Fernando Rogério Lara Ferreira[1,2],
Carlos Augusto de Almeida Silva[2],
Samantha Xena da Costa[2]

# Acute intermittent porphyria, an important and rare differential diagnosis of acute abdomen: case report and literature review

*Porfiria aguda intermitente, um importante e raro diagnóstico diferencial de abdômen agudo: relato de caso e revisão da literatura*

1. Fundação Hospital Adriano Jorge, Manaus (AM), Brazil.
2. Universidade do Estado do Amazonas - UEM - Manaus (AM), Brazil.

This study was conducted at Fundação Hospital Adriano Jorge – Manaus (AM), Brazil.

Submitted on September 25, 2011
Accepted on December 14, 2011

**Conflicts of interest:** None.

**Corresponding author:**
Carlos Augusto de Almeida Silva
Rua Canamari, 15 - Bairro Cidade Nova 1
Zip Code: 69095-130 - Manaus (AM), Brazil.
E-mail: caas.med@live.com

**ABSTRACT**

Porphyrias are metabolic disorders related to heme biosynthesis pathway enzyme dysfunctions. The heme pathway is fundamental for the formation of a number of molecules, and such defects cause noxious precursors (porphyrins) to build up. Porphyrias are heterogeneously manifested by symptoms that can either be neurovisceral, cutaneous, or both, usually during outburst episodes called porphyric crises. This article presents a literature review and reports on a case of porphyric crisis initially diagnosed as acute abdomen and treated with an inconclusive exploratory laparotomy During the postoperative period, the patient progressed with tetraparesis, tetraplegia and respiratory distress, suggesting Guillain-Barre syndrome, which was precluded after cerebrospinal fluid analysis revealed no albumin-cytological dissociation. The patient was admitted to the intensive care unit due to her neurological disorders, which required ventilation support. After admission, she progressed with choluria and seizures. A porphyric crisis was suspected and confirmed upon a 24 hour urine porphyrins test. Supportive therapy was initiated, but due to unavailability in our hospital, heme derivatives were not given. The patient progressed with nosocomial infection, organ dysfunctions and eventually died. Porphyria should be considered as a differential diagnosis in acute abdomen cases of unknown origin and associated with neurological disorders such as paresis, hydroelectrolytic and psychiatric disorders, especially in patients with triggering factors, with a history of recurring crises and a family history of porphyria.

**Keywords:** Porphyria; Liver porphyria; Intermittent acute porphyria; Acute abdomen; Differential diagnosis; Case reports

## INTRODUCTION

Porphyrias are metabolic disorders related to heme biosynthesis pathway enzyme dysfunction and the accumulation of precursors (porphyrins). The clinical manifestations of porphyrias may include neurovisceral symptoms, cutaneous symptoms, or both, and diagnosis is most frequently exclusionary during acute porphyric episodes. Intermittent acute porphyria is the most common type of porphyria and is frequently identified during porphyric crises. The usual clinical presentation is an abdominal pain of unknown origin associated with neurological signs and symptoms, psychiatric and hydroelectrolytic disorders in women > 30 years old with a history of recurrent crises in association with predisposing factors and a family history of porphyria.[1-5]

This article reports on a case of porphyric crisis that had a differential diagnosis of acute abdomen and Guillain-Barre syndrome. In addition, a narrative review is

presented based on data researched on the PubMed, Biomed, ScienceDirect and Scielo databases covering the period from 2000 to 2011 and using the key words porphyria, liver porphyria and acute intermittent porphyria (including both the English and Portuguese languages). Other articles that were not found in these databases were included according to indications from an expert.

## CASE REPORT

A 31-year-old female who lived in Manaus-AM, Brazil was admitted to the emergency room with diffused and severe abdominal pain in association with nausea, vomiting and unmeasured fever. Her physical examinations revealed tachycardia (118 bpm), hypertension (158/100 mmHg) and Blumberg's sign. Complementary tests uncovered intestinal loop distension on abdominal radiography, normochromic and normocytic anemia in association with leukocytosis and hyponatremia.

