

A rare cause for delirium: COPE syndrome

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ABSTRACT

Calcium-alkali syndrome (CAS) (Milk alkali syndrome) is the third most common cause of hypercalcemia. The triad of hypercalcemia, metabolic alkalosis, and variable renal failure constitutes this syndrome. Here, we report a case of CAS in a female with post-thyroidectomy hypoparathyroidism who presented with delirium due to hypercalcemic encephalopathy. CAS can occur even after decades of normocalcemia in hypoparathyroidism, and regular monitoring of calcium levels is required.

Key words: Calcium alkali syndrome, Calcium citrate malate, Cope syndrome, Hypoparathyroidism, Hypercalcemia, Metabolic alkalosis, Milk alkali syndrome

Milk-alkali syndrome (MAS) is characterized by the triad of hypercalcemia, various degrees of renal failure, and metabolic alkalosis due to the ingestion of large amounts of calcium and absorbable alkali. With the introduction of proton pump inhibitors, the incidence of MAS has drastically reduced. There is resurgence of a similar syndrome, calcium-alkali syndrome (CAS), following overzealous treatment of osteoporosis with calcium carbonate and treatment of dyspepsia with calcium-based antacids.

Here, we report the case of CAS presenting as delirium in a patient with hypoparathyroidism following unmonitored use of calcium citrate malate and alfacalcidol.

CASE REPORT

A 69-year-old lady with hypertension of 5 years duration, hypothyroidism and hypoparathyroidism (post-total thyroidectomy 24 years ago) on thyroxine 100 mcg/day, calcium citrate malate 750 mg/day, alfacalcidol 0.75 mcg/day, Vitamin D 1200 IU/day, and cilnidipine 5 mg twice daily presented with drowsiness, reduced food intake, and abnormal behavior for the past 3 days. She has a history of bradykinesia and rest tremor for the last 3 years, for which she is taking levodopa-carbidopa 125 mg half tablet 3 times daily. There was no history of cognitive impairment or bladder symptoms before her present symptoms. There was no history of fever, headache, vomiting, seizure, weight loss, abdominal pain, or bone pain. There was no history of thiazide intake, Vitamin A intake, antacids, or betel nut chewing.

On examination, her blood pressure was 130/80 mm Hg and her pulse rate was 88/min. There were no cataracts or soft tissue calcifications. She was drowsy, disoriented in place and time, and restless. There was bilateral rigidity and rest tremor. She had insomnia and prominent visual hallucinations during her hospital stay, which required antipsychotics.

A computed tomography (CT) head showed calcification in the bilateral basal ganglia and subcortex, which was present in her CT head taken 6 years ago following a fall (Fig. 1). Biochemical evaluation showed severe hypercalcemia (16.8 mg%), hyponatremia, hypokalemia, hypomagnesemia, and metabolic alkalosis. Her serum alkaline phosphatase and vitamin D3 levels were normal. Her thyroid stimulating hormone was low, suggesting mild hyperthyroidism, and thyroxine was reduced to 88 mg/day. Urine potassium: Creatinine ratio was elevated (91 mEq/g, normal <15), as was her urine calcium. Creatinine ratio was 0.62 (normal <0.2). Other investigations are shown in Table 1.

She was treated with normal saline and a single dose of furosemide. Her hypokalemia and hypomagnesemia were corrected with potassium chloride and magnesium tablets. Her metabolic parameters became normal by the 5th day, and delirium subsided. Her blood urea level became 20 mg/dL from her initial value of 43 mg/dL.

DISCUSSION

MAS is characterized by the triad of hypercalcemia, various degrees of renal failure, and metabolic alkalosis due to the ingestion of large amounts of calcium and absorbable alkali [1].

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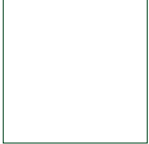
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Figure 1: Computed tomography head showing calcification in bilateral caudate nuclei and lentiform nuclei

Table 1: Laboratory investigations of the patient

Blood parameters	Result (%)	Normal range (%)
Sodium	128.2 mEq/L	135–145 mEq/L
Potassium	3.5 mEq/L	3.8–5.5mEq/L
Calcium	16.8 mg	8.8–10.6 mg
Phosphate	4.12 mg	2.5–4.5 mg
Magnesium	1.7 mg	1.9–2.5 mg/dL
Bicarbonate	35	21–31mmoL/L
Albumin	3.6 g	3.5–5.5 g
Fasting blood sugar	83 mg	70–110 mg
Urea	43 mg	17–43 mg
Creatinine	1.16 mg	0.8–1.2 mg/dL
Ionized calcium	0.91 mmol/L	1.15–1.33 mmol/L
Blood pH	7.611	7.35–7.45
Vitamin D level	74.96 ng/ml	30–100 ng/mL
Thyroid stimulating hormone	0.196 mIU/mL	0.35–5.5mIU/mL

This syndrome was first identified after the medical treatment of peptic ulcer disease with milk and alkali by Bertram Sippy, which was widely adopted at the beginning of the 20th century. Sippy's regime consists of hourly administration of milk and cream with Sippy powders, which are a mixture of sodium bicarbonate with calcinated magnesia or bismuth subcarbonate [2]. With the advent of H₂ receptor blockers and proton pump inhibitors, MAS went into oblivion. The resurgence of MAS has been witnessed recently because of the wide availability and increasing use of calcium carbonate, mostly for osteoporosis prevention, and is now better called CAS. CAS is now believed to be the third most common cause of in-hospital hypercalcemia, after hyperparathyroidism and malignant neoplasms. This evolution in terminology reflects the current pathogenesis of the disorder, which is related to excess calcium supplementation or calcium-containing antacids.

