

# A Forgotten Cause of Recurrent Abdominal Pain: Case Report

Carlos Mauricio Martínez-Montalvo,<sup>1\*</sup> David José Ramírez-Daza,<sup>2</sup> Laura Catalina Gutiérrez-Rueda,<sup>3</sup> David Felipe Olarte-Parra,<sup>4</sup> Laura Otálora-González.<sup>4</sup>

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<sup>1</sup> Internist, Universidad del Rosario. Gastroenterology Fellow, Universidad Nacional de Colombia. Bogotá, Colombia. General Practitioner, Hospital San Juan de Dios. Ituango, Antioquia, Colombia.

<sup>2</sup> Internist, Universidad del Rosario. Fundación Cardioinfantil, La Cardiol. Bogotá, Colombia.

<sup>3</sup> Internist, Universidad del Rosario, Hospital Universitario Mayor Méderi. Bogotá, Colombia.

<sup>4</sup> Medical Student, Universidad del Rosario. Bogotá, Colombia.

\*Correspondence: Carlos Mauricio Martínez-Montalvo. [carlitos220792@gmail.com](mailto:carlitos220792@gmail.com)

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## Abstract

**Introduction:** Porphyrrias are enzymatic disorders of heme synthesis. Acute hepatic porphyrias (AHP) presents with acute neurovisceral symptoms such as abdominal pain, nausea, vomiting, constipation, muscle weakness, neuropathy, tachycardia, and hypertension. 5-aminolevulinic acid dehydratase (ALAD) deficiency is a rare autosomal recessive disorder that results in little or no elevation of porphobilinogen but elevates urinary 5-aminolevulinic acid and coproporphyrin III. There are no records of this type of porphyria in Colombia. Acute management requires comprehensive care, ranging from hemotherapy to liver transplantation. **Case Presentation:** A 24-year-old man with no prior medical history presented with a recurrent and acute episode of abdominal pain associated with changes in urine color, skin lesions, diarrhea, and dysregulation of body temperature. Initial paraclinical workup ruled out common causes of recurrent abdominal pain, with a negative porphobilinogen test, but further testing revealed elevated 5-aminolevulinic acid, confirming the diagnosis of ALAD porphyria. The patient showed improvement with hemotherapy and remission of acute kidney injury. A possible distractor associated with interstitial nephritis and skin manifestations related to nonsteroidal anti-inflammatory drug (NSAID) use was documented. **Conclusions:** ALAD porphyria and all acute hepatic porphyrias should be considered in any patient presenting with unexplained recurrent severe abdominal pain and neuropathy. Despite their relative rarity and complexity, most porphyrias can be easily defined and diagnosed. A common cause of diagnostic delay is the failure to consider porphyria in the differential diagnosis on time. There is still much to learn about ALAD porphyria.

## Keywords

Hepatic porphyria, hemin, abdominal pain.

## INTRODUCTION

Porphyrias are disorders of heme synthesis involving either inherited or acquired enzyme deficiencies, resulting in an overproduction of heme precursors<sup>(1,2)</sup>. Heme is an essential molecule that performs a wide range of functions necessary for aerobic life as a cofactor in hemoproteins<sup>(3,4)</sup>.

Porphyrias are classified into acute hepatic porphyrias (AHP) and photosensitive porphyrias. AHPs result from hepatic overproduction of porphyrin precursors, aminolevulinic acid (ALA), and porphobilinogen (PBG), and include

acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and 5-aminolevulinic acid dehydratase deficiency porphyria (ALAD-P). Clinical manifestations are characterized by acute neurovisceral symptoms, such as abdominal pain, nausea, vomiting, constipation, muscle weakness, neuropathy, tachycardia, and hypertension<sup>(5)</sup>. Symptomatic AHPs affect approximately 1 in 100,000 patients; however, it is estimated that there is a diagnostic delay of more than 15 years from initial presentation<sup>(5)</sup>.

ALAD deficiency is a rare autosomal recessive disorder (with only eight documented cases worldwide) in which

enzyme activity is less than 3% of normal<sup>(6,7)</sup>, resulting in little or no elevation of PBG but marked increases in urinary ALA and coproporphyrin III<sup>(7)</sup>. No cases of this type of porphyria have been documented in Colombia.

The initial approach for an acute porphyria episode is a multidisciplinary management strategy ranging from hospitalization to intensive care, depending on the severity of presentation. Key management principles include avoidance of triggering factors, caloric supplementation, and often hematotherapy<sup>(5,8)</sup>, with liver transplantation as a last resort<sup>(8)</sup>. Long-term complications include liver disease (cirrhosis and hepatocellular carcinoma), hypertension, and chronic kidney disease.

