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Review article

Porphyria cutanea tarda: Recent update

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A B S T R A C T

Porphyria cutanea tarda (PCT) is the most common human porphyria, due to hepatic deficiency of uroporphyrinogen decarboxylase (UROD), which is acquired in the presence of iron overload and various susceptibility factors, such as alcohol abuse, smoking, hepatitis C virus (HCV) infection, HIV infection, iron overload with HFE gene mutations, use of estrogens, and *UROD* mutation. Patients with familial or type II PCT due to autosomal dominant *UROD* mutation also require other susceptibility factors, as the disease phenotype requires hepatic UROD deficiency to below 20% of normal. PCT clinically manifests with increased skin fragility and blistering skin lesions on sun exposed areas. The common age of presentation is 5th to 6th decade and occurs slightly more commonly in males. Although mild liver biochemical profile are common, advanced fibrosis and cirrhosis with hepatocellular carcinoma (HCC) can occasionally develop. Screening for HCC using ultrasound examination is recommended in PCT patients, especially with cirrhosis and advanced fibrosis. PCT is effectively and readily treatable with the use of either repeated phlebotomy or use of 100 mg hydroxychloroquine orally twice a week, and both the treatments are equally effective and safe. With the advent of new or direct antiviral agents for HCV infection, treatment of concomitant HCV has become safer and effective. Data are emerging on the benefit of these drugs as monotherapy for both PCT and HCV. After the achievement of remission of PCT, there remains a potential for relapse, especially when the susceptibility factors are not adequately controlled. Scanty data from retrospective and observational studies shows the relapse rate to be somewhat higher after remission with low-dose hydroxychloroquine as compared to phlebotomy induced remission. Future studies are needed on exploring mechanism of action of 4-aminoquinolines, understanding interaction of HCV and PCT, and relapse of PCT on long-term follow-up.

1. Introduction

Porphyria cutaneous tarda (PCT) is the most common human porphyria. Clinical profile with predominant cutaneous manifestations and its natural history with a chronic course characterized by relapses and remissions, led to the nomenclature of PCT, to differentiate from other cutaneous porphyria such as erythropoietic protoporphyria and congenital erythropoietic porphyria (predominant enzyme defects in the bone marrow) and hepatic porphyria such as variegate porphyria and hereditary coproporphyria, which present with both cutaneous and neurovisceral manifestations.

PCT is a hepatic porphyria, due to intrahepatic deficiency of an enzyme, uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the heme biosynthetic pathway (Fig. 1). The normal function of UROD is to catalyze the conversion of uroporphyrinogen to coproporphyrinogen. This is a four-step decarboxylase reaction, which mediates conversion of eight carbon uroporphyrinogen to hepta-, hexa-, penta, and finally four carbon molecule or coproporphyrinogen, the substrate for next reaction in the heme biosynthetic pathway, conversion to protoporphyrinogen mediated by enzyme coproporphyrinogen oxidase. Decreased activity of the enzyme UROD leads to accumulation of uroporphyrinogen and intermediates, which are then oxidized to uroporphyrins in the presence of CYP1A2 enzymes (Fig. 2). The accumulated uroporphyrins and intermediates spill over into the circulation and are excreted in the urine. This leads to a characteristic porphyrin pattern on biochemical examination of plasma and urine for porphyrins analysis: a) elevation of plasma porphyrins (normal < 1.0 mg/dL), b) peak fluorescence of plasma porphyrins at 618–621 nm wavelength, c) elevation of urine porphyrins (normal < 300 mg), and d) fractionation of porphyrins in urine or plasma with predominant elevation of uroporphyrins and hepta- or hexa- porphyrins. Both I and III isomers of porphyrins are increased, with predominant increase in type III isomers. Urinary amino-levulinic acid (ALA) excretion is normal or slightly increased, with normal excretion of porphobilinogen in urine, to differentiate from acute hepatic porphyria with cutaneous manifestations such as variegate porphyria and hereditary coproporphyrias.

PCT occurs throughout the world. The prevalence of symptomatic disease is 1 in 25,000 in the US, and more common in Czechoslovakia at 1 in 5000 in the general population. The exact incidence rate is unclear due to lack of data and potential for confounding with relapse and remissions in the index case. PCT can occur at any age, although, the peak age group is in the 5th or 6th decade. PCT occurs in both genders, with slightly more common prevalence in males due to higher frequency of susceptibility factors in males, and occurs equally in all the ethnicities.

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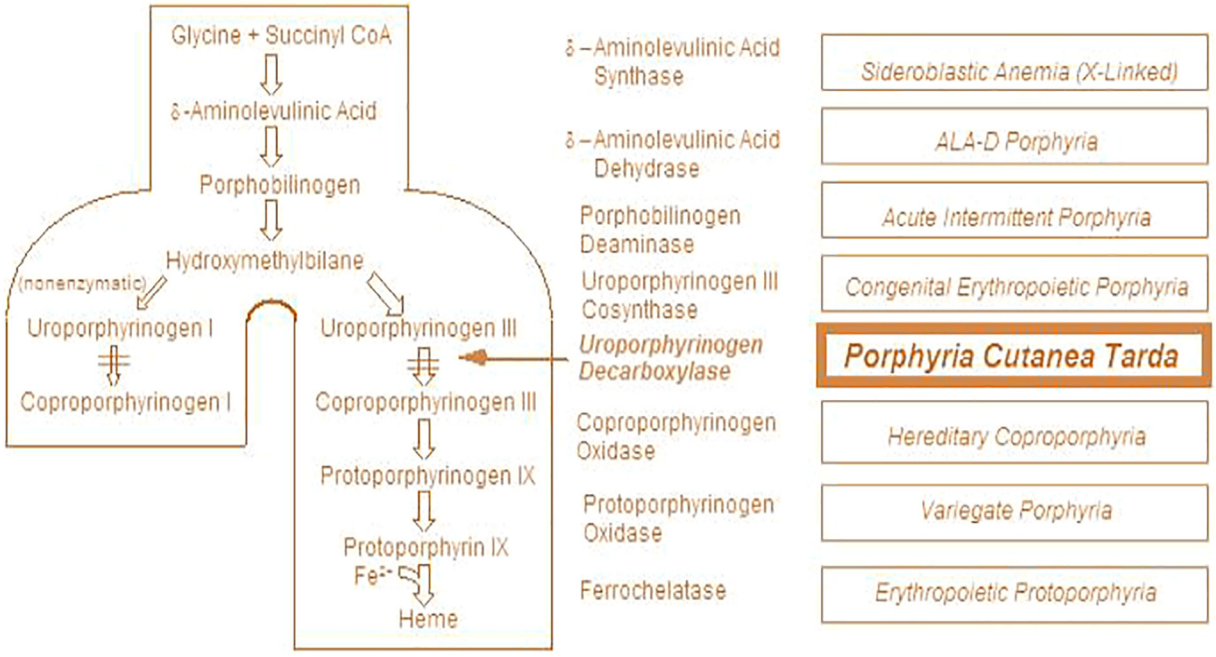

Fig. 1. Heme biosynthetic pathway and enzymatic defect in porphyria cutanea tarda.

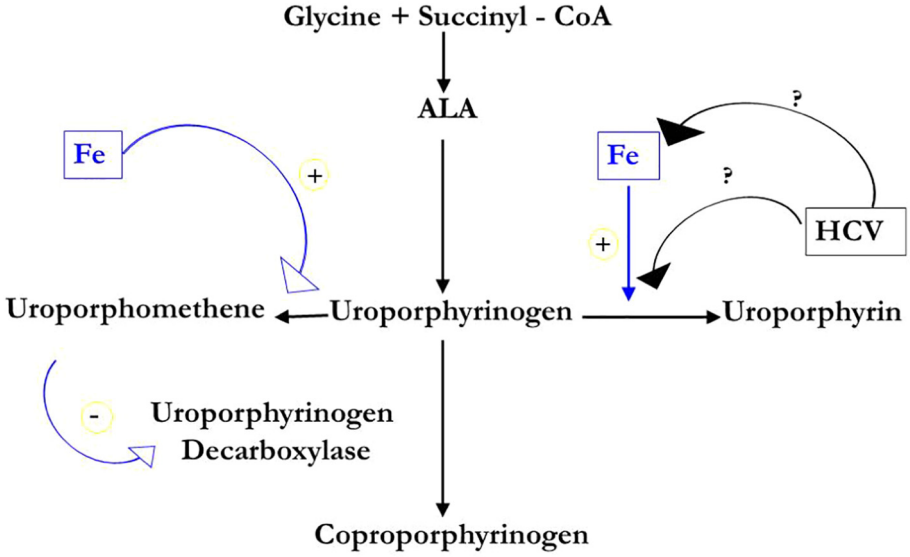

Fig. 2. Mechanism of generation of uroporphomethene, the inhibitor of uroporhyrinogen decarboxylase (UROD).

2. Pathophysiology and disease manifestations

PCT is an acquired porphyria, with deficiency of UROD acquired in the presence of iron overload and many susceptibility factors. Up to 80% of cases of PCT are sporadic with deficiency of the UROD acquired by many susceptibility factors. However, even 20% of cases of PCT which are due to inherited autosomal dominant mutation of UROD, susceptibility factors are needed to cause clinical symptoms and phenotype, as inherited mutation can only lead to 50% of reduction in the enzyme activity, while UROD deficiency to below 20% is needed to cause clinical symptoms and phenotype (Table 1). Accumulated uroporphyrinogen in the cytosol is oxidized to uroporphyrin in the presence of iron and other oxidative stressors [1]. Partial oxidation of uroporphyrinogen produces a molecule uroporphomethene, which can bind the enzyme but cannot be metabolized as a substrate [2]. It is possible that any of the three intermediates resulting from the partial oxidation of uroporphyrinogen III to uroporphomethene can act as UROD inhibitor (Fig. 2).

Based on the UROD activity in red blood cells as measured by enzyme immunoassay or mass spectrophotometric methods [3,4], PCT can be divided into 2 major subtypes: sporadic or type 1 PCT with near normal activity familial or type 2 PCT due to inherited autosomal dominant UROD mutation (type 2 or familial PCT) with erythrocyte UROD activity at about 50% of normal. Rarely patients with sporadic PCT may have a family history of PCT and these patients are known to have type 3 PCT (Table 1). Type 1 PCT constitutes about 80% of PCT pool and these patients do not have family history of PCT. On the other hand, type 2 PCT may often have family history as the UROD mutation is inherited in an autosomal dominant fashion. However, it must be noted that the mutation is not enough to bring down the hepatic UROD activity to around 20% of normal which is needed to manifest PCT, and therefore, even patients with type 2 PCT require additional acquired

Table 1
Types of porphyria cutanea tarda.

