

Is this a seizure?

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Summary

We describe a case of a 65-year-old woman admitted to the hospital for suspected of epileptic crisis. She was affected by diabetes and hiatal hernia for which she was taking Proton Pump Inhibitors (PPIs) for about 8 years. She showed hypocalcaemia, hypomagnesaemia, hyperparathyroidism and severe hypovitaminosis D. We exclude malabsorption and magnesium loss. After restored vitamin D levels, stopped use of PPI, start calcium and magnesium supplementation normal values of the ions were restored. This case underlies the importance of evaluate magnesium routinely, other than calcium and vitamin D, and use PPI more carefully.

KEY WORDS: proton pump inhibitors; magnesium; hypocalcaemia; hypoparathyroidism.

Introduction

Proton Pump Inhibitors (PPIs) are currently routinely used in patients affected by gastric diseases and recently they have been associated with hypomagnesaemia which in turn can induce PTH and calcium imbalance.

Case report

A 65-year-old female was admitted to the hospital for "suspect of epileptic crisis". The patient presented with stiffness and lapse of consciousness, which lasted for about 15 minutes, associated with tongue biting but no sphincter release or tonic-clonic seizures; the patient had no memory of the accident.

The patient had a history of type 2 diabetes complicated with diabetic retinopathy and peripheral artery disease, chronic kidney disease, atrial fibrillation and hypertension. She had hiatal hernia and prior duodenal ulcer since 8 years and chronic hypocalcaemia and hypomagnesaemia.

Her medications included: amlodipine 5 mg ¼ cp day, ramipril 5 mg twice a day, furosemide 25 mg twice a day, doxazosin 2 mg day, metoprolol 100 mg day, glyburide 2,5 mg + phenformin 25 mg three times a day, pantoprazole 40 mg day, ezetimibe 10 mg + simvastatin 40 mg day, warfarin.

The patient underwent a CT brain, an MRI and an EEG none of which showed an organic cause for the epileptic episode, but only a recent small ischemic lesion in the right precentral zone.

Exams showed: sodium 140 mmol/l (normal range 136-145), potassium 3,9 mmol/l (nr 3,4-4,5), hypomagnesaemia (0,14 mmol/l, nr 0,70-1,05) and hypocalcaemia (1,17mmol/l, nr 2,10-2,55), phosphoremia 1,12 mmol/l (nr 0,81-1,4) with elevated PTH levels (71,2 ng/l, nr 4,6-26,8) and hypovitaminosis D 11 nmol/l (nr 75-250), low urine calcium 0,69 mmol/24h (2,5-7,50) and normal urine phosphorus 15,8 mmol/24h (nr 12,9-42,0). The hypocalcaemia was treated for the first three days with intravenous calcium gluconate (4 mg/day) and then with oral supplementation (calcium carbonate 2 g/day). At the same time the patient was started on calcitriol (0.5 mg/day) and cholecalciferol (300.000 UI oral load followed by a regime of 8.000 UI weekly). Likewise the hypomagnesaemia was treated with intravenous and oral supplementation (magnesium sulphate 2 g/day, for the first three days and magnesium pidolate 4,5 g/day, for the next days, respectively). Serum calcemia and magnesemia improved consequently but did not achieve the normal range.

At the same time, there was a decline in PTH level, restored to the normal range.

In order to understand the origin of the ion imbalance we investigated the possible causes of hypocalcaemia and hypomagnesaemia.

We started investigating the hypocalcaemia excluding malabsorption, which could have also explained the hypovitaminosis D. Celiac disease and Inflammatory Bowel Disease (IBD) were also considered: the anti-transglutaminase antibodies determination was negative, the gastric endoscopy with biopsy showed only minimal gastric inflammation, the colonoscopy showed diverticulosis of the colon and the levels of hepatic and pancreatic enzymes were normal.

Investigating the hypomagnesemia we ruled-out the following possible causes:

- 1) Renal loss: it is defined by the presence of hypomagnesaemia and 24-hours urine magnesium greater than 1 mmol/l (1).
 - a) The main causes of renal magnesium wasting are the Gitelman and Bartter syndromes: both are characterized by hypomagnesaemia, hypokalaemia, metabolic alkalosis and normal blood pressure; the main difference between the two diseases is that urinary calcium value is elevated in Bartter syndrome and reduced in Gitelman's (2). Our patient had high-blood

