An 18-Year-Old With Acute-on-Chronic Abdominal Pain

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An 18-year-old woman with a complex past medical history presented with 2 days of vomiting and lower abdominal pain. She had been admitted for the majority of the previous 5 months for recurrent pancreatitis and had undergone a cholecystectomy. Additional symptoms included nausea, anorexia, constipation, and a 40-lb weight loss over 4 months. She appeared uncomfortable, and an examination was remarkable for tachycardia, hypertension, and diffuse abdominal tenderness to light palpation. Her initial laboratory test results revealed mildly elevated liver enzymes (aspartate aminotransferase 68 U/L, alanine aminotransferase 80 U/L) and a normal lipase. She was admitted for pain control and nutritional support. Over the next few days, the lipase increased to 1707 U/L. Despite optimizing her management for acute pancreatitis, the patient's symptoms persisted. Further history gathering and laboratory testing ultimately revealed her diagnosis. Our expert panel reviews her hospital course and elucidates the management of our eventual diagnosis.

CASE HISTORY WITH SUBSPECIALITY INPUT

Dr Corden, Moderator, Pediatric Hospital Medicine

An 18-year-old woman with a history of recurrent abdominal pain attributed to pancreatitis was admitted for 2 days of abdominal pain and nonbloody, nonbilious emesis. The patient reported 8 out of 10 crampy, lower-quadrant, nonradiating abdominal pain. Her pain was not relieved by oral hydromorphone. She reported several days of reduced oral intake because of nausea. She also endorsed worsening of her chronic constipation, with her last bowel movement 2 days before admission. She noted a 40-lb unintentional weight loss over the past 4 months. There were no upper respiratory symptoms, rash, fevers, or chills. There was no recent travel history or trauma. She denied alcohol or illicit drug use.

Her past medical history was unremarkable aside from chronic constipation until 5 months before admission. Since that time, she had been hospitalized on 4 separate occasions for abdominal pain, nausea, and vomiting. These episodes were often accompanied by hypertension, back pain, and intermittent paresthesias of the lips, abdomen, and legs. During each of these episodes she had an elevated lipase, leading to the diagnosis of pancreatitis. She required extensive pain control with hydromorphone patient-controlled analgesia (PCA), mirtazapine, and gabapentin. Her workup included a computed tomography (CT) scan, the results of which were negative for pancreatic inflammation, pseudocysts, or ascites. An abdominal ultrasound demonstrated either biliary sludge or a small gallstone, and she underwent laparoscopic cholecystectomy. Nonetheless, her symptoms persisted. MRI and magnetic resonance cholangiopancreatography (MRCP) revealed intrahepatic biliary ductal dilatation and a heterogeneous pancreas without focal lesions or pseudocysts. Endoscopic retrograde

abstract

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Dr Corden contributed to the design and conception of this case presentation, recruited all specialists involved for writing the manuscript, revised the manuscript, and was involved in the care of the patient; Drs Frediani and Ostrom contributed to the writing of the manuscript, revised the manuscript, created the figures and tables, and were involved in the care of the patient; Dr Xu drafted the initial manuscript, revised the manuscript, and was involved in the care of the patient; Drs Chen and Liu contributed to the writing of the manuscript and were involved in the care of the patient; Dr Bissell contributed to the writing of the manuscript; and all authors approved the final manuscript as submitted.

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cholangiopancreatography indicated stenosis of the pancreatic sphincter. A stent was placed, resulting in symptom improvement and a decreased lipase.

Despite these interventions, her symptoms recurred. On this admission, her physical exam was notable for tachycardia (110–120 seconds), hypertension (130s over 80s), and diffuse abdominal tenderness to light palpation. Her initial exam was otherwise unremarkable. Her initial laboratory tests were significant for elevated liver enzymes (aspartate aminotransferase 68 U/L, alanine aminotransferase 80 U/L) and a normal lipase. Over the next few days, the lipase increased to 1707 U/L.

Dr Liu, given the patient's history and exam, does her presentation fit with the diagnosis of pancreatitis?

