CLINICAL IMAGE

# PPI-induced hypomagnesemia with secondary hypoparathyroidism and posterior reversible encephalopathy syndrome restricted to the cerebellum

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## **CASE REPORT**

A 42-year-old male presented with anorexia and dyspepsia. His physical exam was unremarkable. His medication list was notable for the chronic use of a proton pump inhibitor (PPI). A chemistry panel revealed a calcium of 7.5 mg/dL. The next day he presented with a severe headache and dizziness. Laboratory studies revealed a calcium of 6.5 mg/dL, magnesium 0.4 mg/dL, and phosphorus of 3.8 mg/dL. Fractional urinary excretion of magnesium was 0.2%. A parathyroid hormone (PTH) level was 22 pg/mL (nl: 14–72 pg/mL). Magnetic resonance imaging (MRI) of the brain (Figure 1) revealed moderate vasogenic edema within the left cerebellar hemisphere and mild vasogenic edema within the right cerebellar hemisphere with a mass effect on the inferior aspect of the fourth ventricle.

The PPI was discontinued. The magnesium and calcium levels normalized with magnesium replacement and the patient's symptoms quickly resolved. A repeat MRI showed significant improvement in the cerebellar edema.

## DISCUSSION

There have been several reports of hypomagnesemia associated with acute/subacute cerebellitis or cerebellar

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Received: 17 June 2020 Accepted: 27 July 2020 Published: 14 September 2020



Figure 1: MRI of the brain revealing moderate vasogenic edema within the left cerebellar hemisphere and mild vasogenic edema within the right cerebellar hemisphere.

edema [1-8]. Nearly all had resolution of clinical signs and symptoms, as well as of MRI changes, with magnesium replacement. There have also been reports of posterior reversible encephalopathy syndrome (PRES) in the setting of PPI-induced hypomagnesemia. Ross Russell et al. reported on three patients with cerebellar syndromes associated with hypomagnesemia with typical PRES findings on MRI who had rapid resolution of both symptoms and MRI changes with magnesium replacement. Two of the three patients had been on a PPI and the third was an alcoholic [7]. Rouco Axpe et al. reported a case of a 43-year-old male with probable PPIinduced hypomagnesemia and vasogenic edema limited to the cerebellum [8]. Li et al. described two patients with PRES limited to the cerebellum and identified nine other cases in the literature [9]. Of note, a retrospective study identified low magnesium levels in many patients during the acute phase of PRES, regardless of its etiology [10, 11].

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## Case Rep Int 2020;9:100085Z06YM2020. *www.casereportsinternational.com*

Magnesium homeostasis is maintained by a balance between intestinal absorption and renal excretion. Intestinal absorption occurs via a paracellular passive transport as well as an active transcellular mechanism involving transient receptor potential melastatin 6 and 7 (TRPM6/7) channels. Magnesium deficiency increases the expression of TRPM6/7 in the intestine which enhances active magnesium transport [12]. It has been shown that PPIs decrease intestinal luminal pH which alters theTRPM6/7 channel affinity for magnesium resulting in decreased absorption. In patients with hypomagnesemia, urinarv PPI-induced excretion of magnesium is low implicating gastrointestinal impairment of magnesium absorption [13]. Danziger et al. confirmed the association of PPIs with hypomagnesemia in hospitalized patients [14]. The inappropriately normal level of parathyroid hormone in our patient supports the diagnosis of secondary hypoparathyroidism. It is known that hypomagnesemia both impairs release of PTH and decreases peripheral tissue sensitivity to PTH leading to a functional secondary hypoparathyroidism [15].

The mechanism whereby magnesium deficiency causes PRES is not known but magnesium deficiency has been shown to promote inflammation. Studies in rat models and humans have linked inflammatory illnesses with hypomagnesemia. Normally, magnesium activates the thiamine pyrophosphate (TTP)-dependent riboswitch which results in increased synthesis of thiazole. Products of thiazole metabolism have been shown to have antiinflammatory and neuroprotective effects and low concentrations of thiazole can, therefore, promote a proinflammatory state. Hypomagnesemia has also be shown to result in elevated levels of tumor necrosis factor alpha (TNF $\alpha$ ) which leads to the transcription of interleukin-6 and interferon-c, two cytokines with pro-inflammatory actions [16]. Furthermore, magnesium plays a role in the suppression of N-methyl-D-aspartate (NMDA) receptors and its deficiency leads to NMDA receptor hyperexcitability. This is further amplified by activation of v-aminobutvric acid (GABA) receptors which are, in part, regulated by magnesium. The increased release of glutamate by NMDA-receptor rich neurons, possibly by the inhibition of voltage-gated calcium channels, leads to an influx of calcium ions into neurons triggering an increased production of toxic reactive oxygen radicals [12]. Magnesium is also intricately linked to vascular function. Endothelial cells contribute to the inflammation and endothelial dysfunction associated with hypomagnesemia in part due to the impairment of release of nitric oxide from those cells [17].

## CONCLUSION

In summary, PPIs are effective but generally over utilized medications in the treatment of chronic gastroesophageal reflux. It has recently become more appreciated that PPI use is linked to a variety of complications, some of which are quite serious. Hypomagnesemia is a well-documented but underappreciated complication of chronic PPI use. The described patient documents a case of PPI-induced prolonged hypomagnesemia leading to PRES limited

**Keywords:** Hypomagnesemia, Posterior reversible encephalopathy syndrome (or PRES), Proton pump inhibitor (or PPI), Secondary hypoparathyroidism

to the cerebellar hemispheres as well as a secondary

## How to cite this article

Mishriki YY. PPI-induced hypomagnesemia with secondary hypoparathyroidism and posterior reversible encephalopathy syndrome restricted to the cerebellum. Case Rep Int 2020;9:100085Z06YM2020.

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Article ID: 100085Z06YM2020

hypoparathyroid state.

doi: 10.5348/100085Z06YM2020CR

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## **Author Contributions**

Yehia Y Mishriki – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation

of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

## **Guarantor of Submission**

The corresponding author is the guarantor of submission.

## Source of Support

None.

## **Consent Statement**

Written informed consent was obtained from the patient for publication of this article.

## **Conflict of Interest**

Author declares no conflict of interest.

## **Data Availability**

All relevant data are within the paper and its Supporting Information files.

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