Gastroenterology 2019;157:365–381

Clinical Guide and Update on Porphyrias

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Physicians should be aware of porphyrias, which could be responsible for unexplained gastrointestinal, neurologic, or skin disorders. Despite their relative rarity and complexity, most porphyrias can be easily defined and diagnosed. They are caused by well-characterized enzyme defects in the complex heme biosynthetic pathway and are divided into categories of acute vs non-acute or hepatic vs erythropoietic porphyrias. Acute hepatic porphyrias (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and aminolevulinic acid dehydratase deficient porphyria) manifest in attacks and are characterized by overproduction of porphyrin precursors, producing often serious abdominal, psychiatric, neurologic, or cardiovascular symptoms. Patients with variegate porphyria and hereditary coproporphyria can present with skin photosensitivity. Diagnosis relies on measurement of increased urinary 5-aminolevulinic acid (in patients with aminolevulinic acid dehydratase deficient porphyria) or increased 5-aminolevulinic acid and porphobilinogen (in patients with other acute porphyrias). Management of attacks requires intensive care, strict avoidance of porphyrinogenic drugs and other precipitating factors, caloric support, and often heme therapy. The non-acute porphyrias are porphyria cutanea tarda, erythropoietic protoporphyria, X-linked protoporphyria, and the rare congenital erythropoietic porphyria. They lead to the accumulation of porphyrins that cause skin photosensitivity and occasionally severe liver damage. Secondary elevated urinary or blood porphyrins can occur in patients without porphyria, for example, in liver diseases, or iron deficiency. Increases in porphyrin precursors and porphyrins are also found in patients with lead intoxication. Patients with porphyria cutanea tarda benefit from iron depletion, hydroxychloroquine therapy, and, if applicable, elimination of the hepatitis C virus. An α-melanocyte–stimulating hormone analogue can reduce sunlight sensitivity in patients with erythropoietic protoporphyria or X-linked protoporphyria. Strategies to address dysregulated or dysfunctional steps within the heme biosynthetic pathway are in development.

Keywords: Therapy; Neurologic; Dermatologic; Clinical.

Porphyrins are essential building blocks in the microcosm of organic life. Because of their ability to absorb electromagnetic radiation from sunlight and their similarity to chlorophyll, which captures energy for photosynthesis, porphyrins are important pigments of life. Porphyrins are ubiquitous precursors of heme, which contains a central iron atom. The heme-bound iron of hemoglobin or myoglobin in blood and tissues reversibly binds and transports oxygen; heme enzymes such as cytochromes, nitric oxide synthases, cyclooxygenases, peroxidases, catalases, and tryptophan pyrrolase catalyze important biochemical reactions in cells. Most of the porphyrins emit red fluorescence when exposed to long-wave (366 nm) ultraviolet light, as exemplified by brown, high protoporphyrin-containing chicken eggshells (Supplementary Figure 1).[1]

The liver synthesizes 20% of heme, which regulates its own production via interaction with 5-aminolevulinate synthase 1 (ALAS1).[2] Most of the remaining 80% of heme is produced in the bone marrow. In contrast to the liver, iron and erythropoietin, instead of heme, regulate the rate-controlling bone marrow enzyme ALAS2.[3] The known porphyrias, rare disorders of heme biosynthesis, produce many symptoms. The acute hepatic porphyrias (AHPs) (acute intermittent porphyria [AIP], variegate porphyria [VP], hereditary coproporphyria [HCP], and aminolevulinic acid dehydratase deficient porphyria [ALADP]) produce mostly abdominal, neurologic, psychiatric, and cardiovascular symptoms. In patients with non-acute porphyrias (porphyria cutanea tarda [PCT], hepatoerythropoietic porphyria [HEP], erythropoietic protoporphyria [EPP], X-linked protoporphyria [XLP], and congenital erythropoietic porphyria [CEP]), porphyrins that were generated by spontaneous oxidation from porphyrinogens accumulate upstream of the affected enzyme to cause skin photosensitivity (photodermatosis) and sometimes severe liver damage.

Porphyrias are diagnosed and differentiated by specific biochemical patterns of elevated porphyrins and porphyrin precursors in urine, feces, and blood (Table 1,

Abbreviations used in this paper: AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinic acid; ALAD, 5-aminolevulinic acid dehydratase; ALADP, 5-aminolevulinic acid dehydratase–deficient porphyria (Doss porphyria); ALAS, 5-aminolevulinic acid synthase; CEP, congenital erythropoietic porphyria; CPOX, coproporphyrinogen oxidase; CQ, chloroquine; CyP450, cytochrome P450; EPP, erythropoietic protoporphyria; FECH, ferrochelatase; HCP, hereditary coproporphyria; HCQ, hydroxychloroquine; HCV, hepatitis C virus; HEP, hepatoerythropoietic porphyria; mRNA, messenger RNA; PBG, porphobilinogen; PBGD, porphobilinogen deaminase; PCT, porphyria cutanea tarda; PPIX, protoporphyrin IX; UROD, uroporphyrinogen decarboxylase; UROS, uroporphyrinogen-III-synthase; VP, variegate porphyria; XLP, X-chromosomal erythropoietic protoporphyria.

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2019.04.050

Table 1. Biochemical, Diagnostic, and Clinical Characteristics of Porphyrias and Lead Poisoning, Ordered by Category and Prevalence

Porphyria and lead poisoning	Enzyme activities	Biochemical testing	Second-line diagnostics	Plasma Screen, *nm*[a]	Neurovisceral symptoms	Cutaneous symptoms	Anemia	Liver damage
AHPs								
AIP	PBGD ↓	Urinary ALA ↑↑, PBG ↑↑, and porphyrins ↑↑	PBGD activity[b] Mutation analysis	615–620	++	−	−	−/+
VP	PPOX ↓	Urinary ALA ↑↑, PBG ↑↑, and porphyrins ↑↑ Fecal PPIX ↑↑ and coproporphyrin III ↑	Mutation analysis	625–627	++	−/+	−	−/+
HCP[c]	CPOX ↓	Urinary ALA ↑↑, PBG ↑↑, and porphyrins ↑↑ Fecal coproporphyrin III ↑	Mutation analysis	615–620	++	−/+	−	−/+
ALADP	ALAD ↓	Urinary ALA ↑↑ and PBG normal or ↑ and coproporphyrin isomer III ↑↑	ALAD activity Mutation analysis	615–619	++	−	−/+	−
Other hepatic porphyrias								
PCT and HEP	UROD ↓	Urinary porphyrins ↑↑	UROD activity[e]	615–620	−	+	−	+
		Uro- >> coproporphyrin[d]	Mutation analysis		−	++	−/+	+
Erythropoietic porphyrias								
EPP	FECH ↓	Erythrocyte metal-free PPIX ↑↑ and Zn-bound PPIX[f] ↑	Mutation analysis	624–635	−	++	−/+	−/+
XLP	ALAS2 ↑	Erythrocyte metal-free PPIX ↑↑ and Zn-bound PPIX[g] ↑↑	Mutation analysis	624–635	−	++	−/+	−/+
CEP	UROS ↓	Urinary and fecal Uro- and coproporphyrin Isomer I ↑↑	Mutation analysis	615–620	−	++	+	−
Other								
Lead poisoning	ALAD ↓	Urinary ALA ↑↑ and PBG normal or ↑ and coproporphyrin isomer III ↑↑[h] Erythrocyte metal-free PPIX ↑ and Zn-bound PPIX ↑↑	ALAD activity Lead concentration ↑↑ (blood, urine)	615–620	++	−	+	+

↑, increased; ↓, decreased; −, clinical feature not present at time of manifestation; −/+, clinical feature variable at time of manifestation; +, clinical feature typically present at time of manifestation.
PPOX, protoporphyrinogen oxidase.
[a]Fluorescence emission maximum (*nm*) of plasma porphyrins on excitation at 405 nm.
[b]Decreased enzyme activity in blood, normal only in the non-erythroid splice site mutation variant.
[c]A specific homozygous mutation or null allele of the CPOX gene leads to the phenotypically different rare harderoporphyria that lacks abdominal and neurologic symptoms.
[d]Increased fecal isocoproporphyrin is a sufficient but not necessary indicator of PCT/HEP, increased metal-free and zinc-bound protoporphyrin in erythrocytes is only found in HEP.
[e]Decreased enzyme activity in blood, normal activity in blood only in acquired (type 1) PCT.
[f]In EPP, the ratio of zinc-bound protoporphyrin to metal-free protoporphyrin is significantly lower (<15%) than in XLP.
[g]In XLP, the ratio of zinc-bound protoporphyrin to metal-free protoporphyrin is >25%.
[h]Lead poisoning affects 3 enzymes involved in heme biosynthesis (ALAD, CPOX, and FECH).

