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The Porphyrias

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Summary

The porphyrias are clinically variable and genetically heterogeneous, predominantly hereditary metabolic diseases, which are caused by a dysfunction of specific enzymes in heme biosynthesis. Here, we provide an overview of the etiopathogenesis, clinic, differential diagnosis, laboratory diagnostics and therapy of these complex metabolic disorders and cover in detail the most common form of porphyria worldwide (porphyria cutanea tarda), the most frequent childhood porphyria (erythropoietic protoporphyria), and the most common neurocutaneous porphyria (variegate porphyria).

Introduction

The porphyrias are a group of complex metabolic diseases caused by a mostly hereditary but more rarely also acquired dysregulation of one or more enzymes in heme biosynthesis. Dysfunction of any one enzyme will result in a specific porphyria (Figure 1). Enzyme deficiency causes accumulation of intermediary metabolic products in various organs, leading to skin and/or neurological symptoms. Since the clinical signs are insufficient for a clear and easy diagnosis, additional biochemical laboratory analysis is required. However, even laboratory analyses may fail to yield a clear-cut diagnosis in some cases, since the various forms of porphyria sometimes show confusing overlaps in laboratory parameters. This may be influenced by time of sampling and type of storage of the relevant materials (blood, urine, feces) until analysis. Interpretation of the biochemical results thus requires a certain amount of experience with porphyria. In difficult cases with ambiguous laboratory results, molecular genetic tests may be required for diagnosis. After diagnosis, patients should if possible be referred to a specialized porphyria center or to a physician who is well versed in this field. Interdisciplinary care can be recommended, especially as regards treatment [1–3].

The porphyrias are complex, mostly hereditary metabolic diseases characterized by skin changes and/or neurological symptoms.

Etiopathogenesis

In heme biosynthesis, eight enzymes catalyze processing of specific substrates.

Starting with the amino acid glycine and succinyl CoA from the citrate cycle, heme biosynthesis occurs in eight steps with eight catalyzing enzymes. The individual substrates of this metabolic pathway are produced either in the cytoplasm or the mitochondrium (Figure 1). Mutations in one of the genes encoding the respective enzymes lead to enzyme dysfunction and deficient or insufficient substrate processing. This in turn leads to accumulation of intermediary metabolites such as porphyrins and/or their precursors 5-aminolevulinic acid (ALA) and porphobilinogen (PBG) in various organs – mainly the skin, liver, blood, and bone marrow. Under the influence of various induction factors such as visible light or UV rays, porphyrinogenic medications, alcohol, or hormones, the accumulated intermediary metabolic products may display cytotoxic or tissue-damaging effects. These result in skin changes and/or acute as well as chronic neurological symptoms typical for the clinical appearance of the disease [4, 5].

Mutations in the genes encoding the respective enzymes result in enzyme dysfunction and consecutive accumulation of intermediary metabolites.

Cytotoxic effects caused by intermediary metabolites lead to skin changes and/or neurological symptoms.

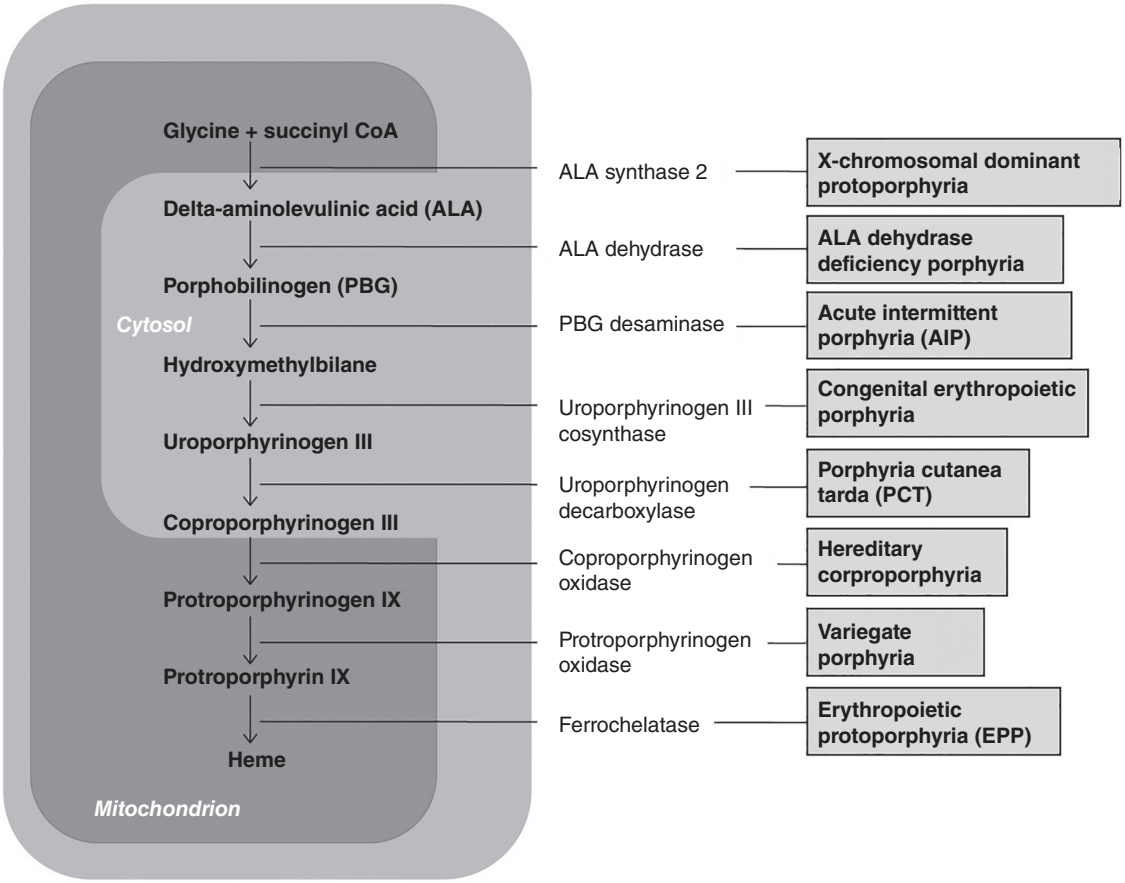

Figure 1 Heme biosynthesis. A dysfunction of each enzyme leads to a specific type of porphyria.

