



## Case Report

## A 39 year-old woman with milk-alkali syndrome complicated by posterior reversible encephalopathy syndrome

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## ABSTRACT

Milk-alkali syndrome (MAS) is characterized by the triad of hypercalcemia, metabolic alkalosis, and acute kidney injury. Once thought to be a rare condition, there has been a resurgence of cases due to the consumption of calcium-containing supplements for osteoporosis prevention and dyspepsia in the general population. We describe the case of a female who presented with acute encephalopathy, hypercalcemia, and new-onset seizure. An extensive hypercalcemia workup and ruling out of other causes led to the diagnosis of MAS from excessive intake of calcium carbonate. Brain magnetic resonance imaging revealed signal abnormalities in the occipital and posterior parietal lobes that were indicative of posterior reversible encephalopathy syndrome. The patient's encephalopathy resolved after treatment of her hypercalcemia with fluid resuscitation and cessation of her calcium supplements. We present our case to highlight this unusual presentation of MAS, challenges in diagnosis, and briefly discuss the pathophysiology underlying hypercalcemia-induced encephalopathy.

## 1. Introduction

Milk-alkali syndrome (MAS) was first described in the 1930s and is recognized by the classic triad of hypercalcemia, metabolic alkalosis, and acute kidney injury (Medarov, 2009; Patel et al., 2013). It is due to the overconsumption of calcium and absorbable antacids (i.e. calcium carbonate). The incidence of MAS substantially decreased by the 1980s due to the advent of histamine-2 receptor blockers and proton pump inhibitors for peptic ulcer disease. In the last several years however, there has been a resurgence of cases due to the widespread use of calcium carbonate for treatment of osteoporosis or dyspepsia (Beall et al., 2006; Yang et al., 2013; Manne, 2016; Tal and Powers, 1996; Kolnick et al., 2011; Etemadi and Bosselmann, 2018). In fact, MAS was found to be the third most common cause of hospitalization for hypercalcemia in an academic hospital, after hyperparathyroidism and malignancy (Beall and Scofield, 1995). It remains a diagnosis of exclusion after obtaining a compatible patient history and ruling out alternative causes of hypercalcemia. The signs and symptoms of MAS parallel those of hypercalcemia; in severe cases (Ca > 14 mg/dL), manifestations include lethargy, nausea, vomiting, constipation, or cardiac arrhythmias. There have been rare descriptions of potentially life-threatening central nervous system (CNS) manifestations such as hypertensive encephalopathy or seizures (Dinnerstein et al., 2008;

Nardone et al., 2016; Kashouty et al., 2011; Juvarrá et al., 1985). In fact, a few cases of hypercalcemia associated with posterior reversible encephalopathy syndrome (PRES) have recently been reported (Choudhary and Rose, 2005; Camara-Iemmarroy et al., 2014; Chan et al., 2019; Moussawi et al., 2018). Although the mechanism underlying this association remains elusive, it is thought to involve reversible vasoconstriction, neuronal excitotoxicity, or inflammatory responses (Chan et al., 2019; Moussawi et al., 2018; Chen et al., 2004).

## 2. Case report

A 39 year-old female with a history of pre-eclampsia presented with acute changes in mental status. Two days before presentation, the patient had symptoms of general malaise, posterior headache, and multiple episodes of vomiting. She decided to take a nap at home, but 15 min later, her family members found her confused, actively vomiting, and speaking nonsensically.

The patient was brought to our emergency department. On initial evaluation, her blood pressure was 240/144 mmHg and heart rate was 140 bpm. The patient was awake but inattentive with frequent bouts of nonpurposeful and repeated speech, and left gaze palsy. After undergoing emergent head computed tomography (CT) scan, she developed two witnessed tonic clonic seizures with shaking of her left arm, and

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additional vomiting. Due to worsening hypoxia and unresponsiveness, the patient was intubated and transferred to the neurological intensive care unit (NICU).

Upon further history, the patient had been taking calcium carbonate (1.5 g daily) for the past five years for dyspepsia. Due to worsening dyspepsia symptoms, she had been increasing her intake in excess of 6.0 g during the week prior to presentation. Other than pre-eclampsia with two previous pregnancies (two and five years ago), the patient had no other past medical history and was not on any other home medications. She had no prior history of seizure, head trauma, hypertension, cancer, atherosclerotic disease, kidney disease, or neurological disease. She reported consuming up to six alcoholic beverages daily but denied any other recreational drugs.

