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Case Report

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A Rare Case of Seizures Secondary to Proton Pump Inhibitors-Induced Hypomagnesemia

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Abstract

Hypomagnesemia is a side effect in patients in treatment with proton pump inhibitors (PPI) for more than one year. It can cause arrhythmias, tetany, seizure, and it can be a life-threatening condition. We describe the case of a 78-year-old man with history of relapsing tonic clonic seizures (TCZ), remote stroke, who presented to emergency department for another episode of TCZ. At blood tests, he had severe hypomagnesemia (0.39 mmol/L). After excluding other causes for hypomagnesaemia, chronic use of PPIs was considered a plausible cause. Therefore, substitutive therapy was initiated to restore blood levels of magnesium, and PPIs were discontinued.

Keywords: Proton-Pump Inhibitors, Hypomagnesemia, Seizures

Introduction

Proton pump inhibitors (PPIs) are commonly used in clinical practice for prevention and treatment of conditions like gastroesophageal reflux disease (GERD), esophagitis, peptic ulcer disease (PUD), and non-steroid anti-inflammatory drug (NSAID)-induced mucosal damage. Hypomagnesemia (serum magnesium <0.7 mmol/L) <0.7mmol/L) has been recognized as a side effect in patients in treatment with PPIs for more than one year. A medium prevalence of 19-27 % has been reported. The mechanism is not so clear, but it seems that PPIs affect magnesium gastrointestinal absorption. Low levels of magnesium in the bloodstream can cause a series of side effects like tiredness, instability, tetany, convulsions, cardiac arrhythmias, seizures, coma, and increased risk for hospitalization [1,2].

Case Report

A 78-year-old man with medical history of remote stroke, chronic ischemic heart disease, hypertension, pulmonary embolism, and cerebral vascular encephalopathy, presented at the emergency department with generalized tonic clonic seizures (TCZ). He also had a recent hospitalization in neurology department for TCZ. His home therapy was omeprazole (20 mg daily and more than one year intake), atenolol, olmesartan/hydrochlorothiazide, levetiracetam, atorvastatin, and rivaroxaban. On arrival, he had dehydrated skin, mixed speech, rhinolalia, and mild expressive dysphasia. Vital signs were in range: systolic blood pressure 135 mmHg, diastolic blood pressure 85 mmHg, heart rate 95 bpm, body temperature 36°C, oxygen saturation 96% FiO2 0.21%. Intravenous (iv) access was taken, and Lorazepam was administered at 0,1 mg/kg/dose [3]. Laboratory tests showed moderate hypokalemia at 2.5 mEq/L (normal values 3.5 to 5.2 mEq/L) that was treated with iv potassium 30 mEq in sodium chloride 0.9% solution. He had no history of neck surgery, remote or recent alcoholism, starvation, chronic diarrhea, steatorrhea, or malabsorption, and he didn't experience prolonged vomiting nor diarrhea. Hydrochlorothiazide therapy was suspended at hospital admission. During the hospitalization he had relapsing episodes of TCZ treated with diazepam at rectal dosage: 0,2-0,5 mg/kg [3]. Brain CT scan was negative for acute lesions. However, he continued to experience episodes of TCZ, so he also underwent a brain magnetic resonance imaging (MRI) which did not show an organic cause for the epileptic episode. At this point, a more enlarged set of blood tests was requested, and we observed a severe hypomagnesemia at 0.3 mEq/L (normal values 1.7 to 2.2 mg/dL). Electrolyte supplementation was initiated with 10% magnesium sulfate (MgSO4) (1g/10ml). Potassium levels normalize, but despite therapy, magnesium levels didn't raise. To understand the ion imbalance, we started to investigate the possible causes of hypomagnesemia. In the suspicion of a gastrointestinal

malabsorption, the patient underwent colonoscopy, which showed a sessile polyp at the level of the caecum (which was removed), and gastroscopy that showed a hyperplasic micropolypoid-like mucosa, indicative of chronic gastropathy (figure 1,2). Biopsies were executed, and histologically all specimens showed chronic inflammation of the lamina propria of the stomach. Celiac disease was also considered, but tissue transglutaminase and anti-endomysial antibodies resulted negative. We ruled out all the other causes of hypomagnesemia, such as alcohol abuse, use of diuretics, primitive aldosteronism, and intestinal surgical resections, thus, we concluded for a proton pump inhibitor's PPIs-induced hypomagnesemia. Substitutive therapy with magnesium sulfate was continued, and omeprazole was interrupted. After few days, we observed a gradual normalization of the blood levels of magnesium (figure 3). Subsequently, patient was discharged at home without any significant neurologic deficits.

