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Hypomagnesemia - An Unusual Cause of Parkinsonism: A Case Report

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Abstract: ***Proton pump inhibitors are used in the prevention and treatment of peptic ulcer, gastroesophageal reflux disease, gastritis, esophagitis [1]. Chronic use of proton pump inhibitors causes various side effects. One of the life threatening side effects is hypomagnesemia, which may present in the form of arrhythmia, tetany, seizures and encephalopathy. We present the case of a 70 year old woman who presented with encephalopathy and parkinsonism due to hypomagnesemia. This case exemplifies that hypomagnesemia should be on the differential diagnosis among patients who present with metabolic encephalopathy with history of long term proton pump inhibitor consumption***

Keywords: Metabolic encephalopathy, Magnesium, Proton pump inhibitors, Hypomagnesemia

1. Background

One of the most abundant intracellular divalent cations and the fourth most abundant element in the body is Magnesium. The majority of this mineral is localized in the bones and soft tissues, only 1 % resides in the extracellular fluids [2]. Magnesium balance is maintained by intestinal absorption in the small bowel, mostly in the ileum and distal part of jejunum, and renal excretion. Magnesium plays a major role in energy metabolism, protein synthesis, stabilizing vascular endothelium, and regulating neurotransmitter function and myocardial metabolism, Calcium homeostasis, and endothelium - dependent vasodilation.

Metabolic encephalopathy (ME) depicts a syndrome of temporary or permanent disturbance of brain functions that occurs in different diseases and varies in clinical presentation. The presentation can vary from subtle changes in cognitive domain to deep coma and death. Most common causes are hypoxia, ischaemia, toxic agents, metabolic disturbances, drugs. Although most of the metabolic encephalopathies are reversible, treatment and prognosis depends upon the etiology, severity of disease. [3]

Objective

We describe the case of a 70 year old female, on long term proton pump inhibitor therapy, who presented with complaints of generalized tiredness, decreased food intake, vomiting and anxiety for 1 month. She was diagnosed with severe hypomagnesemia and improved markedly after intravenous magnesium supplementation. This case outlines the importance of keeping hypomagnesemia among the differential diagnosis for patients with a history of long term PPI consumption who present with encephalopathy.

2. Case Report

This is a 70 year old Indian woman with a past medical history of Systemic hypertension on telmisartan, Type 2 Diabetes Mellitus on glimepiride, metformin and insulin, who presented to emergency department with complaints of generalized tiredness, decreased food intake, vomiting and anxiety for 1 month. She was evaluated and managed initially at a private hospital, diagnosed with Parkinson's disease/ anxiety disorder, started on SSRI/benzodiazepines/ syndopa but her symptoms persisted and gradually worsened.

Physical examination revealed tremors and cogwheel rigidity. Notable laboratory values are present in Table 1. She had an episode of generalized tonic clonic seizures while at ward and she was shifted to Intensive care unit for close monitoring. Diagnostic evaluation for seizures revealed severe hypomagnesemia and hypocalcemia, which was corrected promptly with intravenous magnesium and calcium supplementation. On reviewing her history, it was found that she had been on omeprazole for 2 years, which was immediately stopped. Brain CT with contrast was suggestive of small vessel ischemic changes and age related cerebral atrophy. Serial monitoring of serum Magnesium levels were done. Fractional Magnesium excretion in urine was calculated, which was 1.42%. Her serum magnesium levels gradually normalized with intravenous magnesium supplementation. Patient's symptoms improved dramatically with correction of hypomagnesemia with resolution of tremors, rigidity and improved appetite and mentation.

Labs	Value	Reference Range
Calcium	5.96 mg/dl	8.7 - 10.7
Potassium	2.82 mmol/L	3.5 - 5.3
Magnesium	<0.50 mg/dL	1.6 - 2.4
Urea	11.6 mg/dL	17 - 49
Parathyroid Hormone	128.3	06- 80
Vitamin D, 25 Hydroxy (Total)	18.9 ng/mL	30 - 100
Hemoglobin A1c	11%	04 - 5.6
Glucose	243 mg/dL	70 - 105

3. Discussion

Hypomagnesemia commonly occurs secondary to conditions like alcoholism, diabetes, gastrointestinal loses like biliary or intestinal fistula, large - volume diarrhea or vomiting), renal disease and drugs (loop and thiazide diuretics, cisplatin, cyclosporine aminoglycosides, amphotericin, pentamidine and foscarnet, proton pump inhibitors, antibiotics,) endocrine causes (hyperaldosteronism, hyperparathyroidism, syndrome of inappropriate antidiuretic hormone secretion, hypercalcemia, hypercalciuria),

malabsorption (Crohn's disease, ulcerative colitis, coeliac disease, short bowel syndrome. In 2006 it was first described thathypomagnesemia is a possible complication for proton pump inhibitors. [4]