Classification

Porphyrias can be classified in various ways. Since most forms present with acute and/or chronic skin symptoms and changes, dermatologists tend to distinguish between cutaneous and non-cutaneous forms (Table 1). We will use this classification in the further course of this overview.

The porphyrias are classified either as cutaneous and non-cutaneous, or as acute and non-acute.

On the other hand, distinguishing between acute and non-acute porphyrias makes more practical sense in most medical disciplines and is thus used more commonly, since this also considers the potentially life-threatening acute neurovisceral attacks (Table 2) [1–3].

Table 1 Classification of the porphyrias into cutaneous and non-cutaneous forms.

Cutaneous porphyrias	Non-cutaneous porphyrias
– Porphyria cutanea tarda	– Acute intermittent porphyria
– Hepatoerythropoietic porphyria	– ALA dehydratase deficiency porphyria
– Variegate porphyria	
– Hereditary coproporphyria	
– Congenital erythropoietic porphyria	
– Erythropoietic protoporphyria	
– X-chromosomal dominant protoporphyria	

Table 2 Classification of porphyrias into acute and non-acute forms. The neurocutaneous porphyrias are marked by an asterisk (*).

Acute porphyrias	Non-acute porphyrias
– Acute intermittent porphyria	– Porphyria cutanea tarda
– ALA dehydratase deficiency porphyria	– Hepatoerythropoietic porphyria
– Variegate porphyria*	– Congenital erythropoietic porphyria
– Hereditary coproporphyria*	– Erythropoetic protoporphyria
	– X-chromosomal dominant protoporphyria

Cutaneous porphyrias

The group of cutaneous porphyrias includes porphyria cutanea tarda (PCT), erythropoietic protoporphyria (EPP), variegate porphyria (VP), hereditary coproporphyria, congenital erythropoietic porphyria, X-chromosomal dominant protoporphyria, and hepatoerythropoietic porphyria (Table 1) [1–3].

Non-cutaneous porphyrias

Non-cutaneous porphyrias include acute intermittent porphyria (AIP), and ALA dehydratase deficiency porphyria (Table 2). These two are the only forms of porphyria that never present with skin changes, so we will not cover them in detail. Nevertheless, we would like to note that AIP is actually the most common form of acute porphyria world-wide, and constitutes an important differential diagnosis for a large number of gastrointestinal, neurological, and psychiatric diseases [1–3]. Since the leading symptom of AIP is acute abdominal pain, it is important that emergency physicians be familiar with this disease [6].

Pathophysiology of cutaneous symptoms

Porphyrins accumulated in the skin absorb electromagnetic radiation especially in the Soret peak (400–410 nm), resulting in a phototoxic reaction to visible light and UV rays.

Porphyrins accumulated in the skin, particularly uroporphyrin, penta-, hexa-, and heptacarboxylated porphyrins, as well as protoporphyrin IX, lead to increased photosensitivity. This results from the fact that the metabolites absorb electromagnetic radiation including visible light and UV rays, especially in the so-called Soret peak (400–410 nm), and can cause phototoxic reactions. These are accompanied by the formation of free oxygen radicals and lipid peroxides in the skin, leading to membrane destruction and increase of inflammatory cytokines such as interleukin (IL)-1 und IL-6, as well as collagenases [1, 2].

Pathophysiology of the neurological symptoms

The causes of porphyria attacks are accumulation of the porphyrin precursors 5-amino levulinic acid and/or porphobilinogen, combined with the influence of endogenous and exogenous triggers, particularly porphyrinogenic medications.

The sudden neurological symptoms in acute porphyria attacks are caused by excessive accumulation of the porphyrin precursors ALA and/or PBG. Lack of heme is also discussed as a possible cause. Apart from the abovementioned biochemical alterations, acute porphyria attacks are triggered by various other exogenous and endogenous factors. These include porphyrinogenic drugs (such as barbiturates, sulfonamides, tricyclic antidepressants, and contraceptives), intake of hormones (such as estrogens and progestins), or an intrinsic hormonal imbalance, excessive

alcohol consumption, severely limited calorie intake in low-carbohydrate diets or fasting periods, and recurrent infections [1, 7].

Clinical appearance

Skin changes in cutaneous porphyria are strictly limited to areas exposed to light.

In patients with cutaneous porphyria, skin symptoms are strictly limited to the skin areas exposed to light. It is, however, important to note that two forms of cutaneous porphyria show both skin changes and acute neurological symptoms: variegate porphyria, and hereditary coproporphyria. These two forms are also called neurocutaneous porphyrias [8].

Non-cutaneous porphyrias, on the other hand, are characterized by sudden neurovisceral and psychiatric symptoms that persist over several hours or even days. These symptoms may in some cases become life-threatening and are very hard to differentiate from other diseases [9]. Acute porphyria attacks may present with diffuse, colicky abdominal pain, nausea and vomiting, tachycardia, paralysis that may develop into paraplegia or tetraplegia, or even respiratory paralysis and respiratory coma [1, 7].

Acute porphyria attacks are difficult to differentiate from other diseases and may become life-threatening.