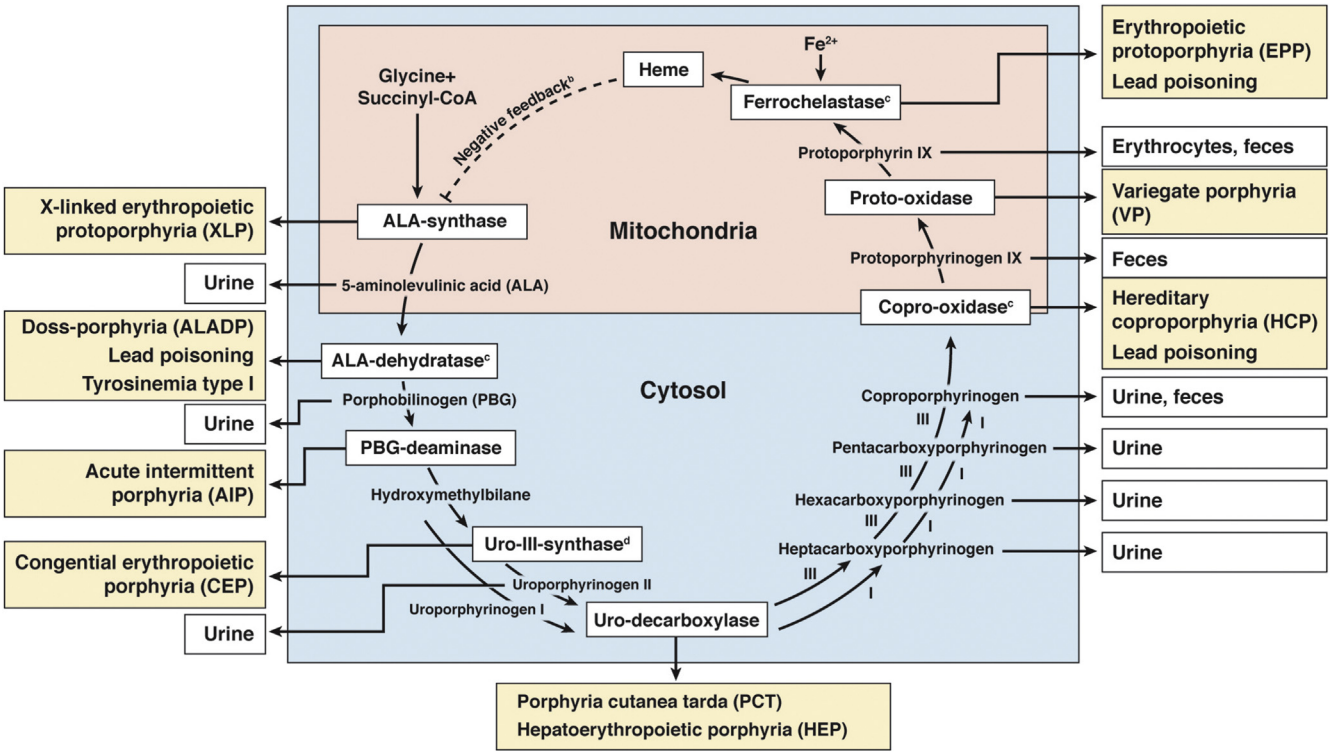

Figure 1. Heme biosynthesis and localization of characteristic enzyme defects in patients with porphyrias or lead poisoning.[a] [a]Porphyrinogens shown are excreted after oxidation to form porphyrins. [b]In the liver, heme regulates the first enzyme ALAS1 via a negative feedback loop. In contrast to the liver enzyme ALAS1, the rate-limiting bone marrow enzyme ALAS2 is regulated by iron and erythropoietin instead of heme. [c]Lead poisoning affects 3 enzymes involved in heme biosynthesis (modified from Blau et al[144]). [d]Two isomers of uroporphyrinogen (I and III) derive from hydroxymethylbilane are converted to coproporphyrinogen I and III. Importantly, only the isomer III is used for heme synthesis, whereas the non-functional isomer I is excreted in feces via the hepatobiliary pathway or in urine via the kidneys.

Figure 1).[4–6] Furthermore, a plasma fluorescence scan can discriminate the characteristic emission maxima of the metabolites and support the biochemical diagnosis (Table 1).[6] Beside the hepatic and erythropoietic porphyrias, secondary elevation in porphyrins have been found in patients with other diseases—especially in patients with chronic liver diseases (Supplementary Table 1).[7–13] We review the pathogenesis, symptoms, and treatment of the most frequent porphyrias (PCT, AIP, and EPP) (Table 2).[5,6,14] We present typical cases, diagnoses, and treatments and discuss therapeutic strategies in development. We also review symptoms and pathologies of lead intoxication that affect enzymes that mediate heme synthesis and share features with porphyrias.

Genetics

Porphyrias are caused by a range of mutations in many genes (Table 2). Most patients are heterozygous for these mutations because homozygous disruption of some of these genes can be lethal. However, some patients have homozygous mutations that result in a reduced but residual enzyme activity. Porphyria-associated mutations are listed in the Human Gene Mutation Database (www.hgmd.cf.ac.uk).

Porphyrias are often autosomal dominant disorders, with variations in penetrance and phenotype; they can also be caused by combinations of genetic alterations. ALADP and CEP are autosomal recessive diseases.[2] XLP is caused by mutations on the X-chromosome.[15] More than 95% of patients with EPP have a loss of function mutation in 1 allele of the ferrochelatase (*FECH*) gene and a single-nucleotide polymorphism in the other allele. This reduces FECH activity to <35% and leads to overt disease.[6,16] Few other homozygous or compound heterozygous functional mutations in the *FECH* gene have been found.

Compound heterozygous mutations (different mutations in each allele of a gene) have been associated with ALADP, CEP, and HEP, as well as in rare cases of severe AHP.[17–19] The genetic factors associated with AIP were investigated in a recent study from France.[20] Exome sequencing was performed in 602 patients with overt AIP, 1968 of their relatives, and in population controls, to reveal 42 genetic variants of the hydroxymethylbilane synthase gene (HMBS or porphobilinogen deaminase [PBGD]). These were expressed in *Escherichia coli* and their enzyme activity determined. In this study, the minimal prevalence of AIP in France was estimated at 1 of 1299. Notably, 22.9% penetrance was found in families with AIP, but only 0.5%–1.0% penetrance in the general population. This indicates that disease susceptibility is affected not only by inheritance of an autosomal dominant variant of PBGD, but other genetic or environmental factors.

Table 2. Protein and Genetic Features and Prevalence of Porphyrias

Porphyria	Deficient enzyme	Gene locus	No. of mutations reported	No. diagnosed [a,b]	Prevalence[c] reported	OMIM no.
ALADP	ALA-dehydratase	9q33.1	12	3	Rare[d,e]	612740
AIP	PBG deaminase	11q23.3	390	878	5.9[f]	176000
CEP	Uroporphyrinogen III synthase	10q25.2-10q26.3	48	35	Rare[e,g]	263700
PCT, HEP[h]	Uroporphyrinogen decarboxylase	1p34	121	3131	21[i]	176100
HCP	Coproporphyrinogen oxidase	3q12	50[j]	78	0.9[i]	121300
VP[k]	Protoporphyrinogen oxidase	1q22	174	133	3.2	176200
EPP	Ferrochelatase	18q21.3	189	289	9.2[l]	177000
XLP	ALA synthase 2	Xp11.21	4	3	Rare[e]	300752

OMIM, Online Mendelian Inheritance in Man.
[a]Data from the German Competence Center for Porphyria Diagnostics and Consultation; cases diagnosed between 1965 and 2017.
[b]The proportion among 4550 porphyrias was PCT:AIP:EPP:VP:HCP:CEP = 89:25:8:4:2:1.
[c]Prevalence is cases per 1 million inhabitants.[14]
[d]Six cases have been described.[35,140,145]
[e]Rare means that prevalence values are below the lowest estimated prevalence of 0.9 per 1 million for HCP.
[f]High prevalence in Sweden.[14,146]
[g]Two hundred cases with CEP have been described.[135]
[h]Forty cases with HEP have been described.[147]
[i]Because, in general, prospectively analyzed data are lacking, prevalence values were approximated according to the relative prevalence of the large German cohort of 4550 porphyrias in footnote *a* and the only (European) prospective study that found 5.9 cases of AIP per 1 million.[14] Thus, we estimated a prevalence of PCT that is 3.56-fold higher than for AIP, that is, 21 cases per 1 million, and lower prevalence for the other porphyrias. These numbers may, however, differ in other countries or regions of the world, depending on variant genetic and environmental factors.
[j]A variant of HCP is harderoporphyria, with 13 known mutations.[40]
[k]High prevalence in South Africa (founder effect).[148]
[l]After the discovery of XLP in 2008, up to 10% of EPP cases were reallocated to XLP.[15,111]

Rare cases of dual porphyrias (biochemical findings of 2 porphyrias) have been identified and confirmed by mutation analyses. Patients were identified that showed deficiencies in coproporphyrinogen oxidase (CPOX) combined with 1 ALAD mutation or with acquired PCT.[21,22]

