Porphyria Cutanea Tarda Associated With Cys282Tyr Mutation in *HFE* Gene in Hereditary Hemochromatosis: A Case Report and Review of the Literature

Lorraine C. Young, MD

GOAL

To understand porphyria cutanea tarda (PCT) and hereditary hemochromatosis (HH) to better manage patients with these conditions

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Identify clinical symptoms of HH.
2. Discuss the genetic and hormonal factors in iron regulation.
3. Describe the association of PCT with HH.

CME Test on page 422.

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Porphyria cutanea tarda (PCT) typically presents with complaints of fragile skin, dorsal hand vesicles, erosions, and scars, and increased levels of uroporphyrins. A case of PCT caused by iron overload associated with hereditary hemochromatosis (HH) is reported. The laboratory workup revealed the patient was homozygous for the Cys282Tyr mutation in the HFE *(hemochromatosis) gene. The associated diagnosis of HH was critical because without early treatment, damage to vital organs and premature death could occur. This report highlights the important association of PCT with HH and reviews*

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Dr. Young is Associate Clinical Professor of Medicine and Co-Chief of Clinical Services in Dermatology, Department of Medicine, Division of Dermatology, David Geffen School of Medicine, University of California, Los Angeles.

Reprints: Lorraine C. Young, MD, Department of Medicine, Division of Dermatology, David Geffen School of Medicine, University of California, Los Angeles, 200 Medical Plaza, Suite 450, Los Angeles, CA 90095 (e-mail: lcyoung@mednet.ucla.edu).

the role of key genetic and hormonal factors in iron regulation.

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Case Report

A 41-year-old white woman presented with a 3-month history of fragile skin and blisters on her hands. She took oral contraceptives and occasionally consumed alcoholic beverages. There was no family history of liver disease. A full skin examination revealed erosions; scars; and 1-mm, firm, white papules consistent with milia on the dorsal hands.

Based on the complaint of fragile skin and the physical findings, porphyria cutanea tarda (PCT) was suspected. To confirm this suspicion, porphyrin levels were obtained. The level of uroporphyrin was elevated and the coproporphyrin level was within reference range, consistent with PCT. The patient was advised to discontinue her use of oral contraceptives and alcohol, and to protect herself from the sun.

Because PCT can be associated with iron overload and liver disease, the patient underwent additional testing. Her serum ferritin level was elevated, but other liver studies, including transaminases and hepatitis serologies, were within reference range.

To further characterize the iron overload, additional studies were performed, including genetic testing for hereditary hemochromatosis (HH). These studies revealed that the patient was homozygous for the Cys282Tyr mutation in the *HFE* (hemochromatosis) gene; therefore, the cause of the patient's PCT was almost certainly HH. A phlebotomy treatment program was instituted, both to treat the PCT-associated skin lesions and to prevent sequelae of systemic iron overload (eg, diabetes mellitus, cirrhosis of the liver, hepatocellular carcinoma, cardiomyopathy, early death). Lifelong monitoring of iron stores was recommended.

Comment

This patient's laboratory workup for PCT identified HH, an autosomal recessive disease associated with iron overload. HH was almost certainly responsible for the PCT because iron overload causes decreased uroporphyrinogen decarboxylase activity. HH is common; it is the most frequent genetic disease in individuals of Northern European descent. Because the patient described here had no family history of HH, iron overload was not suspected prior to the diagnosis of PCT. HH should be suspected when the serum ferritin level is elevated and when the transferrin saturation exceeds 55%.

Early clinical symptoms of HH generally are nonspecific, such as fatigue, arthralgia, and arthritis. Later findings can include generalized metallic gray hyperpigmentation of the skin, diabetes mellitus, cirrhosis of the liver, hepatocellular carcinoma, and congestive heart failure, all of which are secondary to iron overload.[1] Premenopausal women with HH are partially protected from end-organ damage because of the loss of iron during menstruation. Early diagnosis and treatment can prevent serious end-organ damage,[2] and individuals with HH can expect a normal lifespan if the excess iron stores are depleted prior to the development of cirrhosis. Environmental factors are important in hemochromatosis; for example, ethanol intake accentuates the risk of morbid complications of HH, including cirrhosis of the liver and cancer.[3] Life expectancy is reduced if there is a delay in diagnosis and treatment.[4]

