Aging Medicine and Healthcare 2021;12(1):26-28. doi:10.33879/AMH.121.2020.02005

Aging Medicine and Healthcare
https://www.agingmedhealthc.com

Case Report

A Case of Delirium Induced by Milk-Alkali Syndrome in the Elderly

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ABSTRACT

An 80-year old woman with intake of calcium carbonate and sodium bicarbonate, admitted with delirium, hypercalcemia and metabolic alkalosis. The mechanism of milk-alkali syndrome, diagnosis and management is described.

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Received 12 February 2020
Accepted 14 June 2020

Keywords
Milk-alkali syndrome, hypercalcemia

1. CASE REPORT

An 80-year old woman, was admitted to the department of Geriatrics in our hospital with consciousness disorder. The patient had increased daytime sleep, nyctohemeral rhythm inversion, slowed responses, and decreased physical activity ten days before admission, and experienced abdominal pain, nausea, and vomiting four days before admission, accompanied by confusion and irritability. Her past medical history is rheumatic polymyalgia, hypertension, chronic renal disease (stage III CKD), osteoporosis, and hypothyroidism. Findings on physical examination were unremarkable except mild pitting edema of both lower extremities, without focal neurologic findings. Her medication was as follows: prednisone 5mg/7.5mg alternately taken every other day; calcium carbonate (1000 mg, three times a day); sodium bicarbonate (1000 mg, three times a day); calcitriol (0.25μg, twice a day); compound α-ketoacid tablets (630 mg, three times a day); amlodipine besylate (2.5mg, twice a day); bisoprolol (5 mg, once a day); and levothyroxine sodium (50 μg, once a day).

The comprehensive geriatric assessment revealed that her hearing and visual loss, but had no impact on her daily life. She scores 7 out of 14 on the Mini-nutrition assessment-short form. She presented acute confusion onset and fluctuating course with inattention and disorganized thinking. The Confusion Assessment Method evaluating delirium was positive. Her grip strength is 16 kg. Her score on the activities of daily living (ADL) assessment was 4 out of 6, and the score on instrumental activities of daily living (IADL) assessment was 1 out of 8. She was a widow and lived with her daughter. Laboratory and radiologic investigations were arranged. The results of laboratory examination are shown in Table 1. The complete blood count, liver function and thyroid function were all within normal limits. MRI of the head revealed

age-related brain changes. Ultrasound of parathyroid gland is normal. She was diagnosed on admission with delirium, hypercalcemia, hypokalemia, stage IV CKD, metabolic alkalosis, fall risk, polypharmacy, malnutrition, frailty.

The factors that precipitated the patient to delirium was hypercalcemia and metabolic alkalosis. The patient had received calcium carbonate supplementation due to osteoporosis and CKD. The daily intake of calcium from calcium carbonate and compound α-ketoacid tablets was 1350mg. The dietary habit of the patient was to drink milk and yoghurt 500ml every day, containing about 600 mg calcium. Therefore, the patient received a total daily amount of around 2000mg calcium. Meanwhile, the patient was given active vitamin D to promote calcium absorption, combined with basic CKD that affected kidney calcium excretion, leading to hypercalcemia. Hypercalcemia led to nausea, vomiting, and insufficient volume, which further caused renal impairment and decline in HCO_{3-} excretion in the kidney, and the patient also received sodium bicarbonate, which resulted in metabolic alkalosis. Taken together, the patient was diagnosed with milk-alkali syndrome. Other common causes of hypercalcemia, such as primary hyperparathyroidism and malignant tumors, were excluded after the examination.

In terms of treatment, calcium supplementation and vitamin D drugs were stopped. Salmon calcitonin was injected subcutaneously 100U every 8 hours a day, and fluid and potassium were supplemented. After three days, calcium decreased to 2.17mmol/L, potassium increased to 3.2mmol/L, and the patient returned to normal mental status. The nutritionist recommended intake of 500mg of calcium carbonate once every other day. As for the patient's diet, intake of high-quality protein and increase in vegetable were recommended. After two weeks, she scored 26 out of 30 on the Mini-Mental State Examination. Her score on the ADL assessment was 5 and on the IADL assessment was 4. Serum creatinine was 1.4mg/dL.

