INTRODUCTION

Porphyria cutanea tarda is caused by the partial deficiency of uroporphyrinogen-decarboxylase (Urod) activity, inherited or acquired, with resultant accumulation of uroporphyrin (URO) and 7-carboxyl porphyrinogen, mostly in the liver. The word porphyria originates from the Greek word porphura, which means purple color, and was chosen because of the urine reddish to purplish staining of patients with porphyria.

In 1911, Günther described “chronic hematoporphyrinuria” including cases, which nowadays are recognized as porphyria cutanea tarda (PCT) and porphyria variegata (PV). In 1937, Waldenström renamed this group as “porphyria cutanea tarda”, not distinguishing from PV, but in 1957, he acknowledged the difference between the two disorders.

PCT is universal and the most frequent porphyria. The disease usually appears in middle-age individuals, the majority of them over 40 years old. In the past, it was found mostly in men, but the current incidence in women, is increasing due to the intake of estrogens and to the increase in alcohol consumption.

The disclosure of low Urod activity in PCT promoted its subdivision.

Sporadic porphyria cutanea tarda (Type I, symptomatic or acquired) – It encompasses 72% to 84% of cases, and the enzyme deficiency is restricted to the liver, with normal erythrocyte Urod activity. There is no family history. The specific enzyme defect is not caused by mutation in the Urod locus, and the cDNA sequences of hepatic, extra-hepatic Urod, as well as the promoter region of the gene are normal.

Familial porphyria cutanea tarda (Type II or inherited) – It comprises 16% to 28% of cases. Urod activity is reduced to half normal in all tissues (erythrocytes and liver) due to reduction in enzyme synthesis or stability. Differentiation between PCT types I and II cannot be solely based on erythrocyte Urod activity, which may be at the lower limit in PCT type II and below the normal interval in PCT type I.

Thus, DNA testing is preferred for the identification...
of familial cases. Mutations in the Urod gene discriminate familial from sporadic forms. Many Urod mutations (more than 40) in the 1p34 chromosome diminish enzyme stability or cause altered pre-RNAm splicing. It is an autosomal dominant disorder with low clinical penetrance; less than 10% of affected subjects are symptomatic. As most individuals who inherit the enzyme defect do not manifest the disorder, it is suggested that additional genetic or non-genetic factors are needed for expressing the disease. The age at onset of the disease, severity of the symptoms, sex distribution, liver enzyme and iron profiles are not different between types I and II.

Type III porphyria cutanea tarda – It is biochemically indistinguishable from type I (normal erythrocyte Urod), but it affects more than one family member. It occurs in a small number of patients (<5%). The promoter region and the coding DNA sequence of Urod are normal, suggesting that other loci are involved in its pathogenesis, and these may be genes affecting tissue iron.

Toxic porphyria cutanea tarda – It occurs after the exposure to hexachlorobenzene (HCB) 20 and tetrachlorodibenzo-p-dioxin (TCDD), which diminish hepatic Urod activity.

PATHOGENESIS

Biosynthesis of heme and inhibition of uroporphyrinogen-decarboxylase

The main sites of heme synthesis are the bone marrow (85%) and the liver. Heme biosynthesis is depicted in Figure 1. The fifth enzyme of the heme biosynthesis chain, is a polypeptide of approximately 42kDa, coded by a single gene in 1p34 chromosome, with 10 exons distributed in 3kb. It is a cytoplasmic enzyme and it catalyzes the sequential decarboxylation (oxidative) of four acetyl groups of uroporphyrinogen (Urogen), yielding 7-, 6-, 5- and 4-carboxyl porphyrinogen or coproporphyrinogen (Coprogen). In PCT there is an inversion in the action sequence of the enzymes Urod and Coprogen oxidase; the latter may initially cause decarboxylation of 5-carboxyl porphyrinogen, yielding dehydroisocoproporphyrinogen, which is decarboxylated by Urod, resulting in harderoporphyrinogen (Harderogen) that goes back to the heme biosynthesis chain or may be hydrated forming isocoproporphyrinogen (Isocopro), thus explaining its increase in the stools of PCT patients.

