

Porphyria Cutanea Tarda and Spherocytosis: A Non-random Association?

Aurélie Du-Thanh¹, Patricia Aguilar-Martinez², Cecilia Enescu¹, Séverine Cunat², Bernard Guillot¹ and Olivier Dereure¹

¹Department of Dermatology, and ²Laboratory of Haematology, University of Montpellier I, University Hospital, Hospital Saint-Eloi, 80 avenue Augustin Fliche, FR-34295 Montpellier cedex 5, France. E-mail: a-du_thanh@chu-montpellier.fr

Accepted Aug 28, 2012; Epub ahead of print Oct 23, 2012

Porphyria cutanea tarda (PCT) results from an anomaly of hepatic haem metabolism. However, little is known about the possible association between PCT and congenital haemolytic disorders implicating increased erythrocyte turnover. We report here the first case of PCT associated with hereditary spherocytosis (HS) and discuss the potential pathophysiological implications of these combined conditions.

CASE REPORT

A 52-year-old woman was referred for blistering lesions and skin fragility with bruises occurring after minor trauma, located on sun-exposed areas and evolving since the previous summer. Her face was slightly greyish, a clinical manifestation she had not noticed previously. Her medical history was remarkable for hereditary spherocytosis with splenectomy during her first year of life. She had been taking substitutive hormone therapy during the previous 5 years, a combination of topical oestrogen and oral progesterone. She denied any excessive alcohol consumption. Clinical examination revealed the presence of rare blisters, along with crusts, erosions and scars, on the dorsum of her hands. Histological examination of a bullous lesion revealed subepidermal blister and mild inflammatory infiltrate surrounding ecstasic vessels in the papillary dermis, reminiscent of PCT. Biological investigations showed classical signs of splenectomized hereditary spherocytosis: spherocytes and Jolly's bodies on the blood film, thrombocytosis (related to splenectomy), normal number of reticulocytes, decreased haptoglobin (0.11 g/l, normal >0.3 g/l) with a negative Coombs test. Osmotic fragility tests including the pink test showed pathological haemolysis. Flow cytometry showed the characteristic decrease in band 3 (a red cell membrane protein) in the eosin-5-maleimide test. There were no clues for chronic viral hepatitis, but hyperferritinaemia (1,139 ng/ml, normal <200 ng/ml), elevated transferrin saturation up to 79.4% and fully confirmed PCT with total urinary porphyrins up to 3,762 nmol/24 h (normal <300 nmol/24 h) and a predominant increase of uroporphyrins (40% of the total urinary porphyrins, i.e. 1,505 nmol/24 h, normal <30%). The ratio of urinary porphyrins to urinary creatinine was >500. Uroporphyrinogen decarboxylase (UROD) activity was 50% decreased in erythrocytes in a first analysis before any treatment and elevated up to 5-fold the upper limit in a second analysis performed 6 months after the end

of the phlebotomies, supporting the hypothesis that chronic haemolysis and a probable induced hyperreticulocytosis dramatically disturb this analysis. Nevertheless, the second analysis was performed under better technical conditions, which tends to conclude to a normal value of UROD activity. No mutation in the gene encoding UROD could be detected. We could not perform family investigations because the patient had been abandoned at birth and did not know her biological relatives. Magnetic resonance imaging (MRI) of the liver showed significant iron overload, with a hepatic iron concentration of 170 µmol/g, whereas analysis of the *HFE* gene revealed no C282Y or H63D mutation.

A protracted complete clinical remission was obtained after repeated phlebotomies (450 ml each, every 2–3 weeks) and discontinuation of the hormonal therapy: bullae disappeared after the fourth phlebotomy, but skin fragility and greyish hyperpigmentation of the face persisted until the tenth, along with hyperferritinaemia. The total blood subtraction needed was 4,500 ml (approximately 2.7 g iron), with no modification of the blood haemoglobin concentration before and at the end of the blood subtractions (mean 14 g/dl). One year after the end of blood subtractions, complete clinical remission was still ongoing, but urinary porphyrins remain increased up to 550 nmol/24 h (normal <300 nmol/24 h).

DISCUSSION

The final diagnosis in this patient was a sporadic PCT, and multiple triggering factors probably led to the occurrence of the symptoms. Sporadic and familial PCT share the same triggering factors: iron overload, hepatitis C chronic infection, alcohol-abuse and oestrogens are the most common acquired causes (1). Here, menopause with the interruption of blood loss through menstruation, which may have triggered the development of iron overload due to chronic haemolysis, along with the prescription of oestrogen replacement therapy, could be considered as key factors. However, oestrogen replacement therapy had been used for 5 years prior to onset of PCT and a previous report does not support its putative causative role (2).

Among the possible triggering factors we were particularly interested in the putative role of the chronic haemolytic anaemia due to HS. To our knowledge, this association has not been reported previously.

HS is an inherited haemolytic anaemia occurring with a prevalence of 1/3,000 (3) in North European populations, with a predominantly autosomal dominant mode of

inheritance. Clinical severity is very heterogeneous, from symptom-free carriers to severe haemolysis. A direct, causative relationship between HS and PCT is possible in our patient. Indeed, inhibition of hepatic UROD activity may result from an iron overload process: the increased red cell turnover due to HS may have led to hepatic iron overload and consequently to UROD activity inhibition with accumulation of uroporphyrin. Indeed, chronic haemolysis is likely to result in hepatic iron overload, which was present in our patient as in a majority of PCT cases, even though its relevancy in PCT mechanisms is still a matter of debate (4–9). However, this biochemical abnormality should have led to earliest clinical manifestations given the congenital nature of the haematological disorder. Thus, other, more recent, triggering factors, such as menopause and its hormonal treatment, are necessary to explain the occurrence of the symptoms in middle-age in our patient. In addition, recent pathophysiological hypotheses have been proposed that overt disease, both in familial and sporadic PCT, may occur when UROD catalytic activity is inhibited in an iron-dependant manner to approximately 20% of normal activity (10). The theory is that uroporphyrinogen, the substrate of the enzyme, is transformed by an iron-dependent oxidation reaction into a competitive inhibitor of UROD (10, 11). High reticulocyte count accompanied by high UROD activity has not been investigated thoroughly, but Aarsand et al. found that UROD activity is not correlated with reticulocyte percentage (12).

To conclude, this original case of sporadic PCT associated with a congenital haemolytic disorder emphasizes, once more, the need for further research into coexisting congenital factors and the role of acquired risk factors.

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