

Milk-alkali syndrome: The forgotten diagnosis for altered sensorium

Yap Wai Leong, MD¹, Andey Rahman, MMed^{1,2}, Kamarul Aryffin Baharuddin, MMed^{1,2}

¹Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia,

²Hospital Universiti Sains Malaysia, Jalan Raja Perempuan Zainab 2, Kubang Kerian, Kelantan, Malaysia

SUMMARY

Milk-alkali syndrome (MAS) is one of the causes of hypercalcaemia. We report a case of a 75-year-old lady with a history of thyroidectomy, presented with an altered mental state and had an extremely high calcium concentration of 4.96mmol/L. The hypercalcaemia was attributed to the ingestion of large doses of calcium supplements, including calcium carbonate and calcium lactate, leading to MAS. She was managed with intravenous fluids, diuretics and withdrawal of calcium supplements. The patient responded well to treatment and regained consciousness. Details of the case including clinical presentations, electrocardiogram (ECG) findings and treatment plan, are discussed in this article.

INTRODUCTION

Altered sensorium (AS) is one of the commonest presentations in the Emergency Department (ED) and is always a diagnostic challenge for ED residents. Most cases of AS are related to neurological causes and a thorough neurological examination is essential. In addition, electrolyte imbalance like hypercalcaemia may be a cause of AS. Milk-alkali syndrome (MAS), once among the commonest cause of hypercalcaemia, is now considered rare.¹ Failure or forgotten to diagnose is not uncommon¹ and may lead to continuing excess intake of calcium carbonate. Recently, the incidence has resurgent secondary to the use of calcium carbonate to prevent and treat osteoporosis. We report a case of AS secondary to MAS in a 75-year-old lady following ingestion of the calcium supplements.

CASE REPORT

A 75-year-old lady was brought to ED of the Hospital Universiti Sains Malaysia, Malaysia with AS for one day. She had had a total thyroidectomy done in June 2021 for thyroid cancer and was recently admitted for hypocalcaemia with corrected calcium level of 1.89mmol/L. She was discharged a few days later with calcium and vitamin D supplements (calcium carbonate 1.5g BD, calcium lactate 1.2g TDS, and calcitriol 0.5mcg BD), antihypertensive medications (amlodipine 10mg OD and hydrochlorothiazide 12.5mg BD) and thyroid hormone supplement (L-thyroxine 100mcg OD). However, she had not been eating much and appeared tired and lethargic at home.

Two days prior to the presentation at the ED, her condition worsened, and she required assistance for ambulation. On the day of presentation, which was a week post-discharged, a family member noticed that she was less responsive, had no eye response, and did not answer upon call. There was no history of head injury or fall. No seizure or abnormal movements were noticed by the family member. No chest pain or angina symptoms were told by her to the family member.

Upon arrival, she was pink but severely lethargic and dehydrated. She was drowsy with GCS 9/15 (E3V1M5) and her pupils were 2mm reactive bilaterally. She had shown minimal movements of her limbs upon call. Her initial vital signs were blood pressure of 100/68mmHg, heart rate of 99 beats per minute, the temperature of 36.4°C, respiratory rate of 10 breaths per min, oxygen saturation of 99% under room air and capillary blood sugar of 5.5mmol/L. Neurological examination showed generalized muscle weakness and symmetrical hyporeflexia involving all 4 limbs. There were no focal signs or meningeal signs. Other systems were unremarkable.

Results from the point-of-care test (POCT) in ED showed hemoglobin (Hb) level of 13.6g/dL, white cell count (WCC) of 18.8x10³μL, and platelet of 804x10³μL. Her venous blood gas (VBG) confirmed metabolic alkalosis with pH 7.560, pCO₂ 56.3 mmHg, pO₂ 51.9 mmHg, and HCO₃ 44.5 mmol/L. Her electrolytes values from the VBG showed hypercalcaemia, hyponatremia and hypokalemia with ionized calcium (Ca) of 2.60 mmol/L, sodium (Na) of 127 mmol/L, potassium (K) of 2.7 mmol/L. An electrocardiogram (ECG) showed ventricular bigeminy with R-on-T phenomenon, Osborn waves and prolonged QT interval (Figure 1).

