Calcium-alkali syndrome in post-surgical hypoparathyroidism

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Introduction

Milk-alkali syndrome or its up-to-date definition ‘calcium-alkali syndrome’ (CAS),1 is characterized by the triad of hypercalcemia, metabolic alkalosis and various degrees of renal failure, due to the intake of variable amounts of calcium and absorbable alkali. Its initial description dates back to the early 20th century when ‘alkali powders’ became a popular therapy for peptic ulcer disease. In 1923, two researchers from the Mayo Clinic, Leo Hardt and Andrew Rivers,3 described the adverse effects of this treatment, and in the three following decades communications about toxicity of Sippy’s protocol were frequent.4

CAS has become a rare cause of hypercalcemia (<1% of cases) since proton pump inhibitor therapy was introduced in the 1990s.5,6 Nevertheless, it remains the third most common cause of hypercalcemia and the second most frequent cause of severe hypercalcemia among inpatients.5 The main reason for the rise of incidences of CAS is the increase of calcium carbonate use for prophylaxis and treatment of osteoporosis in post-menopausal women.

Notably, any situation in which an overload of calcium and alkaline element coexist fosters a risk for CAS. We describe three patients who developed this syndrome in the setting of a post-surgical hypoparathyroidism.

Patients

Case 1

A 71-year-old woman was admitted to our hospital with a 10-day history of nicturia, polyuria, fatigue, nervousness, insomnia and headache. Her past medical history included hypertension, treated with lisinopril and hydrochlorothiazide (20/12.5 mg/day), mild chronic renal failure (creatinine, 1.6 mg/dl) and primary hyperparathyroidism. She had undergone total thyroidectomy and parathyroid resection 2 years earlier and required a second intervention 1 year later because of a new mediastinal parathyroid adenoma. At the time she developed permanent post-operative hypothyroidism and hypoparathyroidism, and calcium carbonate (900 mg/day), calcitriol (1 μg/day) and levothyroxine (100 μg/day) were started.

At admission laboratory results were as follows: serum creatinine, 2.4 mg/dl; urea, 104 mg/dl; phosphate, 3.4 mg/dl; and serum calcium, 12.7 mg/dl. Intact PTH (iPTH) levels were <1 pg/ml, ionized calcium, 1.46 mM and venous blood pH, 7.48.

Calcium, vitamin D and antihypertensive agents were discontinued and intensive oral hydration was started. The patient showed a progressive and rapid improvement in renal function. Her serum and ionized calcium levels fell below the reference values (8.5–10 mg/dl and 1.16–1.35 mM, respectively), even with signs of hypocalcemia...
(Trouseau sign). Hence, calcium and vitamin D were reintroduced and thiazide was permanently withdrawn. At discharge, serum creatinine was 1.9 mg/dl and serum calcium levels remained at the lower limit of the reference range.

Case 2
A 52-year-old woman was admitted with a 2-month history of gastric fullness and dyspepsia. She also complained about nausea, vomiting, holocranial headaches and epigastralgia in the last 24 h. She had undergone total thyroidectomy with lateral lymphadenectomy 3 years earlier because of a papillary thyroid carcinoma with left supraclavicular lymph node extension. She was on calcium carbonate (1200 mg/day), calcitriol (1 µg/day) and levothyroxine (150 µg/day) due to postoperative hypoparathyroidism and hypothyroidism.

At admission, serum creatinine was 4.1 mg/dl; urea, 113 mg/dl; serum calcium, 14.8 mg/dl; phosphate, 4 mg/dl; and iPTH: <6 pg/ml.

Calcium and vitamin D were discontinued and intravenous fluids followed by furosemide were started. The patient showed a rapid recovery, with improvement in renal parameters. As serum calcium level remained in the low reference range calcium carbonate and calcitriol were reintroduced at half dose. At discharge, serum creatinine was 2.1 mg/dl and serum calcium 9 mg/dl.

She was readmitted 2 years later with similar symptoms during the last 4 days. Serum creatinine and urea were 2.4 and 87 mg/dl, respectively, and serum calcium was 11.8 mg/dl. Calcium carbonate and vitamin D were withdrawn (doses prescribed in the previous admission were not modified) and she was treated with intravenous fluids. There was a rapid improvement in serum creatinine levels, urea and calcium (up to 8.2 mg/dl). iPTH levels were <5 pg/ml; 25 OHD, 15 ng/ml; 1.25 OHD, 10 pg/ml; and ionized calcium, 1.22 mM. Venous pH was 7.49 and serum bicarbonate 26.7 mEq/l. At discharge serum creatinine was 1.6 mg/dl and corrected calcium level 8.5 mg/dl. Calcitriol was restarted (0.5 µg /day).

Case 3
A 67-year-old woman was admitted with intense fatigue, gait instability and confusion, lasting for one week. She also developed nausea and vomiting during the previous 72 h. She had hypertension, treated with perindopril (4 mg/day) plus indapamide (1.5 mg/day), and multinodular toxic goiter. She had undergone total thyroidectomy a year earlier. A non-functioning adenoma was found during surgery and thus a lower left parathyroidectomy was performed. She developed permanent hypothyroidism and hypoparathyroidism, and levothyroxine (75 µg/day), calcium carbonate (3 g/day) and calcitriol (0.5 µg/day, except Saturdays and Sundays—0.75 µg/day) were started.