Type	Frequency	UROD mutation	Family history	Hepatic UROD activity	RBC UROD activity
Type 1	75–80%	No	No	< 20% of normal	Normal
Type 2	15–20%	Yes	Often	< 20% of normal**	~50% of normal
Type 3	< 5%	No	Yes	< 20% of normal	Normal

UROD: Uroporphyrinogen decarboxylase.

susceptibility factors for the disease phenotype. Another variant of toxic PCT has been described in 1950s from Turkey due to exposure to a fungicide, hexachlorobenzene (HCB) [5], or to tetrachlorodibenzo-p-dioxin (TCDD) [6].

2.1. Iron overload

Mild to moderate iron overload with increased serum ferritin levels and hepatic siderosis has been described in up to 90% of PCT, [7–12] and iron deficiency is protective [13]. Although associated susceptibility factors can cause iron overload such as mutations in the hemochromatosis gene (*HFE*) [14], downregulation of hepcidin from associated alcohol use and HCV infection [15], increased iron absorption and decreased levels of hepcidin are documented in PCT [16–19]. Further, phlebotomy with reduction in iron overload is an effective therapy for PCT [20,21].

2.2. Susceptibility factors

PCT is manifested biochemically and/or clinically when the hepatic UROD activity is reduced to about 20% of normal [22,23]. This clearly means that there are other disease modifiers or susceptibility factors which are needed for manifestation of the disease phenotype. Multiple susceptibility factors are associated in PCT patients (Table 2) [24–26]. Although, PCT can rarely occur without susceptibility factor, about 90% of patients have 3 or more susceptibility factors [25]. These include:

2.3. Alcohol use

Heavy alcohol use of > 40 g/day is considered an important susceptibility factor and is reported in about 60 to 90% of PCT cases, [27–30] although, only about 2% of subjects with chronic heavy alcohol use in one study were reported to have PCT [31]. Mechanisms of PCT development by alcohol are unclear and speculated to be due to down regulation of hepcidin resulting in increased iron absorption [32], and alcohol induced oxidative stress [33].

2.4. Smoking

Like alcohol use, cigarette smoking is also highly prevalent in PCT patients (Table 2). Mechanisms of smoking mediating development of PCT are speculated to be increased oxidative stress and induction of hepatic cytochrome P450 enzymes. However, no mechanism is clearly identified, and additional susceptibility factors are invariably present.

Table 2
Frequency of susceptibility factors in patients with porphyria cutanea tarda.

	Jalil (N = 143) [24]	Singal (N = 30) [26]	PC (N = 167) [90]
Smoking	81%	81%	90%
Alcohol use	87%	93%	72%
HCV infection	69%	81%	48%
HFE mutation	53%	58%	50%
Estrogen use	30%	20%	30%
UROD mutation	17%	8%	15%
HIV infection	13%	12%	2%

HCV: Hepatitis C virus; HFE: Hemochromatosis; UROD: Uroporphyrinogen decarboxylase; HIV: Human immunodeficiency virus.

2.5. Hepatitis C

About 70–80% of PCT patients in the US have associated HCV infection (Table 2). However, there is wide geographic variation in the prevalence of this infection in PCT with prevalence of antibodies to HCV, probably reflecting variations in the prevalence of at-risk populations [34,35]. There is no association of PCT with any specific HCV genotype. HCV is an important true susceptibility factor, and was the only factor varied between sporadic and familial PCT patients in a study from Scandinavia [36]. Mechanisms for association of HCV and PCT are unclear and may include oxidative stress and dysregulation of hepcidin expression with HCV infection [15,37].

2.6. HFE mutations

Mutations of the hemochromatosis gene (*HFE*) (Table 2) are more common in PCT than in the general population [14,30,38–48]. Data from several large studies have shown that any *HFE* mutation is present in 21–73% of cases, C282Y mutation in 2–42%, homozygous for the C282Y mutation 0–19% and heterozygous for H63D mutations in 23–50% of cases [35]. In a meta-analysis from 202 studies on over 66,000 PCT cases and over 200,000 controls, the odds of any HFE mutation was over two fold, with about 48 fold risk for C282Y homozygous mutation in PCT patients [49]. Iron overload is mild to moderate and clinically overt hemochromatosis is very rare [35].

2.7. Human immunodeficiency virus (HIV) infection

Since the first report of association of HIV infection and PCT in 1987, many such cases have been described [50,51]. Although, HIV infection has been documented in the absence of HCV infection in PCT patients [52], more and more data are emerging that most PCT cases associated with HIV infection have concomitant HCV infection, and HIV by itself may not be a true susceptibility factor [53].

2.8. Estrogens

Use of estrogens was first identified in men as a PCT susceptibility factor during hormonal treatment for prostate cancer [54,55]. Later, many reports confirmed this association in women using oral contraceptives, hormone replacement therapy, or use of tamoxifen for breast cancer (Table 2) [38,56,57]. Mechanisms by which estrogens cause PCT remain unclear. If needed for medical reasons, transdermal estrogen patch may be used once the disease activity is reduced and PCT remission is achieved [58].

2.9. Other conditions

PCT is also associated with systemic lupus erythematosus [59], end-stage renal disease on hemodialysis [59,60], diabetes mellitus [61], hepatic steatosis and hematological malignancies [62]. Advanced renal disease is often associated with iron overload, and PCT in this setting is

often more severe, because the porphyrins that accumulate are poorly dialyzable.

The role of cytochrome P4501A2 (CYP1A2) in the pathogenesis of PCT remains controversial. Although *Cyp1A-2* −/− mice can develop PCT with deletion of the *UroD* gene (*UroD* ±) and iron loading [63], genetic variants of *CYP1A2* have been reported to be associated with PCT in some human studies [64–66], while not confirmed in other cohorts [67,68].

3. Genetics of porphyria cutanea tarda

PCT is inherited with an autosomal dominant mutation of the *UROD* gene in only 20% of cases, the familial or type 2 PCT (Table 1). Approximately 110 UROD mutations (60% missense and 40% nonsense or deletion or insertion) are known and about 75% are located between exons 5 and 10 [69,70]. A detailed account of the described mutations can be found at the human gene mutation database [71]. Even patients with inherited mutation of the *UROD* gene need presence of iron overload and other susceptibility factors for the development of biochemical abnormalities and clinical manifestations, like the remaining 80% cases with sporadic PCT.

Severe UROD deficiency due to homozygous or compound heterozygous mutation of the *UROD* gene, inherited as autosomal recessive pattern can occur, with development of more severe and debilitating PCT like symptoms in young children. This is known as hepatoerythropoietic porphyria or HEP, a very rare porphyria. Unlike PCT is not amenable to specific therapy such as phlebotomy or 4–aminoquinolines.

4. Clinical manifestations

4.1. Skin lesions

Photosensitivity with skin lesions on sun exposed areas is a characteristic feature of PCT. Although, blistering lesions are hallmark of the disease (Fig. 3A), more often patients report increased skin fragility with peeling of skin after minor or trivial trauma and/or delayed wound healing in the sun exposed areas (Fig. 3B) [61]. Accumulated uroporphyrins and highly carboxylated porphyrins in the liver freely circulate in the plasma and capillaries, which get activated on exposure to sunlight, resulting in immune mediated reaction, release of free radicals, and damage of the lower dermis and basement membranes (Fig. 4). [72,73] Skin histology shows sub-epidermal blister formation, periodic-acid-Schiff positive amorphous hyaline material around the walls of capillaries at the dermal-epidermal junction (Fig. 5), which on immunofluorescence is deposits of IgG or IgM [74,75] Patients with chronic lesions may develop fibrotic reaction, appearing like systemic sclerosis [76].

Common sites of involvement are dorsal aspects of hands, forearms, neck, face, and ears [61,77–79]. Patients often report pain in these lesions which sometimes can be severe requiring analgesics. Lesions occasionally may be complicated by secondary bacterial infection with abscess formation and purulent drainage [77]. Patients with frequent relapses and remissions and those with prolonged severe symptoms may develop hypertrichosis, hyper- and hypopigmentation, hirsutism, and scarring, which sometimes can be severe enough to resemble scleroderma [61] [80], (Fig. 3C–D). Eyes can be rarely involved with development of scleral necrosis, corneal and conjunctival scarring, and ectropion [81].

4.2. Liver disease

Minor liver biochemical abnormalities with elevation of liver enzymes are common in PCT, with liver histology often revealing nonspecific changes such as iron deposition, fatty change, portal and/or lobular inflammation, and periportal fibrosis [61,82,83]. Although, associated susceptibility factors of alcohol use and HCV can cause cirrhosis of the liver, this complication has been described due to long term liver damage from accumulated porphyrins within the hepatocytes (Fig. 6) [61,84], which appear as birefringent needle shaped inclusions.

Hepatocellular carcinoma has been described as a long-term complication of PCT [82,85,86]. In one study, the risk for hepatocellular carcinoma in PCT patients compared to general population was over 21 folds, however, how much of this risk was due to concomitant alcohol use or HCV, was not clear [87]. In another prospective study, the risk of hepatocellular carcinoma was reported over five folds in 53 PCT cases

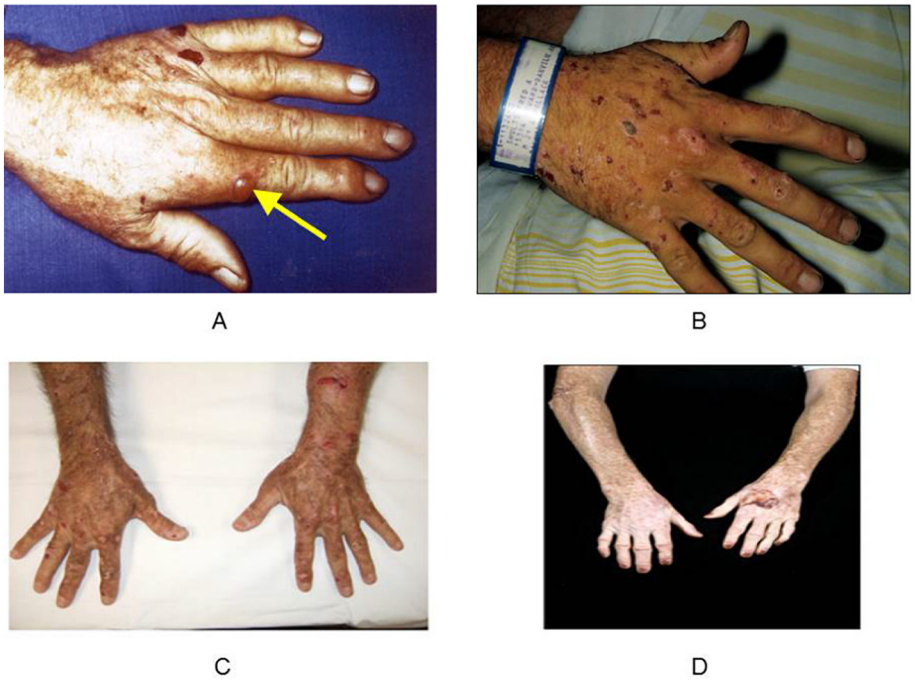

Fig. 3. Skin manifestations of porphyria cutanea tarda A) blistering lesion, B) lesions with easy fragility of skin, C) hyperpigmented skin, and D) thickened skin in chronic cases.