Even though her electrolytes values from the VBG were abnormal and no focal signs, a computerized tomographic (CT) scan of the brain was done due to sudden history of AS. The finding of the CT scan was normal. Her chest radiograph showed left lower zone haziness.

Formal the laboratory investigation results came back four hours later and showed severe hypercalcaemia, hyponatremia, hypomagnesemia, and hypokalemia with renal impairment (Na 126mmol/L, K 3.0mmol/L, Urea 9.0mmol/L, Creatinine 120μmol/L, Ca 4.96mmol/L

This article was accepted: 27 October 2021

Corresponding Author: Andey Rahman

Email: andey@usm.my

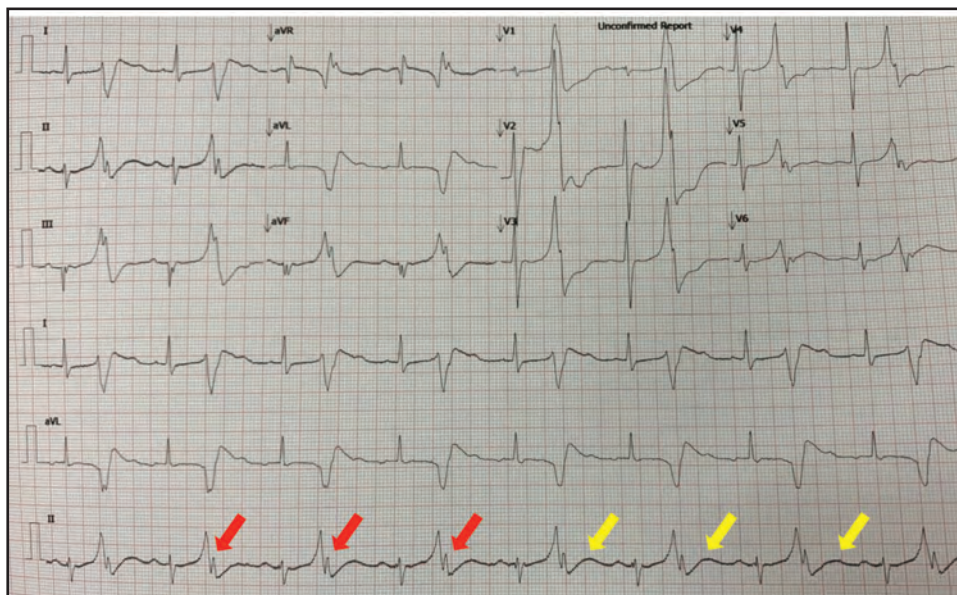


Fig. 1: ECG upon presentation. It appeared as ventricular bigeminy with prolonged QT interval along the sinus beats. Each premature ventricular complex (PVC) was very close to the T wave, represents R-on-T phenomenon. There was prolonged PR interval. Along the PVCs we could appreciate an upstroke of J point (red arrows), representing the Osborn wave. There was upright wave after the PVCs, which represents U wave (yellow arrow).

