Milk alkali syndrome in an infant with chronic kidney disease

Jameela A Kari
Sherif M El Desoky
Department of Pediatrics and Pediatric Nephrology Unit, King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia

Abstract: We report a case of milk alkali syndrome in a 15-month-old infant who had chronic kidney disease. His kidney function worsened, with creatinine raised from 1.11 mg/dL (98 µmol/L) to 3.98 mg/dL (350.3 µmol/L), normal 0.4–1.0 mg/dL (35–91 µmol). He had hypercalcemia, serum calcium level 3.11 (normal 2.1–2.6) mmol/L, and metabolic alkalosis, HCO3 48.7 (normal 21–26) mmol/L. His kidney function returned to its base level and his calcium and bicarbonate levels normalized with adjustment of calcium carbonate and sodium bicarbonate doses. We report this case to highlight an unusual complication and to review the literature on milk alkali syndrome which is rare in children.

Keywords: milk alkali syndrome, infants, chronic kidney disease

Introduction
Milk alkali syndrome consists of hypercalcemia, various degrees of renal failure, and metabolic alkalosis due to ingestion of large amounts of calcium and absorbable alkali. This syndrome was first identified after medical treatment of peptic ulcer disease when milk and alkali were widely adopted at the beginning of the 20th century.1 After the introduction of histamine 2 blockers and proton pump inhibitors, the occurrence of milk alkali syndrome became rare; however, a resurgence of milk alkali syndrome has been witnessed because of the wide availability and increasing use of calcium carbonate, mostly for osteoporosis prevention.1 Oral calcium carbonate is now the predominant source of calcium and alkali associated with the development of milk alkali syndrome (with or without milk intake).2–4 Milk alkali syndrome is currently believed to be the third most common cause of in-hospital hypercalcemia in adults, after hyperparathyroidism and malignant neoplasm.5 Because milk alkali syndrome is rare in children, we report a case of a young child who developed milk alkali syndrome as a complication of conservative management of chronic kidney disease by using calcium carbonate and sodium bicarbonate.

Case report
This case concerns a 15-month-old boy with stage 3 chronic kidney disease. His renal impairment was accidentally discovered at the age of 6 months, after an episode of febrile seizure following pertussis-diphtheria-tetanus vaccination. He was born at term by emergency cesarean section due to fetal distress. Birth weight was small for dates at 2 kg. He needed admission to the neonatal intensive care unit for 33 days and required mechanical ventilation for a few days. He was found to have a small ventricular septal
defect, 5.5 mm in diameter, for which he was commenced on captopril and furosemide for 9 months.

He was referred to our hospital at 12 months of age, with severe failure to thrive, a weight of 5 kg and length of 64 cm (both below the 3rd centile for age). Renal ultrasound showed echogenic kidneys, with no evidence of hydronephrosis or back pressure. The underlying etiology of his chronic kidney disease remains unknown. His calculated glomerular filtration rate by Schwartz formula was 30 mL/min/1.73 m². His albumin was 3 g/L, and his serum ionized calcium was 2.65 mmol/L (normal level 2.15–2.55 mmol/L). His serum phosphorus was 1.36 mmol/L (normal level 0.8–2.0 mmol/L) to 3.98 mg/dL (normal level 0.4–1.0 mg/dL). His serum sodium was 132 mmol/L (normal level 135–145 mmol/L) to 124 mmol/L (normal level 135–145 mmol/L). His serum bicarbonate was 23 mmol/L (normal level 22–28 mmol/L) to 10 mmol/L (normal level 22–28 mmol/L). His serum creatinine was 183 µmol/L (normal level 54–130 µmol/L) to 3.98 mg/dL (normal level 0.4–1.0 mg/dL). His serum uric acid was 550 µmol/L (normal level 195–900 µmol/L) to 743 µmol/L (normal level 195–900 µmol/L). His serum potassium was 3.6 mmol/L (normal level 3.5–5.5 mmol/L) to 2.7 mmol/L (normal level 3.5–5.5 mmol/L). His glucose was 4.4 mmol/L (normal level 4.4–6.1 mmol/L) to 5.1 mmol/L (normal level 4.4–6.1 mmol/L). His blood urea nitrogen was 21 mg/dL (normal level 8–20 mg/dL) to 145 mg/dL (normal level 8–20 mg/dL). His serum albumin was 3 g/L (normal level 3.5–5.5 g/L) to 2.4 g/L (normal level 3.5–5.5 g/L). His serum total protein was 32 g/L (normal level 40–70 g/L) to 21 g/L (normal level 40–70 g/L). His serum total cholesterol was 4.6 mmol/L (normal level 4.0–6.2 mmol/L) to 11.3 mmol/L (normal level 4.0–6.2 mmol/L). His serum triglyceride was 1.4 mmol/L (normal level 0.6–2.2 mmol/L) to 16.5 mmol/L (normal level 0.6–2.2 mmol/L). His liver enzymes were normal. His serum iron was 25 µmol/L (normal level 20–60 µmol/L) to 40 µmol/L (normal level 20–60 µmol/L). His serum ferritin was 230 µg/L (normal level 10–400 µg/L) to 400 µg/L (normal level 10–400 µg/L). His serum ferritin index was 350.3 µg/L, and his serum ferritin index was 350.3 µg/L. His serum ferritin index was 350.3 µg/L to 5.5 mm in diameter, for which he was commenced on captopril and furosemide for 9 months.