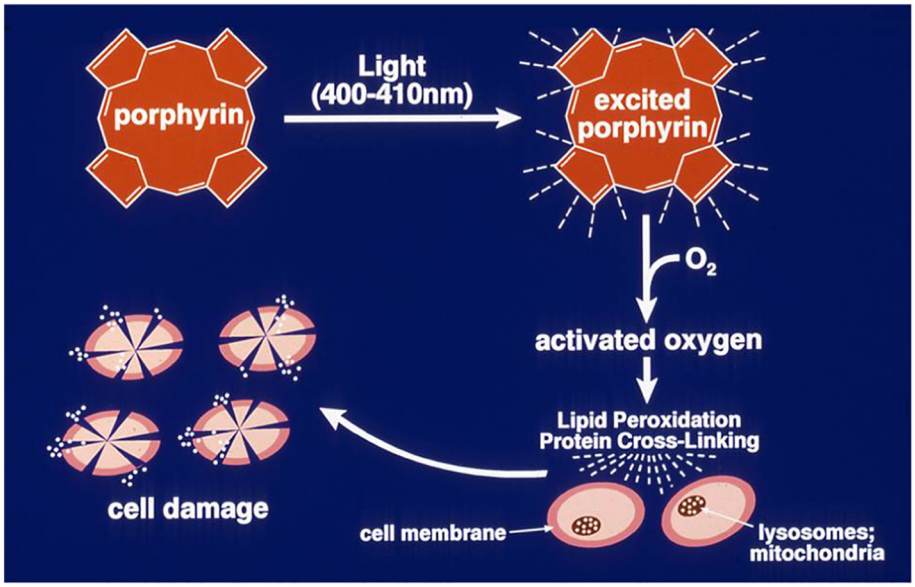

Fig. 4. Mechanism of skin damage by porphyrins in porphyria cutanea tarda.

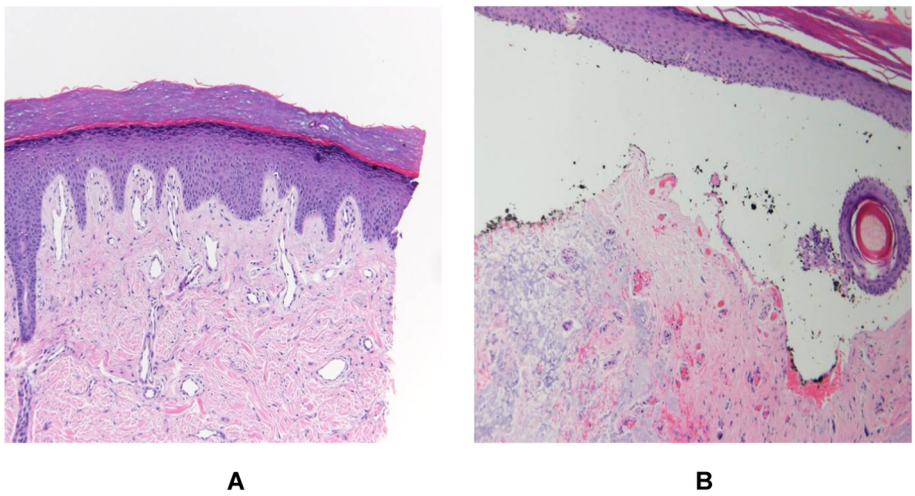

Fig. 5. Histology of skin in porphyria cutanea tarda showing A) superficial ulceration of skin with keratinocytes in the epidermis and B) dermal fibrosis and perivascular hyalinization of PAS positive material, which on immunofluorescence shows deposits of immunoglobulins and complement.

followed for median period of six years compared to 53 matched controls [88]. Although, the relative risks seem high, the development of this complication in routine practice may not be that common. For example, in one prospective study on 39 PCT cases followed for median of about 10 years, only one case of hepatocellular carcinoma occurred with overall risk of 0.26% per year [89]. The sole patient with liver cancer in this study reported chronic alcohol use and had concomitant HCV infection, with liver biopsy showing advanced bridging fibrosis (stage 3 disease), which was done over 3 years prior to the development of hepatocellular carcinoma [89]. Similarly, none of the 192 patients enrolled in a longitudinal study of the porphyria consortium in the US has been reported with development of hepatocellular carcinoma or receipt of liver transplantation [90].

5. Diagnosis

5.1. Clinical and routine laboratory evaluation

Detailed history should be obtained about previous episodes, associated susceptibility factors including alcohol use, smoking, high risk behavior for HCV infection (Table 3). Majority of PCT patients have mild to moderate iron overload. Other routine laboratory tests usually are unhelpful in making the diagnosis of PCT, however should be obtained to make decision on choosing the specific between phlebotomy and 4-aminoquinolines for specific treatment of PCT (*refer to treatment section described later*). Appropriate laboratory tests should be obtained to screen for associated susceptibility factors (HCV, HIV, HBV, *HFE* gene mutations), as these can impact disease course and response to treatment [35,91]. Genetic test for *UROD* gene mutation is not routinely obtained for diagnosis given that 80 of PCT cases are sporadic. However, this may be obtained among patients with family history of PCT, to screen family members of the proband case, when suspecting hepatoerythropoietic porphyria in children, and for research purposes.

5.2. Porphyrins biochemical profile

The porphyrins biochemical profile in PCT is characteristic: a) elevation of urinary porphyrins (normal < 300 nmol/24 h), b) elevation of plasma porphyrins (normal < 1.0 μg/dL), c) peak plasma fluorescence at 618–621 nm wavelength, and d) fractionation of porphyrins in urine or plasma with uroporphyrins, hepta- and hexa- porphyrins as predominant fraction in contrast to coproporphyrins in healthy people

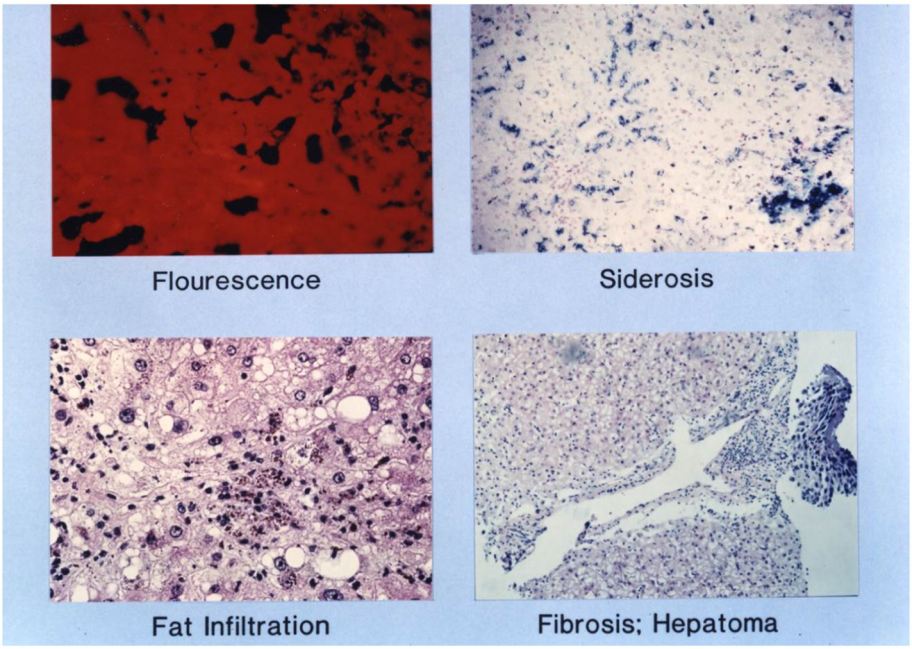

Fig. 6. Liver histology showing A) accumulation of uroporhyrins in the hepatocytes on fluorescence examination of liver tissue. In addition, routine hematoxyline and eosin staining of the liver tissues may show B) mild to moderate iron overload or siderosis and C) fat infiltration of steatosis. Rarely PCT may be associated with D) fibrosis with advanced fibrosis, cirrhosis and hepatocellular carcinoma.

Table 3
Initial and follow up evaluation among patients with porphyria cutanea tarda.

A. Initial evaluation
a) Biochemical porphyrin profile
b) Susceptibility factors
- History of alcohol use, smoking, estrogens use
- Iron status: serum ferritin and Transferrin saturation
- HCV (Ab and RNA), HBV (HBsAg), HIV (Ab and RNA)
- DNA test for *HFE* mutations
- DNA test for *UROD* mutation
- Red blood cell UROD activity

c) Assessment for liver disease
- Liver biochemical profile
- Ultrasound and elastography
- Liver biopsy if needed to assess disease stage

B. Selection of specific treatment regimen
- Examination of peripheral veins
- Complete blood count
- Basic metabolic panel
- Hepatic biochemical panel
- Urine pregnancy test
- Retinal examination if any eye symptoms
- G-6PD deficiency

C. Monitoring during treatment
- Clinical evaluation for skin lesions
- Control of susceptibility factors
- Complete blood count with ferritin for phlebotomy regimen
- Biochemical porphyrin profile

D. Follow up after achievement of remission
- Annual clinical and biochemical porphyrins evaluation
- Annual serum ferritin and liver chemistry panel
- Annual ultrasound examination for high risk groups (HCV, alcohol, hemochromatosis)

[92]. Fecal porphyrins are normal or modestly (occasionally markedly) increased in PCT [92]. Urinary excretion of δ-aminolaevulinic acid is normal or modestly increased, and of porphobilinogen is normal, differentiating from acute porphyria with cutaneous manifestations such as variegate porphyria and hereditary coproporphyria. Accumulated uroporphyrinogens in PCT are unable to inhibit PBG deaminase, unlike inhibition of protoporphyrinogen oxidase and coproporphyrinogen oxidase by the accumulated porphyrins in variegate porphyria and hereditary coproporphyria respectively, explaining absence of acute attacks and normal porphobilinogen excretion in PCT patients. However, porphobilinogen elevation with development of acute neurovisceral symptoms has been described in a confirmed patient with PCT with concomitant occurrence of another porphyria (dual porphyria) due to mutation of *PBG deaminase* gene [93].