Diagnostics

A careful medical history and especially family history as well as a comprehensive physical examination are essential when porphyria is suspected. All patients require

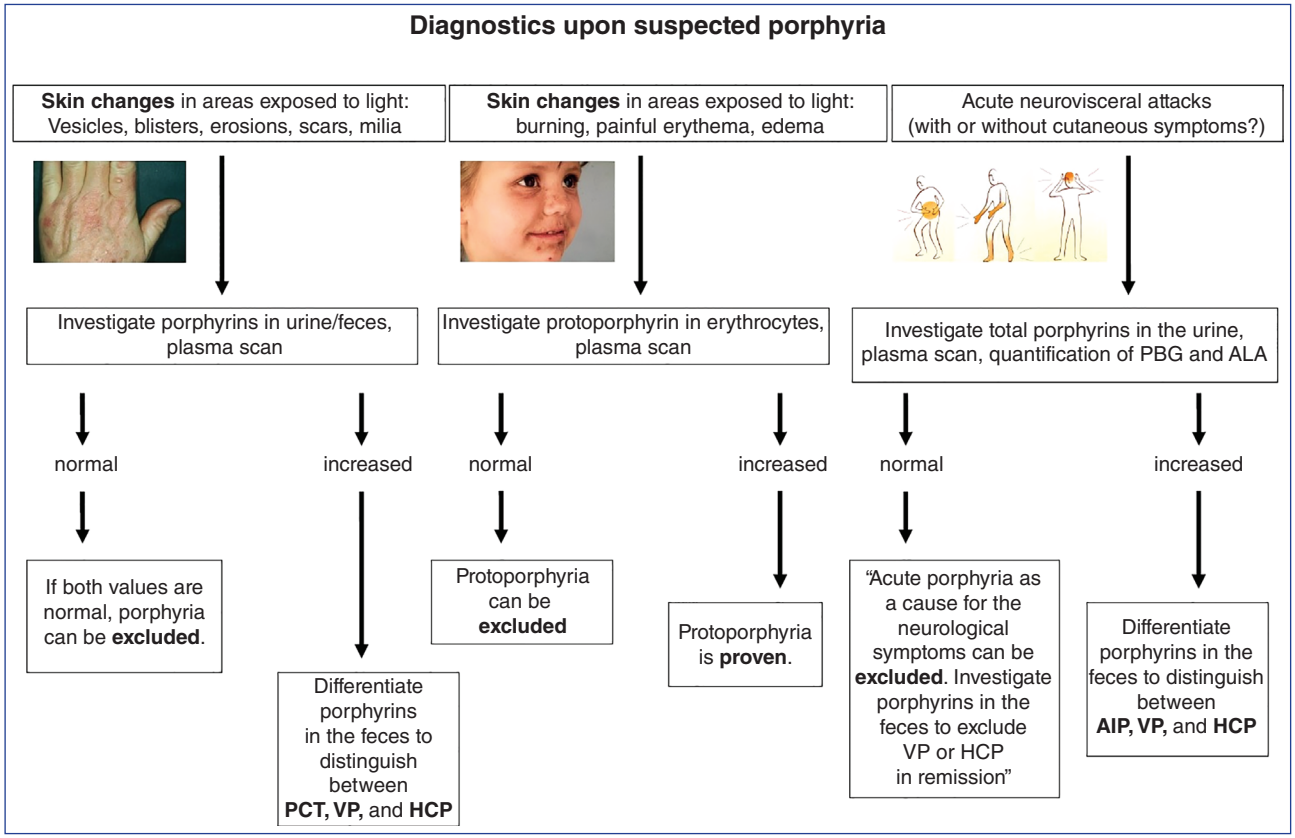

Figure 2 Diagnostic algorithm for the presumptive diagnosis of porphyria.
Abbr.: PCT, Porphyria cutanea tarda; HCP, hereditary coproporphyria; PBG, porphobilinogen; ALA, δ-Aminolevulinic acid; VP, variegate porphyria; AIP, acute intermittent porphyria.

an initial fluorescence-based plasma scan (spectrometric detection of the various porphyrins in plasma or serum, based on their specific fluorescence maximum), as well as a biochemical analysis of porphyrins and their precursors ALA and PBG in the blood, urine, and feces (Figure 2). If this is insufficient for a clear diagnosis of the porphyria variant present in this patient, molecular diagnostics need to be performed. In the past, enzyme activity analyses were offered by a limited number of laboratories specializing in porphyria diagnostics, but these have proven too complicated and unsuitable for routine diagnostics [9].

If cutaneous porphyria is suspected as the most likely diagnosis, skin biopsies should usually be avoided since the technique lacks specificity and does not contribute sufficiently to the diagnosis. This is especially important when porphyria is suspected in children, since biopsies at this young age are inappropriately invasive, and patients with cutaneous porphyria usually show impaired wound healing and delayed scar formation. Liver biopsies used to be performed frequently in the past but have become very rare nowadays since hepatic involvement can be diagnosed with sufficient certainty via modern imaging procedures [10].

All porphyrias can be diagnosed with non-invasive or minimally invasive laboratory and/or molecular genetic investigations.

Following, we will describe three forms of cutaneous porphyria in detail: The most common form of porphyria world-wide, the most common childhood porphyria, and the most common neurocutaneous porphyria. The main characteristics of these three porphyrias as well as those of the other porphyria variants are also contained in Table 3.

Porphyria cutanea tarda (PCT)

Porphyria cutanea tarda is the most common form of porphyria world-wide.

Porphyria cutanea tarda (PCT; MIM 176090 und 176100) is the only form of porphyria that occurs in an acquired form as well as in a hereditary form [11]. The disease was first described by Waldenström in 1937 [12]. With an estimated prevalence of 1 : 10,000, this is the most common form of porphyria world-wide [13].

There are at least two different forms of PCT, with some authors differentiating three. All forms share an enzymatic deficiency of uroporphyrinogen decarboxylae (UROD), the fifth enzyme in the biosynthesis of heme (Figure 1). In the acquired form, also called sporadic or type I PCT, hepatic UROD enzyme activity alone is decreased by about 20 %. In contrast, hereditary PCT (also called familial PCT or type II PCT) shows decreased enzyme activity by about 50 % in all tissues, and hepatic UROD activity is severely decreased with a residual activity of only 20 %. Hereditary PCT is caused by heterogeneous germline mutation in the *UROD* gene encoding UROD, and is inherited in an autosomal dominant manner. The rare type III PCT shows familial clustering, hepatic UROD activity decreased to about 20 %, normal UROD activity in extrahepatic tissues, and no evidence of mutations in the *UROD* gene [14]. The ratio of type I PCT to type II PCT is about 4 : 1 on average.