Transport of Magnesium in the loop of Henle is mainly passive via paracellular diffusion between the cells which is facilitated by a tight junction protein, claudin - 16, that is encoded by the paracellin - 1 gene. The distal reabsorption of magnesium is explained as it enters the tubular cells through magnesium channels present in the luminal membrane, and the exit mechanism in the basolateral membrane occurs through sodium - magnesium exchange [1]

Gastrointestinal absorption and renal excretion are the major mechanisms involved in magnesium homeostasis [4]. Absorption occurs mainly by intracellular diffusional and solvent drag mechanism [5]. Renal Magnesium excretion was found to be markedly reduced in patients with PPI - associated hypomagnesemia, eliminating the kidney as the cause of Magnesium loss. Impaired intestinal absorption was found as the primary culprit in PPI - induced hypomagnesemia [4]. Studies have shown that passive paracellular Magnesium absorption is intact, but active transport via TRPM6/7 channels is disrupted. It appears that a PPI - induced decrease in intestine luminal pH of 0.5 (a 3.5 - fold increase in protons) alters TRPC6/7 channel affinity for Magnesium thoughthe pathophysiology has not been definitively determined.

Modeling experiments proved that increased intestinal protons seen with Proton pump inhibitors reduce the ionized/unionized ratio of the residues which results in decreased channel affinity for Magnesium and thus reduces its absorption. These data suggest that PPIs can impair active Magnesium transport via TRPM6/7 channels and lead to hypomagnesemia over time [4]

Published cases suggest that hypomagnesemia commonly affects females among the elderly age group. It also develops mainly after chronic PPI ingestion, generally over many years (up to 13 years), with no obvious dose relationship [5].

Acute hypomagnesemia can produce different symptoms depending on the severity of the deficiency. Early signs produced by hypomagnesemia are non - specific and include loss of appetite, lethargy, nausea, vomiting, fatigue and weakness. Lower magnesium levels can result in tremor, muscle cramps, tetany and generalized seizures. [6]

Plasma magnesium concentrations are frequently very low (about 0.12–0.85 mg/dl) and are often accompanied by hypokalemia and hypocalcemia [7]. It may present with neuromuscular and cardiovascular manifestations. Neuromuscular manifestations include . muscle cramps or weakness, carpopedal spasm, tetany, vertigo, ataxia, seizures, depression, psychosis. Cardiovascular complications include ventricular arrhythmias, torsades de pointes, supraventricular tachycardia and increased sensitivity to digoxin [Gastrointestinal symptoms like nausea, vomiting, and diarrhea may also be present [7].

Hypomagnesemia is accompanied by hypocalcemichypoparathyroidism and hypokalemia [9] . Our patient had hypocalcemia and hypokalemia as well. Management involves discontinuing PPI and replacement of Magnesium. Associated electrolyte abnormalities also need to be corrected. Symptoms usually improve around 4 days after discontinuing PPI. Intravenous magnesium will rapidly correct serum concentrations while oral Magnesium seems to have less effect [10]. In patients with heart block or myocardial damage, parenteral administration of Magnesium should be avoided [11]. During IV administration, blood pressure and heart rate should be closely monitored. [12]

In patients with diabetes hypomagnesemia can occur due to renal Magnesium wasting. [13]. Physiological concentrations of insulin induce a specific increase in the renal excretion of magnesium [14]. Increased blood glucose levels in diabetic patients will cause hyperfiltration and increased renal urinary flow Increased glomerular filtration will results in high urinary flow rate and hence reduces Mg2+ reabsorption in diabetic patients [15]

There are several advances demonstrating the role of insulin in regulation of Magnesium reabsorption through TRMP6 in the kidney Hence people with diabetes may end up in hypomagnesemia [16]. In hypomagnesemic patients fractional excretion of magnesium (FEMg) is a very useful tool in the diagnostic approach of hypomagnesemia [17]. The fractional excretion of Magnesium in urine in our patient was 1.42% (a value more than 4 per cent is indicative of renal magnesium wasting), which proved that hypomagnesemia was not due to diabetes induced renal Magnesium wasting [17]. Our patient was initially diagnosed as a case of parkinson's disease and anxiety disorder elsewhere and even started on levodopa and carbidopa along with SSRI. The development of seizure prompted us to check the serum magnesium and calcium levels which ultimately lead to the correct diagnosis. Upon correction of Hypomagnesaemia, she had complete resolution of her parkinsonism and greatly improved cognitive capacity.

4. Recommendations

This unique casereport demonstrates that patients with prolonged proton pump inhibitor intake can develop hypomagnesemia which can manifest with encephalopathy and parkinsonism. We therefore make the following recommendations.

First, given the high degree of morbidity associated with Metabolic encephalopathy. hypomagnesemia should remain on the differential diagnosis especially in patients with prolonged proton pump inhibitor intake. Second, Long - term PPI users should be monitored for unexplained hypomagnesemia, hypocalcemia, functional hypoparathyroidism and associated symptoms.

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