

Acute Intermittent Porphyria

Mubashir A. Shah, MD

Roderick Remoroza, MD

Khalid Aziz, MBBS, MRCP(UK), MRCP(Ire), FACC

Porphyrins are a heterogeneous group of disorders caused by deficiencies of specific enzymes of the heme biosynthetic pathway. When clinically expressed, these disorders are associated with striking accumulations of heme pathway intermediates. Most porphyrias are inherited, but their clinical severity is also determined by other factors, such as diet and medications. Acute intermittent porphyria (AIP), the most common type of porphyria, is an autosomal dominant disorder that results from an approximately 50% deficiency of porphobilinogen (PBG) deaminase. This enzyme is deficient in all persons who inherit a mutant PBG deaminase gene, and the deficiency remains fairly constant over time; however, most people with PBG deaminase deficiency remain asymptomatic. More prevalent and more often manifested in adults than are most metabolic diseases, porphyrias are likely to be encountered by physicians in many disciplines. Prompt diagnosis and early treatment with carbohydrates are vital for improvement of symptoms.

This article reports a case of an 18-year-old woman in whom AIP was diagnosed, based on her history of abdominal pain associated with menstruation, clinical evidence of hyponatremia, and pertinent laboratory data. The etiology, epidemiology, pathophysiology, clinical features, diagnosis, and management of AIP will be discussed.

CASE PRESENTATION

History and Initial Evaluation

An 18-year-old woman came to the emergency department because of a 5-day history of severe abdominal pain. She had had intermittent, localized, severe, sharp epigastric and periumbilical pain associated with mild nausea but no vomiting for the previous 6 months. The pain usually started 2 to 3 days prior to the beginning of her menstrual cycle and generally lasted the length of the cycle; there were no other obvious exacerbating (or relieving) factors. She reported having discoloration of her urine during these episodes of pain but no burning or additional pain on micturition and no fevers, chills, diarrhea, constipation, melena, hema-

tochezia, shortness of breath, or chest pain. The patient, who was menstruating at the time of presentation, was taking no medications. She lived with her parents and was a senior in high school.

Medical history was significant for 2 previous hospital admissions, at which time extensive work-ups had been performed to determine the cause of her hyponatremia, irregular menstruation, and abdominal pain; no specific diagnosis had been reached on these occasions. The patient had no history of psychiatric illness, sexual intercourse, sensitivity to the sun, smoking, drinking, or illicit drug use. Menarche occurred at age 12 years.

Physical examination revealed a thin white woman in mild distress. Heart rate was 108 bpm. The abdomen was scaphoid, with mild tenderness on deep palpation (mostly periumbilical); there was no hepatosplenomegaly. Auscultation of the abdomen revealed reduced bowel sounds. Pelvic examination revealed no cervical motion or adnexal tenderness; there were no visible ulcers or lesions. Her stool was heme negative.

Results of serum electrolyte measurement were notable for a serum sodium level of 132 mEq/L (normal, 135–145 mEq/L). Other serum electrolyte levels and plasma levels of urea nitrogen, creatinine, and glucose were within normal limits. Results of a complete blood count and liver function tests also revealed no abnormalities. Results of urinalysis showed a few erythrocytes. Ultrasonography of the abdomen was unremarkable, but a computed tomography scan of the abdomen showed mild ileus.

The unexplained hyponatremia and history of urinary discoloration and recurrent abdominal pain associated with menstruation in this 18-year-old woman, who had no apparent predisposing factors, suggested the presence of AIP, and subsequent serologic and urinary

Dr. Shah is a Resident in Internal Medicine, Dr. Remoroza is a Fellow in Gastroenterology/Hepatology, and Dr. Aziz is an Assistant Professor of Medicine and Associate Program Director, Department of Gastroenterology, University of Connecticut, Farmington, CT.

Table 1. Laboratory Measurements in the Case Patient

Substance Measured	Result
Porphobilinogen (urine)	95 µmol/L (normal, 0–8.8 µmol/L)
5-Aminolevulinic acid (urine)	724 µmol/L (normal, 0–35 µmol/L)
Porphobilinogen deaminase (erythrocytes)	2 mU/g (normal, 2.1–4.3 mU/g)

tests confirmed the diagnosis. Pertinent laboratory data are shown in **Table 1**.