HH caused this patient's PCT. Strongly suggestive of PCT are complaints of fragile skin worsened by trauma or sunlight, along with the findings of vesicles or bullae on the hands or evidence of resolution of these lesions, such as erosions, scars, or milia.[5] Other bullous diseases, including bullous pemphigoid and epidermolysis bullosa acquisita, also should be considered, but these diagnoses generally are excluded by the physical examination and histologic results. Two hereditary porphyrias—variegate porphyria and hereditary coproporphyria—as well as pseudoporphyria can present with skin findings similar to PCT.[5] However, both variegate porphyria and hereditary coproporphyria commonly are associated with extracutaneous manifestations, and pseudoporphyria is associated with renal failure. In addition, different porphyrin profiles make it possible to distinguish PCT from the other porphyrias.

PCT is the most common porphyria, with an incidence of approximately 1 per 70,000 people.[6,7] PCT is caused by decreased activity of uroporphyrinogen decarboxylase.[8] Estrogens, iron, alcohol, hepatitis C,[9] and human immunodeficiency virus[10] can be associated with PCT. It is poorly understood how they interfere with the activity of uroporphyrinogen decarboxylase, but iron overload is thought to be a common feature.[5]

When PCT is suspected, a laboratory evaluation is obtained to assess iron stores and liver function. Serum ferritin levels usually are at the upper limits of the reference range or elevated in patients with PCT.[11]

The understanding of iron overload has been enhanced by the identification of the *HFE* gene[12] and the genes for the transferrin receptor 2 (*TFR2*)

Genetic Variants of Iron Overload*

HFE mutations associated with hemochromatosis (eg, Cys282Tyr, Hy63Asp, Ser65Cys)

TFR2 mutations (eg, Leu490Arg, Val561Xaa)

HJV mutations

**HFE* indicates hemochromatosis; *TFR2,* transferrin receptor 2; *HJV,* hemojuvelin.

and hemojuvelin (*HJV*)(Table). The locus that most frequently accounts for HH is *HFE*, the class I major histocompatibility complex–related protein on chromosome 6p21.3.[13] At least 37 different *HFE* mutations causing HH have been detected,[14] including Cys282Tyr, Hys63Asp, and Ser65Cys. The most common mutation, the substitution of a tyrosine for a cysteine at protein residue 282 (Cys282Tyr), is caused by a G-to-A substitution at nucleotide 845 of the *HFE* transcript.[15]

Genetic testing revealed that the patient described here was homozygous for the Cys282Tyr mutation, which was not particularly surprising because this mutation is most common in patients with a Northern European ancestry. About 85% to 90% of patients of Northern European descent with HH are Cys282Tyr homozygotes.[16] This mutation is almost certainly associated with increased iron absorption, though population surveys have revealed that some Cys282Tyr homozygotes do not have elevated iron stores.[17]

The Cys282Tyr mutation is most common in white individuals, but this mutation does not account for iron overload in nonwhite individuals, including Pacific Islanders and Asians.[18] In addition, several other genes have been implicated in iron overload. The Leu490Arg and Val561Xaa mutations in the *TFR2* gene have been identified in Japanese patients with hemochromatosis lacking mutations in *HFE*.[19] Also, mutations in the *HJV* gene have been identified in patients with juvenile HH.[20]

Hepcidin is a key hormone in iron regulation.[21] Its expression is decreased by mutations in *HFE*, *TFR2*, and *HJV*, all of which can contribute to iron overload in patients with HH. Hepcidin is a 25–amino acid peptide that was first identified in urine and plasma during a search for antimicrobial peptides.[22] When there are increased iron stores in the body, *HFE* triggers hepcidin expression, which decreases the level of iron in the blood.[21] The loss of hepcidin in upstream stimulatory factor 2 knockout mice is associated with increased intestinal iron absorption and increased circulating iron levels, akin to HH.[23] Reduced hepcidin expression occurs in HH regardless of the genetic etiology. Although current treatment for HH is phlebotomy, a future treatment may be exogenous hepcidin.[21]

Conclusion

The homozygous Cys282Tyr mutation in the *HFE* gene was identified as the cause of PCT and HH in a 41-year-old woman. An understanding of iron overload has been enhanced by the identification of genes that control hepcidin, including *HFE*, *TFR2*, and *HJV*. Mutations in these genes are associated with reduced levels of hepcidin, resulting in iron overload observed in HH.

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