Dr Liu, Pediatric Gastroenterology

To make the diagnosis of pancreatitis the patient must have 2 out of 3 of the following: clinical symptoms of abdominal pain, back pain, or nausea; serum levels of pancreatic amylase and/or lipase ≥3 times the upper limit of normal; and/or radiographic evidence of pancreatic edema on ultrasound or CT.[1] Important historical data include trauma, gallstones, medication or toxin exposures, and recent infections. Serum lipase is 90% to 100% sensitive and 99% specific, resulting in a positive predictive value of 90% for the diagnosis of pancreatitis.[2] Although less specific, amylase can be helpful early in the course as it rises quickly but has a shorter half-life than lipase.[2] Other laboratory tests may help a physician to uncover the etiology or assess severity, including calcium level, triglycerides, liver enzymes, bilirubin, albumin, white blood cell count, and blood urea nitrogen level.[3]

The mainstay of therapy for patients with acute pancreatitis is fluid resuscitation, pain control, nutritional support, and preventing adverse events, including infection, thrombosis, or systemic inflammatory response syndrome. Fifteen percent to thirty-six percent of patients have recurrent acute pancreatitis after their initial episode.[4] Recurrent pancreatitis requires interim resolution of pain for at least 1 month or interim normalization of lipase between episodes. Lucidi et al[5] and Kumar et al[6] have investigated the underlying etiology in recurrent pancreatitis, demonstrating genetic mutations in *CFTR*, *CPINK1*, and *PRSS1*. Other etiologies included biliopancreatic malformations, lithiasis, congenital pancreatic polycytosis, dyslipidemia, and drugs.[5,6]

The objective in management of recurrent pancreatitis is to control symptoms and prevent progression to chronic pancreatitis. In our patient's case, it was appropriate to first evaluate anatomic causes. With ongoing symptoms, testing for hyperlipidemia (triglyceride levels ≥800 mg/dL), autoimmune pancreatitis (elevated immunoglobulin G4 levels), and hereditary pancreatitis (genetic mutation testing) would be appropriate. Other causes such as mediator-release pancreatitis (from exposure to azathioprine, polyethylene glycol 3350, or diuretics), alcohol abuse, and trauma were less likely in her case.

Her initial presentation largely fits with a diagnosis of recurrent acute pancreatitis, even if the episodes were fairly prolonged. Her constipation could have been explained by ileus, commonly seen with pancreatitis. Cholecystectomy was an appropriate initial intervention, given the biliary sludge seen on her initial ultrasound. With endoscopic retrograde cholangiopancreatography revealing pancreatic sphincter stenosis, stent placement was a logical next step. However, her symptoms recurred. One element of her history that could not be explained by pancreatitis was her initial complaint of paresthesias of the lips and legs.

Dr Ostrom, Pediatric Hospital Medicine

On this admission, she was made nil per os and given intravenous fluids. Her pain and nausea were again difficult to manage, requiring PCA with high-dose, continuous opioid infusion. Her constipation persisted, and she developed urinary retention, both of which were attributed to her large doses of narcotics. Nonetheless, she had sustained tachycardia and hypertension, which suggested to us that her pain remained poorly controlled.

Dr Chen, what was your approach to pain management given the complexity of our patient's pain?

Dr Chen, Pediatric Anesthesiology and Pain Management

Given the patient's clinical presentation and laboratory results in the context of abdominal pain with radiation to the back, the source of her pain appeared to be secondary to pancreatic inflammation. Pancreatic pain can be classified into 3 types: nociceptive, neuropathic, and neurogenic. Nociceptors sense and respond to either impending or actual injury as nociceptive pain. At the same time, tissue inflammation causes release of bradykinins, prostaglandins, and substance P that further activate nociceptors. Neuropathic pain is due to malfunctioning of the peripheral or central nervous system, which can be initiated by nociceptive activation. Neuropathic pain is characterized by hyperalgesia attributed to central sensitization. Lastly, neurogenic

inflammation may result from tissue inflammation and cell death.[7]

These sources of pancreatic pain create a challenge to provide adequate analgesia during each episode of pancreatitis, requiring treatments that target each subtype to create a multimodal approach while minimizing potential side effects.[8] Nociceptive pain can be managed with a combination of parenteral opioids and epidural analgesia, whereas nonsteroidal anti-inflammatory drugs reduce tissue inflammation. Gabapentin targets neuropathic pain. The multimodal management did not eliminate our patient's pain completely. In fact, her pain seemed out of proportion to both examination and laboratory findings, suggesting an alternative or more complex source of her pain.

Dr Ostrom

On hospital day 5, the patient began staring blankly into space and was minimally responsive to verbal or tactile stimulation. She developed bilateral weakness in wrist flexion and reduced grip strength. She was found to be hyponatremic (sodium 114 mEq/L). After slow correction with hypertonic saline, her mental status improved, but her distal muscle weakness persisted. Neurology was consulted, but the patient's findings did not correspond with a particular pathology. The neurologists recommended outpatient electromyography.