Individuals with PCT seem to be inherently predisposed to present Urod deficiency in response to hepatic injury. PCT results in progressive inactivation of Urod (structurally normal) in the liver, by a specific process affecting the catalytical site, not affecting the main epitopes. Liver Urod activity decreases to less than 25% of normal, which generates enough quantities of porphyrins to cause photosensitization. Although this process is described in sporadic PCT, it is also likely to occurs in familial form.

In 1998, Elder reviewed which factors interfered in the inactivation mechanism of Urod in the hepatocytes, in experimental models, and observed
...that three main factors accelerated inactivation: iron overload, cytochrome P450 induction and increased supplementation of delta-aminolevulinic acid (ALA).\(^{126}\) Iron acts by promoting the formation of oxygen reactive factors (ORF),\(^{27}\) which act by oxidating Urogen, generating URO and non-porphyrin (non-characterized) oxidated products which cause Urod inactivation. Oxidation occurs by means of hydroxyl radicals.\(^{25}\) Cyclic hydrocarbons induce cytochrome P450.\(^{28}\) Human cytochrome is less active than that of rodents in catalizing Urogen oxidation.\(^{29}\) ALA has an accelerating effect, likely due to the fact it acts as Urogen supplier, Urod substrate which is inhibited.\(^{30}\)

The interaction among inherited and acquired factors implicit in Urod inactivation are depicted in Figure 2 and it is based in a pathogenetic model suggested by Thunell and Harper.\(^{14}\) In normal conditions, just about all Urogen III is converted in Coprogen III. In the presence of iron, the oxidated proportion of URO and of non-porphyrin oxidation products is increased. Urod inactivation is self-supported. Iron acts as a switch which controls the generation and the inhibition of Urod, beginning a vicious cycle of its inactivation; its removal allows restoring Urod activity.\(^{11}\) There are several genes that may induce PCT: mutations in the Urod locus and other likely loci would be genes involved in iron metabolism, in production of hepatic heme (ALA formation) and in induction of cytochrome P450; other susceptibility genes, besides those of hemochromatosis, have not been identified yet. Iron may be increased due to dietary ingestion, increased intestinal absorption (alcohol and estrogens) or because a chronic viral infection releases the iron bound to ferritin. Alcohol and cyclic hydrocarbons may also induce the ALA-synthetase gene, increasing Urogen, the precursor of Urod inhibitors.\(^{31}\) Some authors suggest that auto-antibodies may be involved in the inhibition of Urod catalytic activity in patients with hepatitis C.\(^{31}\)

**Pathophysiology of skin lesions**

The photosensitization capacity of porphyrins was demonstrated by Meyer-Betz in 1912, when he self-injected hematoporphyrin.\(^{32}\) Porphyrin exposure to the spectrum of the Soret band (400 to 410nm) results in the emission of two fluorescence peaks in the region of 600 to 610nm and of 640 to 669nm.\(^{23}\) The photosensitization mechanism is not well defined. The interaction among several factors is likely to be responsible for the pathogenesis of skin lesions, such as oxygen reactive factors, cells (mast cells and fibroblasts), soluble mediators (complement and eicosanoid systems) and matrix metaloproteinases.\(^{25}\)

**Oxygen reactive factors (ORF)** – Porphyrins (URO and Copro) absorb light energy generating a porphyrin molecule in the excited singlet state, which converts spontaneously to the triplet state of lower energy level and longer average life, facilitating the reaction with biological substrates. Porphyrins in the triplet state transfer energy to oxygen (O\(_2\)) molecules, producing the ORF, such as the singlet oxygen (\(^1\)O\(_2\)), superoxide anion (O\(_2^-\)), hydroxyl radicals (OH), hydrogen peroxide (H\(_2\)O\(_2\)) and lipid peroxides, which interact with cell membranes causing tissue injury and release of pro-inflammatory mediators. Singlet oxygen (\(^1\)O\(_2\)) is probably the main mediator of tissue injury.\(^{35}\) This process is called photodynamic reaction. Several studies support the participation of

