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Case Report

Early presentation of adult-onset conditions: A dual diagnosis of hereditary hemochromatosis and porphyria cutanea tarda

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A B S T R A C T

Asymptomatic aminotransferase elevation has a broad differential in the pediatric population. We report an 11-year old male with a history of urine discoloration found to have persistently elevated aminotransferases. Biochemical evaluation was notable for elevated uroporphyrin, consistent with porphyria cutanea tarda (PCT). Genetic testing revealed biallelic pathogenic variants in *HFE* and a pathogenic variant in *UROD*, consistent with a diagnosis of hereditary hemochromatosis (HHC) and PCT, respectively. Dual diagnosis likely explains the pediatric onset of these typically adult-onset conditions.

1. Introduction

Persistent, asymptomatic aminotransferase elevation has a broad differential in the pediatric population, including autoimmune, viral, and metabolic disease, and can be a harbinger of severe and progressive liver disease. For many diagnoses, early and correct diagnosis is critical for initiating early treatment and improving patient outcomes.

There are many genetic syndromes that cause adult-onset liver disease, but may have subtle manifestations in childhood. This is best described for alpha-1 antitrypsin deficiency, where liver disease can present as early as the neonatal period [1]. Unlike alpha-1 antitrypsin deficiency, which is a well-known and screened condition in the pediatric population, hereditary hemochromatosis (HHC) and porphyria cutanea tarda (PCT) are two treatable, common conditions that can present with elevated aminotransferases that rarely manifest during childhood and are therefore not evaluated as part of the standard pediatric workup of elevated aminotransferases.

Here we present an 11-year old male with a history of asymptomatic aminotransferase elevation, found to have significant elevation of urine heptacarboxyl porphyrin and uroporphyrin as well as elevated serum ferritin and transferrin saturation. Genetic testing was notable for biallelic pathogenic *HFE* gene variants as well as a pathogenic *UROD* gene variant, consistent with a diagnosis of both HHC and PCT. This dual diagnosis likely explains the pediatric onset of these typically adult-onset conditions. Early identification allowed for immediate initiation of appropriate medical therapy.

2. Case presentation

Patient is an 11-year old male with Trisomy 21 complicated by developmental delay, intellectual disability, skin-picking behaviors, and hypothyroidism. At 7 years of age he presented to Nephrology clinic with a one-year history of orange and red urine. Comprehensive metabolic panel was notable for an elevated creatinine suggestive of stage II chronic kidney disease felt to be a consequence of his Trisomy 21, and elevated aminotransferases (ALT 117, normal < 45; AST 96, normal < 60). He was subsequently evaluated by Gastroenterology, and a broad workup to evaluate for autoimmune, viral, and metabolic etiologies of disease was notable for an elevated serum ferritin (121 ng/mL). Urine porphyrins were measured given the history of urine discoloration and were notable for significant elevation of urine heptacarboxyl porphyrin (362 μg/L, normal < 2) and uroporphyrin (474 μg/L, normal < 20). Abdominal ultrasound was notable for small right kidney and increased heterogeneous liver echotexture. He was referred to Genetics for further evaluation.

Physical examination in Genetics clinic was notable for typical facies of Trisomy 21, hypotonia, ligament laxity, frequent skin picking, tan-skin, and scattered scabs and well-healed scars on the hands. Serum and stool porphyrins were measured to further address a possible diagnosis of porphyria. Stool porphyrins were negative, and serum porphyrins showed significant elevations of total plasma porphyrin (71 nmol/L, normal < 15), uroporphyrin (2.5 μg/dL, normal < 1) and heptacarboxyl porphyrin (1.6 μg/dL, normal < 1), consistent with PCT.

PCT is most commonly associated with environment exposures, infections, alcohol, medications or iron overload and not with a primary

genetic defect. Based on this and the patient's history of elevated serum ferritin, serum ferritin and transferrin saturation were measured, and were elevated, with a transferrin saturation of 56% (normal < 40%) and a serum ferritin of 106.3 ng/mL (normal < 77 ng/mL), consistent with mild iron overload. Due to the presence of both iron overload and biochemical porphyria, *UROD* and *HFE* gene sequencing was performed for diagnosis of PCT and HHC, respectively. Testing identified a pathogenic *UROD* gene variant (c.430C > T; p.R144X) and biallelic pathogenic *HFE* variants (c.187C > G; p.H63D and c.845 G > A; p.C282Y), consistent with a genetic diagnosis of both HHC and PCT in addition to underlying Trisomy 21. He was referred to Hematology for initiation of therapeutic phlebotomy.

3. Discussion

Persistent aminotransferase elevation has a broad differential that includes viral, autoimmune and genetic/metabolic etiologies. Though many overlaps exist, there is a distinct differential for pediatric and adult populations. Here we present a case of pediatric manifestation of two typically adult-onset liver diseases, PCT and HHC, highlighting the importance of considering adult-onset conditions in the evaluation of pediatric patients.

