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Calcium Alkali Thiazide Syndrome

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Introduction

- Acute Kidney Injury (AKI) frequently presents with metabolic acidosis except in the occasional case, when it is associated with metabolic alkalosis and hypercalcemia.
- The triad of AKI, metabolic alkalosis and hypercalcemia is the hallmark of Milk Alkali syndrome. The term Milk Alkali was originally described in 1930s as a complication of a Sippy diet, a diet containing milk, calcinated magnesia and sodium bicarbonate, hence high calcium, for the treatment of peptic ulcer disease.
- Although in the modern era the Sippy diet has been replaced by medications with different mechanism of action, yet calcium intake is the third most common cause of hypercalcemia in hospitalized patients. This is mainly due to over the counter (OTC) calcium and vitamin D supplements, used primarily, but not exclusively, by postmenopausal women for prevention and treatment of osteoporosis.
- Nowadays, due to these changes in epidemiology and pathophysiology, Milk Alkali syndrome is preferably called Calcium Alkali syndrome. In our case report, hypercalcemia was exacerbated by the concomitant use of chlorthalidone, which is why we called it Calcium Alkali Thiazide Syndrome.

Case Report

- Here we present the case of a 57 year-old lady, with past medical history (PMH) of hypertension and primary hyperparathyroidism causing persistent hypercalcemia and nephrolithiasis despite partial parathyroidectomy.
- She presented to the Emergency Department (ED) with severe generalized body weakness affecting her mobility, legs achiness, feet numbness, dizziness, nausea, vomiting, abdominal pain, constipation, mild confusion and occasional palpitations.
- Approximately 3 weeks before she underwent total parathyroidectomy along with partial thyroidectomy for persistent hypercalcemia. She was then placed by her surgeon on calcium carbonate 1 g three times daily, calcitriol 0.5 mcg twice daily and cholecalciferol 10,000 units daily, on top of her usual chlorthalidone 25 mg daily and irbesartan 300 mg daily.
- She was also religiously drinking a glass of milk after each meal. On physical examination she presented with: temperature 97.9°F, heart rate 87 bpm, respiratory rate 16/min and blood pressure 163/67 mmHg.
- On presentation she was alert and oriented but confused; a symmetrically decreased muscle strength was noticed in all four extremities although reflexes were normal. There was also mild generalized abdominal tenderness. Otherwise physical exam appeared normal.
- Patient's labs upon presentation showed
  - WBC count 15.5 k/mm^3, hemoglobin 15.6 g/dL, platelet count 370 k/mm^3,
  - creatinine 1.9 mg/dL (baseline 0.8-0.9),
  - BUN 45 mg/dL, eGFR 27 mL/min (baseline >60ml/min),
  - bicarbonate 33 MEQ/L, chloride 94 MEQ/L,
  - potassium 2.5 MEQ/L, sodium 135 MEQ/L,
  - **calcium 23 mg/dL**, confirmed with **free ionized calcium 12.03 mg/dL,**
  - phosphate 1.3 mg/dL, PTH 0 pg/mL,
  - 25-hydroxy vitamin D level 61 ng/mL (30-100 ng/mL) and
  - 1,25-dihydroxy vitamin D level 31 pg/mL (18-72 pg/mL)
- The patient had some nonspecific ST-T wave changes on ECG with negative troponin. She was started on IV normal saline at 200 mL/hour, the first 4 liters were given within the first 24 hours, along with 40 mg of furosemide twice daily as we aimed a urine output of 100-150 mL/hr.
- After consultation with endocrinology, as she did not show any life-threatening features, it was decided to continue only with current treatment.
- She improved quickly and was discharged on day 5 with total calcium of 10.3 mg/dL and a trending down creatinine of 1.4 mg/dL.

Labs	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Calcium (mg/dl)	23	17.9	14.7	14.5	11.7	10.3
Ionized Calcium (mg/dL)	12.03	9.26	8.76	-	6.48	5.77
Creatinine (mg/dL)	1.9	1.9	1.7	1.9	1.5	1.4
eGFR (ml/min)	27	27	31	27	36	39
HCO3 (MEQ/L)	33	31	30	28	25	26
pH (7.32-7.42)	7.59	7.47	7.46	-	7.47	7.42
Phosphate (mg/dL)	1.3	5.7	-	-	2.7	-

Discussion

- High calcium level alerts every ED physician and sometimes leads to unnecessary diagnostic testing in pursuit of malignancy.
- A thorough history is mandatory to identify benign causes of hypercalcemia, focusing also on supplementation, OTC medications and diet. Thanks to an exhaustive PMH this patient was spared from redundant testing.
- Three different types of Milk Alkali syndrome have been described: acute, subacute and chronic. It is important to note that classically 4 g of daily calcium intake is required to develop acute Milk Alkali syndrome but cases with only 1-1.5 g daily have been reported.
- This case appeared to be an acute event, although the patient might have had a baseline calcemia above the upper normal limit given the primary hyperparathyroidism.
- Without a doubt the supplementation with 3 different medications along with thiazide and milk consumption, had a central role in developing such high level of calcemia. Our literature review showed that maximum serum calcium levels reported with Milk Alkali syndrome do not exceed 16-17 mg/dL (higher levels have been only described in cases of parathyroid adenoma).
- Our patient proved it can be higher. One important difference between Calcium Alkali syndrome and Milk alkali syndrome caused by a Sippy diet is that the latter was associated with hyperphosphatemia due to phosphate-rich milk and cream in the Sippy diet.
- As no extra milk and cream is taken in the modern era, Calcium Alkali syndrome is associated with normal or low serum phosphorus: this is caused by the phosphate-binding capacity of calcium carbonate, which decreases the absorption of phosphate in the gut.

Conclusion

- Although simple in its diagnosis and resolution, this case stands out for its high level of calcemia, which can be associated with major complications, fortunately not seen in this patient.
- It also gave us the opportunity to focus on differential diagnosis of hypercalcemia and on Calcium Alkali syndrome.
- Due to the current diffusion of vitamin supplementation in the general population and in particular in post-menopausal women, along with the frequent use of thiazide diuretics, this syndrome needs to be kept in mind as a frequent cause of benign hypercalcemia.
- A comprehensive history is mandatory to spare patients from costly and unnecessary testing looking for malignancy. The association with AKI and metabolic alkalosis definitely helps its recognition.

Disease	Cancer	Milk alkali syndrome and thiazides	Familial hypocalciuric Hypocalcemia	Hyperpara thyroidism	Vitamin D Excess	Chronic Renal Failure
Calcium	High	High	High	High	High	Low
PTH	Low	Low	Increased or Normal	High	Low	High
PO4	Low	Low	Low	Low	High	High
25-(OH)D	Low or Normal	Normal	Normal	Low or Normal	High	Variable
1.25 (OH)2D	High	Normal	Normal	High	Variable	Decreased

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