Three months later, he developed frequent vomiting, weakness, polydipsia, and polyuria, with dehydration of insidious onset and a progressive course. Laboratory findings showed an acute rise in blood urea nitrogen and creatinine, together with hypercalcemia and hypochloremic metabolic alkalosis (Table 2).

His clinical picture was suggestive of acute on chronic renal failure mediated by vomiting and dehydration. However, after correction of his dehydration with intravenous fluids, the patient continued to have sustained hypochloremic metabolic alkalosis, with progressive deterioration of renal function tests, together with hypercalcemia. His creatinine increased from 1.11 mg/dL (98 µmol/L) to 3.98 mg/dL (350.3 µmol/L), normal level 0.4–1.0 mg/dL (35–91 µmol/L). Therefore, a diagnosis of milk alkali syndrome or calcium alkali syndrome was made, and readjustment of his chronic renal failure. However, after correcting dehydration with intravenous fluids, the patient continued to have sustained hypochloremic metabolic alkalosis, with progressive deterioration of renal function tests, together with hypercalcemia. His creatinine increased from 1.11 mg/dL (98 µmol/L) to 3.98 mg/dL (350.3 µmol/L), normal level 0.4–1.0 mg/dL (35–91 µmol/L). Therefore, a diagnosis of milk alkali syndrome or calcium alkali syndrome was made, and readjustment of his chronic renal failure was made. Table 2 summarizes the laboratory results, showing that milk alkali syndrome occurred 4 months after his presentation to our hospital and improved after adjustment of calcium carbonate and withholding sodium bicarbonate. Oral sodium bicarbonate was withheld for a few weeks then restarted cautiously (Table 2). Figure 1 demonstrates the positive correlation of worsening kidney function with degree of alkalosis and hypercalcemia.

The Pearson’s correlation test showed a positive correlation between pH and creatinine (P = 0.016), creatinine and bicarbonate (P = 0.001), and pH and bicarbonate (P = 0.002), while no correlation was found between serum calcium and pH, bicarbonate, and serum creatinine (P = 0.17, P = 0.4, and P = 0.8, respectively). At peak serum creatinine, a peritoneal catheter was inserted, which was not used because we observed rapid improvement of kidney function tests after adjustment of doses. With correction of the ongoing metabolic alkalosis that was associated with hypercalcemia, serum creatinine and blood urea slowly went back to base levels and the peritoneal catheter was removed after 4 months because his laboratory results showed continuous improvement of renal function tests (Table 2). He had a normal vitamin D3 level of 117 (75–200) nmol/L.

