Unusual Neurological Manifestation of Proton Pump Inhibitor: A Case Report of Acute Disseminated Encephalomyelitis and Severe Hyponatremia After Brief Use of Proton Pump Inhibitor

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Abstract

Hyponatremia is commonly reported after the use of proton pump inhibitors (PPI). While omeprazole is most likely to cause hyponatremia, almost all the PPIs have been reported to cause hyponatremia. The underlying mechanism of PPI-induced hyponatremia is a syndrome of inappropriate antidiuretic hormone (SIADH) secretion which leads to hyponatremia. The hyponatremia can develop with only a few days of exposure to PPI. We present a case of a 56-year-old previously healthy female who was prescribed omeprazole for trivial acid reflux symptoms when she presented to the emergency room for evaluation of generalized weakness. She was discharged home from the emergency room after clinical evaluation as she had essentially normal lab work including a negative COVID PCR test. She subsequently developed progressive weakness of extremities and slurred speech over the next three days. She returned back to the emergency room and was found to have profound hyponatremia with MRI evidence of acute disseminated encephalomyelitis (ADEM). She was treated with hypertonic saline to correct hyponatremia and omeprazole was discontinued. The patient also received pulse dose steroids with improvement in her symptoms.

Keywords: Internal Medicine, Neurology

Introduction

Drug-induced hyponatremia has been described with a number of medications including non-steroidal anti-inflammatory drugs (NSAIDs), antipsychotics, selective serotonin reuptake inhibitors (SSRIs), and proton pump inhibitors (PPI) [1]. However, there are very few case reports of acute disseminated encephalomyelitis (ADEM) associated with drug-induced hyponatremia [2,3]. ADEM is acute inflammatory neurological disorders of several etiologies. Brighton collaboration has established case definitions for ADEM [4]. ADEM is diagnosed based on clinical and radiological abnormalities which are best seen on MRI imaging of the brain, brainstem, and spinal cord. MRI findings are best seen on T2 weighted images, fluid-attenuated inversion recovery (FLAIR) sequence, and Gadolinium contrast-enhanced images. MRI findings that raise suspicion for ADEM include deep white matter and subcortical lesion of variable size, location and symmetry involving the brain, brainstem and spinal cord. These disorders typically occur one to two weeks after bacterial, viral infections, or vaccination. In some patients, the presentation may be delayed up to three months [5]. Vaccine-induced ADEM has been associated with influenza, human papilloma virus (HPV), pneumococcal conjugate vaccine (PCV), rabies, diphtheria-tetanus-polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, and hepatitis B [6,7]. Pallegrino et al. reported that Flu and HPV were most commonly associated with ADEM and together accounted for one-third of cases [7,8]. We now report a case of ADEM related to the use of PPI Omeprazole that developed briskly and led to neurological deficits.

Case Presentation

A 56-year-old previously healthy female presented to the emergency room for evaluation for generalized weakness, body aches and pains as well as trivial acid reflux. Evaluation in the emergency room showed normal clinical examination and lab work including a negative COVID PCR test. She was discharged home from the emergency room after clinical evaluation as she had essentially normal lab work including a negative COVID PCR test. Over the next four days, the patient developed progressive weakness of extremities and slurred speech over the next three days. She returned back to the emergency room and was found to have profound hyponatremia with MRI evidence of acute disseminated encephalomyelitis (ADEM). She was treated with hypertonic saline to correct hyponatremia and omeprazole was discontinued. The patient also received pulse dose steroids with improvement in her symptoms. She was discharged home from the emergency room as she had essentially normal lab work including a negative COVID PCR test.
minute, temperature 37 °C, oxygen saturation of 94% on room air. Her BMI was 28.3 kg/m². Her Glasgow Coma Scale (GCS) was normal at 15/15. Physical examination was remarkable for a normal cardiac, respiratory, and abdominal examinations. Neurologically, there was evidence of 4/5 weakness in bilateral upper extremities and 2/5 weakness in bilateral lower extremities. There was generalized hyporeflexia. There was no sensory impairment. Gait could not be tested. Pertinent laboratory test results are outlined in Table 1.

