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Hepatic porphyrias: diagnosis and management

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"King George III, who was held in low regard on both sides of the Atlantic as the stubborn monarch whom the American colony fought for their independence, was not a well man. . .. the much maligned king suffered spells of a painful and delirious metabolic disease. . .." [1].

Porphyrias are a group of metabolic disorders in which there are defects in the normal pathway for the biosynthesis of heme, the critical prosthetic group for numerous hemoproteins such as hemoglobin, myoglobin, catalase, and microsomal cytochromes b_5 and P-450. The term porphyria comes from the Greek word *porphyra*, which means purple. The derivation is apt because the biochemical hallmark of the porphyrias is overproduction and overexcretion of compounds called porphyrins, which have a deep red or purple color. It is not certain to this day whether George III truly had variegate porphyria. The first clinical reports of porphyria appeared in the late nineteenth century, describing a patient with severe cutaneous photosensitivity and brown pigmentation of the bones, characteristic of congenital erythropoietic porphyria. Soon thereafter, the first case of an inducible acute porphyria was described in a drug addict who passed urine the color of port wine and later died after taking the hypnotic drug sulfonmethane.

The clinical manifestations of the porphyrias can be highly varied, and patients may present to general physicians and be referred to a wide variety of subspecialists because of these manifestations. However, two major clinical forms are represented by the so-called "acute" porphyrias, in which patients suffer

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recurrent bouts of pain, especially pain in the abdomen, and the "cutaneous" porphyrias, in which patients have painful skin lesions.

Elucidation of the heme biosynthetic pathway provided the basis for exploring the chemical reasons for the abnormal accumulation of metabolic intermediates in patients with porphyrias. Characterization of the intermediates involved in heme biosynthesis and the enzymes responsible for their formation, together with observed patterns of the excretion of metabolites in patients with porphyria, suggested which enzyme would be deficient in each type of porphyria (Fig. 1). Knowledge of the factors chiefly responsible for regulating the rate of synthesis of heme has helped to explain how drugs and other factors may cause porphyria. Knowledge of the physical and chemical properties of porphyrins also forms an important part of the foundation for understanding the clinical manifestations of these diseases. Thus, the porphyrias can best be understood after reviewing the chemical properties of porphyrins and heme and the control of their biosynthesis [2,3].

Normal physiology and biochemistry of porphyrin and heme metabolism

Structures and properties of porphyrins and heme

Porphyrins are cyclic tetrapyrroles in which the four pyrrole rings are linked by methene bridges (−CH =), as shown in Fig. 2. All naturally occurring porphyrins have side chains attached to the carbon atoms of the pyrrole rings that are not attached to the ring nitrogen. For uroporphyrins, these side chains are acetate and propionate; for coproporphyrins, they are methyl and propionate; and for protoporphyrins, they are methyl, propionate, and vinyl groups (see Fig. 2). Naturally occurring uroporphyrin and coproporphyrin are of two of four possible isomer types, either the I-isomer, in which the acetate and propionate side chains alternate, or the III-isomer in which one of the pyrrole rings (the D ring) has been flipped 180 degrees, so that the two propionate groups on the C and D rings are vicinal, rather than trans, in their relative orientations (see Fig. 2). In the case of protoporphyrin, which has three side chains, 15 isomers are possible. Only one (called protoporphyrin IX, following the numbering and nomenclature originally proposed by Fischer and Orth) occurs in nature.

Porphyrins are planar, highly stable compounds that absorb light strongly around 400-nm wavelength (the Soret band). They also are strongly fluorescent and emit intense red light when excited by light of the Soret band wavelength. These properties are due to the high degree of resonance of the system of conjugated double bonds (see Fig. 2). These optical properties facilitate detection of porphyrins, even at very low concentrations. In contrast, the porphyrinogens, which are hexahydro- or reduced porphyrins and are the actual intermediates for most of the steps of heme synthesis (see Fig. 1), lack this resonance structure due to the fact that the bridges are all reduced to methylene moieties, which lack double bonds. The porphyrinogens do not absorb light of 400-nm wavelength,

Step	Enzyme defect	Type of porphyria	Urine	Stool	Plasma	RBCs
Glycine + Succinyl-CoA						
↓	ALA synthase					
5-Aminolevulinate (ALA)						
↓	ALA dehydratase	ALA dehydratase deficiency (ADP)	ALA	—	ALA	Zn PROTO
Porphobilinogen (PBG)						
Hydroxymethyl bilane	PBG deaminase	Acute intermittent porphyria (AIP)	ALA, PBG	—	ALA, PBG	—
Nonenzymatic ↓	Uroporphyrinogen III	Congenital erythropoietic porphyria (CEP)	URO,	COPRO	URO	URO,
Uroporphyrinogen III	Synthase (cosynthase)		COPRO			COPRO
UROGEN I						
↓	Uroporphyrinogen III	Porphyria cutanea tarda (PCT)	URO	ISOCOPRO	URO	—
Coproporphyrinogen III	Decarboxylase	Hepatoerythropoietic porphyria (HEP)	URO	ISOCOPRO	URO	Zn PROTO
COPROGEN I						
↓	Coproporphyrinogen III	Hereditary coproporphyria (HCP)	ALA, PBG	COPRO	COPRO	—
Protoporphyrinogen IX	Oxidase		COPRO	(PROTO)		
↓	Protoporphyrinogen	Variegate porphyria (VP)	ALA, PBG	PROTO	PROTO	—
Protoporphyrin IX	Oxidase		COPRO	(COPRO)	(COPRO)	
Fe^{2+} ↓	Ferrochelatase	(Erythropoietic) Protoporphyria ([E]PP)	—	PROTO	PROTO	PROTO
Heme						

Fig. 1. Heme biosynthetic pathway showing the sites of enzyme defects in the porphyrias and the major biochemical abnormalities in biochemically active disease. Only the major increases in the urine, stool, plasma, and erythrocytes (RBCs) are shown. The dashes (–) represent no abnormalities. For several of the diseases, many patients are biochemically silent ("latent") carriers of the enzymatic defects for most of their lives. COPRO, coproporphyrin; COPROGEN, coproporphyrinogen; ISOCOPRO, isocoproporphyrin; PROTO, protoporphyrin; URO, uroporphyrin; UROGEN, uroporphyrinogen; Zn, zinc.

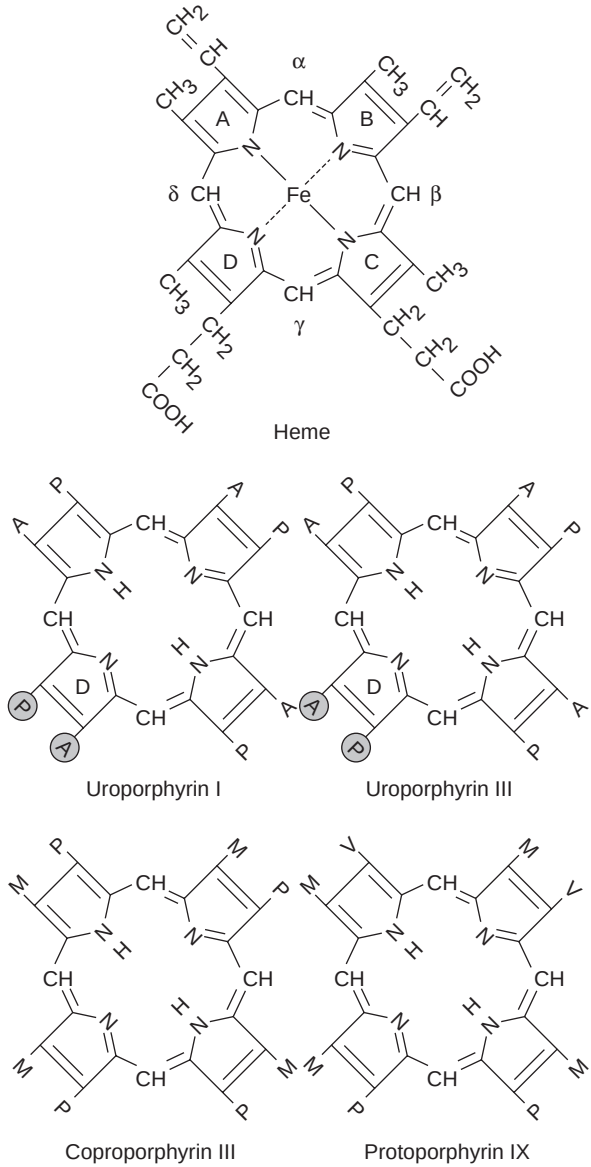


Fig. 2. Structures of heme and selected porphyrins. All porphyrins have the same basic ring structure but differ in the side-chains that are attached to the pyrrole rings. Porphyrinogens are reduced (hexahydro) forms in which the methane bridges linking the pyrroles are replaced by methylene ($-CH_2-$) groups, and all four nitrogens are linked to hydrogens. A, acetate; M, methyl; P, propionate; V, vinyl. (*Modified from* Bloomer JR, Straka JG. Porphyrin metabolism. In: Arias IM, Jakoby WB, Popper H, Schachter D, Shafritz DA, editors. The Liver: biology and pathobiology. New York: Raven Press; 1988. p. 451–66; with permission.)

are colorless, and do not fluoresce. However, they are readily oxidized to the corresponding porphyrins. Such oxidation may occur within cells in the body, as well as in excreted urine or stool. Heme differs from protoporphyrin only in that an iron atom has been inserted into the tetrapyrrole ring. This increases stability of the structure and also causes it to lose its fluorescent properties. Other metalloporphyrins, such as zinc protoporphyrin, may also form in intact animals.

Pathway of heme biosynthesis

The enzymes of the pathway are compartmentalized within the cell. The first and last three steps of the pathway take place in mitochondria, whereas intermediate steps take place in the soluble fraction of the cell cytoplasm. In the first step, the enzyme 5-aminolevulinate (ALA) synthase catalyzes the formation of ALA from glycine and succinyl-CoA in the presence of pyridoxal phosphate. The ALA formed diffuses or is transported from the mitochondria into the soluble fraction, where the second enzyme of the pathway, ALA dehydratase or porphobilinogen (PBG) synthase, condenses two molecules of ALA to form the monopyrrole PBG. In the next step, the enzyme PBG deaminase (sometimes called hydroxymethylbilane synthase) carries out the stepwise polymerization of four molecules of PBG to form the linear tetrapyrrole hydroxymethylbilane. This latter compound is highly unstable and rapidly undergoes cyclization with ring closure spontaneously in the absence of further enzymatic activity. Normally, however, the cytoplasmic fraction contains a large excess of uroporphyrinogen III cosynthase, the next enzyme of the pathway, which leads to the formation of the III-, rather than the I-isomer of uroporphyrinogen. The next enzyme of the pathway, uroporphyrinogen decarboxylase, carries out the stepwise decarboxylation of the four acetate side chains of uroporphyrinogen III, with the eventual formation of coproporphyrinogen III. This enzyme is also capable of decarboxylating uroporphyrinogen I to coproporphyrinogen I, although it does so at a lower rate than for the III-isomer. Coproporphyrinogen III is then transported back into the mitochondria, where the enzyme coproporphyrinogen oxidase catalyzes the stepwise oxidative decarboxylation of the propionic acid side chains on rings A and B to form vinyl groups at these positions. This gives rise to the intermediate protoporphyrinogen IX. Although protoporphyrin readily forms nonenzymatically from protoporphyrinogen in the presence of oxygen, the enzyme protoporphyrinogen oxidase is responsible for this reaction in normal animals. In the final step of the pathway, ferrous iron is inserted into the protoporphyrin ring by the enzyme ferrochelatase to form heme, the end product of the pathway.

