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CLINICAL SCIENCE LETTERS

Porphyria Cutanea Tarda and Hemochromatosis in Spain

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To the Editor:

We present the case of a 31-year-old woman with no relevant medical history, who consulted because of lesions on the backs of the hands related to minor traumas; the lesions worsened in the summer leaving residual hyperpigmentation (Figure). The patient had phototype III skin and displayed discrete hypertrichosis in the zygomatic areas. Photosensitive dermatosis was suspected and a battery of tests was requested to measure liver function, serum iron, transferrin and ferritin levels, blood and urine porphyrins, and photosensitivity.

High levels of porphyrins were found in the 24-hour urine collection: 2104 µg/L (normal values: <200 µg/L), 85 % of which were uroporphyrins.

Levels of porphyrins in the plasma were 25 µg/L, exceeding the normal range (< 10 µg/L). Levels for serum iron were 2104 µg/L (normal values: 92-155 µg/dL); transferrin: 310 mg/dL (normal values: 205-365 mg/dL); and ferritin: 175 µg/mL (normal values: 13-160 µg/mL); all of which were high or at the upper limit of the accepted normal range. Liver ultrasound showed no abnormalities.

A diagnosis of porphyria cutanea tarda (PCT) was reached on the basis of the symptoms, clinical indicators, and test results. The patient reported no family history of skin lesions or liver disease. Oral contraceptives (OC) taken by the patient for 6 months prior to consultation were initially considered a possible trigger for the PCT, but the lesions continued to appear after this medication was suspended. There were no other apparent triggers as the patient was not a habitual drinker and tests for hepatitis were negative.

Genetic studies for the most common hemochromatosis mutations (C282Y, H63D) showed the patient to be heterozygous for C282Y. This could explain the discreet abnormalities seen in the iron metabolism and, in conjunction with the use of OC, could have contributed to her developing PCT. In view of the patient's wish to start a family, her husband was tested for hemochromatosis. He was found to be heterozygous for the H63D mutation.

Treatment consisted of phlebotomies at 2 week intervals and this led to remission of the skin lesions and a return to normal porphyrin levels in both plasma and urine.

We were unable to determine the enzymatic activity of erythrocyte uroporphyrinogen decarboxylase (URO-D) as follow-up of the patient was incomplete.

PCT is the outcome of a deficit in or inactivation of the URO-D enzyme, resulting in the accumulation of photosensitive metabolites that are excreted in the urine and feces.[1]

There are three main types of PCT: I, II, and III.[2] Type I—the sporadic variety—is most common, with inactivation limited exclusively to the liver in patients with no previous family history. Type 2—the familial variant—is characterized by the inactivation or deficiency of the URO-D enzyme in all tissues. Type III is characterized by inactivation in the liver where there has been some previous family history of the condition.

Onset tends to occur in adulthood, and there are several known triggers: viral hepatitis, alcohol, OC and hormone replacement therapy, polychlorinated hydrocarbons, hemodialysis, and situations leading to iron overload like hemochromatosis.[3,4] The most common trigger varies according to age, sex, and geographical location. In men, alcohol abuse and chronic viral hepatitis are the most common triggers, while in women, hormone therapy is the single factor implicated in a large percentage of cases. Exposure to hydrocarbons has been identified as a trigger in developing nations, while infection by the hepatitis C virus is a more common element in the Mediterranean and Latin American countries.[2]

Hemochromatosis is a autosomal recessive genetic condition with a prevalence of 1/200.[5] It is characterized by increased intestinal absorption of iron that

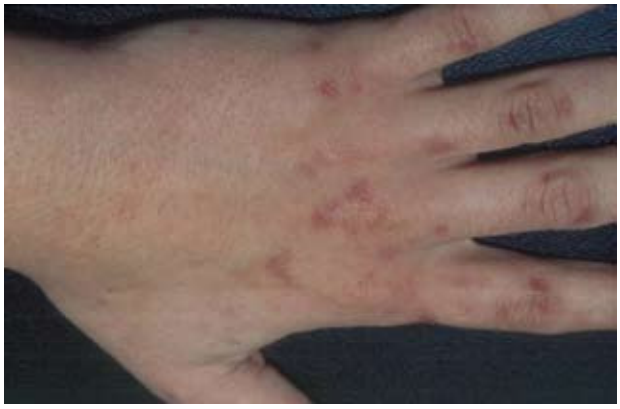

Figure 1. Residual hyperpigmented lesions on the back of the hands.