On further history, her mother noted that the patient's urine had been red-colored during her hospitalization. Her urine test results were negative for blood or infection. With these new findings, we were prompted to consider an acute porphyria as a unifying diagnosis. Urine porphobilinogen (PBG) was elevated at 116.8 mg/L, confirming our suspicion. Given the limited experience with the porphyrias at our institution, we consulted hematology.

TABLE 1 Differentiating the Acute Hepatic Porphyrias

		AIP	HC	VP	Our Patient
Urine porphyrins	PBG, ALA	++	++	++	++
	Uroporphyrin	+	+	+	++
	Coproporphyrin	±	+	+	+
Stool porphyrins	Total	Nml	+	+	Not done
	Coprophyrin III	Nml	+++	±	Borderline +
	Protoporphyrin	Nml	+	+++	Nml
Plasma porphyrins	Total	±	Nml	+++	+

HC, hereditary coprophyria; Nml, normal; VP, variegate porphyria.

Dr Frediani, when you received this consult, what were your diagnostic approach and initial recommendations?

Dr Frediani, Pediatric Hematology

The patient's symptoms of recurrent abdominal pain, intractable nausea, hypertension, hyponatremia, and muscle weakness in the setting of a significantly elevated urine PBG were consistent with the diagnosis of an acute hepatic porphyria. Because each subtype of acute hepatic porphyria has unique short- and long-term treatment strategies, identifying the subtype is imperative.[9] We recommended obtaining a urine δ-aminolevulinic acid (ALA) and quantitative urine porphyrins, fecal porphyrin levels, plasma porphyrins, and erythrocyte PBG deaminase levels. The urine samples are typically sent as a spot sample rather than a 24-hour collection because testing is more cost-effective and readily available and results are comparable.[10] These tests should be sent before initiating treatment because the levels of these porphyrins may drop rapidly with definitive measures. Given the rarity of this condition in pediatrics (<5% of cases),[11] we consulted with our adult hematology colleagues, who agreed with the above diagnostic approach.

While awaiting the results of the tests, prompt treatment with hematin is the standard of care, provided it is available. In the meantime, a trial of intravenous glucose loading (at least 300 g/day) has demonstrated some efficacy in mild cases of porphyria (eg, those without paresis, hyponatremia, etc). Otherwise, symptomatic relief and trigger avoidance remain the mainstay of therapy.[12] We recommended consulting the drug database through the Porphyria Foundation (www.porphyriafoundation.com) to ensure her current medications were not contributing to her ongoing exacerbation.

Dr Corden

While waiting for hematin to be delivered, the patient remained strictly nil per os and was receiving 485 g of carbohydrate daily through her total parenteral nutrition. We treated her pain with intravenous acetaminophen and PCA with a continuous hydromorphone infusion. Nausea was controlled with granisetron and prochlorperazine. Hyponatremia persisted despite fluid restriction. Hypertension was managed with a calcium channel blocker. Her hand weakness had some improvement through occupational therapy. Psychiatry was involved to assist with the patient's anxiety and depression. Throughout this period, her lipase remained elevated.

After being hospitalized for more than 3 of the previous 5 months, the patient's laboratory evaluation helped confirm her underlying diagnosis, acute intermittent porphyria (AIP) (Table 1).

TABLE 2 Clinical Symptoms of AIP

Category	Symptom
Increased sympathetic activity	Tachycardia[a]
	Hypertension[a]
	Palpitations and/or arrhythmias
	Sweating
	Urinary retention[a]
Visceral symptoms	Abdominal pain (steady and poorly localized)
	Constipation[a]
	Nausea and/or vomiting[a]
Neurologic symptoms	Headache
	Muscle weakness[a]
	Neuropathic pain[a]
	Tremors
	Seizure
	Sensory loss
Psychiatric symptoms	Anxiety[a]
	Depression[a]
	Disorientation and/or hallucinations
	Insomnia
	Paranoia
	Restlessness

[a] Symptoms experienced by our patient.

Dr Bissell, what exactly is AIP, and does this case reflect the usual course of presentation?