---

**FIGURE 2: The inactivation mechanism of uroporphyrinogen-decarboxylase in hepatocytes and interaction between inherited and acquired factors in porphyria cutanea tarda (pathogenetic model) source: Thunell S et al.\(^{14}\)**
ORF in photosensitivity induced by porphyrins.34,55

Physicochemical properties of porphyrins – Porphyrin distribution in tissues depends on its physicochemical properties. URO and Copro are hydrophilic and accumulate majorly in the lower epidermis and upper dermis; on the other hand, protoporphyrin (Proto) has greater affinity with lipid membranes (endothelial cell and lysosome membrane). This explains the clinical differences between erythropoietic protoporphyrina (EPP) and PCT.4

Complement participation – Its participation in the genesis of the skin injury was suggested by immunofluorescence studies which identified complement (C’) on vessels walls and on the dermal-epidermal junction (DEJ).60-68 In vitro irradiation of serum of PCT patients results in C’ activation.29 Porphyrin-induced photosensitization is suppressed in animals with C’ depletion and congenitally C5 deficient.60 Chemotaxis generation due to C5 is also seen after skin exposure to radiation at Soret band in PCT patients.55 Light irradiated porphyrin presumably generates ORF, especially singlet oxygen, which in turn, activates C’.41

Fibroblast proliferation and fibrosis – Enhanced biosynthesis of collagen occurs after incubation of fibroblasts with URO, irrespective of light radiation.42 C’ activation causes generation of anaphylotoxin (C5a),43 releasing histamine form mast cells, which stimulate collagen production.45 Fibrosis may also be secondary to vascular injury.56

Eicosanoid metabolism – In vitro incubation of peritoneal macrophages of rats or of fibrosarcoma cells with hematoporphyrin derivatives, followed by radiation of 630nm, results in the generation of prostaglandin E2 (PGE2).44 It is known that the PCT blister fluid contains PGE2.45

Matrix metaloproteinases (MMP) – In vitro photoexcited URO induces interstitial collagenases [MMP-1, MMP-2 (type IV collagenase) and MMP-3 (stromelysin-1)] in fibroblasts of human dermis, suggesting that the degradation of the dermis and basal membrane may be caused by such enzymes.56

The cause of pigment changes and hypertrichosis was not elucidated yet.

TRIGGERRING FACTORS

The factors that often contribute to the occurrence of PCT are alcohol, estrogens, iron, hepatitis C virus (HCV), human immunodeficiency virus (HIV), polychlorinated hydrocarbons and hemodialysis in patients with chronic renal failure (CRF). At least one of these factors is present in most patients, regardless of the PCT type.5

Alcohol – Alcoholism has been acknowledged as an important triggering factor of PCT.7 Since most of the alcoholics do not develop PCT, it is clear that alcohol only acts in synergism with other factors in predisposed subjects.49 This is possibly linked to the inheritance of mutations associated to hemochromatosis (Cys282Tyr).49 The analysis of urinary porphyrin excretion and of hepatic porphyrin concentration in alcoholics with chronic liver disease suggests that the biochemical changes consistent with Uro deficiency are more frequent than the diagnosis of PCT.50 Chronic alcoholism leads to suppression of erythropoiesis and increases dietary iron absorption.51 Alcohol induces cytochrome P450 isoenzyme causing the consumption of the hepatic heme and affecting ALA-synthetase expression, increasing Urogen generation and overloading Uro, inhibited or genetically altered, promoting the enzyme deficit manifestation.52

Estrogens – The use of estrogens for contraception, post-menopause hormonal replacement or hormonal therapy in men with prostate cancer, may be associated to PCT.4 Estrogens are the single triggering factor in over 25% of women with PCT,55 and its interruption is usually enough for remission, when used for a short time.55 The mechanism by which they act for PCT expression is not yet established. Estrogens induce hepatic ALA-synthetase, but this does not explain the excretion pattern of porphyrins in PCT.55 Estrogens may also act inhibiting Urod in the liver of patients with genetically reduced enzyme.56