With a hypothesis of acute abdomen, the patient underwent an exploratory laparotomy, which failed to detect any abdominal organ changes. The patient remained hospitalized for six days and was discharged to home with improved signs and symptoms. Two days later, she returned to the emergency department with worsening of the initial signs and symptoms and reporting parenthesis of her extremities. She was readmitted to the hospital and, within seven days, progressed with choluria, tetraparesis followed by tetraplegia and respiratory distress, requiring admission to the intensive care unit (ICU) and respiratory support. Additional tests results were similar to the first hospitalization, a head computed tomography demonstrated no changes, and cerebrospinal fluid analysis revealed no albumin-cytological dissociation, precluding the hypothesis of Guillain-Barre syndrome.

During her ICU stay, the patient had seizures, and a porphyric crisis was suspected. This diagnosis was confirmed upon a 24 hour urine delta-aminolevulinic acid and porphobilinogen dosage test. Overall porphyric crisis support was provided, except for the use of heme derivatives (unavailable in our hospital). The patient progressed with nosocomial infection unresponsive to therapy, multiple organ dysfunction and eventually died 23 days after her admission to the ICU.

## DISCUSSION

Porphyrins are metabolic heme precursors and are metabolized by the heme biosynthesis pathway, which is found in all mitochondrial cells (particularly erythropoietic and liver cells). This pathway provides the heme required to form several relevant molecules (e.g., hemoglobin, myoglobin and cytochrome).[1,2]

Porphyrias are metabolic disorders related to the dysfunction of one of the eight enzymes that are part of the heme biosynthesis pathway. The clinical manifestations of porphyrias are characterized by neurovisceral symptoms, cutaneous symptoms, or both. The clinical features are not dependent of the reduced synthesis of heme but instead on the type of accumulated porphyrin, the site where it is produced (liver or bone marrow) and accumulates, the way it is excreted and the toxicity mechanism (neurotoxicity, photosensitivity or both).[1-5]

There are eight types of porphyria, which are related to each specific enzyme. The disease is categorized according to the site of enzyme inactivity (erythropoietic or hepatic) and to its presentation (either acute or chronic) (Table 1). Acute hepatic porphyrias are characterized by neurovisceral attacks and, in specific cases, by cutaneous manifestations. Acute intermittent porphyria is the most common form of porphyria.[4-8]

**Table 1 - Categories of porphyrias**

| | | |
|---|---|---|
| Chronic porphyrias | Erythropoietic porphyrias | Congenital erythropoietic porphyria<br>Erythropoietic protoporphyria |
| | Chronic hepatic porphyrias | Late cutaneous porphyria<br>Hepatoerythropoietic porphyria |
| Acute porphyrias | Acute hepatic porphyrias | ALA dehydratase deficiency porphyria<br>Acute intermittent porphyria<br>Hereditary coproporphyria<br>Variegate porphyria |

Source: Dinardo CL, Fonseca GH, Suganuma LM, Gualandro SFM, Chamone DA. Porfirias: quadro clínico, diagnóstico e tratamento. Rev Med (São Paulo). 2010;89(2):106-14.[2]

## EPIDEMIOLOGY

Acute intermittent porphyria has a prevalence of 1-2 cases per 100 thousand inhabitants. However, this estimation should take into consideration some limitations, such as geographic aspects, undiagnosed cases and incomplete penetrance. Approximately 80% of the patients remain asymptomatic. Further, the disease rarely manifests before puberty and is commonly observed in women > 30 years old in connection with conditions predisposing to reduced enzyme activity (Table 2). When these conditions are not resolved or controlled, porphyric crises become recurrent.[8-10]

**Table 2 - Porphyric crisis triggering factors**

| Triggering factors |
|---|
| Drugs |
| Fasting |
| Smoking |
| Alcoholism |
| Illicit drugs (e.g., marijuana, ecstasy, amphetamines and cocaine) |
| Infections |
| Physical and emotional stress |
| Menstrual periods |

Source: Thadani H, Deacon A, Peters T. Diagnosis and management of porphyria. BMJ. 2000;320(7250):1647-51.[5]

## PHYSIOPATHOLOGY

Acute intermittent porphyria is an autosomal dominant disease that is related to an 11q24.1 - 11q24.2 gene mutation, leading to reduced porphobilinogen deaminase enzyme activity, which is the third heme biosynthesis pathway enzyme. Carriers of this mutation remain asymptomatic until a critical enzyme activity boundary, which is usually 50% activity, is reached. Below this point, porphyric crisis manifestations are observed.[8-10]

