Porphyria cutanea tarda – When skin meets liver

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Porphyria cutanea tarda (PCT) is the most frequent type of porphyria worldwide and results from a catalytic deficiency of uroporphyrinogen decarboxylase (UROD), the fifth enzyme in heme biosynthesis. At least two different types of PCT are currently distinguished: an acquired variant, also referred to as sporadic or type I PCT, in which the enzymatic deficiency is limited to the liver; and an autosomal dominantly inherited form, also known as familial or type II PCT, in which there is a decrease of enzymatic activity in all tissues. The cutaneous findings include increased photosensitivity, skin fragility, blistering, erosions, crusts, and miliae on the sun-exposed areas of the body. Additionally, hyperpigmentation, hypertrichosis, sclerodermoid plaques, and scarring alopecia might be observed. In patients with type I PCT, there is a significant association with liver disease that can be triggered by genetic and environmental factors, such as alcohol abuse, iron overload, haemochromatosis, polychlorinated hydrocarbons, and hepatitis C virus infection. The diagnosis of PCT can be made based on the skin symptoms, a characteristic urinary porphyrin excretion profile, and the detection of isocoproporphyrin in the feces. In red blood cells of individuals with type II PCT, UROD activity is decreased by approximately 50% due to heterozygous mutations in the UROD gene. Here we provide an update on clinical, diagnostic and therapeutic aspects of PCT, a disorder that affects both skin and liver.

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Introduction

The porphyrias are a clinically and genetically heterogeneous group of metabolic diseases, which arise from a predominantly inherited dysfunction of specific enzymes in the heme biosynthetic pathway [1,2]. Porphyria cutanea tarda (PCT; OMIM 176100) was described for the first time by Walsdenström in 1937 [3]. It is the only type of porphyria that is not exclusively inherited as a monogenetic trait since an acquired and a hereditary form can be distinguished. The disease is due to a decrease in the activity of uroporphyrinogen decarboxylase (UROD; E.C.4.1.1.37), the fifth enzyme in heme biosynthesis that catalyzes the conversion of uroporphyrinogen to coproporphyrinogen (Fig. 1). As a consequence, impaired UROD activity leads to an accumulation of uroporphyrin and other highly carboxylated porphyrins in various organs, including the skin and liver [1,2,4].

Epidemiology

PCT is the most common type of porphyria worldwide. It has an estimated prevalence of 1:10,000 and the sex ratio is approximately equal [5]. The disease usually becomes clinically manifest in middle-aged individuals but can also develop earlier [1,2,4]. Prior to the widespread use of oral contraceptives, PCT was seen predominantly in males. The ingestion of oestrogens in oral contraceptives or hormone supplements, however, could explain the rising incidence of PCT in females [2]. In line with this notion, males undergoing adjunctive oestrogen therapy in the treatment of prostate carcinoma have been reported to develop PCT [6].

Fig. 1. The heme biosynthetic pathway. Porphyria cutanea tarda results from a catalytic deficiency of uroporphyrinogen decarboxylase, the fifth enzyme along the pathway.
Classification

PCT belongs to the group of the cutaneous and chronic hepatic porphyrias (Tables 1 and 2). At least two clinically similar forms of the disease can currently be distinguished, both associated with decreased UROD activity: (i) acquired PCT, also referred to as sporadic or type I PCT; and (ii) hereditary PCT, also known as familial or type II PCT [1,2,4].

In type I PCT, UROD deficiency is restricted to the liver only. By contrast, type II PCT is an autosomal dominant disorder with incomplete penetrance. Decreased levels of residual UROD activity by approximately 50% are found in all tissues, including red blood cells and skin fibroblasts [2,4].

Of note though, not every patient with a positive family history will have type II PCT. There is a subset of PCT patients with one or more relatives presenting the typical clinical features of PCT but with normal erythrocyte UROD activities. This latter disease variant has been designated type III PCT, indicating that not all facets of the disease have been elucidated yet [2,4,7].

A small percentage of affected individuals carry mutations on both alleles of the UROD gene. Such homozygous or compound heterozygous patients suffer from hepatoerythropoietic porphyria (HEP) and reveal more severe clinical features than those encountered in the three aforementioned types of PCT (Tables 1 and 2) [2,4,8,9].

