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CASE REPORT

Needle in a Haystack: Acute Intermittent Porphyria, an Often-missed Differential Diagnosis of Abdominal Pain

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Abstract

Acute intermittent porphyria (AIP) is a rare disease that arises due to deficiency of the biosynthetic enzyme porphobilinogen deaminase (PBGD) involved in heme synthesis. Acute attacks can present with abdominal pain and neurological symptoms, although vague in nature. Recurrent hospitalizations for idiopathic intermittent abdominal pain should warrant investigation for AIP. Posterior reversible encephalopathy (PRES) presents with visual disturbances and seizure-like activity and can be, although rarely, associated with AIP. It is noteworthy to know that antiepileptic medication used in management of PRES can in turn worsen AIP.

Keywords: Abdominal pain, Acute intermittent porphyria, PRES, Seizures, SIADH

1. Introduction

Acute intermittent porphyria (AIP) is a rare metabolic autosomal dominant disease from heme biosynthesis dysfunction in the liver because of mutations in the gene encoding for the enzyme porphobilinogen deaminase (PBGD).[1] More than 400 mutations in the PBGD gene have been identified thus far, which can explain the multiple clinical variants of the disease.

Abdominal pain is the most typical clinical manifestation during acute crises. However, due to its nonspecific clinical picture, AIP is often missed. This often leads to numerous clinical encounters both on an out-and in-patient basis. When untreated, AIP can lead to cirrhosis, hepatocellular carcinoma, cholangiocarcinoma, paralysis, and renal disease.

We describe a patient with recurrent abdominal pain crises in which diagnosis of AIP was delayed.

2. Case presentation

A 26-year-old female with past medical history of ruptured ovarian cyst, currently on oral contraceptive medications (OCPS), presented with a 5-day history of worsening abdominal pain. Prior to presenting to our hospital, she had sought medical attention on multiple occasions at several other facilities. Multiple pelvic examinations and 3 computerized tomography (CT) imaging studies were unremarkable. A bedside transvaginal ultrasound showed an ovarian cyst, but no other concerning findings were seen. The abdominal pain was severe, generalized, non-radiating and associated with constipation. Of note, the patient had

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recently been engaging in significant exercises, and was in the luteal phase of her menstrual cycle. On prior hospitalizations, her recurrent abdominal was assumed to be secondary to a ruptured ovarian cyst.

On presentation, initial laboratory studies showed hypokalemia (potassium 3.4 mmol/L, reference range 3.5–5.1 mmol/L), and an elevated creatinine 1.14 mg/dl (baseline around 0.80 mg/dl). Pelvic examination was again benign. A small bowel follow-through showed significant delay in contrast transit, which was managed conservatively (Fig. 1).

Patient also reported tingling sensation in her hands and red discoloration of urine. On hospital day 2, serum sodium decreased abruptly from 136 mmol/L to 127 mmol/L (range: 135–145 mmol/L). Serum osmolality was low at 271 mOsm/kg (range: 280–300mOsm/kg), urine sodium was markedly elevated at 168 mmol/L and urinalysis was remarkable for increased urine specific gravity (>1.042). A diagnosis of Syndrome of Inappropriate Antidiuretic Hormone secretion (SIADH) was made, and water restriction and salt tablet intake were initiated. Early hospital course was complicated by significant hypertension (systolic blood pressure 180 mm Hg), acute visual disturbances followed by seizure and postictal confusion. Magnetic Resonance (MR) imaging showed subtle symmetric parenchymal edema in the occipital and posterior parietal lobes, suggestive of PRES and Levetiracetam was initiated (Fig. 2).

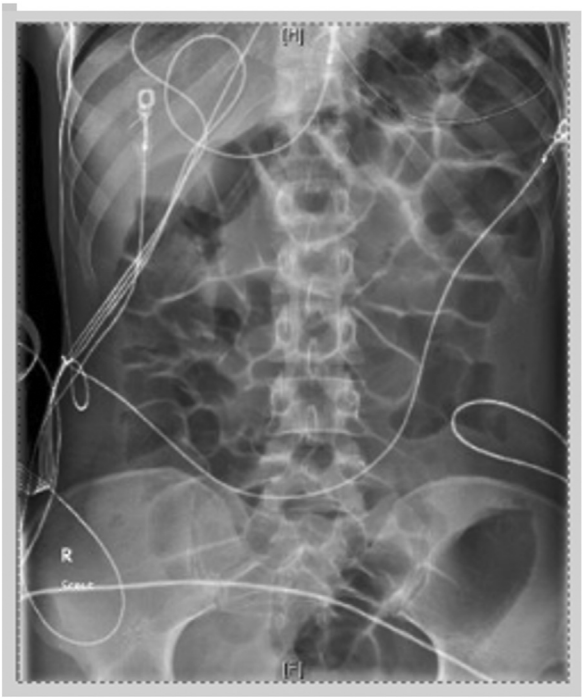

Fig. 1. Small bowel follow-through showing significant delay in transit of contrast through the small bowel with some small bowel distension.

