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Iron overload and porphyria cutanea tarda

Camille Francès, Paris

Springer Healthcare

Notes are linked to the references page.

Iron overload is a key determinant in the pathogenesis of porphyria cutanea tarda: it must always be investigated and the findings will have significant therapeutic implications.

BACKGROUND

Porphyria cutanea tarda (PCT), the most common form of porphyria accounting for 80–90% of all cases[1,2] is due to uroporphyrinogen decarboxylase (UROD) deficiency. In different countries, its prevalence varies between 1/5000 and 1/70,000 (Table 1.).

Tableau 1. : Prevalence of porphyria cutanea tarda in different countries.[1]

Country	Prevalence per 100,000
Czech Republic and Slovakia	20
Sweden	10
United States	4
Western Europe	4
Norway	1
United Kingdom	0,2-0,5

The 3.6 kb gene that encodes UROD is located on chromosome 1P34 (short arm). UROD is found in all tissues and deficiency is only clinically expressed if its activity is reduced to less than 25% of normal. Where UROD acts in the pathway of haem synthesis is shown in Table 2.

Different forms are recognised. In type I or sporadic PCT—the most common (75–80% of cases)—UROD deficiency is restricted to liver cells and it fluctuates from marked deficiency at times of flare-up to normal levels during periods of remisssion or in response to treatment. Deficiency manifests as diminished UROD catalytic activity accompanied with normal or even elevated assay results in radio-immunological tests. This is associated with liver damage. This form tends to appear relatively late in life, starting in the fourth

decade, and is more common in men. Type II PCT (20–25% of cases) is hereditary with heterozygous UROD deficiency. It is transmitted as a dominant autosomal trait with low penetrance: probably fewer than 10% of carriers express deficiency. UROD activity is halved in all cells in the body, notably in red blood and liver cells. Homozygous UROD deficiency is very rare but can lead to hepato-erythropoietic porphyria, a condition similar to congenital erythropoietic porphyria (Gunther's disease). In types I and II, various different factors contribute to symptoms, including iron overload. The third form—the rarest (<1% of cases)—also runs in families but the genetic basis is as yet unknown. It causes hepatic UROD deficiency with normal levels in red blood cells. Whether a type IV exists or not is controversial, but if it exists it corresponds to a toxic phenomenon in which UROD activity in the liver is compromised by an exogenous chemical (hexachlorobenzene or dioxin). Symptoms are severe with major photosensitivity (possibly persisting for years after the poisoning event), intense, frequent hypertrichosis, arthritis and thyroid hypertrophy.

Tableau 2. : Haem synthesis.

Succinyl coenzyme A + glycine	
↓ Delta aminolevulinic acid synthetase	X-linked hereditary sideroblastic anaemia
Delta aminolevulinic acid	
····· Exit from the mitochondrion	
Delta aminolevulinic acid	
↓ Delta aminolevulinic acid dehydratase	Porphyria due to delta aminolevulinic acid dehydratase deficiency
Porphobilinogen	
↓ Porphobilinogen deaminase	Acute intermittent porphyria
Hydroxymethylbilane	
↓ Uroporphyrinogen III synthase and cosynthase	Congenital erythropoietic porphyria
Uroporphyrinogen III and I	
↓ **Urophorphyrinogen III decarboxylase**	**Porphyria cutanea tarda**
Coproporphyrinogen III and I	
····· Exit from the cytosol, re-entry into the mitochondrion	
Coproporphyrinogen III	
↓ Coproporphyrinogen III oxidase	**Hereditary coproporphyria**
Protoporphyrinogen IX	
↓ Protoporphyrinogen IX oxidase	Porphyria variegata
Protoporphyrin IX	
↓ Ferrochelatase	Erythropoietic protoporphyria
Haem	
+ globin / + apoprotein	
Haemoglobin / Cytochromes	

CLINICAL ASPECTS

Symptoms are similar in all forms of PCT. Dermatological manifestations predominate, especially on exposed skin as a result of sensitivity related to the porphyrins that build up in the dermis.[3] The peak absorption of these compounds is between 400 and 410 nanometres with a secondary band in the visible range between 580 and 650 nanometres.

Cutaneous fragility is the main skin manifestation, with serous or haemorrhagic blisters and erosions after minor trauma, especially on the backs of the hands (Figure 1.). Bullae may also form on skin exposed to ultraviolet (UV) radiation and these usually give way relatively quickly to erosions, brown scabs and, secondarily, milia (Figure 2.). Mucous membranes remain entirely unaffected.