Acute Hepatic Porphyrias

Pathophysiology

AIP, HCP, and VP are caused by defects in enzyme (PBGD, CPOX, and protoporphyrinogen oxidase, respectively) and are promoted by excess activity of the first enzyme in hepatic heme synthesis, ALAS1 (Figure 1). ALAS1 is induced via induction of cytochrome P450 (CyP450), such as by xenobiotics, smoking, excess alcohol consumption, fasting, and female sex hormones.[2] Xenobiotics also directly induce ALAS1. Induction of ALAS1 in AHPs leads to an exaggerated accumulation of the neuropharmacologic active porphyrin precursors.[23] However, it is unclear whether ALA and PBG are the relevant neurotoxins. Their accumulation in HCP and VP results from allosteric inhibition of PBGD by metabolites, especially coproporphyrinogen and protoporphyrinogen, which accumulate downstream of the affected enzyme.[24] A paradoxical increase of porphyrins downstream of the enzyme defect that is apparently mediated by the induced synthesis of ALA and an excessive accumulation of PBG, corresponds clinically to red-colored or darkening urine in severe cases. The mechanism of this phenomenon is ill-defined.[23,25] Moreover, a drug-responsive sequence in the ALAS1 gene mediates a direct transcriptional activation via drugs such as barbiturates, hydantoins, and metyrapone.[26–29]

Glucose activation of peroxisome proliferator-activated receptor γ–coactivator 1α prevents transcription of *ALAS1*. This might account for the ability of intravenous glucose and other nutritional carbohydrates or gluconeogenic amino acids to attenuate signals of a fasting state, resulting in increased expression of ALAS1.[30] This is the reason that patients should avoid glucose-lowering drugs and conditions. Interestingly, the synthesis of fibroblast growth factor 21, a glucose-lowering hormone that is largely produced in the liver and induces a fasting state, is blocked by heme that is used in the treatment of acute attacks.[31] Heme is not a direct inhibitor of ALAS1 at physiologically achievable concentrations, but rather decreases stability of *ALAS1* messenger RNA (mRNA) and therefore its protein expression. Moreover, heme inhibits mitochondrial uptake of pre-ALAS1 and promotes the cytosolic breakdown of the mature

enzyme.[32] The overexpression of heme oxygenase-1 under conditions of inflammation, fasting, or physical or oxidative stress increases heme degradation and thereby removes feedback inhibition of ALAS1, promoting disease.[23,33]

ALADP is a rare autosomal recessive disease.[34,35] ALAD is a lead-sensitive enzyme. Patients who are heterozygous for a mutation that reduces ALAD activity by 50% develop acute porphyria symptoms once they have an even slight increase in lead exposure.[36] Interestingly, all mutations in ALAD associated with disease cause formation of functionally compromised enzyme hexamers that are dominant to normal, high-activity octamers.[37]

Clinical Presentation

AHPs usually do not manifest before puberty. Women more frequently develop symptoms than men, and some unfortunate women suffer from monthly attacks with onset during the luteal phase of their menstrual cycle. Typically, patients have abdominal pain, which is intermittent and colicky and can extend to the back and extremities. This is often accompanied by constipation, nausea, vomiting, and symptoms of ileus and paresthesia. Tachycardia coupled with hypertension and a reddish dark urine are further diagnostic signs (Figure 2*A*). The pain of acute attacks of porphyria typically arises gradually, often with a stereotypic prodrome, gradually building over hours and lasting for days. Some patients have pain chiefly in the chest, back, or extremities, although the more usual presentation is that of severe abdominal pain.

When these symptoms are misdiagnosed and pathogenesis is promoted by inadequate treatment (especially porphyrinogenic medications, hypocaloric feeding, and inadequate pain treatment leading to increased stress), patients may gradually develop peripheral motor neuropathy that first affects the upper proximal extremities and may progress to paralysis of extensor muscles of the hands and arms (Figure 2*B*), tetraparesis, and respiratory arrest. Some patients present with anxiety, confusion, and overexcitement, including hallucinations, psychosis, or seizures. An inappropriately high secretion of antidiuretic hormone (Schwartz–Bartter syndrome) leads to a potentially life-threatening severe hyponatremia, another diagnostic feature of acute porphyrias. With frequent attacks, the risk of hypertensive renal damage and of hepatocellular carcinoma is increased. A variant of kidney peptide transporter 2 (PEPT2*1*) has high affinity for ALA and promotes its reabsorption, likely contributing to renal damage.[38] PEPT2*1 is also found in the choroid plexus and may be important in pumping variable amounts of toxic ALA into the brain, which could explain the variable susceptibility to neuropsychiatric symptoms in patients.[39] HCP and VP can also cause skin photosensitivity that in AIP only occurs when severe renal disease leads to further accumulation of plasma porphyrins. Overall, there is significant variation among individuals in clinical manifestations of all hepatic porphyrias. Rare patients with homozygous acute porphyrias present in childhood with abdominal attacks (AIP, HCP), cutaneous symptoms (HCP, VP), or skeletal abnormalities (VP). Harderoporphyria, a variant form of homozygous HCP, presents predominantly in early childhood, mostly with hematologic abnormalities. The cause is a dysfunctional homozygous mutation or a null allele in exon 6 of the *CPOX* gene.[40] Although in HCP, mutations occur in the same gene, the *CPOX* mutation that causes harderoporphyria does not produce abdominal or neurologic symptoms as in HCP.[41,42]

A subgroup of patients without clinical symptoms but high urinary ALA, PBG, and porphyrin levels have been classified as asymptomatic high excreters. On the other hand, attacks recur in as many as 5% of patients with clinically manifest AIP, causing high medical costs, absence from work, and often unemployment.[14,43,44]

Diagnosis

Laboratory analysis of the precursors and porphyrins in a sample of spot urine, transported in a dark vessel is mandatory and suffices in most cases (Table 1). A more than 4-fold increase in ALA and PBG (normal level $<$6.3 mmol/mol and $<$1.4 mmol/mol creatinine, respectively) in urine is used to identify patients with AIP, VP, or HCP.[45] However, this is not the case for the rare ALADP or lead poisoning (Figure 1, Table 1).[34] Patients with rare ALADP or lead poisoning have a more than 10-fold increase in urine level of ALA, in the absence of a significant increased PBG (Table 1). Type 1 tyrosinemia is not a primary disorder of porphyrin metabolism but indirectly leads to similar biochemical changes and porphyria-like symptoms as in ALADP, caused by the accumulation of succinyl acetone, a potent inhibitor of ALAD.[46] No enzymatic test is readily available to confirm HCP and VP. However, fecal porphyrins, which are increased in patients with HCP (coproporphyrin III) or VP (coproporphyrin III and protoporphyrin IX [PPIX]), can discriminate among acute porphyrias (Table 1). Mutational analysis can further secure the diagnosis. In patients with AIP, urinary excretion of the porphyrin precursors ALA and PBG and of porphyrins decreases quickly (within 3–6 days) during remission, but can remain significantly increased over years.[2,45,47] A single analysis of urine level of PBG identified most patients (90%) with AIP in remission.[48] However, only repeated analysis for urine level of ALA and PBG during symptomatic periods can identify all patients with AHP. Urinary ALA and PBG are also increased in acute HCP and VP, but fall more rapidly upon remission, while elevated porphyrins may persist.

Because individual cases and disease phases can have different patterns and because of the relative rarity and complexity of the porphyrias, a final evaluation should always be performed by specialists at porphyria centers (www.porphyriafoundation.com, www.porphyria.uct.ac.za, www.porphyria.eu). The metabolic (and clinical) activity of the acute porphyrias and the efficacy of therapy can be monitored by assessing metabolite excretion. An annual examination is also recommended for asymptomatic patients. If urine analysis identifies an acute (hepatic) porphyria, it is necessary to measure the activity of PBGD in erythrocytes and perform genetic analyses, to confirm a

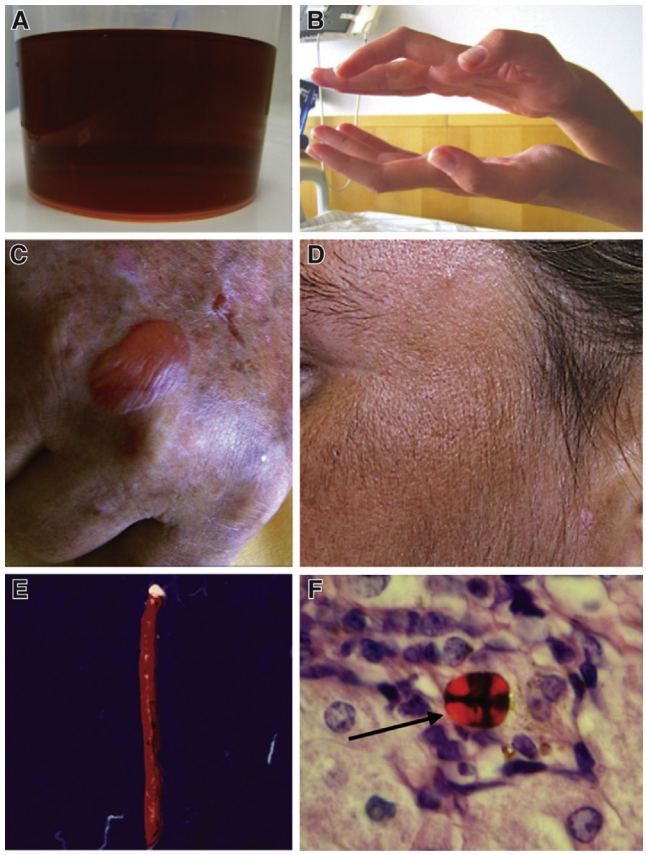

Figure 2. Clinical signs of different porphyrias. (*A, B*) AHP. (*A*) A dark-red urine that further darkens under air/oxygen; (*B*) motor neuropathy of the hand extensors 6 months after the first manifestation. (*C–E*) PCT. (*C*) vulnerability, blisters and scars on sunlight exposed skin; (*D*) hypertrichosis on cheeks; (*E*) liver biopsy showing an intense red fluorescence under long-wave ultraviolet light (366 nm, Wood's lamp). (*F*) EPP. Liver biopsy with spherical structures displaying red birefringence under polarized light and with a dark Maltese cross in the center (original magnification ×400).