Regulation of hepatic heme metabolism

Under normal conditions in both developing erythrocytes and other tissues such as the liver, the first enzyme of the pathway (ALA synthase) is the rate-controlling enzyme. There are two forms of ALA synthase in higher animals: ALA synthase 1, a ubiquitous housekeeping form, and ALA synthase 2, the

erythroid form, which is expressed principally in developing erythrocytes. These two enzymes are regulated quite differently: ALA synthase 1 is downregulated by heme, whereas ALA synthase 2 is downregulated by lack of sufficient iron, through a typical iron responsive element located in its promoter. Thus, under physiologic conditions of iron sufficiency ALA synthase 2 is expressed robustly in developing erythrocytes. In contrast, under physiologic conditions in liver cells, ALA synthase 1 is present in relatively low amount, and the maximal rate at which it is capable of functioning is less than for any of the other enzymes of the pathway. ALA synthase 1 in the liver has a short life span (approximately 1 hour), as does the mRNA coding for it (approximately 3 hours). Therefore, agents that alter the rate of synthesis of the mRNA for ALA synthase 1 or the rate of translation of the message have a rapid (within minutes) and dramatic effect on the amount of ALA synthase 1 in the cell and thus on the rate of synthesis of porphyrins and heme.

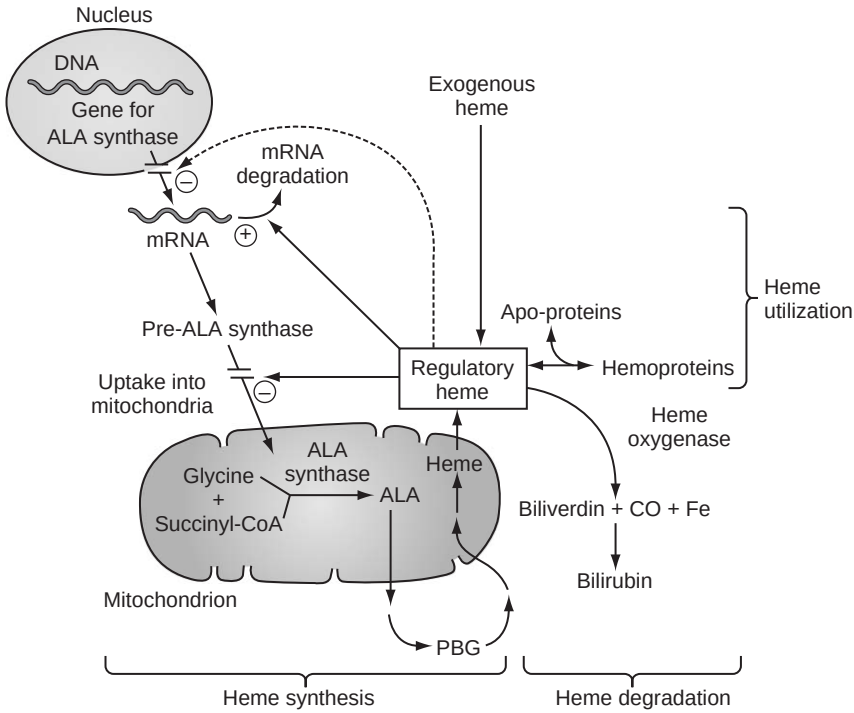


Fig. 3. Regulation of the hepatic heme biosynthetic pathway and subcellular localization of the enzymes of the pathway. Schematic of the synthesis of heme and its regulation. The regulatory heme pool acts to stimulate (+) or downregulate (−) the indicated steps. Those steps indicated as not within the nucleus or mitochondrion take place in the cytosol. The dashed line indicates a still controversial regulatory effect of heme to decrease transcription of the gene for ALA synthase 1. ALA, 5-amino-levulinate; CO, carbon monoxide; CoA, coenzyme A; PBG, porphobilinogen.

Chemicals that cause porphyria in rodents (and probably in humans) also profoundly affect hepatic heme metabolism at sites other than ALA synthase 1. All are believed to decrease the size of a small but critical regulatory heme pool in liver cells. Such a depletion is envisioned to lead to a secondary increase in activity of ALA synthase 1 as the hepatocyte attempts to replenish its regulatory heme pool. The most efficient classical porphyrogenic chemicals produce rapid and profound reduction of the heme of cytochromes P-450, leading, in turn, to reduction of the regulatory heme pool and thus to induction of ALA synthase 1. There is no doubt that heme in hepatocytes downregulates activity of ALA synthase 1, although the exact site(s) of action of heme is still somewhat controversial. There is consensus that heme decreases the stability of the mRNA for ALA synthase 1 and that it also blocks the uptake of ALA synthase into mitochondria.

Some chemicals that are capable of producing experimental porphyria (eg, hydantoins) do not produce depletion of liver heme but rather induce both ALA synthase and cytochromes P-450. Such chemicals are generally lipid soluble, and recent evidence indicates that they upregulate the expression of the genes for Cyp P-450s and for ALA synthase 1 by interaction with consensus drug regulatory elements, which are found in the 5′-untranslated regions of these genes [4]. Parenterally administered heme is capable of entering hepatocytes and of repleting the regulatory heme pool and downregulating the levels of ALA synthase 1. The overall regulation of the pathway is summarized in Fig. 3.

Nutritional status plays an important role. The activity of hepatic ALA synthase is increased by fasting or starvation, whereas the feeding of carbohydrates decreases the basal activity and markedly diminishes the induction of the enzyme produced by porphyrogenic chemicals. Proteins, probably owing to their content of gluconeogenic amino acids, can exert similar effects to that of glucose. The exact mechanism for the glucose effect on ALA synthase is still not understood, but it is of considerable clinical significance. A mainstay of therapy of the acute porphyrias is the administration of large amounts of glucose, which in itself may be sufficient for therapy of mild attacks of the disease.

Overview of the porphyrias

The main clinical manifestations of the porphyrias are cutaneous photosensitivity and neurologic dysfunction, most often presenting as abdominal pain. The porphyrias are a group of metabolic disorders characterized by the excessive accumulation and excretion of porphyrins and their precursors. They result from specific enzyme defects in the heme synthetic pathway, which may be inherited or acquired. Many patients with the enzyme defects do not have clinical manifestations. Porphyric attacks can be fatal, so the early diagnosis of carriers and affected individuals is important to be able to advise the avoidance of precipitating factors for an acute attack, typically drugs, fasting, or alcohol. If neurovisceral symptoms suggest an acute porphyric attack, a rapid screening test for PBG should be performed. If a cutaneous porphyria is suspected, screening

tests for increased erythrocytic porphyrins should be done (if solar urticaria and acute photosensitivity suggest erythropoietic protoporphyria [EPP]), or screening tests for urinary porphyrins (if vesiculobullous formation and skin fragility suggest porphyria cutanea tarda [PCT], hereditary coproporphyria [HCP], or variegate porphyria [VP]). Positive screening tests should be confirmed by specific quantitative tests. Enzymic assays and DNA-based tests are useful for kindred evaluation, genetic diagnosis, and the pinpointing of causative mutations but are not needed for rapid diagnosis of symptomatic patients. Prevention is a central component of management of patients with porphyria. Intravenous hematin, high carbohydrate intake, and pain control are central in the treatment of acute neurovisceral attacks. Sun avoidance and skin protection are important to reduce cutaneous manifestations and complications [2,3,5–9].

Classification

The porphyrias are classified based on the principal site of expression of the enzymic defect, as either hepatic or erythroid (Table 1). They are also classified based on the dominant clinical presentation, whether with cutaneous manifestations only or with neurovisceral features (with or without cutaneous manifestations) (Table 2). The hepatic porphyrias are ADP, AIP, HCP, VP, PCT, and HEP. The "acute" or "inducible" hepatic porphyrias are the first four of these: ADP, AIP, HCP, and VP. The erythropoietic porphyrias are congenital erythropoietic porphynia (CEP) and EPP. HEP may be classified as both hepatic and erythroid.

For the most part, the porphyrias are inherited as autosomal dominant disorders (AIP, HCP, VP, EPP, and the familial form of PCT); some are inherited in a recessive fashion (ADP, HEP, CEP). The majority of PCT patients have an

Table 1
Classification of the porphyrias

Hepatic	Hepatic acute inducible	Erythropoietic
ADP	ADP	
AIP	AIP	
HCP	HCP	
VP	VP	
PCT		
HEP		(HEP)
		CEP
		EPP

The porphyrias are listed as hepatic, acute inducible hepatic, or erythropoietic porphyrias. HEP may be considered both a hepatic and erythropoietic porphyria.

Abbreviations: ADP, ALA dehydratase deficiency porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinate; CEP, congenital erythropoietic porphyria; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; HEP, hepatoerythrocytic porphyria; PCT, porphyria cutanea tarda; VP, variegate porphyria.

Table 2
Summary of major clinical features of the porphyrias

		Clinical manifestation	
Type of porphyria	Neurovisceral	Cutaneous	Liver damage
ADP	Yes	No	No
AIP	Yes	No	No
HCP	Yes	Yes (bullae, fragility)	No
VP	Yes	Yes (bullae, fragility)	No
PCT	No	Yes (bullae, fragility)	Yes
HEP	+/–	Yes (bullae, fragility)	Yes
CEP	No	Yes (bullae, fragility)	Occasional
EPP	Rarely[a]	Yes (urticaria, erythema)	Yes (10%)

The porphyrias are listed with respect to their dominant symptomatology with neurovisceral or cutaneous manifestations and the presence of potential liver damage. (*Modified from:* Hahn M, Bonkovsky HL. Disorders of porphyrin metabolism. In: Wu G, Israel J, editors. Diseases of the liver and bile ducts: a practical guide to diagnosis and treatment. Totowa, NJ: Humana Press; 1998. p. 249–72; with permission.)