A porphobilinogen deaminase defect causes porphyrins (delta aminolevulinic acid and porphobilinogen) to accumulate, while intracellular heme levels are reduced. This imbalance leads to a loss of heme negative feedback for the entire enzyme pathway, increasing the production of porphyrins and leading to tissue accumulation and increased excretion (Figure 1). The symptoms are not correlated with reduced heme production, as even low production levels are sufficient to maintain homeostasis. Instead, the symptoms are correlated with the increased porphyrin concentrations.[10-13]

Porphyrins are toxic, and their effects on tissues are not fully understood. In cases presenting with predominantly neurovisceral symptoms, as in acute porphyria and especially in acute intermittent porphyria, excess porphyrins are neurotoxic and lead to degenerative disorders of the central nervous system and the inhibition of GABA release. In cases with cutaneous manifestations, porphyrins accumulate in the skin and, under light stimulation, increase the local production of free radicals, which damage the skin.[12,13]

## CLINICAL PRESENTATION

The clinical manifestations of acute intermittent porphyria crises involve a number of neurovisceral symptoms, as well as hydroelectrolytic and psychiatric disorders (Table 3).

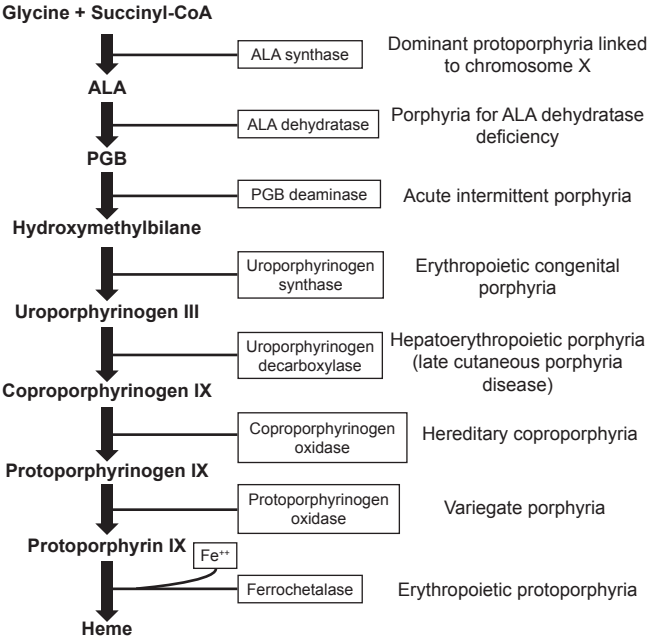


**Figure 1 - Illustrative flowchart of the heme biosynthesis pathway and the relationship between enzyme defects and specific types of porphyria.**

ALA - delta-aminolevulinic acid; PBG - porphobilinogen; $Fe^{++}$ - ionic iron.

Source: Adapted from: Puy H, Gouya L, Deybach JC. Porphyrias. Lancet. 2010;375(9718):924-37. Review.[9]

**Table 3 - Symptom frequency in porphyric crises**

| Porphyric crises most frequent presentation | (%) |
|---|---|
| Female | 60 – 80 |
| Neurovisceral symptoms | |
| Abdominal pain | 85 – 95 |
| Nausea and vomiting | 43 – 88 |
| Obstipation | 48 – 84 |
| Tachycardia | 64 – 85 |
| Arterial hypertension | 36 – 55 |
| Neurological symptoms | |
| Pain in extremities, back, chest and head | 50 – 70 |
| Paresis | 42 – 68 |
| Respiratory palsy | 9 – 20 |
| Neuropsychiatric disorders | |
| Agitation, confusion, hallucinations and depression | 40 – 58 |
| Seizures | 10 – 20 |

Source: Bloomer JR, McGuire BM. Intermittent unexplained abdominal pain: is it porphyria? Clin Gastroenterol Hepatol. 2007;5(11):1255-8.[11]

Neurovisceral symptoms affect the peripheral, central, autonomic and visceral nervous systems. Severe diffused abdominal pain is present in 90% of the cases. Pain in

the extremities, chest and back are also reported. Other neurovisceral symptoms include predominantly motor neuropathy with muscle weakness, which is initially proximal and may progress to tetraplegia and respiratory and bulbar palsy within hours or days, resembling the Guillain-Barre syndrome. The psychiatric changes are insomnia, agitation, confusion and seizures, which may progress to coma. Hyponatremia resulting from the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is the most frequent hydroelectrolytic disorder.[1,5,11-13]