Hexachlorobenzene (HCB) – Used as a fungicide, caused an “epidemic” of toxic PCT in southeast Turkey in 1952. It was also used as a pesticide in wheat seeds, but due to famine, thousands of people, mostly children ate bread made with this wheat and presented toxic PCT.56 Toxic porphyria may be caused by other chlorated hydrocarbons, such as polychlorinated biphenyl (PCB) and 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD), byproducts in the synthesis of herbicides.57

Hemochromatosis and iron metabolism – Iron overload ranges from mild to moderate in most patients, and clinical hemochromatosis is uncommon.22 Some degree of hepatic siderosis is present in 80% of patients with PCT.5,58,59 PCT is frequent where alcoholism is due to iron-rich beer and wine, like in South Africa and Italy.50 Cys282Tyr in the hemochromatosis gene was identified as a susceptibility factor for acquired or familial PCT.7 People homozygous for this mutation with hemochromatosis have up to 60-fold greater risk of having PCT53 and have earlier onset of skin lesions.59 In southern Europe, another mutation in the hemochromatosis gene which also may be associated to PCT is H63D.60

Viral infections – The role of hepatotropic viruses in triggering PCT has been reported since 1992.61 The prevalence of anti-HCV antibodies ranges
from 8% to 90%, and it is related to its endemicity in the population,9,11,62 being higher in some regions of Europe (France,63 Spain,64 Italy3,64 e Poland3) and in the United States.5,5 There is no predominance of HCV genotype in porphyrias.66 These patients have additional benefit from phlebotomy, because lowering iron improves hepatic inflammation and response to interferon treatment.57 There must be a predisposition for Urod deficiency, because most patients with hepatitis C do not develop PCT.68 As PCT may be the first indication of an HCV infection, it is important to be searched in all patients.69 The hypotheses explaining the role of HCV in PCT encompass: (1) lower Urod activity secondary to hepatocyte injury;64,70 (2) changes in the cytochrome P450 oxidase-dependent system;70 and (3) increased auto-immune response in the liver.31 Auto-antibodies would occur due to a mechanism of molecular mimicking72 and they act as inhibitors of the Urod catalytic activity.72 There is also slight increase in the prevalence of hepatitis B.73

The association of HIV with PCT was first recognized in 1987,74 and in the early records, PCT usually occurred in the late phase of the infection.75 Currently, in most cases reported, the diagnosis of HIV is concomitant to that of PCT;76 therefore, ordering HIV sorology should be considered in all PCT patients. Other triggering factors are usually associated, such as alcohol, hepatitis B and hepatitis C. It is likely that the combination of these factors causes hepatic injury, and the HIV infection enhances the injury.75

Hemodialysis – PCT may occur in patients with CRF treated by hemodialysis.77,78 Predisposition to PCT is likely due to preexistent reduction of hepatic Urod activity.79 Iron overload in these patients also contributes to reducing Urod activity.80

CLINICAL MANIFESTATIONS

Vesicles and bullae, followed by erosions and crusts occur mainly in sun and trauma exposed areas, such as face, back of hands (Figure 3) and feet.6,81 Just about all patients present skin fragility. Bullae are tense, not surrounded by inflammation, and their content is usually clear, occasionally hemorrhagic. Hypopigmented or hyperpigmented scars with milia occur mainly in the fingers and the back of hands.82 Another skin change is the diffuse hyperpigmentation of the face and of the photoexposed areas.6,69,91 Hyperpigmentation may be the first sign of the disease in women (Figure 4).83 Hair is usually of lanugo type but may vary in thickness and color, occurring in the frontotemporal and upper malar regions.81 Sclerodermiform plaques occur in 1.6% to 18% of patients69,84 and usually appear after long duration of the disease.84,85 Plaques are white-yellowish, hardened and they occur in photoexposed or protected areas.45

