

Epigastric Pain and Hyponatremia Due to Syndrome of Inappropriate Antidiuretic Hormone Secretion and Delirium: The Forgotten Diagnosis

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For Editorial see page 283

A previously healthy 30-year-old female presented to the emergency department (ED) with abdominal epigastric pain that began 2 weeks prior to her admission. The pain was accompanied by nausea and vomiting. There were no fevers, chills, heartburn, rectal bleeding, or diarrhea. The pain was not related to meals and did not radiate to the back. She denied any previous history of dyspepsia, weight loss, decreased appetite, or previous attacks of abdominal pain. There was no prior use of non-steroidal anti-inflammatory drugs nor any alcohol consumption. On arrival, the patient's blood pressure was 134/82 mmHg, heart rate 85 beats per minute, temperature 36.7°C, respiratory rate 14 per minute, and oxygen saturation 98% at room air. On examination, she had mild epigastric tenderness. Peristalsis was normal and there was no hepatosplenomegaly. The rest of the physical examination was unremarkable.

In a 30-year-old healthy female, with subacute symptoms of abdominal pain, nausea, and vomiting, the initial and most common differential diagnosis includes peptic ulcer disease (PUD), biliary colic, cholecystitis, pancreatitis, gastroenteritis, and gastroesophageal reflux disease (GERD). The possibility of GERD appears less likely in the absence of heartburn. In biliary colic, the pain usually appears in relation to meals. Furthermore, the possibility of gastroenteritis is less likely due to the absence of diarrhea and the fact that the symptoms were still ongoing after 2 weeks. At this point, the medical professional should obtain basic laboratory tests, including complete blood count, liver enzymes, and amylase.

Complete blood count, liver enzymes, alanine aminotransferase (ALT), aspartate transaminase (AST), gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALK), total bilirubin, serum electrolytes, and creatinine level were all normal. C-reactive protein (CRP) and amylase levels were normal as well.

The combination of atypical abdominal pain and mild epigastric tenderness, together with normal liver enzymes and amylase levels, excluded the diagnosis of hepatitis and pancreatitis. Although normal liver enzymes cannot dismiss biliary colic, the absence of typical symptoms indicative of biliary pathology and the normal inflammatory markers (white blood cell count and CRP) decreased the likelihood of biliary colic and cholecystitis, as well as an infectious gastroenteritis. Thus, the impression was that the patient's symptoms may be from PUD. Since the patient was not over 45 years of age and she had no symptoms such as weight loss, dysphagia, or night sweats, our recommendation was to perform a breath test for *Helicobacter pylori* and to treat symptoms with proton pump inhibitors, and administer antibiotic treatment only if *H. pylori* was positive. The patient was discharged from the ED after treatment with intravenous (IV) fluids and IV histamine (H₂) blockers.

The breath test for *H. pylori* was negative and the patient was treated with esomeprazole 40 mg once daily, without improvement. She was referred again after 1 week to the ED due to worsening of the abdominal pain.

We expanded the differential diagnosis after assuring the correct administration of esomeprazole (recommended 30 minutes before meals). Repeat blood tests and abdominal imaging studies, ultrasonography and computed tomography (CT) were performed.

The patient took the esomeprazole correctly. Repeated laboratory tests (same as the tests obtained above) were all normal. Abdominal ultrasonography was normal, with no pathology in the biliary tract. Abdominal CT scan was normal as well, and no pathology was seen in the liver, spleen, pancreas, stomach, and gynecological organs.

Although no specific diagnosis had been reached, we admitted the patient for in-hospital observation and symptomatic treatment.

The patient was admitted to the internal medicine ward for treatment with analgesics, nothing per mouth OS (NPO), IV fluids, and IV esomeprazole.

Despite these treatment measures, the patient continued to be symptomatic, with debilitating epigastric abdominal pain and vomiting. Thus, the next step was to perform an endoscopic assessment.

Prior to the endoscopic assessment, the patient developed an acute episode of delirium. Blood tests at this point revealed severe hyponatremia of 110 mmol/L. Thus, the endoscopy was postponed until correction of the hyponatremia. Further tests revealed high urine osmolality (520 MOSM/KGH20) and low serum osmolality (225 MOSM/KGH 20). Urinary sodium was elevated while the patient was in an euvolemic state.

The hyponatremia in our patient was related to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The main treatment is restriction of exogenous fluid intake. It is most likely that the development of hyponatremia was secondary to persistent pain and vomiting which are known predisposing causes of SIADH. However, other causes such as medications, Addison disease, hypothyroidism, and malignancy warranted investigation.

The patient was not prescribed any other medications. Morning cortisol and thyroid-stimulating hormone (TSH) levels were within normal limits and no malignancy was seen by imaging studies. A few days following oral fluid restriction, there was an improvement in the serum sodium level.

After the improvement in serum sodium levels, the patient was scheduled for endoscopy.

An upper endoscopy was performed after fasting for 36 hours, which showed significant food remnants in the stomach, without endoscopic signs of esophago-gastro-duodenitis or PUD [Figure 1].

The relatively normal endoscopic assessment coupled with the normal radiological assessment and laboratory tests ruled out the above mentioned differential diagnosis. However, the unusual (and surprising) finding of a large amount of residual food in the stomach after 36 hours fasting raised the suspicion of delayed gastric emptying and gastroparesis. Thus, tests excluding diabetes mellitus were performed and a neurologi-

cal exam was performed to exclude neurological autonomic dysfunction.

