Answer to Dermacase *continued from* ***page 749***

3. Porphyria cutanea tarda

Porphyrias are genetic metabolic disorders resulting from deficient or absent enzymes in heme biosynthesis (which primarily occurs in bone marrow erythroblasts and hepatocytes).[1,2] Porphyrias can be classified into *acute hepatic porphyrias* and *nonacute porphyrias.* In general, acute porphyrias are associated with neurologic symptoms, whereas nonacute subtypes are associated with cutaneous photosensitivity to UV radiation in the Soret band (400 to 410 nm). Accumulation of porphyrins or porphyrin precursors, combined with exposure to UV radiation, results in the production of reactive oxygen species that destroy cell membranes and cause cell lysis.[1-3] Acute hepatic porphyrias involve heme pathway dysregulation, while chronic hepatic porphyrias result in porphyrin accumulation[4] (**Table 1**[1,2,5,6]). Porphyria can be an indicator of and is often associated with underlying systemic disease resulting in considerable morbidity and mortality if it goes undiagnosed or untreated. However, recognizing this condition can be challenging without clinical suspicion of the entity.

Table 1. General overview of heme synthesis

STEP	DESCRIPTION	PORPHYRIA
1	Glycine + succinyl-coenzyme A → ΔALA *Enzyme:* **ALA synthase** *Location:* Mitochondria	Rate-limiting step in porphyrin synthesis
2	ΔALA + ΔALA → PBG *Enzyme:* **ALA dehydratase** *Location:* Cytosol	ADP
3	PBG → hydroxymethylbilane intermediate *Enzyme:* **PBG deaminase** *Location:* Cytosol	IAP
4	Hydroxymethylbilane intermediate → uroporphyrinogen III *Enzyme:* **UROS** *Location:* Cytosol	CEP
5	Uroporphyrinogen (uroporphyrinogen III or abnormal uroporphyrinogen I) → coproporphyrinogen III intermediate *Enzyme:* **UROD** *Location:* Cytosol	PCT
6	Coproporphyrinogen III intermediate → decarboxylation → protoporphyrinogen IX *Enzyme:* **Coproporphyrinogen oxidase** *Location:* Mitochondria	HCP
7	Protoporphyrinogen IX → protoporphyrin IX *Enzyme:* **PPO** *Location:* Mitochondria	VP
8	Protoporphyrin IX → heme synthesis *Enzyme:* **Ferrochelatase** *Location:* Mitochondria	EPP

ADP—ALA dehydratase deficiency porphyria, ALA—aminolevulinic acid, CEP—congenital erythropoietic porphyria, EPP—erythropoietic protoporphyria, HCP—hereditary coproporphyria, IAP— intermittent acute porphyria, PBG—porphobilinogen, PCT—porphyria cutanea tarda, PPO—protoporphyrinogen IX oxidase, UROD—uroporphyrinogen decarboxylase, UROS—uroporphyrinogen III synthase, VP—variegate porphyria.
Data from Sassa,[1] Puy et al,[2] Poblete-Gutiérrez et al,[5] and Murphy.[6]

Acute hepatic porphyrias

Acute hepatic porphyrias include intermittent acute porphyria, aminolevulinic acid dehydratase deficiency porphyria, hereditary coproporphyria, and variegate porphyria. Porphobilinogen deaminase deficiency is rarely seen before puberty[1,5] (**Table 2**[1,2,5,7]). With the exception of variegate porphyria, acute hepatic porphyrias typically present with systemic symptoms rather than cutaneous findings.

Nonacute porphyrias

Nonacute porphyrias are further subclassified into *erythropoietic porphyrias* (ie, congenital erythropoietic porphyria and erythropoietic protoporphyria) and *chronic hepatic porphyrias* (ie, porphyria cutanea tarda and hepatoerythropoietic porphyria) as summarized in **Tables 3** and **4,** respectively.[1,2,5,7] These nonacute porphyrias demonstrate cutaneous manifestations and systemic findings, but are typically not associated with any neurologic symptoms.

Discussion

Porphyria cutanea tarda (PCT) is the most common porphyria. History and clinical examination reveal photosensitivity, skin fragility, and bullae formation, as well as healed scars with milia formation and hyperpigmentation on photodistributed regions of the body, particularly the dorsa of the hands and arms, and, less commonly, hypertrichosis and sclerodermoid skin changes.[5] Clinical symptoms and a positive urinary porphyrin profile are often adequate to make the diagnosis of PCT.[5] Porphyrin excretion ceases in the remission phase.[2] Uroporphyrinogen decarboxylase activity in erythrocytes can also be measured in some laboratories. A skin biopsy is considered unnecessary; however, histologic examination will demonstrate subepidermal, cell-poor bullae with festooning of the dermal papillae.[5]

Differential diagnoses for porphyrias include other blistering disorders such as polymorphic light eruptions, bullous lupus erythematosus, epidermolysis bullosa acquisita, photoinduced bullous drug reactions, solar urticaria, and hydroa vacciniforme. All of these conditions have normal (ie, negative) urine, fecal, and serum porphyrin levels.