Pseudoporphyria cutanea tarda (also referred to as pseudoporphyria) summarizes a group of conditions closely resembling the clinical hallmarks of PCT. This disease is usually seen in patients with chronic renal insufficiency or individuals undergoing haemodialysis [2,10].

Aetiology and pathogenesis

Clinically overt PCT is due to hepatic accumulation of uroporphyrin, the oxidized substrate of UROD, which circulates in plasma and is finally excreted in the urine. Uroporphyrin is the agent responsible for the photochemical skin reaction on the sun-exposed areas of affected individuals. For clinical symptoms to manifest, the residual UROD activity must be ~25% of the normal level [2]. Recent studies have shown that this substantial decrease in enzyme activity is caused by oxidation of uroporphyrinogen to uroporphomethene, which acts as a competitive inhibitor of UROD in the liver. This oxidation reaction is iron-dependent [11].

Genetics

The human UROD gene has been mapped to chromosomal region 1p34 and spans approximately 3.6 kb [12]. The gene contains a single promoter and 10 exons, which encode a polypeptide of 367 amino acids with a molecular weight of approximately 41 kD [13]. The active human UROD protein is a homodimer that belongs to the (α/β)8 barrel family [14]. To date, more than 100 mutations in the UROD gene have been identified in patients with type II PCT or HEP, reflecting the high degree of molecular heterogeneity in familial PCT ([15–21]; for a more comprehensive overview see also the Human Gene Mutation Database at www.hgmd.cf.ac.uk/ac/index.php).

Table 1
Classification of the porphyrias into cutaneous and non-cutaneous forms. Both porphyria cutanea tarda and hepatoerythropoietic porphyria belong to the group of the cutaneous porphyrias.

<table>
<thead>
<tr>
<th>Cutaneous porphyrias</th>
<th>Non-cutaneous porphyrias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphryia cutanea tarda</td>
<td>Acute intermittent porphyria</td>
</tr>
<tr>
<td>Variegated porphyria</td>
<td>δ-aminolevulinic acid dehydratase deficiency porphyria</td>
</tr>
<tr>
<td>Erythropoietic protoporphyria</td>
<td></td>
</tr>
<tr>
<td>Hereditary coproporphyria</td>
<td></td>
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<tr>
<td>Congenital erythropoietic porphyria</td>
<td></td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td></td>
</tr>
</tbody>
</table>
Clinic – the skin

Clinically, type I and type II PCT are indistinguishable. Symptoms exclusively manifest on the sun-exposed areas of the body and predominantly comprise cutaneous photosensitivity, increased skin fragility, vesicles, bullae, erosions and crusts, which occur predominantly in areas subject to repeated trauma, e.g. the back of the hands (Fig. 2a). As the lesions resolve, hyper- or hypopigmented scars (Fig. 2b) and milia (Fig. 2c) can develop. Hypertrichosis of the non-virilizing type is more apparent in females and particularly prominent on the temples and the cheeks. In severe cases, however, it can also involve the trunk and extremities. Rarely, sclerodermoid changes may be observed, which consist of scattered, waxy yellow to white, indurated plaques that closely resemble morphea or scleroderma (Fig. 2d). Another rare skin symptom is a purplish red (‘heliotrope’) suffusion of the central part of the face.

<table>
<thead>
<tr>
<th>Porphyria type</th>
<th>Incidence</th>
<th>Age of onset</th>
<th>Important aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Most common porphyria worldwide</td>
<td>Third to fourth decade of life; usually not before puberty</td>
<td>Most frequent type of porphyria worldwide; acquired and hereditary variants exist; moderate to severe photosensitivity; cutaneous symptoms include vesicles and bullae, erosions, crusts, miliae, scarring, hyperpigmentation, and hypertrichosis; undistinguishable from variegate porphyria</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>Very rare (~25 cases reported)</td>
<td>Early infancy</td>
<td>Recessive variant of porphyria cutanea tarda; reported in the USA and Europe; markedly increased photosensitivity and severe clinical course possible; vesicles and bullae, erosions, excoriation, crusts, miliae, scarring, and hypertrichosis; mutilation can occur</td>
</tr>
</tbody>
</table>

Fig. 2. Porphyria cutanea tarda. (a) Blisters and erosions on the back of the hands. (b) Erosions, hyperpigmentation and hypopigmented scars on the forehead. (c) Milia on the back of the hand. (d) Sclerodermoid changes in the neck.
face, particularly involving the periorbital areas, which may bear a striking resemblance to the plethora seen in polycythemia rubra vera [2,4,22]. HEP usually presents during early childhood, with dark urine in the diapers usually being the first clinical sign. Upon exposure to UV light, severe cutaneous photosensitivity develops, associated with blistering, pruritus, hypertrichosis, hyperpigmentation and scleroderma-like scarring [2,4,8,9]. In pseudoporphyria cutanea tarda, skin fragility, blisters, erosions and scarring have a predilection for the dorsal aspect of the hands, the face, and the extensor surfaces of the legs [2,10].