Given suspicion of acute porphyria, urine porphobilinogen was measured and was found to be elevated at 188.4 mg/L (range: 0.0–2.0 mg/L). 24-hour urine Uroporphyrin was also significantly elevated at 135.6mg/24hr (range: 0.0–1.5mg/24hr). Delta-Aminolevulinic Acid (ALA) and PBGD urine tests were ordered. Since Hemin treatment was unavailable at our facility, patient was transferred to a tertiary center. Patient was treated with Hematin, and symptomatic improvement ensued (Table 1).

3. Discussion

In patients with recurrent idiopathic abdominal pain and unremarkable extensive work-up, AIP should be considered as a possible etiology. AIP is rare, presents with vague symptomatology, and is often missed or its diagnosis delayed. The use of porphyrinogenic drugs can also worsen its clinical course.[2]

In AIP, deficiency in PBGD leads to an uncontrolled modulation of delta-aminolevulinic acid synthase 1 (ALAS-1), resulting in accumulation of porphyrin precursors i.e., porphobilinogen and aminolevulinic acid (ALA).[1] Acute attacks occur due to a combination of enzyme deficiency as well as precipitating factors such as OCPs and low caloric intake or rapid weight loss. Other medications/conditions that could trigger crises include anticonvulsants, reproductive hormonal changes, cytochrome P450 inducers, sulfonamides, alcohol, acute illness, stress, and surgery.[3]

In AIP, abdominal pain remains the most common clinical manifestation. It is often generalized, associated with nausea, vomiting and constipation. It is caused by intestinal spasm from autonomic dysfunction and is typically unresolved with pain medications.[4] A dark-reddish urine discoloration due to abnormal accumulation of porphyrins in the urine is common and can be misinterpreted as hematuria. Most patients are misdiagnosed with an acute surgical abdomen or pain from a gynecological etiology. Moreover, female patients who have monthly attacks during the luteal phase of their menstrual cycle can be mislabeled as malingering.

Central nervous system (CNS) involvement typically presents as seizures and PRES. Seizures in AIP can be difficult to manage as some antiepileptic medications i.e., phenytoin can induce enzymatic activities in the heme pathway and therefore aggravate symptoms. Although seizures in these patients could be due to PRES, the inherent

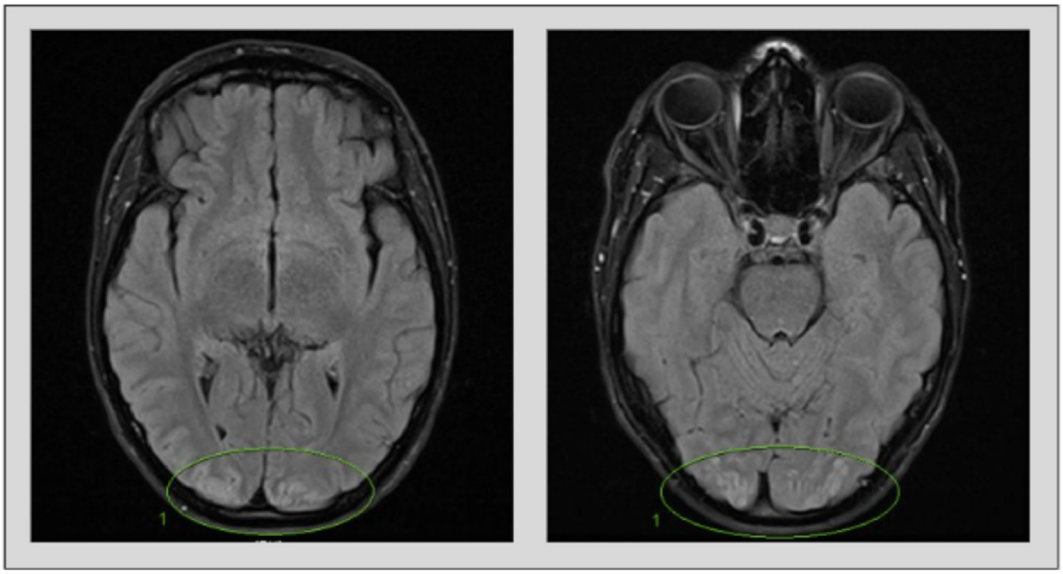

Fig. 2. Subtle cortical and subcortical edema in both occipital and posterior parietal lobes best seen on the magnetic resonance imaging FLAIR sequences.