Three different subtypes of porphyria cutanea tarda have been described, all of them caused by a partial deficiency of uroporphyrinogen decarboxylase.

For the appearance of clinical symptoms, additional trigger factors apart from the partial UROD deficiency are required. These include increased serum iron levels, abuse of alcohol and nicotine, infection with hepatitis C virus, mutations in the hemochromatosis (*HFE*) gene, estrogen, and HIV infection [10, 11, 15].

Known trigger factors that may promote clinical manifestation of porphyria cutanea tarda include increased iron levels in the serum, alcohol and nicotine abuse, HCV infection, mutations in the hemochromatosis (*HFE*) gene, estrogens, and HIV infection.

PCT is usually chronic or chronic-recurrent and in most cases appears in adults of middle age from the 5th decade of life onwards. Women and men are affected equally. Clinical appearance is characterized by primary lesions (vesicles and blisters on erythematous skin), and secondary lesions such as erosions, crusts, milia, hyperpigmented and hypopigmented scars (Figure 3). In addition, some patients develop hypertrichosis and pseudo-scleroderma characterized by yellowish-white, waxy sclerodermiform papules and plaques [16, 17]. Calcifications and diffuse

Table 3 Epidemiological, clinical and genetic aspects of the cutaneous and non-cutaneous porphyrias.
Abbr.: AD, autosomal dominant; AR, autosomal recessive; ASD, autosomal semidominant; XD, X-chromosomal dominant.

Porphyria (MIM)	Incidence	Age of manifestation	Clinical appearance	Protein	Gene/Gene locus	Heredity
Porphyria cutanea tarda	Most common porphyria world-wide; 1 per 10,000	4th to 5th decade of life, usually not before puberty	Mild to moderate photosensitivity; increased skin fragility, skin changes exclusively in areas exposed to light: vesicles/blisters, erosions, crusts, milia, scars, hyperpigmentation, sclerodermiform papules and plaques, hypertrichosis; possible complication: hepatic cirrhosis, hepatocellular carcinoma	Uroporphyrinogendecarboxylase	*UROD; 1p34*	Acquired (type I); AD (type II); unknown (type III)
Hepatoerythropoietic porphyria	Extremely rare	Early childhood	Moderate to severe photosensitivity, increased skin fragility, skin changes exclusively in areas exposed to light: vesicles/blisters, erosions, crusts, milia, scars, hyperpigmentation, hypertrichosis, mutilations	Uroporphyrinogendecarboxylase	*UROD; 1p34*	Homozygous variant of porphyria cutanea tarda type II
Variegate porphyria	Rare; 3 per 1,000 in the light-skinned population of South Africa	3rd to 4th decade of life, usually not before onset of puberty	Mild to moderate photosensitivity; increased skin fragility, skin changes exclusively in areas exposed to light: vesicles/blisters, erosions, crusts, milia, scars, hyperpigmentation, hypertrichosis; Note! Acute neurological attacks; possible complication: hepatocellular carcinoma	Protoporphyrinogen oxidase	*PPOX; 1q22-23*	AD
Hereditary coproporphyria	Very rare	Usually not before puberty	Skin changes are much rarer than in variegate porphyria: Mild to moderate photosensitivity; increased skin fragility, skin changes exclusively in areas exposed to light: vesicles/blisters, erosions, crusts, milia, scars, hyperpigmentation; Note! Acute neurological attacks; possible complication: hepatocellular carcinoma	Coproporphyrinogen oxidase	*CPOX; 3q12*	AD
Congenital erythropoietic porphyria	Very rare	Early childhood/ infancy	Moderate to very severe photosensitivity; increased skin fragility, skin changes exclusively in areas exposed to light: vesicles/blisters, erosions, crusts, milia, scars, hyperpigmentation, hypertrichosis	Uroporphyrinogensynthase III	*UROS*	AR

Continued

Table 3 Continued.

Porphyria (MIM)	Incidence	Age of manifestation	Clinical appearance	Protein	Gene/Gene locus	Heredity
Erythropoietic protoporphyria	Second most common cutaneous porphyria; 1 per 130,000; most common porphyria in children	Early childhood; late manifestation is very rare	Moderate to severe photosensitivity. Subjective complaints: pruritus, burning, stinging and pain of the skin directly after exposure to light. Objective symptoms: Diffuse erythema and edema, more rarely petechiae and purpura. Very rarely vesicles/blisters. Lichenification, post-inflammatory hyperpigmentation, scarring; scar-like hyalinoses (bridge of the nose, knuckles). Complications: cholelithiasis, liver failure.	Ferrochelatase	*FECH; 18q21.3*	ASD
X-chromosomal dominant protoporphyria	Very rare	Early childhood	Moderate to severe photosensitivity. Subjective complaints: pruritus, burning, stinging and pain of the skin directly after exposure to light. Objective symptoms: Diffuse erythema and edema, more rarely petechiae and purpura. Very rarely vesicles/blisters. Lichenification, post-inflammatory hyperpigmentation, scarring; scar-like hyalinoses (bridge of the nose, knuckles). Complications: cholelithiasis, liver failure.	Aminolevulinic acid synthase 2	*ALAS2; Xp11.21*	XD
Acute intermittent porphyria	Most common acute porphyria; 0.5–1 per 100,000	3rd to 4th decade of life, usually not before onset of puberty	Acute neurological attacks, no skin changes; possible complication: hepatocellular carcinoma	Porphobilinogen deaminase;	*PBGD; 11q23.3*	AD
ALA dehydratase deficiency porphyria	Extremely rare	Variable; manifestation reported in both children and adults	Acute neurological attacks, no skin changes	Aminolevulinic acid dehydratase	*ALAD; 9q34*	AR