diagnosis of AIP (Table 1). Both analyses are necessary because in a subvariant of AIP, which occurs in about 5% of cases, the activity of PBGD in erythrocytes is normal.[49] With knowledge of the mutation of the index patient, a targeted genetic analysis can be offered to all first-degree relatives to identify asymptomatic carriers and to inform them about porphyria triggers. Notably, >95% of gene carriers remain asymptomatic throughout life.[20,50]

Therapy

There are specific therapies for AHPs (see Table 3). Once neurologic symptoms occur, heme therapy is indicated. With early intravenous administration of heme, patients begin to improve within 48 hours. Intravenous heme (Normosang; Orphan Europe, Puteaux, France, in Europe and some other regions, and Panhematin; Recordati Rare Diseases, Lebanon, NJ, in the United States, Mexico, and elsewhere) acts as a transcription factor that reduces expression of the rate-limiting hepatic enzyme ALAS1. Studies with heme therapy date back to 1971.[51] Data from 15 uncontrolled studies on 420 patients with AHP have been published.[52–58] Taken together, biochemical remission with a significant drop in urinary excretion of ALA and PBG was usually achieved after 3–6 days, but not all of the treated patients were judged to be responders to heme therapy. In 1 report, only half of patients benefited from heme infusions.[55] Inadequate responses to heme have been attributed to an insufficient dosage (<3 mg/kg/d), probably non-porphyria–related symptoms, delayed onset of therapy, and chronic porphyria-related pathology, such as irreversible neurologic damage.[52,59] In the only prospective randomized placebo-controlled trial of heme, comprising 12 patients, there was a significantly more rapid decrease in urine levels of ALA and PBG in patients given heme compared to placebo. However, there was only a trend for clinical improvement in this underpowered study.[60] Notably, as many as one-third

Table 3. Therapy for Acute Porphyrias

Therapy	Description
Discontinuation of porphyrinogenic drugs and intensive medical monitoring	www.drugs-porphyria.org
Sufficient caloric support (carbohydrates, protein)	Intravenous and/or oral carbohydrates as preferred source of energy; beware of dilutional hyponatremia; serum sodium, magnesium, and phosphate must be monitored daily
Heme treatment	For severe cases, neurologic manifestations and associated hyponatremia: heme arginate (eg, Normosang), 3 mg/kg body weight/d in 100 mL human Albumin (5%–20%), infused in 15 min, for up to 4 consecutive days
Symptom measures	
For pain	Acetylsalicylic acid, morphine derivatives, gabapentin
For tachycardia and hypertension	Propranolol, metoprolol, valsartan
For restlessness or vomiting	Chlorpromazine, lorazepam, ondansetron
For symptoms of ileus	Neostigmine
For respiratory relief	Assisted or controlled ventilation (possibly tracheotomy)
For infections	Penicillin, cephalosporins, imipenem, gentamicin, amikacin, vancomycin
Physiotherapeutic measures from the very beginning	

of attacks resolved with supportive care, whereas the other two-thirds required heme therapy.[57]

Sufficient caloric support (carbohydrates, protein) is essential for treatment of AHP—especially when attacks are induced or amplified by low caloric intake, nausea, and vomiting, which are usually present in these patients.[5,61–63] After emergency intravenous glucose, oral nutrition with carbohydrates should be initiated as soon as possible. Patients presenting with hyponatremia should receive heme therapy because hyponatremia can worsen with glucose infusions.

Pain should be addressed immediately and strictly prevented. Pain stress contributes to neuroendocrine reactions that activate ALAS1 and exacerbate symptoms. Well-tolerated drugs such as opiates and gabapentin, which do not induce ALAS1 in the liver and are excreted via the kidneys, are often insufficiently dosed.[64] Pain therapists are frequently not trained in management of patients with AHP. Moreover, the usually long period of misdiagnosis coupled with a traumatic path of suffering and frustration with physicians who are not familiar with the disease can lead to anxiety, depression, and the need for expert psychotherapy, supported with antidepressive or anxiolytic medication.

Patients with recurrent attacks (more than 3 per year) often receive prophylactic administration (interval therapy) of heme. However, frequent heme infusions often lead to venous obliteration due to heme degradation products that bind to endothelial cells, platelets, and clotting factors.[63,65] Therefore, patients with recurrent attacks often receive intravenous ports and sometimes arteriovenous shunts for blood sampling and intravenous therapy. Side effects can be mitigated by administration of heme bound to albumin (Table 3). The frequency of clinical manifestations requiring intravenous heme may require up to once weekly dosing in some cases.[2] High dosages of intravenous heme (250 mg/d) can lead to overexpression of heme oxygenase 1, resulting in heme degradation and loss of feedback inhibition of ALAS1. This was demonstrated in PBGD-deficient mice.[66] A 4.4-fold increase of reported AIP patients with recurrent attacks since the introduction of heme therapy (from 4 of 230 in 1985 to 40 of 536 in 2008) may be due to several reasons, including induction of heme oxygenase 1, but also improved survival by heme therapy.[66] Therefore, high-frequency heme infusions should be avoided. Overall, the rigorous elimination of precipitating factors in daily life remains the mainstay of prevention and therapy.

Patients with chronic complications, such as loss of venous access, or progressive neurologic symptoms despite adequate therapy, should be transferred to a porphyria center for therapy optimization. There, they might be able to participate in clinical trials of therapeutic agents in development. Nanoparticular *PBGD* RNA was recently shown to target hepatocytes, restore deficient enzyme activity, and protect from induced porphyria attacks in mice.[67]

Notably, a novel agent (Givosiran, Alnylam Pharmaceuticals, Cambridge, MA) that addresses the underlying pathology of AIP promises high efficacy with a tolerable side effect profile. Givosiran is a small interfering RNA that neutralizes excess *ALAS1* mRNA in hepatocytes. The small interfering RNA is conjugated to trimeric N-acetyl-galactosamine. After subcutaneous injection, Givosiran is directed to and endocytosed by hepatocytes that carry the N-acetyl-galactosamine binding asialoglycoprotein receptor. Once endocytosed, the small interfering RNA is cleaved from the conjugate to potently reduce levels of *ALAS1* mRNA and protein.[68] The phase 1 trial with once monthly Givosiran demonstrated high efficacy in reducing acute attacks in 6 patients with AIP.[69] An interim analysis from a phase 3 trial (Envision) in 94 randomized patients with AHP and at least 2 attacks within 6 months before enrollment has been made public in April 2019, showing a significant reduction in the annualized rate of porphyria attacks, days of administered heme, and urinary ALA levels with Givosiran. Only 1 patient had to be discontinued due an 8-fold elevation of alanine aminotransferase, while mild–moderate alanine aminotransferase elevations subsided with ongoing therapy. Ninety-three of 94 patients elected to continue the treatment beyond the 6 months of the study.[70]

A final option is liver transplantation.[71,72] Ten patients from the United Kingdom who underwent successful liver transplantation developed biochemical and symptomatic remission. However, 4 developed hepatic artery thrombosis. Therefore, post-transplantation anticoagulation is recommended.[73] Notably, 3 patients with end-stage non-porphyria liver disease who were not eligible for standard transplantation received livers from patients with AIP. Two survived and 1 developed symptoms of AIP (abdominal pain and neuropathy) within 3 weeks. This was accompanied by increased urinary levels of ALA, which confirmed liver as the primary source of increased porphyrin precursors.[74]

New and alternative therapies are summarized in Supplementary Table 2. International porphyria emergency identification cards are provided free of charge by Orphan Europe (www.orphan-europe.com). Furthermore, MedicAlert (www.medicalert.org) provides bracelets and wallet cards that contain information on acute porphyrias.

Case Report

A 24-year-old woman was admitted with generalized abdominal pain, constipation, and recurrent vomiting for 6 days. She had no history of alcohol, nicotine, or drug abuse. She had normal weight (body mass index 19 kg/m^2) and appearance. Physical examination revealed abdominal tenderness, reduced bowel sounds, and pain on palpation of the upper abdomen. Pregnancy was excluded and abdominal ultrasound showed normal findings. Laboratory analysis revealed a striking hyponatremia (117 mEq/L; normal >133 mEq/L) with increased urine level of sodium (154 mEq/L). Because the patient vomited, intravenous infusion of 10% glucose and saline was started. After 4 hours, the hyponatremia worsened (110 mEq/L) and generalized convulsions necessitated the administration of levetiracetam, intubation, stepwise careful compensation of hyponatremia with intravenous sodium chloride (3%), and mechanical ventilation for 2 days. Brain magnetic resonance imaging, electroencephalograms, cerebrospinal fluid analysis, drug screening, and extensive laboratory tests did not

reveal any pathologic features. After extubation, she was transferred to standard care with the diagnosis of syndrome of inadequate antidiuretic hormone secretion of unknown etiology. Subsequent interviews raised the suspicion of a pre-existing eating disorder and she was referred to a psychiatric clinic for 4 weeks.