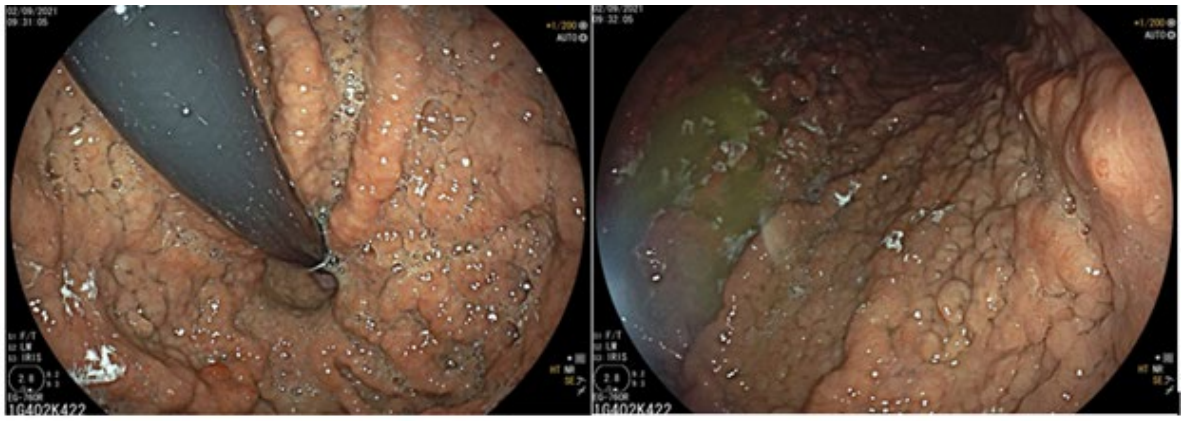

Figure1,2: Gastroscopy showing hyperplasic micropolypoid-like mucosa.

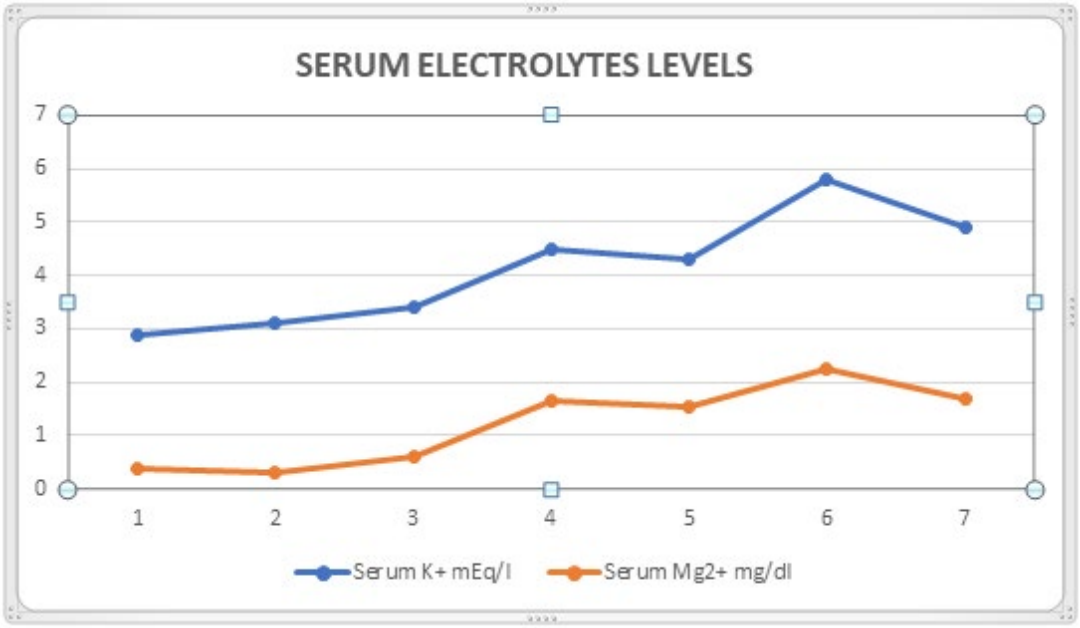

Figure 3: Potassium and magnesium serum levels during hospitalization.