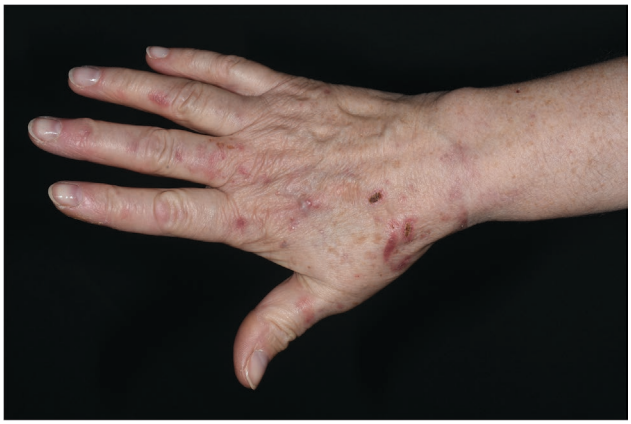

Figure 3 Erosions, crusts, milia and scars on the right hand of a patient with porphyria cutanea tarda.

actinic elastosis in the facial area have also been reported. The skin symptoms are often accompanied by iron and hemosiderin deposition in the liver, which is reflected by the red fluorescence of the liver punch cylinder in liver biopsies that were often performed in the past [10, 11].

Differential diagnoses for porphyria cutanea tarda include other blistering cutaneous porphyrias, epidermolysis bullosa acquisita, polymorphic light dermatosis, bullous photoaggraveted drug reactions, bullous phototoxic contact dermatitis, and hydroa vacciniformia.

Differential diagnoses of PCT include other forms of blistering porphyria, especially pseudoporphyria cutanea tarda (bullous photosensitivity reactions that look like PCT both clinically and histologically but are not associated with pathological changes of porphyrins in the urine or serum), variegate porphyria, hereditary coproporphyria, and mild forms of hepatoerythropoietic porphyria. Other differential diagnoses that need to be excluded are epidermolysis bullosa acquisita, polymorphic light dermatosis, UV-aggravated bullous drug reactions, bullous phototoxic contact dermatitis, and hydroa vacciniformia [4, 11, 16, 17].

Increased accumulation of iron in various organs will result in increased serum levels of iron, as well as ferritin and transferrin. The patient's urine will show a marked increase in total porphyrins, uroporphyrin, and highly carboxylated porphyrins. Detection of heptacarboxylated porphyrins, as well as detection of isocoproporphyrin in the feces, is pathognomonic for PCT. To differentiate type II PCT from the other forms, molecular genetic analysis can be performed to detect a mutation in the *UROD* gene [9].

After a diagnosis of PCT, the patient should first be informed about the known trigger factors and advised of the importance of appropriate light protection. This includes clothing that covers the arms and legs, and broad-brimmed, light-proof hats. Only mineral (physical) sunscreens are suitable for topical photoprotection. Patients should avoid alcohol and nicotine, and any medical hormone use should be critically reviewed [4, 11, 17].

Phlebotomy and low-dosed hydroxychloroquine are used for treating porphyria cutanea tarda.

There are two therapeutic strategies for treating PCT. Phlebotomy according to Ippen has been an established treatment for decades [18]. Although there are various regimens, it is generally recommended to draw about 400–500 ml blood every two weeks until blisters cease to appear, clinical remission has commenced, and serum ferritin is ~40–50 ng/ml [19]. Note that the cutaneous symptoms usually resolve long before the laboratory values have normalized [10]. Apart from phlebotomy, low-dose treatment with 100 mg hydroxychloroquine twice a week is also an option. Hydroxychloroquine increases water solubility of uroporphyrin accumulated in the liver, as well as of highly carboxylated porphyrins, and thus facilitates their excretion via the urine. It is essential to adhere to this low dose regimen since any

overdose will or even worsen the disease. Before hydroxychloroquine treatment, porphyrin excretion in the urine should be determined as a baseline value, and during treatment this should be monitored every two months. With this treatment, as well, clinical remission will precede the biochemical normalization of porphyrin excretion [10]. The average duration of treatment is nine to twelve months [11, 17]. Chloroquine was frequently used in the past and is very effective [10, 11], but it was withdrawn from the German market in 2019 and is now, unfortunately, unavailable for PCT treatment. There is currently no treatment option for hypertrichosis, a complaint which is unpleasant especially for affected women.

Possible complications of porphyria cutanea tarda are liver cirrhosis and hepatocellular carcinoma.

Possible complications of PCT include liver cirrhosis caused by accumulation of porphyrins in the hepatocytes over long periods of time. Histologically, porphyrin accumulation appear as birefringent, needle-shaped inclusions in the hepatocytes [20]. Regular monitoring with upper abdominal sonography and investigation of alpha-1 fetoprotein levels is recommended for prophylaxis. High concentrations of this glycoprotein may also indicate the development of hepatocellular carcinoma which has been reported several times as a possible complication of PCT [21, 22].

Erythropoeitic protoporphyria

Erythropoietic protoporphyria is the most common porphyria in children.

Erythropoietic Protoporphyrie (EPP; MIM 177000) is the second most common cutaneous porphyria and the most common form of porphyria in childhood. The disease was first reported in 1953 by Kosenow and Treibs who described a child with increased photosensitivity and accumulation of porphyrins in the blood [23]. Eight years later, Magnus et al. characterized the disease as a porphyria and coined the name EPP [24]. This disease has an estimated prevalence of 1 in 130,000; it affects male and female patients equally and is found in all ethnicities [1, 2].

The disease results from ferrochelatase deficiency, inherited in an autosomal semidominant pattern.

EPP is inherited in an autosomal semidominant pattern and is caused by partial deficiency of ferrochelatase (FECH), the eighth enzyme in the heme biosynthesis pathway. FECH deficiency results in massive accumulation of lipophilic protoporphyrin (PP) in the skin, the erythrocytes, the liver, and other organs. Protoporphyrin is a metal-free porphyrin with an absorption maximum in the blue wavelength range of visible light between 400 and 410 nm (Soret peak) which acts as a photosensitizer [1, 25, 26].

On the one hand, enzymatic dysfunction of FECH is caused by heterozygous mutations in the *FECH* gene. However, these mutations in a single parental allele will only yield a ~ 50 % decrease in residual enzyme activity, which is not enough to cause clinical symptoms. Clinical manifestation only occurs is FECH activity is reduced by another 30–35 % by *FECH* polymorphism in *trans* on the second parental allele, with a residual activity of FECH of just 15–20 % [27–29].

