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Case report

Emergency Department Encounter with Acute Intermittent Porphyria

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Acute intermittent porphyria (AIP) is a rare autosomal dominant disorder characterized by deficiencies in porphobilinogen deaminase (PBGD) and the toxic accumulation of metabolites in the heme biosynthesis pathway. Diagnosing AIP is challenging due to its low prevalence and nonspecific symptoms, often resulting in delayed diagnosis and management. We present the case of a 39-year-old female with a five-year history of recurrent emergency department visits for severe intermittent abdominal pain with unremarkable laboratory workup and imaging each time. The patient was eventually diagnosed with AIP following genetic testing. Despite initial symptom improvement with intravenous heme therapy, the patient experienced recurrent episodes due to limited access to prophylactic treatment. Transitioning to givosiran reduced symptom frequency and improved her quality of life. This case highlights the diagnostic challenges of AIP, emphasizing the importance of taking detailed histories to identify patterns and potential triggers in patients with recurrent unexplained symptoms. Early identification and targeted management of AIP can prevent acute exacerbations and reduce complications. Increased clinician awareness can facilitate earlier recognition and management of this rare condition. Accurate identification of such cases may also inform further research into AIP's prevalence and deepen understanding of its pathophysiology.

INTRODUCTION

Acute intermittent porphyria (AIP) is a rare genetic disorder, with an estimated prevalence of approximately 1 in 20,000 (<0.0005%).[1,2] It predominantly affects women more than men, with a reported ratio of 1.5-2 to 1, and is most commonly diagnosed in individuals between 18 and 40 years of age.[3] AIP is caused by an autosomal dominant mutation in the hydroxymethylbilane synthase (HMBS) gene, which encodes porphobilinogen deaminase (PBGD), an enzyme essential in the heme biosynthetic pathway. Deficiency in PBGD activity leads to the overproduction and toxic accumulation of upstream metabolites, including aminolevulinic acid (ALA) and porphobilinogen (PBG).[1,3,4]

The clinical presentation of AIP is often broad and nonspecific, making diagnosis challenging, especially given the disease's low prevalence. Common symptoms include intermittent severe abdominal pain, vomiting, constipation, hypertension, tachycardia, and various peripheral and central nervous system manifestations.[1,4,5] Acute exacerbations typically progress through three phases: the prodromal phase, the visceral symptom phase, and the neurological phase.[1] The prodromal phase may present nonspecific symptoms such as nausea, fatigue, dizziness, weakness, headache, and myalgia. During the visceral phase, patients experience severe abdominal pain, often accompanied by vomiting. The neurological phase is characterized by neuropsychiatric symptoms, ranging from peripheral neuropathy, anxiety, and depression to severe manifestations such as encephalopathy, seizures, or even paralysis. While symptoms are initially episodic and occur as acute flares, they may later evolve into a chronic disease course.[1,4]

When AIP is suspected, diagnostic evaluation includes measuring urine aminolevulinic acid and urine +/- serum porphobilinogen levels, which are elevated during acute attacks. Confirmation of the diagnosis is achieved through genetic testing, identifying mutations in the HMBS gene.[3,6]

Management of AIP focuses on reducing the production of ALA and PBG. This involves a combination of adequate caloric intake, heme therapy (e.g., hemin), and symptomatic management during an acute episode.[1,3,4] Intravenous administration of heme is the most effective treatment for acute attacks. Carbohydrate loading is an alternative approach in cases where heme is unavailable or for mild episodes.[4] Both methods work by down-regulating ALA synthase-1, leading to decreased production of porphyrin precursors and symptomatic improvement. Emerging therapies include givosiran, a synthetic small interfering RNA targeting ALA synthase-1. For definitive treatment in refractory cases, liver transplantation may be considered.[3,4]

CASE PRESENTATION

We present the case of a 39-year-old female with a five-year history of recurrent visits to the emergency department (ED) for abdominal pain. The pain was described as intermittent, colicky, and primarily localized to the epigastric region and left upper quadrant. Her episodes were occasionally accompanied by nausea, vomiting, headaches, and peripheral neuropathy characterized by pain, tingling, and numbness. The patient had a history of depression and anxiety managed with bupropion but reported no other significant medical or family history.