Subsequent Hospital Course

The patient was admitted to the medical service and treated with oral administration of analgesics and antiemetics and intravenous administration of dextrose. On the third hospital day, serum sodium level decreased to 120 mEq/L; urine sodium level was 169 mEq/L, serum osmolality was 265 mOsm/kg H₂O (normal, 275–295 mOsm/kg H₂O), and urine osmolality was 642 mOsm/kg H₂O (normal 50–1400 mOsm/kg H₂O). These laboratory findings were all consistent with the syndrome of inappropriate secretion of antidiuretic hormone. Intravenous administration of fluids was discontinued, and she was placed on fluid restriction, which increased her serum sodium level. The patient was discharged 2 days later with complete resolution of symptoms. She was placed on a high-carbohydrate diet and told to avoid prolonged periods without eating and to use medications only after consulting with her family physician.

DISCUSSION

Etiology and Epidemiology

AIP, also known as *pyroloporphyria* or *Swedish porphyria*, is the most common acute porphyria and is caused by a deficiency of hepatic PBG deaminase activity. The inheritance pattern is autosomal dominant with variable penetrance. Women are more commonly affected than are men. Affected persons have a 50% reduction in PBG deaminase activity in their erythrocytes.

The prevalence of AIP varies, with a higher incidence reported in England, Ireland, and Scandinavia.¹ The estimated gene prevalence is 1 in 10,000 to 20,000 persons in the United States. However, the majority of affected persons do not exhibit clinical disease. For example, the gene prevalence in Sweden is 7.7 per

10,000 persons, but the clinical incidence of AIP is estimated to be 1.5 per 100,000 persons.² Moreover, there is a higher incidence of AIP in psychiatric populations than in the general population, with rates as high as 2.1 per 100,000 reported in the United States.³

Pathophysiology

Porphyryns are byproducts of intermediates in the heme biosynthetic pathway (**Figure 1**). The precursors glycine and succinyl coenzyme A are converted to δ-aminolevulinic acid (ALA) in a reaction catalyzed by ALA synthetase. This reaction is considered the rate-limiting step in heme biosynthesis and is subject to feedback regulation by heme, the end product of the pathway. Two molecules of ALA combine to form porphobilinogen. Only protoporphyrin is used in heme synthesis. The other porphyryns (eg, uroporphyrin, coproporphyrin) have no physiologic function and must be excreted. Their fluorescent properties account for the diagnostic appearance of urine in some patients.

AIP results from partial deficiency of PBG deaminase, leading to accumulation and excess urinary excretion of porphobilinogen and ALA. The gene for PBG deaminase has been cloned and sequenced. Located on chromosome 11,⁴ this gene consists of 2 promoter sites, with the distal promoter being erythroid specific and the proximal promoter serving a housekeeping or constitutive function. Types of AIP are based on the ratio of cross-reactive immunologic material (CRIM) to enzyme activity in the tissues of affected persons. Enzyme mutations that result in excess amounts of CRIM are classified as CRIM-positive, whereas CRIM-negative mutations have normal or reduced amounts of CRIM. Two CRIM-positive patterns of disease and 2 CRIM-negative patterns have been described; most persons affected with AIP have CRIM-negative defects. Normal controls are described as having 100% PBG deaminase activity and 100% CRIM, with a ratio of enzyme activity to CRIM of 1. A ratio of 1 has also been correlated with CRIM-negative defects.

Clinical Features

Clinical features of AIP consist of heterogeneous manifestations of acute neurovisceral attacks; there is no cutaneous involvement. The most common signs and symptoms of AIP are abdominal pain (80%), constipation (50%), nausea and vomiting (50%), tachycardia (40%), hypertension (31%), urine discoloration (25%), and fever (16%).⁵ The neuropsychiatric signs and symptoms of AIP are diverse and nonspecific.