The association with scleroderma is rare86 Other cutaneous changes are cicatryptal alopecia,69 precocious aging with solar elastosis and comedones,81,82 and onycholysis.81 Non-cutaneous manifestations are peripheral neuropathy,87 Van der Hoeve scleromalacia perforans,86 palmar fibromatosis,86 deafness, insomnia, personality changes, conjunctivitis and epiphora.89 Nausea, anorexia, diarrhea and constipation are other symptoms described.82

ASSOCIATED CONDITIONS

Hepatic changes – Hepatic disease is unusual, despite hepatic enzyme changes and increased hepatic porphyrin, with precipitated uroporphyrinogen crystals inside hepatocytes.86 The crystals are needle-shaped brownish cytoplasm inclusions, showing double refringence under polarized light and specific of PCT;91 but their contribution to the progression of the hepatic disease is controversial.91 Cirrhosis occurs in less than 15% of patients, who have greater risk of developing hepatocellular carcinoma (HCC) than those with cirrhosis of other causes.59,92,93 The incidence of HCC in PCT ranges from 5% to 16%, and, in autopsies, from 40% to 50%, indicating that these tumors are asymptomatic and slow progressing.87 The coexistence of factors, such as viral hepatitis, alcohol and iron overload may explain the occurrence of HCC in patients with PCT.92 The risk of HCC increases in men older than 50 years, with symptomatic PCT for 10 years or longer and with cirrhosis.93, 94 The risk of HCC decreases with early effective treatment.94 The patients should be monitored with ultra-sound and serum alpha-fetoprotein measurements for the early detection of HCC.95 Surgery and the intratumoral injection of absolute ethanol, to cause tumor necrosis, are successful procedures in small tumors with no associated cirrhosis. Regardless of the treatment

employed, metastases are frequent, even in small tumors, because of microscopic vascular invasion.\textsuperscript{14}

\textbf{Glucose intolerance} – It is often mentioned in PCT, and in some reports the incidence of diabetes mellitus is greater than 40%, especially in men.\textsuperscript{6} In one study, 77% of participants had altered glucose tolerance test (GTT),\textsuperscript{48} but in another research, the GTT of 20 PCT patients was compared with controls and no differences were found.\textsuperscript{96} Some authors associate glucose intolerance to the presence of the hemochromatosis gene rather than to PCT.\textsuperscript{97}

\textbf{Other associated conditions} to PCT are systemic lupus erithematosus\textsuperscript{98} or discoid lupus,\textsuperscript{99} dermatomyositis,\textsuperscript{6} systemic sclerosis,\textsuperscript{86} hematological disorders,\textsuperscript{100} sideroblastic anemia,\textsuperscript{11} thalassemia\textsuperscript{11} and cytomegalovirus infection.\textsuperscript{80}

\section*{DIAGNOSIS AND LABORATORY FINDINGS}

The diagnosis of PCT is made clinically, histopathologically and by the analysis of urinary, fecal and blood porphyrins.

\section*{Porphyrin analysis}

The screening test, with the Wood lamp, is positive in urine (+ +) and in feces (+ +) and negative in blood (erythrocytes).\textsuperscript{101} If the screening test is positive or dubious, the quantitative test must be performed.

Urinary porphyrins may be quantified by the HPLC (High Performance Liquid Chromatography) method.\textsuperscript{102} The six porphyrin fractions are detected and identified with this test – uroporphyrin (URO), 7-, 6- and 5-carboxyl porphyrin, and coproporphyrin (Copro) – in 24-hour urine. In PCT, the characteristic pattern is the increased excretion of URO (50 times) and of 7-carboxyl porphyrin. 6- and 5-carboxyl porphyrins may also be increased. Copro is less increased. than URO is.\textsuperscript{14,50} The URO/Copro ratio is usually greater than 3:1, while in physiological conditions this ratio is about 1:4.\textsuperscript{25} The biochemical marker to assess response to treatment is the quantification of urinary porphyrins.\textsuperscript{69}

Fecal porphyrin of patients with PCT is increased and is primarily represented by Isocopro, 7-carboxyl porphyrin and, in lesser amounts, by URO and Copro. The 24-hour fecal protein excretion is greater than the total amount excreted in urine.\textsuperscript{25}