Abbreviations: ADP, ALA dehydratase deficiency porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinate; CEP, congenital erythropoietic porphyria; EPP, erythropoietic protoporphyria; HCP, hereditary coproporphyria; HEP, hepatoerythrocytic porphyria; PCT, porphyria cutanea tarda; VP, variegate porphyria.

[a] EPP with end-stage liver disease, especially just after liver transplantation, may rarely be associated with neurovisceral manifestations.

acquired disease, albeit perhaps with a genetic predisposition. Because the principal focus of this article is on the hepatic porphyrias, they are described in the order listed previously, first the acute hepatic porphyrias (ADP, AIP, HCP, VP), then the other hepatic porphyrias (PCT, HEP). EPP is also described because the major complications of EPP affect the liver and biliary tree. A summary overview of the porphyrias with diagnostic essentials is shown in Fig. 1.

Pathophysiology

Neurovisceral features

Abdominal pain, which is the dominant symptom of most porphyrias (especially in the acute porphyrias ADP AIP, HCP, and VP), is probably due to an autonomic neuropathy affecting the gut. The pathogenesis of the neurologic manifestations likely relates either to excess ALA or PBG, usually precipitated by an increase in liver ALA synthase 1 activity or to a deficiency of heme within neurons or other tissues (Fig. 4). It has been proposed that ALA or PBG may be directly neurotoxic or that ALA may interact with receptors for the inhibitory neurotransmitter gamma-amino butyric acid or affect motor nerve conduction velocity, acetylcholine release, Na/K ATPase activity, or other aspects of neuronal function. Heme deficiency within neurons may compromise mitochondrial cytochrome levels and impair ATP production. A deficiency of hepatic heme may lead to increased levels of 5-hydroxytryptophan and tryptamine (5HT, serotonin) in the nervous system, which may mediate or exacerbate neurovisceral features of the acute porphyrias.

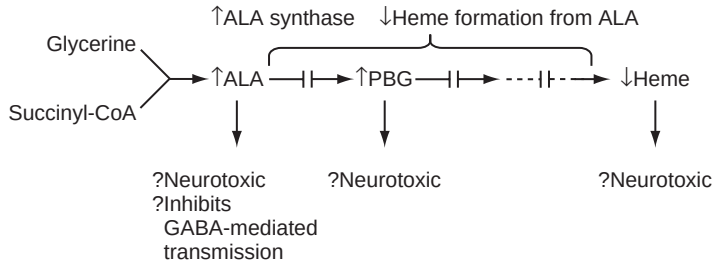


Fig. 4. Pathogenesis of the neurovisceral features of the acute porphyrias. An increase in ALA and PBG levels, accompanied by reduced heme concentrations in the liver and nervous system, likely causes the neurovisceral features. ALA, 5-aminolevulinate; PBG, porphobilinogen.

Cutaneous features

Photocutaneous lesions, due to the photosensitizing effects of the excess porphyrins in the skin or in the dermal blood vessels, may occur in most of the porphyrias (HCP, VP, PCT, HEP, CEP, EPP) but not in ADP and AIP (as the enzyme deficiencies in these last two porphyrias precede porphyrin formation). Skin exposed to light may manifest porphyrin-induced photosensitivity in two ways: either formation of vesicles or bullae and increased fragility as a result of mild trauma to light-exposed skin, or acute erythema with burning and itching but with less chronic injury. When exposed to Soret band radiation the porphyrins emit two major fluorescence emission peaks at 600 to 610 and 640 to 660 nm. The Soret band light excites porphyrin electrons into an activated "triplet state." Some of this energy is then transferred to biological membranes or molecular oxygen, forming reactive "singlet" oxygen. Singlet oxygen damages the skin through several mechanisms, including lipid peroxidation of membranes and cross-linking of membrane proteins. Release of mediators and enzymes from mast cells and polymorphonuclear leukocytes contributes to an inflammatory response modulated by the effects of the porphyrins on the complement and other pathways. The pathophysiology of the cutaneous features of the porphyrias is summarized in Fig. 5. The Soret band light that excites porphyrins passes through ordinary window glass; therefore porphyric patients are not protected from skin photosensitivity damage by remaining indoors. Typical sunburn reactions and other photosensitivities result from light of shorter wavelength (290 to 320 nm), which is absorbed by window glass.

Hepatic features

Some acute porphyrias have mild hepatic abnormalities. Data from Scandinavia and France show an increased risk of hepatocellular carcinoma in patients with acute porphyria. More severe liver damage may occur in PCT and EPP, and to a lesser degree in HEP. Liver biopsies from patients with PCT show red fluorescence, hemosiderosis, fatty infiltration, and variable fibrosis and necrosis. Chronic injury may result in cirrhosis and hepatocellular carcinoma. There is a high incidence of alcohol excess, HCV infection, iron overload, and hetero-

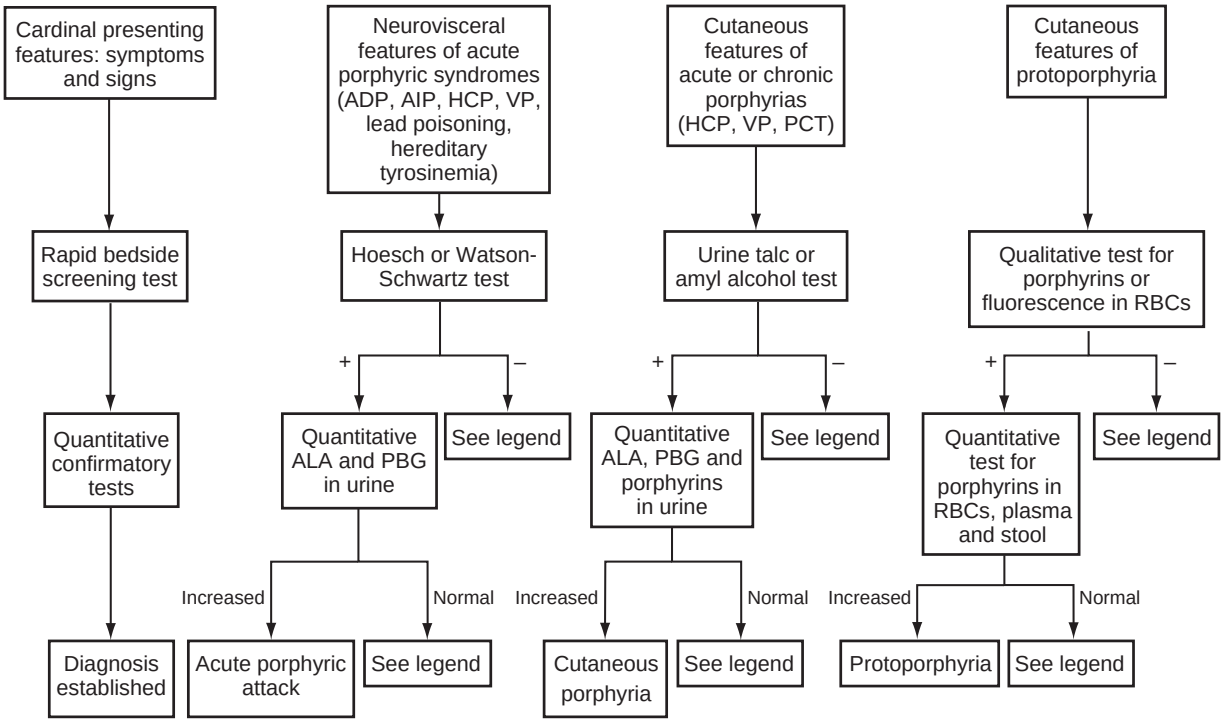


Fig. 5. Pathogenesis of the cutaneous features of the porphyrias. Elevated concentrations of porphyrins in the skin are activated by light of the Soret band. Some of their energy may be transferred to oxygen, activating it to the higher energy (singlet) state. The activated oxygen may produce numerous additional reactions, leading to cell and tissue damage, an inflammatory response, complement pathway activation, and skin damage. ADP, ALA dehydratase deficiency porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinate; HCP, hereditary coproporphyria; PBG, porphobilinogen; PCT, porphyria cutanea tarda; RBCs, erythrocytes; VP, variegate porphyria.

zygosity for hereditary hemochromatosis in PCT patients. In protoporphyria there is an increased risk of developing pigment gallstones, with rare cases developing pigmentary cirrhosis and fatal liver damage.

Enzymatic defects

The enzymatic defects in the heme biosynthetic pathway responsible for the porphyrias are outlined in Fig. 1. The assay of many of these enzymes is available only in a research setting. The enzyme abnormality affecting heme biosynthesis may not by itself be sufficient to cause disease expression. Many patients with a deficient enzyme activity do not have clinical or biochemical manifestations of porphyria. Any induction of hepatic ALA synthase 1 may enhance the production of porphyrin precursors and exacerbate a porphyria. As most of the porphyrias are genetic disorders, the enzyme defects can be detected in several tissues. For example, in EPP a defect in the ferrochelatase-catalyzed insertion of iron into protoporphyrin has been shown in liver, bone marrow cells, peripheral blood mononuclear cells, and cultured skin fibroblasts. Much progress had been made in recent years in defining the genetic defects responsible for the porphyrias. A summary of molecular aspects of the genes and enzymes involved in the porphyrias is shown in Table 3.

Traditional methods of diagnosis of the porphyrias, based on urine, serum, and stool levels of porphyrins or porphyrin precursors or liver and erythrocyte enzyme assays, are still probably best when a specific mutation is not known. Mutational screening in such cases is laborious. The diagnostic essentials for each of the porphyrias are shown in Fig. 1. When a specific mutation is suspected in a

Table 3
Summary of the enzymatic defects causing the porphyrias, showing the sizes and chromosomal locations of the genes and sizes of the gene products

Disease	Enzyme	Size of gene (kb)	#Exons	Chromosomal location	#AAs	MW (kDa)
ADP	ALA dehydratase			9q34	307	36.3
AIP	PBG deaminase	10	15	11q24.1	344/361	37/39
CEP	Urogen III cosynthase			10q25	265	28.6
PCT/HEP	Urogen decarboxylase	3	10	1p34	365	41
HCP	Coprogen oxidase	14	7	3q12	354	41
VP	Protogen oxidase	5.5	13	1q23	354	51
EPP	Ferrochelatase	45	11	18q	423	47.8

Two numbers are given for the amino acids and molecular weights of PBG deaminase, because there are two forms of this enzyme, which are products of alternate splicing (see Fig. 6). The gene size and number of exons of human ALA dehydratase and urogen III cosynthase are not yet known.
Abbreviations: #AAs, number of amino acids; ADP, ALA dehydratase deficiency porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinate; CEP, congenital erythropoietic porphyria; EPP, erythropoietic protoporphyria; COPROGEN, coproporphyrinogen; HCP, hereditary coproporphyria; HEP, hepatoerythrocytic porphyria; kb, kilobases; MW kDa, molecular weight of the enzyme in kilodaltons; PBG, porphobilinogen; PCT, porphyria cutanea tarda; PROTOGEN, protoporphyrinogen; UROGEN, uroporphyrinogen; VP, variegate porphyria.

family or geographic cluster, a variety of molecular methods may simplify making the diagnosis. However, "clustering" of a frequent mutation may not necessarily imply a familial relationship or implicate a founder effect.