5.3. Differential diagnosis

Although photosensitivity is a characteristic feature of PCT, this is not specific and can occur in other skin conditions or pseudo porphyria and in other porphyria such as erythropoietic protoporphyria, variegate porphyria, hereditary coproporphyria, and congenital erythropoietic porphyria. Sub epidermal blisters with immunofluorescence findings as described earlier on skin histology is not specific for the diagnosis of PCT, and can occur in pseudo porphyria (Table 4) Lack of classical skin lesions in the history and examination, normal iron status, and absence of susceptibility factors should raise doubt on the clinical diagnosis of PCT. However, the diagnosis of should be confirmed by obtaining the biochemical porphyrin profile [94]. The porphyrins profile also helps in differentiating PCT from other porphyria with cutaneous manifestations. Characteristic biochemical porphyrins profile for each of the other cutaneous porphyria can be found in other chapters dealing with the specific porphyria.

5.4. Assessment for complications

Ultrasound examination of the liver at diagnosis of PCT should be obtained to screen for cirrhosis and for hepatocellular carcinoma, especially in the presence of concomitant heavy alcohol use, hemochromatosis, or HCV/HBV/HIV infection. There are no current guidelines for surveillance of hepatocellular carcinoma in PCT patients. However, given that PCT is a chronic disease, ultrasound every 6–12 months should be performed for patients with advanced fibrosis or

Table 4
Drugs causing pseudo porphyria with cutaneous blistering photosensitivity.

- Dapsone
- NSAID
- Furosemide
- Tetracycline
- Nalidixic acid
- Pyridoxine or Vitamin B6

cirrhosis. Recommendations for ultrasound surveillance for hepatocellular carcinoma remain unclear for patients without cirrhosis especially in the absence of heavy alcohol use, HCV/HBV/HIV infection, or hemochromatosis (Table 3).

6. Treatment of porphyria cutanea tarda

6.1. General measures

Patients should avoid exposure to sunlight by wearing protective clothing and use sunscreen applications when going out in sun. Patients are also instructed to abstain from alcohol use, stop smoking, and avoid medications which can worsen the PCT especially use of oral contraceptive pills and estrogen treatment [95–97]. Analgesics may be needed for pain from skin lesions. For secondarily infected skin lesions, antibiotics may be required.

6.2. Specific treatment

PCT can be effectively treated with achievement of remission (clearance of skin lesions and normalization of porphyrins biochemical profile) by phlebotomy or a low dose regimen of either HCQ or chloroquine [79].

6.3. Repeated phlebotomy

Based on the rationale of reducing iron overload and decreasing the formation of UROD inhibitor within the hepatocytes, phlebotomy has been successfully tried in the treatment of PCT ever since 1961 [98]. Since then, many open label studies have confirmed demonstrated the safety and efficacy of this therapy for treatment of PCT [20,99–107]. Although various regimens are used, a common approach is to remove 450 mL every 2 weeks [105]. Follow up laboratory assessment on phlebotomy regimen includes hematocrit to assess for safety and tolerance, serum ferritin to assess iron status, and porphyrin biochemical profile for assessment of response to treatment [108–110]. It is recommended to discontinue further phlebotomy when the serum ferritin level is lower limit of normal, 20 ng/mL [21,111].

Plasma porphyrins although normally elevated at this time, usually follow downward trend to then normalize with achievement of remission. Although, number of phlebotomies needed depends on severity of iron overload at the beginning of treatment regimen, median of 5–7 phlebotomies are needed to normalize serum ferritin and achieving biochemical remission of PCT [79,91,102]. Clinical remission occurs much earlier than biochemical remission. After second or third phlebotomy usually, new skin lesions stop forming. After biochemical remission, if there are no further relapse, chronic skin changes of hypertrichosis, hyperpigmentation, scarring and sclerodermatous changes may also clear [99,102,104]. Liver function and histology were reported to improve in some studies but not in others [101].

6.4. 4-aminoquinolines (chloroquine and hydroxychloroquine)

Both chloroquine and hydroxychloroquine are equally effective, although HCQ is preferred given its larger clinical experience and safety profile in other conditions such as rheumatoid arthritis and lupus. Initial use in the 1960s showed clinical and biochemical efficacy, but was associated with worsening of skin lesions and hepatotoxicity (*"chloroquine reaction"*), due to use of high doses of these drugs [27,112–115]. Later, a lower dose with twice weekly use of 125 mg of chloroquine or 100 mg of HCQ showed similar efficacy with better safety profile. The drug is discontinued with the achievement of remission, which may take from 3 to 27 months, with median time to remission of about 7 months in most studies [83,116–121]. Dose in children is recommended to be 3 mg/kg twice a week [122]. Similar to phlebotomy, clinical improvement occurs first within about 2–4 months of starting the medication, followed by biochemical remission [118,119]. Most patients achieve remission provided patients comply with treatment. In one study, three of 62 patients with severe iron overload due to hemochromatosis and *HFE* gene C282Y mutations failed to achieve remission of PCT with over one year of low dose HCQ therapy [123].

Mechanism of action of 4–aminoquinolines remains unclear. The most accepted mechanism is that these drugs bind porphyrins within the hepatocytes and consequent their urinary excretion [75]. Indirect evidence for this comes from clinical studies showing increase in urinary porphyrins along with 50% decrease in hepatic porphyrins and moderate increase in transaminases after brief course of 0.-1 g of chloroquine administration [112]. In animal model of PCT, the maximum localization of chloroquine is within the mitochondria and lysosomes, and it is believed that chloroquine binds the porphyrins within the lysosomes and excretes them in the urine [75]. Other speculated mechanisms are effect on membrane permeability, [124] decrease in iron overload [26,125], inhibition of autophagy, [126] and decreased activity of delta-ALA activity [120].

6.5. Comparison of phlebotomy and 4-aminoquinolines

Three studies on head to head comparison of phlebotomy and 4-aminoquinolines have shown mixed results. For example, in one prospective non-randomized study on 48 patients, phlebotomy and low dose chloroquine were equally effective with median of 7 phlebotomies or 4–11 months use of chloroquine [127]. Similar results were reported in a randomized study, with median of 7 phlebotomies and about 7 g of low dose HCQ per patient for achieving remission of PCT [26]. Careful assessment of safety in this study showed that both modalities were safe with no hepatic toxicity from HCQ. In this study, of the 13 non-compliant patients, 12 were in the phlebotomy arm [26]. In another randomized study on 61 PCT patients, both phlebotomy and 200 mg twice weekly of HCQ achieved remission in all the patients. However, urinary porphyrins normalized much more frequently with HCQ (73% vs. 32%, $p < .01$) at one year of treatment [128]. However, compliance was not compared for the two treatments, which could have explained the difference in the two arms. Patients in the HCQ group did show worsening of inflammation and fibrosis on liver biopsy.

6.6. Optimal therapy of PCT

Although both the regimens and treatment options for managing PCT are equally safe and effective, one of the two treatments may be preferred over the other depending on patient's or physician choice, and more importantly based on initial comprehensive evaluation prior to starting treatment (Table 5). For example, it is recommended to avoid 4-aminoquinolines in patients with severe liver damage (e.g. serum bilirubin > 3 mg/dl, INR > 1.4, or AST or ALT > 200 IU/L), renal

Table 5
Comparison of phlebotomy and low dose hydroxychloroquine in the treatment of porphyria cutanea tarda [26].

	Phlebotomy	Low dose HCQ
Regimen	450 mL q 2 weeks	100 mg twice a week
End point	Serum Ferritin	Not well defined
Median duration	3 months	8 months
Median time remission	6 months	7 months
Compliance	May be poor	Good
Convenience	Inconvenient	Convenient
Cost	Expensive	Cheap
Contra-indications	Anemia	Severe liver/renal disease
	ESRD	Retinopathy
	Poor veins	↓G-6PD
		Homozygous C282Y
		Pregnancy

insufficiency (serum creatinine > 3 mg/dl), pre-existent retinopathy, G-6PD deficiency, and pregnancy. Further, careful assessment for toxicity should be made among patients at higher risk such as older age and children and higher cumulative dose > 100 g [129]. Similarly, phlebotomy may be difficult among patients with pre-existing anemia, end-stage renal disease, and patients with poor venous access. Further, other factors such as lower cost and ease of administration with 4-aminoquinolines compared to phlebotomy potentially result in better compliance with 4-aminoquinolines. On the other hand, phlebotomy is an optimal choice in patients with severe iron overload, especially in the presence of *HFE* genotypes that are consistent with hereditary hemochromatosis due to C282Y homozygotes or C282Y/H63D compound heterozygotes.

6.7. Treatment of PCT in patients with end-stage renal disease

Patients with End-stage renal disease have much higher levels of plasma porphyrins with more severe symptoms, as the porphyrins cannot be excreted in the urine due to renal failure, and these are not dialyzable also. The treatment is also complicated due to concern for tolerance to phlebotomy secondary to anemia in these patients, and for renal safety of low dose HCQ. Phlebotomy with removal of 50 mL blood every two weeks has been reported to be successful in one patient with end-stage renal disease, who had active PCT with concomitant HCV infection. Deferoxamine, an effective iron chelator can be used instead of phlebotomy [107,130,131], however, this drug may be limited by its slower response, longer time to remission, and potential low efficacy [125,132]. Another option is to use erythropoietin as an adjuvant to phlebotomy, with effective in reducing iron load and achieving the target ferritin level [133]. Repeated plasmapheresis with 20 sessions over 24 weeks, removing 250 mL at each session and replaced by equal amount of saline has also been successfully used in a patient with active PCT with end-stage renal disease [134]. Although, traditionally HCQ and 4-aminoquinolines are not advised for use in patients with serum creatinine > 3 mg/dL, there have been anecdotal reports of successful use of low dose HCQ for 1–2 years and normalization of plasma porphyrin levels.