Diagnosis of CAS is important, as approximately 10% of patients with CAS underwent unnecessary parathyroid exploration in one series. The true incidence of CAS is unknown. In a recent retrospective study at a single center, from 1998 to 2003, CAS was

the third most common cause of hypercalcemia (8.8%) and the second most common cause of severe hypercalcemia (>14 mg/dL). The traditional MAS is characterized by elevated serum phosphate concentrations, probably secondary to the ingestion of phosphate-rich milk and cream in the Sippy diet. In contrast, CAS is associated with hypophosphatemia, or a low-normal serum phosphorus level, as a result of the phosphate-binding capacity of calcium carbonate and other calcium-containing supplements, resulting in decreased phosphate absorption. Hypercalcemia causes a furosemide-like effect by inhibiting secretory potassium channel activity through actions initiated by the calcium-sensing receptor in the thick ascending limb of Henle's loop. Metabolic alkalosis favors calcium reabsorption [3,4].

CAS can be acute (Cope's syndrome), subacute, or chronic (Burnett's syndrome). Normalization of renal function and calcium levels within a few days indicates the acute type. Nowadays, CAS is seen in: (a) post-menopausal women prescribed calcium carbonate and vitamin D supplements to prevent or treat osteoporosis; (b) pregnant women taking calcium supplements; (c) bulimic patients suffering from chronic alkalosis; (d) persons undergoing dialysis and treatment based on active vitamin D and calcium carbonate supplementation; and (e) persons being treated for hypoparathyroidism [4]. The metabolic alkalosis might be essential to the development of the MAS without a high calcium and absorbable alkali intake [5].

As per the US preventive services task force (Rockville, MD, USA), evidence is insufficient for the benefit beyond 400 IU of Vitamin D₃ and more than 1000 mg of calcium for the primary prevention of fractures in non-institutionalized post-menopausal women. According to the national osteoporosis foundation (Washington, DC, USA), dietary calcium intake in excess of 1200–1500 mg may increase the risk for cardiovascular disease or kidney stones. Recommended dietary allowances for calcium and vitamin D in 50–70-year-old females are 1200 mg and 600 IU, respectively [6].

Our patient with post-thyroidectomy hypothyroidism and hypoparathyroidism presented with encephalopathy, and evaluation showed hypercalcemia, metabolic alkalosis, and mild azotemia, suggesting CAS. Probable precipitating factors are mild hyperthyroidism and excess calcium intake on a background of irregular follow-up. Even though she was taking more than the recommended dose of vitamin D, her vitamin D levels were normal, as Vitamin D toxicity can cause hypercalcemia. There are similar cases of CAS in patients with hypoparathyroidism in the literature [7]. Drugs influencing the glomerular filtration rate (angiotensin receptor blockers, aldosterone receptor antagonists, thiazide diuretics), changing the calcium carbonate supplementation, dehydration, a diet rich in pH-basic foods (i.e., a vegetarian diet), pregnancy, and other associated conditions are listed among the factors triggering CAS in patients with hypoparathyroidism. There are expert opinions regarding the management of hypocalcemia in hypoparathyroidism to prevent the development of CAS [8].

The syndrome has been reported after ingestion of doses as low as 1 g of elemental calcium daily. However, most reported

cases of the syndrome document ingestion of at least 4 g of elemental calcium per day. Although a daily intake of 2 g of calcium is considered safe for the general population, smaller doses of 1.2–1.5 g daily should be used when patients have risk factors that increase their likelihood of developing the CAS. The elderly and patients with chronic kidney disease are more susceptible because they will have a lower glomerular filtration rate and decreased calcium clearance. Thiazide diuretic use may also pre-dispose to CAS by enhancing renal tubular calcium absorption and by promoting volume depletion and alkalosis. Furthermore, any medications that reduce the glomerular filtration rate, such as non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors, can contribute to the development of the syndrome [8]. There are many recent case reports and reviews about CAS [9,10].

CONCLUSION

CAS (MAS) is the third most common cause of hypercalcemia. The triad of hypercalcemia, metabolic alkalosis, and variable renal failure constitutes this syndrome. It can be precipitated by changes in food or drug habits and new prescription medications for hypertension or endocrine disorders. Regular monitoring of calcium levels is important in hypoparathyroidism, as CAS can occur even after decades of normocalcemia.

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