**Discussion**

Here we report a case of milk alkali syndrome in a young child aged 15 months with chronic kidney disease. To our knowledge, milk alkali syndrome has not been reported before in the pediatric age group. At presentation to our unit, the child had mild metabolic acidosis and was therefore treated with rather high doses of sodium bicarbonate (6 mmol/kg/day) and acceptable doses of calcium carbonate according to the European guidelines. When he presented with frequent vomiting and weakness, this could be easily confused with metabolic alkalosis caused by losing acid due to repeated vomiting, resulting in dehydration and acute on chronic renal failure. However, after correcting dehydration in the previous scenario, one would expect correction of the alkalosis or even return of acidosis caused by chronic kidney disease. Progression of chronic kidney disease was another possibility. However, persistent metabolic alkalosis, hypercalcemia, and worsening of kidney function are indicators of milk alkali syndrome.

The diagnosis of milk alkali syndrome requires a history of excessive calcium and absorbable alkali ingestion and

<table>
<thead>
<tr>
<th>Table 1 Summary of medications used before, during, and after the episode of milk alkali syndrome (shaded area)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At presentation (0–12 months)</strong></td>
</tr>
<tr>
<td>Alfalcaldiol 15–30 ng/kg/day</td>
</tr>
<tr>
<td>Calcium carbonate 300 mg 3–4 times/day</td>
</tr>
<tr>
<td>NaHCO3, initially 1–2 mmol/kg, to be adjusted</td>
</tr>
<tr>
<td>Erythropoietin alfa/week 75–150 IU/kg three times/week</td>
</tr>
<tr>
<td>Elemental iron 3–6 mg/kg/day</td>
</tr>
<tr>
<td>Folic acid 1–2 mg/day</td>
</tr>
</tbody>
</table>

**Note:** Usual doses are written next to the name of each medication.

**Abbreviations:** bid, twice daily; tid, three times daily.
findings of hypercalcemia, metabolic alkalosis, and variable 
degrees of renal impairment. The symptoms may develop 
within several days to several weeks and months after the 
start of therapy with absorbable alkali and calcium. Three 
forms of milk alkali syndrome have been described, ie, 
acute, subacute (Cope’s syndrome), and chronic (Burnett’s 
syndrome). These three forms should be considered a con-
tinuum, because there is overlap between them. Milk alkali 
syndrome was described first in middle-aged men with peptic 
ulcer disease. More recently, milk alkali syndrome has been 
reported in older women who received calcium supplements 
for osteoporosis. Clinically, these patients present in an 
acute hypercalcemic crisis, responding rapidly to hydration 
with no need for bisphosphonates because the phosphorus 
level is usually normal to low. The chronic form of milk alkali 
syndrome is usually asymptomatic, with the incidental 
finding of hypercalcemia and renal failure.

Milk alkali syndrome is considered as one of the main 
causes of hypercalcemia in adults. It was reported in a new 
series as a cause of hypercalcemia in around 12% of cases. 
Picolos et al reported that among 125 adult patients with 
hypercalcemia, milk alkali syndrome was the third leading 
cause of hypercalcemia of any degree and the second cause 
of severe hypercalcemia among inpatients without end-stage 
renal failure. In children, hypercalcemia was reported to 
be associated with acute kidney injury in two immobilized 
children and a third child with malignancy. However, milk alkali 
syndrome as a cause of hypercalcemia or acute kidney 
injury has not been reported before in children. Abnormalities 
in serum calcium concentration may have profound effects 
on the neurological and gastrointestinal systems as well 
as on renal function. It is also associated with metastatic 
calcifications, pancreatitis, and reversible cardiac conduc-
tion abnormalities. Our patient did not have any of those 
complications, apart from vomiting and dehydration.

Hypercalcemia in milk alkali syndrome could be explained 
by high calcium influx into the extracellular fluid from the intestine and/or bone which exceeds the efflux to 
test results suggesting milk alkali syndrome after 4 months from presentation (shaded area) which improved after adjusting medications.