Familial PCT (OMIM #176100) is an autosomal dominant, adult-onset condition characterized by skin-blistering rashes, liver inflammation and fibrosis, and discolored urine. The causal gene, *UROD,* encodes the enzyme uroporphyrinogen decarboxylase, which catalyzes the fifth step in heme biosynthesis, converting uroporphyrinogen III to coproporphyrinogen [2]. Reduced UROD activity causes hepatic and cutaneous accumulation of uroporphyrinogen and heptacarboxyl-porphyrin. Within the skin, uroporphyrinogen is oxidized by sunlight and initiates a delayed inflammatory response that causes the skin blistering and discoloration characteristic of PCT [3]. The pathogenesis of liver disease in PCT is incompletely understood, but is believed to be a consequence of uroporphyrinogen hepatotoxicity as well as toxicity from hepatic iron accumulation [4, 12]. Importantly, PCT is incompletely penetrant, with less than 40% of individuals harboring pathogenic *UROD* variants manifesting disease. Indeed, pathology emerges when UROD activity is below 20%, as opposed to the theoretical 50% reduction conferred by *UROD* gene variants. This suggests that pathogenic *UROD* variants are a risk factor for disease development, but there is an important contribution from additional genetic and environmental factors, most notably alcohol, certain medications, and hepatic infections, which all affect porphyrin metabolism and UROD activity [5]. Indeed, most PCT patients do not harbor pathogenic *UROD* variants.

A well-described genetic risk factor for both familial and sporadic PCT is HHC (OMIM #235200) [6–8], an autosomal recessive, classically adult-onset condition caused by biallelic pathogenic variants in the *HFE* gene. *HFE* encodes the human homeostatic iron regulator protein, and its deficiency results in intestinal iron hyper-absorption and systemic iron overload with deposition in multiple tissues, leading to liver cirrhosis, bronze skin, heart failure, diabetes, polyarthropathy and adrenal insufficiency [9]. Like PCT, HHC is also incompletely penetrant, suggesting that genetic background and environment strongly influence phenotype.

A pediatric presentation of PCT is highly unusual, though has been reported previously, precipitated by stress from chemotherapy [10,11]. Our patient's history is negative for precipitating medications and environmental exposures; however, his pathogenic *UROD* variant coupled with biallelic pathogenic *HFE* variants would be predicted to produce a more severe and earlier-onset phenotype, as *HFE* deficiency would lead to iron overload, a known risk factor for PCT[12] (Fig. 1). Indeed, biochemical PCT and early-onset skin disease in a child with familial PCT and HHC has been reported. Liver findings were not described [13].

Given the elevated aminotransferase levels consistent with symptomatic PCT and HHC, treatment was initiated immediately. PCT can be
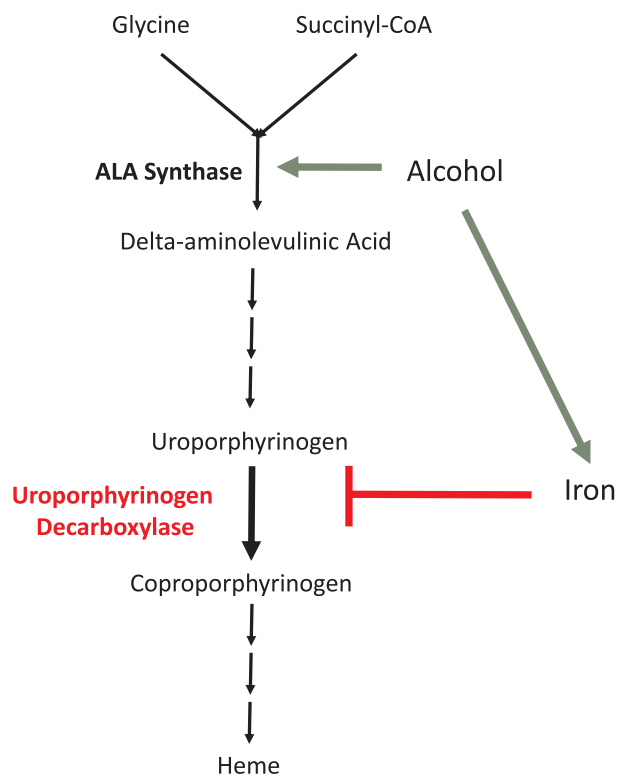

Fig. 1. *Porphyrin biosynthesis pathway*. Aminolevulinic acid synthase catalyzes the production of delta-aminolevulinic acid from glycine and succinyl-CoA. Three subsequent reactions convert delta-aminolevulinic acid to uroporphyrinogen, which is converted to coproporphyrinogen by uroporphyrinogen decarboxylase (UROD). Three subsequent reactions result in the formation of heme. Familial porphyria cutanea tarda (PCT) is an autosomal dominant condition, caused by pathogenic variants in the *UROD* gene. Reduction in UROD activity below 20% causes accumulation of uroporphyrinogen, which deposits in the skin and liver causing the skin-blistering and hepatic injury characteristic of PCT. *UROD* pathogenic variants alone are insufficient to cause disease, and most cases of PCT are sporadic. Hepatic iron accumulation is required for both familial and sporadic disease. Specifically, hepatic iron is suspected to promote synthesis of a UROD inhibitor through a yet unknown oxidation reaction. Alcohol increases flux through the porphyrin pathway, increases iron absorption and contributes to formation of the UROD inhibitor.

treated with hydroxychloroquine, which promotes solubilization of deposited porphyrin metabolites and urinary excretion versus therapeutic phlebotomy, which promotes iron and porphyrin mobilization, and also increases endogenous UROD activity by relieving its inhibition from accumulated iron [14]. Neither treatment has demonstrated superiority [15]. HHC is treated principally by phlebotomy. Given our patient's dual diagnosis of HHC and PCT, it was felt that phlebotomy would be the most effective first-line treatment.

In summary, we present a pediatric patient with elevated aminotransferases found by biochemical and genetic testing to have both PCT and HHC. We suggest that a dual diagnosis of familial PCT and HHC should be considered in children not only with cutaneous findings, but also with signs of liver pathology and iron overload, and propose that these conditions be evaluated in children with idiopathic aminotransferase elevation.

Financial disclosures

None.

Declaration of Competing Interest

None.

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