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CASE REPORT

Milk alkali syndrome in an infant with chronic kidney disease

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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, HCO_3 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 inhospital 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

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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[6] was 30 mL/min/1.73^2. His chronic kidney disease was managed conservatively and he continued taking alfacalcidiol 0.5 μg once a day, calcium carbonate 250 mg four times a day, sodium bicarbonate 10 mmol three times a day, erythropoietin 2000 IU once a week, folic acid 1 mg once a day, and ferrous hydroxide 40 mg once a day (Table 1).

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). Therefore, a diagnosis of milk alkali syndrome or calcium alkali syndrome was made, and readjustment of his chronic kidney disease medication doses 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.[7] 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.[1,8]

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

Table 1 Summary of medications used before, during, and after the episode of milk alkali syndrome (shaded area)

	At presentation (0–12 months)	4 months	4.5 months	8 months
Alfacalcidiol 15–30 ng/kg/day	0.5 μg	0.5 μg	0.2 μg	0.1 μg
Calcium carbonate 300 mg 3–4 times/day	250 mg qid	250 mg qid	100 mg qid	100 mg tid
$NaHCO_3$ initially 1–2 mmol/kg, to be adjusted	10 mEq tid	5 mEq tid	Withheld temporarily	2 mEq bid
Erythropoietin alfa/week 75–150 IU/kg three times/week	2000 IU	2000 IU	2000 IU	20000 IU
Elemental iron 3–6 mg/kg/day	40 mg	40 mg	50 mg	50 mg
Folic acid 1–2 mg/day	1 mg	1 mg	2 mg	2 mg

Note: Usual doses are written next to the name of each medication.
Abbreviations: bid, twice daily; tid, three times daily.

Table 2 Laboratory results suggesting milk alkali syndrome after 4 months from presentation (shaded area) which improved after adjusting medications

Laboratory test (normal range)	0 (presentation)	1 month	4 months	4.5 months	5 months	6 months	7 months	8 months	12 months
pH (7.35–7.45)	7.305	7.461	7.49	7.535	7.51	7.415	7.45	7.382	7.34
pCO_2 (4.7–6.1) kPa	4.28	5.22	5.95	7.85	7.1	5.17	4.92	5.8	5.7
HCO_3 (21–26) mmol/L	15.6	27.3	32	48.7	34	24.3	25.1	25.3	21
BE (<2) mmol/L	−10.7	3.5	10	26.1	12	−0.2	1.1	0.2	−2.5
iPTH (1.6–6.9) pmol/L	17.81	8.78	8.5	10	11.15	5.24	7	6.4	7.9
Na (136–145) mmol/L	135	138	133	132	134	139	138	142	134
K (3.5–5.1) mmol/L	4.9	4.6	3.7	3.9	4.1	5.6	4.4	4.6	5.3
Cl (98–107) mmol/L	104	98	73	76	92	101	99	104	105
BUN (2.5–6.4) mmol/L	23.7	23.6	39.3	52.2	31.5	28.8	20.9	20.4	15
Creatinine (0.4–1.0) mg/dL	1.11	1.17	2.84	3.98	1.93	1.48	1.45	1.25	0.79
Ca (2.1–2.5) mmol/L	2.59	2.71	2.67	2.66	3.11	2.75	2.68	2.55	2.66
PO_4 (0.81–1.58) mmol/L	1.63	2.05	3.35	2.76	1.79	1.89	1.7	1.55	1.59
ALP (50–136) U/L	124	156	109	103	110	90	103	129	200

Abbreviations: ALP, alkaline phosphatase; BE, base excess; BUN, blood urea nitrogen; iPTH, intact parathyroid hormone.

findings of hypercalcemia, metabolic alkalosis, and variable degrees of renal impairment.[1] 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 continuum, because there is overlap between them.[3,9] 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.[10] 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.[11] 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.[12] In children, hypercalcemia was reported to be associated with acute kidney injury in two immobilized children and a third child with malignancy.[13] 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.[11] It is also associated with metastatic calcifications, pancreatitis, and reversible cardiac conduction abnormalities.[14] 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 intestine, bone, and/or kidneys.[15] Acute kidney injury usually improves with cessation of calcium and alkali ingestion, but occasionally dialysis is needed.[8] Our patient was about to be dialyzed, but improvement in his laboratory results made dialysis unnecessary. The doses of calcium carbonate used in our patient were not high,[7] but the occurrence of milk alkali syndrome could be explained by the relatively high doses of sodium bicarbonate (6 mmol/kg/day), or another remote possibility is receiving higher doses of calcium carbonate by mistake from his parents. The latter possibility is

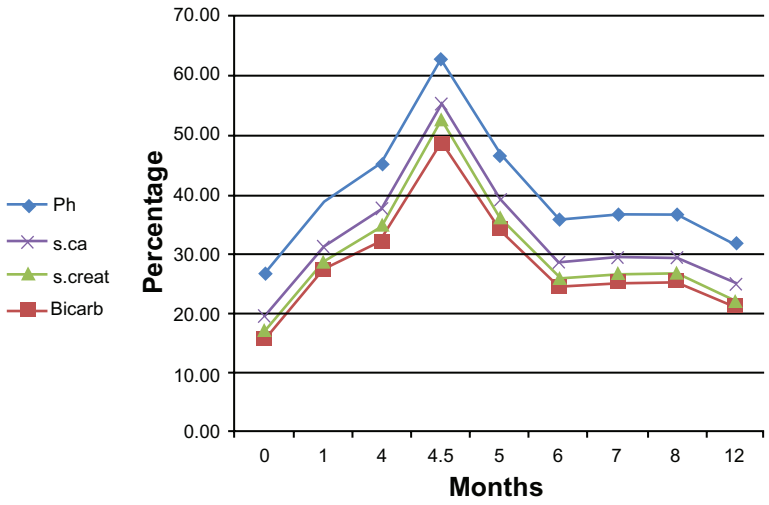

Figure 1 Line chart expressing percentage of changes in pH, bicarbonate, serum creatinine, and serum calcium at presentation (0 months), and peak of milk alkali syndrome at 4.5 months and return back to normal base level after 12 months.
Abbreviations: s.Ca, serum calcium; s.Creat, serum creatinine; bicarb, bicarbonate.

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 alfacalcidiol 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.

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