Dr Bissell, Adult Gastroenterology

The underlying cause of AIP is mutation of 1 allele of the hydroxymethylbilane synthase gene (also termed PBG deaminase). This is the third of 8 enzymes mediating heme synthesis, catalyzing the conversion of PBG to uroporphyrinogen. The disease is autosomal dominant, with affected individuals having ~50% of normal hydroxymethylbilane synthase activity. The mutation potentially leads to accumulation of ALA and PBG. Under most circumstances, however, 50% hydroxymethylbilane synthase activity is sufficient for homeostasis, with many carriers showing no biochemical or clinical evidence of disease. The deficiency becomes critical when hepatic demand for heme increases, which can be due to medications that induce hepatic cytochrome P450 or severe caloric deprivation. Spontaneous attacks do occur but almost exclusively in younger women (16–45 years). They may be cyclical, coming during the second half of the menstrual cycle when progesterone secretion peaks. Overall, <10% of adult carriers experience attacks, but a larger subgroup may have chronic complaints including fatigue, depression, intermittent low-grade pain, and constipation. ALA coming from the liver is believed to be neurotoxic, affecting both the autonomic and peripheral nervous systems (Table 2).[13] Central nervous system involvement manifests as seizures (~20% of acute flares) and hyponatremia; the latter may be due to hypothalamic or pituitary dysfunction.

The presentation of an acute attack of AIP, although notoriously nonspecific, has characteristic features.[14] The patient invariably describes worsening pain and nausea that has been present for a few days. Pain that arises and resolves within 24 hours in a naïve patient is rarely due to acute porphyria. More commonly, the pain is described as diffuse but "deep" and intense; occasionally it may be localized, suggesting an acute abdomen. Analgesics, including oral opioids, provide little relief.[15] Examination often reveals a well-appearing patient in whom the physical findings do not match the symptoms. Laboratory and imaging studies are essentially normal. Dark urine is a tip-off but not always present because ALA and PBG, as porphyrin precursors rather than porphyrins, are colorless.

The symptoms in acute attacks are largely neurologic in nature but may not be recognized as such because in the early stage they represent autonomic dysfunction only: tachycardia, systolic hypertension, and ileus on abdominal imaging. AIP becomes a diagnostic consideration only after the appearance of motor neuron signs (extremity weakness or paresis) or seizures. Hyponatremia is seen in a substantial minority of acute attacks and suggests the diagnosis in a young woman without known chronic disease. Poor prognostic factors include extensive muscle weakness, need for mechanical ventilation, bulbar palsy, altered levels of consciousness, and hyponatremia.[16] The progression of motor neuropathy to respiratory failure and the development of life-threatening arrhythmias because of autonomic neuropathy make AIP a potentially fatal disease.[17]

Delay in arriving at the diagnosis of AIP is not uncommon and has been associated with an increase in mortality.[18] In an observational study of 108 patients with acute porphyrias in the United States, the diagnosis was delayed by 15 years, on average, from the time of first symptom onset.[19] As in our patient, case reports demonstrate that extensive testing and interventions are often pursued before reaching the correct diagnosis.[20–25] Once a diagnosis is reached, DNA testing of family members is recommended for identifying carriers and genetic counseling.

Given this patient's classic presentation, I would treat with hematin as soon as it can be obtained. Hematin shuts down ALA

overproduction through a negative feedback loop to ALA synthase. There is usually a delay of 2 to 3 days in providing the medication because hospital pharmacies do not stock it. The caveats with hematin are as follows: (1) it is mildly alkaline and may cause a painful phlebitis if infused into a small vein, and (2) in solution it is unstable and must be given as soon as the vial is ready. These challenges can be overcome by doing the following: (a) establishing (usually) central venous access before hematin is ordered; (b) reconstituting hematin with human serum albumin rather than sterile water, which avoids the development of a transient coagulopathy and reduces the risk of forming degradation products that bind to endothelial cells, platelets, and coagulation factors[26]; and (c) coordinating with the pharmacy to ensure prompt delivery to the bedside. Once therapy has been initiated, the patient's clinical response can be monitored by trending heart rate, blood pressure, pain scores, and sodium levels (if abnormal).

Dr Corden

After an initial 4-day course of hematin, the patient's abdominal pain had completely resolved. However, nausea persisted despite regularly scheduled antiemetics, and her hand weakness was unchanged. Because there are patients in the literature who had continued improvement with multiple treatments,[27] we gave another course of hematin, during which her nausea resolved and her hand weakness improved. Interestingly, the patient's lipase level continued to rise in the setting of a normal abdominal exam and imaging (ultrasound and MRCP). Her diet was advanced, and after receiving a total of 12 doses of hematin, the patient was weaned off narcotics and antiemetics and was having slow but noticeable improvement in her distal motor weakness (neurologic recovery does not occur with hematin treatment but requires axonal regeneration). She was discharged from the hospital with outpatient occupational therapy.

