Acute porphyria presenting as abdominal pain in pregnancy

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A 29-year-old White woman who had a history of hypothyroidism and a remote partial bowel resection for perforated appendix presented to our hospital with a few days of sudden-onset cramping, diffuse and nonradiating lower abdominal pain, nausea, vomiting and watery diarrhea. After confirmation of a 4-week intrauterine pregnancy, she was discharged from the emergency department with a diagnosis of nausea and vomiting in pregnancy (morning sickness). However, on her third presentation over 2 days with progressive symptoms, she was admitted for parenteral fluids and analgesia.

The patient had been highly functioning before this acute episode and had no history of recurrent abdominal pain, allergies, medication or supplement use, recreational drug use, heavy metal exposure, recent travel or sick contacts. Her partner confirmed this information. Systems review did not point to other causes of acute abdominal pain (Box 1).¹ On examination, she was afebrile, with a blood pressure of 144/87 mm Hg and heart rate 82 beats/min, and her oxygen saturation was 100% by pulse oximetry on room air. She had a diffusely tender abdomen, and the results of her neurologic, cardiovascular, respiratory and skin examinations were unremarkable.

Over the next few days, her pain became progressively worse, requiring up to 20 mg of hydromorphone daily via a continuous ambulatory delivery device pump. She also became hypertensive and described urinary hesitancy; we treated her with labetalol for blood pressure control, and pyridoxine-doxylamine, dimenhydrinate and metoclopramide for nausea.

The results of laboratory investigations were mostly within normal limits, apart from slight metabolic acidosis likely secondary to starvation ketosis (with normal blood glucose). The patient had hyponatremia consistent with a syndrome of inappropriate antidiuretic hormone secretion (SIADH), and her aminotransferase (ALT) level was mildly elevated (Box 2). A chest radiograph was normal, and electrocardiogram showed normal sinus rhythm with possible sinus arrhythmia. Given her surgical history, we ordered an abdominal ultrasound and magnetic resonance imaging scans, which, aside from a simple, left hydrosalpinx, revealed no hepatobiliary, genitourinary or gastrointestinal tract pathology. Doppler ultrasound of the portal vein did not show any thrombus to account for the elevated ALT.

KEY POINTS

- Acute porphyrias are rare genetic disorders that present with neurologic and systemic symptoms, including abdominal pain, hyponatremia and seizures.
- When porphyria is suspected, a urine screening should be undertaken.
- If a urine porphyria screen is positive, treatment for acute porphyria should not be delayed.
- Identifying and avoiding triggers, high-carbohydrate diet, use of intravenous hemin and supportive care are the mainstay therapies of acute porphyria.

In light of the patient's normal leukocyte count, lack of fever, negative cervical swabs for chlamydia and gonorrhea, negative nasopharyngeal swab for coronavirus disease 2019, and normal urinalysis and urine culture, we ruled out an infectious cause for her abdominal pain and nausea. A normal C-reactive protein level and abdominal imaging argued against inflammatory bowel disease and other autoimmune conditions.¹ Because of the patient's surgical history, our working diagnosis at this time was scar-mediated pain from a gravid uterus.

However, given her ongoing intractable abdominal pain, urinary hesitancy, hypertension suggestive of autonomic dysregulation and SIADH, we considered the possibility of porphyria and ordered a urine porphyria screen, which came back positive on day 10 (Box 2). We diagnosed acute porphyria, likely triggered by pregnancy. Quantitative testing from the same urine sample verified an elevated urine porphobilinogen-creatinine ratio. Complete urine and stool porphyrin analysis showed substantially elevated coproporphyrin levels with normal protoporphyrin, which confirmed a diagnosis of hereditary coproporphyria.

Because of the severity of the attack, we decide to start an infusion of a hemin infusion product available via Canadian Blood Services (Panhematin), which corrects heme deficiency in the liver and downregulates porphyrin precursors that cause acute attacks.² After consulting the American Porphyria Foundation website, we discontinued pyridoxine-doxylamine, dimenhydrinate and metoclopramide, as they can potentially exacerbate acute porphyria episodes.³ We also prescribed a high carbohydrate load. The patient's symptoms improved