One month after her dismissal from psychiatry she was readmitted due to epigastric colicky cramps for 4 days. Laboratory analysis again showed severe hyponatremia (112 mEq/L) with a urine sodium level of 114 mEq/L. Careful substitution with 3% sodium chloride was started, with intensive monitoring and hourly controls of serum sodium to prevent pontine myelinolysis. However, her systolic blood pressure increased to 190 mmHg. A dark-reddish urine elicited the suspicion of AHP, and a more than 10-fold increase in concentration of urine ALA and PBG led to the diagnosis of AIP (Supplementary Table 3).

She was treated with heme arginate 3 mg/kg body weight/d for 4 days. Porphyrinogenic medications were strictly avoided, and with oral and intravenous carbohydrates and other nutrients, she recovered quickly. In retrospect, it was apparent that a vicious cycle of fasting, worsening vomiting, and abdominal pain, likely induced by a mild eating disorder, caused excessive induction of hepatic ALAS1. With adherence to expert advice to avoid trigger factors for AIP, especially fasting, she remained stable and free of further acute attacks during a 3-year follow-up period.

Porphyria Cutanea Tarda

Pathophysiology

Low activity (<20%) of hepatic uroporphyrinogen decarboxylase (UROD) underlies all cases of PCT (acquired type 1 or familial type 2).[75] Patients heterozygous for mutations in *UROD* (type 2 PCT) have a 50% reduction in enzyme activity in all tissues, which is necessary but not sufficient to cause overt disease.[76] A further decrease of hepatic UROD activity that finally triggers overt clinical disease is usually due to several cofactors (Supplementary Figure 2). Iron is the most important cofactor and hemochromatosis gene mutations (HFE) (mostly heterozygous) are found in up to two-thirds of the patients.[77] Iron does not directly inhibit UROD. In the presence of iron, CyP450 enzymes catalyze the conversion of uroporphyrinogen into uroporphomethene, an inhibitor of UROD, as shown in mice. Moreover, ferrous iron was found to generate uroporphomethene independently of CyP450-enzymes.[75,78] This mechanism has only been confirmed in homogenates of human liver biopsies, where an inhibitor of UROD has been identified in patients with PCT. Patients with PCT usually carry polymorphic variants of CyP450 genes, leading to higher enzyme activities, whereas patients with familial PCT express a polymorphic variant of glycerol phosphate O-acyltransferase that is associated with iron accumulation in HFE-associated hemochromatosis. The resultant even modest increase in hepatic iron in the setting of low UROD activity in familial PCT then appears to promote clinical PCT.[79,80] Hexachlorobenzene, a fungicide that was used in agriculture until 1984, inhibits UROD and causes PCT in humans and animals.[81,82] Other factors that can cause this disease are infection with hepatitis C virus (HCV) and human immunodeficiency virus.[83–87] HEP is a rare severe form of type 2 PCT that arises in patients with homozygous or compound heterozygous mutations in *UROD*.

Clinical Presentation

The most striking signs and symptoms of PCT are chronic photo-cutaneous damage, often with blisters, bullae, milia, hyper- or hypo-pigmentation, and hypertrichosis on cheeks, temples, and eyebrows (Figure 2*C* and *D*). In patients with PCT, urinary porphyrin excretion >3390 nmol/d indicates severe hepatic porphyrin overload. Liver biopsies, which are frequently collected to assess fibrosis in these patients, have intensive red fluorescence when exposed to long-wave ultraviolet light (366 nm, Wood's lamp) (Figure 2*E*).

Latent or subclinical PCT can occasionally be found in patients with otherwise unexplained elevations of liver enzymes, and confirmed by elevated plasma or urine levels of porphyrins (Table 1). Latent PCT does not cause skin symptoms. If liver biopsies are exposed to long-wave ultraviolet light, those from PCT produce red fluorescence. Abdominal ultrasound may reveal hyperechogenic focal liver lesions, possibly regions of steatosis, that have isoenhancement in contrast imaging and disappear after treatment.

Diagnosis

In patients with PCT, but also in patients with HEP, levels of porphyrins are greatly increased in urine and plasma, with uro- and heptacarboxy-porphyrins predominating (Table 1, Supplementary Figure 3). Renal failure with loss of urinary excretion requires porphyrin analysis in serum or plasma. Another characteristic finding is the fecal excretion of isocoproporphyrin, which is a sufficient but not necessary indicator of PCT.

Therapy

Patients are advised to avoid known precipitating factors, especially alcohol and smoking, that up-regulate CyP450 enzymes and thus the heme synthetic machinery. Alcohol further contributes by down-regulating hepcidin and enhancing oxidative stress. Women must discontinue hormonal contraception or replacement therapy. Photoprotection, phlebotomy, and treatment with low-dose 4-aminoquinolines, chloroquine (CQ) or hydroxychloroquine (HCQ) (125 mg or 100 mg twice per week, respectively), are effective first-line therapies.[88–90] The aim of phlebotomy, introduced in 1977, is the removal of excess iron.[91] Usually, phlebotomy up to 500 mL biweekly is recommended, and monitoring of serum ferritin concentrations helps guide individually adapted iron depletion and avoid iron deficiency. A target ferritin near the lower limit of normal is recommended. Both oral iron chelators or low-dose 4-aminoquinolines are alternatives when phlebotomy is not possible, as in severe anemia.[92] Phlebotomy or low dose

4-aminoquinolines are likewise effective treatments in the majority of patients with PCT.

Low-dose CQ or HCQ are more convenient than phlebotomy.[93,94] They mobilize intracellular porphyrin depots that are mainly eliminated via the urine.[6,95,96] During the first 3 months after patients begin receiving 4-aminoquinolines, urinary porphyrin excretion usually increases more than 2-fold and skin photosensitivity can worsen, but thereafter decreases, resulting in clinical remission and improved liver enzyme activities in 95% of patients.[77,90,97] In 207 patients with PCT treated exclusively with low-dose CQ, 5% of patients with HFE who were homozygous for C282Y (3 of a subgroup of 62 patients that were genotyped) did not benefit, whereas all patients heterozygous for C282Y or H63D and those without disease-associated variants in *HFE* responded to CQ therapy.[77] Another study reported more non-responders among patients with PCT who were heterozygous for the C282Y mutation.[98] Patients with PCT and iron overload/HFE mutations should be preferentially treated with phlebotomy.

HCQ and CQ are effective and safe therapies. However, HCQ is less toxic and should be the first option.[99] Because retinopathy is a side effect of 4-aminoquinolines, baseline and later annual ophthalmologic screening is recommended.[100] Phlebotomy (in case of increased serum concentrations of ferritin) combined with simultaneous or subsequent low-dose 4-aminoquinolines appears to shorten the time to remission. This is supported by 1 study comparing phlebotomy or CQ alone with the combined regimen in 15, 24, and 20 patients who underwent remission within 12.5, 10.2 and 3.5 months, respectively.[101] More evidence is needed to favor a combined regimen as first-line option. Liver damage and siderosis—especially in patients homozygous for the *HFE* C282Y mutation—can regress after phlebotomy and CQ therapy.[59,97,102]

In patients with chronic HCV infection, highly effective antiviral therapy coupled with iron depletion induces rapid clinical and biochemical remission.[103] All 16 patients with PCT and HCV infection (12 co-infected with human immunodeficiency virus) who did not respond to phlebotomy or 4-aminoquinolines achieved clinical and biochemical remission after HCV eradication with direct-acting antivirals, qualifying this approach as first-line therapy in PCT patients with HCV infection.[103] Treatment can be discontinued when urinary porphyrin excretion stabilizes (approximately 407 nmol/d). Mild porphyrinuria can persist during clinical remission, especially in patients with PCT type 2 (Supplementary Figure 3). However, clinical and biochemical relapse can occur in 36% and 20% of patients within 1 year after pharmacologic treatment or phlebotomy, repectively.[104]

Case Report

A 50-year-old man was referred from a dermatologist, presenting with increased skin vulnerability, fluid-filled blisters, and "badly healing wounds." The lesions occurred on sunlight-exposed skin areas, prominently on the dorsal hands and forearms (Figure 2*C*). He reported that his urine sometimes turned "dark reddish brown." His body mass index was 29.9 kg/m^2 and he received a diagnosis of type 2 diabetes 10 years earlier. He smoked as many as 20 cigarettes per day for 15 years and his alcohol consumption was 4 drinks per week. An abdominal ultrasound demonstrated a hyperechoic liver suggesting steatosis. His level of alanine aminotransferase was 1.0 μmol/L/s (normal $<$0.85 μmol/L/s) and his level of ferritin was 1434.8 pmol/L (normal $<$844 pmol/L). Results from serologic tests for hepatitis B virus, HCV, or human immunodeficiency virus infection were negative. Genetic analysis revealed that he was homozygous for the H63D mutation and negative for the C282Y mutation in HFE. Urinary excretion of coproporphyrin, ALA, and PBG was within the normal range, but total porphyrins, uroporphyrin, and heptacarboxyporphyrin were increased 22-fold, 66-fold, and 100-fold, respectively. All laboratory parameters are shown in Supplementary Table 4. Based on the characteristic pattern of urinary porphyrins and normal level of porphyrin precursor, the patient received a diagnosis of PCT.