6.8. Treatment of PCT in pregnancy

The clinical course of PCT during pregnancy is unpredictable and it can improve or worsen during this physiological state. Pregnancy in active PCT is considered a high risk pregnancy, with fetal risk of perinatal death, small for gestational age, and low birth weight [135]. Phlebotomy has been used safely and successfully in one pregnant woman with active PCT [136]. The drug has not been classified to any high risk category by the FDA. Exposure to HCQ during pregnancy for rheumatic diseases has been found to be safe with no overt risk to the mother or the fetus [137,138]. However, it is not recommended to use HCQ during pregnancy in routine clinical practice.

6.9. Treatment of PCT in HCV patients

Treatment of HCV infection in the presence of PCT has traditionally been difficult in the interferon era. In one study, sustained virologic response to HCV treatment was only 5% to interferon based treatment in the presence of PCT, and 25% among HCV patients without PCT [139]. However, with the availability of newer direct acting antiviral agents, the sustained virologic response rates have improved tremendously with over 95% response rates among PCT patients, which are similar to response rates in patients without PCT [140]. On the other hand, effect of interferon and ribavirin based HCV treatment has shown mixed response with benefit on PCT in some and worsening of the disease in other reports [141,142]. With the newer direct antiviral agents, worsening of PCT has not been described. Data are emerging on the benefit of these drugs in killing two birds with one stone with excellent HCV cure rates and at the same time resulting in remission of PCT [140,142]. Prospective studies are ongoing within the porphyria consortium in the US, examining utility of sofosbuvir and ledipasvir combination among active PCT patients who are infected with genotype-1 HCV, as sole therapy to cure HCV and induce remission of PCT. The study will examine the time to remission of PCT and compare with the median time to remission of 6–7 months reported historically in these patients with either phlebotomy or low dose hydroxychloroquine [26].

6.10. Relapse of PCT

Frequency of relapse of PCT after achieving remission with either of the two treatments has not been studied well. Various studies have reported on relapse rates, however, the data in these studies are heterogeneous for duration of follow up after achieving remission, initial treatment regimen used (monotherapy, combination, or sequential therapy with phlebotomy followed by 4-aminoquinolines), dose and duration of the agent used for initial treatment, and end-point used for defining remission [27,99,100,104,115,117,118,143–147]. Further, susceptibility factors especially relapse to alcohol use and HCV treatment status have not been analyzed with granularity in most of these studies, which are important variables to impact relapse of PCT. In one study on 30 PCT patients, relapse rate tended to be higher after remission (normalization of plasma porphyrins) of PCT with low dose HCQ as compared to remission with phlebotomy for clinical (53 vs. 37%, $P > 0.05$) as well as biochemical (69 vs. 47%, $P > 0.05$) relapse [148]. Alcohol use, HCV treatment, and smoking rates in the two groups were similar after achieving remission of PCT. However, this study was limited by a short median follow up duration of one year and use of normalization of plasma porphyrins and not urinary porphyrins as other studies have used, especially for patients in the HCQ arm [148]. In a pooled meta-analysis of 13 (12 observational each on one regimen and one randomized study comparing phlebotomy and low dose HCQ) studies, relapse rates were analyzed after achieving remission of PCT in 195 patients with high dose 4-aminoquinoline in 5 studies (2 combined with and 3 without phlebotomy) [27,115,143–145], in 242 with low dose 4-aminoquinoloine in 5 studies [117,118,146–148], and in 102 with phlebotomy in 4 studies [99,100,104,148]. Pooled relapse rate reported as relative risk (RR) and 95% confidence intervals (CI) were 8.6% (3.9–13.3%) in the high dose group, 17.5% (8.9–25.3%) in the low dose group, and 6.5% (1.2–11.7%) in the phlebotomy group [149]. Clearly, there is a need for prospective larger multicenter data with longer follow up to examine true relapse rates after achieving remission with either phlebotomy or HCQ, and the impact of susceptibility factors on these relapse rates. These data would be useful to derive evidence based recommendations for prevention of relapses after index remission with either treatment regimen among patients with PCT.

7. Summary and future perspectives

PCT is a common hepatic acquired porphyria and requires multiple susceptibility factors. It is a chronic disease with a tendency for relapses and remissions. Although, mild to moderate iron overload and liver disease often accompany, PCT can occasionally be associated with advanced liver disease and hepatocellular carcinoma. It is readily treatable with either phlebotomy or low-dose hydroxychloroquine. However, there remain certain unsolved issues in the field of PCT. These include a) impact of UROD mutation on the disease phenotype, b) role of systemic inflammation and mitochondrial dysfunction in its pathogenesis, c) mechanism of action of HCQ in the treatment of PCT, and d) mechanisms to understand the interaction of hepatitis C and PCT. Data are also awaited from prospective studies in the US porphyria consortium on the use of direct acting antivirals as sole therapy for hepatitis C and PCT. Most importantly, robust multicenter long-term

prospective data are needed to define relapse rate of PCT, overcoming limitations of the existing retrospective observational status.

References

[1] J.D. Phillips, F.G. Whitby, J.P. Kushner, C.P. Hill, Structural basis for tetrapyrrole coordination by uroporphyrinogen decarboxylase, EMBO J. 22 (23) (2003) 6225–6233.

[2] J.D. Phillips, H.A. Bergonia, C.A. Reilly, M.R. Franklin, J.P. Kushner, A porphomethene inhibitor of uroporphyrinogen decarboxylase causes porphyria cutanea tarda, Proc. Natl. Acad. Sci. U. S. A. 104 (12) (2007) 5079–5084.

[3] H. de Verneuil, C. Beaumont, J.C. Deybach, Y. Nordmann, Z. Sfar, R. Kastally, Enzymatic and immunological studies of uroporphyrinogen decarboxylase in familial porphyria cutanea tarda and hepatoerythropoietic porphyria, Am. J. Hum. Genet. 36 (3) (1984) 613–622.

[4] Y. Wang, C.R. Scott, M.H. Gelb, F. Turecek, Direct assay of enzymes in heme biosynthesis for the detection of porphyrias by tandem mass spectrometry, Porphobilinogen deaminase, Anal. Chem. 80 (7) (2008) 2606–2611.

[5] C. Can, G. Nigogosyan, Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. Report of 348 cases caused by this fungicide, JAMA 183 (1963) 88–91.

[6] G.M. Calvert, M.H. Sweeney, M.A. Fingerhut, R.W. Hornung, W.E. Halperin, Evaluation of porphyria cutanea tarda in U.S. workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin, Am. J. Ind. Med. (1994) 559–571.

[7] O. Dereure, N. Jumez, D. Bessis, B. Gallix, B. Guillot, Measurement of liver iron content by magnetic resonance imaging in 20 patients with overt porphyria cutanea tarda before phlebotomy therapy: a prospective study, Acta Derm. Venereol. 88 (4) (2008) 341–345.

[8] A. Bygum, F. Brandrup, Iron overload in porphyria cutanea tarda, Br. J. Dermatol. 143 (5) (2000) 1116.

[9] H.L. Bonkovsky, R.W. Lambrecht, Y. Shan, Iron as a co-morbid factor in non-hemochromatotic liver disease, Alcohol 30 (2) (2003) 137–144.

[10] O. Lundvall, A. Weinfeld, P. Lundin, Iron storage in porphyria cutanea tarda, Acta Med. Scand. 1–2 (1) (1970) 37–53.

[11] G.H. Elder, Porphyrin metabolism in porphyria cutanea tarda, Semin. Hematol. 14 (2) (1977) 227–242.

[12] M. Sampietro, G. Fiorelli, S. Fargion, Iron overload in porphyria cutanea tarda, Haematologica 84 (3) (1999) 248–253.

[13] K.G. Jones, F.M. Cole, G.D. Sweeney, The role of iron in the toxicity of 2,3,7,8-tetrachlorodibenzo-(p)-dioxin (TCDD), Toxicol. Appl. Pharmacol. 61 (1) (1981) 74–88.

[14] H.L. Bonkovsky, M. Poh-Fitzpatrick, N. Pimstone, J. Obando, A. Di Bisceglie, C. Tattrie, et al., Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America, Hepatology 27 (6) (1998) 1661–1669.

[15] K. Miura, K. Taura, Y. Kodama, B. Schnabl, D.A. Brenner, Hepatitis C virus-induced oxidative stress suppresses hepcidin expression through increased histone deacetylase activity, Hepatology 48 (5) (2008) 1420–1429.

[16] A. Turnbull, H. Baker, B. Vernon-Roberts, I.A. Magnus, Iron metabolism in porphyria cutanea tarda and in erythropoietic protoporphyria, Q. J. Med. 42 (166) (1973) 341–355.

[17] R.S. Ajioka, J.D. Phillips, R.B. Weiss, D.M. Dunn, M.W. Smit, S.C. Proll, et al., Down-regulation of hepcidin in porphyria cutanea tarda, Blood 112 (12) (2008) 4723–4728.

[18] E. Darwich, J. To-Figueras, R.A. Molina-Lopez, R. Deulofeu, G. Olbina, M. Westerman, et al., Increased serum hepcidin levels in patients with porphyria cutanea tarda, J. Eur. Acad. Dermatol. Venereol. 27 (1) (2013) e68–e74.

[19] A. Du Thanh, P. Aguilar-Martinez, S. Cunat, D. Bessis, B. Guillot, O. Dereure, Hemojuvelin and hepcidin gene mutations in patients with porphyria cutanea tarda from Southern France, Acta Derm. Venereol. 91 (1) (2011) 66–67.

[20] C.A. Ramsay, I.A. Magnus, A. Turnbull, H. Baker, The treatment of porphyria cutanea tarda by venesection, Q. J. Med. 43 (169) (1974) 1–24.

[21] S. Ratnaike, D. Blake, D. Campbell, P. Cowen, G. Varigos, Plasma ferritin levels as a guide to the treatment of porphyria cutanea tarda by venesection, Australas. J. Dermatol. 29 (1) (1988) 3–8.

[22] M.J. Moran, A. Fontanellas, E. Brudieux, I. Hombrados, V. de Ledinghen, P. Couzigou, et al., Hepatic uroporphyrinogen decarboxylase activity in porphyria cutanea tarda patients: the influence of virus C infection, Hepatology 27 (2) (1998) 584–589.

[23] J.D. Phillips, T.L. Parker, H.L. Schubert, F.G. Whitby, C.P. Hill, J.P. Kushner, Functional consequences of naturally occurring mutations in human uroporphyrinogen decarboxylase, Blood 98 (12) (2001) 3179–3185.

[24] S. Jalil, J.J. Grady, C. Lee, K.E. Anderson, Associations among behavior-related susceptibility factors in porphyria cutanea tarda, Clin. Gastroenterol. Hepatol. 8 (3) (2010) (297-302, e1).