Box 1: Considerations for differential diagnosis of acute abdominal pain¹

Surgical	<ul style="list-style-type: none"> • Bowel obstruction • Perforated viscus • Ischemic colitis • Biliary tree pathology • Pancreatitis • Ureteric obstruction • Abdominal aortic aneurysm • Ovarian torsion • Trauma
Drugs and toxins	<ul style="list-style-type: none"> • Cocaine use • Lead poisoning
Infectious	<ul style="list-style-type: none"> • Gastroenteritis • Hepatitis • Genitourinary infection • Herpes zoster
Metabolic	<ul style="list-style-type: none"> • Inflammatory bowel disease • Diabetic ketoacidosis • Hypercalcemia • Adrenal insufficiency • Acute porphyria
Referred pain	<ul style="list-style-type: none"> • Cardiac: Myocardial infarction, pericarditis • Pulmonary: pneumonia, pulmonary embolism, pleural pathology such as effusion or pneumothorax • Esophageal: esophageal spasm, gastric reflux • Musculoskeletal such as rib pain • Spinal cord or nerve root compression • Testicular torsion
Others	<ul style="list-style-type: none"> • Irritable bowel syndrome • Lactose intolerance • Functional abdominal pain • Psychiatric disorders • Familial Mediterranean fever • C1 esterase inhibitor deficiency

after 4 days of hemin infusion and she was discharged home on a low dose of hydromorphone, which was discontinued soon afterward.

At 1-month follow-up, the patient's nausea had improved, her pain was well controlled with minimal analgesia, and her blood pressure and plasma sodium levels had normalized. The patient's family confirmed that her paternal grandmother had reported intermittent episodes of purple urine. The patient and her father eventually tested positive for the gene mutation responsible for hereditary coproporphyria, although her father remains asymptomatic. In preparation for labour and delivery, we monitored for recurrence of any clinical symptoms and signs of acute porphyria and avoided hypoglycemia and medications known to trigger attacks. The patient delivered a healthy baby.

Box 2: Summary of patient's laboratory results

Investigation	Result (normal range)
Hemoglobin (g/L)	149 (115–155)
Mean corpuscular volume (fL)	83.9 (80–100)
Leukocytes ($\times 10^9/L$)	7.5 (3.5–10.5)
Thrombocytes ($\times 10^9/L$)	184 (130–380)
Sodium (mmol/L)	139 (136–144)
Potassium (mmol/L)	4.1 (3.5–5.1)
Creatinine ($\mu\text{mol/L}$)	49 (49–84)
Bicarbonate (mmol/L)	20 (19–30)
Calcium (mmol/L)	2.42 (2.24–2.58)
Albumin (g/L)	46 (36–47)
Aspartate aminotransferase (IU/L)	24 (2–25)
Alanine aminotransferase (IU/L)	31 (6–30)
Alkaline phosphatase (IU/L)	49 (46–118)
Total bilirubin ($\mu\text{mol/L}$)	18 (≤ 11)
Lactate (mmol/L)	1.2 (0.25–2.5)
Lipase (IU/L)	31 (14–85)
Human chorionic gonadotropin (mIU/mL)	1672 (≤ 5)
Urine sodium (mEq/L)	172
Osmolality (mOsm/kg)	269 (280–295)
Urine osmolality (mOsm/kg)	794 (50–1200)
C-reactive protein (mg/L)	0.4 (< 10)
Thyroid-stimulating hormone (mIU/L)	1.88 (0.27–4.2)
Urine porphyria screen	Positive
Porphyrin quantitative analysis	
Serum porphobilinogen deaminase ($\mu\text{mol/L}$)	27 (29–49)
Urine porphobilinogen to creatinine ratio ($\mu\text{mol}/\text{mmol Cr}$)	4.3 (< 0.8)
Urine aminolevulinic acid to creatinine ratio ($\mu\text{mol}/\text{mmol Cr}$)	14.1 (< 5)
Urine porphyrin quantification (nmol/mmol Cr)	<ul style="list-style-type: none"> • Uroporphyrin I: 204.6 (elevated) • Uroporphyrin III: 34.4 (elevated) • Coproporphyrin I: 316.8 (elevated) • Coproporphyrin III: 1113.6 (elevated)
Fecal porphyrin quantification (nmol/g)	<ul style="list-style-type: none"> • Coproporphyrin III: 2376.1 (≤ 12) • Coproporphyrin I: 252.2 (≤ 13) • Protoporphyrin: 6.5 (≤ 38)

Discussion

Epidemiology

The term “acute porphyria” refers to a group of rare genetic disorders characterized by various enzyme deficiencies in the heme biosynthesis pathway.^{4,5} The most common subtype of acute porphyria is acute intermittent porphyria; others include variegate porphyria, hereditary coproporphyria, and the very rare aminolevulinic acid dehydratase porphyria.^{4,5} Combined, symptomatic porphyrias have an estimated prevalence of 10 per million in European populations, with acute intermittent porphyria about twice as common as variegate porphyria and 6 times as common as hereditary coproporphyria.⁶ These conditions are autosomal dominant, with incomplete penetrance, and, as such, carriers of a gene mutation may never have acute attacks.⁶ Symptoms typically manifest in young women in the second to fourth decade of life.^{5,7}