On excitation at 405 nm, his plasma emitted a peak fluorescence at 619 nm and UROD activity in erythrocytes was 85% (normal $>$80%), confirming the diagnosis of PCT type 1. The patient was advised to avoid precipitating factors, especially alcohol and smoking. Treatment was started with biweekly phlebotomy of 500 mL for the first 5 months and low-dose HCQ 100 mg twice a week was given for 9 months.

After 9 months, the skin lesions had regressed and urinary porphyrin excretion normalized (Supplementary Table 4). We terminated iron depletion when clinical remission was achieved because the patient refused another phlebotomy. The patient had given up smoking and reduced alcohol consumption to 1 drink per week. Follow-up with urinary porphyrin determinations every 6 months confirmed stable remission.

Protoporphyrias

Pathophysiology

EPP is caused by a partial deficiency of FECH, which catalyzes the final step in heme synthesis (Figure 1). There are at least 189 known (pathogenic) mutations in *FECH* (Table 2).[105,106] FECH deficiency increases levels of metal-free erythrocyte PPIX, in contrast to secondary elevations of zinc-bound erythrocyte protoporphyrin that are caused by iron deficiency, lead intoxication, or hemolytic anemia.[12] The lipophilic PPIX, which is eliminated via bile, is hepatotoxic at high concentrations, causing varying degrees of liver damage.[107–109] Protoporphyrin-containing crystals can be detected as pathognomonic Maltese crosses upon histologic examination of liver sections under polarized light (Figure 2*F*).[110] As many as 23% of patients with EPP develop protoporphyrin-containing gallstones that emit red fluorescence under long-wave ultraviolet light.[111]

C-terminal deletions in the *ALAS2* gene, which is expressed in the bone marrow, in a small percentage of patients with suspected EPP led to their reclassification as

patients with XLP. XLP is characterized by hypermorphic gain-of-function mutations in *ALAS2*. These mutations increase the enzymatic activity of ALAS2 and cause accumulation of metal-free and zinc-bound PPIX.[15] EPP and XLP share clinical and biochemical features, such as usually severe acute photosensitivity, liver damage, and increased levels of (metal-free) PPIX in erythrocytes. A mutation in the caseinolytic mitochondrial matrix peptidase chaperone subunit gene (CLPX) was associated with a disease that resembles XLP. This mutation promotes ALAS protein stability and increases ALA, leading to accumulation of PPIX.[112]

Clinical Presentation

In patients with EPP or XLP, photosensitivity usually develops during early childhood. Patients have symptoms of burning, itching, pain, erythema, and edema on sun-exposed skin areas, sometimes but not always resembling sunburn. Patients' pain and cutaneous symptoms with exposure to light are severe, forcing them to strictly avoid light, which substantially decreases their quality of life. In a small proportion of patients, the cutaneous symptoms are associated with abdominal pain, about one-quarter display abnormal liver enzyme activities and rarely develop severe hepatobiliary injury, including jaundice and liver cirrhosis, can occur.[108,111] Therefore, EPP or XLP should be considered for cases of unexplained cholestasis, and physicians should ask patients if they are photosensitive because patients often do not report this spontaneously. Finally, patients often present with iron deficiency and corresponding microcytic anemia.

Diagnosis

Diagnoses of EPP or XLP are made based on increased levels of metal-free protoporphyrin (>4.500 nmol/L, normal <89 nmol/L) in hemolyzed anticoagulated whole blood. Specialized porphyria laboratories report levels of total erythrocyte, metal-free, and zinc-protoporphyrin.[113] The proportion of zinc-protoporphyrin to metal-free protoporphyrin is significantly higher in patients with XLP (>25%) than in those with EPP (up to 15%). Notably, urinary porphyrins are normal in protoporphyrias. However, with deterioration of liver function, urinary coproporphyrin excretion (especially isomer I) increases.[109] Noninvasive measurement of liver stiffness (with ultrasound or magnetic resonance elastography) should be useful for early diagnosis but has not been validated in patients with XLP or EPP.[114]

Therapy

Adequate sun protection is indispensable, and skin should not be exposed to intensive artificial light sources. Importantly, because photosensitivity is due mainly to visible blue light (Soret band: near 400 nm), conventional sunscreens are less effective. Skin should be protected from sunlight with zinc oxide or titanium oxide paste. Uncontrolled trials and retrospective case series (including a study of 337 patients) reported the efficacy of oral β-carotene (moderate or strong effects in 28% and 54% of patients, respectively). However, a small controlled cross-over study found no benefit on light-dependent symptoms in 9 of 11 patients.[115]

Patients learn to prevent pain by avoiding sunlight, and this impairs quality of life. Light avoidance necessitates vitamin D substitution. The α-melanocyte–stimulating hormone analogue afamelanotide (Scenesse, Clinuvel Pharmaceuticals, Melbourne, VIC, Australia) increases skin pigmentation independent of sunlight via the activation of the melanocortin-1 receptor on melanocytes, improving sunlight protection significantly.[116–119] In a pilot study, 5 patients with EPP were treated with 2 subcutaneous implants of afamelanotide over 120 days, which increased tolerance to artificial light from a mean of 2.2 minutes to 13.3 minutes. Furthermore, 168 patients with EPP from Europe or the United States who were included in 2 phase 3, multicenter, randomized, double-blind, placebo-controlled trials, received 16 mg of afamelanotide, implanted at intervals of 60 days (for as long as 120 days in the United States and as long as 240 days in Europe). Duration of pain-free exposure to sunlight in both studies was significantly longer in the afamelanotide group, coupled with an improved quality of life and a lack of serious adverse events. Afamelanotide has been approved by the European Medicines Agency in 2014 for patients with EPP or XLP, whereas approval by the Food and Drug Administration is pending.

Uncontrolled observations suggest successful treatment with ursodeoxycholic acid that may increase hepatic clearance, and with cholestyramine that may bind protoporphyrin and interrupt its enterohepatic circulation.[120,121] Erythrocyte concentrates that suppress erythropoiesis and plasma exchange that removes excess metal-free protoporphyrin have been used to treat liver failure or prevent further decompensation.[122,123] Patients with advanced cholestasis or cirrhosis should receive liver transplants. Before transplantation, excess PPIX in circulating blood must be removed by plasmapheresis. During the procedure or other major abdominal procedures, special yellow filters are used to prevent light-induced damage of visceral organs.[72,124] Sixty-two liver transplants in erythropoietic porphyrias have been reported worldwide.[72] In contrast to patients with AHP, liver transplantation does not cure patients with EPP or XLP because the bone marrow is the source of the excessively elevated PPIX. However, a PPIX reduction of up to 85% and a resolution of inflammatory liver damage have been reported after allogeneic hematopoietic stem cell transplantation, even when performed before or after liver transplantation.[125,126]

Drug restriction, as required for AHP, is not required for patients with EPP or XLP. Interestingly, iron substitution can decrease protoporphyrin concentrations and improve symptoms in patients with XLP—sufficient iron as second substrate promotes conversion of toxic PPIX to heme by FECH.[127,128] In contrast, iron substitution can worsen EPP by stimulating the bone marrow enzyme ALAS2.[129] Moreover, mild iron deficiency might protect patients with EPP. Iron substitution in patients with EPP, if necessary, such as in patients with significant anemia, may be considered during the darker seasons when the intensity of sunlight is low. Gene therapies are also being explored. Administration of an

antisense oligonucleotide that prevents the abnormal splicing of the nascent mutant *FECH* mRNA in developing human erythroblasts of a patient with EPP increased the production of functional FECH and reduced the accumulation of PPIX.[130]

Case Report

A 67-year-old female patient presented with pronounced photosensitivity (burning, stinging pain, swelling, and itching) on light-exposed skin areas (prominent in the face and on the back of the hands) since early childhood. Exposure to light caused her levels of 8 on the pain scale (which ranges from 1 to 10). As long as she could recall, she could hardly be outdoors, had only few friends, and was teased at school. She chose a job with an indoor activity. After many misdiagnoses, dermatology at a tertiary care center made a diagnosis of EPP 35 years ago, and she was informed that the disease was incurable. Sunscreen (UVA and UVB protection) and β-carotene for a few years were without noticeable effect. She continued to wear light-protective clothing (long-sleeved tops, gloves, long trousers, closed shoes, and socks) and used windows with blinds at home. Before seeing us in March 2017, she experienced at least monthly episodes of painful skin reactions after even short sunlight exposure and lasting up to 2 days. Cold water and ice packs did not help. Avoiding pressure and heat, and especially showering with lukewarm water, relieved the symptoms to some degree. Laboratory tests confirmed the diagnosis of EPP and severe vitamin D deficiency (Supplementary Table 5). Physical examination, ultrasound, and laboratory values did not reveal signs of hepatobiliary involvement. Vitamin D was substituted orally with 20,000 IU of cholecalciferol per week. In late March, June, and August, we implanted a small depot stick of Scenesse (16 mg afamelanotide) into the subcutaneous fat above the iliac crest via a 14-gauge needle. Photosensitivity decreased dramatically, while her protoporphyrin level remained unchanged. The patient could now spend as many as 6 hours in normal daylight. In autumn and winter, therapy with afamelanotide was not required.