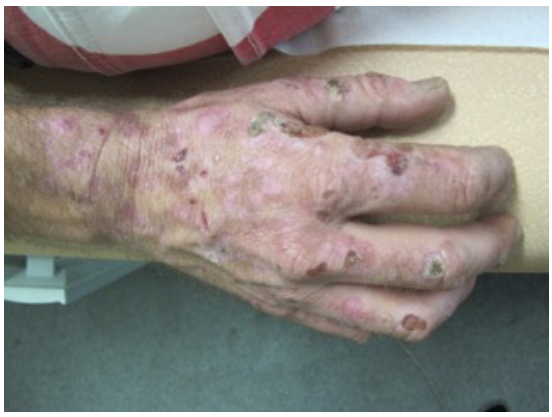

Figure 1. Bullae and excoriation on the back of the hands due to fragile skin

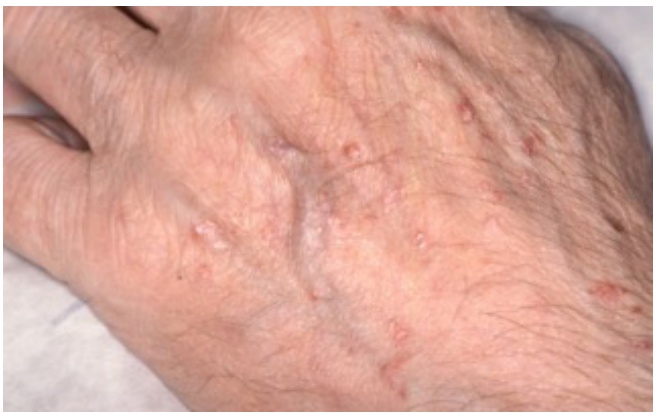

Figure 2. : Milia secondary to bulla formation on exposed skin

Other manifestations may be seen. Pruritus on exposed patches has no prognostic significance. Temporomalar hypertrichosis varies in intensity but is usually modest with a few tufts of long hair growing on the cheeks and at the side of the eyes; elsewhere it tends to be more diffuse (Figure 3.). The hair on the head can darken and dyschromia is common with either uniform pigmented areas or heterogeneous spattered patches, sometimes interspersed with bleached areas. Sometimes heliodermatitis-like symptoms are seen corresponding to photo-induced premature ageing with elastosis and deep wrinkles.

Figure 3. : Malar hypertrichosis

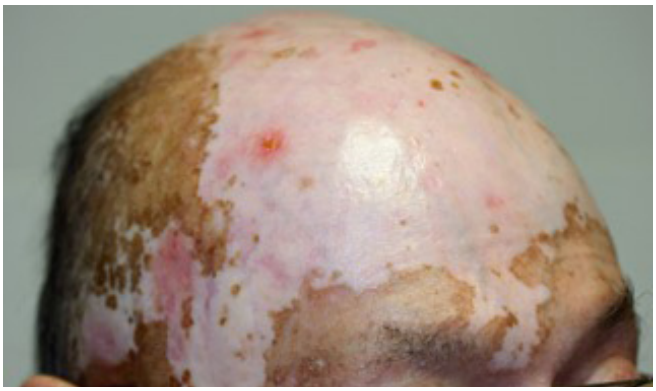

Figure 4. : Sclerodermiform appearance of the scalp with secondary alopecia

In about a third of cases, sclerodermiform lesions develop later on the face, neck, upper chest, trunk and scalp with alopecia (Figure 4.). This could be secondary to the stimulation of collagen synthesis by uroporphyrin I—independently of any solar irradiation—as has been demonstrated *in vitro* in cultured fibroblasts.[4] Calcium deposition in these plaques (a potential cause of atonic ulcers) is rare.