Neurological examination was completely normal and laboratory tests excluded diabetes mellitus.

At this point, the combination of severe epigastric unresolving pain, coupled with hyponatremia secondary to SIADH and suspected gastroparesis as shown by incomplete gastric food emptying after 24 hours, caused us to consider an alternative diagnosis of porphyria. Thus, a urine biochemical analysis of porphyrin was performed. In addition and in parallel, another rapid test was conducted to strengthen our diagnosis: exposure of the patient's urine to sunlight.

Indeed, the urine was exposed to the sunlight, and its color changed from light yellow to dark orange color [Figure 2], which is highly suspicious for porphyria. Subsequently, the diagnosis of porphyria was confirmed by the presence of porphobilinogen (PBG) in the urine. The patient was treated with IV glucose and hematin, with clinical improvement and resolution of the hyponatremia. The patient was discharged 2 weeks later, in good condition with a recommendation of a high carbohydrate diet.

Figure 1. Endoscopic image demonstrating food remnants in stomach and duodenum following 36 hours, without signs of duodenitis

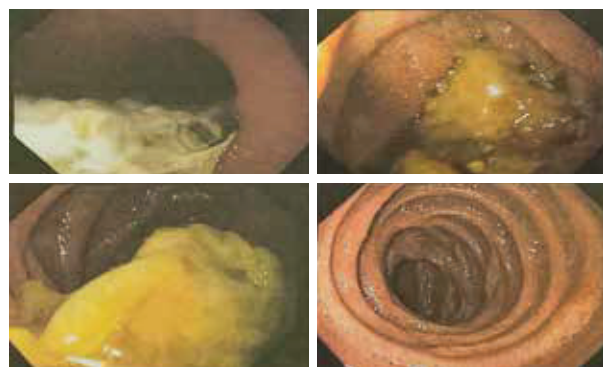


Figure 2. Urine sample demonstrating the change of urine color from yellow bright to deep orange after exposure to sun light



COMMENT

This patient presented with a rare cause of a frequent symptom, which made this case particularly challenging to diagnose. Abdominal epigastric pain is one of the most common symptoms to be referred to the ED. Most often, this symptom is attributed to several diseases, including PUD and pain from biliary origin or pancreatitis. The investigation of epigastric abdominal pain includes a careful medical history, physical examination, and basic laboratory tests. In our patient, the features of the pain, coupled with the initial normal electrolytes, kidney function, liver enzymes, and amylase levels, ruled out pain from a pancreatic or hepatobiliary origin. Furthermore, ultrasound and CT imaging confirmed the absence of abdominal visceral pathology. Usually, the initial management of epigastric pain in the absence of other identified pathology, such as weight loss, melena, dysphagia, and anemia, is a trial of proton pump inhibitors, which was not helpful in our patient. However, our patient was diagnosed with acute intermittent porphyria (AIP) based on the additional signs of hyponatremia due to SIADH and visceral neuropathy as manifested by delayed gastric emptying.

AIP is a rare metabolic disease with an autosomal dominant pattern of inheritance. AIP has incomplete genetic penetrance so that over 85% of patients have latent disease with a clinical and laboratory asymptomatic course throughout life [1]. The symptomatic disease rate is 1–2 per 100,000 [2,3]. AIP is characterized by accumulation of porphyrin precursors such as delta-aminolevulinic acid (ALA) and PBG is due to an enzyme deficiency, porphobilinogen deaminase [4]. Women are more affected than men with onset usually occurring at adolescence [5]. Porphyria can be exacerbated by several drugs, infectious processes, alcohol, and menstruation-induced hormonal changes [2].

In our case, the attack of acute porphyria was most probably precipitated by an acute viral infection 1 week before symptom onset. Previous studies showed that almost 30% of porphyria exacerbations were secondary to an infection [6]. The mainstay treatment of AIP includes intravenous hemein and glucose. Hemein is a heme preparation that is isolated and purified from human red blood cells, which induce suppression of heme precursor synthesis.

In addition, avoidance of analgesics as well as barbiturates and sulfa-containing antibiotic medications is recommended [7]. Our patient was treated with IV glucose in addition to hemein with both clinical improvement and sodium normalization. In most cases, the diagnosis of AIP with neurovis-

cer involvement is often delayed for several years due to its rarity. In one study, a lag period of more than 10 years was reported [8]. Notably, our patient was diagnosed 3 weeks after the first symptomatic appearance due to visceral neurological involvement (gastroparesis), acute persisting abdominal pain (90% of attacks), severe hyponatremia, and orange colored urine on exposure to sunlight [9,10]. The fact that our patient manifested the full spectrum of findings in AIP made early diagnosis possible. The pathophysiology of abdominal pain is related to autonomic neuropathy mediated by the neurotoxic effects of porphyrin precursors. [11]. The pathophysiology of hyponatremia is poorly understood, however, SIADH is the most common underlying cause [9].

CONCLUSIONS

A high clinical suspicion and knowledge of the associated manifestations are needed to diagnose AIP. Early diagnosis is crucial since severe attacks of AIP can be life-threatening. Early diagnosis and treatment can be potentially lifesaving.

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“We must be willing to let go of the life we have planned, so as to have the life that is waiting for us”

E.M. Forster (1879–1970), English novelist, short story writer, essayist and librettist. Many of his novels examined class difference and hypocrisy