


# A Perfect Storm: Abdominal Pain and Ileus Explained by Acute Intermittent Porphyrinemia Caused by Prehospitalization and Intrahospitalization Factors

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## Abstract

Acute intermittent porphyria (AIP) is a rare autosomal dominant inherited disease, predominantly seen in female patients, caused by mutations in the hydroxymethylbilane synthase gene. When impaired, elevated heme biosynthesis precursor levels accumulate in the liver, resulting in neurological symptoms, psychiatric disturbances, darkened urine color, abdominal pain, nausea, vomiting, and ileus. We present a 22-year-old Hispanic female with diffuse abdominal pain and no bowel movements for 8 days. She reported recent antibiotic and oral contraceptive pill use. Computerized tomography of her abdomen revealed a dilated small bowel and marked colonic distension. A colonoscopy found mild nonspecific inflammation in the rectosigmoid and terminal ileum. Her abdominal pain persisted despite interventions and improvements in appetite, bowel movements, abdominal imaging, and treatment of an identified *Clostridium difficile* infection. A random urine porphobilinogen was then obtained and found to be elevated. Fractionation of plasma and urine porphyrins was suggestive of AIP. Her symptoms improved with 3 days of intravenous (IV) hematin and IV dextrose. This is a unique case of a rare disease due to her clinical presentation with ileus, unremarkable past medical history, family history, and the prehospitalization and intrahospitalization factors that likely exacerbated the patient AIP.

## Keywords

acute intermittent porphyria, porphyria, abdominal pain, constipation, gastroenterology

## Introduction

Acute intermittent porphyria (AIP) is an autosomal dominant inherited disease caused by mutations in the hydroxymethylbilane synthase (HMBS) gene. HMBS converts porphobilinogen (PBG) into hydroxymethylbilane within the heme biosynthesis pathway. When impaired, increased levels of succinyl CoA, glycine, and increased levels of substrates (including PBG) accumulate in the liver and result in symptoms such as autonomic, neurological symptoms (neuropathy and seizures); psychiatric disturbances (anxiety, depression, and psychosis); vague abdominal pain; and the classical darkened urine coloration.<sup>1</sup>

Factors that trigger AIP episodes include commonly used medications (such as oral contraceptives, anti-epileptics, antibiotics, and calcium channel blockers), infections, excessive consumption of alcohol, and hormonal imbalances. Although the literature suggests low penetrance of the disease (2%–3%), acute attacks have a slight female predilection.<sup>2</sup>

Long-term complications of untreated AIP can result in primary liver cancer, kidney failure, and hypertension.

## Case Presentation

A 22-year-old Hispanic female with a past medical history of dysmenorrhea and recurrent urinary tract infections (UTIs), previously diagnosed by her primary care physician, presented with an 8-day history of no bowel movements and diffuse abdominal pain. The abdominal pain was described

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**Figure 1.** Computerized tomography of abdomen pelvis with contrast. (A) There is new diffuse marked colonic distention with fecal dilatation measuring up to 9 cm. There is a transition point at the sigmoid colon of unclear etiology. (B) In addition, there is a progression of small bowel dilatation, which is now fluid- and fecal-filled.

as a fullness or bloating sensation. She had tried multiple laxatives for symptom relief. She also reported frequent antibiotic usage, most recently ciprofloxacin, for recurrent UTIs. She had previously been prescribed an oral contraceptive for dysmenorrhea, but it was recently discontinued due to severe nausea and negligible improvement of her abdominal pain.

On presentation, she was afebrile (36.7°C), had a normal heart rate (85 beats per minute), normal respiratory rate (16 breaths per minute), and was normotensive (121/80 mmHg). On physical examination, the patient was alert and oriented to time, place, and person without any objective signs of anxiety, depression, psychosis, or other appreciable psychiatric disturbances. The abdomen was soft, nondistended, with mild upper abdominal and periumbilical tenderness. Laboratory examinations were remarkable only for hyponatremia of 130 mEq/L and hypoalbuminemia at 3.4 g/dL. Urine analysis with reflex culture was negative for leukocyte esterase and nitrites. Urine osmolality was 410 mOsm/kg and urine sodium was 100 mEq/L, indicating a syndrome of inappropriate antidiuretic hormone secretion (SIADH). Her initial computerized tomography (CT) scan of the abdomen and pelvis (Figure 1) revealed a diffusely dilated small bowel filled with fecal matter and marked colonic distention with cecal dilatation measuring 9 cm.

