Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

Hypoventilation: a risk factor for milk alkali syndrome?

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Summary

A 67-year-old woman was admitted to the hospital due to progressive mental changes, nausea and vomiting after a dose increase of an intrathecal morphine pump. We found severe hypercalcaemia due to milk alkali syndrome (MAS). Her symptoms resolved quickly after normalisation of hypercalcaemia.

Similar to the original and the modern versions of the syndrome, ingested carbonate was the main source of bicarbonate in our case. The main trigger was a morphine overdose with volume contraction due to vomiting and a further aggravation of chronic compensatory elevation of bicarbonate due to hypoventilation leading to MAS; thus, suggesting hypoventilation as a risk factor for MAS.

BACKGROUND

The milk alkali syndrome (MAS), with its classical triad of hypercalcaemia, metabolic alkalosis and renal failure, has been known for many years. It was originally described in patients ingesting large amounts of calcium through milk for the treatment of peptic ulcer disease.¹ In the 1970s, the incidence of the syndrome virtually disappeared with the introduction of more potent antacids. In the late 1980s a modern day version of the syndrome was observed in patients with excessive intake of calcium carbonate supplementation for osteoporosis prophylaxis.^{2–5} MAS was now more common in women in contrast to the male prevalence in the original MAS.^{3–6} In a recent analysis, the MAS was found to be the third most common cause of hypercalcaemia in patients admitted to hospital.⁶

We report a new risk factor for the MAS that should be taken into account in case of otherwise unexplained hypercalcaemia, alkalosis and renal failure.

CASE PRESENTATION

A 67-year-old woman was admitted to the hospital due to progressive mental changes, nausea and vomiting for 2 days. She had a history of poliomyelitis in childhood with paraparesis, severe osteoporosis with vertebral compression fractures, chronic back pain and weight gain of 40 kg during the last 4 years. She had long-term calcium carbonate supplementation for osteoporosis and a thiazide diuretic. She also suffered from obesity induced chronic hypoventilation syndrome. The chronic pain syndrome was treated with an intrathecal morphine pump. Three days before admission the morphine dose was increased. On physical examination an obese (body mass index 46 kg/m²), somnolent, patient was found. Blood pressure was 155/71 mm Hg and heart rate was 77 bpm. The arterial oxygen saturation was 100% while the patient was breathing 8 l oxygen per min.

INVESTIGATIONS

Blood tests showed severe hypercalcaemia (total calcium 4.68 mmol/l, ionised calcium 2.34 mmol/l, albumin 45 g/l), mild hyperphosphataemia (phosphorus 1.51 mmol/l), mild renal insufficiency with a creatinine of 97 µmol/l (recent creatinine 40 µmol/l) and low serum chloride (84 mmol/l). Arterial blood gas analysis revealed primary respiratory acidosis (pH 7.32) with severe hypercapnia (pCO₂ 10.8 kPa) and concomitant metabolic alkalosis (HCO₃ 41 mmol/l). Calcium excretion in the spot urine was not increased (calcium to creatinine ratio 0.44 mmol/mmol; normal range 0–0.7 mmol/mmol). No evidence of malignancy associated hypercalcaemia was found. Serum and urinary protein electrophoresis were normal; bone scan showed no signs of metastatic bone lesions and parathyroid hormone (PTH) related protein was not detectable. Hyperparathyroidism was ruled out by suppressed intact PTH (7.6 pg/ml; normal range 10–75 pg/ml). Hypervitaminosis D was excluded by normal 25-hydroxyvitamin D (84 nmol/l; normal range 50–250 nmol/l) and suppressed calcitriol (29 pmol/l; normal range 48–160 pmol/l) levels. The patient was immobilised for several months, but there were no signs of high bone turnover as a source of hypercalcaemia. The alkaline phosphatase was initially slightly elevated (142 U/l; normal range <104 U/l), but normalised quickly by day 3 (84 U/l) and before administration of bisphosphonates.

DIFFERENTIAL DIAGNOSIS

A differential diagnosis of hypercalcaemia includes increased bone resorption (eg, malignancy, hyperparathyroidism, hyperthyroidism, and immobilisation), increased calcium uptake (eg, hypervitaminosis D, calcium supplementation) and reduced renal calcium excretion (eg, renal failure, thiazide diuretics). Severe hypercalcaemia (calcium >3.5 mmol/l) in the absence of significant renal disease usually is caused by malignancy, primary hyperparathyroidism or MAS.

TREATMENT

Treatment with calcium carbonate supplementation and thiazide diuretic was stopped. Consciousness did not improve after naloxon administration. The patient was admitted to the intensive care unit and treated with sodium chloride 0.9% infusion at a rate of 200 ml/h, intravenous furosemide and subcutaneous calcitonin. Due to persistent elevated calcium (total calcium 2.8 to 3.1 mmol/l), a single dose of zoledronic acid was administered at day 3.