DIAGNOSTIC TESTS

The work-up sets out to confirm PCT, define the type and cause of any liver problems, and investigate any significant factors that might be relevant to the therapeutic strategy.[1,2]

PCT is diagnosed on the basis of finding high levels of uroporphyrin (carboxylated form 8 with 60% isomer I and 40% isomer III, carboxylated 7 and 6 forms with 90% isomer III) and coproporphyrin in the urine with a uroporphyrin:coproporphyrin ratio of over 3. Pink fluorescence in the urine under Wood illumination is unreliable. In the faeces, isocoproporphyrin derived from isomer III is dominant. Currently, which isomers are present is no longer routinely analysed and their simple presence at levels well above normal in urine and

faeces is enough to confirm a diagnosis of porphyria. Assays on liver samples — were they to be carried out — would detect elevated levels of uroporphyrin and carboxylated porphyrin 7. Blood tests show porphyrin profiles similar to those measured in urine.

A skin biopsy is only usually analysed if the diagnosis is suspected on the basis of the clinical picture. Histological analysis of a bulla can point to PCT if there is sub-epidermal detachment, no cells in the detached tissue and a festooned floor. Direct immunofluorescence can show deposits of immunoglobulin and complement around capillaries in the superficial dermis and less often the dermo-epidermal junction.

It is vital to investigate cofactors that might be contributing to the pathogenesis of PCT: an iron work-up is essential as are liver function tests and a whole blood count. In addition, haemochromatosis as well as serological status vis-à-vis viral hepatitis and HIV could be investigated.

DIFFERENTIAL DIAGNOSIS

Porphyria variegata shares dermatological symptoms with PCT[1] but these are accompanied by abdominal signs (pain, vomiting, constipation) and neurological signs (muscle weakness, confusion, coma) that are also seen in acute intermittent porphyria. There is no parallel between internal signs and dermatological manifestations (which can start years before). It is a dominant autosomal disease due to a deficiency in protoporphyrinogen oxidase in lymphocytes and fibroblasts. The uroporphyrin:coproporphyrin ratio in the urine is different and faecal protoporphyrin levels are high.

Dialysis patients can develop genuine porphyria but concomitant infection with a hepatitis virus or pseudoporphyria should be investigated without the typical abnormalities seen in PCT. In this last case, test-based diagnosis can be inconclusive because most dialysed patients—whether they have cutaneous manifestations or not—tend to have slightly elevated porphyrin levels in the blood and sometimes moderate UROD deficiency.[5] In patients on ambulatory peritoneal dialysis, porphyrins are usually less elevated and there is no UROD deficiency.[5]

Drug-induced photosensitivity reactions can give clinical pictures resembling PCT but without either hypertrichosis or pigment problems. The drugs that cause these are the tetracyclines, nalidixic acid, furosemide, disulone and naprosyne. Porphyrin assay results are normal.

Finally, like PCT, epidermolysis bullosa is associated with fragile skin, bulla formation following minor injury and milia. It can be differentiated from it: because mucous membranes may be involved; concomitant inflammatory enteropathy is common; on the basis of the results of biopsy analysis, direct immunofluorescence and electron immunomicroscopy; and the absence of any porphyrin abnormality.

PORPHYRIA CUTANEA TARDA AND IRON METABOLISM

The relationship between PCT and iron overload is long established, with iron overload seen in most cases (60–70%). Reducing iron reserves induces improvements in both clinical and test parameters whereas increasing them induces exacerbation. Mutations have been detected in the regulatory sequences of four genes involved in iron homoeostasis (ceruloplasmin, cytochrome B reductase 1, hepcidin, an antimicrobial peptide and solute carrier family 40 member 1.[6]

Haemochromatosis is associated with PCT as shown in a 2007 meta-analysis covering 66,000 cases of the former disease and 226,000 controls.[7] The presence of *C282Y/C282Y* mutations increases the risk of PCT with an odds ratio of 48 (24–95, $I^2 = 3\%$, 0–62%), 61 (28–130, $I^2 = 0\%$, 0–55%) for sporadic PCT, and 47 (14–160, $I^2 = 0\%$, 0–68%) for hereditary PCT. The presence of *C282Y/H63D* mutations increases the risk of PCT with an odds ratio of 8.1 (3.9–17, $I^2 = 0\%$, 0–47%), 9.1 (3.5–24, $I^2 = 0\%$, 0–53%) for sporadic PCT, and 15 (4.6–51, $I^2 = 0\%$, 0–0%) for hereditary PCT. For the heterozygous *C282Y* mutation, the odds ratio is 3.6 (1.8–7.3, $I^2 = 47\%$,

0–73%) and 4.7 (1.7–13, I2 = 53%, 0–79%) for sporadic PCT. The odds ratio for double *H63D/H63D* mutation is 3 (1.6–5.6, I^2 = 0%, 0–30%) and 3.1 (1.4–6.6, I^2 = 0%, 0–55%) for sporadic PCT. The heterozygous *H63D* mutation is not associated with any increase in the prevalence of PCT.