[25] N.G. Egger, D.E. Goeger, D.A. Payne, E.P. Miskovsky, S.A. Weinman, K.E. Anderson, Porphyria cutanea tarda: multiplicity of risk factors including HFE mutations, hepatitis C, and inherited uroporphyrinogen decarboxylase deficiency, Dig. Dis. Sci. 47 (2) (2002) 419–426.

[26] A.K. Singal, C. Kormos-Hallberg, C. Lee, V.M. Sadagoparamanujam, J.J. Grady, D.H. Freeman Jr.et al., Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda, Clin. Gastroenterol. Hepatol. 10 (12) (2012) 1402–1409.

[27] E. Tsega, Long-term effect of high-dose, short-course chloroquine therapy on porphyria cutanea tarda, Q. J. Med. 65 (247) (1987) 953–957.

[28] N. Tsukazaki, K. Tanaka, H. Irifune, H. Yoshida, M. Watanabe, T. Ohgami, et al., Relationship between porphyria cutanea tarda (PCT) and viral hepatitis, J. Dermatol. 21 (6) (1994) 411–414.

[29] M. Kondo, Y. Horie, J. Okano, A. Kitamura, N. Maeda, H. Kawasaki, et al., High prevalence of hepatitis C virus infection in Japanese patients with porphyria cutanea tarda, Hepatology 26 (1) (1997) 246.

[30] K.A. Stuart, F. Busfield, E.C. Jazwinska, P. Gibson, L.A. Butterworth, W.G. Cooksley, et al., The C282Y mutation in the haemochromatosis gene (HFE) and hepatitis C virus infection are independent cofactors for porphyria cutanea tarda in Australian patients, J. Hepatol. 28 (3) (1998) 404–409.

[31] J. Hallen, H. Krook, Follow-up studies on an unselected ten-year material of 360 patients with liver cirrhosis in one community, Acta Med. Scand. 173 (1963) 479–493.

[32] T. Ohtake, H. Saito, Y. Hosoki, M. Inoue, S. Miyoshi, Y. Suzuki, et al., Hepcidin is down-regulated in alcohol loading, Alcohol. Clin. Exp. Res. 31 (1 Suppl) (2007) S2–S8.

[33] P.R. Sinclair, N. Gorman, I.B. Tsyrlov, U. Fuhr, H.S. Walton, J.F. Sinclair, Uroporphyrinogen oxidation catalyzed by human cytochromes P450, Drug Metab. Dispos. 26 (10) (1998) 1019–1025.

[34] M.G. Kristiansen, M.L. Lochen, T.J. Gutteberg, E. Falk, L. Mortensen, J. Florholmen, et al., Hepatitis C virus infection was not found in patients with sporadic porphyria cutanea tarda, membranoproliferative glomerulonephritis or membranous glomerulonephritis in Northern Norway, Scand. J. Gastroenterol. (2009) 1–3.

[35] A.P. Singal, G. Ferreira (Ed.), J. Porphyria Cutanea Tarda, World Scientific Publishing Co. Pte. Ltd., Hackensack, NJ, USA, 2014.

[36] C. Munoz-Santos, A. Guilabert, N. Moreno, J. To-Figueras, C. Badenas, E. Darwich, et al., Familial and sporadic porphyria cutanea tarda: clinical and biochemical features and risk factors in 152 patients, Medicine 89 (2) (2010) 69–74.

[37] M. Korenaga, M. Okuda, K. Otani, T. Wang, Y. Li, S.A. Weinman, Mitochondrial dysfunction in hepatitis C, J. Clin. Gastroenterol. 39 (4 Suppl 2) (2005) S162–S166.

[38] Z.J. Bulaj, J.D. Phillips, R.S. Ajioka, M.R. Franklin, L.M. Griffen, D.J. Guinee, et al., Hemochromatosis genes and other factors contributing to the pathogenesis of porphyria cutanea tarda, Blood 95 (5) (2000) 1565–1571.

[39] K. Kratka, M. Dostalikova-Cimburova, H. Michalikova, J. Stransky, J. Vranova, J. Horak, High prevalence of HFE gene mutations in patients with porphyria cutanea tarda in the Czech Republic, Br. J. Dermatol. 159 (3) (2008) 585–590.

[40] A.L. Martinelli, M.A. Zago, A.M. Roselino, A.B. Filho, M.G. Villanova, M. Secaf, et al., Porphyria cutanea tarda in Brazilian patients: association with hemochromatosis C282Y mutation and hepatitis C virus infection, Am. J. Gastroenterol. 95 (12) (2000) 3516–3521.

[41] A.G. Roberts, S.D. Whatley, R.R. Morgan, M. Worwood, G.H. Elder, Increased frequency of the haemochromatosis Cys282Tyr mutation in sporadic porphyria cutanea tarda, Lancet 349 (9048) (1997) 321–323.

[42] M. Santos, H.C. Clevers, J.J. Marx, Mutations of the hereditary hemochromatosis candidate gene HLA-H in porphyria cutanea tarda, N. Engl. J. Med. 336 (18) (1997) 1327–1328.

[43] A. Ivanova, N. von Ahsen, D. Adjarov, Z. Krastev, M. Oellerich, E. Wieland, C282Y and H63D mutations in the HFE gene are not associated with porphyria cutanea tarda in Bulgaria, Hepatology 30 (6) (1999) 1531–1532.

[44] L. Malina, E. Zd'arsky, S. Dandova, H. Michalikova, M. Cerna, M. Cimburova, Significance and prevalence of the C282Y gene mutation of primary hemochromatosis in the pathogenesis of pophyria cutanea tarda, Cas. Lek. Cesk. 139 (23) (2000) 728–730.

[45] M. Sampietro, A. Piperno, L. Lupica, C. Arosio, A. Vergani, N. Corbetta, et al., High prevalence of the His63Asp HFE mutation in Italian patients with porphyria cutanea tarda, Hepatology 27 (1) (1998) 181–184.

[46] M. D'Amato, A. Macri, D. Griso, G. Biolcati, F. Ameglio, Are His63Asp or Cys282Tyr HFE mutations associated with porphyria cutanea tarda? Data of patients from central and southern Italy, J. Invest. Dermatol. 111 (6) (1998) 1241–1242.

[47] K. Furuyama, M. Kondo, K. Hirata, H. Fujita, S. Sassa, Extremely rare association of HFE mutations with porphyria cutanea tarda in Japanese patients, Hepatology 30 (6) (1999) 1532–1533.

[48] L. Christiansen, C. Ged, I. Hombrados, J. Brons-Poulsen, A. Fontanellas, H. de Verneuil, et al., Screening for mutations in the uroporphyrinogen decarboxylase gene using denaturing gradient gel electrophoresis. Identification and characterization of six novel mutations associated with familial PCT, Hum. Mutat. 14 (3) (1999) 222–232.

[49] C. Ellervik, H. Birgens, A. Tybjaerg-Hansen, B.G. Nordestgaard, Hemochromatosis genotypes and risk of 31 disease endpoints: meta-analyses including 66,000 cases and 226,000 controls, Hepatology 46 (4) (2007) 1071–1080.

[50] P.S. Wissel, P. Sordillo, K.E. Anderson, S. Sassa, R.L. Savillo, A. Kappas, Porphyria cutanea tarda associated with the acquired immune deficiency syndrome, Am. J. Hematol. 25 (1) (1987) 107–113.

[51] C. Drobacheff, C. Derancourt, H. Van Landuyt, D. Devred, B. de Wazieres, B. Cribier, et al., Porphyria cutanea tarda associated with human immunodeficiency virus infection, Eur. J. Dermatol. 8 (7) (1998) 492–496.

[52] N. Nomura, S. Zolla-Pazner, M. Simberkoff, M. Kim, S. Sassa, H.W. Lim, Abnormal serum porphyrin levels in patients with the acquired immunodeficiency syndrome with or without hepatitis C virus infection, Arch. Dermatol. 132 (8) (1996) 906–910.

[53] P. Aguilera, M. Laguno, J. To-Figueras, Human immunodeficiency virus and risk of porphyria cutanea tarda: a possible association examined in a large hospital, Photodermatol. Photoimmunol. Photomed. 32 (2) (2016) 93–97.