Table. Studies Including a Series of Healthy Patients With Porphyria Cutanea Tarda (PCT) in Which the C282Y and H63D Mutations Were Observed to be More Common in Patients Affected by PCT

Study	*Mutation*	*PCT*	*Controls*	*Country*
Roberts (1997)	C282Y	44 %	11 %	United Kingdom
Santos (1997)	H63D	23 %	4 %	The Netherlands
Sanpietro (1998)	H63D	29 %	13 %	Italy
Martinelli (2000)	C282Y	17 %	4 %	Brazil
Bulaj (2000)	C282Y	34 %	13 %	USA
	H63D	22 %	20 %	
Chiaverini (2003)	C282Y	18 %	1 %	France
	H63D	54 %	37 %	
Frank (2006)	C282Y	15 %	5 %	Germany
	H63D	35 %	29 %	

accumulates in the tissue (liver, pancreas, myocardium, skin, joints), where it produces clinical symptoms. Hemochromatosis is suspected in premenopausal women where there is transferrin saturation of more than 50% or ferritin levels of above 200 µg/L.[6] Even though 80% of patients with PCT have hepatic siderosis and 60% have hyperferremia, less than 20% fulfill the criteria of hemochromatosis.[7]

Various mutations associated with this disease have been identified recently.[8] The most common of these—C282Y and H62D—are found on the HFE gene on the short arm of chromosome 6. In the former, tyrosine is replaced by cysteine at amino acid 282, while in the latter, histidine replaces aspartic acid at position 63.[8] Eighty percent of these patients are homozygous for C282Y, and 20% are double heterozygous for both this and H62D.

The prevalence of these mutations varies from one population to another. The former is predominant in Nordic and central European countries and among the Celtic populations of Spain (Galicia and Asturias),[9] while the second is common in the Mediterranean area. In Spain, there is 1.7% prevalence of C282Y, while there is more than 20% prevalence of H63D.[10] However, the clinical diagnosis of hemochromatosis is far less common, which leads us to suppose low penetrance and late clinical diagnosis.

These mutations appear to be more common in patients with PCT due to the fact that homozygotes, heterozygotes, and double heterozygotes for these mutations are more likely to produce iron overload, which acts as a trigger for PCT, either alone or concomitantly. The H63D mutation in heterozygosis is not significant in iron overload and the development of PCT, but its role increases in double heterozygosis.[4]

Several studies with a series of patients have demonstrated the previous association. Thus, in most of Europe, including Spain, the United States, and South America, C282Y is the most common mutation,[3,4,10-16] while in Italy, mutation H63D is more widespread[17] (Table).

The treatment of choice for PCT is phlebotomies at 2 week intervals, extracting 200-500 mL according to tolerance. Clinical response is seen within 2 to 3 months and tests prove normal at 12 months. Serum iron levels of less than 25 µ/g/L are sufficient to control the disease.[18] Other accepted treatment options include the antimalarial drugs chloroquine and hydroxychloroquine, which help achieve faster results when combined with bleeding.[3,17] There is a poorer response to antimalarials in those cases of significant iron overload that tend to occur in patients homozygous for C282Y, and it may therefore be necessary to combine the 2 options.[3,18]

Trigger factors like hormone therapy, alcohol, liver failure, and viral hepatitis must be corrected or minimized.

This article aims to call attention to the fact that genetic screening for hemochromatosis can be useful in patients with PCT in whom no clear trigger can be identified, as this test is readily available within the Spanish health system and can help to diagnose these latent hemochromatoses. Also, as these are relatively common mutations (up to 20% of the population may be carriers) genetic testing and counseling could be provided for couples where one member is known to have PCT and some of the mutations described above.[11]

In this case, both members of the couple were carriers of the most common mutations for hemochromatosis. This situation gives them a 25% chance of heterozygous descent, although penetrance of this disease is known to be low and therefore the possibility of their children suffering hemochromatosis will be lower.

The subtype of PCT could not be reliably established for this patient as the erythrocyte URO-D and URO-D genetic tests were not undertaken. As a result, even though there was no previous family history of photodermatosis or liver disease, type II PCT could not be entirely ruled out. Although this matter has little bearing on treatment options in such cases, the information would prove useful as a basis for providing genetic counseling, above all for young women experiencing PCT in the absence of other triggers.[19]

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Conflicts of Interest
The authors declare no conflicts of interest.

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Melanoma in a Patient With Parkinson Disease

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To the Editor:

There has been discussion of the link between melanoma and Parkinson disease (PD) in the literature, along with the possible causal relationship between levodopa and rasagiline therapy and the appearance of melanoma. We present the case of an 81-year-old woman, Caucasian, phototype III, home maker, with no history of sunburn or family history of melanoma, who consulted for a pigmented lesion on the right cheek that had appeared a year earlier. Pathologic study led to a diagnosis of lentigo maligna and the lesion was excised. The patient had a personal medical history of idiopathic PD treated with Sinemet (levodopa/carbidopa) and Azilect (rasagiline) for the last 18 months. We reviewed the literature in order to