteronism induced by magnesium depletion might be functionally significant with respect to the pathogenesis of the concomitant renal potassium wasting. The improvement in renal handling of potassium in Cases 1 and 2 might be therefore the consequence of reduced levels of aldosterone. However, the unchanged PAC in Case 3 presumably reflected other mechanisms that improved renal potassium wasting.

Cellular depletion of magnesium in the loop of Henle may be the major cause of the renal potassium wasting since the reabsorption of potassium in the loop of Henle is dependent upon reabsorption of sodium and the driving force for sodium reabsorption is generated by the activity of a magnesium-dependent enzyme, namely Na-K-ATPase localized in the basolateral membrane. However, magnesium repletion failed to improve significantly fractional distal chloride reabsorption in all cases. Persistent abnormality in distal fractional chloride reabsorption after magnesium supplements in all three cases may support the contention that impairment in salts reabsorption in the loop of Henle is the proximate cause of Bartter’s syndrome. Correction of renal potassium, sodium and chloride reabsorption after magnesium supplement in this study, therefore, indicates that hypomagnesemia decreases the compensatory increase in salts reabsorption in nephron sites other than the thick ascending limb of Henle.

Distal delivery from the proximal tubule as estimated by \( C_{\text{H}_{2}O} + C_{\text{Cl}} \) was persistently subnormal and unchanged in three siblings even after magnesium infusion (Table 1). The enhanced reabsorption of sodium and chloride in the proximal tubule has been suggested when reabsorption of these ions is decreased in the ascending limb of the loop of Henle (17). Since magnesium infusion can curtail urinary potassium, sodium and chloride without a significant change in distal delivery, the site where magnesium correction is exerted might not be the proximal tubules. Thus, hypomagnesemia (presumably, intracellular low magnesium) would inhibit the compensatory increases in salts reabsorption in nephron segments beyond the loop of Henle.

In summary, the present data demonstrate that there are derangements of both sodium, potassium and chloride transport, and magnesium reabsorption in this familial Bartter’s syndrome. Magnesium depletion may undermine the compensatory increase in reabsorption of potassium, sodium and chloride in the nephron beyond the loop of Henle. Magnesium deficiency could be a deleterious factor causing electrolytes and volume loss in familial Bartter’s syndrome. We conclude that magnesium depletion may be responsible, at least in part, for the deranged reabsorption of sodium, chloride and potassium in familial Bartter’s syndrome associated with hypomagnesemia.

Acknowledgements: We would like to express cordial thanks to Dr. Shunya Uchida of the Division of Nephrology, Showa General Hospital and Dr. Toshiro Fujita of the Fourth Department of Internal Medicine, University of Tokyo for their valuable suggestions and discussions.

References