Clinical features

General comments on diagnosis

Diagnosis of the porphyrias is usually made by clinical history in association with increased amounts of porphyrins or porphyrin precursors in the urine, feces, and blood [2,3,6,9]. Rapid screening tests are useful in the initial evaluation. The Watson-Schwartz and Hoesch tests detect PBG in the urine by its reaction with Ehrlich's reagent to produce a red color. Urine PBG is increased in most acute porphyric attacks that manifest neurologic abnormalities. In patients with a positive screening test, subsequent specific quantitative tests of urinary ALA and PBG should be done because false positives do occur. If clinical features suggest a cutaneous porphyria, then for solar urticaria and acute photosensitivity (suggesting EPP), screening tests for increased erythrocyte porphyrins should be done; for vesiculobullous formation (suggesting PCT, HCP, or VP), a screening test for urinary porphyrins should be done. The diagnostic essentials are shown in Fig. 1; the normal urine and serum levels of the porphyrins and their precursors are shown in Table 4. The porphyrin precursors ALA and PBG are excreted in the urine; during acute porphyric attacks these levels are markedly increased. The porphyrinogens spontaneously, or after the addition of oxidizing agents, are converted to their corresponding porphyrins, which are then measured. The water solubility and hence excretion of a porphyrin in urine depends on the number of its carboxylic acids groups. Thus uroporphyrin with

Table 4
Normal urinary, fecal, and blood levels of porphyrins and precursors

	Urine		Feces μg/g	Erythrocytes	
Analyte	μg/g Cr	μg/24 h	dry wt	μg/dL packed RBCs	Plasma μg/dL
ALA	<3000	<4000	–	–	15–23
PBG	<2500	<3500	–	–	–
URO	10–60	<80	<5	<2	<2
COPRO	50–250	<280	<50	<2	<1
PROTO	–	–	<120	<90	<2
ISOCOPRO	–	–	–	–	–
Porphyrins (Total)	35–300	50–400	<175	–	<2

Typical normal values for adults are tabulated; there is some variability in normal levels, depending on the laboratory performing the tests and methods used. Normal urine creatinine (Cr) = 0.8–2.0 g/24 hours, Dashes (–) indicate no detectable levels or not routinely tested.
Abbreviations: ALA, 5-aminolevulinate; COPRO, coproporphyrin; ISOCOPRO, isocoproporphyrin; PBG, porphobilinogen; PROTO, protoporphyrin; URO, uroporphyrin.

8 carboxyl groups is predominantly excreted in the urine; coproporphyrin with 4 carboxyl groups is excreted in both urine and feces; protoporphyrin with only two carboxyl groups is poorly water soluble and excreted only in feces after its secretion into bile.

Acute porphyrias

The "acute attacks" of porphyria, with episodic neurologic dysfunction give these porphyrias their name rather than any acute hepatic involvement in these life-long genetic disorders. AIP is the commonest acute hepatic porphyria in the United States and probably the most common "genetic" porphyria; it is usually used as the paradigm for all the acute hepatic porphyrias.

Acute intermittent porphyria

Epidemiology. Acute intermittent porphyria (AIP), also known as Swedish porphyria or pyrroloporphyria, is the most common acute porphyria. It is autosomal dominant with variable penetrance. The true incidence varies from region to region. The prevalence of the defective gene is ~5 to 10 per 100,000 in the United States; it may be about three times higher in hospitalized psychiatric patients. The highest prevalence of AIP is in Scandinavia, especially among the Samis in northern Sweden at 1 in 1500. The United Kingdom is another high incidence region.

Presenting/associated features. Symptomatic AIP occurs more commonly in women than men. Typically women develop symptoms after puberty in their twenties; men develop symptoms in their thirties. Attacks often result from a precipitating factor, which most likely induces ALA synthase 1, such as drugs (especially barbiturates, sulfonamides and hydantoins), hormonal changes, or fasting (Box 1). Barbiturates are still used commonly for the rapid induction of general anesthesia. Sulfonamides may directly inhibit PBG deaminase. The drugs that can precipitate porphyric attacks in susceptible individuals are listed in

Box 1. Precipitating factors for porphyric attacks

- Porphyrogenic drugs and chemicals
- Ethanol
- Fasting/ low calorie diet
- Steroids (gonadal, endogenous and exogenous)
- Infections
- Intercurrent illness
- Surgery (including dental extraction)

Table 5. Some women have cyclic menstrual attacks, progesterone increases heme catabolism, and synthetic estrogens and progesterones induce porphyria. Sex steroid metabolites induce hepatic ALA synthase 1.

The four most common symptoms of AIP are abdominal pain, extremity pain or paresthesias, constipation, and vomiting (Table 6). There are no cutaneous manifestations. The abdominal pain is usually colicky, in the lower abdomen, and may last for hours to days. While the patient may complain of severe abdominal pain, and acute crises have been mistaken for conditions requiring surgical intervention, the abdomen is soft. An autonomic neuropathy may manifest as tachycardia, systemic arterial hypertension, postural hypotension, vomiting, constipation, diarrhea, diaphoresis, and abnormal bladder function. The neuropathic features are diverse; virtually any type of neuropathy may occur (Box 2). In the peripheral nervous system a motor neuropathy is more common than a sensory one [8]. Back, chest, and extremity pain and paresthesias are common and can occur in the absence of abdominal pain. Urinary symptoms of retention, incontinence, dysuria, and frequency may occur. Severely affected patients may also have CNS symptoms. Symptoms such as depression and anxiety may be reactive secondary to the illness of porphyria rather than a direct consequence of it. Seizures, delirium, and coma can occur from the porphyria itself or secondary to hyponatremia attributed to salt losses or to hypothalamic antidiuretic hormone (ADH) release. Attacks that prove fatal often result in prolonged respiratory paralysis and subsequent infectious complications.

The four most frequent presenting signs in patients hospitalized for AIP are tachycardia, dark urine, confusion, and a peripheral motor deficit (see Table 6). The white blood cell count may be elevated because of stress or intercurrent infection. Serum sodium and magnesium concentrations may be decreased. Other abnormalities noted include increased serum T4, thyroxine binding globulin (but AIP patients are usually euthyroid, only rarely frankly thyrotoxic), and elevated cholesterol and low-density lipoprotein (LDL), simulating an exaggerated estrogen effect.

A presumed deficiency of hepatic cytochrome P-450 may account for altered metabolism of some drugs such as salicylamide, antipyrine, and aminopyrine. European series of deceased patients with AIP had an increased incidence of hepatocellular carcinoma, but this has not yet been documented in the United States.

Nature of the metabolic defect in acute intermittent porphyria. AIP is caused by a deficiency of PBG deaminase resulting in an accumulation of PBG and ALA. Porphyric attacks are precipitated by inducers of ALA synthase 1 in AIP carriers. There is one human PBG deaminase gene but two PBG deaminase enzyme isoforms that differ in size by 2 Kd. These two tissue-specific forms arise by alternate splicing from two different promoters using overlapping transcription units but producing two distinct mRNAs (Fig. 6A). The first or upstream promoter is active in all cells and transcribes exons 1 and 3–15. Exon 2 is split out and the result is the so-called “ubiquitous,” “housekeeping,” or “nonerythroid”

Table 5
Drugs and chemicals in acute hepatic porphyrias

	Drug action indication		
Drug	Unsafe	Risky	Safe
Analgesics			
Nonopioids	Danazol	Phenacetin	Acetaminophen
	Diclofenac	Tramadol	Acetylsalicylic acid
	Oxyphenbutazone		Sulindac
	Phenylbutazone		Ibuprofen
	Piroxicam		Naproxen
			Indomethacin
			Paracetamol
Opioids	Dextropropoxyphene	Dezocine	Codeine
	Pentazocine	Fentanyl	Meperidine
		Hydrocodone	Methadone
		Nalbuphine	Morphine
		Oxycodone	
Anesthetics and muscle relaxants	Enflurane	Alcuronium	Bupivacaine
	Fluroxene	Halothane	Butacaine
	Ketamine	Isoflurane	Cyclopropane
	Lidocaine	Propofol	Ether
	Mepivicaine	(single dose)	Nitrous oxide
	Methoxyflurane	Veronal	Procaine
	Propofol		Succinylcholine
	(high doses)		
Anticholinergics		Propantheline	Atropine
			Benzhexol
Anticonvulsants	Barbiturates[b]	Diazepam	Bromides
	Carbamazepine[b]	(high doses)	Gabapentin
	Clonazepam		Magnesium sulfate
	(high doses)		Vigabatrin
	Felbamate		
	Hydantoins[b]		
	Lamotrigine		
	Oxcarbazepine		
	Phenytoin[b]		
	Tiagabine		
	Topiramate		
	Valproate		
Antibiotics/antifungals	Chloramphenicol	Isoniazid	Acyclovir
	Dapsone	Mefenamic acid	Aminoglycosides
	Doxycycline	Miconazole	Amphotericin
	Erythromycin	Nalidixic acid	Cephalosporins[a]
	Griseofulvin	Rifampicin	Ethambutol
	Ketoconazole	Sulfinpyrazone	Flucytosine
	Metronidazole	Sulpiride	Norfloxacin
	Pyrazinamide	Tinidazole	Ofloxacin
	Sulfonamides		Penicillin
	Trimethoprim		Tetracycline[a]
Antihypertensives/ cardiovascular drugs/diuretics	Furosemide	Dipyridamole	Atropine
	α-Methyldopa	Pentoxifyline	Acetazolamide
	Amiodarone	Ticlopidine	Amiloride

(continued on next page)

Table 5 (*continued*)