Differential diagnosis

Classic PCT must be distinguished in the first place from other types of cutaneous porphyrias that manifest with blistering. These include variegate porphyria, hereditary coproporphyria, mild variants of HEP and congenital erythropoietic porphyria, and pseudoporphyria cutanea tarda [2,4]. The latter has a well-established association with the ingestion of specific drugs, including non-steroidal anti-inflammatory drugs (e.g. naproxen, nabumetone, and ketoprofen), furosemide, antibiotics (e.g. nalidixic acid and tetracyclines) and retinoids. Furthermore, epidermolysis bullosa acquisita, polymorphous light eruption, phototoxic and bullous drug eruptions, and hydroa vacciniforme should be excluded. All aforementioned diseases can easily be differentiated from PCT by measuring urinary and stool porphyrins [2].

Associations and complications – the liver

A variety of triggering factors has been reported to precipitate the clinical manifestations of PCT, among them alcohol, iron, inheritance of specific mutations in the HFE gene which underlie classic haemochromatosis, oestrogens, polychlorinated hydrocarbons, and hepatitis C virus infection [1,2,4].

Alcohol

Alcohol ingestion is well-known to exacerbate the disease [2]. Ethanol is a potent inducer of hepatic ALA synthase in patients with PCT [23]. However, the fact that ALA synthase is increased in patients with hepatic cirrhosis without porphyria raises questions concerning the relevance of alcohol effects on ALA synthase in the clinical expression of PCT [24]. Erythrocyte UROD activity is diminished in healthy subjects following acute ethanol ingestion and in chronic alcoholics. Ethanol can also inhibit the activity of other enzymes in the heme pathway, including ALA dehydratase and ferrochelatase [25]. Chronic alcoholism leads to suppression of erythropoiesis and increased absorption of dietary iron [26], probably linked to inherited mutations associated with haemochromatosis (see below).

Iron

Serum iron and ferritin concentrations are elevated or in the upper range of normal in PCT, confirming the important role of iron in the pathogenesis of the disease. Hepatic iron overload accompanies clinically overt PCT in basically all patients, and elevation of plasma iron is found in up to one-half of affected individuals [27]. In PCT, the quantity of iron that can be mobilized by phlebotomy indicates that total iron stores are approximately twice normal. Ferrokinetic studies in patients with PCT are said to be normal. The long remissions that follow repeated phlebotomy and the apparent ineffectiveness of this treatment if supplemental iron is administered concomitantly suggest that iron plays a role in the excessive hepatic porphyrin production of PCT. PCT is particularly common where alcoholism and iron overload occur together.

The role of iron in the pathogenesis of PCT is complex, and several hypotheses have been proposed to explain it. Iron may directly inhibit UROD. However, studies on purified UROD prepared from human erythrocytes show that the purified enzyme is not inhibited by Fe^{2+} or Fe^{3+} [27,28]. Chronic iron overload can produce peroxidative damage to lipid-rich mitochondrial and microsomal membranes in the liver of experimental animals, but the relationship of this toxic effect to changes in hepatic heme synthesis has not been clearly defined [29].
Iron may have a permissive effect on the inhibition of UROD by halogenated hydrocarbons, and it can also enhance the induction response of hepatic ALA synthase to drugs [30]. Although such an iron-augmented increase in ALA synthase activity could lead to enhanced porphyrinogenesis, this alone would not explain the porphyrin excretion pattern seen in PCT. Kushner et al have shown that addition of ferrous iron to liver in vitro causes a marked increase in porphyrin synthesis and inhibits the enzymatic activity of uroporphyrinogen III synthase, thereby providing an explanation for the excess of uroporphyrin I isomer that is characteristic for PCT [28,31]. More recently, the same group developed a mouse model of type II PCT in which one UROD allele is disrupted. Subsequently, these animals were crossed with mice homozygous for an HFE gene defect and intercrossed animals developed a PCT-like phenotype [32].

