Case Report with Review of Literature

Hypercalcemic encephalopathy due to milk alkali syndrome and injection teriparatide

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ABSTRACT

An 82-year-old male, a known case of severe osteoporosis with vertebral fracture and prostatic carcinoma, was treated with gonadotropin releasing hormone analogue, calcium carbonate, cholecalciferol sachet and injection teriparatide. His diet consisted of milk and curd. He developed altered behavior and generalized weakness, and on investigation, hypercalcemia, hypokalemia, and metabolic alkalosis with low parathyroid hormone levels were detected. Injection teriparatide was stopped and he was managed with forced saline diuresis and injection zoledronic acid. He was diagnosed as a case of milk alkali syndrome in whom teriparatide and prolonged immobilization played a permissive role in the development of hypercalcemic encephalopathy.

Key words: Hypercalcemic encephalopathy, milk alkali syndrome, osteoporosis, teriparatide

Introduction

Metabolic encephalopathies are among one of the common causes of admission to hospital in the elderly age group.[1] Hypercalcemia is rare among these patients. Depending on the severity and rate of development of hypercalcemia, patient can present with mild drowsiness to coma. In more than 90% of cases, hyperparathyroidism is the cause; however, in an emergency setting, malignancy related hypercalcemia is the commonest cause.[1] Milk alkali syndrome (MAS) can cause acute, subacute or chronic hypercalcemia, which has been reported as early as in 1923, though the term MAS was coined in 1949.[2] Though it became uncommon after some time, recently it has witnessed resurgence after increased general awareness about osteoporosis and overuse of calcium carbonate and vitamin D.[2] Injection teriparatide is known to cause transient hypercalcemia up to 6 hours of its administration;[3] severe hypercalcemia causing encephalopathy is not known. Here, we report a case of hypercalcemic encephalopathy caused by MAS in which a permissive role was played by injection teriparatide and other factors.

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Case Report

An 82-year-old male presented to emergency with history of sudden onset with gradual deterioration of mental sensorium of 8 days duration. Other history elicited from attendants revealed that the patient suffered from low impact fracture of third and fourth lumbar vertebrae 3 months back for which he was evaluated and found to have osteoporosis (L1–L4 vertebrae: T-score 3.1, Z-score 1.1; femur neck: T-score 3.0, Z-score 0.7). During evaluation, he was detected to have prostatic carcinoma for which he was being treated with depot preparation of injection treptorelin acetate [gonadotropin-releasing hormone (GnRH) analogue] 11.25 mg once in 3 months. He was prescribed oral calcium carbonate 500 mg thrice daily and cholecalciferol 60,000 U monthly. However, the patient was consuming 5–6 tablets of calcium carbonate (each tablet containing 500 mg elemental calcium) and his diet consisted of milk (1.5 l/day) and plenty of curd. He was started on injection teriparatide 20 μg daily 10 days back in view of severe osteoporosis. At this time, his serum calcium (9.9 mg/dl), phosphorus (3.8 mg/dl) and 25(OH)

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vitamin D (84.4 ng/ml) levels were normal. His sensorium gradually worsened after starting injection teriparatide. He had limited physical activity in view of his age and disability. On examination, he had normal vital parameters with normal systemic examination except drowsiness and disorientation. Investigations revealed hypercalcemia (serum calcium 14.3 mg/dl), normal phosphate levels (3.1 mg/dl), normal alkaline phosphatase (174 U/l), acute kidney injury as evidenced by raised serum creatinine (2.3 mg/dl as compared to basal creatinine levels of 0.9 mg/dl), metabolic alkalosis (pH 7.56, HCO^{3-} 39 mEq/l, $PaCO_2$ 47 mm of Hg) and hypokalemia (serum potassium 2.3 mEq/l). His serum parathyroid hormone (PTH) level was 7 pg/ml (10–74 pg/ml). He was euthyroid [T_3 1.2 ng/ml, T_4 9.45 μg/dl, thyroid stimulating hormone (TSH) 4.5 μIU/ml] and eucortisolemic (cortisol basal 8.3 μg/dl, post ACTH cortisol 24 μg/dl). He had low serum testosterone levels (0.1 ng/ml) consistent with GnRH therapy.