The subjective complaints of the young patients – pruritus, burning, stinging, and pain in the skin – are in discrepancy to the objective cutaneous signs.

As early as infancy, patients become agitated after a brief outdoor exposure to visible and UV light and complain of itching, burning, stinging, and pain in the skin within minutes of light exposure. The challenge with EPP is that at the time of first manifestation, the subjective symptoms of the mostly young patients are markedly different from the objective signs seen on the skin. These will frequently appear only half an hour to several hours after exposure to light, and may even then be discrete and difficult to see [30]. The subjective symptoms of acute photosensitivity are accompanied by diffuse erythema and edema in the areas exposed to light (Figure 4a). Petechiae and purpura may develop more rarely (Figure 4b) [25, 26, 31]. The phototoxic reaction usually occurs without vesicles or blisters. Only if the patient has to stay exposed to the sun for longer periods of time – for example because adults will not take the child's complaints seriously, suspect that the child is making up the complaints, or is just "being difficult" – vesicles or bullae

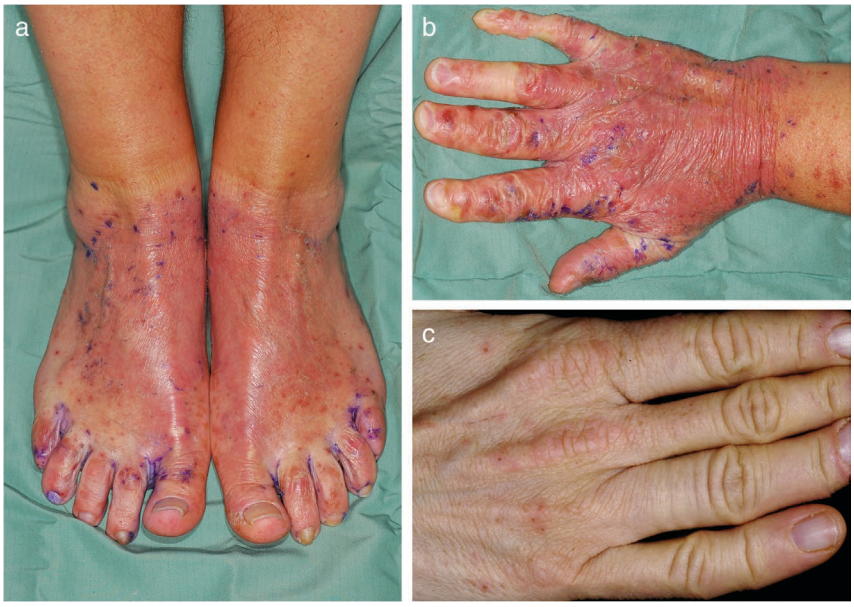

Figure 4 Erythema and petechiae on the back the feet and extensor digitorum of the toes of a patient with erythropoietic protoporphyria. Note that the non-light-exposed portions of the distal lower legs are free of skin erythema (a). Erythema and edema on the back and extensor digitorum of single fingers of the right hand of a patient with erythropoietic protoporphyria (b). Hyalinosis cutis over the metacarpophalangeal joints II and III of the right hand of a patient with erythropoietic protoporphyria (c).

Currently, the only effective treatment is afamelanotide, a synthetic analog of alpha-melanocyte stimulating hormone.

may develop in rare cases. This will resemble severe sunburn (solar dermatitis). Symptoms will mainly occur in spring and summer, and since diagnosis is usually delayed for several years, continued exposure to light may lead to lichenification, post-inflammatory hyperpigmentation, and scarring. In this connection, the development of scar-like hyalinoses especially over the knuckles and the bridge of the nose is pathognomonic (Figure 4c) [25, 26, 30].

First and foremost, EPP must be differentiated from X-chromosomal dominant protoporphyria. This is impossible based only on clinical appearance. Other differential diagnoses include diseases characterized by increased photosensitivity, such as solar urticaria, polymorphic light dermatosis, phototoxic or photoallergic dermatitis, Bloom syndrome, and Rothmund-Thompson syndrome [32].

In diagnostics, the plasma scan will show a characteristic emission maximum of 634 nm. PP is markedly increased in both blood and feces, but investigation of the blood is sufficient. If EPP is the leading suspected diagnosis, analysis of the urine is unnecessary since PP is liophilic and is not excreted via urine. Determination of residual FECH activity will show decreased values with only 15–25 % enzyme activity compared to the normal value. To differentiate EPP from X-chromosomal dominant protoporphyria, molecular genetic analysis of the *FECH* gene may be performed [32, 33].

In an acute situation with pruritus, burning, and pain in the skin, patients should seek darkened rooms without exposure to light and cool the affected skin areas, either with running water, moist poultices, or cool packs. Afamelanotide (Scenesse®), a synthetic analog of α-melanocyte stimulating hormone, is an effective medication for preventing phototoxicity in adult patients with EPP [32, 34]. It is only approved for patients aged 18 or above, and is thus unfortunately unavailable for exactly those patients who need treatment most urgently: children

and adolescents. An additional drawback is the manufacturer's restrictive policy which has remained unchanged for years: Only a small, select group of physicians specialized in EPP and working in porphyria centers are permitted to administer the drug by implanting a subcutaneous appliance every two months. Afamelanotide may only be administered by physicians who have been trained and accredited by the marketing authorization holder. These restrictions have led to a situation where adult EPP patients remain underserved and cannot receive afamelanotide, as the capacities of the few centers are limited.

In some earlier publications, systemic treatment with β-carotene or vitamins E and C was reported to have positive effects, but this is nowadays discouraged, as these effects appear at best to be small and non-reproducible [32].

Possible complications of EPP include cholelithiasis, liver cirrhosis with hepatic insufficiency, as well as fulminant and terminal liver failure.

