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HEPATOERYTHROPOIETIC PORPHYRIA WITH COEXISTING *BTD* AND *CNGB1* GENETIC MUTATIONS: A FIRST CASE REPORT

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ABSTRACT

Introduction: Hepatoerythropoietic porphyria (HEP) is an uncommon autosomal recessive disorder marked by deficiencies in enzymes involved in heme biosynthesis. This results in the build-up of porphyrins and their precursors. Here, we describe a case study of a 17-year-old male who has experienced symptoms of porphyria since early childhood.

Case description: The patient exhibited initial symptoms of porphyria, including dark-coloured urine, abdominal pain, constipation and cutaneous lesions. Genetic testing at age 17 confirmed a homozygous mutation in the *UROD* gene, diagnosing HEP. Additional mutations in the *CNGB1* and *BTD* genes contributed to retinitis pigmentosa and biotinidase deficiency, respectively. The patient also experienced complications such as thumb amputation and finger developmental anomalies.

Conclusion: This case underscores the diagnostic challenges and multidisciplinary management required for patients with complex genetic profiles and rare porphyria subtypes such as HEP. Further research is essential to enhance understanding and treatment strategies for such intricate genetic conditions.

KEYWORDS

Porphyria, biotinidase deficiency, retinitis pigmentosa

LEARNING POINTS

- This is a first report of hepatoerythropoietic porphyria with coexisting *BTD* and *CNGB1* genetic mutations.

INTRODUCTION

Porphyria encompasses a set of rare inherited metabolic disorders resulting from enzyme deficiencies in the heme biosynthesis pathway. This leads to the accumulation of porphyrins and their precursors, causing a range of clinical manifestations, including abdominal pain, neuropsychiatric

symptoms and skin lesions. The severity and type of symptoms vary depending on the specific form of porphyria and the affected enzymes[1].

Hepatoerythropoietic porphyria (HEP) is an extremely rare subtype within the porphyria spectrum, characterised by both hepatic and cutaneous manifestations. It is caused by changes in the *UROD* gene, which makes the enzyme uroporphyrinogen decarboxylase. This enzyme plays an important role in the process of making heme[2]. HEP typically presents early in life with signs such as skin lesions and abdominal pain, and it follows an autosomal recessive inheritance pattern. While the clinical features of HEP may initially overlap with other forms of porphyria, its confirmation requires genetic testing to identify mutations in the *UROD* gene. At first, the patient was diagnosed with erythropoietic protoporphyria (EPP), a type of porphyria that shares some symptoms with HEP, such as skin problems and sensitivity to light. However, further genetic testing showed a mutation in the *UROD* gene, confirming the patient actually had HEP instead of EPP. This highlights the importance of genetic testing to ensure an accurate diagnosis and to distinguish between similar types of porphyria. In addition to the genetic mutation associated with HEP, the patient exhibited mutations in the *CNGB1* and *BTD* genes, which contributed to retinitis pigmentosa and biotinidase deficiency, respectively. These additional genetic factors further complicated the clinical picture, as both conditions have overlapping dermatological features with porphyria.

This report aims to highlight the complexities of diagnosing rare porphyrias such as HEP, especially when complicated by other genetic mutations, and to underscore the importance of a multidisciplinary approach in treatment and management.

CASE DESCRIPTION

We present a case of a 17-year-old male who initially sought medical attention for a range of symptoms suggestive of porphyria, including dark-coloured urine *(Fig. 1)*, abdominal pain, constipation and characteristic skin lesions at infancy. The patient's medical history indicated normal percentiles at birth, with the initial signs of porphyria, such as skin lesions and abdominal pain, emerging during early childhood *(Fig. 2)*. The clinical presentation raised the possibility of EPP, which was initially diagnosed at the age of 3.

Diagnostic testing included a urine porphobilinogen test, which was positive, along with a 24-hour urine collection showing significantly elevated levels of uroporphyrin 1 and 3, coproporphyrin 3, heptacarboxyporphyrin and hexacarboxyporphyrin, consistent with porphyria. However, genetic analysis at the age of 17 revealed a homozygous mutation in the *UROD* gene, which led to the revision of the diagnosis from EPP to HEP. This genetic confirmation was essential in distinguishing between the two porphyrias, both of which exhibit overlapping cutaneous and hepatic manifestations.