Dr Bissell, is there a known etiology for elevated lipase in the setting of an attack of AIP? Or is there a possible association between an episode of pancreatitis and an attack of AIP?

Dr Bissell

An association between pancreatitis and AIP has been largely unexplored despite reports of lipase elevation during acute attacks of porphyria.[28–32] Causation cannot be established on the basis of the limited information available. A latent AIP carrier who develops pancreatitis is at risk for an attack of porphyria because of reduced caloric intake. On the other hand, the metabolic changes of porphyria may induce mild pancreatitis. The latter would be analogous to the increase in alanine aminotransferase and aspartate aminotransferase that is seen commonly in acute attacks and is entirely subclinical. Because the transaminases normalize as the attack resolves, they were thought to be unimportant. That view is changing given long-term data from researchers who indicate that older patients with a history of porphyria flares over many years are at risk for liver and kidney disease, possibly because of chronic elevation of blood ALA.[33–35] Ongoing natural history studies may shed light on an association between AIP and chronic pancreatic injury.[19]

Dr Liu

It is important to note that an elevated lipase alone is not diagnostic for pancreatitis; however, levels 3 times greater than normal are rarely because of other causes. In this patient, as well as many of those described in the literature, a high index of suspicion for other potential causes of abdominal pain is important. Unquestionably, an attack of AIP can mimic the presentation of acute pancreatitis. However, once initial investigations demonstrate that pancreatitis is a less likely cause of the patient's symptoms, alternative diagnoses should be explored. In our patient, the results of a previous CT scan, the gold standard for radiologic diagnosis,[36] were negative for pancreatic pathology. Although the initial MRCP revealed a prominent pancreatic duct, this finding can be a normal variant. Further investigations could not identify a cause of pancreatitis. In retrospect, distinguishing features of this patient's presentation that might have led us to consider alternative diagnoses earlier included urinary retention, hyponatremia, and the persistence of tachycardia and hypertension despite treatment with seemingly adequate analgesia.

Dr Corden

The patient was hospitalized 6 more times over the course of the following year because of symptoms consistent with AIP flares. Each hospitalization lasted no more than a week, as hematin was administered promptly on admission. Usually, lipase levels (when checked) with each of her subsequent admissions stayed low. However, one of her most recent flares, triggered by inappropriate trimethoprim and sulfamethoxazole administration at a local clinic, resulted in the largest elevation in lipase and decrease in sodium since her original diagnosis (Fig 1).

Dr Frediani, what is her ongoing care plan?

Dr Frediani

Treatment of AIP focuses on prevention and prompt treatment of flares with hematin. The most common triggers are prolonged fasting or dieting, menses, smoking or alcohol use, psychological and