Possible complications of EPP include cholelithiasis, liver cirrhosis with hepatic insufficiency, and as the most severe complication fulminant and terminal hepatic failure. For prophylaxis, regular monitoring of liver and cholestasis parameters as well as yearly upper abdominal sonography is recommended. All abovementioned complications are caused by massive accumulation of PP, which are insoluble in water, in the biliary tract and the liver [25, 35].

Variegate porphyria

Variegate porphyria belongs to the neurocutaneous porphyrias.

Variegate porphyria (VP; MIM 176200) is the most common neurocutaneous porphyria, characterized by large clinical variability and genetic heterogeneity. The disease is sometimes also called "mixed hepatic porphyria", or "South African porphyria", and was first described in 1951 by Barnes [36]. The general incidence and prevalence of VP are unknown, but in the light-skinned population of South Africa its incidence is estimated at about 3 : 1,000 due to a so-called "founder effect" [37, 38].

The disease is caused by dysfunction of protoporphyrinogen oxidase, and is inherited in an autosomal-dominant pattern.

The disease is inherited in an autosomal-dominant pattern and is caused by dysfunction of protoporphyrinogen oxidase (PPOX), the seventh enzyme in heme biosynthesis. The catalytic deficiency of this enzyme results from mutations in the *PPOX* gene which are usually heterozygous but may be compound heterozygous or homozygous in rare cases [39, 40].

Clinically, variegate porphyria may present with skin changes and/or acute neurological and psychiatric symptoms during an acute porphyria attack.

Clinical manifestation usually occurs only after the onset of puberty. Skin changes in areas exposed to light and/or acute neurological or psychiatric symptoms may develop. Primary skin lesions such as intact vesicles or blisters are relatively rare, but secondary lesions such as erosions, crusts, milia, and scars are common. As in PCT, hypertrichosis especially in the facial area is common (Figure 5) [8, 41, 42]. Neurological-psychiatric symptoms may occur in acute porphyria attacks, either alone or in combination with skin changes. Abdominal pain is the leading symptom, which may be accompanied by nausea, vomiting, diarrhea (but also constipation), paresthesia, motoric or sensory dysfunction, and paralysis, and may even culminate in paraplegia or tetraplegia.

The skin changes are impossible to differentiate from those occurring in other blistering porphyrias such as PCT, hereditary coproporphyria, or milder variants of hepatoerythropoietic porphyria or congenital erythropoietic porphyria. It is also impossible to differentiate the neuropsychiatric symptoms from those of acute intermittent porphyria, hereditary coproporphyria, or ALA dehydratase deficiency porphyria. In addition, differential diagnosis of acute porphyria/acute porphyria attacks includes any disease presenting with acute abdominal pain, as well as many neurological and/or psychiatric diseases [7, 8, 41].

For diagnosis of VP, a characteristic fluorescence emission maximum of 625–626 nm in the spectrophotometric analysis of plasma from affected patients was described as early as 1980 [43]. This pathognomonic plasma emission peak

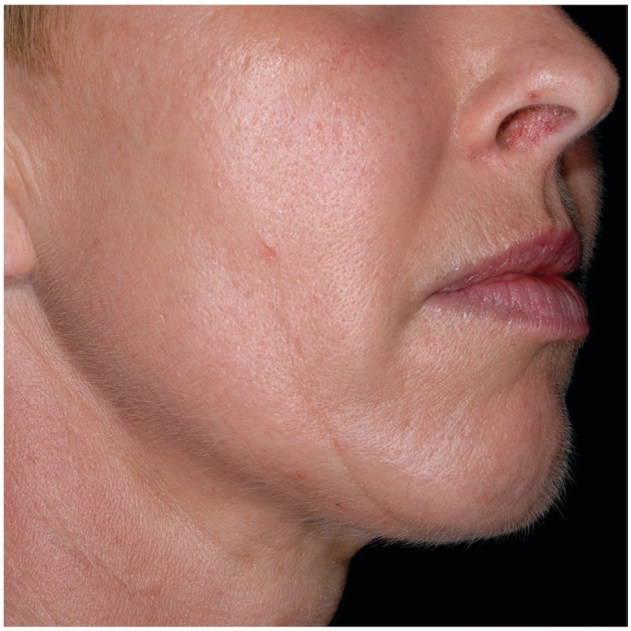

Figure 5 Facial hypertrichosis in a patient with variegate porphyria.

is sufficiently specific to differentiate VP from PCT and other acute porphyrias in symptomatic adult patients. In children and non-symptomatic adults, however, a plasma scan is not sensitive enough [41]. During an acute porphyria attack, urinalysis will reveal moderately to greatly increased excretion of the porphyrin precursors ALA and PBG but cannot differentiate VP from other forms of acute porphyria. This requires analysis of the feces with evidence of increased excretion of proto- and coproporphyrin. The levels of protoporphyrin are usually higher than those of coproporphyrin. If the biochemical results remain ambiguous, molecular genetic analysis with sequencing of the *PPOX* gene may be performed [8, 33, 41].

There is no specific treatment for the cutaneous symptoms of VP, therefore general photoprotective measures as described for PCT should be taken. Phlebotomy has no effect, and treatment with antimalarials as described for PCT therapy is strongly discouraged. These drugs are potentially porphyrinogenic and may trigger exacerbation of acute porphyria attacks. There is a fixed scheme for treating an acute porphyria attack, based on the consensus recommendations of the European Porphyria Initiative (EPI) and its successor, the European Porphyria Network (EPNET) (https://porphyria.eu/de/content/treatment-acute-attack) [2, 7, 8]:

Treatment of acute porphyria attacks follows a fixed scheme based on the consensus recommendations of the European Porphyria Network (EPNET).

1. Identification and elimination of possible porphyrinogenic trigger factors.
2. Initial monitoring in an intensive care unit if indicated, with adequate supportive treatment using analgesics, antiemetics, neuroleptics, and antihypertensives.
3. Specific treatment with intravenous heme preparations: in Europe with heme arginate (Normosang®), in the US, South America, and Middle America with hemin (Panhematin®).
4. There is a new treatment option for prophylaxis of recurrent porphyria attacks: givosiran (Givlaari®), based on RNA interference and proven to be very effective in clinical studies [44]. It blocks ALA synthase and thus the rate-determining step in heme biosynthesis. Development of severe homocysteinemia when using givosiran has been observed by several authors [45–47].