Iron stimulates uroporphyrin production at three different levels (Figure 5.): (1) by raising oxidative stress leading to oxidation of uroporphyrinogen and heptacarboxylporphyrinogen to generate porphyrin derivatives; (2) by reducing UROD activity through the production of an inhibitor, probably derived from hydroxymethylbilane or uroporphyrinogen; (3) by stimulating the synthesis of delta-aminolevulinic acid, a precursor of uroporphyrinogen.[2] Hydroxymethylbilane is the tetrazole precursor for uroporphyrinogen. Formation of an inhibitor of UROD in liver cells results from an oxidation phenomenon that is promoted by iron, cytochrome P-4501A2 activity, alcohol and oestrogen. In two murine models, mass spectroscopy identified the inhibitor as uroporphomethene, a compound that is closely related to uroporphyrinogen (from which it differs through the presence of an oxidised carbon bridge).[8] Isomer III is more potently inhibited than isomer I.

Lowering hepcidin stimulates iron absorption in the digestive tract.[9]

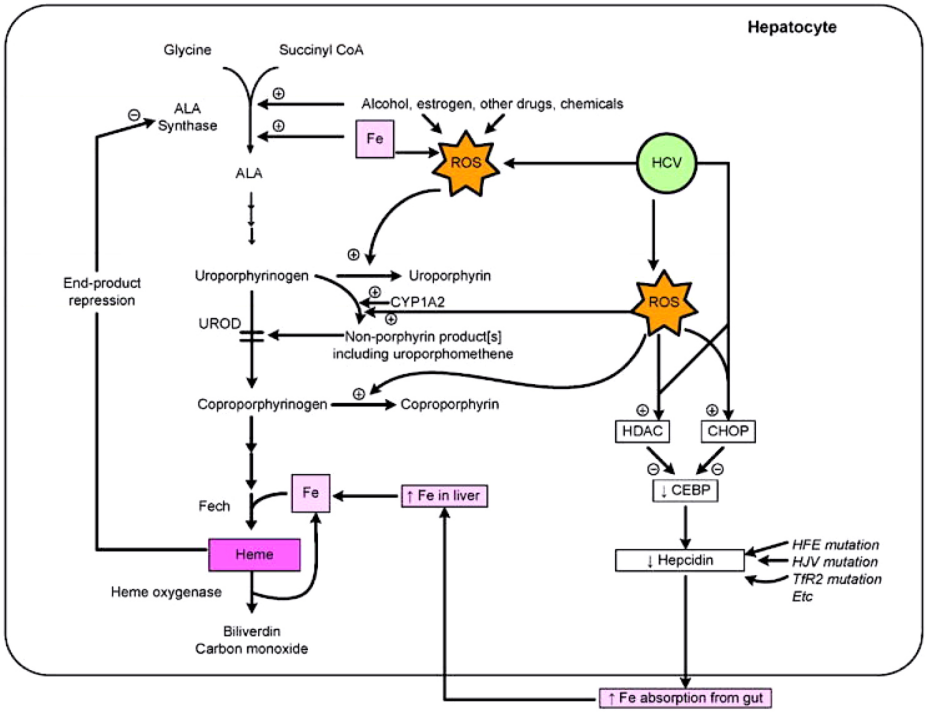

Figure 5. : Various points at which iron is involved in porphyrin metabolism in liver cells[17]
Abbreviations: Fe: iron; ALA: delta aminolevulinic acid; SO: oxidative stress; HCV: hepatitis C virus; FC: ferrochelatase; TD: digestive tract; ROS: reactive oxygen species.

OTHER COFACTORS ASSOCIATED WITH PCT

Many different factors are associated with prevalence varying according to PCT form and geographical location.

Between 30% and 90% of patients with PCT are heavy drinkers, especially those with the sporadic form. Alcohol stimulates iron absorption as well as the synthetase that makes aminolevulinic acid, promotes the dissociation of iron from its protein ligands, inhibits UROD and induces the generation of free radicals.