[54] H.H. Roenigk Jr., M.E. Gottlob, Estrogen-induced porphyria cutanea tarda. Report of three cases, Arch. Dermatol. 102 (3) (1970) 260–266.
[55] F.T. Becker, Porphyria cutanea tarda induced by estrogens, Arch. Dermatol. 92 (1965) 252–256.
[56] R. Agarwal, T.J. Peters, R.C. Coombes, D.M. Vigushin, Tamoxifen-related porphyria cutanea tarda, Med. Oncol. 19 (2) (2002) 121–123.
[57] M.J. Cruz, S. Alves, T. Baudrier, F. Azevedo, Porphyria cutanea tarda induced by tamoxifen, Dermatol. Online J. 16 (9) (2010) 2.
[58] Z.J. Bulaj, M.R. Franklin, J.D. Phillips, K.L. Miller, H.A. Bergonia, R.S. Ajioka, et al., Transdermal estrogen replacement therapy in postmenopausal women previously treated for porphyria cutanea tarda, J. Lab. Clin. Med. 136 (6) (2000) 482–488.
[59] G.E. Gibson, M.T. McEvoy, Coexistence of lupus erythematosus and porphyria cutanea tarda in fifteen patients, J. Am. Acad. Dermatol. 38 (4) (1998) 569–573.
[60] S. Seubert, A. Seubert, K.W. Rumpf, H. Kiffe, A porphyria cutanea tarda-like distribution pattern of porphyrins in plasma, hemodialysate, hemofiltrate, and urine of patients on chronic hemodialysis, J. Invest. Dermatol. 85 (2) (1985) 107–109.
[61] M.E. Grossman, D.R. Bickers, M.B. Poh-Fitzpatrick, V.A. Deleo, L.C. Harber, Porphyria cutanea tarda. Clinical features and laboratory findings in 40 patients, Am. J. Med. 67 (2) (1979) 277–286.
[62] D.B. McKenna, M. Browne, R. O'Donnell, G.M. Murphy, Porphyria cutanea tarda and hematologic malignancy—a report of 4 cases, Photodermatol. Photoimmunol. Photomed. 13 (4) (1997) 143–146.
[63] J.D. Phillips, J.P. Kushner, H.A. Bergonia, M.R. Franklin, Uroporphyria in the Cyp1a2−/− mouse, Blood Cells Mol. Dis. 47 (4) (2011) 249–254.
[64] L. Christiansen, A. Bygum, A. Jensen, K. Thomsen, F. Brandrup, M. Horder, et al., Association between CYP1A2 polymorphism and susceptibility to porphyria cutanea tarda, Hum. Genet. 107 (6) (2000) 612–614.
[65] A. Fontanellas, M. Martinez-Fresno, M.C. Garrido-Astray, T. Perucho, M.J. Moran-Jimenez, M. Garcia-Bravo, et al., Smoking but not homozygosity for CYP1A2 g-163A allelic variant leads to earlier disease onset in patients with sporadic porphyria cutanea tarda, Exp. Dermatol. 19 (8) (2010) e326–e328.
[66] J.K. Wickliffe, S.Z. Abdel-Rahman, C. Lee, C. Kormos-Hallberg, G. Sood, C.M. Rondelli, et al., CYP1A2*1F and GSTM1 alleles are associated with susceptibility to porphyria cutanea tarda, Mol. Med. 17 (3–4) (2011) 241–247.
[67] O. Dereure, P. Aguilar-Martinez, D. Bessis, F. Blanc, D. Larrey, B. Guillot, et al., No significant association between CYP1A2 polymorphism and porphyria cutanea tarda, Acta Derm. Venereol. 84 (3) (2004) 254–255.
[68] D. Tchernitchko, A.M. Robreau, T. Lefebvre, J. Lamoril, J.C. Deybach, H. Puy, Comprehensive cytochrome P450 CYP1A2 gene analysis in French caucasian patients with familial and sporadic porphyria cutanea tarda, Br. J. Dermatol. 166 (2) (2012) 425–429.
[69] E. GH, Porphyria cutanea tarda and related disorders, in: K.S.K. Kadish, R. Guilard (Eds.), Sn Diego Elsevier Science, 2003.
[70] M. Mendez, M.V. Rossetti, S. Gomez-Abecia, M.J. Moran-Jimenez, V. Parera, A. Batlle, et al., Molecular analysis of the UROD gene in 17 Argentinean patients with familial porphyria cutanea tarda: Characterization of four novel mutations, Mol. Genet. Metab. 105 (4) (2012) 629–633.
[71] Available from: http://www.hgmd.cf.ac.uk/ac/index.php.
[72] I.A. Magnus, Cutaneous porphyria, Clin. Haematol. 9 (2) (1980) 273–302.
[73] H.W. Lim, M.B. Poh-Fitzpatrick, I. Gigli, Activation of the complement system in patients with porphyrias after irradiation in vivo, J. Clin. Invest. 74 (6) (1984) 1961–1965.
[74] B. Maynard, M.S. Peters, Histologic and immunofluorescence study of cutaneous porphyrias, J. Cutan. Pathol. 19 (1) (1992) 40–47.
[75] P.L. Scholnick, J. Epstein, H.S. Marver, The molecular basis of the action of chloroquine in porphyria cutanea tarda, J. Invest. Dermatol. 61 (4) (1973) 226–232.
[76] H.P. Stevens, L.S. Ostlere, C.M. Black, M.H. Rustin, Generalized morphoea secondary to porphyria cutanea tarda, Br. J. Dermatol. 129 (4) (1993) 455–457.
[77] J.M. Mascaro, The porphyrias: a brief overview based on 25 years of experience (1969-1994) by the Department of Dermatology of the Hospital Clinic and Faculty of Medicine of Barcelona, Spain, J. Dermatol. 22 (11) (1995) 823–828.
[78] G.H. Elder, Porphyria cutanea tarda and related disorders, in: R. Guilard (Ed.), Kadish KM SK, Elsevier Science, USA, 2003, pp. 67–92.
[79] K.E.S.S. Anderson, D.F. Bishop, R.J. Desnick, C.R. Scriver, W.S. Sly, D. Valle, B. Childs, B. Vogelstein (Eds.), Disorders of Heme Biosynthesis: X-Linked Sideroblastic Anemias and the Porphyrias, 8th ed., Mc Graw Hill, New York, 2001, pp. 2991–3062.
[80] G. Varigos, J.R. Schiltz, D.R. Bickers, Uroporphyrin I stimulation of collagen biosynthesis in human skin fibroblasts. A unique dark effect of porphyrin, J. Clin. Invest. 69 (1) (1982) 129–135.
[81] U.E. Altiparmak, Y. Oflu, F.A. Kocaoglu, Y.A. Katircioglu, S. Duman, Ocular complications in 2 cases with porphyria, Cornea 27 (9) (2008) 1093–1096.
[82] J.M. Cortes, H. Oliva, F.J. Paradinas, C. Hernandez-Guio, The pathology of the liver in porphyria cutanea tarda, Histopathology 4 (5) (1980) 471–485.
[83] A. Chlumska, J. Chlumsky, L. Malina, Liver changes in porphyria cutanea tarda patients treated with chloroquine, Br. J. Dermatol. 102 (3) (1980) 261–266.
[84] E. Baravalle, J. Prieto, Serum antibodies against porphyric hepatocytes in patients with porphyria cutanea tarda and liver disease, Gastroenterology 84 (6) (1983) 1483–1491.
[85] V. Kordac, Frequency of occurrence of hepatocellular carcinoma in patients with porphyria cutanea tarda in long-term follow-up, Neoplasma 19 (2) (1972) 135–139.
[86] M.S. Linet, G. Gridley, O. Nyren, L. Mellemkjaer, J.H. Olsen, S. Keehn, et al., Primary liver cancer, other malignancies, and mortality risks following porphyria: a cohort study in Denmark and Sweden, Am. J. Epidemiol. 149 (11) (1999) 1010–1015.
[87] M.S. Linet, G. Gridley, O. Nyren, L. Mellemkjaer, J.H. Olsen, S. Keehn, et al., Primary liver cancer, other malignancies, and mortality risks following porphyria: a cohort study in Denmark and Sweden, Am. J. Epidemiol. 149 (11) (1999) 1010–1015.
[88] A.L. Fracanzani, E. Taioli, M. Sampietro, E. Fatta, C. Bertelli, G. Fiorelli, et al., Liver cancer risk is increased in patients with porphyria cutanea tarda in comparison to matched control patients with chronic liver disease, J. Hepatol. 35 (4) (2001) 498–503.
[89] J.P. Gisbert, L. Garcia-Buey, A. Alonso, S. Rubio, A. Hernandez, J.M. Pajares, et al., Hepatocellular carcinoma risk in patients with porphyria cutanea tarda, Eur. J. Gastroenterol. Hepatol. 16 (7) (2004) 689–692.
[90] A.K.N.J. Singal, J. Overbey, M. Balwani, L. Liu, B. Wang, C. Parker, S. Keel, A. Erwin, C. Levy, J.R. Bloomer, D.M. Bissell, H.L. Bonkovsky, J. Phillips, R.J. Desnick, K.E. Anderson, Porphyria cutanea tarda: profile of 189 patients from the porphyrias consortium in the United States, Gastroenetrology 152 (2017) S1156 (Abstract).
[91] G.H. Elder, Porphyria cutanea tarda, Semin. Liver Dis. 18 (1) (1998) 67–75.
[92] S.G. Smith, K.R. Rao, A.H. Jackson, The prophyrins of normal human urine, with a comparison of the excretion pattern in porphyria cutanea tarda, Int. J. BioChemiPhysics 12 (5–6) (1980) 1081–1084.
[93] J.R. Harraway, C.M. Florkowski, C. Sies, P.M. George, Dual porphyria with mutations in both the UROD and HMBS genes, Ann. Clin. Biochem. 43 (Pt 1) (2006) 80–82.
[94] K.E. Anderson, Pseudoporphyria versus porphyria cutanea tarda, J. Pediatr. 123 (5) (1993) 841–842.
[95] G.C. Topi, A. Amantea, D. Griso, Recovery from porphyria cutanea tarda with no specific therapy other than avoidance of hepatic toxins, Br. J. Dermatol. 111 (1) (1984) 75–82.
[96] H.F. Haberman, F. Rosenberg, I.A. Menon, Porphyria cutanea tarda: comparison of cases precipitated by alcohol and estrogens, Can. Med. Assoc. J. 113 (7) (1975) 653–655.
[97] G. Leonhardi, K.H. Klahn, J. Gurenci, Treatment of porphyria cutanea tarda with and without phlebotomy (author's transl), MMW Munch Med. Wochenschr. 119 (2) (1977) 43–46.
[98] H. Ippen, General symptoms of late skin porphyria (porphyria cutanea tarda) as an indication for its treatment, Dtsch. Med. Wochenschr. 86 (1961) 127–133.
[99] J.H. Epstein, A.G. Redeker, Porphyria cutanea tarda. A study of the effect of phlebotomy, N. Engl. J. Med. 279 (24) (1968) 1301–1304.
[100] O. Lundvall, The effect of phlebotomy therapy in porphyria cutanea tarda. Its relation to the phlebotomy-induced reduction of iron stores, Acta Med. Scand. 189 (1–2) (1971) 33–49.
[101] J. Chlumsky, L. Malina, A. Chlumska, The effect of venesection therapy on liver tissue in porphyria cutanea tarda, Acta Hepatogastroenterol. (Stuttg.) 20 (2) (1973) 124–130.
[102] H. Ippen, Treatment of porphyria cutanea tarda by phlebotomy, Semin. Hematol. 14 (2) (1977) 253–259.
[103] R. Enriquez de Salamanca, R. Rico, M.L. Pena, F. Romero, A. Olmos, J. Jimenez, Patterns of porphyrin excretion in porphyria cutanea tarda under venesection treatment, Int. J. BioChemiPhysics 12 (5–6) (1980) 861–868.
[104] O. Lundvall, Phlebotomy treatment of porphyria cutanea tarda, Acta Derm Venereol Suppl (Stockh). 100 (1982) 107–118.
[105] C. Di Padova, L. Marchesi, T. Cainelli, G. Gori, S.A. Podenzani, P. Rovagnati, et al., Effects of phlebotomy on urinary porphyrin pattern and liver histology in patients with porphyria cutanea tarda, Am J Med Sci 285 (1) (1983) 2–12.
[106] D. Adjarov, M. Donov, E. Ivanov, E. Naidenova, Phlebotomy treatment in porphyria cutanea tarda combined with beta-thalassaemia, Dermatologica 169 (4) (1984) 184–187.
[107] E. Rocchi, P. Gibertini, M. Cassanelli, A. Pietrangelo, A. Borghi, M. Pantaleoni, et al., Iron removal therapy in porphyria cutanea tarda: phlebotomy versus slow subcutaneous desferrioxamine infusion, Br. J. Dermatol. 114 (5) (1986) 621–629.
[108] G.M. Addison, M.R. Beamish, C.N. Hales, M. Hodgkins, A. Jacobs, P. Llewellin, An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload, J. Clin. Pathol. 25 (4) (1972) 326–329.
[109] G.O. Walters, F.M. Miller, M. Worwood, Serum ferritin concentration and iron stores in normal subjects, J. Clin. Pathol. 26 (10) (1973) 770–772.
[110] J.D. Cook, D.A. Lipschitz, L.E. Miles, C.A. Finch, Serum ferritin as a measure of iron stores in normal subjects, Am. J. Clin. Nutr. 27 (7) (1974) 681–687.
[111] E. Rocchi, P. Gibertini, M. Cassanelli, A. Pietrangelo, A. Borghi, E. Ventura, Serum ferritin in the assessment of liver iron overload and iron removal therapy in porphyria cutanea tarda, J. Lab. Clin. Med. 107 (1) (1986) 36–42.
[112] B.F. Felsher, A.G. Redeker, Effect of chloroquine on hepatic uroporphyrin metabolism in patients with porphyria cutanea tarda, Medicine (Baltimore) 45 (6) (1966) 575–583.
[113] W.R. Vogler, J.T. Galambos, S. Olansky, Biochemical effects of chloroquine therapy in porphyria cutanea tarda, Am. J. Med. 49 (3) (1970) 316–321.
[114] G.D. Sweeney, S.J. Saunders, E.B. Dowdle, L. Eales, Effects of chloroquine on patients with cutaneous porphyria of the "Symptomatic" type, Br. Med. J. 1 (5445) (1965) 1281–1285.
[115] G. Wennersten, A.M. Ros, Chloroquine in treatment of porphyria cutanea tarda. Long-term efficacy of combined phlebotomy and high-dose chloroquine therapy, Acta Derm. Venereol. Suppl. (Stockh) 100 (1982) 119–123.
[116] C. Wolff, R. Armas, P. Krause, A. Parraguez, J. Ramon Soto, Treatment of porphyria cutanea tarda with chloroquine and its effect on associated liver disease: retrospective analysis, Rev. Med. Chil. 124 (4) (1996) 456–460.