Management of PCT includes UV protection, avoidance of triggers (the most common being excessive alcohol consumption or estrogens), biweekly phlebotomy (ie, approximately 500 mL every 2 weeks) to reduce serum ferritin, and treatment of underlying

Table 2. Overview of acute hepatic porphyrias

TYPE OF PORPHYRIA	CLINICAL SYMPTOMS	ENZYME DEFECT	BIOCHEMICAL INVESTIGATIONS	MANAGEMENT
IAP *Inheritance:* Autosomal dominant	*Skin*: None *Systemic:* Abdominal pain, diffuse pain, hypertension, tachycardia, hyponatremia, muscle weakness, sudden death from arrhythmia *Neurologic*: Confusion, seizures, sensory loss	PBGD deficiency Type I and III: Decreased erythrocyte PBGD activity Type II: Decreased non–erythrocyte PBGD activity	*Urine:* Acute—PBG, ALA, uroporphyrin, coproporphyrin Latent—PBG, ALA Dark red urine contains porphobilin, an oxidized product of PBG *Fecal and serum*: Normal	Avoidance of agents that inhibit ALAD activity (sulfonamides, barbiturates, hormones) *Other precipitants:* Fever, infection, physiologic stress, surgery, starvation *Treatment:* IV glucose and hematin with acute attacks
VP *Inheritance:* Autosomal dominant among South Africans; mixed skin and neurologic symptoms	*Skin:* Photosensitivity, chronic bullae and erosions, milia on skin exposed to UV radiation, hypertrichosis, sclerodermoid changes *Systemic:* Abdominal pain, gallstones, diffuse pain, hypertension, tachycardia, hyponatremia, muscle weakness, sudden death from arrhythmia *Neurologic:* Confusion, seizures	PPO deficiency	*Urine:* Coproporphyrin, protoporphyrin Acute—ALA, PBG, and uroporphyrin *Fecal:* Protoporphyrin, coproporphyrin *Serum:* Plasma porphyrin (fluoresces at 626 nm)	Avoid alcohol and other precipitants (dapsone, barbiturates, anticonvulsants, sulfonamides, hormones, griseofulvin) *Treatment:* IV glucose and hematin with acute attacks
HCP *Inheritance:* Autosomal dominant (rare)	Identical to IAP and VP *Skin*: None *Other:* Hemolytic anemia, risk of hepatocellular carcinoma	Coproporphyrinogen oxidase deficiency	*Urine:* Coproporphyrin III Acute—ALA, PBG, and uroporphyrin *Fecal*: Coproporphyrin III *Serum*: Normal	Avoid precipitants (alcohol, barbiturates, hormones)
ADP *Inheritance:* Autosomal recessive (very rare; < 10 cases reported)	Identical to IAP *Skin*: None	ALAD deficiency	*Urine:* ALA, coproporphyrin, uroporphyrin *Fecal:* Coproporphyrin, protoporphyrin *Serum*: Protoporphyrin	Avoid precipitants (alcohol, physiologic stress) *Treatment:* IV glucose and hematin with acute attacks

ADP—ALA dehydratase deficiency porphyria, ALA—aminolevulinic acid, ALAD—ALA dehydratase, HCP—hereditary coproporphyria, IAP—intermittent acute porphyria, IV—intravenous, PBG—porphobilinogen, PBGD—porphobilinogen deaminase, PPO—protoporphyrinogen IX oxidase, VP—variegate porphyria.
Data from Sassa,[1] Puy et al,[2] Poblete-Gutiérrez et al,[5] and Köstler and Wollina.[7]

Table 3. Overview of nonacute erythropoietic porphyrias

TYPE OF PORPHYRIA	CLINICAL SYMPTOMS	ENZYME DEFECT	BIOCHEMICAL INVESTIGATIONS	MANAGEMENT
CEP *Inheritance:* Autosomal recessive (very rare; about 150 reported cases) Severe clinical course	*Skin:* Severe photosensitivity, bullae, scarring, cartilage destruction, hypertrichosis, hyperpigmentation *Ocular:* Photophobia, conjunctivitis, symblepharon, blindness *Systemic:* Mild to severe hemolysis, transfusion-dependent anemia, splenomegaly, erythrodontia particularly later in life	UROS deficiency	*Urine:* Uroporphyrin I, coproporphyrin I *Fecal:* Coproporphyrin I *Serum:* Uroporphyrin I, coproporphyrin I	UV protection Blood transfusions (for anemia), splenectomy, activated charcoal, hydroxyurea and bone marrow transplantation
EPP *Inheritance:* Autosomal dominant	*Skin:* Photosensitivity, diffuse edematous plaques with UV exposure, scarring *Systemic:* Porphyrin gallstones, liver disease (cirrhosis, jaundice)	Ferrochelatase partial deficiency	*Urine:* Normal *Fecal:* Protoporphyrin *Serum:* Protoporphyrin (red blood cell)	UV protection High-dose beta-carotene (children: 30-90 mg/d, adults: 60-180 mg/d); cholestyramine, blood transfusions, activated charcoal