OUTCOME AND FOLLOW-UP

Total serum calcium declined to 3.47 mmol/l after 24 h. Neurological symptoms disappeared and kidney function normalised (creatinine 41 µmol/l). Normalisation of calcium occurred after 6 days but mixed acid-base disorder with hypoventilation and compensatory hyperbicarbonataemia persisted (pH 7.42, pCO₂ 6.82 kPa, HCO₃ 32.9 mmol/l). An overnight pulse oxymetry test showed severe desaturation (apnoea-hypopnoea index >40/h) compatible with obesity hypoventilation syndrome. Treatment with continuous positive airway pressure was started with a sustained normalisation of acid-base disorder (pH 7.41, pCO₂ 5.98 kPa, HCO₃ 27.3 mmol/l) and hypercalcaemia (ionised calcium 1.18 mmol/l).

DISCUSSION

Severe hypercalcaemia (calcium >3.5 mmol/l) in the absence of significant renal disease usually is caused by malignancy, primary hyperparathyroidism or MAS.⁶ As malignancy and hyperparathyroidism could be ruled out MAS remained the most probable cause of hypercalcaemia in our case.

Development of MAS usually begins with hypercalcaemia by high calcium carbonate supplementation. Hypercalcaemia produces a decrease in glomerular filtration due to increased sodium and water excretion,⁷ and by direct glomerular vasoconstriction.⁸ The combined effects of increased alkali intake, a fall in glomerular filtration rate (GFR) and hypercalcaemia then lead to metabolic alkalosis. The alkalosis further enhances the hypercalcaemia by decreasing calcium excretion in the distal nephron.⁹ Vomiting, diuretics, and the natriuretic effects of hypercalcaemia further aggravate hypercalcaemia and alkalosis.

Our patient was treated for several years with calcium carbonate containing supplementation for osteoporosis and thiazide diuretics but her calcium level in the past remained in a high-normal range (total calcium 2.54 mmol/l) until 6 months before admission. Metabolic alkalosis was induced by: (i) calcium carbonate supplementation, (ii) volume contraction due to vomiting, thiazide diuretics and hypercalcaemia, and (iii) acid loss by vomiting. High bicarbonate levels persisted during the follow-up despite discontinuation of calcium carbonate and thiazide diuretics and vigorous volume substitution. The condition with chronic compensatory elevation of bicarbonate due to hypoventilation in normal circumstances does not lead to MAS. But

given the patient's known condition with several risk factors for the development of MAS (calcium carbonate containing supplementation, thiazide diuretics and immobilisation), the morphine overdose induced vomiting with further volume contraction aggravated hypoventilation and increased compensatory renal bicarbonate generation, which finally led to MAS. How much the different factors contributed to the development of MAS in this case is unclear. As in the original and the modern version of the syndrome, ingested carbonate was probably the main source of bicarbonate. However, compensatory generation of bicarbonate due to aggravation of hypoventilation may contribute to the metabolic alkalosis and is probably not negligible.

Learning points

- ▶ MAS should always be considered in patients with severe hypercalcaemia.
- ▶ Today's polymedication in the elderly with calcium carbonate containing supplementation for osteoporosis, thiazide diuretics, calcium carbonate containing antacids and reduced capacity to handle calcium (impaired GFR, reduced bone uptake of calcium) exposes them to a higher risk for MAS.
- ▶ Chronic hypoventilation associated with compensatory high bicarbonate levels seems to be another risk factor that should be taken into account.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Burnett CH**, Commons RR. A syndrome characterized by hypercalcemia, calcinosis, and renal insufficiency following prolonged intake of calcium and alkali. *J Clin Endocrinol Metab* 1948;**8**:584.
2. **Beall DP**, Henslee HB, Webb HR, *et al*. Milk-alkali syndrome: a historical review and description of the modern version of the syndrome. *Am J Med Sci* 2006;**331**:233–42.
3. **Beall DP**, Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. Report of 7 patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. *Medicine (Baltimore)* 1995;**74**:89–96.
4. **Vanpee D**, Delgrange E, Gillet JB, *et al*. Ingestion of antacid tablets (Rennie) and acute confusion. *J Emerg Med* 2000;**19**:169–71.
5. **Kapsner P**, Langsdorf L, Marcus R, *et al*. Milk-alkali syndrome in patients treated with calcium carbonate after cardiac transplantation. *Arch Intern Med* 1986;**146**:1965–8.
6. **Picolas MK**, Lavis VR, Orlander PR. Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) inpatients. *Clin Endocrinol (Oxf)* 2005;**63**:566–76.
7. **Brown EM**. Physiology and pathophysiology of the extracellular calcium-sensing receptor. *Am J Med* 1999;**106**:238–53.
8. **Humes HD**, Ichikawa I, Troy JL, *et al*. Evidence for a parathyroid hormone-dependent influence of calcium on the glomerular ultrafiltration coefficient. *J Clin Invest* 1978;**61**:32–40.
9. **Sutton RA**, Wong NL, Dirks JH. Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney. *Kidney Int* 1979;**15**:520–33.

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