Hepatitis C virus (HCV) is also important in many cases of PCT, being found in 20–80% of patients (depending on geographical origin). Most of these correspond to active infection with viral RNA detected and elevated transaminase activities. However, the pathogenic mechanisms underlying this association remain poorly

understood, although it is believed that iron overload or cytochrome P450 may be involved.[2]
The role of HIV is difficult to establish because many patients have other cofactors, including medications, alcohol abuse and HCV infection.

The most common type of drug that induces flare-ups is high-dosage oestrogen prescribed to treat prostate cancer, but oral contraceptives can also do so. In rats, oestrogens are known to augment iron stocks although pregnancy does not always exacerbate the disease.[10] Other drugs known to be 'porphyrinogenic' include barbiturates, hydantoin, sulfamides, rifamycin, griseofulvin, vitamin B12, methotrexate, cyclophosphamide, busulfan, simvastatin and pravastatin. A regularly updated list of drugs to be avoided in different forms of porphyria is available on the web site of the *Centre Francais des Porphyries* (www.porphyrie.net).

Hexachlorobenzene, used as a fungicide in agriculture, caused wholesale epidemics of PCT in Turkey in the 1950s. This compound has been shown to inhibit hepatic UROD in animals, resulting in a PCT-like condition. Other chlorinated hydrocarbons such as dioxin, a potent activator of delta aminolevulinic acid synthetase, can also induce PCT. Occupational exposure to toxins may cause some cases of PCT.[11]

TREATMENT

Exposure to sunlight—especially in the 400–410 nanometre range of wavelengths—should be avoided as much as possible. PCT sufferers should wear clothing that covers the body (hat, long sleeves, etc.), and sunscreen should be applied to exposed parts, especially products containing zinc or titanium dioxide.

Avoiding trigger factors such as alcohol and oestrogen is also important. Reducing dietary iron consumption is recommended, with red meat and liver kept to a minimum because of their high haem content.

If such preventive measures fail to resolve the problems, symptomatic treatment may be indicated, essentially bleeding or synthetic antimalarial drugs.

Bloodletting can lower iron levels.[2] Taking out 300–500 mL every week or 2 weeks is recommended until the ferritin concentration drops below 25 ng/ml. Before each bleed, haemoglobin should be over 11 g/dL. Clinical remission is usually obtained once 2–4 litres of blood have been removed; improvements in test parameters usually follow later (after about 13 months). Bullae disappear within 2–3 months and skin resistance is restored after 6–9 months. Maintenance treatment with monthly bleeds is not essential. Pre-existing anaemia, protein deficiency (which can be associated with cirrhosis or haemorrhagic disease) contraindicate therapeutic phlebotomy.

Synthetic antimalarial drugs are usually prescribed at low dosage (125 mg chloroquine every other day or 200 mg hydroxychloroquine twice a week). These bind to 7 and 8-carboxylated porphyrins forming soluble complexes that accumulate inside lysosomes and are eventually cleared from the tissues via the kidneys. They inhibit delta-aminolevulinic acid synthetase. Transaminase activities and porphyrin levels are often elevated—usually moderately—at the beginning of a course of treatment, returning to normal within 2 months. Clinical remission is obtained after 3 months but treatment should be continued for 2–18 months (with porphyrin levels normalising in 4–16 months). At high doses, antimalarial drugs can induce lysis of liver cells and although short courses of high-dosage treatment (750 mg hydroxychloroquine a day for 3 days)—possibly after preliminary phlebotomy—have been proposed,[12] this would be unwise because of the risk of hepatic toxicity.

Desferrioxamine (Desféral) is useful if bloodletting is contraindicated (refractory or haemolytic anaemia). Its therapeutic effects are comparable to those of bleeding whether it is administered by slow subcutaneous injection (40–50 mg/kg over 8–10 hours, 5 days a week until test result normalisation and thereafter 5–10 days every 2 months) or intravenously (200 mg/kg in 500 mL normal saline once a week).[13]

Oral chelators such as deferasirox and deferiprone can also be prescribed, especially if ferritin levels are very high. These have proved effective in small studies and individual case histories.[14] Other treatment modalities are indicated in exceptional cases, including plasmapheresis and vitamin E. Erythropoietin can be used, especially in patients on dialysis with iron depletion during the dialysis.[15] Kidney transplantation can cure PCT.[16]

In conclusion, iron overload plays a central role in the pathogenesis of PCT and reducing it is a fundamental issue in treatment.

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