Drug	Drug action indication		
	Unsafe	Risky	Safe
	Hydralazine		Bethanidine
	Enalapril		Amlodipine
	Lidocaine		Captopril
	Nifedipine		Clonidine
	Spironolactone		Digoxin
	Thiazides		Diltiazem
	Verapamil		Doxazosin
			Epinephrine
			Ethacrynic acid
			Guanethidine
			Irbesartan
			Lisinopril
			Losartan
			Nadolol
			Nitroglycerine
			Norepinephrine
			Prazosin
			Procainamide
			Propranolol
			Quinidine
			Reserpine
			Triamterine
			Valsartan
Anti-inflammatory agents (Nonsteroidal)	Valdecoxib	Celecoxib Rofecoxib	
Antidepressants/ sedatives/ tranquilizers	Alprazolam Chlordiazepoxide Flurazepam Glutethimide Meprobamate Nefazodone nitrazepam Thioridazine Tricyclic antidepressants Troxidone	Bupropion Chlorazepate Diazepam Loprazolam Lorazepam Midazolam Nitrazepam Nordazepam Oxazepam Phenazone Prazepam Tetrazepam Trazodone	Chloral hydrate Chlorpromazine Fluoxetine Lithium Lofepremine Paraldehyde Paroxetine Promazine Temazepam
Antineoplastic agents	Azathioprine Busulfan Cyclophosphamide 5-Fluorouracil Hexamethylmelamine Procarbazine	Cyclophosphamide Tamoxifin	Chlorambucil Dacarbazine Melphalan
Miscellaneous/other	Aminophylline Bemegride Ergotamine Estrogens[b,c]	Dexfenfluramine Hydroxyzine Probenecid Ranitidine	Allopurinol Benzserazide Chlorpheniramine Cimetidine

(continued on next page)

Table 5 (*continued*)

Drug	Drug action indication		
	Unsafe	Risky	Safe
	Eucalyptol	Stanozolol	Colchicine
	Metoclopramide		Corticosteroids
	Progestagens[b,c]		Coumarin
	Sulfonylureas		Heparin
	Theophylline		Insulin
			Laxatives
			Leuprolide
			Levodopa
			Loperamide
			Metformin
			Probucol
			Vitamins A, B, C, D, E
			Warfarin

[a] These agents are either theoretically risky or reports are controversial.
[b] These chemical are the worst offenders.
[c] The female sex steroids are porphyrogenic but in low doses as oral contraceptives may help to prevent cyclic monthly attacks of acute porphyria in some women.
Modified from Hahn M, Bonkovsky HL. Disorders of porphyrin metabolism. In: Wu G, Israel J, editors. Diseases of the liver and bile ducts: a practical guide to diagnosis and treatment. Totowa, NJ: Humana Press; 1998. p. 249–72.

form of PBG deaminase. Use of the second or downstream promoter preceding exon 2, active only in erythroid cells, results in the transcription and translation of exons 3–15 (because exon 2 does not have a start signal) to produce the shorter erythrocyte specific enzyme (17 amino acids shorter). Activity of this form is measured in erythrocyte lysates.

Table 6
Symptoms and signs of attacks of acute intermittent porphyria (AIP)

Clinical features of AIP in hospitalized patients			
Symptom	%	Sign	%
Abdominal pain	87	Tachycardia	90 (38)
Nausea, vomiting	60	Dark urine	74
Extremity pain/paresthesia	50	Mental confusion	53
Constipation	50	Peripheral motor deficit	47
Back or chest pain	41	Bulbar involvement	46
Diarrhea	7	Hypertension	40
		Absent reflexes	29
		Peripheral sensory deficit	26
		Postural hypotension	21
		Palpable dilated bowel loops	21
		Seizures	20
		Fever	9 (31)

The symptoms and signs refer to patients with AIP based on reported large series of AIP patients. Numbers in parentheses refer to percentages from individual large series with discrepant frequencies.

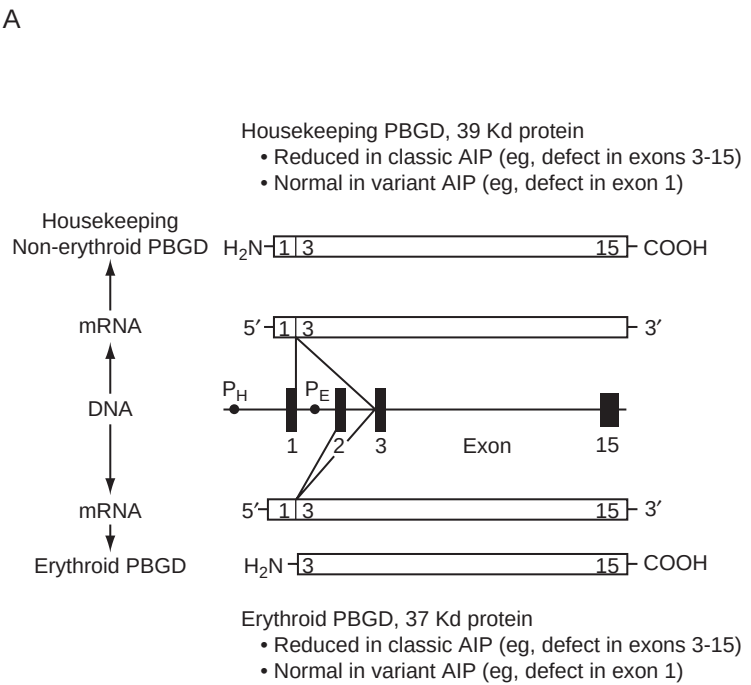
Box 2. Neurologic manifestations of the acute porphyries (listed in descending order of frequency)

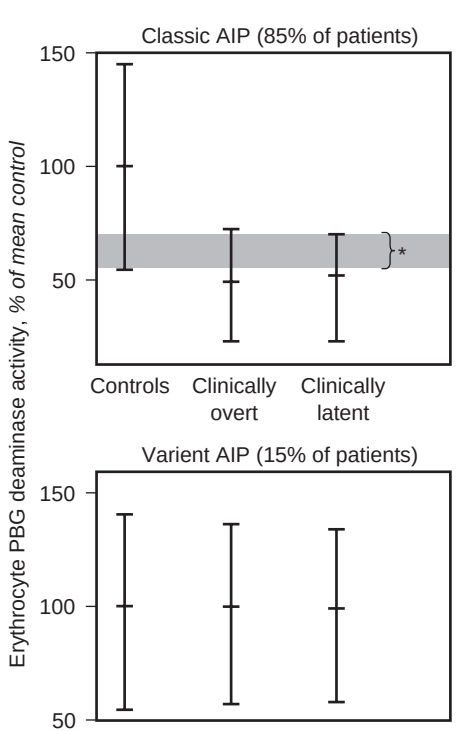
- Autonomic neuropathy (cardiovascular, bladder, bowel)
- Peripheral neuropathy (predominantly motor)
- Sensory loss over the trunk
- Neuropsychiatric manifestations (anxiety, depression, insomnia, disorientation, hallucinations, paranoia)
- Cranial neuropathy (mostly lower cranial nerves, VII and X)
- Seizures or coma
- Rarely, cerebellar, optic nerve, basal ganglion. or pyramidal tract involvement

AIP is associated with half-normal activity of hepatic PBG deaminase consistent with a heterozygous state. Most carriers (80%) are asymptomatic throughout their lives (ie, have latent AIP). The diagnosis of asymptomatic heterozygotes is crucial for the prevention of potentially life-threatening acute attacks by the avoidance of known precipitating factors (see Box 1). AIP is the most virulent of the acute porphyrias because hepatic PBG deaminase activity is only marginally more active than the rate-limiting step catalyzed by ALA synthase 1. Therefore a 50% reduction in PBG deaminase activity often becomes critical, particularly in association with other factors such as a markedly increased ALA synthase 1 activity, and precipitates an acute porphyric attack. The other acute porphyrias are less often clinically expressed and are less severe. For example, the enzyme ALA dehydratase has a much higher usual activity; therefore the expression of ADP requires a more marked reduction of ALA dehydratase (>90% reduction) for clinical expression.

The major pathologic findings in AIP are in muscle and nerve. Electromyography (EMG) studies may be consistent with muscle denervation. There is a reduced motor nerve conduction velocity, edema and irregularity of the myelin sheaths, thinned axons with vacuolization, and degeneration. CNS findings include vacuolization of neurons and focal demyelination. There are few morphologic abnormalities in the liver even though the underlying defect in classic AIP is expressed in the liver.

Diagnosis of acute intermittent porphyria. Latent gene carriers of the AIP gene defects may not have any urinary abnormality in ALA or PBG excretion. However, all patients with true signs and symptoms of AIP will have increased urinary ALA and PBG often up to 25 to 100 mg ALA per day, 50 to 200 mg PBG per day during an attack. This is the sine qua non for the diagnosis of AIP. In AIP the milligram amount of urinary PBG is greater than that of ALA. If this is not the case another diagnosis is more likely. In other porphyrias and in lead poisoning or hereditary tyrosinemia the amount of ALA usually exceeds PBG, even though the


A
Housekeeping PBGD, 39 Kd protein
• Reduced in classic AIP (eg, defect in exons 3-15)
• Normal in variant AIP (eg, defect in exon 1)
Housekeeping
Non-erythroid PBGD
H2N
1 3
15
COOH
mRNA
5′
3′
DNA
PH
PE
1
2
3
Exon
15
mRNA
Erythroid PBGD
Erythroid PBGD, 37 Kd protein
• Reduced in classic AIP (eg, defect in exons 3-15)
• Normal in variant AIP (eg, defect in exon 1)


B
Classic AIP (85% of patients)
Erythrocyte PBG deaminase activity, % of mean control
150
100
50
*
Controls
Clinically overt
Clinically latent
Varient AIP (15% of patients)
150
100
50

clinical manifestations may resemble AIP. PBG in urine may be converted nonenzymically to uroporphyrin; therefore, even though the molecular defect in AIP is in hepatic PBG deaminase, there may be increased uroporphyrin and coproporphyrin in the urine of AIP patients. Their urine may turn dark red (due to porphyrins) or black (due to porphobilin formation) by exposure to air and light [2,3,6,9].

The diagnosis of AIP can usually be made by determining erythrocyte PBG levels (~85% to 95% of cases). There is some overlap in erythrocyte PBG deaminase activities between normal controls and AIP patients, which can result in ambiguous assay results (the "indeterminate zone") (Fig. 6B). For these reasons one cannot depend on erythrocyte PBG deaminase assays to diagnose or exclude AIP. Activity of erythrocyte PBG deaminase is higher in young than in old cells. Thus, erythrocyte PBG deaminase is increased in hemolytic diseases, hepatic diseases, and neonates; it is decreased in uremia. The so-called "variant AIP" (~5% to 15% of AIP patients) is caused by defects in exon 1 so that the nonerythroid transcript is defective while the erythroid-specific transcript is normal and unaffected (Fig. 6A). The diagnosis of type II or variant AIP requires the demonstration of either PBG deaminase deficiency in nonerythroid cells (eg, lymphocytes or cultured fibroblasts) or DNA hybridization using oligonucleotides specific for the mutated allele.