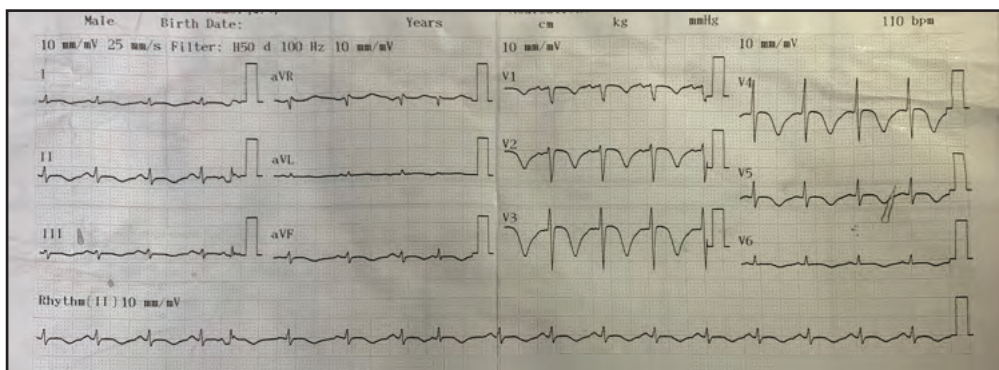


Fig. 2: ECG in ward. There were T inversions in all the leads (except lead aVR) with prolonged QT interval, which was due to the low levels of magnesium and potassium. Previously seen ventricular bigeminy, R-on-T phenomenon, U waves and Osborn J waves had resolved.

(corrected), phosphate (PO₄⁻) 1.14mmol/L, and magnesium (Mg) 0.48mmol/L). Troponin T result came back to be normal (5ng/L).

She was diagnosed with AS secondary to symptomatic hypercalcemia attributed to ingestion of calcium supplements, complicated by hospital acquired pneumonia. She was given aggressive intravenous fluid administration, a single bolus dose of diuretic and withdrawal of calcium supplements. Antibiotic was started and she was admitted to the general medical ward for further management.

During the admission, her conscious level had improved and calcium levels normalized. Her magnesium (0.52mmol/L) and potassium (2.8mmol/L) levels were slowly corrected. ECG done in the ward revealed changes caused by the electrolyte imbalances (Figure 2) prior to complete correction. Parathyroid hormone (PTH) level was low at < 0.127pg/ml.

She was not treated with bisphosphonates during the admission.

DISCUSSION

MAS was first described in 1920s as a complication of excessive use of milk and alkali to treat gastric ulcers. However, the incidence has greatly diminished with the introduction of acid reducing drugs like H₂-receptor antagonists or proton pump inhibitors.² However, since over-the-counter use of calcium for the supplement has increased and complicated with MAS, some authors suggested changing the name to calcium-alkali syndrome.^{1,3,4}

The triad of MAS includes hypercalcaemia, metabolic alkalosis, and renal insufficiency. Our patient had profound symptomatic hypercalcaemia, which caused lethargy, cognitive disturbance, and muscle weakness. Life-threatening

central nervous system manifestations may also occur like encephalopathy and seizure.⁵ In this case, she was initially treated for hypocalcaemia post thyroidectomy, and she was discharged with high doses of calcium with thiazides. Thiazides are known to reduce calcium excretion, promote intravascular depletion and alkalemia.² Moreover, hypercalcaemia is well-known to have natriuretic and diuretic effects that eventually worsen the intravascular status.²

Hypercalcaemia usually becomes symptomatic at a concentration of 3 to 3.5mmol/L.⁶ The symptoms are predominantly related to gastrointestinal, genitourinary, musculoskeletal and central nervous system. These include abdominal pain, reduced appetite, nephrolithiasis, depressed mood, headache, confusion, lethargy, and muscle weakness. Studies have found that the mean of calcium level among 78 MAS patients was 4.30mmol/L (range, 2.78-6.88mmol/L).⁷ In this patient, her calcium was 4.96mmol/L with moderate hypomagnesaemia and hyponatremia with mild hypokalaemia. Concurrent electrolyte abnormalities are common in MAS like hypomagnesaemia, hyponatremia and hypokalaemia.¹ Her serum creatinine (120µmol/L) was slightly high compared to the mean of serum creatinine (106.1µmol/L) in MAS patients.¹

ECG changes are very important for a high index of suspicious cases, particularly to look for QT/QTc interval shortening and often non-hypothermic J waves.⁴ During the initial presentation (Figure 1), there were normothermic Osborn J wave, prominent U waves, PR prolongation, QT interval prolongation, ventricular bigeminy, and R-on-T phenomenon. The presence of normothermic Osborn J wave in a hypercalcaemic patient is not considered as arrhythmogenic that lead to ventricular fibrillation⁸ compared to R-on-T phenomenon. R-on-T phenomenon occurs as a result of the increment of T wave duration and therefore, it increases the chance of premature ventricular contraction (PVC) to fall on the T wave. It is well known that hypercalcaemia causes decreased in ventricular conduction velocity and shortening of the refractory period that trigger PVC.⁹ Prominent U waves and prolonged PR interval can occur in patients with severe hypercalcaemia.