[117] R.E. Ashton, J.L. Hawk, I.A. Magnus, Low-dose oral chloroquine in the treatment of porphyria cutanea tarda, Br. J. Dermatol. 111 (5) (1984) 609–613.
[118] V. Kordac, R. Papezova, M. Semradova, Chloroquine in the treatment of porphyria cutanea tarda, N. Engl. J. Med. 296 (16) (1977) 949.
[119] A. Freesemann, M. Frank, I. Sieg, M.O. Doss, Treatment of porphyria cutanea tarda by the effect of chloroquine on the liver, Skin Pharmacol. 8 (3) (1995) 156–161.
[120] G. Goerz, K. Bolsen, H. Merk, Influence of chloroquine on the porphyrin metabolism, Arch. Dermatol. Res. 277 (2) (1985) 114–117.
[121] V. Kordac, P. Martasek, M. Kalab, M. Semradova, R. Papezova, Chloroquine in the treatment of porphyria cutanea tarda symptomatica. Twelve years of experience in 307 patients (author's transl), Cas. Lek. Cesk. 120 (40) (1981) 1225–1227.
[122] A.J. Bruce, I. Ahmed, Childhood-onset porphyria cutanea tarda: successful therapy with low-dose hydroxychloroquine (Plaquenil), J. Am. Acad. Dermatol. 38 (5 Pt 2) (1998) 810–814.
[123] U. Stolzel, E. Kostler, D. Schuppan, M. Richter, U. Wollina, M.O. Doss, et al., Hemochromatosis (HFE) gene mutations and response to chloroquine in porphyria cutanea tarda, Arch. Dermatol. 139 (3) (2003) 309–313.
[124] G. Goerz, T. Krieg, K. Bolsen, Letter: Porphyria cutanea tarda: normalization of porphyrin-excretion following treatment with p-amino-benzoic acid (Potaba) (author's transl), Arch. Dermatol. Res. 255 (3) (1976) 331–335.
[125] L. Marchesi, C. Di Padova, T. Cainelli, A. Reseghetti, F. Di Padova, P. Rovagnati, et al., A comparative trial of desferrioxamine and hydroxychloroquine for treatment of porphyria cutanea tarda in alcoholic patients, Photo-Dermatology 1 (6) (1984) 286–292.
[126] K.L. Cook, A. Warri, D.R. Soto-Pantoja, P.A. Clarke, M.I. Cruz, A. Zwart, et al., Hydroxychloroquine inhibits autophagy to potentiate antiestrogen responsiveness in ER+ breast cancer, Clin. Cancer Res. 20 (12) (2014) 3222–3232.
[127] T. Cainelli, C. Di Padova, L. Marchesi, G. Gori, P. Rovagnati, S.A. Podenzani, et al., Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda, Br. J. Dermatol. 108 (5) (1983) 593–600.
[128] T. Cainelli, C. Di Padova, L. Marchesi, G. Gori, P. Rovagnati, S.A. Podenzani, et al., Hydroxychloroquine versus phlebotomy in the treatment of porphyria cutanea tarda, Br. J. Dermatol. 108 (5) (1983) 593–600.
[129] I. De Waziers, P.H. Cugnenc, C.S. Yang, J.-P. Leroux, P.H. Beaune, Cytochrome P 450 isoenzymes, epoxide hydrolase and glutathione transferases in rat and human hepatic and extrahepatic tissues, J. Pharmacol. Exp. Ther. 253 (1990) 387–394.
[130] E. Rocchi, M. Cassanelli, A. Borghi, F. Paolillo, M. Pradelli, S. Pellizzardi, et al., Liver iron overload and desferrioxamine treatment of porphyria cutanea tarda, Dermatologica 182 (1) (1991) 27–31.
[131] P. Vasconcelos, H. Luz-Rodrigues, C. Santos, P. Filipe, Desferrioxamine treatment of porphyria cutanea tarda in a patient with HIV and chronic renal failure, Dermatol. Ther. 27 (1) (2014) 16–18.
[132] J.J. Munoz, J. Garcia-Cabezas, J. Martinez-Verano, C. Perez-Oteyza, R. Enriquez de Salamanca, Desferrioxamine in the treatment of porphyria cutanea tarda: ineffectiveness of intramuscular administration, J. Dermatol. 17 (5) (1990) 329–331.
[133] K.E. Anderson, D.E. Goeger, R.W. Carson, S.M. Lee, R.B. Stead, Erythropoietin for the treatment of porphyria cutanea tarda in a patient on long-term hemodialysis, N. Engl. J. Med. 322 (5) (1990) 315–317.
[134] S. Miyauchi, S. Shiraishi, Y. Miki, Small volume plasmapheresis in the management of porphyria cutanea tarda, Arch. Dermatol. 119 (9) (1983) 752–755.
[135] M.C. Tollanes, A.K. Aarsand, S. Sandberg, Excess risk of adverse pregnancy outcomes in women with porphyria: a population-based cohort study, J. Inherit. Metab. Dis. 34 (1) (2011) 217–223.
[136] G. Rajka, Pregnancy and porphyria cutanea tarda, Acta Derm. Venereol. 64 (5) (1984) 444–445.
[137] R.A. Levy, V.S. Vilela, M.J. Cataldo, R.C. Ramos, J.L. Duarte, B.R. Tura, et al., Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study, Lupus 10 (6) (2001) 401–404.
[138] O. Diav-Citrin, S. Blyakhman, S. Shechtman, A. Ornoy, Pregnancy outcome following in utero exposure to hydroxychloroquine: a prospective comparative observational study, Reprod. Toxicol. 39 (2013) 58–62.
[139] I. Fernandez, G. Castellano, R.E. de Salamanca, F. Colina, A.G. de la Camara, M.J. Moran, et al., Porphyria cutanea tarda as a predictor of poor response to interferon alfa therapy in chronic hepatitis C, Scand. J. Gastroenterol. 38 (3) (2003) 314–319.
[140] A. Combalia, J. To-Figueras, M. Laguno, M. Martinez-Rebollar, P. Aguilera, Direct-acting antivirals for hepatitis C virus induce a rapid clinical and biochemical remission of porphyria cutanea tarda, Br. J. Dermatol. 177 (2017) e183–e184.
[141] D.R. Berk, S.B. Mallory, E.B. Keeffe, A. Ahmed, Dermatologic disorders associated with chronic hepatitis C: effect of interferon therapy, Clin. Gastroenterol. Hepatol. 5 (2) (2007) 142–151.
[142] A.K. Singal, K.V.R. Venkata, S. Jampana, F.U. Islam, K.E. Anderson, Hepatitis C treatment in patients with porphyria cutanea tarda, Am J Med Sci 353 (6) (2017) 523–528.
[143] F.D. Malkinson, L. Levitt, Hydroxychloroquine treatment of porphyria cutanea tarda, Arch. Dermatol. 116 (10) (1980) 1147–1150.
[144] C.S. Petersen, K. Thomsen, High-dose hydroxychloroquine treatment of porphyria cutanea tarda, J. Am. Acad. Dermatol. 26 (4) (1992) 614–619.
[145] I. Rossmann-Ringdahl, R. Olsson, Porphyria cutanea tarda: effects and risk factors for hepatotoxicity from high-dose chloroquine treatment, Acta Derm. Venereol. 87 (5) (2007) 401–405.
[146] V. Valls, J. Ena, R. Enriquez-De-Salamanca, Low-dose oral chloroquine in patients with porphyria cutanea tarda and low-moderate iron overload, J. Dermatol. Sci. 7 (3) (1994) 169–175.
[147] U. Wollina, E. Kostler, A. Koch, H. Riedel, U. Stolzel, Does chloroquine therapy of porphyria cutanea tarda influence liver pathology? Int. J. Dermatol. 48 (11) (2009) 1250–1253.
[148] A.K.G.E. Singal, M. Rizwan, M. Albuerne, C.K. Hallberg, K.E. Anderson, Relapse of porphyria cutanea tarda after achieving remission with phlebotomy or low dose hydroxychloroquine, Hepatology 62 (Supplement) (2015) (1231-2A).
[149] M.A.K. Rizwan, A.K. Singal, Relapse of porphyria cutanea tarda after achieving remission: a meta-analysis, Hepatology 62 (Supplement) (2015) 1238A.