Initial laboratory studies were notable for elevated calcium of 15 mg/dL (corrected for a mildly decreased albumin of 3.7 g/dL), creatinine 2.96 mg/dL, serum bicarbonate 34 mmol/L, white blood cell count of 12,000 cells/mm<sup>3</sup>, potassium 2.5 mEq/L, and magnesium 1.2 mg/dL. Arterial blood gas analysis revealed pH of 7.384, pO<sub>2</sub> 70.0 mmHg, and pCO<sub>2</sub> 46.4 mmHg. A pregnancy test was negative. Creatine kinase, serum alcohol, urinalysis, urine culture, blood culture, head CT, and head/neck CT angiography were unremarkable. Lumbar puncture was performed and other than a mildly elevated cerebrospinal fluid (CSF) glucose of 86 mg/dL and protein of 53 mg/dL, CSF was negative for bacteria, herpes simplex virus I and II DNA, and enterovirus RNA. However, brain magnetic resonance imaging (MRI) without contrast showed mild FLAIR signal abnormalities and cortical swelling of both occipital and posterior parietal lobes, consistent with PRES (Figs. 1 and 2). Electroencephalogram (EEG) revealed diffuse disorganization with occasional admixed synchronous and asynchronous delta activity of both hemispheres, attributable to a post-ictal state.

A hypercalcemia workup was performed. Parathyroid hormone (PTH) was at the lower range of normal (24.7 pg/mL). Serum thyroid stimulating hormone, phosphate, cortisol, alkaline phosphatase, serum and urine protein electrophoresis (with urine immunofixation), 25-hydroxyvitamin D, and vitamin A were within normal limits. Levels of 1,25-dihydroxyvitamin D and PTH-related peptide were appropriately suppressed at 5.9 pg/mL and < 2.0 pmol/L, respectively. A random urinary calcium/creatinine ratio was > 0.7, consistent with hypercalciuria (see Table 1 for reference ranges for biochemical data).

After excluding primary hyperparathyroidism, malignancy, and other causes of hypercalcemia, we diagnosed the patient with milk-alkali syndrome due to calcium carbonate overingestion.

The patient's hypercalcemia, hypertension, and other lab abnormalities resolved with fluid resuscitation, pamidronate, calcitonin, and medical management of hypertension and seizures. She was extubated by day 5 and upon regaining her normal mental status, was able to confirm her medical history and details of her present illness. Other than residual dysmetria on finger-to-nose exam and difficulty with fine motor tasks, the patient had an otherwise normal neurological exam with intact speech, executive functioning, and no other motor or sensory deficits. She had no additional seizures throughout her hospital stay and was counseled on the nature of her diagnosis and alternative medications for dyspepsia.

### 3. Discussion

Milk-alkali syndrome, originally named in association with the use of milk and absorbable antacids for treatment of peptic ulcer disease, is experiencing a resurgence in recent years. This is partly due to the use of calcium-containing supplements for treatment or prevention of osteoporosis, and treatment of dyspepsia. Among patients hospitalized for hypercalcemia in an academic medical center, MAS was estimated to be the third most common cause behind primary hyperparathyroidism and cancer (Beall and Scofield, 1995). The diagnosis relies on excluding other causes of hypercalcemia, such as thyrotoxicosis, malignancy, hyperparathyroidism, granulomatous diseases, adrenal insufficiency, rhabdomyolysis, and certain medications. Despite our patient's PTH level technically remaining in the low-normal range, the diagnosis of milk-alkali syndrome was reached with a high degree of certainty given the compatible history of calcium carbonate overingestion during the few days prior to admission, the acute nature of her symptoms, and the characteristic triad of hypercalcemia, metabolic alkalosis, and acute kidney injury seen in MAS. Moreover, cases of PTH-independent hypercalcemia are almost always correlated with PTH levels below 20–25 pg/mL (Haden et al., 2000). Primary hyperparathyroidism typically presents in post-menopausal women with minimal to no symptoms, with labs showing an increased serum 1,25-dihydroxyvitamin D (Kinoshita et al., 2005; Moosgaard et al., 2006; Silverberg et al., 1999); the lack of these characteristics further argued against primary