A variety of molecular methods has been used to assist in the molecular diagnosis of the porphyrias. The source of the DNA or RNA is customarily blood leukocytes, sometimes immortalized, but readily mailed hair roots have been used as a source of DNA to facilitate family studies. DNA analysis from paraffin-embedded tissue blocks has also been described. The molecular methods are beyond the scope of this article but have recently been reviewed [9]. These molecular methods are not commercially available, and the molecular diagnosis of AIP is complicated by the large allelic heterogeneity with >100 mutations reported to date (most in exons 10, 12, and 14) [10]. The molecular methods are of greatest benefit when the specific mutation within a family or geographic cluster of patients is already known, for example, the Arg116Tyr mutation in the Dutch AIP population or the G to A mutation in exon 10 (Tyr198X), the major AIP mutation in Sweden [11]. In such cases gene carriers can be identified or excluded with greater accuracy than is possible with conventional biochemical tests.

Fig. 6. The enzymatic defects in acute intermittent porphyria (AIP): the two forms of porphobilinogen deaminase (PBGD) and how the diagnosis of variant AIP is missed by measuring erythrocytic PBGD activity. The PBGD gene with 15 exons is illustrated. (*A*) Use of the housekeeping promoter (PH) results in the 39-kDa nonerythroid PBGD derived from exons 1 and 3–15. Use of the erythroid promoter (PE) results in a 37-kDa protein derived from exons 3–15. *B*. When erythroid PBGD is measured in classic AIP, there is an ~50% reduction compared with controls. An indeterminate zone of PBGD activity (*) overlaps the lower range of control values and those seen in some AIP patients. In variant AIP there is no reduction in erythrocytic PBGD levels. The graphs illustrate the mean and range of measurements anticipated for hypothetical groups of patients with classic and variant AIP.

Management. Prevention is key. Patients should wear a medical alert bracelet. Carriers of the gene defect should be counseled to avoid situations that may precipitate acute attacks. AIP patients should be advised to use as few drugs as possible. Drugs that are used should be "safe" based on experimental and clinical experience (see Table 5) (other drug lists are available on the worldwide web at www.porphyriafoundation.com; http://www.porphyria-europe.com; www.uct.ac.za/depts/liver/drugname.htm; http://www.cpf-inc.ca/links.htm; http://www.porphyrias2003.cz/program.html. Oral carbohydrate intake should always be adequate, and starvation and fad diets should be avoided. Infections should be treated promptly. Stresses should be avoided if possible. Relatives who are at risk for AIP should be screened for the disease, probably best done at centers with special expertise in the diagnosis and management of porphyria.

The treatment aim is to reduce the activity of hepatic ALA synthase 1. The essentials of treatment of the acute porphyric attacks are given in Box 3. Mild attacks may be treated with general supportive measures. Discontinue all known or potentially harmful drugs that might have precipitated an acute attack. Provide at least 300 g of carbohydrate per day enterally or parenterally; glucose or another readily metabolized carbohydrate should be used. Replace fluids, particularly if patients have poor oral intake or have been vomiting. Monitor patients for potential hyponatremia or hypomagnesemia and modify administration of electrolytes and water appropriately. Pain control can be achieved with regular and frequent doses of morphine or meperidine, although such narcotics may exacerbate urinary retention or constipation. The intermittent nature of the symptoms or attacks means that narcotic addiction is unusual. Agitation and anxiety can be treated with chlorpromazine (50 to 400 mg/day). Sympathetic hyperactivity may be treated with propranolol (in the absence of contraindications). The tachycardia and hypertension can be quite labile.

Box 3. Essentials of treatment of acute porphyric attacks

- Discontinue all known or potentially harmful drugs (see Table 5)
- 300 g of carbohydrate intake/day
- Fluid replacement (fluid restriction if syndrome of inappropriate secretion of antidiuretic hormone [SIADH])
- Monitor for potential hyponatremia ± hypomagnesemia
- Pain control: meperidine (400 to 1600 mg/day) or morphine (32 to 128 mg/day)
- Agitation and anxiety: chlorpromazine (50 to 400 mg/day).
- Sympathetic hyperactivity: propranolol (40 to 200 mg/day).
- IV heme (3 to 5 mg/kg body weight/day).
- Prompt treatment of infection
- Treatment of intercurrent diseases

The treatment of choice for any acute attack of porphyria that is severe enough to warrant hospital admission is prompt therapy with intravenous heme [12–14]. The only preparation currently available for use in the United States is panhematin (Ovation Pharmaceuticals, Deerfield, Illinois, Hematin Hot Line 1-800-622-2688; 1-800-455-1141 for questions from health care providers). The usual dose is 3 to 5 mg hematin/kg body weight once daily for 3 to 5 days. Resuspension of lyophilized hematin powder in human serum albumin will prolong its usually very limited stability (1 vial of panhematin, 313 mg of heme, is dissolved in 132 mL of 25% human serum albumin, and administered over 1 hour) [15]. Haem arginate (Normosang, Medica, Helsinki, Finland) is available in many other countries. In most patients with acute porphyria given IV heme, there is normalization of the hepatic overproduction and over-excretion of ALA and PBG within 2–3 days and the porphyric symptoms improve, especially if they are of recent onset. After IV heme therapy is discontinued, the overproduction of ALA and PBG increases rapidly, but fortunately patients do not generally redevelop symptoms. Patients with AIP may overexcrete ALA and PBG for years after an acute attack. There are risks associated with the use of IV hematin, including a coagulopathy due to adverse effects on the clotting factors and platelets, vasculitis, hemolysis, and, if large doses are used, transient renal failure. A phlebitis or thrombophlebitis is frequent. Frequent treatment with hematin may induce heme oxygenase and reduce its therapeutic benefit. The duration of effectiveness of heme may be increased significantly if an inhibitor of heme oxygenase such as tin or zinc meso- or protoporphyrin is given with heme [7,16–18], but this approach is not yet approved.

Women with cyclical porphyric attacks during the luteal phase of their menstrual cycles may benefit from oral contraceptives to block their endogenous cyclic sex hormone production. Leutinizing hormone releasing hormone (LH-RH) analogues, which block the effects of LH-RH at the pituitary, and the cyclic secretion of LH and follicle stimulating hormone are also useful. Leuprolide (Lupron, TAP Pharmaceuticals, Chicago, Illinois) has been used most widely for this purpose. Alternatively, prophylactic IV heme (given once, twice, or thrice weekly) may help these women.

The treatment of seizures complicating porphyria is especially difficult because many of the usual drugs are contraindicated in porphyria (see Table 5). Clonazepam may benefit some patients and is less likely than hydantoins or barbiturates to worsen porphyric atttacks. Parenteral magnesium may be useful but not for chronic therapy. Among newer anticonvulsants, gabapentin and vigabatrin appear to be safe, whereas felbamate, lamotrigine, and tigabine are not [19].

Prognosis. Attacks may last for a few days to months; in some patients a chronic porphyria syndrome develops, but most are asymptomatic between attacks. The prognosis in AIP is generally good, especially if patients who carry a gene defect are counseled to avoid drugs and other precipitants of an acute attack and if acute attacks are treated early and vigorously with IV hematin. Patients with a chronic paresis may be left with a residual deficit, usually a foot drop or wrist drop or

wasting of the intrinsic hand muscles, or they may slowly recover fully. Chronic renal failure, perhaps partly secondary to sustained arterial hypertension or analgesic nephropathy, occurs with an increased incidence in AIP.

ALA dehydratase deficiency porphyria

ALA dehydratase deficiency porphyria (ADP) is a rare syndrome with symptoms similar to AIP. Most ADP patients have had severe repeated porphyric attacks, with different phenotypes but with no skin photosensitivity. The typical symptoms are vomiting, extremity pain, and neuropathy including paralysis and abdominal pain.

ADP results from a severe deficiency of ALA dehydratase (<10% of normal) with secondary induction of hepatic ALA synthase 1 and overproduction of ALA. ADP patients excrete large amounts of urinary ALA and coproporphyrin. For reasons that are not clear, despite markedly decreased activities, ALA dehydratase levels are ~3% of normal, but erythrocyte coproporphyrin III and protoporphyrin levels are elevated ~100 fold. The treatment of ADP is suggested to be the same as for AIP, but not all patients have responded. Some had exacerbations after alcohol, stress, or hunger [20]. The prognosis is guarded at best.

Hereditary coproporphyria

Hereditary coproporphyria (HCP), an inherited autosomal dominant disorder, is less common than AIP, though latent HCP and HCP carriers are being increasingly recognized. In Denmark the prevalence of HCP has been estimated to be 2 per million. The clinical features of HCP may be neurovisceral as in AIP but milder or cutaneous (in ~30%) with a vesiculobullous eruption, resembling that in PCT. Attacks have been precipitated by drugs (barbiturates) but also by the menstrual cycle, contraceptive steroids, and pregnancy. Some patients have had jaundice and hepatic dysfunction.

HCP results from a deficiency of coproporphyrinogen oxidase. Most patients have ~50% of normal enzyme activity. The livers of patients with active HCP have increased coproporphyrin levels, and they fluoresce red when exposed to light of the Soret band. Many molecular defects in coproporphyrinogen oxidase (CPO) give rise to HCP, with a variable phenotype. Many HCP patients have a moderately to markedly increased excretion of coproporphyrin III in the feces (both during and between attacks) and to some extent in the urine. During acute porphyric attacks urine ALA and PBG are also increased; typically urinary ALA PBG excretion (in mg/24 h) exceeds that of PBG but these levels usually normalize between attacks of HCP, unlike AIP. There are silent carriers, just as with AIP, who carry mutations in CPO, but in whom the excretion of porphyrins and their precursors is normal.

The avoidance of precipitating factors is crucial for managing HCP. Acute attacks of HCP are treated in the same way as for AIP. Opaque sunscreens and the avoidance of sunlight are recommended in the treatment of cutaneous manifestations and their prevention. Beta-carotene may be of some benefit in reducing

the severity of photosensitivity. Although the disease is usually relatively mild, death from respiratory paralysis has been reported.