Table 1. Laboratory examination

Items	Admission
Creatinine	2.8 mg/dL (0.6~1.1)
Calcium	3.12 mmol/L (2.13~2.70)
Corrected serum calcium	3.19 mmol/L
Potassium	2.3 mmol/L (3.5~5.5)
Arterial blood gas	pH 7.52, PaO_2 76 mmHg, $PaCO_2$ 40 mmHg, base excess 9.0 mmol/L (-3.0~+3.0)
Serum [HCO_{3-}]	32.7 mmol/L (21.8~26.2)
Serum parathyroid hormone (PTH)	42.9 pg/ml (12.0~68.0)
1,25 (OH) Vitamin D	0.71 pg/ml (19.6~54.3)
Urinary calcium	3.85 mmol/24h

2. DISCUSSION

Milk and alkali were widely adopted in the treatment of peptic ulcers in the early 20th century. Milk-alkali syndrome was first described in 1923,[1] and it was recognized that excessive intake of alkali could cause alkalosis and kidney injury. With the wide availability of histamine H2-receptor antagonists and proton pump inhibitors for treatment of peptic ulcer, the incidence of milk-alkali syndrome has declined. However, a resurgence of milk-alkali syndrome has been noted as a result of the widespread use of calcium carbonate in the prevention and treatment of osteoporosis and renal osteopathy. Some studies have shown that milk-alkali syndrome is the third most common cause of hypercalcemia in hospitalized patients, following hyperparathyroidism and malignancy, with an incidence ranging from 9 to 12%, and it is the second leading cause of severe hypercalcemia (corrected serum calcium >3.5mmol/l).[2,3] Milk-alkali syndrome, also known as Calcium-alkali syndrome, is characterized by hypercalcemia, metabolic alkalosis, and acute renal injury caused by ingestion of large amounts of calcium and absorbable alkali. The exact pathogenesis of milk-alkali syndrome remains uncertain. When the continuous intake of excessive calcium and active vitamin D supplementation can increase in blood calcium, which decreases glomerular filtration rate (GFR) and effects calcium excretion by contracting renal vessels and injuring renal tubules. The calcium-induced diuresis results in volume insufficiency, which stimulates the renal tubular absorption of bicarbonate. The combined effects of increased alkali intake, insufficient volume, and decreased GFR lead to metabolic alkalosis.[4] It has been reported that the presence of kidney disease may be a predisposing factor of milk-alkali syndrome.[5] In addition, medications that affect calcium excretion, such as thiazide diuretics, have also been considered to be risk factors for the disease.[6]

The diagnosis of milk-alkali syndrome is based on the history of excessive calcium and alkali intake, the presence of clinical and laboratory features, and the exclusion of other causes of hypercalcemia. Milk-alkali syndrome can present in a variety of forms, depending in part on the amount and duration of the calcium and alkali intake, as well as the presence of risk factors such as the use of thiazide diuretic and dehydration. Historically, patients presented with symptoms of nausea, vomiting, weakness, altered sensorium, and pruritus, and, renal impairment is not always relieved after normalization of the plasma calcium depending upon the duration of hypercalcemia. Older individuals suffering from multimorbidity and polypharmacy are at higher risk for the development of milk-alkali syndrome, because of most of them taking calcium and Vitamin D, at risk for dehydration (including thiazide diuretics use), a propensity to decreased renal function. They

Table 2. Differential diagnosis of laboratory examination

Disease	Laboratory examination				
	PTH	Serum calcium	Urinary calcium	eGFR	1,25 OHD
Milk-alkali syndrome	Generally low	Elevated	Normal or elevated	Low	Low
Hyperparathyroidism	High	Elevated	Normal or elevated		Normal, low-normal or low
Malignancy	Low	High	Generally high	Normal or low	Normal or elevated

eGFR : estimated glomerular filtration rate; PTH: parathyroid hormone.

may have atypical symptoms and changes in mental state characterized by delirium or decreased levels of consciousness. It is important to be aware of the possibility of incident delirium induced by milk-alkali syndrome in the older adults. Milk-alkali syndrome should be distinguished from hypercalcemia caused by hyperparathyroidism and malignancy. The clinical presentations of these diseases are sometimes asymptomatic and atypical, and laboratory examinations can usually help identify them (see Table 2). Treatment is supportive and involves hydration and withdrawal of calcium and alkali intake. In severe cases, furosemide can be used to enhance urinary calcium excretion.[7] Bisphosphonates, which cause a prolonged suppression of the serum calcium, can produce hypocalcemia in patients with milk-alkali syndrome and should be avoided.[3]

Nowadays, with the increasing awareness of osteoporosis and the extensive use of calcium supplements for prevention, the incidence of milk-alkali syndrome is increasing. Physicians should be aware of the potential adverse effects of excessive amounts of calcium carbonate intake and public education on the correct calcium supplement should be communicated. It is generally considered safe to consume no more than 2g of elemental calcium daily; however, milk-alkali syndrome may still occur if additional predisposing factors, such as renal insufficiency, use of thiazide diuretics, and dehydration, are present. Therefore, when prescribing calcium supplement therapy for the elderly, it is necessary to check the medications at the same time, whether to take alkaline agents and drugs that affect calcium excretion. When predisposing factors of milk-alkali syndrome are present, the choice of dosage, the form of calcium supplement, and close monitoring of blood calcium need to be carefully considered.

CONFLICTS OF INTEREST

All authors have no conflicts of interest to declare.

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