**Haemochromatosis**

Hereditary haemochromatosis is an autosomal recessive disease of iron metabolism wherein excess iron accumulates in different organs, including the liver [33]. Classic haemochromatosis is most often caused by mutations in the *haemochromatosis* (*HFE*) gene on chromosome 6p21.3 [34]. Inheritance of two specific *HFE* gene mutations, C282Y and H63D, is considered an important susceptibility factor for the development of PCT [27,35]. Although another mutation in the *HFE* gene, S65C, was also shown to be associated with a mild form of iron overload [36], several studies indicate that this mutation does not play a crucial role in the pathogenesis of PCT [37].

Interestingly, homozygosity for the *HFE* gene mutation C282Y has been found to be associated with an earlier onset of cutaneous lesions in both sporadic and familial PCT, the effect being more marked in familial PCT [38].

**Oestrogens**

The widespread use of oestrogens as contraceptive agents or as hormone supplements for post-menopausal replacement therapy in females and as adjunctive hormonal therapy in males with prostatic carcinoma has been associated with PCT [22]. However, the mechanisms by which oestrogens exert their effects on disease expression have not yet been fully elucidated and although diethylstilbesterol, an oestrogen, induces hepatic ALA synthase [39] this would not explain the distinctive porphyrin excretion pattern observed in PCT. More importantly, the vast majority of patients receiving oestrogens do not manifest the biochemical abnormalities associated with PCT [40].

**Hexachlorobenzene and 2,3,7,8-tetrachlorodibenzo-p-dioxin**

The fungicide hexachlorobenzene (HCB) caused an epidemic PCT-like syndrome in southeastern Turkey in the 1950s. It was added as a preservative to wheat intended for planting, but, because of a famine, several thousand individuals of diverse ethnic origin, mostly children, ingested the seed wheat and subsequently developed cutaneous symptoms resembling PCT. These findings were also associated with the characteristic porphyrin excretion pattern of the disease. Over 4000 cases were reported from 1956 to 1961 [41,42].

In animal models, the chronic administration of HCB causes an excessive porphyrin accumulation in the liver in a pattern quite similar to that seen in PCT in humans [43]. These data are consistent with the hypothesis that chlorinated hydrocarbons, such as HCB, or their metabolites inhibit hepatic UROD, leading to massive accumulation of uroporphyrin and other acetate substituted porphyrins in the liver [44,45]. Further studies have shown that HCB can also inactivate UROD thereby abolishing catalytic activity without changing the amount of immunoreactive protein [46].

Chemical porphyria, similar to PCT, can be caused by other chlorinated hydrocarbons such as the polychlorinated biphenyls and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a by-product in the synthesis of the herbicide 2,4,5-trichlorophenoxyacetic acid [47]. TCDD is a toxic environmental pollutant chemical. Among its numerous effects in experimental animal models and perhaps also in humans are chloracne, liver damage, and hepatic porphyria. It has been shown that the hepatic porphyrinogenic effect of TCDD can be abolished in mice by first depleting them of iron [48]. Furthermore,
it is known that highly inbred mouse strains vary in their susceptibility to induction of hepatic porphyria by TCDD, indicating that the porphryrogenic effect of this hydrocarbon may be modulated by different genetic factors [49].

Additional studies on the porphyrinogenic effects of chlorinated hydrocarbons suggest that metabolic activation of the compounds mediated by cytochrome P450 1A2 and involving iron-generated reactive oxygen species is associated with an attack on the catalytic site of UROD [28].

**Hepatitis C virus**

There is an association between PCT and hepatitis C virus (HCV) infections as well as combined HCV and HIV infection [39,50]. However, the specific role of these viruses in the pathogenesis of PCT is not yet clear although some connection with the *HFE* gene mutation H63D has been suggested [51]. It is also possible though that the connection is fortuitous and secondary to non-specific hepatotoxic effects of this virus.

**Hepatic siderosis and cirrhosis**

Patients with PCT characteristically have chronic liver disease. Between 60 and 70% of them will develop hepatic siderosis and are prone to liver cirrhosis [52,53]. Further, they were thought to have an increased risk for hepatocellular carcinoma although new studies rather indicate this risk seems to be low [54].