This case report presents a clinical phenotype of ALAD deficiency porphyria with a history of urine discoloration and recurrent abdominal pain. The initial diagnostic approach was diverted due to a suspected diagnosis of paroxysmal nocturnal hemoglobinuria, further complicated by cutaneous manifestations and interstitial nephritis likely associated with the patient's intake of nonsteroidal anti-inflammatory drugs (NSAIDs) for symptom management. Mutation confirmation was not possible due to discontinuation of follow-up by the patient, but this case contributes to the literature by providing an approach to diagnostic testing and a review of relevant studies.

## CASE DESCRIPTION

This case involves a 24-year-old male with no significant medical, toxicological, family, or perinatal history. He presented with a four-day clinical course characterized by severe epigastric and bilateral lumbar pain, described as stabbing and rated 10/10 on the visual analog scale (VAS). These symptoms were associated with changes in urine color (**Figure 1**), pruritic skin lesions, loose stools, emesis episodes, and a documented fever of 38.7°C.

Initial evaluation recorded normal vital signs, diffuse abdominal tenderness on palpation without masses, organomegaly, or peritoneal irritation. Erythematous-edematous pruritic plaques with central pallor were observed, primarily affecting the upper limbs and trunk (**Figure 2**).

Initial laboratory findings showed elevated nitrogenous waste, consistent with acute kidney injury (AKI) classified as KDIGO stage III, a slight increase in lactate dehydrogenase (**Table 1**), and a diffuse increase in liver echogenicity on abdominal ultrasound.

Subsequently, during a follow-up interview, the patient reported outpatient management for recurrent abdominal pain occurring every three months, for which he had self-medicated with N-butylscopolamine bromide and diclofenac without clinical improvement. His recent diclof-

enac use had increased over the past four days, with an approximate daily dose of 300-400 mg. Outpatient studies included abdominal imaging, which showed no abnormalities, normal PBG levels, a negative autoimmune profile, and negative infectious disease testing, including for human immunodeficiency virus (HIV), hepatotropic viruses, and rapid plasma reagin (RPR). Additionally, electrophoresis and immunofixation were negative, although flow cytometry detected paroxysmal nocturnal hemoglobinuria (PNH) clones in monocytes (12.9%), granulocytes (12.5%), and erythroid cells (1.2%). Given the abdominal pain, acute kidney injury (AKI), and urine discoloration, an episode of PNH with secondary abdominal-renal thrombotic events was initially considered as a diagnostic impression. However, this was ruled out due to the low clinical significance of the small PNH clone populations and the absence of a clinical phenotype consistent with PNH.



**Figure 1.** Urine discoloration observed in the patient. Source: Author's File.

Due to persistent renal impairment without indications for urgent dialysis, but with reduced urine density and polyuria, a renal biopsy was performed. Histopathology revealed tubulointerstitial nephritis without glomerular involvement or chronic changes. The patient experienced a stationary clinical course with persistent symptoms of limiting visceral pain, associated with somnolence and neuropathy manifesting as dysesthesias in the extremities and tongue. Given the intermittent and temporally related nature of symptoms, as well as a reported association with physical and emotional stress and alcohol intake, additional



**Figure 2.** Pruritic skin lesions presenting as erythematous-edematous plaques with central pallor, predominantly on the upper limbs and trunk. Source: Author's File.

inpatient studies were conducted. The reports showed elevated urinary ALAD levels, normal porphobilinogen, and elevated 24-hour urinary porphyrins. This clinical presentation was considered compatible with a probable phenotype of ALAD porphyria, leading to treatment initiation with dextrose solution and subsequent administration of human hemin at 4 mg/kg/day (260 mg) via infusion for three days. Improvement was observed in both the reported symptoms and follow-up laboratory values, including a gradual reduction in nitrogenous waste.

The skin manifestations were interpreted as likely related to NSAID-induced skin toxicity or a gastrointestinal infectious agent, and were treated with ampicillin-sulbactam for five days. However, due to spontaneous resolution within 24 hours of admission, a skin biopsy was not pursued. The patient did not continue follow-up, and due to administrative constraints, the mutation panel needed to confirm the type of porphyria could not be completed. Consequently, the case was managed as a probable ALAD porphyria phenotype with initial diagnostic distractions, no PNH phenotype, and complications from NSAID overuse.

