ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

Time is of the Essence: Using Extended Hemin Treatment for a Case of Severe Acute Intermittent Porphyria

Smriti Rajita Kumar, MD, EdM[1], Diana Byrnes, MD[1], Mahmoud Mahfouz, MD[1], Joseph Rosenblatt, MD[2], and Cynthia Levy, MD[3]

[1]*Department of Medicine, University of Miami Miller School of Medicine, Miami, FL*
[2]*Department of Hematology and Oncology, University of Miami Miller School of Medicine, Miami, FL*
[3]*Division of Digestive Health and Liver Diseases, University of Miami Miller School of Medicine, Miami, FL*

ABSTRACT

Acute intermittent porphyria (AIP) is a disorder that affects heme synthesis, leading to accumulation of upstream precursors, and can cause an array of visceral and neurological symptoms. These can be severely debilitating and even fatal if not diagnosed and treated in a timely fashion. We outline a rare case of severe AIP masquerading as ascending polyneuropathy and how it was correctly diagnosed and treated with an extended course of hemin despite initial barriers to biochemical testing for AIP.

INTRODUCTION

Acute intermittent porphyria (AIP) is a genetic disorder, caused by porphobilinogen (PBG) deaminase deficiency, which affects 2 of 10,000 people.[1] AIP attacks occur primarily in female patients, aged 15–45 years, with abdominal pain as the most common symptom often accompanied with nausea, vomiting, and constipation. In addition, patients may demonstrate mild transaminase elevation.[2] Neurological manifestations of AIP usually follow the visceral symptoms, resulting from an increased production of harmful porphyrin precursors, δ-aminolevulinic acid (ALA), and PBG, which are released from the liver.[1] These neurological symptoms classically start with motor neuropathy and can progress to respiratory distress, seizures, weakness, encephalopathy, and autonomic dysfunction.

Although gene mutation testing is the gold standard for diagnosis of the specific acute hepatic porphyrias, it is not recommended as first-line testing because of low penetrance. It is the elevation of urinary ALA and PBG during an attack that implicates acute hepatic porphyrias as the cause of acute symptoms.[3] Timely access to hemin therapy is critical for survival in patients especially with severe presentations of AIP.[1] We summarize a case of severe AIP with neurovisceral manifestations initially misdiagnosed as Guillain-Barre syndrome (GBS) and describe successful extension of hemin therapy for optimal response.

CASE REPORT

A 21-year-old woman presented to a hospital in Ecuador 11 days after right ovarian cyst removal with abdominal pain, intermittent diarrhea, and constipation. One day before admission, she experienced tonic-clonic seizures with associated loss of consciousness and cyanosis that spontaneously resolved.

On admission, she reported moderate hypogastric pain alleviated with oxycodone and accompanied with generalized weakness, decreased appetite, and intermittent vomiting. She revealed that she had initiated oral contraceptives 2 weeks earlier. Vitals were notable for mild tachypnea. Physical examination was remarkable for disorientation, diffuse abdominal tenderness and subcutaneous emphysema, positive retroperitoneal signs, and 3 of 5 bilateral upper and lower extremity strength. Magnetic resonance imaging of the brain suggested posterior reversible encephalopathy syndrome. Laboratory test results revealed mild leukopenia and iron deficiency anemia, with mild hyponatremia, which rapidly improved. Computed tomography imaging showed a double collecting system with pneumoperitoneum and

ACG Case Rep J 2022;9:e00827. doi:10.14309/crj.0000000000000827. Published online: July 11, 2022

Correspondence: Cynthia Levy, MD (clevy@med.miami.edu).

subcutaneous emphysema consistent with an acute abdomen. This was believed to be a complication from prior ovarian cyst resection. One day later, she underwent ex-laparotomy with lysis of adhesions, but with no evidence of abscess/collections.

She was started on anticonvulsants. Electroencephalogram was indeterminate, and electromyogram revealed symmetric distal polyneuropathy. Nine days after admission, intravenous immune globulin was initiated because of concern of GBS because she experienced worsening ascending polyneuropathy.

Without improvement on intravenous immune globulin, her symptoms raised concern for porphyria. Diagnosis was limited because porphyria biochemical testing is not available in Ecuador. She progressed with respiratory failure, was subsequently intubated, and was then airlifted to our facility.

Initial laboratory tests at our hospital were notable for hyponatremia and mild transaminase elevation. Liver ultrasound showed normal morphology and patent vasculature. Owing to suspicion for AHP, hemin infusions 5 mg/kg daily were initiated while laboratory tests were pending. Cerebrospinal fluid analysis was unrevealing. Repeat electromyogram demonstrated porphyric neuropathy. Later, urine studies unveiled an elevated total urine porphyrin of 25.6 (normal 1.0–5.6) μg/L, urine PBG level of 184.92 (normal <0.22) mg/gCre/12 h, and urine D-ALA of 105.1 (normal <5.4) mg/gCre/12 h consistent with AHP, later confirmed by a genetic test, which showed a pathogenic variant in the hydroxymethylbilane synthase gene (c.874C>T (p.Gln292*)). Moreover, infectious, autoimmune, and metabolic workup for liver disease was negative.

