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CASE REPORT

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A novel mutation c.457C > T p.Q153 in the HMBS gene in a Mexican woman with acute intermittent porphyria

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Key Clinical Message

The detection of a novel HMBS gene mutation (c.457C > T) in a Mexican woman with acute intermittent porphyria underscores the importance of expanding genetic analyses in diverse populations to improve diagnosis, management, and knowledge of the disease's clinical implications.

Abstract

Acute intermittent porphyria (AIP) is an autosomal dominant disorder caused by a deficiency in the enzymatic activity of porphobilinogen deaminase (HMBS), resulting in the accumulation of toxic heme metabolites. In this report, we present the case of a Mexican woman with AIP who experienced recurrent episodes of severe abdominal pain, weakness, vomiting, and insomnia. Despite the challenges in diagnosis and treatment, genetic analysis revealed a novel HMBS mutation, c.457C > T (p.Q153X), located in exon 9. This mutation induces a premature translational stop codon and had not been previously reported in medical literature among individuals with AIP. Remarkably, the patient exhibited a positive response to RNA interference therapy. We hypothesize that this novel HMBS mutation may potentially account for the more severe clinical presentation observed in this case. However, further research is necessary to establish a definitive link between this specific mutation and disease severity. The prevalence and genetic variants of AIP in Mexico remain largely unknown, underscoring the importance of conducting additional research and expanding genetic analyses to gain a better understanding of the clinical implications associated with these mutations.

KEYWORDS

acute intermittent porphyria, hydroxymethylbilane synthase, mutation

1 | INTRODUCTION

Acute intermittent porphyria (AIP) represents an autosomal dominant disorder stemming from a partial deficiency in the enzymatic activity of porphobilinogen deaminase, which is also referred to as hydroxymethylbilane synthase (HMBS), the third enzyme involved in the synthesis of heme. This deficiency leads to the accumulation of toxic heme metabolites, namely aminolevulinic acid (ALA), and porphobilinogen (PBG).[1] The precise mechanisms through which porphyrin precursors trigger the symptoms of AIP are not fully understood.[1,2]

AIP presents with a range of clinical manifestations that can be categorized into three distinct phases: the prodromal phase, the visceral symptom phase, and the neurological phase. Prominent clinical symptoms include the occurrence of acute neurovisceral episodes, marked by intense abdominal pain, mental disturbances, and heightened sympathetic activity.[2]

Acute attacks of porphyria can be precipitated by a range of factors, comprising alcohol ingestion, stress, fasting, menstruation, surgical procedures, infection, and the administration of certain drugs.[1,3] Preliminary assessment for AIP involves the detection of markedly elevated porphyrin levels in urinary, stool or serum during an acute attack, followed by subsequent genetic analysis to confirm the presence of HMBS gene mutations.[4] The management of AIP encompasses a comprehensive approach that includes the management of acute attacks, prevention of future episodes, long-term monitoring, and the treatment of associated complications.[2]

Among the various acute porphyrias, AIP is recognized as a prevalent condition on a global scale, being both the most common and severe form among the acute hepatic porphyrias.[5] AIP affects both males and females, however, in the context of AIP episodes, females tend to experience more severe impacts in terms of higher frequencies of attacks, longer durations of attacks, and an increased likelihood of requiring hospitalization.[6]

The HMBS gene is situated at the chromosomal position 11q23.3 and has been linked to more than 400 pathogenic mutations.[5] Individuals harboring pathogenic variants of the HMBS gene, regardless of their symptomatic or latent status, are prone to experiencing acute attacks. Furthermore, chronic complications such as hepatocellular carcinoma, hypertension, and chronic renal failure can manifest in both symptomatic individuals with AIP and those who are asymptomatic but carry pathogenic HMBS variants.[7]

To date, limited knowledge exists regarding certain variants of pathogenic HMBS, particularly in low and middle-income countries such as Mexico. Consequently, there is uncertainty about the disease behavior in these individuals. Further research is warranted to address these gaps and enhance our understanding of AIP management in this specific patient population.

2 | CASE REPORT

We present the case of a 28-year-old Mexican woman who came to our clinic because she had been experiencing recurring episodes of intense abdominal pain, weakness in her upper and lower extremities, uncontrollable vomiting, and insomnia since the age of 17. These symptoms required frequent visits to the emergency department. Despite undergoing normal biochemical and imaging tests, not responding to pain relief medications, and even undergoing abdominal surgery for suspected acute appendicitis, her symptoms persisted. After enduring nearly 3 years of almost daily symptoms, an episode of elevated urine PBG during a crisis finally confirmed the diagnosis of AIP.