Variegate porphyria

Variegate porphyria (VP), also known as the Royal malady, protocoproporphyria, and South African porphyria, is inherited as an autosomal dominant disorder of low penetrance. Its prevalence is much higher in South Africa than elsewhere, especially among Afrikaners (prevalence ~3 per 1000): there is strong evidence for a founder effect from 17th century Dutch immigrants to South Africa. The presentation of VP is variable, hence its name. Photosensitivity and photodermatitis may develop, as in HCP and PCT, but at an earlier age than PCT with bullae, erosions, or ulcers after mild trauma of light-exposed skin and similar chronic skin changes. Acute neuropsychiatric attacks occur, as in AIP, with abdominal pain, vomiting, constipation, tachycardia, hypertension, psychiatric symptoms, and possible quadriplegia. Hepatic involvement is usually absent.

VP usually results from a heterozygous deficiency of ~50% protoporphyrinogen oxidase (PPO) activity. Four homozygotes or compound heterozygotes with more profound reduction of PPO activity have been described. If hepatic ALA synthase 1 is induced, there is a marked overproduction of ALA, PBG, coproporphyrin, and protoporphyrin associated with acute attacks and cutaneous manifestations. VP is characterized by increased fecal protoporphyrin and also coproporphyrin. In the urine there is increased ALA, PBG, and coproporphyrin. The Arg59Trp mutant in PPO creates a *Sty*1 endonuclease cut site [21]; a combination of restriction enzyme and single strand confirmational polymorphism (SSCP) analysis now allows a rapid diagnosis of VP in South Africa. The enzyme defect in other geographic regions is not dominated by the Arg59Trp mutation.

Avoidance of precipitating factors similar to AIP (barbiturates, contraceptive steroids, other drugs, low carbohydrate intake) is crucial for management. Therapy of the acute attacks is the same as for AIP, whereas that of the cutaneous changes is the same as for HCP. Protective clothing is important, and canthraxanthrin (a beta-carotene analogue) may be helpful. Phlebotomy and antimalarials are not effective. The prognosis for VP is good, although it has a life-threatening potential after ingestion of precipitating drugs.

Other hepatic porphyrias

Porphyria cutanea tarda

Epidemiology. Porphyria cutanea tarda (PCT), synonymous with symptomatic porphyria, idiosyncratic porphyria, chemical porphyria, or acquired hepatic porphyria, is the most common form of porphyria in the United States. The sporadic form (s-PCT) may be purely acquired, although a genetic predisposition is likely present in many patients. The familial form (f-PCT) is inherited in most families as an autosomal dominant disorder with low clinical penetrance.

Presenting/associated features. Sporadic and familial PCT usually presents in adults. PCT patients do not present with acute neurologic attacks. Symptoms are usually limited to the skin. In PCT the photosensitizing skin lesions of increased skin fragility affect mostly the dorsum of hands and forearms; the hands may present with bullae, vesicles, blisters, and sores (Fig. 7). These lesions are not from acute photosensitivity but result from mild trauma in sun-exposed areas. Milia are 1- to 5-mm pearly white subepidermal inclusions, particularly on the hands and fingers. Lesions can also be seen on the forehead, ears, neck, and other sun-exposed areas. The lesions often become infected and tend to heal slowly and leave residual areas of hypo- or hyperpigmentation or sclerodermatous changes. Increased facial hair occurs, which is more noticeable in women. Alopecia may develop at sites of repeated skin damage. The characteristic histopathologic finding of PCT in the skin is subepidermal bullae with minimal inflammation. The undulating base of dermal papillae is termed "festooned."

A typical patient with PCT is a middle-aged man who consumes excess alcohol and has evidence of hepatic disease with elevated serum amino-transferases and gamma glutamyl transpeptidase. Alcohol induces hepatic ALA synthase 1 in patients with PCT and reduces erythrocyte uroporphyrinogen decarboxylase (UROD) activity. Alcohol also inhibits other enzymes in the heme pathway, and chronic alcoholism suppresses erythropoiesis and increases dietary iron absorption. Other patient groups with a relatively high incidence of PCT are those with diabetes mellitus, young women who use oral contraceptives, men with prostate cancer who take estrogens, and chronic hemodialysis patients. These last patients often have iron overload from multiple blood transfusions. The livers of patients with PCT contain high concentrations of uroporphyrins and hepta-carboxyl porphyrins, and when exposed to light from a Wood's lamp, they show an intense red fluorescence. They also often have fat deposition, inflammation, and variable necrosis and fibrosis. Some degree of siderosis is present in 80% of PCT patients on liver biopsy, and most PCT patients have

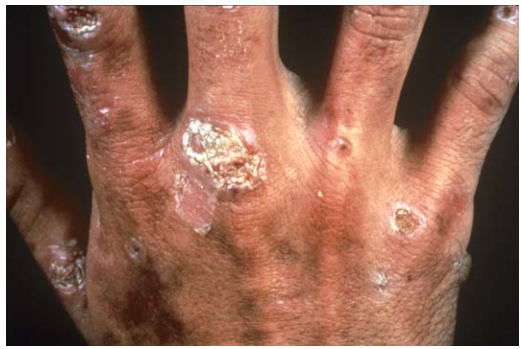


Fig. 7. Manifestations of porphyria cutanea tarda. Typical cutaneous lesions with bullae, vescicles, and erosions on the dorsal hands.

increased ferritin, serum iron, and iron-binding saturation. Iron in the liver plays an important role in the pathogenesis of PCT. Cirrhosis develops in 30% to 40% of PCT cases. The incidence of hepatocellular carcinoma in PCT is greater than normal. There is a high prevalence of HCV antibody markers in PCT patients, with significant variation between countries (5% in Germany, 12% in the United Kingdom, 56% in the United States, and 75% to 90% in Italy and Spain) [22].

Nature of the metabolic defect in porphyria cutanea tarda. PCT results from a defect in UROD. There is an inherited or acquired reduction in hepatic UROD activity, but a 50% reduction per se is insufficient to cause disease. There may be formation of an inhibitor of UROD from iron and breakdown products of uroporphyrinogen. The pathogenesis of PCT is complex. It involves increased oxidative stress in the liver, which may be mediated by multiple exogenous or endogenous factors, for example by alcohol, iron, estrogens, porphyrins, chronic hepatitis C virus infection, polychlorinated biphenyls (PCBs), and polychlorinated cyclic hydrocarbons (the fungicide hexachlorobenzene contaminated wheat in Turkey and resulted in ~4000 cases of PCT in the 5 or 6 years up to 1961). With respect to estrogens, their use in therapy of prostate cancer, postmenopausal replacement, contraception, and their increase in pregnancy have been reported to precipitate PCT. With respect to iron, it is present both in hepatocytes and in Kupffer cells. Inheritance of one or more hemochromatosis genes is an important susceptibility factor for sporadic PCT. Thus, heterozygosity for HLA-linked hereditary hemochromatosis is frequently present in patients with PCT and probably is the major factor causing hepatic iron deposition [22,23]. All patients with PCT should undergo screening for HFE gene mutations and for hepatitis C infection. All forms of human PCT have reduced liver UROD activity. A sporadic form (s-PCT or type I PCT) accounts for ~75% to 85% of PCT patients with decreased UROD activity confined to the liver. The inherited familial autosomal dominant forms (f-PCT or types II and III PCT) account for the remaining ~15% to 25% of PCT patients.

Diagnosis. PCT is characterized by a marked increase in urinary uro- (mostly the I isomer) and heptacarboxy porphyrins. Urinary ALA is often slightly elevated, but PBG is usually normal. A variety of fecal porphyrins is present in PCT. Much of the fecal coproporphyrins are isocoproporphyrins (unlike HCP and VP); therefore elevated stool isocoproporphyrin/coproporphyrin is almost diagnostic of PCT. Urinary uroporphyrin > coproporphyrin favors PCT; urinary coproporphyrin > uroporphyrin favors VP or HCP.

Management. Cutaneous symptoms of PCT are treated by stopping precipitating factors such as the ingestion of alcohol or estrogens. If the urinary uroporphyrin excretion is very high (>2 mg/day), other measures may be necessary. Patients should wear protective clothing, avoid strong sunlight, and apply opaque

sunscreens such as zinc oxide paste. Sunscreens that protect against sunburn are not adequate because they do not screen out the Soret band of light radiation.

Phlebotomy to remove iron from the liver is curative in sporadic PCT and results in the normalization of activity of hepatic UROD. Initially, 450 mL of blood is removed one to two times per week, then with increasing intervals. The aim is to produce a mild degree of iron deficiency (hematocrit <35% and serum ferritin <10 ng/mL), which usually requires removal of 12 to 16 units of blood (3 to 4 g of iron removal). Phlebotomy may induce clinical remission, reduce urinary porphyrins, be associated with regression of the scleroderma-like skin changes, but it is not proven to improve liver histology. About 10% to 20% relapse within 1 year but will likely respond again to phlebotomy if there are no other causative factors. Chloroquine and other antimalarials form water-soluble complexes with octa- and hepta-carboxyl porphyrins and facilitate their excretion in the urine. Treatment should be initiated at a low dose (125 mg, two to three times per week) to reduce the likelihood of acute hepatic injury (fever, right upper quadrant pain related to massive uroporphyrin removal from the liver) and retinopathy. Improvement or remission typically takes 6 to 9 months. Patients with chronic hepatitis C and PCT may experience porphyric remissions after interferon therapy of the viral hepatitis.

Prognosis. Although the prognosis is good for PCT patients who avoid alcohol, the general prognosis depends on the nature and severity of the underlying liver disease.

Hepatoerythropoietic porphyria

Hepatoerythrocytic porphyria (HEP) is a rare form of porphyria. It is caused by a marked deficiency of UROD due to homozygous or compound heterozygous defects. The clinical manifestations of HEP, which are similar to those of congenital erythropoietic porphyria, occur in early childhood, within the first year of life, as a skin disease with severe photosensitivity, skin fragility, and subepidermal bullae. There is excess facial hair, and erythrodontia has been noted. Hepatosplenomegaly has been noted, and hepatic disease develops later. The liver shows portal inflammation and a red fluorescence; serum amino-transferases may be mildly elevated. Serum iron is usually normal. Adults with HEP have a mild normocytic anemia; the erythroid precursors in the bone marrow fluoresce.

HEP is genetically heterogeneous. As the name implies, excess porphyrins are synthesized both in the liver and bone marrow. The clinical diagnosis of HEP is based chiefly on elevated urinary uro- and heptacarboxyl-porphyrins, mostly type I isomers; additionally zinc protoporphyrin in erythrocytes is elevated. Isocoproporphyrin, greater or equal to coproporphyrin, is detected in stool (and urine). Several mutations and deletions have been described. Management of HEP is the same as for PCT and includes avoidance of the sun. Gene therapy

might prove effective in the future. The prognosis of HEP is poor due to the severe defect in UROD activity.