The most common presenting symptom of an acute attack is abdominal pain.⁶ Other common initial

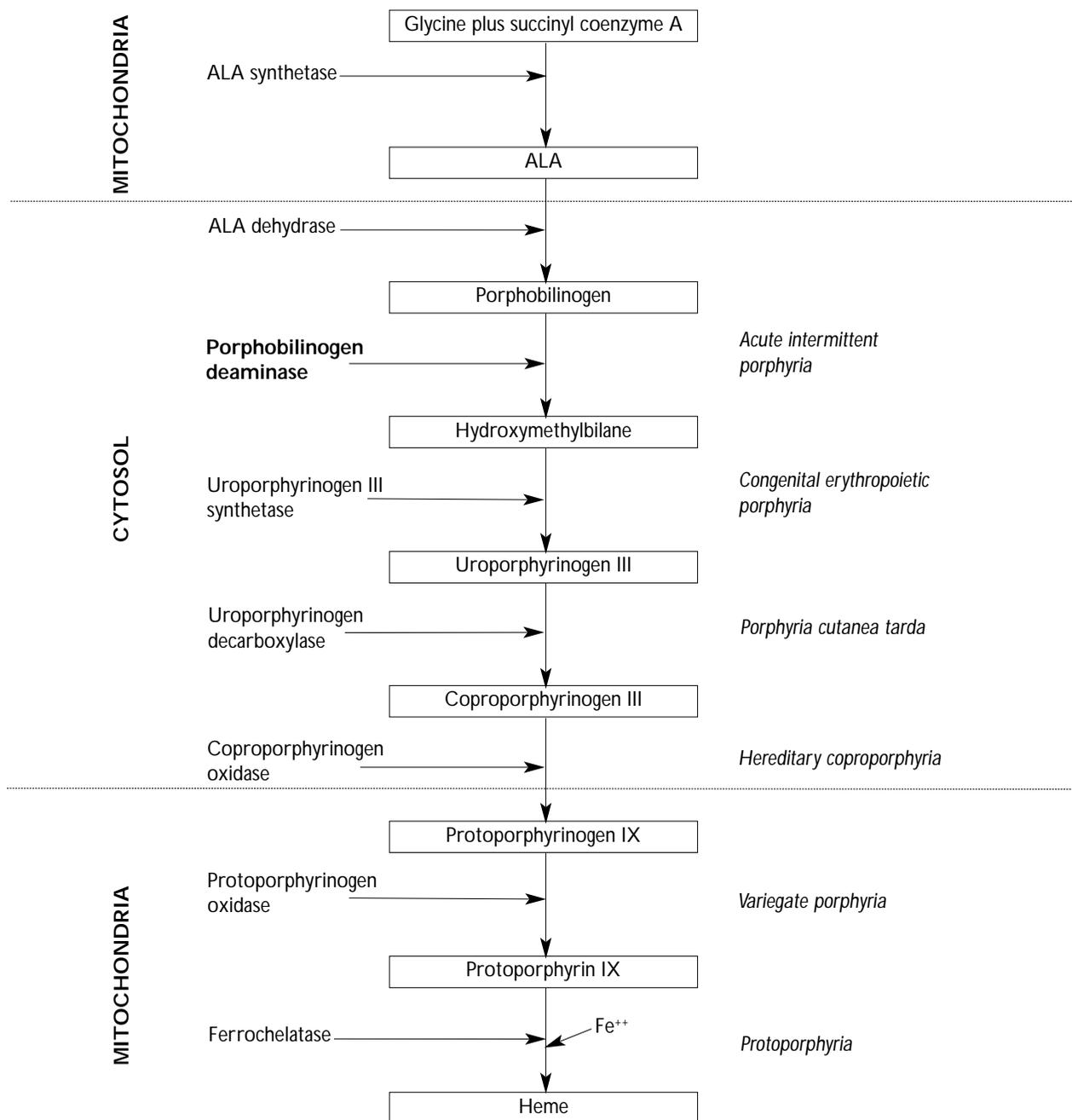


Figure 1. Algorithm illustrating the heme biosynthetic pathway and associated porphyrias. ALA = δ -aminolevulinic acid; Fe^{++} = ferrous form of iron.

symptoms include nausea and vomiting, constipation, confusion, stupor, coma, and seizures. Although constipation is most common, there are also reports of intestinal hyperactivity and diarrhea. The abdominal pain tends to be quite intense, and acute crises have been mistaken for conditions requiring surgical intervention.

