Hereditary coproporhyria

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Abstract

Hereditary coproporphyria (HCP) is a congenital, autosomal dominant disorder which occurs in approximately two to five people per million inhabitants, worldwide. It is a diagnostic challenge in patients with acute abdominal pain. We present the case of a 17-year-old adolescent who debuted with atypical abdominal pain with no clear etiology. Elevated urinary porphobilinogen was found, which was treated with hematin. A genetic study concluded that the adolescent was a heterozygous carrier of the c.717T>A; p.Cys239 pathogenic nonsense mutation in the CPOX gene, leading to a diagnosis of hereditary copropophyria. The available national literature has presented cases diagnosed with acute intermittent porphyria in patients with abdominal pain of unknown origin, without covering the existing classifications of hepatic porphyrias and without detailing the genetic diagnosis; thus, this case is a contribution to the national case studies. **(Acta Med Colomb 2021; 46. DOI: https://doi.org/10.36104/amc.2021.1950).**

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Introduction

Porphyrias are a group of metabolic disorders secondary to heme biosynthesis enzyme deficiencies which are characterized by the accumulation of porphyrins and their toxic precursors such as porphobilinogen and aminolevulinic acid (1). Five main types of hepatic porphyrias have been described: intermittent acute porphyria (IAP), variegate porphyria (VP), hereditary coproporphyria (HCP) and 5-aminolevulinic acid dehydratase deficiency porphyria (ADP) (2-4).

Hereditary coproporphyria is caused by an alteration of the coproporphinogen oxidase enzyme due to a mutation of the *CPOX* gene located on chromosome band *3q12* (1). Symptoms appear after puberty and include neurovisceral manifestations due to the accumulation of toxic porphyrin precursors, such as abdominal pain along with acute neuropathies and nonspecific signs: constipation, vomiting, hypertension, and tachycardia, among other neurological and psychiatric manifestations, which make it difficult to establish an etiology (2, 5-7). Lack of clinical recognition, delayed diagnosis and the use of unnecessary resources cause delays in treatment (8).

The importance of this case lies in its clinical and genetic diagnosis, which is not described in case reports in the national literature. The objective is to contribute to the regional and national published case studies and contribute elements to the current discussion on the approach to and treatment of HCP.

Case presentation

A 17-year-old female college student from Pereira, with no significant medical history, presented to the emergency room due to a four-day history of intense, burning epigastric abdominal pain which subsequently migrated to the right iliac fossa, associated with multiple episodes of vomiting and hyporexia. On admission to the tertiary care center, the physical exam showed an abdomen painful to palpation in the right iliac fossa, a positive psoas sign and McBurney's point tenderness, leading to a presumptive diagnosis of acute appendicitis. She was seen by a pediatric surgeon who oriented the case towards a urogenital disease. A urinalysis and abdominal ultrasound were ordered, reporting a urinary tract infection and a normal ultrasound, ruling out a surgical condition. Outpatient antibiotic treatment was ordered, and the patient was discharged.

Two days later, the patient consulted once again due to exacerbated abdominal pain with no response to analgesic treatment. Her symptoms were treated, and a complete blood count was ordered, with no abnormalities. A urinalysis showed no pathological findings; and a beta sub-unit qualitative urine chorionic gonadotropin test was negative. She was hospitalized and began treatment with dipyrone (40 mg/kg/day, intravenous) and morphine (2 mg/dose, intravenous) without achieving pain control. Subsequently, magnesium sulfate treatment was begun due to lab-reported

hypomagnesemia, with a level of 1.2 mg/dl.

The patient reported abdominal-pelvic pain along with dysuria and had bilateral fist-percussion induced kidney pain. The urinary tract ultrasound reported predominantly right pyelocalyceal dilation, which pointed to an obstructive uropathy etiology, but a urinary tract tomography was negative for this presumptive diagnosis.

She subsequently had dissociative episodes with psychomotor agitation associated with hyponatremia (111 mg/dl) and hypocalcemia (2.28 mg/dl), leading to a suspicion of porphyria with neuropsychiatric symptoms. The Hoesch and Watson-Schwartz tests were positive, in addition to high 24-hour urine levels of: 5-aminolevulinic acid (12 mg/g, reference range 0-5 mg/g) and porphobilinogen (18 mg/24 hours, reference range less than 4 mg/24 hours). Haptoglobin and antinuclear antibodies were ordered, which were within normal limits. She was transferred to intensive care due to severe symptomatic hyponatremia. Hematin was begun at 4 mg/kg/day intravenously for one week, with progressive recovery.

A genetic study of sequencing and deletions-duplications was performed using next generation sequencing (NGS) for porphyria genes, analyzing the *ALAD, ALAS2, C15ORF41, COPX, FECH, HFE, HMBS, PROX, SLC19A2, UROD, and UROS* genes, all analyzed with 100% coverage. The conclusion was that the patient was a heterozygote carrier of the c.717T>A;p.Cys239 nonsense variant on the CPOX gene. The results of this molecular study supported the diagnosis of HCP.

After hospital discharge, the patient continued treatment with nutrition and hematology. She has had no further crises and her condition is currently stable.

Discussion

Intermittent acute porphyria is the most frequent porphyria, with 1.5 per 100,000 people worldwide. However, HCP es even more rare, with one to nine cases per million (9, 10).