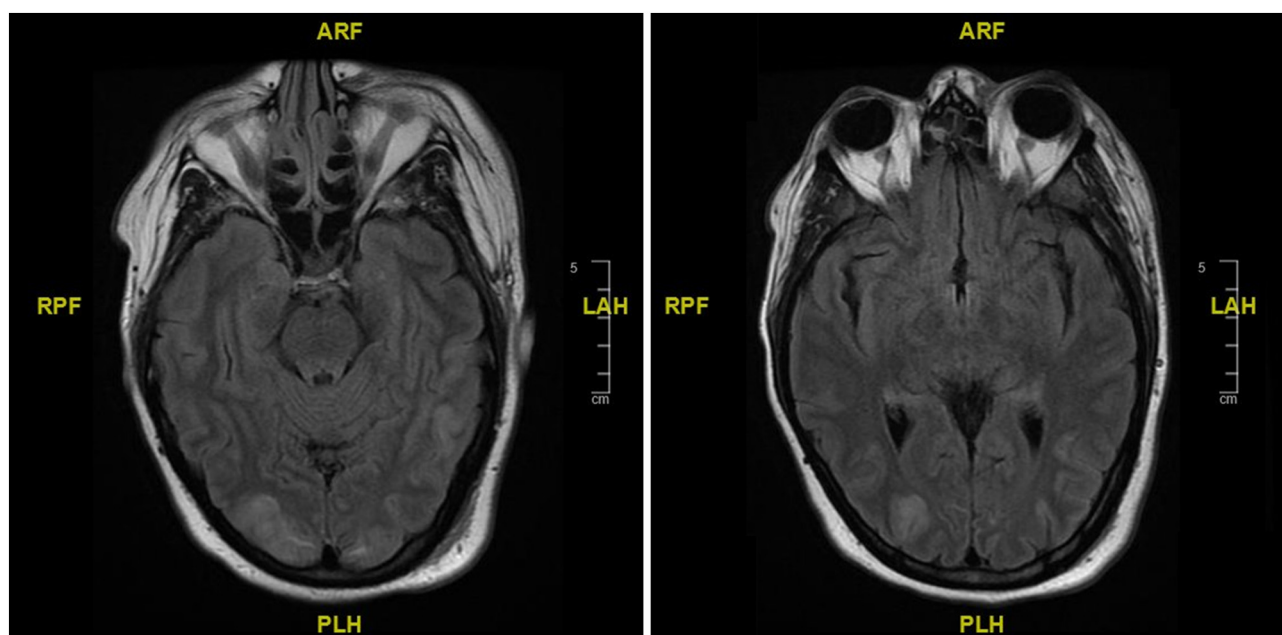


Fig. 1. Brain MRI demonstrating mild cortical fluid-attenuated inversion recovery (FLAIR) abnormalities in the occipital and posterior parietal lobes symmetrically.