The main plasma porphyrin is uroporphyrin, which can be measured in a qualitative test, by plasma dilution in phosphate buffered saline and read in a spectrophotometer. It is further subjected to 410nm wave length, producing a characteristic emission peak between 618 and 620nm.\textsuperscript{505}

\textbf{Other biochemical changes} – Virtually all patients have increased serum iron, iron saturation, and ferritin.\textsuperscript{2,23} Approximately 50% of them have increased serum transaminases and $\gamma$-glutamyltranspeptidase.\textsuperscript{4}

\section*{HISTOPATHOLOGY}

PCT displays histopathologically characteristic subepidermal bulla that distinguishes it from other porphyrias, suggesting that in PCT an additional unknown pathologic event occurs.\textsuperscript{56,57,104} In the base of the subepidermal bulla, dermal papillae extend to the internal bulla cavity (Figure 5). This phenomenon called festonamento is explained by the rigidity of the upper dermis induced by eosinophilic material in vessel walls.\textsuperscript{36,37,104} Inflammatory infiltrate is mild or absent. In sclerodermiform lesions, dermis sclerosis is caused by increased collagen I, similar to systemic scleroderma,\textsuperscript{36,84} and there is a significant number of mast cells in the inflammatory infiltrate.\textsuperscript{43} Exposed skin often displays considerable solar elastosis.\textsuperscript{56}

With PAS (periodic acid Schiff) staining, hyaline material, PAS-positive and diastase-resistant is found in the upper dermis vessel walls and in the DEJ (Figure 6).\textsuperscript{36,37,37} Hyaline deposits are the response to repeated episodes of injury in vessel walls with content leakage.\textsuperscript{106} Electron microscopy demonstrated that thickening is due to multiple layers of basal lamina, thin collagen fibers and filamentous and amorphous material.\textsuperscript{56,57,104} Histochemical studies demonstrated that the hyaline deposits contain tryptophan, originated in the blood, not found in the dermis.\textsuperscript{107} The structural changes in the DEJ are identical to those described in vessels.\textsuperscript{56,57}

Direct immunofluorescence (DIF) detects IgG, IgA, IgM, and C3 within the vessel walls and in DEJ (Figure 7).\textsuperscript{38} Circulating auto-antibody against vascular, perivascular antigens and anti-basal membrane, or immunocomplexes, were not identified; therefore
it is unlikely that such deposits result from an immunological phenomenon. Several authors suggest that deposit occurs due to the entrapment of immunoglobulins and complement in the hyaline material. Since the DEJ deposits correspond to the vessel deposit, it is likely that they are leaking plasma components. The immunoglobulin deposits cannot be blamed for fragility because they also occur in EPP, in which there is no fragility. It is believed that such difference is related to solubility of the involved porphyrins.

Some studies using electron microscopy and immunomapping (antigenic immunomapping of the dermal-epidermal junction) observed different bulla cleavage levels: basal keratinocytes, lamina lucida, dense sublamina and papillary dermis.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of PCT must be made with hereditary coproporphyria, porphyria variegata, hepatoerythropoietic porphyria, late onset congenital erythropoietic porphyria (Günther disease), pseudoporphyria, acquired bullous epidermolysis and scleroderma. All these disorders can be differentiated on clinical, histological grounds, immunofluorescence or by the study of porphyrins.

**TREATMENT**

After the identification and suppression of the triggering factor of the disease, especially alcohol and estrogens, there is gradual improvement.