She was kept nil per os, except for medications, and a nasogastric tube was placed for bowel decompression. A colonoscopy found only granular and punctate erythematous



**Figure 2.** Computerized tomography of abdomen pelvis with contrast. (A) Moderate dilation of the colon with fluid and stool which is improved when compared with prior computerized tomography. No small bowel dilation.

mucosa in the rectum and sigmoid colon with mild nonspecific ileitis and successfully decompressed the dilated colon. A few days after decompression, she developed several watery bowel movements and continued to have abdominal pain. Rapid stool studies were obtained and returned positive for *Clostridium difficile* antigen and toxin A&B. She was treated with oral vancomycin for 10 days. A repeat CT scan of her abdomen (Figure 2) noted no further small bowel dilation, free air, or free fluid. CT enterography showed no bowel wall thickening or imaging features to suggest inflammatory bowel disease.

Her appetite improved, but her abdominal pain persisted despite the antibiotic course, and pain remained out of proportion to her physical examination. The differential was broadened to include AIP. A random urine PBG was elevated at 99.9 mg/g (normal < 0.22 mg/g), with a urine delta aminolevulinic acid (ALA) elevated at 71.9 mg/g (normal < 5.4 mg/g). The fractionation of porphyrins in plasma (Table 1) and urine (Table 2) was suggestive of a biochemical diagnosis of AIP.

Intravenous (IV) hematin 1 mg/kg/d and IV dextrose were given for 3 days. After hematin/dextrose therapy, her abdominal pain and bowel symptoms resolved. On subsequent questioning, it was found that she had no family history of porphyria, history of skin lesions, previous hospitalizations due to abdominal pain, history of urinary color changes, or any prior positive urine cultures within our medical institution. She improved clinically and was later discharged with

**Table 1.** Plasma Porphyrin Fractionation and Values.

Porphyrin type	Value (µg/L)	Normal range (µg/L)
Uroporphyrin	7.5 (H)	≤0.2
Heptacarboxyporphyrin	0.9 (H)	≤0.2
Hexacarboxyporphyrin	1.1 (H)	≤0.3
Pentacarboxyporphyrin	1.2 (H)	≤0.4
Coproporphyrin	1.7 (H)	≤0.8
Protoporphyrin	2.8	0.4-4.8
Total porphyrins	15.2 (H)	1.0-5.6

The table illustrates the plasma fractionation of porphyrins and their measured values compared with the normal range.

Abbreviation: H, high.

education on how to reduce AIP acute attacks and followed as an outpatient by hematology. Two weeks after discharge, the patient was seen by her primary care physician and noted significant improvements in her appetite and abdominal pain without recurrence of constipation or diarrhea.

## Discussion

We present a case of AIP triggered by a “perfect storm” of precipitating factors that synergistically contributed to the patient’s hospital presentation. The characteristic objective finding in her clinical presentation is the significant new-onset ileus discovered on imaging and other notable findings, including SIADH, found on basic investigations and her abdominal pain out of proportion to examination. AIP is an autosomal dominant disorder secondary to deficiency of PBG deaminase in the heme biosynthetic pathway. Among the acute porphyrias, AIP is the most common, with low penetrance.<sup>3</sup> Studies in Europe estimated the incidence and prevalence of AIP to be 0.13 cases/year/million patients over a 3-year period.<sup>3,4</sup> Women are most affected and presentation is usually in the third or fourth decades of life.<sup>5</sup> Factors that exacerbate AIP attacks include hormonal-state fluctuations, various medications (antimicrobials, oral contraceptive pills, antihypertensives, and nonsteroidal anti-inflammatory drugs), and infections.<sup>5</sup> This is particularly significant given our patient’s history of dysmenorrhea and treatment with oral contraceptive use and frequent antibiotic usage for her recurrent UTIs. The latter contributed to her underlying *C. diff* colitis found during hospitalization, further providing an additional precipitant for an acute AIP attack.

Clinical presentations of AIP and their severity vary, from asymptomatic to severe symptoms. Abdominal symptoms are nonspecific, including generalized abdominal pain (often described as cramping), vomiting, constipation, ileus, diarrhea, and bloating.<sup>6-8</sup> Abdominal pain is usually disproportionate to physical examination findings and does not respond well to narcotic pain medications present in up to 95% of cases.<sup>7</sup>

**Table 2.** Urine Porphyrin Fractionation and Values.

Porphyrin type	Value (µg/g creatinine)	Normal range (µg/g creatinine)
Uroporphyrin I	2860.7 (H)	3.6-21.1
Uroporphyrin III	2771.3 (H)	≤5.6
Heptacarboxyporphyrin	99.0 (H)	≤3.4
Hexacarboxyporphyrin	27.5 (H)	≤6.3
Pentacarboxyporphyrin	121.0 (H)	≤4.1
Coproporphyrin I	150.9 (H)	6.5-33.2
Coproporphyrin III	683.6 (H)	4.8-88.6
Total porphyrins	6714.0 (H)	27.0-153.6

The table illustrates the urine fractionation of porphyrins and their measured values compared with the normal range.

Abbreviation: H, high.