In addition to the diagnosis of HEP, the patient's clinical picture was further complicated by the presence of additional genetic mutations. Notably, mutations in the *CNGB1* gene, responsible for retinitis pigmentosa, were identified. This condition, which is a form of hereditary retinal degeneration, did not result in active complaints from the patient, but it contributed to the complexity of his genetic profile. Furthermore, a mutation in the *BTD* gene led to biotinidase deficiency, a disorder that impairs the recycling of biotin and can result in both dermatological and neurological symptoms.

The patient's medical history also included the loss of his left thumb, which required amputation due to an infection, as well as incomplete development of the index fingers during embryological formation *(Fig. 3)*. These additional physical anomalies added to the multifactorial nature of his

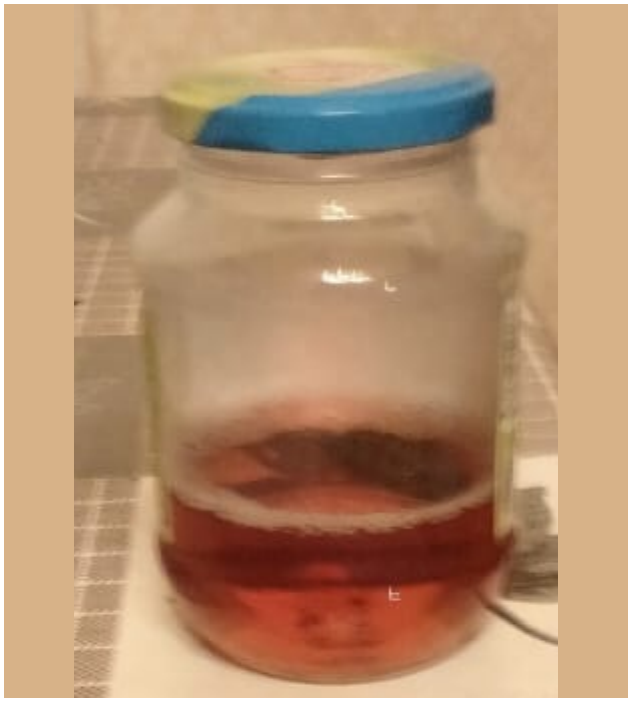

Figure 1. Dark urine.

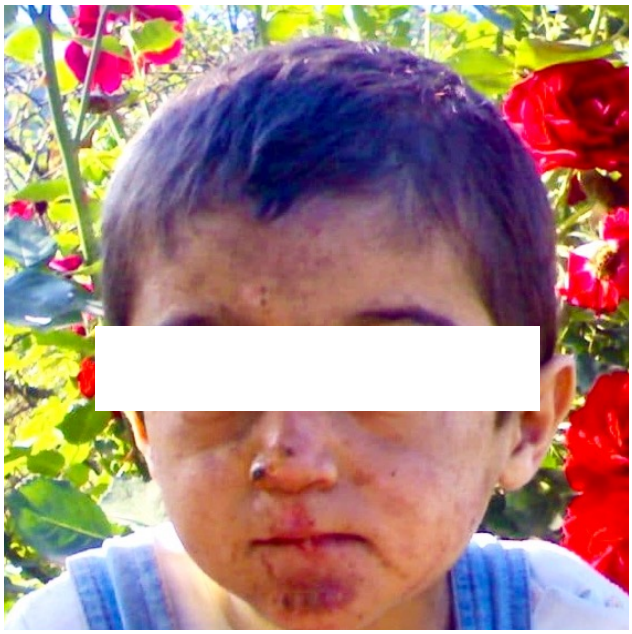

Figure 2. Lesions due to sunlight, black scars on the face in childhood.

clinical presentation. The patient had no history of smoking or alcohol consumption, and no other first-degree family members exhibited similar symptoms, with the exception of his mother, who began to experience similar skin lesions after childbirth, leading to the suspicion of PCT.