## DIAGNOSIS

Acute intermittent porphyria diagnosis during an episode of porphyric crisis requires a high degree of suspicion in a patient with abdominal pain in whom a possible acute abdomen was precluded and in the presence of other signs such as proximal and symmetric upper limb muscle weakness, paresis, hydroelectrolytic and psychiatric disorders, tachycardia and choluria. Other relevant factors include a history of previous episodes of porphyric crises, a family history suggesting porphyria and the presence of possible triggering factors (e.g., drugs, alcohol, and premenstrual symptoms).[2,3,9,11-13]

The gold standard for porphyria diagnosis is DNA analysis. However, in addition to its considerable costs, this test is not applicable for acute porphyric crises. Indeed, DNA analysis is more suitable for appropriately detecting the exact type of porphyria during remission periods and, additionally, for family screening. The most important test for the diagnosis of porphyric crises is measuring urinary porphobilinogen levels, which are usually increased during crises. Other alternatives for porphyric crises diagnosis are testing urinary delta-aminolevulinic acid and porphyrins, plasma and stool porphyrins and erythrocytic porphobilinogen deaminase levels.[1-3,8,9,11-13]

## TREATMENT

The treatment is based on four aspects: family screening, removal or management of triggering factors, overall supportive measures and the use of heme derivatives.[1,2,11,12]

All first-degree relatives should be tested for the disease; DNA analysis is the most applicable test. The risk of hepatocellular carcinoma is another relevant screening issue for which imagery liver tests are suggested for patients > 50 years old.[1,3,11-13]

Triggering factors (Table 2) should be prevented or managed. Lists with safe and unsafe medicines are useful. The patients should also be advised to either control or suppress drinking alcohol and smoking, as well as to avoid the use of illicit drugs. Female patients should be advised respecting hormone therapy and menstrual periods.[1,2,11-13]

Overall supportive measures during crises are limited to removal of triggering factors, symptom management using safe drugs and a hyper-caloric diet based on carbohydrates. Admission to the ICU or to reference centers is advised because peripheral neuropathy may quickly progress to respiratory failure and bulbar involvement (Table 4). Heme derivatives act by reactivating the negative heme feedback to the ALA synthase enzyme, reducing toxic precursor production. Heme derivatives should be used early, especially in severe porphyric crises' patients with bulbar palsy or other progressive neuropathies.[1,2,11-13]

**Table 4 - Therapeutic schedule for porphyric crises.**

| Therapeutic strategy according to the porphyric crisis features | |
|---|---|
| Neurovisceral symptoms | Conventional therapy |
| | Triggering factor(s) identification and removal |
| | Appropriate pain management with opiates |
| | Emesis control (e.g., chlorpromazine) |
| | Hydroelectrolytic disorder and fluid balance management |
| | Psychiatric disorder and seizure management (e.g., gabapentin) |
| | Hyper-caloric diet; 300 g carbohydrates/day |
| | Admission to intensive care units or porphyria units |
| | Specific therapy |
| | Hematine or heme arginate: 3-4 mg/kg/day, once daily for 4 days. |
| Cutaneous symptoms | Prevent sunlight exposure and trauma |
| | Photo-protection |

Source: Siegesmund M, van Tuyll van Serooskerken AM, Poblete-Gutiérrez P, Frank J. The acute hepatic porphyrias: current status and future challenges. Best Pract Res Clin Gastroenterol. 2010;24(5):593-605.[1]

## CONCLUSIONS

Acute intermittent porphyria is a genetic disease with heterogeneous manifestations and should be considered as a differential diagnosis in cases of acute abdomen of unknown origin and associated with neurological disorders (e.g., paresis and hydroelectrolytic and psychiatric disorders), especially in patients with triggering factors, a history of recurring crises and a family history of porphyria.