Treatment with hematin derivatives (Normosang®, Panhematin®) was initiated, resulting in partial improvement. However, subsequent years witnessed progressively severe crises, some accompanied by paralysis and kidney injury. Remarkably, elevated urine PBG was even detected during asymptomatic periods. Notably, her first cousin was also diagnosed with AIP and had a similar clinical presentation.

A molecular genetic study was conducted at a reference center in Belgium. All coding exons (1, 3–15), including parts of the adjacent intronic sequences and regions of the 5′- and 3′-UTR of the HMBS gene, were PCR-amplified from genomic DNA. The amplicons underwent direct sequencing using capillary electrophoresis and the BigDye technology (Applied Biosystems). Data alignment and comparison with the wildtype sequence (NM_000190.3) were performed using the GenBank Database. This analysis revealed a heterozygous state mutation, c.457C > T (p.Q153, exon 9, HMBS gene).

At the age of 38, she enrolled in a clinical trial for Givosiran, an RNA interference therapeutic targeting ALAS1 mRNA. Remarkably, she exhibited a notable response to the treatment and continued it even after the trial. Over the past years, her symptoms have been sporadic, and she has not required hospitalization. The patient is now 42 years old.

3 | DISCUSSION

Genetic testing plays a confirmatory role in diagnosing acute porphyria and is also useful for screening family members, enabling genetic counseling and future trigger avoidance.[4] Analysis of exomic and genomic databases

has revealed a substantially increased prevalence of pathogenic HMBS variants in individuals who do not present any apparent symptoms, indicating the presence of unidentified modifying genes or environmental factors.[5]

To date, the majority of mutations in the Human Gene Mutation Database (HGMD), approximately 187 of them, are classified as missense/nonsense mutations. The frequency and patterns of these mutations are highly diverse and distributed among different ethnic populations. In a 2019 study by Fu et al., distinct distribution patterns were reported among various ethnic groups. For instance, the nonsense mutation c.C499>T (p.R167W) is most frequent in the Finnish population, while in African populations, it is C.G955>A (p.0319N), and in South Asia, it is c.G532>A (p.D178N). When specifically examining Latino populations, mutations such as c.G842>A (p.R281H) and c.G532>A (p.D178N) were less common, whereas mutations like c.C76>T (p.R26C) and C.A634>G (p.M212V) were more prevalent.[8]

The estimated clinical penetrance of mutations in the HMBS gene is around 0.5%–1% in the general population, with certain families showing higher penetrance ranging from 10%–30%. Multiple HMBS mutations lead to loss of function, with most being considered "private" and affecting only a single or few families. However, certain founder mutations inherited across generations have been identified, such as HMBS c.593G>A (p.W198X) in Sweden and Norway, or c.331G>A (p.G111R) in Argentina.[5] Founder effects can significantly increase the prevalence of AIP in specific regions. For instance, southeastern Spain has a prevalence of 17.7 cases per million, while in Sweden, it reaches 23 cases per million. Notably, northern Sweden has an astonishing prevalence of 192 cases per million.[5]

The detected mutation c.457C>T in exon 9 is a nonsense mutation that results in a premature translational stop codon at amino acid position 153 of the HMBS gene. This mutation, recently classified as pathogenic based on a single submission to the National Center for Biotechnology Information, had not been previously reported in medical literature among individuals with AIP, particularly when the patient presented to us in 2009.[9] In 2022, a study conducted in China examined the prevalence of pathogenic HMBS variants and identified the c.457C>T mutation. Interestingly, this mutation was detected in a single allele and was found exclusively in individuals categorized as "American mixed race".[10]

AIP has rarely been reported in Mexico, and the exact incidence and prevalence of the condition are unknown. This characterization is relevant because different mutations can be associated with more severe clinical symptoms.[8] Based on our literature review, there is a lack of information regarding the prevalence and genetic variants of porphyria in Mexican patients. As a result, the implications of this specific variant at a population level remain unknown. It remains unclear whether the atypical features of this case, such as frequent recurrences and resistance to treatment, which led to the patient's enrollment in a clinical trial with interference RNA, are related to the patient's genotype or other demographic characteristics. Specifically, this mutation could be a specific variant found in Mexico or the Americas.

We conclude that expanding access to genetic analyses in patients and their family members is necessary. Future studies will help characterize the clinical implications of this and other genetic variants in the pathogenesis of AIP.

AUTHOR CONTRIBUTIONS

Jose Malagon-Rangel: Conceptualization; supervision. **Jose Gabriel-Solis:** Conceptualization; writing – original draft. **Luis Fernando Zavala-Jonguitud:** Conceptualization; writing – original draft. **Martín Roberto Basile-Alvarez:** Conceptualization; writing – review and editing. **Andrea Malagon-Liceaga:** Conceptualization; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

We declare that we have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

CONSENT

Written informed consent was obtained from the patient in accordance with the journal's patient consent policy.

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