The patient's medication history revealed the use of metamizole sodium, a drug known to precipitate porphyria attacks, which was subsequently discontinued to prevent further exacerbations. To manage his porphyria, the patient was prescribed hydroxychloroquine 200 mg daily for 6 months, a treatment known to be effective for skin lesions associated with porphyria. During episodes of acute porphyria, confirmed by positive urine porphobilinogen tests, haemarginine (also known as heme arginate) was administered intravenously at a dose of 4 mg/kg until the urine porphobilinogen test became negative. In addition, the patient was treated for biotinidase deficiency with oral biotin, 5,000 µg twice daily.

Further investigations revealed moderately low levels of lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and biotin, further suggesting a compromised metabolic state due to the combined effects of the patient's multiple genetic mutations. The patient also reported ongoing symptoms of muscle weakness in the arms and hands, difficulty flexing his fingers, and writing, fatigue and hair loss.

Abdominal ultrasound findings were unremarkable, effectively ruling out any structural liver abnormalities. Despite the complex genetic background and ongoing symptoms, the patient had not exhibited any acute hepatic dysfunction up to this time. As the patient continued to experience progressive muscle weakness and fatigue, regular follow-up and multidisciplinary management remained crucial for optimising his care and addressing the multifaceted aspects of his condition.

It is worth mentioning there was no documented consanguinity in the patient's family history, nor was there any indication that the patient came from a remote location with a small gene pool where consanguinity might be more likely. The patient's genetic profile and family history did not suggest any increased risk related to consanguinity, and no specific geographical or familial factors were identified that would contribute to a higher prevalence of inherited genetic mutations.

DISCUSSION

The nomenclature 'hepatoerythropoietic' underscores the involvement of the liver (hepato-) and bone marrow (erythropoietic) in the pathology of this subtype, as these organs are pivotal for heme synthesis. It manifests as both hepatic and cutaneous porphyria. HEP is an exceptionally rare subtype within the broader spectrum of porphyria disorders. Its inheritance pattern is autosomal recessive, indicating that individuals with this condition inherit mutations in both copies of the relevant gene, typically from each parent. The principal genes implicated in hepatoerythropoietic porphyria contribute to the synthesis of *UROD*, an indispensable enzyme crucial for the proper functioning of the heme biosynthetic pathway[2].

As seen in this case, the patient was initially diagnosed with EPP, but after genetic testing, the diagnosis was changed to HEP. This emphasises the importance of differentiating between these two diseases, which share symptoms such as skin sensitivity to light and abdominal pain. EPP is a type of porphyria that causes the build-up of protoporphyrin IX, mostly in the blood-forming tissues, leading to skin sensitivity and blistering when exposed to sunlight. It is caused by mutations in the *FECH* gene, which provides instructions for making ferrochelatase, the enzyme that helps add iron to protoporphyrin to create heme[3].

This defect leads to the build-up of protoporphyrin which, when exposed to sunlight, induces oxidative damage to the skin, causing the hallmark symptoms of painful skin blistering, erythema and hypertrichosis. Treatment options for EPP include sun avoidance and protective clothing,