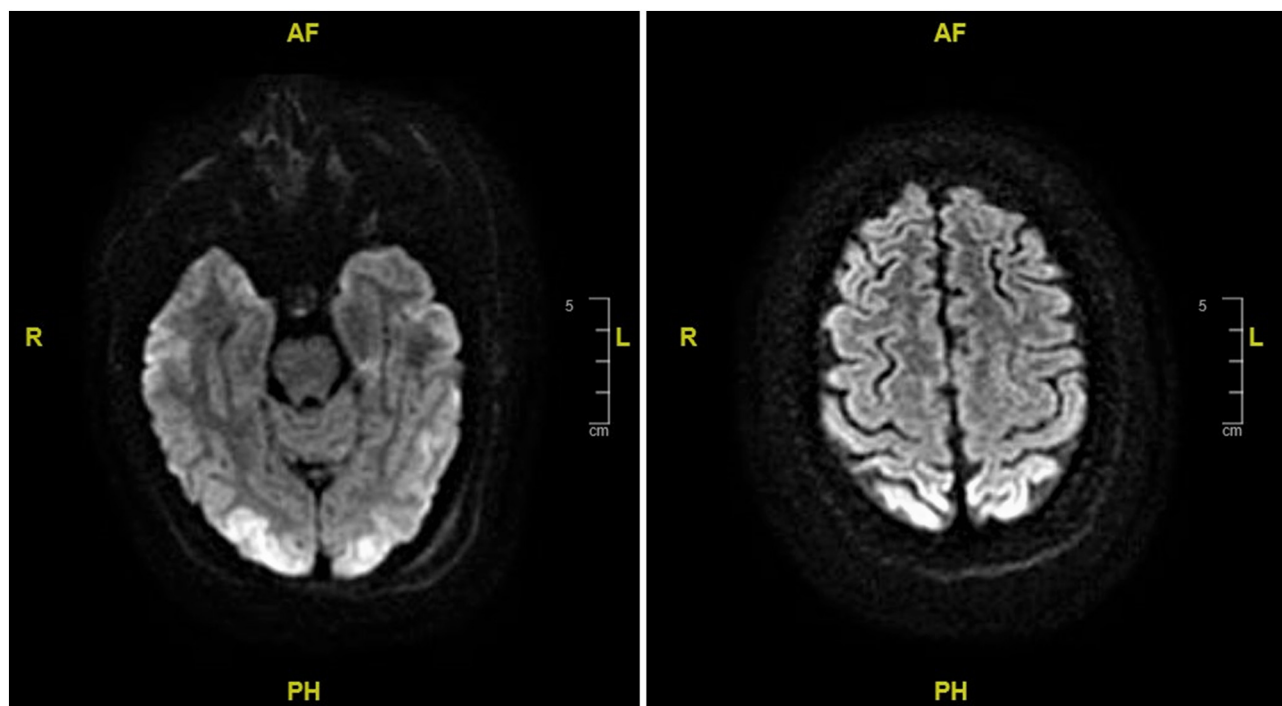


Fig. 2. Brain MRI demonstrating mild cortical restricted diffusion within the occipital and posterior parietal lobes on diffusion-weighted imaging (DWI).

Table 1

Reference intervals of selected biochemical data compared with patient's values.

| Parameter                  | Reference range | Patient's value |
|----------------------------|-----------------|-----------------|
| Total calcium              | 8.5–10.1 mg/dL  | 15.0 mg/dL      |
| PTH                        | 18.5–88 pg/mL   | 24.7 pg/mL      |
| PTH-related peptide        | < 2.5 pmol/L    | < 2.0 pmol/L    |
| 1,25-Dihydroxyvitamin D    | 19.9–79.3 pg/mL | 5.9 pg/mL       |
| Urinary calcium/creatinine | < 0.14          | > 0.70          |
| pH                         | 7.35–7.45       | 7.384           |
| pO <sub>2</sub>            | 80.0–100.0 mmHg | 70.0 mmHg       |
| pCO <sub>2</sub>           | 35.0–45.0 mmHg  | 46.4 mmHg       |
| Bicarbonate                | 21–32 mmol/L    | 34 mmol/L       |

hyperparathyroidism.

Our case was complicated by the development of new-onset seizure and brain MRI findings suggestive of posterior reversible encephalopathy syndrome. PRES is a clinical syndrome consisting of headache, acute encephalopathy, visual disturbances, seizure activity, and vasogenic edema predominantly affecting the parietal and occipital lobes. It typically develops in the setting of severe hypertension, pre-eclampsia, and certain immunosuppressive agents (Camara-lemarroy et al., 2014; Chen et al., 2004; McKinney et al., 2007; Bhagavati and Choi, 2008). Management involves blood pressure control and addressing suspected triggers. Several reports have pointed to hypercalcemia, regardless of the cause, as an additional risk factor associated with PRES (Choudhary and Rose, 2005; Camara-lemarroy et al., 2014; Chan et al., 2019; Moussawi et al., 2018). The exact mechanism remains uncertain, but several lines of evidence point to reversible vasoconstriction in the posterior cerebral arteries, neuronal excitotoxicity, inflammatory responses, or hypertensive encephalopathy (Chan et al., 2019; Moussawi et al., 2018; Chen et al., 2004).

Although hypercalcemia is considered to be a risk factor for PRES, it is difficult to ascertain whether it was the definitive cause in our patient. On presentation, there were concurrent findings of malignant hypertension and hypomagnesemia; these are considered risk factors for PRES but are also known to be direct manifestations of

hypercalcemia (Moussawi et al., 2018). Alcohol consumption, as in our patient, is also thought to be a culprit in recent reports (McKinney et al., 2007; Bhagavati and Choi, 2008; Ishikawa et al., 2013). Furthermore, due to the shared cellular processes of vasospasm and membrane instability that underlie both eclampsia and PRES (Moussawi et al., 2018), we speculate whether our patient's history of pre-eclampsia conferred additional risk. The pathophysiology of PRES is an evolving area that will be better elucidated with further clinical experience and investigation.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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