## DISCUSSION

Acute hepatic porphyrias (AHP) are rare, with estimated prevalence rates of five per 100,000 people<sup>(3)</sup>. Among these,

ALAD deficiency is the rarest form, with only eight cases documented in the literature, and is the least understood type of porphyria<sup>(8)</sup>, with no cases reported in Colombia. The ALAD gene is located on chromosome 9q34 and catalyzes the condensation of two ALA molecules to form PBG<sup>(8)</sup>. Its mutation, an autosomal recessive disorder, results in enzyme activity of less than 10%. All individuals affected by this mutation experience severe disease onset early in life<sup>(3)</sup>, with all reported cases being male, as is true for this patient, who has had intermittent symptoms since the age of 13.

Clinically, AHPs manifest as intermittent, progressive, colicky abdominal pain radiating to the lumbar region and extremities, along with nausea, vomiting, urine discoloration, and constipation<sup>(5,6)</sup>. However, diarrhea can sometimes occur<sup>(8)</sup>, as in this case. ALA, PBG, and other hepatic heme precursors can cross the blood-brain barrier, exerting agonistic and antagonistic effects on gamma-aminobutyric acid (GABA) receptors in the central and peripheral nervous systems, leading to delirium, confusion, neuropathies, muscle weakness, seizures, tetraparesis, and respiratory arrest<sup>(3,5)</sup>. Physical examination may reveal tachycardia and hypertension due to sympathetic hyperactivity during acute attacks<sup>(6,7)</sup>. These episodes may also be associated with hyponatremia and hypomagnesemia, attributed to a combination of hypovolemia and syndrome of inappropriate



**Table 1.** Laboratory Report

Laboratory Tests	Patient Values	Reference Values	Unit of Measure
Lactate dehydrogenase	510.31	120-246	U/L
Chloride	102	98-107	mmol/L
Sodium	137	136-145	mmol/L
Potassium	4.32	3.5-5.1	mmol/L
Prothrombin time	10.50	9.9-11.8	s
INR	0.98	0.90-1.15	mg/dL
Partial thromboplastin time	28.7	25.0-31.3	s
Blood urea nitrogen	55.52	9-23	mg/dL
Alkaline phosphatase	94.84	46-116	U/L
Glucose	71	74-106	mg/dL
Total bilirubin	0.61	0.3-1.2	mg/dL
Direct bilirubin	0.24	0-10	mg/dL
Indirect bilirubin	0.37		mg/dL
Glutamic-oxalacetic transaminase	27.95	<34	
Creatinine	11.24	0.6-1.1	
Haptoglobin	138.9	40-280	
Parathyroid hormone	200.1	18.5-88	
Antinuclear antibodies	Negativo		
Anti-DNA antibodies	Negativo		
Hepatitis B	<0.10	0-50	
Hepatitis C antibody	0.08	0-1.0	
HIV 1/2 antibodies	Negativo		
Cardiolipin IgM antibodies	10.543	<20	
Cardiolipin IgG antibodies	1.927	<20	
$\beta_2$ glycoprotein IgM	6.537	0-20	
$\beta_2$ glycoprotein IgG	1.927	0-20	
Myeloperoxidase	1.6	<20	
$\delta$ -aminolevulinic acid	14.1	1-7	

DNA: deoxyribonucleic acid; IgG: immunoglobulin G; IgM: immunoglobulin M; INR: international normalized ratio; HIV: human immunodeficiency virus. Author's own research.

ate antidiuretic hormone secretion. Given its incomplete penetrance, triggering factors—such as excessive alcohol intake, smoking, drug use, fasting, or starvation—are necessary and likely act directly to increase hepatic ALA synthase-1 (ALAS1) mRNA levels, which is rate-limiting in heme production, thereby creating a vicious cycle<sup>(3)</sup>.

Renal disease associated with porphyria can occur in approximately 59% of patients, with an annual decline in glomerular filtration rate of around 1 mL/min per 1.73 m<sup>2</sup>. Literature suggests that causes may include endoplasmic reticulum stress mediated by ALA and PBG, apoptosis, and phenotypic changes in proximal tubular epithelial cells leading to renal injury, as well as the action of a variant of the human peptide transporter 2 expressed by proximal tubular cells that mediates ALA reabsorption<sup>(3)</sup>. Due to the deterioration in renal function, a renal biopsy was performed on this patient, which reported tubulointerstitial nephritis, considered multifactorial: the effect of porphyria combined primarily with chronic NSAID use, with an increase in consumption prior to admission. Liver enzymes may be elevated in 13% of patients during acute attacks, and while cases of cirrhosis have been reported, the cause of elevated liver enzymes and hepatic fibrosis remains poorly understood; thus, abnormal liver enzymes should prompt diagnostic evaluation for alternative etiologies<sup>(6)</sup>.