Congenital Erythropoietic Porphyria

Pathophysiology

In CEP, another rare porphyria, the activity of uroporphyrinogen-III-synthase (UROS) is low, due to mutations in UROS or GATA1.[131,132] GATA1, encoded by a gene on the X chromosome, is a transcription factor that regulates heme biosynthesis.[133,134] This leads to accumulation of hydroxymethylbilane, spontaneously (non-enzymatically) forming uroporphyrinogen I, that is further metabolized to the non-functional end product coproporphyrinogen I. Spontaneous oxidation of the porphyrinogens generates porphyrins that accumulate in tissues.

Clinical Presentation, Diagnosis, and Therapy

Photodermatosis is severe, with mutilations already occurring in infancy and early childhood. Most of the patients display red-colored urine.[135] Anemia and splenomegaly may develop later. A prominent clinical manifestation is erythrodontia (reddish-brown discoloration of the teeth). Patients have increased plasma, urine, and fecal levels type I isomer uro- and coproporphyrins (Table 1). Analysis of mutations in UROS and studies of its enzymatic activity confirm diagnosis.

Light protection and vitamin D supplementation are the basis of treatment. Some patients with anemia benefit from splenectomy. Because clinical presentations vary, including the need for transfusion and consequences of an enlarged spleen (eg, thrombocytopenia), the indication for splenectomy should be personalized. Allogeneic hematopoietic stem cell transplantation is curative. It is recommended at a young age.[135,136] In 1 case, iron depletion with deferasirox, which reduces the activity of ALAS2, was reported to improve photosensitivity.[137] In support of this mechanism, an ALAS2 gain-of-function mutation was reported to increase the severity of CEP.[138] Proteasome inhibitors or chemical chaperones might stabilize abnormal UROS variants to increase its activity and reduce porphyrin accumulation and skin photosensitivity in patients with CEP.[139]

Lead Poisoning

Lead affects 3 enzymes involved in heme biosynthesis: ALAD, CPOX, and FECH (Figure 1). Primarily due to inhibition of ALAD, its clinical and biochemical features resemble those of ALADP. Lead poisoning is likely in patients with microcytic anemia (which is untypical for ALADP), abdominal symptoms, and in some cases neuropsychiatric symptoms.

In contrast to ALADP, in lead poisoning, the enzyme activity of ALAD in patients' lysed erythrocytes can be restored completely by adding ionic zinc.[140] Patients with lead poisoning also have basophilic stippling of erythrocytes in blood smears and a lead line (bluish pigmentation on the gum–tooth line). Increased blood and urine levels of lead confirm the diagnosis. Lead intoxication causes a 10-fold increase in urine levels of ALA and normal or only slight increases in urine levels of PBG, as in ALADP porphyria. Erythrocyte zinc-protoporphyrin and urinary coproporphyrin isomer III are increased (Table 1). Heme therapy can relieve symptoms of lead intoxication and ALADP.[46] The primary measure is removal from lead exposure and the use of chelating agents such as 2,3-dimercaptosuccinic acid (succimer) or calcium disodium ethylenediamine-tetraacetate.

Secondary Elevation in Porphyrins

Apart from the genetically determined erythropoietic and hepatic porphyrias, clinically asymptomatic secondary elevation in porphyrins (urine, plasma, erythrocytes, and stool) can be detected in several disorders or under certain medications. These are clinically asymptomatic and usually consist of coproporphyrin (plasma, urine) or protoporphyrin (blood) (mostly zinc bounded protoporphyrin) (Supplementary Table 1). Increased plasma levels of porphyrins, especially zinc protoporphyrin and coproporphyrin, are found in patients with diseases other than

Table 4. Clinical and Biochemical Features of Porphyrias

AHP (Patients after puberty)	PCT (Adult patients Aged >18 y)	Protoporphyrias (Children or adolescents)
Unexplained gastrointestinal complaints (colic, vomiting, subileus) Neurologic symptoms (paresthesia, seizures, paresis) Mental abnormalities (depression, anxiety, hallucination) Tachycardia, hypertension Red-colored urine without erythrocytes or hemoglobin Serum hyponatremia	Blister-forming dermatosis on light-exposed skin areas Increased skin vulnerability Hyper- and hypopigmentation on light-exposed skin Hypertrichosis of cheeks, temples, and the eyebrows, often associated with: Iron overload HCV infection HIV infection Alcohol consumption Hormone (replacement) therapy Toxic agents (eg, hexachlorobenzene)	Burning pain Erythema/redness on light-exposed skin areas Angioedema-like swelling on the face, on the back of the hands and on the forearms Often microcytic anemia Possible family history
Key biochemical features		
>4-fold elevated ALA and PBG in urine	ALA and PBG in urine normal, elevated total porphyrins in urine with uroporphyrin > coproporphyrin	ALA and PBG in urine normal, metal-free erythrocyte protoporphyrin increased in blood

HIV, human immunodeficiency virus.

porphyrias, such as in colorectal adenocarcinoma.[141] Secondary elevations of porphyrins are often misinterpreted, but can be differentiated by analyzing porphyrin precursors and porphyrins in urine, stool, plasma, and heparinized blood, as performed by specialized porphyria laboratories or centers (Table 1).[142,143]

Synopsis

The initial diagnosis and differential diagnosis of porphyrias continue to rely on biochemical, quantitative determinations of the porphyrin precursors and porphyrins in urine, stool, plasma and heparinized blood. The following principles and simplified 3 scenarios (Table 4) are helpful in clinical practice. Think of porphyria when a patient presents with unexplained abdominal and neuropsychiatric symptoms and/or photosensitivity. Clinically classify and compile the medical history and obtain basic and supportive laboratory data. Use key diagnostic tools, such as the (extended) porphyria laboratory diagnostics efficiently and correctly.

Information and Contacts

www.porphyrie.de
www.drugs-porphyria.org
www.hgmd.cf.ac.uk
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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.04.050.

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Received June 27, 2018. Accepted April 10, 2019.

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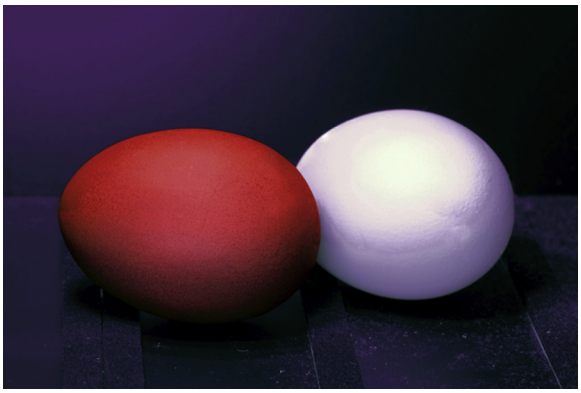
Acknowledgments
The authors thank Herbert L. Bonkovsky for valuable comments, Thomas Stauch for fruitful discussions and expert laboratory porphyria analyses, and Ilja Kubisch for help preparing tables, figures, and references. The histologic pictures were kindly provided by J.O. Habeck.

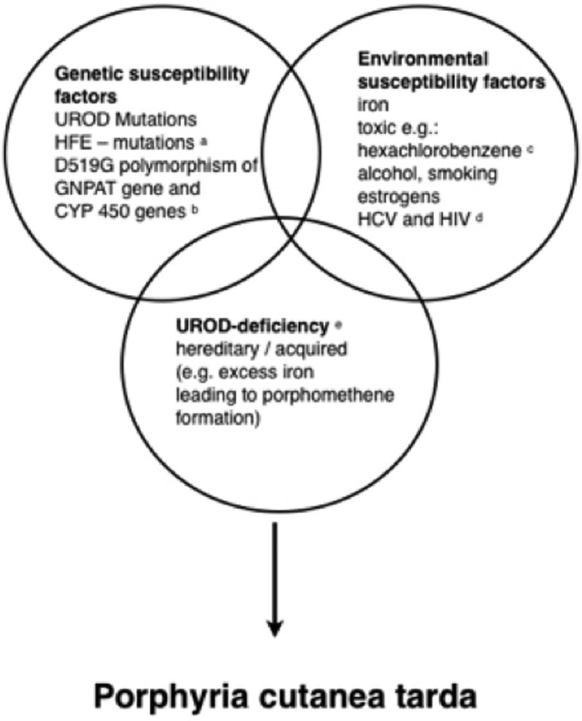
Author contributions: Ulrich Stölzel: Idea, composition, literature research, writing, and editing all aspects of the manuscript, creating figures, and tables. Manfred Otto Doss: Providing historical and mechanistic information, especially as regards mechanisms and laboratory diagnosis, editing the manuscript. Detlef Schuppan: Idea, composition, literature research, writing, and editing all aspects of the manuscript, creating figures, editing tables, and proofreading.