There is an increased risk of cirrhosis and hepatocellular carcinoma in patients with untreated AIP.<sup>5</sup> There are also reported instances of cardiac arrhythmias, electrolyte abnormalities (secondary to SIADH), hypertension, hyperthyroidism, and bladder dysfunction (such as urine retention with urgency to void).<sup>5,9</sup> As noted in our patient, SIADH is a common presentation in approximately 25% to 60% of patients, and intriguingly, the degree of hyponatremia can indicate the gravity of the AIP exacerbation.<sup>5</sup>

Clinical symptoms present in bouts of acute attacks with associated periods of remission. Due to the neuropathic nature of the pain, patients generally have minimal physical examination findings, such as seen in our patient, given her abdominal pain was out of proportion to her physical examination. Interestingly, sensory or motor neuropathy can precede gastrointestinal symptoms in acute attacks, which can be a marker of an upcoming episode in patients with a known diagnosis of AIP.<sup>10</sup> Electromyography findings in these patients reveal primary axonal motor neuropathy.<sup>9</sup> Autonomic symptoms due to autonomic nervous system involvement are common and include blood pressure irregularities, anxiety, agitation, restlessness, and tachycardia, the most common clinical sign during acute attacks.<sup>11</sup>

Diagnostic modalities include measuring urine (spot urinary PBG), the plasma level of PBG, and stool (spot stool PBG). Baseline urine PBG levels are typically less than 2 mg/L. Urinary PBG levels can range between 20 and 200 mg/L during an acute attack,<sup>12</sup> as previously illustrated by our patient’s elevated PBG levels. When interpreting PBG levels, it is essential to note that diagnostic levels depend on the reference interval and methodology, as the absolute levels in normal individuals can vary. In addition, laboratory studies can normalize PBG values to creatinine or in a 24-hour volume versus depending on just the raw concentration. Stool PBG can be obtained to assist in differentiating between different porphyrias if urine and serum analyses are not conclusive with a particular culprit porphyria. Our

patient's urine PBG and fractionation of serum and urine porphyrin studies provided us with a diagnosis of AIP.

Few established treatment modalities prevent disease development in symptomatic mutation carriers, given that some carriers of the pathogenic variant may remain asymptomatic.<sup>1</sup> Most patients with diagnosed AIP follow strict lifestyle measures to avoid recurrence of symptoms. Treatment often includes pain medication and increased caloric and fluid ingestion in mild exacerbations. Thus, not all exacerbations necessitate hospitalization. Hematin infusions are the current preferred treatment for sporadic AIP attacks. This helps restore hepatic heme levels and downregulates the ALAS1 gene through negative feedback, decreasing heme precursors.<sup>13</sup> In addition, as noted in our clinical case, high-carbohydrate content infusions are used as a stand-alone treatment or as a combination with hematin in acute attacks.<sup>14</sup> Orthotopic liver transplant remains the only cure for AIP, with patient survival rates nearing 80%; however, there remains an elevated risk of thrombosis within the hepatic artery within 9 months.<sup>15</sup>

Novel therapies are currently emerging for the treatment of AIP. These therapies include enzyme replacement and liver gene therapy. Enzyme replacement therapy administers doses of recombinant human HMBS proteins that help reduce PBG plasma and urinary accumulation; it has succeeded in some individuals who became symptom-free but has mostly been unsuccessful due to the inability of HMBS to be explicitly targeted to the liver.<sup>1</sup> Liver gene therapy uses 2 mechanisms of action. The first approach involves the administration of viral vectors to deliver normal HMBS gene and RNA to hepatocytes, which has shown promising pre-clinical study results.<sup>16</sup> The second approach involves aiming small interfering RNA (siRNA) against ALA synthase, which has resulted in decreased delta ALA within 1 day and up to 30 days with minimal side effects.<sup>16</sup> This siRNA treatment, Givosiran (Givlarri), is US Food and Drug Administration–approved for the treatment of acute hepatic porphyrias as it has been shown to decrease rates of porphyria attacks substantially.<sup>17</sup>

Our case presentation contains several distinctive features in addition to the presentation with ileus. After evaluating her medical history further, one of the unique findings in our patient is her previous diagnoses of dysmenorrhea and recurrent UTIs. Given that her prior treatments did not improve her abdominal pain, it is possible that she was misdiagnosed and masked her actual underlying pathology of AIP. AIP is known to present with abdominal pain associated with fluctuations in hormonal levels and bladder symptoms. The management of her dysmenorrhea and recurrent UTIs, and concomitant *C diff* colitis were probable aggravating factors of her underlying condition. It is important to note that the severity of AIP exacerbations can vary, thus not always requiring hospitalization.

In conclusion, we present this case of AIP to emphasize the underdiagnosis of AIP and the importance of maintaining

an extensive differential diagnosis when assessing acute onset abdominal pain with an accompanying new ileus and electrolyte abnormalities. AIP should specifically be included as a potential culprit when abdominal pain persists despite treatment of underlying factors and exploration of the more common etiologies.

### Authors' Note

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### Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

### Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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