Discussion

Magnesium homeostasis is vital for many intracellular processes. It is regulated by a dynamic relationship between gastrointestinal absorption, bone reservoir exchange, renal absorption/excretion [4]. It plays a central role in muscle contraction, and in central nervous system, it is important for nerve transmission and neuromuscular coordination; it also protects against excessive excitation leading to cell death [5]. Magnesium levels are affected by renal or gastrointestinal (GI) losses, or changes in extracellular fluid. GI tract cause include severe diarrhea or vomiting, malabsorption (for example after surgical intestinal resection), vitamin D deficiency, or chronic use of PPIs (more than one-year intake). Impaired renal tubular reabsorption includes some genetic disorder (such as Gitelman and Bartter syndrome), acquired tubular necrosis, decreased tubular reabsorption, toxins, or drugs, like alcohol and diuretics. Other causes are post-parathyroidectomy, extensive burns, metabolic acidosis. PPIs-induced hypomagnesemia was first reported in 2006 [6], and since then numerous studies have confirmed this hypothesis. As patients with mild hypomagnesemia (±0.6mmol/L) are often asymptomatic, this condition is easily

missed and underestimated because magnesium is not dosed during routine blood examinations [7]. The exact mechanism is still unclear, but hypothesis have been formulated. Apparently, PPIs may impair gastrointestinal absorption of magnesium, via alteration of intestinal mucosal pH and interference with transient potential melastatin-6 (TRPM6)-mediated active absorption of magnesium [8], and seem to have a relation with gut microbiome disturbances. There are some studies suggesting that omeprazole induces a shift in microbial composition that may result in impaired magnesium absorption [5,9]. Previous studies suggest that hypomagnesemia may only affect a small proportion of patients with genetic or clinical predisposition as chronic renal impairment or concomitant use of diuretics, diabetes mellitus, higher dose of PPIs, female gender, and lower BMI. Diuretics and renal impairment both cause hypomagnesemia via renal losses [8,10,11]. Blood levels of magnesium recover within 4 days after discontinuing PPIs and can recur if readministration occurs [12]. Magnesium levels also affects potassium levels. Although exact mechanism is not so clear, it seems that magnesium deficiency impairs Na-K-ATPase, which would decrease cellular uptake of potassium [13]. Chronic use of PPIs induces histopathological changes such as protrusion of parietal cells into the gland lumen and cystic dilation of gastric fundic glands. Furthermore, endoscopic changes have been reported, such as formation of fundic gland polyps (13.6%), hyperplastic polyps (8.9%), cobblestone-like mucosa (9 to 35%) [14]. In our case gastroscopy showed a micropolypoid-like aspect of the mucosa at the level of the fundus and body of the stomach. Biopsy confirmed the presence of chronic inflammation of the lamina propria.

Conclusion

The actual epidemiology of PPIs induced hypomagnesemia is currently not established. It is directly proportional to the duration of the therapy, and it is reversible if PPIs are discontinued [11]. The peculiarity of this case is that our patient recovered from a life-threatening condition caused by hypomagnesemia as he interrupted PPIs therapy. This case also underlies what is already described in literature about the importance of routine assessment of magnesium in patients using PPIs for prolonged periods, as hypomagnesemia can be easily missed because serum magnesium is not dosed during routine blood examinations [6]. Furthermore, it should be remarked in all PPIs users that there are formal indications for their use, and they need to be used cautiously. Physicians should consider the rare but serious side effects of PPIs and check the indications for their chronic use of PPIs to prevent potential hypomagnesemia episodes which could cause a life-threatening side effects.

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