epileptogenic properties of some upstream metabolites in AIP such as ALA has been demonstrated to interact with glutamate and gamma-aminobutyric acid receptors.[5] Metabolic disturbances such as hyponatremia could also be a possible etiology.[5] Other features of PRES such as delirium, cortical blindness, and CT/MRI finding of symmetric parenchymal edema in focal regions were seen in our case.[6] The mechanism of PRES in AIP remains unknown. However, it has been postulated that increased vasoconstriction and edema occur due to depletion of nitric oxide synthase, a hemoprotein in AIP.[7] Other hypotheses that have been put forth include blood–brain barrier disruption, focal vasospasm, and decreased sympathetic innervation of blood vessels in posterior regions.[5] Additionally, hypertension from autonomic dysfunction can also predispose to PRES. Other possible neuropsychiatric manifestations in AIP include peripheral neuropathy, depression and bipolar disorder as previously reported in the English literature.[2] In very severe cases, patients can develop ascending motor weakness in bilateral lower extremities and neuropathies in other nerve distributions that may progress to respiratory paralysis.

Table 1. Urine porphyrin values.

Porphyrin type	Value	Reference range
24-hour Porphobilinogen (mg/24hr)	135.6 (H)	0–1.5
Quantitative Urine Porphobilinogen (mg/L)	188.4 (H)	0–2
24-hour Uroporphyrin (ug/24hr)	8924 (H)	0–24
Timed Heptacarboxyl 7-CP (ug/L)	61 (H)	0–4
Pentacarboxyl 5-CP (ug/24hr)	143 (H)	0–4
24-hour Coproporphyrin (ug/24hr)	137 (H)	0–24
Coproporphyrin CPIII (ug/24hr)	368 (H)	0–74
24-hour Hexacarboporphyrin (ug/24hr)	0	0–1

The most common electrolyte abnormality is hyponatremia. The pathophysiology is complex, with injury to the supraoptic nuclei of the hypothalamus causing SIADH, gastrointestinal losses, nephrotoxicity, and excessive renal sodium excretion which have all been implicated.[8] SIADH-induced hyponatremia is typically treated with fluid restriction, but 3% hypertonic saline infusion can be used in severe cases.

AIP should be suspected in patients who experience episodic abdominal pain, autonomic symptoms, muscle weakness, psychiatric symptoms, and/or hyponatremia. Given its low penetrance, a family history will likely be unhelpful. Initial measurements of urinary PBG level and total porphyrins can help establish the diagnosis of acute porphyria, leading to urgent initiation of treatment. In patients with renal insufficiency, serum/plasma PBG testing can be done. Of note, urine samples should be protected from sunlight exposure. Additional testing to differentiate AIP from other types of porphyria include urinary ALA and porphyrins as well as plasma and stool porphyrins. Preferably, all samples for investigations should be collected prior to treatment. The diagnosis for AIP is confirmed with evidence of decreased erythrocyte PBGD and/or a pathogenic variant in the HMBS/PBGD gene. In an acute attack, predisposing factors should be addressed such as discontinuing any offending drug, and Carbohydrate loading (10% glucose

infusion) can be used in the interim while awaiting availability of Hemin.

The treatment of choice is intravenous Hemin. It acts through negative inhibition by suppressing the hepatic heme biosynthesis pathway, hence reducing the accumulation of toxic metabolites and subsequently lessening symptoms.[8] Heme preparations are generally well tolerated. Reported adverse effects include coagulopathy, anaphylactic reactions, renal insufficiency, circulatory collapse, and thrombophlebitis.[9]

Other treatment modalities for individuals with recurrent attacks include Givosiran, a gene silencing medication which acts by reducing delta-ALA synthase-1 levels, and Gonadotropin-Releasing Hormone (GnRH) analogues for females with frequent attacks during the luteal phase of the menstrual cycle.[10]

In conclusion, AIP should be included in the differential diagnosis of recurrent abdominal pain especially after robust evaluation for common causes are unremarkable. To prevent complications and recurrent attacks, prompt treatment should be started when diagnosis is suspected, and patients should be educated about common triggers of an acute crises.

Conflict of interest

None.

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