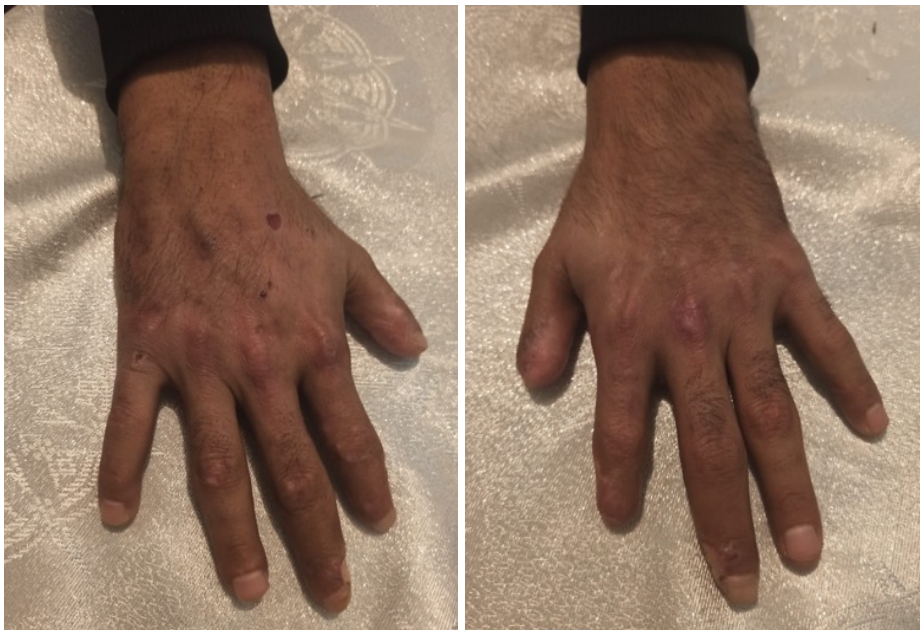

Figure 3. Undeveloped fingers (right hand) and amputated thumb due to infection, undeveloped index finger (left hand).

along with beta-carotene therapy, which has been shown to decrease photosensitivity by acting as an antioxidant. In severe cases, light-protective measures such as the use of UV-blocking window films and special lighting are employed. In some cases, hematin therapy may be used to help reduce protoporphyrin production[4].

HEP typically presents with symptoms in early childhood, similar to EPP, but with the added complication of hepatic involvement, which can lead to hepatomegaly, liver dysfunction and, in severe cases, cirrhosis. Treatment strategies for HEP include sun protection and hydroxychloroquine, which helps to reduce the skin lesions associated with photosensitivity. For acute attacks, haemarginine is used to decrease porphyrin levels and manage symptoms. Management also includes discontinuation of porphyrinogenic drugs, which may exacerbate symptoms. The prognosis for HEP can be complicated by hepatic involvement, and liver function must be monitored regularly. However, with proper treatment and management, many patients with HEP can maintain a good quality of life[5,6]. A total of 100 cases of HEP have been documented in the literature. The clinical features of EPP and HEP overlap considerably, particularly regarding photosensitivity and skin lesions. Both conditions can present with painful blistering upon sun exposure, making it challenging to differentiate them based solely on clinical presentation. However, the key differentiating factor lies in the underlying genetic defect. Laboratory tests, including urine porphobilinogen testing, measurement of porphyrin levels and genetic testing, are critical for making an accurate diagnosis[7].

Biotinidase (BTD) deficiency is an uncommon autosomal recessive metabolic disorder resulting from inadequate biotin metabolism, leading to the inability to effectively recycle the vitamin biotin. Biotinidase serves as the sole enzyme capable of breaking down biocytin, a by-product of the proteolytic digestion of holocarboxylases. A severe deficiency in biotinidase (falling below 10% of the average normal activity in serum) is an autosomal recessive disorder that can result in neurological and cutaneous abnormalities. Remarkably, the prevalence of BTD deficiency is higher in Turkey when compared to global incidence rates[8].

Untreated profound biotinidase deficiency presents with specific features, including an eczematous skin rash, alopecia, conjunctivitis, candidiasis and ataxia. Additional symptoms encompass seizures, hypotonia, respiratory problems (hyperventilation, laryngeal stridor and apnoea), developmental delay and sensory impairments such as hearing loss and optic atrophy. Early detection and intervention are crucial to address the diverse health implications of this condition[9].

The skin manifestations of biotinidase deficiency can overlap with those of porphyrias, posing further diagnostic challenges. As a result, a comprehensive approach, including genetic testing and a careful clinical evaluation, is essential for differentiating these disorders.

A mutation in the *CNGB1* gene is a recognised cause of autosomal recessive retinitis pigmentosa (RP), recently linked to olfactory dysfunction; RP is the most prevalent form of hereditary retinal degeneration. Initial visual symptoms typically involve night blindness and a narrowing of the visual field (primary rod dysfunction). As the disease progresses, reduced daylight vision and central vision loss occur, attributed to secondary cone involvement in the advanced stages. Despite its progressive nature, RP displays significant phenotypic diversity, aligning with well-established genetic heterogeneity[10].

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