## RESUMO

As porfirias são distúrbios metabólicos relacionados à disfunção enzimática da cadeia de biossíntese do heme, componente fundamental para formação de diversas moléculas. Tal defeito ocasiona um acúmulo de precursores (porfirinas) nocivos ao organismo. As porfirias se manifestam de maneira heterogênea através de sintomas neuroviscerais, cutâneos ou ambos, geralmente durante episódio de agudização denominado crise porfírica após a exposição a algum fator precipitante. No presente artigo é relatado caso de crise porfírica inicialmente diagnosticado como abdômen agudo e tratado com laparotomia exploradora inconclusiva, seguido de revisão de literatura. Durante o pós operatório o quadro evoluiu com sinais neurológicos de tetraparesia, tetraplegia e desconforto respiratório que sugeriam o diagnóstico de síndrome de Guillain-Barré, hipótese afastada após análise do líquor que não mostrou dissociação albumino-citológica. Admitida em unidade de terapia intensiva, dado o quadro neurológico e a necessidade de suporte ventilatório, apresentou colúria e crises convulsivas sendo feita a hipótese de crise porfírica, confirmada com a dosagem de porfirinas na urina de 24 horas. Iniciado o tratamento de suporte, porém, sem o uso de derivados do heme devido a indisponibilidade, a paciente evoluiu com infecção hospitalar, disfunção orgânica e óbito. A porfiria deve ser levada em consideração nos casos agudos de dor abdominal de causa desconhecida, associada a sinais neurológicos como paresias, distúrbios hidroeletrolíticos e psiquiátricos, especialmente em pacientes com presença de fatores precipitantes, história de crises recorrentes e história familiar positiva para porfiria.


**Descritores:** Porfirias; Porfirias hepáticas; Porfiria aguda intermitente; Abdômen agudo; Diagnóstico diferencial; Relatos de casos

## REFERENCES


1. Siegesmund M, van Tuyll van Serooskerken AM, Poblete-Gutiérrez P, Frank J. The acute hepatic porphyrias: current status and future challenges. Best Pract Res Clin Gastroenterol. 2010;24(5):593-605.
2. Dinardo CL, Fonseca GH, Suganuma LM, Gualandro SFM, Chamone DA. Porfirias: quadro clínico, diagnóstico e tratamento. Rev Med (São Paulo). 2010;89(2):106-14.
3. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet. 2010;375(9718):924-37. Review.
4. Jorge SG. Porfirias hepáticas [Internet]. Hepcentro 2007 [citado 2011 out 1]. Disponível em: http://www.hepcentro.com.br/porfiria.htm
5. Thadani H, Deacon A, Peters T. Diagnosis and management of porphyria. BMJ. 2000;320(7250):1647-51.
6. Gásquez Sisteré I, Luján Mavila K, Chordá Ribelles J, Touzón López C. La porfiria aguda intermitente, un problema diagnóstico. Gastroenterol Hepatol. 2010;33(6):436-9.
7. Asselbergs FW, Kremer Hovinga TK, Bouwsma C, van Ingen J. Acute intermittent porphyria as a cause of respiratory failure: case report. Am J Crit Care. 2009;18(2):180, 178-9.
8. Lopes DA, Valle MA, Taguti J, Taguti RCTC, Betônico GN, Medeiros FC. Porfiria aguda intermitente: relato de caso e revisão da literatura. Rev Bras Ter Intensiva. 2008;20(4):429-34.
9. Puy H, Deybach JC, Lamoril J, Robreau AM, Da Silva V, Gouya L, et al. Molecular epidemiology and diagnosis of PBG deaminase gene defects in acute intermittent porphyria. Am J Hum Genet. 1997;60(6):1373-83.
10. Shah MA, Remoroza R, Aziz K. Acute intermittent porphyria. Hosp Physician. 2002;38(2):67-71.
11. Bloomer JR, McGuire BM. Intermittent unexplained abdominal pain: is it porphyria? Clin Gastroenterol Hepatol. 2007;5(11):1255-8.
12. Herrick AL, McColl KE. Acute intermittent porphyria. Best Pract Res Clin Gastroenterol. 2005;19(2):235-49. Review.
13. Pimstone NR, Anderson KE, Freilich BL. Acute porphyrias: emergency room recommendations [Internet]. Houston (TX): American Porphyria Foundation; 2008. [cited 2011 Aug 24]. Available from: http://www.porphyriafoundation.com/themes/apf_one/ERGuidelinesAcutePorphyria.pdf