<table>
<thead>
<tr>
<th>Laboratory test (normal range)</th>
<th>0 (presentation)</th>
<th>1 month</th>
<th>4 months</th>
<th>5 months</th>
<th>6 months</th>
<th>7 months</th>
<th>8 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH (7.35–7.45)</td>
<td>7.305</td>
<td>7.461</td>
<td>7.468</td>
<td>7.49</td>
<td>7.535</td>
<td>7.51</td>
<td>7.415</td>
<td>7.34</td>
</tr>
<tr>
<td>pCO2 (4.7–6.1) kPa</td>
<td>4.28</td>
<td>5.22</td>
<td>6.95</td>
<td>7.32</td>
<td>7.12</td>
<td>7.1</td>
<td>8.1</td>
<td>6.7</td>
</tr>
<tr>
<td>HCO3 (21–26) mmol/L</td>
<td>15.6</td>
<td>27.3</td>
<td>32</td>
<td>48.7</td>
<td>34</td>
<td>24.3</td>
<td>25.1</td>
<td>21.5</td>
</tr>
<tr>
<td>BE (–2) mmol/L</td>
<td>–10.7</td>
<td>3.5</td>
<td>10</td>
<td>12.3</td>
<td>10.1</td>
<td>12.6</td>
<td>12.6</td>
<td>9.2</td>
</tr>
<tr>
<td>iPTH (1.6–6.9) pmol/L</td>
<td>17.81</td>
<td>8.78</td>
<td>10.8</td>
<td>11.5</td>
<td>11.5</td>
<td>12.8</td>
<td>12.1</td>
<td>12</td>
</tr>
<tr>
<td>Na (136–145) mmol/L</td>
<td>135</td>
<td>138</td>
<td>133</td>
<td>133</td>
<td>133</td>
<td>134</td>
<td>138</td>
<td>134</td>
</tr>
<tr>
<td>K (3.5–5.1) mmol/L</td>
<td>4.6</td>
<td>4.6</td>
<td>4.0</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
<td>4.1</td>
</tr>
<tr>
<td>Cl (98–107) mmol/L</td>
<td>104</td>
<td>98</td>
<td>76</td>
<td>76</td>
<td>76</td>
<td>76</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>BUN (2.5–6.4) mmol/L</td>
<td>23.7</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
<td>23.6</td>
</tr>
<tr>
<td>Creatinine (0.8–1.5) mg/dL</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
<td>1.11</td>
</tr>
<tr>
<td>Ca (2.1–2.5) mmol/L</td>
<td>1.63</td>
<td>1.63</td>
<td>1.63</td>
<td>1.63</td>
<td>1.63</td>
<td>1.63</td>
<td>1.63</td>
<td>1.63</td>
</tr>
<tr>
<td>ALP (50–136) U/L</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Abbreviations: ALP, alkaline phosphatase; BE, base excess; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
unlikely, because the patient required lower doses of calcium carbonate after resolution of milk alkali syndrome to maintain his normal serum calcium. Although the high dose of alfalcacidol might have contributed to the hypercalcemia, vitamin D intoxication is unlikely because the patient had a normal 25-hydroxyvitamin D level, and his intact parathyroid hormone level was not suppressed. Severe metabolic alkalosis could not be explained by vitamin D intoxication alone.16

In our patient, the intact parathyroid hormone level was almost normalized during and after the episode of milk alkali syndrome. The vitamin D3 level was normal, but we did not measure 1,25-dihydroxyvitamin D level. There are limited data suggesting that 1,25-dihydroxyvitamin D and parathyroid hormone levels are suppressed in milk alkali syndrome.12 We observed a rise in serum phosphate which is unusual with the recent form of milk alkali syndrome caused by excessive ingestion of calcium carbonate, because serum phosphate could be normal or low, while in the old form caused by ingestion of phosphorus-rich milk, serum phosphate is expected to be high.1

Our patient had renal impairment which could contribute to the pathogenesis of milk alkali syndrome as it was suggested by previous reports, that interplay between hypercalcemia and alkalosis in the diseased kidney seems to lead to a self-reinforcing cycle, resulting in the clinical picture of milk alkali syndrome in adult patients.1

**Conclusion**

We present a case of milk alkali syndrome in a young child with chronic kidney disease, which improved on adjusting doses of calcium carbonate and sodium bicarbonate. Milk alkali syndrome should be considered in children with chronic kidney disease, worsening of kidney function, hypercalcemia, and metabolic alkalosis.

**Disclosure**

The authors report no conflicts of interest in this work.

**References**