| Laboratory test | Normal values | Initial emergency room presentation (day 1) | Subsequent emergency room presentation and hospital admission on (day 5) | Comments |
|-----------------|---------------|---------------------------------------------|-------------------------------------------------|----------|
| Serum sodium    | 136–145 mmol/L | 137                                         | 116                                             | Abnormal (low) |
| Serum uric acid | 149–349 umol/L |                                             | 140                                             |          |
| Random cortisol | 102–535 nmol/L |                                             | 518                                             |          |
| Serum TSH       | 0.35 – 4.94 mIU/L |                                            | 3.81                                            |          |
| Free T4         | 9 – 19 pmol/L   |                                             | 15.03                                           |          |
| Serum osmolality| 276–294 mOsm/kg |                                             | 236                                             | Abnormal (low) |
| Urine osmolality| 301 – 899 mOsm/kg |                                         | 700                                             |          |
| Urinary sodium  | mmol/L         |                                             | 64                                              |          |
| Urinary potassium| mmol/L        |                                             | 36                                              |          |
| Urinary chloride| mmol/L         |                                             | 89                                              |          |
| CSF appearance  | Clear          | Clear                                       | Clear                                           |          |
| CSF protein     | 0.15–0.4 g/L   | 1.76                                        | Abnormal (elevated)                             |          |
| CSF glucose     | 2.21–3.89 mmol/L |                                          | 4.62                                            | Abnormal (elevated) |
| CSF WBC         | 0 – 5 × 10⁶ /L  | 1                                           | Abnormal (elevated)                             |          |
| CSF RBC         | 0 – 10 × 10⁶ /L | 7                                           |                                                  |          |
| CSF segments    | 0–6 %          | 20%                                         | Abnormal (elevated)                             |          |
| CSF monocytes   | 15 – 45%       | 64%                                         | Abnormal (elevated)                             |          |
| CSF lymphocytes | 40 – 80 %      | 16%                                         | Abnormal (low)                                  |          |
| COVID PCR       |                | Negative                                    |                                                  |          |

**TABLE 1: Pertinent laboratory test results**

Chest X-ray was unremarkable. MRI brain showed patchy areas of asymmetric subcortical lesions on FLAIR.
sequence images which did not show enhancement on contrast-enhanced T1 images with gadolinium (Figure 1). MRI of cervical, thoracic and lumbar spine were normal.

The patient was treated with hypertonic saline 2% with very slow correction of serum sodium over the next 24 hours at the rate of less than 0.5 mEq/hour. Subsequently, serum sodium improved to 133 mEq/L over one week. Serum uric acid also corrected to normal within 48 hours of admission. The patient had taken Omeprazole for four days prior to being admitted to the hospital and was discontinued on admission. The patient received pulse dose steroids using 1 g of methylprednisolone for five days along with physical and occupational therapy. This led to partial improvement of her weakness in lower extremities graded at 3/5 at the time of discharge. The patient did not receive plasmapheresis or intravenous immune globulins (IVIG) during the course of the hospital stay.

Discussion

To the best of our knowledge, this is the first case report of omeprazole-induced hyponatremia presenting as ADEM. ADEM is multifactorial in etiology and the possibility of this being related to co-existing viral syndrome cannot be entirely ruled out. The patient did not take acetaminophen prescribed to her for symptomatic management of aches and pains. Hyponatremia associated with PPI use especially with omeprazole tends to occur with recent use and typically in elderly female patients. While there is no one MRI brain pattern that is diagnostic of ADEM, it is a combination of clinical suspicion and imaging that is helpful in establishing the diagnosis. ADEM is immune-mediated while MS is genetic in nature. ADEM affects children more often and has an acute onset and relatively good prognosis. On the other hand, multiple sclerosis (MS) tends to affect young adults with gradual onset but when it presents in children it can lead to significant disability over time. A follow-up MRI may be needed to distinguish it from MS as ADEM is, in general, a unimodal entity although in children a multimodal pattern like multiple sclerosis has been described. Mori et al. [2] have described a case of ADEM associated with hyponatremia related to the cerebral disease. However, ADEM is a rare complication associated with medication-induced hyponatremia [3]. Neurological manifestations such as dementia from long-term use of PPIs are well known which is attributed to amyloid protein deposition in neurons and vitamin B-12 deficiency [8,9]. Overall, the great
majority of patients with ADEM show significant improvement in neurological deficits over a period of one to six months [10]. While correction of hyponatremia is imperative, for ADEM pulse dose steroids followed by prednisolone taper over subsequent four to six weeks is often needed. Other options for non-responders include IVIG and plasmapheresis [11-13].

Conclusions
Over the past several decades, PPI has become the preferred treatment for erosive esophagitis, peptic ulcer disease, and *Helicobacter pylori* infections. However, because of the easy availability of generic formulations over the counter, public access to this class of medication has also increased. While PPIs are potent acid suppressants, they are not free from serious side effects like electrolyte imbalances, risk for osteoporosis, and predisposition to *Clostridium difficile* infection, to name a few. This case report highlights the importance of recognizing the potential of PPIs to cause serious side effects like hyponatremia which can occur even with brief exposure to these medications. It also mandates that physicians recognize that patients who are taking PPIs may present with unusual or unexplained neurological findings, which may be related to the use of this class of medication. Additionally, it also highlights the importance of judicious use of such medications with close clinical follow-up, especially, in elderly females.

Additional Information

**Disclosures**

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