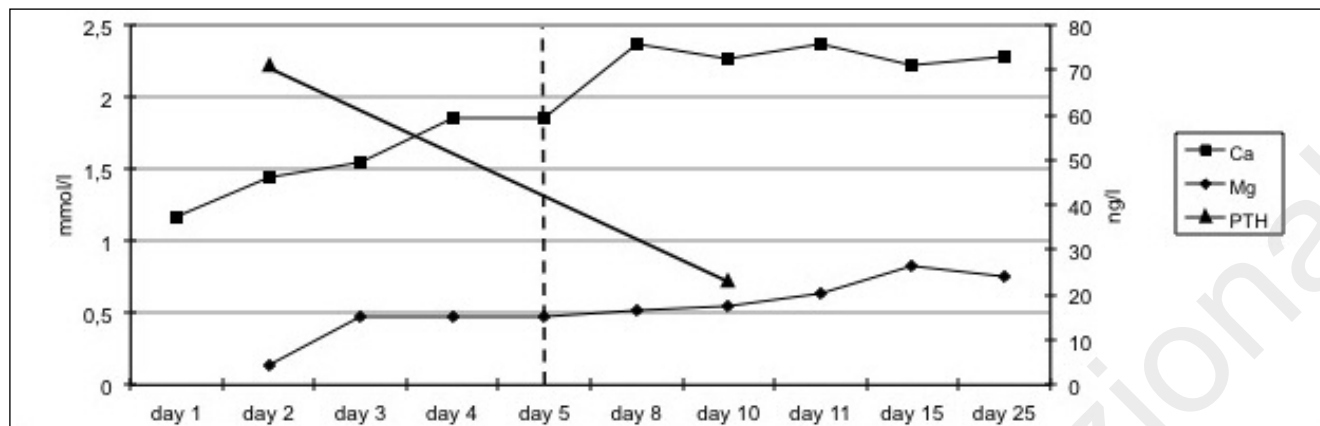


Figure 1 - Serum Parathyroid (PTH), Calcium (Ca) and Magnesium (Mg) in our case, the dotted line indicate the switch from PPI to H2RA and from furosemide to amiloride.

pressure and normal blood levels of potassium, which allowed us to exclude both syndromes.

- b) Diabetes can be a rare cause of renal loss of magnesium because it increases the renal tubular flow.
- The extra-renal causes of hypomagnesaemia (24 hours urine total magnesium lower than 0,5 mmol/l) are represented by intestinal malabsorption such as IBD, chronic pancreatitis and alcoholism (1); these causes had been already excluded in our patient.
 - Iatrogenic: some drugs can induce renal magnesium loss through two mechanisms causing renal toxicity (for example aminoglycosides) or decreasing tubular reabsorption (1) (such as loop diuretics, which were taken by the patient). Proton Pump Inhibitor (PPI) have been recently associated with hypomagnesaemia (3) through mechanisms not yet fully understood, but mainly by reducing the intestinal absorption (4). Among the drugs chronically taken by the patient two could be the cause this ion imbalance: furosemide and pantoprazole.

During the hospitalization we stopped pantoprazole and replaced it with ranitidine, we also replaced furosemide with amiloride and hydrochlorothiazide. We kept the oral supplementation of both calcium and magnesium managing to normalize their blood levels in 10 days (Figure 1). At discharge serum calcium was 2,23 mmol/l and the magnesium was 0,82 mmol/l.

Discussion

Although it was the hypocalcaemia that led to the neurological symptoms, it should be noted that hypomagnesaemia affects calcium homeostasis. The pathophysiological mechanism that correlates the hypomagnesaemia to hypocalcaemia is explained by the so-called paradox of blunted parathormone (PTH) secretion (5): a severe hypomagnesaemia causes a reduction of PTH secretion, thus inducing a functional hypoparathyroidism and a secondary hypocalcaemia; on the other side if magnesium levels are just slightly reduced this induces PTH secretion.

Magnesium homeostasis is regulated by intestinal absorption and renal excretion. PPIs cause electrolyte disturbance through a mechanism not yet fully understood. Among the pathophysiological mechanisms hypothesized there is a decreased magnesium intestinal absorption due to the interference with both the active transport mechanism, mediated by

transcellular transient receptor potential melastatin 6 and -7 (TRPM6 and -7), and the passive transport mechanism (using paracellular channels). In addition, altering the intestinal pH, PPIs modify the function of active transporters inducing hypochlorhydria thus decreasing ingested Mg salt solubility (4). To support the hypothesis for which there is a decrease Mg intestinal absorption in course of PPI therapy there is the evidence that the urinary magnesium in these patients is consequently reduced (6). In March 2011, the US Food and Drug Administration (FDA) issued a safety announcement about the association between PPI use and hypomagnesaemia, although only 1% PPI's adverse effects is represented by hypomagnesaemia. Such an adverse reaction occurs most frequently in elderly patients (mean age 64 aa) taking PPI by a prolonged period of time (mean 5.5 yr) (7) and there is no gender differentiation (4). Moreover, although the effect appears to be a characteristic of the whole pharmacological class, pantoprazole is associated with a greater risk while esomeprazole with a lower risk of developing hypomagnesaemia (7).

Conclusion

The actual PPI-associated hypomagnesaemia (PPIAH) epidemiology is currently unknown. The FDA claims that it represents 1% of all adverse events of PPI (7), while the prospective study published on the American Journal of Kidney Diseases (AJKD) reported 5% of incidence among users of this drug class (8). Both studies reported PPIAH as directly correlated to the duration of therapy and the association with loop diuretics.

PPIAH regresses suspending the drug but recurs if it is reintroduced, this does not happen if the PPI is replaced with a Histamine Receptor Antagonist (H2RA) like ranitidine (4).

Even with the limitation of not having evaluated 24 hours urine total magnesium, we concluded that at the origin of ion imbalance miming an epileptic crisis there was a severe hypocalcaemia associated with hypomagnesaemia. Hypovitaminosis D is often part of the differential diagnosis of calcium imbalance but less attention is drawn to magnesium and the adverse effects due to the use of PPIs. This suggests we have to use PPIs when there is real need and cautiously. Moreover, the control of the serum magnesium might be suggested routinely in patients using PPIs at higher dose and for prolonged periods.

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