The CPOX gene mutation causes mitochondrial dysfunction in the coproporphinogen oxidase enzyme (2). The accumulation of porphobilinogen and aminolevulinic acid is responsible for the neurovisceral and psychiatric manifestations (2), as presented in this case, in which the patient debuted with acute abdominal pain and subsequently experienced psychomotor agitation along with dissociative episodes.

The variety of clinical manifestations made diagnosis difficult, due to the torpid progression of the clinical picture. No clear etiology was found at first, and paraclinical tests ordered which gave rise to different unsuccessful presumptive diagnoses.

Identifying precipitating factors is useful for avoiding acute episodes or exacerbations. These factors include hormonal changes such as increased progesterone, as well as metabolic stress and the use of medications which increase cytochrome P450 activity in the liver, among others (5). Since porphyria was not one of the initial diagnostic considerations, the patient received dipyrone as an analgesic (from the pyrazolone family, associated with acute episodes and considered unsafe in porphyria), exacerbating the neurovisceral manifestations, as well as triggering hyponatremic encephalopathy, increasing the mortality risk (11-13).

In the national literature, porphyria is described as a diagnostic dilemma, due to its nonspecific clinical presentation (8). This concurs with the clinical case described in which there were various presumptive diagnoses, delaying the identification of the etiology.

The most recently published clinical cases in Colombia refer to patients with IAP, such as those described by Torregrosa (14), Erazo (15), Lozano (16) and Latorre (17). In countries like Argentina, we only found one published clinical case report of HCP in a series of porphyria cases (18). Therefore, we believe that this case presentation is useful for the medical community, contributing towards the recognition of this condition and serving as a reminder that there are a variety of hepatic porphyrias which should be considered before making a definitive diagnosis. The findings in this case and the genetic approach differ from the reports presented in these publications.

The existence of epidemiological gaps with regard to the occurrence of HCP at a regional level could possibly be explained by the usual diagnostic method which is based on quantification of urinary PBG levels and the clinical picture. This leads to most cases being oriented towards an IAP type of hepatic porphyria, which is the most common, without conducting adequate confirmation through a specific genetic test. This is supported by Jaramillo et al., who reported that 98% of the hepatic porphyrias in their analysis of 101 patients were diagnosed as IAP with no genetic support to differentiate between this type or HCP or VP (19).

Thus, molecular genetic diagnosis is essential in differentiating HCP from other porphyrias. In this patient, a heterozygote nonsense variant was found on the *CPOX* gene, which consists of a substitution of a thymine for an adenine in position 717 of cDNA *(c.717T>*A), which generates a nonsense modification of a cysteine for a premature stop codon at the protein level (7). This variant has not been reported in the ClinVar databases (20) nor in the Human Gene Mutation Database (HGMD) (21), and it produces a prematurely truncated protein, possibly leading to a loss of its function or a degradation of the mRNA transcript through the nonsense mediated decay (NMD) mechanism (22). In addition, the loss of function is a known pathogenic mechanism in this gene. Mutations of the CPOX gene (OMIM *612732), located on the 3q11.2 chromosome region, cause HCP, which is an autosomal dominant condition (7).

Differences were found between this case and similar descriptions of HCP around the world. Insiripong et al. also reported a case in a young person (21 years old), differing in that our case did not have seizures, hypertension, or respira-

tory failure, nor did she die. Also, a genetic diagnosis was not described in this report. They are similar in that both cases had dark red urine with a positive Watson-Schwartz test, and a clear triggering factor could not be identified, despite a urinary tract infection being found and treated in our patient (23).

On the other hand, our case differs from that published by Sadie et al., who reported the disease in an older patient (39 years old) with a combination of gastrointestinal symptoms and neurocutaneous manifestations (24). With regard to Graziadei et al.'s publication, the presence of a genetic diagnosis is a common factor, although their patient was found to have a new nonsense variant on the coproporphinogen oxidase gene and the *c.1348A>G (p.Arg450Gly)* mutation, which was isolated in three other family members. In addition, their patient did not have urinary PBG abnormalities (25). Unlike the patient described by Lagos et al., in our case there were no renal or neurological disorders (14, 27).

Meanwhile, the management of this patient's acute crisis was appropriate, according to the literature, since hematin, dextrose fluids and magnesium sulfate were administered (14, 27).

An unresolved point is the lack of an extensive genetic study of first-degree relatives to determine the disease's transmission patterns. In this regard, the role of genetic tests in autosomal dominant acute porphyrias (IAP, HCP and VP) is to identify presymptomatic carriers of the family´s specific pathogenic mutation so they can receive counseling on how to minimize the risk of an acute attack (28).

The lack of recognition and low index of suspicion for HCP in differential diagnoses may delay diagnosis and treatment. It also increases healthcare costs due to prolonged hospital or intensive care stays (16).

Due to its low frequency, HCP is a challenge for the attending physician, who must consider this diagnosis as a possible cause of acute abdominal pain when the clinical assessment does not suggest another etiology (29). New studies that could shed light on this disease in Colombia would be supported by the review of cases of acute hepatic porphyrias already performed by some authors such as Jaramillo et al. (19), but the national case reports would need to be complemented with genetic diagnoses which would help determine the exact prevalence of HCP and other varieties in our country.

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