Our patient had a rapid resolution of hypercalcaemia and metabolic alkalosis after aggressive intravenous normal saline and single bolus dose of diuretic were administered. Withdrawal of the offending agent and treatment with isotonic saline usually produces clinical improvement and rapid resolution of the hypercalcaemia and metabolic alkalosis.¹⁰ These combinations are adequate for initial management in ED, but severe cases may require regular diuretics, bisphosphonate and calcitriol.¹⁰ Bisphosphonate takes more than 24 hours to take effect and may cause prolonged suppression of serum calcium.¹ Unless clearly indicated, bisphosphonate should be avoided as the emergent treatment in ED. Once the patient's calcium level returned to normal, the Osborn J wave, R-on-T phenomenon, ventricular bigeminy, and prominent U waves in the ECG recording were resolved (Figure 2).

Generally, MAS has a good prognosis if properly treated.⁶ Complicated MAS cases associated with posterior reversible encephalopathy syndrome may also have a good recovery if adequately managed.⁵ However, a significant number of patients may be left with permanent renal impairment if the diagnosis is forgotten.⁶

CONCLUSION

AS, seizure or encephalopathy may be a presentation for MAS. A high index of suspicion is important in hypercalcaemic patients with metabolic alkalosis and acute kidney injury. A history of taking high doses of calcium supplements should trigger the diagnosis of MAS. Detailed history taking, a complete physical examination and ECG changes are essential for a better diagnosis.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of Department of Emergency Medicine of HUSM and the patient's consent to have her case published.

REFERENCES

1. Picolos 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(5): 566-76.
2. Medarov BI. Milk-alkali syndrome. *Mayo Clin Proc* 2009; 84(3): 261-7.
3. Patel AM, Goldfarb S. Got calcium? Welcome to the calcium-alkali syndrome. *J Am Soc Nephrol* 2010; 21(9): 1440-3.
4. Zayed RF, Millhouse PW, Kamyab F, Ortiz JF, Atoot A. Calcium-Alkali Syndrome: Historical Review, Pathophysiology and Post-Modern Update. *Cureus* 2021; 13(2): e13291.
5. Vu K, Becker G, Eagerton D. A 39 year-old woman with milk-alkali syndrome complicated by posterior reversible encephalopathy syndrome. *Bone Rep* 2020; 12: 100278.
6. Vestergaard P. Current pharmacological options for the management of primary hyperparathyroidism. *Drugs* 2006; 66(17): 2189-211.
7. Scofield RH, Fayyaz A, Sharma R, Griffing GT, Nguyen T-T, Sharief SA, et al. Milk-Alkali Syndrome: Medscape; [updated 09 August 2017; cited August 2021. Available from: <https://emedicine.medscape.com/article/123324-overview#a7>.
8. Maruyama M, Kobayashi Y, Kodani E, Hirayama Y, Atarashi H, Katoh T, et al. Osborn waves: history and significance. *Indian Pacing Electrophysiol J* 2004; 4(1): 33-9.
9. Pedersen CM, Rolighed L, Harsløf T, Jensen HK, Nielsen JC. Primary hyperparathyroidism and recurrent ventricular tachyarrhythmia in a patient with novel RyR2 variant but without structural heart disease. *Clin Case Rep* 2019; 7(10): 1907-12.
10. Watson SC, Dellinger BB, Jennings K, Scott LA. Antacids, altered mental status, and milk-alkali syndrome. *Case Rep Emerg Med* 2012; 2012: 942452.