**Phlebotomy** – Several reports stress the efficacy of this treatment, which was introduced by Ippen, in 1961. Phlebotomy is an outpatient procedure in which approximately 500ml (one unit) of blood are removed weekly or at every two weeks, until hemoglobin reaches 10g/dl or serum iron reaches 50 to 60 ìg/dl. The goal of this treatment is to reduce the iron stores to a level lower than the normal limit. Ferritin does not assess the intensity of iron deposits, because it may be increased by infectious, inflammatory and malignant diseases. Low ferritin levels, on the other hand, always indicate low body iron stores, and thus, phlebotomies must be interrupted when the lower reference limit is reached. Porphyrin excretion may remain low after the interruption of phlebotomies. In 90% of patients treated with phlebotomy, the urinary excretion of URO reaches normal levels after five to 12 months. The remission time is quite variable (four to 85 months). Relapse occurs at about 2.5 years after the end of the treatment, and in most cases, responds to a new treatment. Phlebotomy is the treatment of choice for patients with the hemochromatosis gene, because it prevents iron induced hepatic injury. It is contra-indicated in cases of anemia, cardiovascular disease, hepatic cirrhosis (blood loss increases the need for albumin synthesis) and HIV.

**Antimalarials** – Low dose chloroquine diphosphate (aminoquinolina) is utilized. Hydroxichlorochine is seldom utilized and was associated to early relapse. In 1957, chloroquine was first used to treat PCT, because of its action in some photodermatoses. Chloroquine in antimalarial doses causes severe hepatotoxic reaction associated to intense uroporphynuria and photosensitization. Low doses - 125mg or 250mg - twice a week, were successfully used in several reports. Chloroquine administration is followed by increased...
urine excretion of porphyrins \(^{125}\) and slight increase in hepatic transaminases at the beginning of treatment. \(^{124}\) Chloroquine does not worsen hepatic injury \(^{124,126}\) nor causes retinopathy, when used in low doses. \(^{127}\) Bullae and cutaneous fragility improve in approximately 6 months and the porphyrin excretion normalizes between six to 15 months. \(^{117,122,124,127}\) It is recommended that treatment must not be interrupted until biochemical remission (urine URO < 100ìg/24h) is attained. \(^{122}\) The duration of the remission period varies from 17 to 24 months. \(^{112,122}\) Chloroquine is effective, however relapse occurs earlier than after phlebotomy. \(^{117}\) There are several hypotheses to explain the mechanism of action of chloroquine: (1) it chelates iron from hepatocytes, which is later eliminated; \(^{128}\) (2) it reduces ALA-synthetase activity; \(^{129}\) (3) it forms a complex with uroporphyrin, which is excreted by the liver through the bile; \(^{130}\) but the model utilized is not comparable to human PCT; \(^{129}\) and (4) it increases the excretion of porphyrins by means of exocytosis and has a porphyrinostatic effect, inhibiting porphyrin formation. \(^{124}\) Phlebotomy associated to chloroquine is employed when there is inadequate response the either treatment alone. \(^{151}\)

**Interferon-alpha (IFN-α)** – Its use in patients with HCV may improve the skin lesions and porphyrin excretion. \(^{152,153}\) The reduction in porphyrins may occur with no change in the HCV viral load. \(^{133}\) It is suggested that it acts by inducing reduction of hepatic siderosis \(^{152}\) or by its immunomodulator effect, diminishing the inflammatory response to HCV, which would cause Urod inhibition. \(^{133}\)

**Human recombinant erythropoietin** – In chronic renal failure porphyrins have displayed high affinity with plasma proteins and thus are not dialyzable. Chloroquine cannot be utilized because the complexes it forms with porphyrin are not filtered either, and the associated anemia precludes phlebotomy indication. The use of human recombinant erythropoietin can reduce iron excess. \(^{134,135}\) When the patient does not respond to this treatment, low volume phlebotomy is used. \(^{136}\) Renal transplantation may improve PCT. \(^{137}\)

Other possible treatments are the slow administration of subcutaneous deferoxamine (iron chelating agent), \(^{138}\) cholestiramine \(^{139}\) and oral thalidomide. \(^{140}\)

In the follow-up, the coexisting hepatic disease is supervised and, in order to prevent relapses, urinary porphyrins are measured, because porphyrinuria precedes dermatological manifestations.
REFERENCES


110. Klein GF, Hintner H, Schuler G, Fritsch P. Junctional blisters in acquired bullous disorders of the dermal-

How to cite this article: Vieira FMJ, Martins JEC. Porfiria cutanea tarda. An Bras Dermatol. 2006;81(6):569-80.