During previous ED visits, extensive workups revealed no acute pathology. These evaluations included abdominal and pelvic computed tomography (CT), pelvic ultrasound, complete blood count (CBC), basic metabolic panel (BMP), hepatic function panel, lipase levels, and urinalysis. In most instances, the patient was discharged with instructions for outpatient follow-up with her primary care physician or admitted for symptomatic management until improvement.

One year prior to this visit, the patient was diagnosed with acute intermittent porphyria (AIP) after genetic testing revealed a heterozygous mutation in the PBGD gene, consistent with this diagnosis. Further evaluation with electromyography and nerve conduction studies confirmed sensorimotor polyneuropathy with demyelinating features, a common finding in patients with peripheral neuropathy associated with AIP.

Over the past year, the patient required frequent hospitalizations for AIP exacerbations. Treatment with Hemin (4mg/kg intravenously daily for four days) during these episodes led to significant symptom improvement. Prophylactic administration of Hemin every four weeks was recommended by her hematologist to prevent recurrence; however, she was unable to do adhere to this regimen due to a lack of health insurance coverage. In the last six months, the patient transitioned to givosiran (2.5mg/kg subcutaneous injections every four weeks) as an alternative. Before initiating givosiran, she experienced abdominal pain and associated symptoms approximately twice monthly. With givosiran treatment, these episodes have decreased to about once every two months. The patient has remained compliant with her home medications and continues regular outpatient follow-ups with her hematologist.

DISCUSSION

Abdominal pain is one of the most common chief complaints among patients presenting to the emergency department (ED).[7,8] In the United States, it accounts for more than 7 million ED visits annually.[7] Its variable clinical presentations and broad range of potential etiologies make it a diagnostic challenge. The primary goal in the ED is to identify and manage conditions that, if left untreated, could result in significant morbidity or mortality. For patients with recurrent or severe symptoms but negative workups, a thorough history focused on risk factors, triggers, and associated symptoms can help uncover subacute or chronic conditions. Recognizing patterns and subtle details enables ED clinicians to direct patients toward timely outpatient follow-up for further evaluation and management.

Acute intermittent porphyria (AIP) exemplifies a condition that requires high clinical suspicion due to its low prevalence and nonspecific symptoms. As demonstrated in our case, AIP should be considered in patients with recurrent, severe, colicky abdominal pain lasting several days, and with no acute findings on prior or current workups. Common triggers for AIP attacks include alcohol use, infections, caloric restriction, rapid weight loss, hormonal fluctuations, exogenous steroid hormones, and certain high-risk porphyrogenic drugs such as ketamine, erythromycin, nitrofurantoin, trimethoprim/sulfamethoxazole, risperidone, spironolactone, among others.[3] Our patient was on bupropion, a medication that studies suggest may increase the risk of porphyric attacks in individuals with AIP.[9]

The diagnostic workup for AIP begins with detecting elevated porphobilinogen (PBG) in urine, confirmed by quantitative measurement of PBG, aminolevulinic acid (ALA), and total porphyrins in the same sample. Normal urinary PBG levels are 0 to 4 mg/L, but during acute AIP attacks, they can rise to 50 and 200mg/L, with ALA levels increasing to 25-100 mg/L. A urinary PBG level of 0 to 4 mg/L during acute symptoms effectively excludes acute porphyria as the cause of symptoms. Additional laboratory findings in AIP may include hyponatremia, hypomagnesemia, mild aminotransferase elevations, and mild leukocytosis.

Management of AIP involves preventing attacks, treating acute episodes, and addressing long-term complications. The most critical preventive measure is avoiding known triggers, including porphyrogenic drugs. Patients can be referred to resources like the American Porphyria Foundation (APF), the Norwegian Porphyria Centre (NAPOS), or the Porphyria Drug Safety Finder for guidance on medication safety.[4,9]

Acute attacks are most effectively treated with intravenous heme, which replenishes the hepatic heme pool and downregulates ALAS1 transcription. This reduces the overproduction of ALA and PBG, alleviating symptoms.[3,4] The standard regimen involves administering 3-4 mg/kg/day for four days. For patients experiencing four or more attacks per year, prophylactic heme therapy is recommended at a dose of 3-4 mg/kg once or twice weekly via central venous catheter. Studies have shown that prophylactic heme therapy significantly reduces hospitalizations and ED visits, improving patient's quality of life.[3]