In view of acute hypercalcemia, hypokalemia, metabolic alkalosis, acute kidney injury and history of consumption of 3–4 g of calcium carbonate daily, he was diagnosed as a case of hypercalcemic encephalopathy due to MAS which was probably precipitated by concomitant use of injection teriparatide and immobilization. His drugs (calcium carbonate and teriparatide) were stopped and he was started on intravenous forced diuresis with 3 l of normal saline and 40 mg thrice daily injection of frusemide, with monitoring of cardiovascular status. He was also given injection zoledronic acid 5 mg in 100 ml normal saline over 30 min. His clinical and biochemical parameters normalized in 72 hours (serum calcium 8.6 mg/dl, pH 7.38, potassium 4.6 mEq/l and creatinine 0.7 mg/dl). He was discharged after 6 days of hospital stay on vitamin D sachet (60,000 U) once monthly.

Discussion

Rapidly increasing serum calcium levels have long been associated with changes in mental status. Elderly population is more prone to these changes in cognition with acute hypercalcemia. Hypercalcemia has various causes, and in an emergency setting, primary hyperparathyroidism, malignancy associated hypercalcemia and MAS constitute most of the cases.[4]

Our patient was diagnosed with MAS on the basis of presence of acute hypercalcemia, hypokalemia, metabolic alkalosis, acute kidney injury and history of consumption of 3–4 g daily calcium carbonate, with normal phosphate and low PTH levels.

Milk alkali therapy for treatment of peptic ulcer disease was developed by Sippy in 1910.[5] It constituted bed rest of 4 weeks duration and multiple doses of milk and cream with alkali. Because of paucity of other treatment options, milk alkali treatment rapidly became standard for treatment of peptic ulcer disease. Gradually, several adverse effects of milk alkali therapy were reported. In 1949, Burnett for the first time named this syndrome of hypercalcemia, hyperphosphatemia, metabolic alkalosis and renal dysfunction as MAS.[6] In pathogenesis of MAS, old age, pre-existing renal dysfunction, and ingestion of large dose of calcium carbonate are all known to play a role. Initially, incidence of MAS was reported to be 10–15% which subsequently reduced on account of availability of effective alternate therapies for peptic ulcer disease. But the last two decades have seen resurgence of a modern form of MAS, where calcium carbonate constitutes the source of calcium and alkali, because many doctors are prescribing calcium supplements due to increase awareness about osteoporosis. Modern MAS differs from classical MAS in absence of male preponderance and presence of near-normal phosphate levels.[7]

In the present case, other factors also contributed to the development of hypercalcemic encephalopathy. Firstly, the patient had limited physical activity and was almost bedridden. Immobilization is a risk factor for the development of hypercalcemia.[8] Secondly, at the age of 82, his estimated glomerular filtration rate will be compromised (~53 ml/min by Cockcroft and Gault equation). Normal individuals with normal renal function do not develop hypercalcemia on high calcium diet. There is balance between intestinal calcium absorption and renal calcium excretion.[9] However, in our patient with compromised renal function, excessive calcium intake with vitamin D may have predisposed him to the development of hypercalcemia. Finally, on initiation of injection teriparatide, he developed sudden worsening of sensorium and severe symptomatic hypercalcemia, along with deterioration in renal function and the biochemical features suggestive of MAS.

Injection teriparatide is the only approved anabolic therapy available for treatment of osteoporosis.[10] It was initially suspected that with the use of teriparatide, a synthetic analogue of PTH, the incidence of hypercalcemia would increase. However, mostly transient and mild hypercalcemia is observed but persistent and severe hypercalcemia has been reported.[3]

Hence, our patient developed MAS secondary to excessive intake of calcium where a permissive role was played by age, immobilization and teriparatide for the development of hypercalcemic encephalopathy. Therefore, it is suggested

that when teriparatide therapy is begun, particularly in elderly patients who have limited physical activity, daily total, dietary and supplemental, calcium should be maintained at 1000 mg or less, so as to keep the serum calcium below 10 mg/dl.[3]

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