Erythropoietic porphyrias

Erythopoietic protoporphyria

Epidemiology. Protoporphyria, also called erythropoietic protoporphyria or erythrohepatic protoporphyria (EPP), is the commonest of the erythropoietic porphyrias and second only to PCT in prevalence of all the porphyrias, 10 to 20/100,000. There is no sex predominance, and it affects all ethnic groups.

Presenting/associated features. The clinical expression is highly variable. Photosensitivity is the major clinical manifestation of EPP. It is variable among patients even of the same family. Cutaneous symptoms usually begin in infancy. Symptoms of EPP are summarized in Table 7. They include burning, itching, or pain in the skin on exposure to sunlight. This may occur within a few minutes of exposure. There is subsequent erythema, edema, and occasional urticaria in sun-exposed areas. Only if the sun exposure is prolonged do vesicles develop (in contrast to PCT). Shallow waxy depressed scars or thickening with some wrinkling will develop over the nose, cheeks, or dorsum of hands if there are repeated episodes of photosensitivity.

EPP patients rarely (<10%) develop severe liver disease with cirrhosis and acute cholestasis. Some have died of hepatic failure with livers black and nodular from cirrhosis. Polarization microscopy of such livers shows birefringence due to crystals of protoporphyrin in hepatocytes and Kupffer cells and bile canaliculi. In these patients the erythrocyte protoporphyrin levels have exceeded 2000 μg/dL, higher than is usually seen in EPP patients. Only rarely do patients recover after jaundice supervenes. Usually, the liver failure is not thought to be related to alcohol or viral or drug-induced hepatitis. Cholelithiasis, due to concretions of protoporphyrin, occurs with an increased frequency.

Table 7
Cutaneous and other manifestations in erythropoietic protoporphyria (EPP)

Symptoms and signs	Incidence (%)
Burning	97
Edema	94
Itching	88
Erythema	69
Scarring	19
Vesicles	3
Anemia	27
Gallstones	4

The manifestations in EPP, mostly cutaneous, from 32 patients are listed.
Adapted from DeLeo VA, Poh-Fitzpatrick M, Mathews-Roth M, Harber LC. Erythropoietic protoporphyria. 10 years experience. Am J Med 1976;60:8.

Nature of the metabolic defect. EPP results from a deficiency of ferrochelatase. The defect is in all heme-forming tissues. Although the inheritance of human EPP has usually been autosomal dominant, the activity of ferrochelatase in clinically affected persons is only 15% to 25% of normal, and the parents of many patients are phenotypically normal and asymptomatic, although about one half of them demonstrate decreases in activity of the ferrochelatase [24]. Rare compound heterozygotes with very severe phenotypes, causing liver failure in adolescence, have also been described [25]. Patients with EPP with more severely affected phenotypes, particularly those who develop serious porphyric hepatopathy, have defects in both FC alleles. Usually, there is a missense or other serious mutation in one allele and a less serious variation in the other. The most common example of the latter is a variation at position −48 of intron 3, which leads to a lower level of expression of this allele, albeit with an mRNA and protein that are normal [26].

In EPP excess protoporphyrin is produced mostly in the bone marrow. Protoporphyrin is excreted unaltered by hepatic clearance into the bile and subsequently into the feces. The rate-limiting step is canalicular excretion. If the hepatic load exceeds the excretion capacity, protoporphyrin accumulates in the liver and causes liver damage, involving a vicious cycle of worsening cholestasis and worsening accumulation. This may result in pigmentary cirrhosis and pigmented gallstones associated with hemolysis.

Diagnosis. Erythrocytes, feces, and plasma have increased protoporphyrin, but urinary porphyrins and precursors are normal. The erythrocytic protoporphyrin is free and not the zinc chelate (as in lead poisoning and iron deficiency anemia).

Management. Standard sunscreens are not useful. The only topical sunscreens effective at wavelengths >400 nm have a high sun protection factor (SPF >30) and are light opaque, containing zinc oxide or titanium dioxide, and may be cosmetically unacceptable to some patients. Oral beta-carotene (Lumitene, Tishcon Corporation, Westbury, NY) 30 to 300 mg orally daily (for adults to give a serum beta-carotene level of 600 to 800 mg/dL after 4–6 weeks of therapy) reduces the photosensitivity in ~80% of patients, over a 1- to 3-month period after starting therapy [26]. Beta-carotene causes a faint yellow-orange discoloration in the skin; topical beta-carotene cream is ineffective. Beta-carotene probably acts by quenching activated oxygen radicals. The optimal therapy of EPP is unclear. Several approaches have been proposed and rationalized: (1) RBC transfusion, (2) IV heme, (3) oral iron to reduce protoporphyrin formation when there is an iron deficiency, (4) oral chenodeoxycholic acid, (5) oral cholestyramine, (6) activated charcoal to interrupt the enterohepatic circulation, (7) vitamin E. Patients should be followed for the development of liver disease; however routine liver "function" tests are not reliable indicators of liver damage. Patients with very high protoporphyrin levels (>1500 μg/dL in erythrocytes or >50 μg/dL in plasma) or unexplained abnormalities in liver chemistries should be followed closely with consideration for liver biopsy. Those with necrosis or fibrosis should receive

therapy as outlined previously. Liver transplant has been used but will not correct the underlying defect in the bone marrow and other tissues.

Prognosis. Fortunately, the prognosis of EPP is good in the majority of patients.

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References

[1] Macalpine I, Hunter R. George III and the mad business. New York: Pantheon; 1969.
[2] Bloomer JR, Bonkovsky HL. The porphyrias. Dis Mon 1989;35:5–54.
[3] Bonkovsky HL. Porphyrin and heme metabolism and the porphyries. In: Zakim D, Boyer T, editors. Hepatology: a textbook of liver disease. Philadelphia: Saunders; 1982. p. 351–93.
[4] Fraser DJ, Podvinec M, Kaufmann MR, Meyer UA. Drugs mediate the transcriptional activation of the 5-aminolevulinic acid synthase (ALAS1) gene via the chicken xenobiotic-sensing nuclear receptor (CXR). J Biol Chem 2002;277:34717–26.
[5] Bonkovsky HL. The porphyries. In: Rakel RE, editor. Conn's current therapy. 52nd edition. Philadelphia: Saunders; 2000. p. 447–53.
[6] Hahn M, Bonkovsky HL. Disorders of porphyrin metabolism. In: Wu G, Israel J, editors. Diseases of the liver and bile ducts: a practical guide to diagnosis and treatment. Totowa, NJ: Humana Press; 1998. p. 249–72.
[7] Bonkovsky HL. Advances in understanding and treating "the little imitator," acute porphyria. Gastroenterology 1993;105:590–4.
[8] Windebank AJ, Bonkovsky HL. Porphyric neuropathy. In: Dyck PJ, Thomas PK, Griffin JW, Low PA, Poduslo JF, editors. Peripheral neuropathy. 3rd edition. Philadelphia: Saunders; 1992. p. 1161–8.
[9] Bonkovsky HL, Barnard GF. Diagnosis of porphyric syndromes: a practical approach in the era of molecular biology. Semin Liver Dis 1998;18:57–65.
[10] Grandchamp B. Acute intermittent porphyria. Semin Liver Dis 1998;18:17–24.
[11] Andersson C, Thunell S, Floderus Y, Forsell C, Lundin G, Anvret M, et al. Diagnosis of acute intermittent porphyria in northern Sweden: an evaluation of mutation analysis and biochemical methods. J Int Med 1995;237:301–8.
[12] Lamon JM, Frykholm BC, Hess RA, Tschudy DP. Hematin therapy for acure porphyria. Medicine 1979;58:252–69.
[13] Pierach CA. Hematin therapy for the porphyric attack. Semin Liv Disease 1992;2:125–31.
[14] Bissell DM. Treatment of acute hepatic porphyria with hematin. J Hepatol 1988;6:1–7.
[15] Bonkovsky HL, Healey JF, Lourie AN, Gerron GG. Intravenous heme-albumin in acute intermittent porphyria. Evidence for repletion of hepatic hemoproteins and regulatory heme pools. Am J Gastroenterol 1991;86:1050–6.
[16] Russo SM, Pepe JA, Cable EE, Lambrecht RW, Bonkovsky HL. Synergistic repression of ALA synthase by heme and zinc-mesoporphyrin in a chick embryo liver cell culture model of acute porphyria. Eur J Clin Invest 1994;24:406–15.
[17] Dover SB, Moore MR, Fitzsimmons EJ, Graham A, McColl KE. Tin protoporphyrin prolongs the biochemical remission produced by heme arginate in acute hepatic porphyria. Gastroenterology 1993;105:500–6.
[18] Cable EE, Pepe JA, Karamitsios NC, Lambrecht RW, Bonkovsky HL. Differential effects of metalloporphyrins on mRNA levels of ∂-aminolevulinate synthase and heme oxygenase: studies in cultured chick embryo liver cells. J Clin Invest 1994;94:649–54.

[19] Hahn M, Gildemeister OS, Krauss GL, Pepe JA, Lambrecht RW, Donohue S, et al. Effects of new anticonvulsant medications on porphyrin synthesis in cultured liver cells—potential implications for patients with acute porphyria. Neurology 1997;49:97–106.
[20] The porphyrias. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular bases of inherited disease, vol. 2. New York: McGraw-Hill; 1995. p. 2103–61.
[21] Warnich L, Kotze MJ, Groenewald IM, Groenewald JZ, van Brakel MG, van Heerden CJ, et al. Identification of 3 mutations and associated haplotypes in the protoporphyrinogen oxidase gene in South African families with variegate porphyria. Hum Mol Gen 1996;5:981–4.
[22] Bonkovsky HL, Poh-Fitzpatrick M, Pimstone N, Obando J, Di Bisceglie A, Tattrie C, et al. Porphyria cutanea tarda, hepatitis C, and HFE gene mutations in North America. Hepatology 1998;27:1661–9.
[23] Roberts AG, Whatley SD, Morgan RR, Worwood M, Elder GH. Increased frequency of the hemochromatosis C282Y mutation in sporadic porphyria cutanea tarda. Lancet 1997;349:321–3.
[24] Goerz G, Bunselmeyer S, Bolsen K, Schurer NY. Ferrochelatase activities in patient with erythropoietic protoporphyria and their families. Br J Dermatol 1996;134:880–5.
[25] Serkany RPE, Cox T. Autosomal recessive erythropoietic protoporphyria: a syndrome of severe photosensitivity and liver failure. Quest J Med 1995;88:541–9.
[26] deRooij FWM, Edixhoven A, Wilson JHP. Porphyria: a diagnostic approach. In: Kadish KM, Smith KM, Guilard R, editors. The porphyrin handbook. New York: Elsevier Science; 2003. p. 211–45.