Carbohydrate loading is another therapeutic option, particularly for mild attacks or when heme is unavailable. This involves administering oral glucose or a high-carbohydrate diet. For patients unable to tolerate oral intake, intravenous dextrose (300-500g/day of 10% dextrose in 0.45% normal saline) may be used.[3,4]

Emergent treatments focus on molecular-level interventions. Givosiran, a small interfering RNA (siRNA) targeting hepatic ALAS1 expression, has been shown to rapidly reduce plasma and urinary ALA and PBG levels, decreasing frequency and severity of attacks. The recommended dose

is 2.5 mg/kg administered subcutaneously once monthly.[1,3,4]

Currently, the only definitive cure for AIP is orthotopic liver transplantation, which is reserved for patients with life-threatening acute attacks, recurrent attacks unresponsive to medical therapy, or severe quality-of-life impairment.[3,4]

Complications of AIP include hypertension, chronic kidney disease, chronic neurologic deficits, and increased risk of hepatocellular carcinoma. Close outpatient follow-up is essential for monitoring these conditions and mitigating long-term morbidity.

CONCLUSION

Maintaining a high clinical suspicion for acute intermittent porphyria (AIP) is crucial, particularly in patients with recurrent severe abdominal pain and unremarkable laboratory and imaging findings in the emergency department (ED). Delayed diagnosis can significantly impact patients, leading to prolonged acute episodes, progression to chronic symptoms, and increased risk of complications such as chronic kidney disease and hepatocellular carcinoma. Timely diagnosis allows for appropriate management, including avoiding triggers, initiating effective treatments such as heme therapy or givosiran, and ensuring regular follow-up to address potential complications and improve quality of life.

ETHICS APPROVAL

Consent was obtained or waived by all participants in this study. HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE) issued approval 2022-002.

COMPETING INTERESTS

The authors declare that they have no competing interests

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REFERENCES

1. Kizilaslan EZ, Ghadge NM, Martinez A, et al. Acute Intermittent Porphyria's Symptoms and Management: A Narrative Review. *Cureus*. 2023;15(3):e36058. doi:10.7759/cureus.36058

2. Spiritos Z et al. Acute Intermittent Porphyria: Current Perspectives And Case Presentation. *Therapeutics and clinical risk management*. 2019;15:1443-1451. doi:10.2147/TCRM.S180161

3. Gonzalez-Mosquera LF. Acute intermittent porphyria. StatPearls - NCBI Bookshelf. May 1, 2023. https://www.ncbi.nlm.nih.gov/books/NBK547665/#:~:text=Acute%20intermittent%20porphyria%20is%20a,acute%20attacks%20is%20intravenous%20heme

4. Zhao L, Wang X, Zhang X, et al. Therapeutic strategies for acute intermittent porphyria. *Intractable & rare diseases research*. 2020;9(4):205-216. doi:10.5582/irdr.2020.03089

5. Cerbino GN, Gerez EN, Varela LS, et al. Acute intermittent porphyria in Argentina: an update. *BioMed research international*. 2015;2015:946387. doi:10.1155/2015/946387

6. Neeleman RA, Wensink D, Wagenmakers MAEM, Mijnhout GS, Friesema ECH, Langendonk JG. Diagnostic and therapeutic strategies for porphyrias. *The Netherlands journal of medicine*. 2020;78(4):149-160.

7. Silverio L. Abdominal Pain. Society for Academic Emergency Medicine. September 2019. https://www.saem.org/about-saem/academies-interest-groups-affiliates2/cdem/for-students/online-education/m4-curriculum/group-m4-approach-to/approach-to-abdominal-pain

8. Soeno S et al. Initial assessment in emergency departments by chief complaint and respiratory rate. *Journal of General and Family Medicine*. 2021;22(4):202-208. doi:10.1002/jgf2.423

9. American Porphyria Foundation. Safe/Unsafe Drug Database. 2024. https://porphyriafoundation.org/for-healthcare-professionals/drug-safety/