Considering the aforedescribed effects of alcohol, iron, haemochromatosis mutations, oestrogens, chlorinated hydrocarbons, and viral infections on the heme biosynthetic pathway, each of these factors could contribute to the excessive hepatic porphyrinogenesis characteristic of PCT. There is growing evidence that hepatic siderosis is the critical pathologic endpoint in PCT and that the other agents intensify the ability of iron to attack the catalytic site of UROD. Thus, the clinical expression of PCT is dependent upon the interaction of various factors, both genetic and environmental.

**Laboratory diagnostics**

Historically, a presumptive clinical diagnosis of PCT was followed by an examination of the patient’s urine, both under Wood’s lamp illumination in the dark and after exposure to natural light. Due to the excessive excretion of porphyrins, the urine of PCT patients turns red to brown after several hours of exposure to natural light and it has a pink to red fluorescence when exposed to a UVA light source.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Biochemical characteristics of porphyria cutanea tarda and hepatoerythropoietic porphyria in urine, stool, and blood (plasma and erythrocytes).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine</td>
<td>Uroporphyrin</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>++++</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>++++</td>
</tr>
<tr>
<td>Stool</td>
<td>Uroporphyrin</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>++</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>Normal</td>
</tr>
<tr>
<td>Blood/erythrocytes</td>
<td>Uroporphyrin</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Normal</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>Normal</td>
</tr>
<tr>
<td>Blood/plasma</td>
<td>Uroporphyrin</td>
</tr>
<tr>
<td>Porphyria cutanea tarda</td>
<td>Normal</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>++</td>
</tr>
</tbody>
</table>

*Isocoproporphyrin; + = slightly increased; ++ = moderately increased; +++ = highly increased; ++++ = very highly increased.*
However, these historic bedside observations are neither sensitive nor specific diagnostic tests and cannot be recommended anymore [2].

The diagnosis of PCT can be confirmed by specific biochemical analyses. In the urine, an increased excretion of uroporphyrin (type I isomers > type III isomers), hepta-carboxylated porphyrins (type III isomers > type I isomers), and coproporphyrin can be detected. In the feces, an increased excretion of coproporphyrin and isocoproporphyrin can be detected, the latter being specific and confirmatory for PCT and HEP (Table 3) [2,4].

In the 1980s and early 1990s, some groups proposed the measurement of erythrocyte UROD activity as a screening technique to distinguish between type I and type II PCT [55–57]. While a patient with type I PCT should have a normal erythrocyte UROD activity, the residual enzymatic activity in a patient with type II PCT would be expected to be decreased by about 50% [55,58]. However, this enzymatic test apparently is not very reliable because some patients with type II PCT and a confirmed mutation in the \textit{UROD} gene might reveal residual UROD activities close to the lower limit of the normal range, which may overlap with the lowest values encountered in patients with type I PCT. In such individuals with erythrocyte UROD activity in an intermediate range, additional molecular genetic analysis might be helpful.

Of note, histopathologic examination does not essentially contribute to confirming a presumptive diagnosis of PCT. Rather, external trauma such as a biopsy or excision constitutes an avoidable risk for delayed or dysfunctional wound healing, which is a characteristic feature of all cutaneous porphyrias.

**Therapy**

The avoidance of UV light exposure, sun-protective clothing, and regular application of broad-spectrum sunscreens is crucial, both prophylactically and therapeutically. However, the wavelengths inducing porphyrins are in the range of 400–410 nm range and, thus, most sunscreens are limited in their therapeutic effectiveness, with the exception of titanium dioxide and zinc oxide. Beside the avoidance of well-known triggering factors as, e.g. alcohol and oestrogens, there are two main therapeutic regimens for PCT, phlebotomy and low-dose chloroquine therapy (Table 4) [2].

Different protocols for phlebotomy have been reported, repeated venesection of approximately 500 ml blood every two weeks or weekly phlebotomies of 300 ml blood. This treatment usually leads to resolution of skin fragility and blistering within 2–4 months. However, normalization of urinary porphyrin concentrations will usually take about 9–12 months. While the therapeutic goal is to reduce serum ferritin levels to the lower limit of the reference range, care should be taken to not induce anaemia [2,59].