At admission, serum creatinine was 2.85 mg/dl; phosphate, 3.7 mg/dl; urea, 105 mg/dl; and serum calcium, 22.4 mg/dl. Two hours after intravenous fluid therapy and furosemide, serum calcium was 19.4 mg/dl. Due to severe hypercalcemia the patient was transferred to the ICU. Subcutaneous calcitonin was added and her physical status progressively improved as well as the serum calcium level. Once in the Internal Medicine Department, laboratory parameters were as follow: iPTH: 72 pg/ml, (3 months before, 10 pg/ml), ionized calcium, 1.24 mM; 25 OHD, 11 ng/ml (20–60 ng/ml); 1.25 OHD, <5 ng/ml (12–40 ng/ml); PINP, 9 ng/ml (19–100 ng/ml); and ß-CTX, 0.334 ng/ml (0.112–1.018 ng/ml). Venous pH was 7.46 and serum bicarbonate 31 mEq/l. At discharge, serum calcium level was 8 mg/dl and serum creatinine 1.7 mg/dl.

Discussion
Our patients developed hypercalcemia, metabolic alkalosis and renal failure, that is the triad which defines CAS. They underwent total thyroidectomy, with or without elective parathyroidectomy, and were on oral calcium and calcitriol due to post-surgical hypoparathyroidism.

Hypercalcemia is the most common complication of thyroidectomy. Injury or removal of the parathyroid glands during neck surgery is the most frequent cause of acute and chronic hypoparathyroidism. Although post-thyroidectomy hypoparathyroidism is usually transitory (8.3%) it may persist in 0.4–33% of cases depending on the series and on its definition.7,8 In a strict sense, the definition should rely on the demonstration of undetectable or below normal PTH circulating levels, although a ‘functional’ definition is based on the requirements of calcium treatment 1 year after surgery in order to maintain a normocalcemic status.9 In this context, calcium supplementation is routinely prescribed after thyroidectomy, with the purpose of decrease the risk of symptomatic hypercalcemia, allowing a safer early discharge.10 Serum PTH or calcium levels will guide a subsequent taper in the clinic. The subset of patients who develop a permanent post-surgical hypoparathyroidism receive chronic therapy with calcium salts (calcium carbonate at doses of 1250–2500 mg/day) and vitamin D (usually calcitriol at doses of 0.25–1 µg/day). They also
frequently receive drugs that increase renal tubular reabsorption of calcium, such as thiazides, in order to maintain normal serum calcium levels and avoid chronic hypercalciuria that may lead to renal function impairment.

Calcium carbonate contributes to the onset and maintenance of CAS in two capacities. It is a source of calcium and therefore, depending on the dose and the presence of contributing factors (previous impairment of renal function, use of agents that reduce calciuresis), it may trigger hypercalcemia. Besides, calcium carbonate increases plasma bicarbonate levels by decreasing its renal excretion. Once established, hypercalcemia and metabolic alkalosis interact in a sequence that leads to chronically elevated calcemia. Metabolic alkalosis decreases calcium renal excretion and hypercalcemia contributes to maintain alkalosis.

The physiological suppression of endogenous 1.25 OHD levels in response to hypercalcemia is cancelled, because calcium and phosphorus absorption continues independently of calcemia.

On the other hand, thiazides block the cotransporter Na/Cl in the apical membrane of distal convoluted tubule, and also contribute to alkali overload. Moreover, they decrease glomerular filtration rate and promote the maintenance of alkalosis by stimulating bicarbonate reabsorption in the proximal tubule. Thus, any other cause of hypercalcemia originated in the setting of chronic calcium overload becomes more apparent with the use of thiazides. Therefore, the association of calcium carbonate, calcitriol and/or thiazide diuretics should require a strict control of calcemia, calciuria and renal function.

With regard to our diagnostic approach, it is critical to note that hypercalcemia may frequently be asymptomatic in CAS. It is important to assess the degree of renal function impairment and order a venous blood gas analysis to differentiate an intoxication caused by the combined effect of these drugs (calcium salts, calcitriol and thiazides) and CAS. Other tests may intuitively seem helpful, yet results may be misleading. For example, calcitriol intoxication should correlate with increased 1.25 OHD serum levels. Nevertheless, given its short plasma half-life (6–8 h), values within the normal reference range could be found. Additionally, clinicians may expect a high plasma phosphate levels in case of calcitriol intoxication. Nevertheless, serum phosphate levels are usually within the normal range in ‘modern’ CAS. We found only one case in which calcium and alkaline overload was induced by a combination of alfacalcidol and hydrochlorothiazide, without any oral calcium supplementation.

Regarding the value of iPTH, it could be worth commenting on the serum levels of our third patient. Four days after recovery from severe hypercalcemia (22.4 mg/dl), her iPTH level was 72 pg/ml (<65 pg/ml) coinciding with the lowest levels of serum calcium. Unfortunately, serum PTH was not measured at admission, at the peak of hypercalcemia. However, serum iPTH levels were 10 pg/ml 3 months before the current admission, and we can not rule out a laboratory error. This high PTH value did not preclude from a CAS diagnosis because there have been prior reports of CAS with elevated or inadequately suppressed PTH levels. In some of these, the measured PTH was not the intact fraction but the carboxy-terminal fragment which has a longer half-life (usually 30 min) and is usually increased in renal failure. Alternatively, we could hypothesize that elevated PTH levels could represent a parathyroid gland response to decrease in serum calcium following the treatment of CAS, even although the patient would remain hypercalcemic. A similar phenomenon has been described in the hypercalcemia observed in the polyuric phase of rhabdomyolysis.

In summary, patients with permanent post-surgical hypoparathyroidism on therapy with calcium supplements and calcitriol are at increased risk for developing CAS. Thiazide diuretics pose an additional higher risk when added to the therapeutic regimen. Therefore, clinicians attending these patients should have a high index of suspicion for CAS. If hypercalcemia develops in this context, closely monitoring of renal function and venous blood pH should be advised for an early diagnosis of this syndrome.

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References