Conflicts of interest
The authors disclose no conflicts.

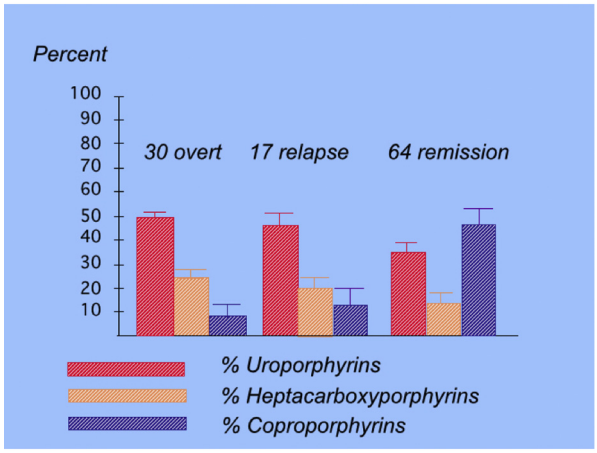
Funding
Part of the authors' work is supported by grants of the German Research Foundation (DFG) collaborative research center project grants DFG CRC 1066/B3 and CRC 1292/08, and by projects EU H2020 under grant no. 634413 for the EPOS consortium and EU IMI under grant no. 777377 for the Litmus consortium to DS.



Supplementary Figure 1. Porphyrins that are concentrated in brown vs white eggshells emit a strong red fluorescence when exposed to long-wave (366 nm) ultraviolet light.



Supplementary Figure 2. Pathophysiologic components of PCT. [a]HFE gene mutations are found in about two-thirds of the patients.[3] [b]Patients with acquired PCT usually harbor polymorphic variants of CyP450 genes, leading to higher enzyme activity, while patients with familial PCT express a polymorphic variant of glycerol phosphate O-acyltransferase (GNPAT) that down-regulates hepcidin and is associated with iron accumulation in HFE-associated hemochromatosis.[4–6] [c]Hexachlorobenzene inhibits UROD and causes PCT in humans and animals.[7,8] [d]Further trigger factors are hepatitis C and HIV infection.[9,10] [e]UROD, uroporphyrinogen decarboxylase.



Supplementary Figure 3. Biochemical characteristics of 111 patients with PCT. Characteristic dominance of urinary uro- and heptacarboxyporphyrin over coproporphyrin in overt disease and relapse, whereas in remission, this ratio is inverted. Total urinary porphyrin concentrations are 5- to 10-fold higher in overt disease or relapse compared to remission ($P < .001$) (not shown).[11]

Supplementary Table 1. Clinical Scenarios That Can Lead to a Secondary Elevation in Porphyrins

Variable	Clinical scenario
Secondary porphyrinurias[a]	Toxic liver damage, lead intoxication
	Alcohol consumption
	Fatty liver disease
	Hemochromatosis
	Hepatitis
	Intra- and extrahepatic cholestasis
	Dubin–Johnson syndrome, Rotor syndrome
	Various anemias
	Diabetes mellitus
	Many drugs, especially inducers of CYPs
Secondary blood protoporphyrin elevations[b]	Iron deficiency
	Lead intoxication

[a]Several hepatobiliary diseases can lead to impaired secretion of porphyrins (especially of coproporphyrin) in bile and feces, with secondary increases in urine, comparable to the signs of enhanced bilirubin turnover.
[b]Iron deficiency causes substrate depletion for ferrochelatase, and lead poisoning inhibits ferrochelatase activity, resulting in elevated concentrations of PPIX, mainly zinc-bound PPIX, in blood.

Supplementary Table 2. Novel and Alternative Therapies for Acute Hepatic Porphyria

Drug or measure	Mechanism	Effectiveness	First author, year, or NCT clinical trial no.
Magnesium intravenously	Inhibition of neuromuscular excitation, treatment of seizures	Case reports Not consistent	Sadeh, 1991[12] Zeiler, 2015[13]
LH-RH agonists[a]	Inhibition of gonadotropin secretion, prevention of ovulo-cyclic manifestations	Case reports Not consistent	Anderson, 1984[14] Gross, 1995[1] De Block, 1999[15] Marsden, 2015[16]
Enzyme replacement therapy (recombinant human PBGD)	Decreasing PBG and 5-ALA	Transient decrease of plasma PBG but not 5-ALA No clinical benefit	Johansson, 2003[17] Sardh, 2007[18]
Transfer of PBGD gene in liver cells by viral vectors	Restoring PBGD function in liver	Phase 1, urinary ALA and PBG not decreased	NCT02076763
Intravenous administration of human PBGD mRNA	Inducing PBGD protein expression in liver	Tested successfully in a mouse model of AIP and nonhuman primates	Jiang, 2018[19]
Hemodialysis	Removing circulating 5-ALA and PBG in plasma	Only successfully treated cases reported; controlled studies are lacking; hepatic synthesis of 5-ALA not inhibited	Attarian, 2017[20]
Pharmacologic chaperone treatment	Enhancing PBGD activity and/or protection against proteolysis	Only tested successfully in PBGD-deficient mouse model	Bustad HL, Bordeaux, France, personal communication
RNAi-mediated silencing (Givosiran)	Inhibition of the hepatic synthesis of 5-ALA	Successfully tested in ALAS1-overexpressing mouse model. Clinical studies show highly efficient ALAS1 suppression in patients with AIP (suppression of ALA and PBG production, reduction of clinical activity)	Givosiran Phase 1 trial, NCT02452372 Phase 3 trial (Envision) NCT03338816

LH-RH, luteinizing hormone-releasing hormone; NCT, National Clinical Trial; RNAi, RNA interference.
[a]Initial treatment with a gonadotropin-releasing hormone agonist, if clinically effective, is preferred. This may later be replaced by oral contraceptives accompanied by regular measurement of urinary porphyrins and porphyrin precursors because this treatment may also induce ALAS1.[1,2]

Supplementary Table 3. Urinary Excretion of Porphyrin Precursors and Porphyrins, and Plasma Porphyrin Scan in a Female Patient With Acute Intermittent Porphyria

Analyte	Level	Normal level corrected for creatinine
5-ALA,[a] *mmol/mol*	45.9	<6.3
PBG,[a] *mmol/mol*	74.1	<1.4
Uroporphyrin,[a] *μmol/mol*	213.8	<4.5
Coproporphyrin,[a] *μmol/mol*	39.1	<20.7
Total porphyrins,[a] *μmol/mol*	306.0	<28.4
Plasma porphyrin scan,[b] *nm*	618	Negative

[a]Corrected for creatinine.
[b]Emission maximum of the plasma fluorescence spectrum on excitation at 405 nm.

Supplementary Table 4. Laboratory Parameters of a Female Patient With Porphyria Cutanea Tarda

Analyte	Level	Normal
ALT, *μmol/L/s*	1.00	<0.85
AST, *μmol/L/s*	0.81	<0.62
GGT, *μmol/L/s*	1.95	<1.02
Serum ferritin, *pmol/L*	1434.8	<844
Serum transferrin saturation, %	71	16–45
Serum antibodies to hepatitis B (HBs, HBc) and C and HIV	Negative	Negative
HFE mutations	H63D +/+, C282Y –/–	Negative
5-ALA,[a] *mmol/mol*[b]	Normal	<6.3
PBG,[a] *mmol/mol*[b]	Normal	<1.4
Uroporphyrin,[a] *μmol/mol*[b]	296.0	<4.5
Heptacarboxyporphyrin,[a] *μmol/mol*[b]	158.0	<1.4
Coproporphyrin,[a] *μmol/mol*[b]	12.4	<20.7
Total porphyrins,[a] *μmol/mol*[b]	615.2	<28.4
Plasma porphyrin scan,[c] *nm*	619	Negative

ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; GGT, serum γ-glutamyltransferase.
[a]Urinary porphyrin precursors and porphyrins.
[b]Corrected for creatinine.
[c]Emission maximum of the plasma fluorescence spectrum on excitation at 405 nm.

Supplementary Table 5. Laboratory Parameters of a Female Patient With Erythropoietic Protoporphyria

Analyte	Value	Normal value
Hemoglobin, *mmol/L*	8.09	>7.45
MCV, *fl*	Normal	>80
Serum ferritin, *pmol/L*	32.9	27.4–316.5
Serum transferrin saturation, %	14.1	16–45
ALT, *μmol/L/s*	Normal	<0.85
AST, *μmol/L/s*	Normal	<0.62
GGT, *μmol/L/s*	Normal	<1.02
25-hydroxy-vitamin D, *nmol/L*	23.9	78–260
Metal-free erythrocyte PPIX, *nmol/L*	36149	<89
Erythrocyte zinc-bound PPIX, *μmol/mol heme*	150	<40
Plasma porphyrin scan, *nm*[a]	634	Negative

ALT, serum alanine aminotransferase; AST, serum aspartate aminotransferase; GGT, serum γ-glutamyltransferase; MCV, mean corpuscular erythrocyte volume.
[a]Emission maximum of the plasma fluorescence spectrum on excitation at 405 nm.

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