Neurological symptoms improved mildly after 5 days of hemin infusion, and the decision was made to extend daily hemin infusions for 14 days. Urine D-ALA and PBG levels continued to trend down over a 14-day period suggesting response to treatment. Over the hospital course, she had slow improvement in extremity strength, was extubated, and was eventually transferred to acute rehabilitation with weekly prophylactic hemin infusions.

The patient continues to receive weekly hemin with improvement in pain and is now able to stand from sitting and walk short distances without assistance. However, she still requires opioids. In efforts to wean her off weekly hemin infusions, reduce the chance of breakthrough attacks, and minimize long-term side effects including iron overload, she was recently started on treatment with RNA interference therapy givosiran, administered subcutaneously once monthly. Effects of this are too soon to be noted.

DISCUSSION

We describe a patient with AIP with delayed diagnosis due to initial concern for GBS. Possible precipitating factors in this case include the use of oral contraceptives, course of anticonvulsants in Ecuador, or surgical stress from ovarian cyst removal. Although few cases of AIP masquerading as GBS have been previously described, many reported fatal outcomes due to diagnosis and hemin administration delay.[4–6]

Fortunately, despite delay, this patient received adequate tailored treatment. Although basic, relatively uniform guidelines for hemin administration exist across the gastrointestinal, hematologic, and liver societies, the recommendations universally fail to address treatment regimens for patients with severe presentation and minimal clinical improvement within the first 4 days of treatment. ALA and PBG results were not available for several days. Delay in laboratory test results compounded with lack of clinical improvement places clinicians in a difficult position to determine effectiveness of hemin infusions.

Many factors may lead to a dampened response to hemin such as delayed initiation of therapy, low dosing <3 mg/kg/d, or chronic irreversible neurologic damage.[7] Efficacious prolonged hemin therapy has been previously described in a patient with AIP flares from repeated lung infections.[8] Currently, no guidelines exist for prolonged hemin use and length of therapy beyond the acute attack.

The latest therapy developed for AIP is givosiran, an RNA interference therapeutic agent targeting hepatic ALA synthetase 1 mRNA, preventing the accumulation of ALA and PBG. In a phase 3 trial, monthly givosiran resulted in a 74% lower annualized rate of composite porphyria attacks with sustained reductions in ALA and PBG levels.[9] In the present time, givosiran is approved only to prevent recurrent attacks. As such, it was initiated for our patient once she recovered from the acute attack.

In conclusion, extended hemin treatments may be beneficial and should be considered by clinicians for patients with AIP refractory to the current guidelines on hemin therapy. Availability of a rapid PBG test could be lifesaving.

DISCLOSURES

Author contributions: All the authors have equal contribution in taking care of the patient and writing and editing the manuscript. Cynthia Levy, MD is the guarantor of the article.

Financial disclosure: None to report.

We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere.

This case was presented as a poster presentation at the annual ACG Conference; 2021; Las Vegas, Nevada.

Received November 13, 2021; Accepted June 6, 2022

REFERENCES

1. Pischik E, Kauppinen R. An update of clinical management of acute intermittent porphyria. *Appl Clin Genet.* 2015;8:201–14.
2. Bissell DM, Wang B. Acute hepatic porphyria. *J Clin Transl Hepatol.* 2015; 3(1):17–26.

3. Wang B. The acute hepatic porphyrias. *Transl Gastroenterol Hepatol.* 2021; 6:24.
4. Mutluay B, Koksal A, Celik RGG, Bulbul HH. A case of acute intermittent porphyria mimicking guillain-barre syndrome. *Noro Psikiyatr Ars.* 2019; 56(4):311–2.
5. Park EY, Kim YS, Lim KJ, et al. Severe neurologic manifestations in acute intermittent porphyria developed after spine surgery under general anesthesia: A case report. *Korean J Anesthesiol.* 2014;67(3): 217–20.
6. Ferreira FR, Silva CA, Costa SX. Acute intermittent porphyria, an important and rare differential diagnosis of acute abdomen: Case report and literature review. *Rev Bras Ter Intensiva.* 2011;23(4):510–4.
7. Stolzel U, Doss MO, Schuppan D. Clinical guide and update on porphyrias. *Gastroenterology.* 2019;157(2):365–81.e4.
8. Cuquemelle E, Ehrmann S, Razazi K, Deybach JC, Brun-Buisson C, Thille AW. An atypical case of guillain-barre syndrome: Acute intermittent porphyria. *Intensive Care Med.* 2012;38(5):913–4.
9. Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. *N Engl J Med.* 2020;382(24):2289–301.