Possible complications of acute porphyria attacks include paralysis of the auxiliary respiratory muscles with transition into respiratory coma. This is why acute porphyrias are classified as potentially life-threatening diseases requiring immediate therapeutic intervention [1, 4, 7, 41].

Conclusion

All porphyrias are caused by a catalytic dysfunction of specific enzymes in the heme biosynthesis pathway. This enzymatic deficiency leads to accumulation of one or more metabolites such as porphyrin precursors and/or porphyrins, which after induction by various trigger factors may cause toxic effects in cells and tissues. Clinically, these effects may present as skin changes as seen in the cutaneous porphyrias PCT and EPP presented here, or as variable cutaneous and/or neurological symptoms as in the case of VP as an example for the neurocutaneous porphyrias. Diagnosis is usually made by biochemical analysis of urine, blood, and feces. If indicated, this may be complemented by molecular genetic diagnostics. An exact diagnosis is essential for differentiating the various forms of porphyria and initiating specific treatment.

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Conflicts of interest

J.F. declares that he was not swayed by economic considerations when preparing this publication. He declares the following potential conflicts of interest:
He received lecture fees and financial support from the companies Genzyme and Shire for participation in the 2nd World Congress for Genodermatology in 2001 in Maastricht, The Netherlands. He received lecture fees and financial support from the companies Roche, Bristol-Myers Squibb, Novartis, MSD, and Orphan Europe Germany GmbH for conducting advanced training courses. He also received travelling cost support from the company Clinuvel for participation in the 23rd World Congress for Dermatology in Vancouver, Canada, and he was study coordinator for two clinical studies (Phase 2 and 3) conducted by Clinuvel. For organizing and conducting the International Congress on Porphyrins and Porphyrias 2015, he received financial support from the companies Alnylam Pharmaceuticals, Orphan Europe, Clinuvel Pharmaceuticals, La Roche-Posay, and Lilly Germany GmbH. He also received honorariums for participating in advisory boards from Alnylam Pharmaceuticals. W.M., M.A.H., and P.P.-G. declare no conflicts of interest.

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CME Questions/Lernerfolgskontrolle

1. Welche der nachfolgend genannten Untersuchungen ist in der Diagnostik der kutanen Porphyrien **nicht wegführend und sollte daher heutzutage unterbleiben?**
a) Inspektion, Eigen-/Fremdanamnese
b) Hautbiopsie
c) Biochemische Untersuchungen
d) Enzymatische Untersuchungen
e) Molekulargenetische Untersuchungen

2. Welches Untersuchungsmaterial benötigen Sie **nicht, um eine Porphyrie-Erkrankung zu diagnostizieren?**
a) Plasma
b) Stuhl
c) Blut
d) Liquor
e) Urin

3. In der Haut abgelagerte Porphyrine können unter Einfluss von UV-Licht eine phototoxische Reaktion auslösen. Welche der nachfolgenden Symptome/klinischen Veränderungen werden bei den Porphyrien üblicherweise **nicht durch diese Reaktion verursacht?**
a) Brennende Schmerzen
b) Blasen
c) Erythem
d) Hauttumoren
e) Ödem

4. Welche Porphyrie-Variante ist weltweit die häufigste?
a) Kongenitale erythropoetische Porphyrie
b) Porphyria variegata
c) Akute intermittierende Porphyrie
d) Hepatoerythropoetische Porphyrie
e) Porphyria cutanea tarda

5. Welche der nachfolgend genannten Porphyrie-Varianten manifestiert sich üblicherweise **nicht bereits im Kindesalter?**
a) Hepatoerythropoetische Porphyrie
b) Porphyria cutanea tarda
c) Erythropoetische Protoporphyrie
d) X-chromosomal dominante Protoporphyrie
e) Kongenitale erythropoetische Porphyrie

6. Neben einer Genmutation bedarf es oft triggernder Faktoren, um bei der Porphyria cutanea tarda klinische Symptome auszulösen. Welcher Faktor gehört **nicht dazu?**
a) Alkohol
b) Östrogene
c) Hepatitis-B-Virusinfektion
d) Erhöhtes Serum-Eisen
e) UV-Licht

7. Bei welcher Porphyrie-Erkrankung treten **nie Hautveränderungen auf?**
a) Porphyria variegata
b) Akute intermittierende Porphyrie
c) Hereditäre Koproporphyrie
d) Hepatoerythropoetische Porphyrie
e) Kongenitale erythropoetische Porphyrie

8. In der Haut abgelagerte Porphyrine absorbieren Licht einer bestimmten Wellenlänge (Soret-Bande) und werden dadurch angeregt. Die Soret-Bande befindet sich im Wellenlängen-Bereich von …
a) 200–250 nm
b) ~ 300 nm
c) 340–370 nm
d) 400–410 nm
e) 450–500 nm

9. Bei welcher der nachfolgend genannten Porphyrie-Erkrankungen können sich sowohl kutane als auch akute neurologische Symptome entwickeln?
a) Porphyria cutanea tarda
b) Akute intermittierende Porphyrie
c) Kongenitale erythropoetische Porphyrie
d) Porphyria variegata
e) Erythropoetische Protoporphyrie

10. Welche dieser Therapieoptionen bietet derzeit die beste Behandlungsmöglichkeit bei der erytheropoetischen Protoporphyrie?“
a) Anwendung topischer Lichtschutzpräparate
b) Umstellung des Tag-Nacht-Rhythmus
c) Afamelanotid
d) β-Carotin
e) Regelmäßige Aderlässe (400–500 ml)

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 31. Mai 2022. Die richtige Lösung zum Thema „Häufige Nagelerkrankungen: Diagnostik und Therapie“ in Heft 12 (Dezember 2021) ist: 1e, 2e, 3e, 4d, 5e, 6a, 7a, 8e, 9c, 10b.

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