CEP—congenital erythropoietic porphyria, EPP—erythropoietic protoporphyria, UROS—uroporphyrinogen III synthase.
Data from Sassa,[1] Puy et al,[2] Poblete-Gutiérrez et al,[5] and Köstler and Wollina.[7]

Table 4. Overview of nonacute hepatic porphyrias

TYPE OF PORPHYRIA	CLINICAL SYMPTOMS	ENZYME DEFECT	BIOCHEMICAL INVESTIGATIONS	MANAGEMENT
PCT *Inheritance:* PCT I: Acquired PCT II and III: Autosomal dominant Most common form of porphyria	*Skin:* Photosensitivity, chronic bullae and erosions, milia on skin exposed to UV radiation, hypertrichosis, sclerodermoid changes *Systemic:* Hepatitis C, hepatocellular carcinoma, increased hepatic iron stores *Other:* HIV, dermatomyositis	UROD deficiency Type I: Decreased hepatic UROD Type II: Decreased hepatic and erythrocyte UROD Type III: Decreased hepatic UROD No increase in ALA or PBG	*Urine*: Uroporphyrin, isocoproporphyrin Red or pink fluorescence of urine *Fecal:* Isocoproporphyrin establishes PCT or HEP diagnosis *Serum:* Increased iron; normal red blood cells	UV protection Biweekly phlebotomy (approximately 500 mL every 2 wk) to reduce serum ferritin and urinary porphyrin concentration; low-dose hydroxychloroquine or chloroquine (125 mg twice/wk) to chelate porphyrins Avoid hepatic UROD inactivators (such as alcohol and estrogen) and chronic hemodialysis for renal failure Treatment of hemochromatosis to reduce hepatic iron content
HEP *Inheritance:* Autosomal recessive (rare)	*Skin:* Severe photosensitivity, bullae, scarring, hypertrichosis, hyperpigmentation *Systemic:* Severe hemolysis, transfusion-dependent anemia, splenomegaly, dark urine in infancy Resembles CEP with hemolytic anemia and splenomegaly	UROD deficiency	*Urine:* Uroporphyrin, heptacarboxylate porphyrin, and isocoproporphyrin *Fecal:* Isocoproporphyrin establishes PCT or HEP diagnosis *Serum:* Erythrocyte porphyrins elevated	Similar to CEP UV protection, blood transfusions, splenectomy, activated charcoal, hydroxyurea, and bone marrow transplantation Note difference in management compared with PCT

ALA—aminolevulinic acid, CEP—congenital erythropoietic porphyria, HEP—hepatoerythropoietic porphyria, PBG—porphobilinogen, PCT—porphyria cutanea tarda, UROD—uroporphyrinogen decarboxylase.
Data from Sassa,[1] Puy et al,[2] Poblete-Gutiérrez et al,[5] and Köstler and Wollina.[7]

conditions (eg, hepatitis, hemochromatosis, HIV). Low-dose hydroxychloroquine or chloroquine (125 mg twice weekly) to chelate porphyrins is also useful, but ineffective in patients with associated hemochromatosis.[1,2,5-7] Alcohol consumption is associated with flares in porphyria as the ethanol molecule decreases the activity of several enzymes including aminolevulinic acid dehydratase, uroporphyrinogen decarboxylase, coproporphyrinogen oxidase, and ferrochelatase.[4] We suspect that substantial alcohol intake (ie, 2 to 4 alcoholic beverages per day) precipitated PCT in our patient.

Finally, it is important to distinguish between acute and nonacute porphyrias, as the former are associated with substantial morbidity, such as neurologic decline (eg, paralysis), respiratory failure, coma, and possibly death, if acute attacks are inadequately managed. Medical history and biochemical porphyrin profiles will help distinguish among the various forms of porphyria. In the future, advances in molecular genetics might be useful for rapid diagnosis and identification of carriers of inherited porphyrias.[1]

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Competing interests
None declared

References

1. Sassa S. Modern diagnosis and management of the porphyrias. *Br J Haematol* 2006;135(3):281-92.
2. Puy H, Gouya L, Deybach JC. Porphyrias. *Lancet* 2010;375(9718):924-37.
3. Lim HW. Pathogenesis of photosensitivity in the cutaneous porphyrias. *J Invest Dermatol* 2005;124(1):xvi-xvii.
4. Doss MO, Kuhnel A, Gross U. Alcohol and porphyrin metabolism. *Alcohol Alcohol* 2000;35(2):109-25.
5. Poblete-Gutiérrez P, Wiederholt T, Merk HF, Frank J. The porphyrias: clinical presentation, diagnosis and treatment. *Eur J Dermatol* 2006;16(3):230-40.
6. Murphy GM. The cutaneous porphyrias: a review. The British Photodermatology Group. *Br J Dermatol* 1999;140(4):573-81.
7. Köstler E, Wollina U. Therapy of porphyria cutanea tarda. *Expert Opin Pharmacother* 2005;6(3):377-83.