The most common physical sign of AIP is tachycardia, which occurs in as many as 80% of patients with

acute attacks.⁷ Tachycardia results, in part, from the release of catecholamine during an acute attack and has been implicated in the sudden death attributed to cardiac arrhythmias.⁸ Motor neuropathy is also common in AIP. The peripheral nerves are usually involved, and symmetrical motor weakness involving the arms is common. The neuropathy is believed to result from axonal degeneration. Cranial nerves can also be impaired in

Table 2. Commonly Used Drugs That Precipitate Acute Attacks in Porphyrias

Barbiturates
Chlordiazepoxide
Chloroquine
Chlorpropamide
Ergot preparations
Estrogens
Ethanol
Glutethimide
Griseofulvin
Imipramine
Meprobamate
Methyldopa
Sulfonamides

cases of AIP, with the facial (VII) and vagus (X) nerves being involved more than the others. Visual impairment, including blindness, has been reported and is believed to be secondary to involvement of the optic (II) nerve or occipital lobes.⁵ Other physical signs include hypertension (which may persist after the acute attack), fever, bulbar paralysis, and sensory deficits.

Hyponatremia is often associated with acute attacks of AIP and may result, in part, from the inappropriate secretion of antidiuretic hormone. Hyponatremia in AIP can occur with or without clinical volume loss⁹ and with a normal adrenal morphology.^{10,11} This hyponatremia can place the patient at increased risk for seizure activity. The exact mechanism of the hyponatremia is not fully understood, but autopsy findings have suggested that damage to the supraoptic nuclei of the hypothalamus may be a contributing factor.¹² Excess renal sodium excretion has also been implicated.¹³ However, hyponatremia is not the only source of seizure activity, because patients without decreased serum sodium levels sometimes also have seizure activity.

There are several theories about the origin of neurologic damage in AIP and other acute porphyrias. Both ALA and PBG may be direct neurotoxins, and serum levels of these compounds are elevated during acute attacks. Heme deficiency has also been suggested as a cause of neurologic dysfunction; there may be decreased heme available for function in the nervous system, as well as decreased hepatic heme. One theory suggests that decreased hepatic heme causes decreased levels of activity of hepatic tryptophan pyrrolase, with resultant decreased metabolic conversion of trypto-

Table 3. Drugs That Are Safe to Use During Acute Attacks of Porphyrias

Acetaminophen
Aspirin
Atropine
Digoxin
Glucocorticoids
Insulin
Narcotic analgesics
Penicillin
Phenothiazines
Streptomycin

phan. The tryptophan may be taken up in the brain, where it activates the synthesis of 5-hydroxytryptamine. Tryptophan administered to healthy persons affects the central nervous system and causes neurologic symptoms that resemble acute episode of porphyria. Yet another theory suggests that the reversible neuro-motor dysfunction may be a result of vasospasm.

Several other factors have been identified that precipitate AIP, including stress, starvation, use of hormones, ethanol intake, infection, use of certain medications, and carbohydrate deprivation with dieting. Both estrogen and progesterone may play a role in AIP; women sometimes experience cyclical symptoms prior to menstruation, as with the case patient. Medications such as sulfonamide antibiotics and barbiturates (Table 2) are known to precipitate acute attacks of AIP.

Diagnosis

Diagnosis of AIP requires the correlation of clinical findings and laboratory data. When AIP is suspected, the demonstration of reduced erythrocyte PBG deaminase activity helps to confirm the diagnosis.¹⁴ Of note, reduced erythrocyte PBG deaminase activity is also encountered in cases of uremia, whereas hepatitis and hemolytic conditions can cause elevations of this activity. Quantitative measurement of urinary ALA and PBG levels should be performed. The urinary excretion of these porphyrin precursors is markedly increased during acute attacks, and the urine may appear reddish brown because of the nonenzymatic formation of porphyrins and other pigments from PBG. The erythrocyte PBG deaminase activity in all affected patients and latent gene carriers is reduced to approximately 50% of normal. ALA and PBG levels are always elevated in the serum and urine during an acute attack. ALA and

PBG levels may occasionally be normal between attacks and in some carriers of the disease who display latent porphyria. Because fecal porphyrin levels are usually within normal limits in patients with AIP, measurement of this variable is usually not helpful in diagnosis.

Treatment

Acute attacks of AIP should be managed with administration of appropriate narcotic analgesics for pain control and appropriate antiemetics for nausea and emesis (Table 3). A minimum daily intake of 300 g of carbohydrates also is required during attacks. If oral intake is inadequate, carbohydrates should be administered intravenously. Dextrose has been shown to decrease the urinary excretion of porphyrin precursors in patients with AIP.¹⁵ Intravenous heme therapy is also effective in managing acute attacks. Early heme therapy for acute attacks is advocated and is associated with improved outcomes, as measured by length of hospitalization.¹⁶ Heme is taken up by hepatocytes, in which it causes negative feedback for the activity and synthesis of ALA synthase, the rate-limiting enzyme. Heme can be administered intravenously as hematin (heme albumin and heme arginate are alternatives) in dosages of 3 to 4 mg/kg body weight per day for 4 days, beginning as soon as possible after onset of the attack. Patients receiving heme therapy should be monitored for complications of coagulopathy, thrombophlebitis, and hemolysis.