The diagnosis of symptomatic AHP requires biochemical testing, specifically showing significantly elevated ALA and PBG levels in urine or plasma, except in ALAD porphyria, where PBG levels do not rise significantly<sup>(5,8)</sup>, as was the case with this patient. It is essential to note that, as precursors of porphyrins, ALA and PBG are not included in standard porphyrin tests. Once biochemical testing indicates ALAD porphyria, confirmation can be achieved through genetic testing with gene sequencing; however, it is not recommended for initial screening<sup>(6)</sup> as it is unnecessary for diagnosis<sup>(9)</sup>. Genetic testing is, however, valuable for family studies and identifying previously unknown mutations<sup>(9)</sup>. In this patient's case, diagnostic challenges included a history of paroxysmal nocturnal hemoglobinuria (PNH), which initially led to distraction from considering ALAD porphyria. Although flow cytometry showed positive PNH clones, these were low-quality and lacked a clinical phenotype of the disease, making PNH diagnosis less probable. Additionally, the skin manifestations, initially interpreted as potential NSAID toxicity, further distracted from an early consideration of ALAD porphyria.

Acute management of AHP involves strict avoidance of porphyrinogenic drugs and triggering factors (such as acute illnesses or infections, physical or psychological stress, excessive alcohol intake, and smoking), intensive care monitoring, caloric support (300 grams of glucose per day), effective

pain management, electrolyte correction, and often hemo-  
therapy<sup>(5,6)</sup>. With early intravenous heme administration,  
patients begin to improve within 48 hours due to decreased  
ALAS1 expression<sup>(4,5)</sup>. The acute phase may involve hypona-  
tremia and hypomagnesemia, attributed to a combination  
of hypovolemia and syndrome of inappropriate antidiuretic  
hormone secretion. For seizures associated with AHP, ben-  
zodiazepines are considered relatively safe, and levetiracetam  
is regarded as a safe option<sup>(6)</sup>. In complex cases, therapeutic  
options include givosiran, a small interfering RNA that  
neutralizes excess ALAS1 mRNA in hepatocytes, with liver  
transplant as a last-resort option<sup>(5)</sup>.

Differential diagnoses should exclude other AHPs (via  
PBG measurement), lead poisoning, and hereditary tyro-  
sinemia type 1. In this case, lead poisoning was ruled out  
due to the absence of anemia, basophilic stippling on  
peripheral smear, and a “lead line” (bluish pigmentation at  
the gum line and teeth), along with a detailed history ruling  
out exposure to lead<sup>(5)</sup>.

AHPs are now considered chronic conditions with a  
significant negative impact on physical and emotional  
health, resulting in a reduced quality of life<sup>(4)</sup>. They pose an  
increased risk of long-term complications, including hepa-  
tocellular carcinoma (HCC) and chronic kidney disease<sup>(6)</sup>,  
requiring annual screening for these complications.

## CONCLUSIONS

It is essential to recognize the clinical phenotype to accu-  
rately interpret porphyria tests; even if initial tests are  
negative, further evaluation should be pursued to consider  
a potential phenotype, such as ALAD porphyria. The  
impact of neurovisceral manifestations often leads to the  
concomitant use of analgesic medications that may cause  
toxicity and should always be considered in patients with

these conditions. Despite their relative rarity and complex-  
ity, most porphyrias can be readily defined and diagnosed.  
One of the most common causes of diagnostic delay is fail-  
ing to consider this entity promptly in differential diagno-  
ses. Much remains to be learned about ALAD porphyria.

## Ethical Approval and Participant Consent

This report was approved by the patient and their family.

## Consent for Publication

Written informed consent was obtained from the patient  
for the publication of this case report and the accompan-  
ying images.

## Data and Material Availability

Data sharing is not applicable to this article as no datasets  
were generated or analyzed during the current study.

## Conflict of Interest

The authors declared no competing interests.

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## Author Contributions

All authors analyzed and interpreted the patient data, wrote  
the manuscript, reviewed and interpreted the imaging, and  
contributed to manuscript preparation. All authors read  
and approved the final manuscript.

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**Una causa olvidada de dolor abdominal recurrente:  
reporte de caso**

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