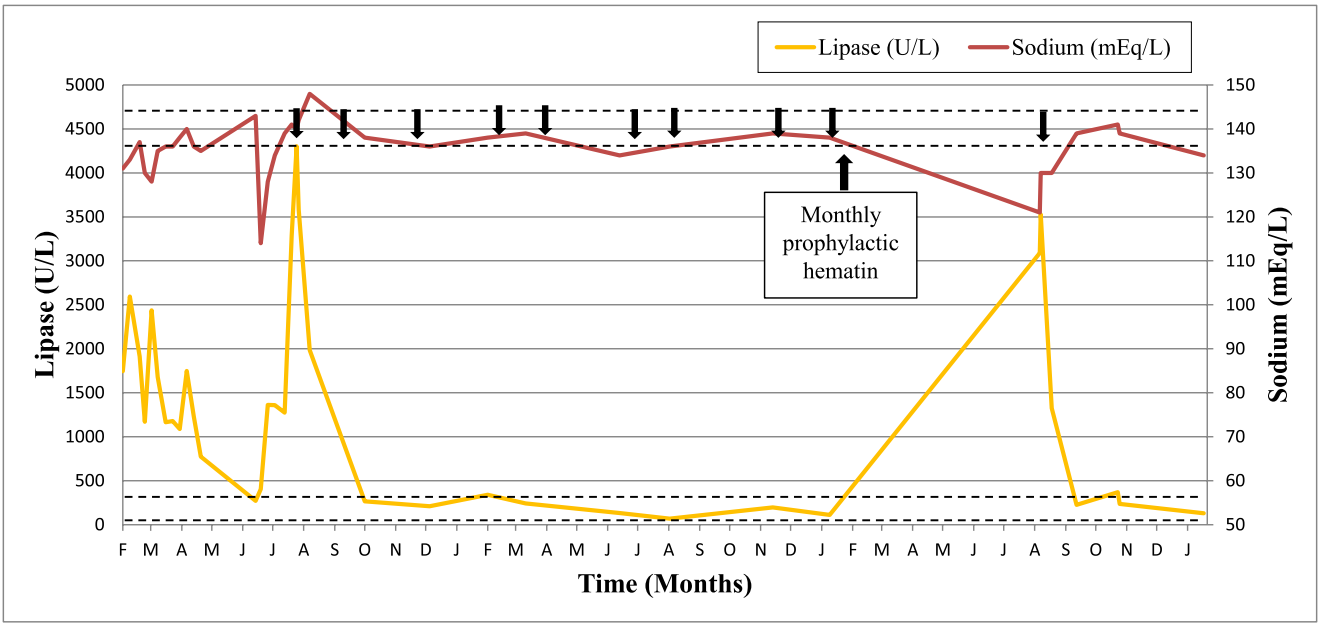

FIGURE 1
Lipase and sodium trends (↓ = hematin administration).

physical stress, and medications that increase hepatic heme production (particularly cytochrome P450 enzymes).[10] During the year after her AIP diagnosis, she continued to have monthly flares ~7 to 10 days before her menses. Symptoms were managed at home with narcotics and antiemetics. Although ovulation suppression with a gonadotropin-releasing hormone agonist (leuprolide, goserelin, and others) was an option, the risk of early menopause outweighed the benefits of such therapy. Severe attacks (intractable nausea, constipation, and abdominal pain refractory to home medications) required inpatient hematin administration. She had complete recovery of her distal neuromuscular weakness.

Fortunately, new treatments are on the horizon. As the liver is the predominant source of excess ALA and PBG production, liver transplantation produces a definitive cure.[37] However, given its cost and morbidity, it is currently reserved for those patients with progressive neurologic disease despite hematin treatment. Additionally, 2 gene-based drugs are in early clinical trials.[38–40]

Because this is a rare disease and predominantly seen in adults, we referred our patient to 1 of 6 porphyria centers through the Porphyrias Consortium, both for a second opinion regarding management and to provide her with the option of participating in clinical trials. Genetic testing, recommended for any patient who might be an index case,[41] revealed a previously undescribed splice site mutation, IVS14-1G>C, in 1 allele of the hydroxymethylbilane synthase gene, consistent with the diagnosis of AIP. Because of the autosomal dominant inheritance pattern and the variable disease penetrance, genetic testing of her older brother was obtained and demonstrated the same gene mutation, although he remains asymptomatic. Her younger sister is 10 years old and will be offered testing when she reaches puberty. After the patient's consultation, we elected to start monthly prophylactic hematin infusions to reduce the frequency and intensity of AIP flares.[10]

Dr Corden

We found this case remarkable for several reasons. Given how rare the case is in pediatrics, the patient ultimately suffered a complex and protracted course before arriving at a diagnosis. Her diagnosis was further delayed because of the negative test results of her family history; in fact, we report a new mutation in this article that was ultimately the cause of the patient's porphyria. Additionally, even after diagnosing AIP, we had to develop a protocol for ordering and administering hematin because it had never been given at our institution.

CONCLUSIONS

AIP can present with a wide variety of symptoms and may mimic more common diseases. A diagnosis of acute porphyria can be considered when the traditional historical elements, physical examination findings, diagnostic parameters, and treatment measures do not follow the typical progression of the working diagnosis. We began suspecting alternative diagnoses to recurrent pancreatitis when we reviewed the

patient's history (paresthesias, red urine), incorporated examination findings (persistent tachycardia and hypertension, altered mental status, hand weakness), and witnessed a lack of response to standard care for recurrent pancreatitis (persistent pain). If the index of suspicion for an acute porphyria is high, immediate treatment with hematin while awaiting the results of the urine and stool porphyrins is critical. Furthermore, all efforts should be made to incorporate a local porphyria expert in the ongoing care and management of the patient. In most cases, as in ours, recognition of the proper type of acute porphyria and prompt treatment with hematin can be life-altering.

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ABBREVIATIONS

AIP: acute intermittent porphyria
ALA: δ-aminolevulinic acid
CT: computed tomography
MRCP: magnetic resonance cholangiopancreatography
PBG: porphobilinogen
PCA: patient-controlled analgesia

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