Recently, cimetidine has been used for hematin-resistant AIP. Cimetidine may be a more cost-effective and easily administered alternative to hematin therapy. The optimal dosage and duration of treatment with cimetidine have not been established and are likely to be patient specific. Daily oral doses of 800 mg have typically been used. In addition to its potential for treatment, cimetidine may also have a role in prophylaxis of acute episodes by maintaining a baseline suppression of ALA synthase activity.¹⁷

CONCLUSION

AIP has protean manifestations, and the physician must consider it in the differential diagnosis of any acute abdominal pain. Intense abdominal pain in the first 24 to 48 hours of an attack can suggest acute cholecystitis, appendicitis, or other surgical diagnoses and so may provoke unnecessary surgery. Attacks are rare before puberty. Treatment includes elimination of possible precipitating drugs, administration of carbohydrates to reverse fasting, analgesia, and supportive management of seizures, delirium, and other neurologic complications. Hematin, a commercial preparation of protoporphyrin IX, has been administered to patients with prolonged

attacks who do not respond to conservative therapy. HP

REFERENCES

1. Kappas A, Sassa S, Galbraith RA, Nordmann Y. The porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Walle D, editors. The metabolic and molecular bases of inherited disease [book on CD-ROM]. 7th ed. New York: McGraw-Hill; 1997:2103-59.
2. Bonkowsky HL, Schned AR. Fatal liver failure in protoporphyria. Synergism between ethanol excess and the genetic defect. *Gastroenterology* 1986;90:191-201.
3. Tishler PV, Woodward B, O'Connor J, et al. High prevalence of intermittent acute porphyria in a psychiatric patient population. *Am J Psychiatry* 1985;142:1430-6.
4. Namba H, Narahara K, Tsuji K, et al. Assignment of human porphobilinogen deaminase to 11q24.1-q24.2 by in situ hybridization and gene dosage studies. *Cytogenet Cell Genet* 1991;57:105-8.
5. Suarez JJ, Cohen ML, Larkin J, et al. Acute intermittent porphyria: clinicopathologic correlation. Report of a case and review of the literature. *Neurology* 1997;48:1678-84.
6. Bustamante M, Moll JL, Sarrion JV, Berenguer J. Acute intermittent porphyria: a possible cause of abdominal pain [in Spanish]. *Gastroenterol Hepatol* 1999;22:497-500.
7. Stein JA, Tschudy DP. Acute intermittent porphyria. A clinical and biochemical study of 46 patients. *Medicine (Baltimore)* 1970;49:1-16.
8. Gross U, Hoffmann GF, Doss MO. Erythropoietic and hepatic porphyrias. *J Inherit Metab Dis* 2000;23:641-61.
9. De Block CE, Leeuw IH, Gaal LF. Premenstrual attacks of acute intermittent porphyria: hormonal and metabolic aspects—a case report. *Eur J Endocrinol* 1999;141:50-4.
10. Hellman ES, Tschudy DP, Bartter FC. Abnormal electrolyte and water metabolism in acute intermittent porphyria. The transient inappropriate secretion of antidiuretic hormone. *Am J Med* 1962;32:734-46.
11. Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967;42:790-806.
12. Perlroth MG, Tschudy DP, Marver HS, et al. Acute intermittent porphyria. New morphologic and biochemical findings. *Am J Med* 1966;41:149-62.
13. Sassa S, Kappa A. Molecular aspects of the inherited porphyrias. *J Intern Med* 2000; 247:169-78.
14. Mastajoki S. Molecular genetics of acute intermittent porphyria in Finland (dissertation). Helsinki: University of Helsinki; 1999.
15. Bonkowsky HL, Magnussen CR, Collins AR, et al. Comparative effects of glycerol and dextrose on porphyrin precursor excretion in acute intermittent porphyria. *Metabolism* 1976;25:405-14.
16. Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993;153:2004-8.
17. Rogers PD. Cimetidine in the treatment of acute intermittent porphyria. *Ann Pharmacother* 1997;31:365-7.