Chloroquine is thought to work by accelerating the secretion of porphyrins and may also inhibit porphyrin synthesis, thereby reducing photosensitivity. The standard therapy consists of 125 mg chloroquine twice weekly and complete remission can be expected within 6–9 months. Chloroquine and phlebotomy can also be used in combination to induce remission faster [2,60,61].

**Table 4**

Therapy of porphyria cutanea tarda and hepatoerythropoietic porphyria at a glance.

<table>
<thead>
<tr>
<th>Porphyria type</th>
<th>Therapy strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porphyria cutanea tarda</td>
<td>1. Photoprotection, e.g. with broad-band sunscreens and/or protective clothing</td>
</tr>
<tr>
<td></td>
<td>2. Avoidance of sunlight exposure and trauma</td>
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<td></td>
<td>3. Cease alcohol ingestion; stop estrogen therapy</td>
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<td></td>
<td>4. Phlebotomy (venesection): 400–500 ml every two weeks over ~ 3–6 months</td>
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<td></td>
<td>5. Low-dose chloroquine treatment: 125 mg twice weekly (e.g. on Monday and</td>
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<td></td>
<td>Thursday) over 6–12 months, until porphyrin excretion is within normal range</td>
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<td></td>
<td>6. Laboratory control of urinary porphyrin excretion for monitoring of</td>
</tr>
<tr>
<td></td>
<td>therapeutic outcome</td>
</tr>
<tr>
<td>Hepatoerythropoietic porphyria</td>
<td>1. Photoprotection, e.g. with broad-band sunscreens and/or protective clothing</td>
</tr>
<tr>
<td></td>
<td>2. Strict avoidance of sunlight exposure and trauma</td>
</tr>
<tr>
<td></td>
<td>3. Change day–night-rhythm</td>
</tr>
</tbody>
</table>

CAUTION – therapeutic approaches used in porphyria cutanea tarda (Phlebotomy; antimalarial) are ineffective!
There are indications that the genetic background of PCT patients with regard to the presence of the common \textit{HFE} gene mutations C282Y and H63D might play an important role in the outcome of chloroquine treatment. Whereas heterozygosity for mutation C282Y and compound heterozygosity for C282Y and H63D did not compromise the therapeutic response to chloroquine, PCT patients homozygous for C282Y seem to retain high serum iron, ferritin, and transferring saturation and, most importantly, failed to respond to chloroquine therapy [62]. Beside the frequency of the two common \textit{HFE} gene mutations C282Y and H63D very little is known to date about the association of other mutations causing haemochromatosis and PCT.

Conclusions

PCT has to be considered as a multi-factorial disease in which visible clinical symptoms can manifest on the skin and characteristic metabolic and histopathological alterations are observed in the liver. The complex interplay of both genetic and environmental factors confers susceptibility to iron overload and subsequent hepatic disease.

\begin{table}[h]
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\begin{tabular}{|l|}
\hline
Practice points \\
\hline
- Most frequently occurring type of porphyria worldwide. \\
- At least three different forms of the disease must be differentiated. \\
- The sporadic variant of the disease arises from liver-specific deficiency of uroporphyrinogen decarboxylase whereas in the hereditary form the enzymatic deficiency is expressed in all tissues. \\
- Age of onset is usually in the third to fourth decade of life; the disorder is uncommon before puberty. \\
- The cutaneous symptoms include moderate to severe photosensitivity, vesicles and bullae, erosions, crusts, milia, sclerodermoid changes and scarring, hyperpigmentation, and hypertrichosis. \\
- The cutaneous features cannot be differentiated from those of variegate porphyria and hereditary coproporphyria. \\
- Liver disease can be precipitated by liver disease that can be triggered by genetic and environmental factors, such as alcohol abuse, iron overload, haemochromatosis, polychlorinated hydrocarbons, and hepatitis C virus infection. \\
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\end{tabular}
\end{table}

\begin{table}[h]
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\hline
Research agenda \\
\hline
- Elucidation of the genetic mechanisms underlying type III PCT. \\
- Unravelling the precise mechanisms by which iron overload leads to exacerbation of PCT. \\
\hline
\end{tabular}
\end{table}

Acknowledgements

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We declare that the study sponsors did not have any influence on the collection, analysis and interpretation of data and in the writing of the manuscript.
None declared.

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