Clinical manifestations

Typical symptoms and signs of acute attacks include diffuse abdominal pain (in up to 90% of patients), nausea, vomiting or change in bowel habits; urine that turns dark when exposed to light; and hyponatremia from inappropriate antidiuretic hormone secretion or renal salt wasting, which may precipitate seizures.⁵ Patients may also present with neuropsychiatric symptoms such as mood disorders, psychosis, behavioural changes, autonomic dysfunction, sensory or motor peripheral neuropathy, and even respiratory compromise.⁵ Bullous skin lesions may be associated with variegate porphyria (50% of patients) and hereditary coproporphyria (< 20% of patients).⁵ One case report describes posterior reversible encephalopathic syndrome in a postpartum patient with known acute intermittent porphyria.⁸

Diagnosis

Given its rarity and spectrum of presentation, it is challenging to diagnose acute porphyria. Patients may undergo multiple abdominal surgeries; a case series reported an average diagnostic delay of 10 years.^{7,9} The diagnosis of acute porphyria requires detection of increased urine porphobilinogen.⁵ Initial urine screening for urine porphyrins may be completed more quickly than definitive quantification, although, in the presence of typical symptoms and absence of secondary causes, screening may be sufficient to initiate treatment.⁵ Fecal or plasma porphyrin quantification is required to subtype the condition.⁵ Genetic studies should be requested in patients with confirmed elevations in porphyrin levels, as well as for patients' first-degree relatives.⁵

A variety of triggers are associated with acute porphyria attacks. These include prescription medications such as antibiotics, oral contraceptives and anticonvulsants, as well as recreational drug use and heavy alcohol intake.⁵ Comprehensive drug databases have been established to facilitate informed choices by health care providers and patients with these disorders.³ Physiologic changes in hormonal concentrations — such as in pregnancy, decreased food intake, stress, or infections — are known triggers.⁵

Secondary causes of porphyrinuria should always be considered, including acute or chronic liver disease, hemoglobin disorders such as thalassemia or sickle-cell disease, and exposure to environmental toxins like lead, mercury or arsenic.¹⁰ Of particular importance is lead toxicity, which can mimic acute porphyria clinically.

Management

In acute attacks, a thorough patient history can identify precipitating triggers.⁵ Adequate analgesia is crucial, and in some cases, patient-controlled analgesia may be favoured.⁵ Careful assessment of urine electrolytes and volume status, particularly to assess hyponatremia, should be performed. Carbohydrates can inhibit the intrinsic heme biosynthesis pathway, and increased intake in the short term (300–500 g/d) may suffice in treating mild attacks.⁵ Dietitians can help to ensure adequate carbohydrate intake.

In patients who have neurologic symptoms, hyponatremia or clinical instability, treatment with intravenous hemin is the mainstay of therapy.⁵ In Canada, hemin is available through the Canadian Blood Services only.² Although efficacy has not been proven in randomized trials, it is considered to alleviate symptoms faster and reduce the risk of complications.⁵ Hemin has been used successfully in pregnant patients, and the combination of hemin, glucose and magnesium sulphate has been an effective treatment strategy for postpartum posterior reversible encephalopathy syndrome.⁸ Benzodiazepines may also be safe for seizures in the acute setting.⁵ Sun protection is recommended for such patients, given their predisposition to photosensitivity.⁵ Although recurrent attacks are rare, prophylactic hemin infusions may be considered.

Over the long term, patients with acute porphyrias may develop complications including neurologic compromise and chronic kidney disease, and they are at increased risk for hepatocellular carcinoma.⁵ Rarely, liver transplant may be the only curative option.⁵ Data on prognosis are scarce and, although attacks can rarely be fatal, expert opinion supports early recognition and management to reduce complications.⁵

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The section Cases presents brief case reports that convey clear, practical lessons. Preference is given to common presentations of important rare conditions, and important unusual presentations of common problems. Articles start with a case presentation (500 words maximum), and a discussion of the underlying condition follows (1000 words maximum). Visual elements (e.g., tables of the differential diagnosis, clinical features or diagnostic approach) are encouraged. Consent from patients for publication of their story is a necessity. See information for authors at www.cmaj.ca.

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