Porphyrinogens, Porphyrins, and Porphyrias

The porphyrias are emotionally distressful and potentially lethal disorders that are evidenced prominently with neurologic and dermatologic expressions. Congenital erythropoietic porphyria (CEP) is evidenced in infancy, but the porphyrias of other types have been evidenced almost entirely in adulthood in most cases and only rarely during childhood.

Acute Intermittent Porphyria (AIP), Coproporphyria (CP), and Variegate Porphyria (VP) are 3 of the mild-to-severe abdominal pain and psychiatric distress ranging from depression to psychosis.

The episodes of abdominal pain may be so severe as to indicate a need for immediate surgical exploration and intervention. Whether mild or severe, in most cases of AIP and CP, the recurring abdominal discomfort has been the unnerving factor that has caused patients to seek examination.

Additional episodic characteristics of lesser frequencies include hypertension, paresthesias, fever, and seizures.

AIP, CP, and VP can cause episodes of neuromuscular weakness that can progress quickly to paraparesis and whole-body paralysis with life-threatening respiratory paralysis; onset of neuromuscular weakness is clearly a signal for expeditious establishment of a diagnosis and prompt medical intervention.

Expression of AIP does not include skin problems, however, 20-30% of known cases of CP and most, if not all, cases of VP are photosensitive and/or have increased physical fragility of the skin, increased sensitivity to chemical contact, and increased susceptibility to "neurodermatitis." Hypertrichosis and regional alopecia may occur in more severely expressed cases of CP and VP. Dermopathy resulting from the photosensitivity of CP and VP includes erythema, urticaria, and blistering and vesicular lesions.

During acute episodes of AIP, CP, and VP, the production and urinary excretion of delta-aminolevulinic acid (δ-ALA) and porphobilinogen (Pbg) are increased; therefore, quantitation of urinary δ-ALA and Pbg during suspected acute episodes is helpful.

AIP may be diagnosed in either the acute state or latent state by quantitation of δ-ALA dehydratase and Pbg deaminase (uroporphyrinogen I synthase) activities in erythrocytes. Initial screening for suspected cases of AIP should include an analysis of a 24-hour urine collection for porphobilinogen and urine porphyrins. Urinary δ-ALA analysis may, additionally, be helpful. CP and VP can be detected by analysis of the fecal porphyrins: coproporphyrin excretion is increased in CP, and both fecal coproporphyrins and protoporphyrins are increased in VP. During acute episodes, urinary porphobilinogen and porphyrins will be increased.

Acute attacks of AIP, Hereditary Coproporphyria, and VP can be provoked by medications (barbiturates and antibacterials are among the best known offenders) and alcohol; other suspect substances that may precipitate an acute attack include household or industrial chemicals, agricultural pesticides, industrial chemical wastes, garden chemicals, and chemicals used in hobby crafts — such as mineral pigments used in ceramics work and degreasing solvents used in automotive and other mechanical repair work.

Congenital Erythropoietic Porphyria is readily recognizable in early life by photosensitivity and voiding of pink, wine-red, or dark urine. Diminished activity of uroporphyrinogen (Upg) III synthase (co-synthase) in erythrocytes is definitive evidence for a diagnosis.

Porphyria Cutanea Tarda is characterized by photosensitivity, increased urinary excretion of uroporphyrin, heptacarboxylporphyrin, and increased plasma porphyrins. It is potentiated by a partial deficiency of Upg decarboxylase, and can be provoked into a metabolically active form by factors such as excessive storage of iron, chronic abuse of alcohol, and hepatitis C infection.

Protoporphyria is relatively mild but potentiates the victim for acute solar urticaria and chronic solar eczema. The chemical features include increased erythrocyte protoporphyrin and increased fecal excretion of protoporphyrin.

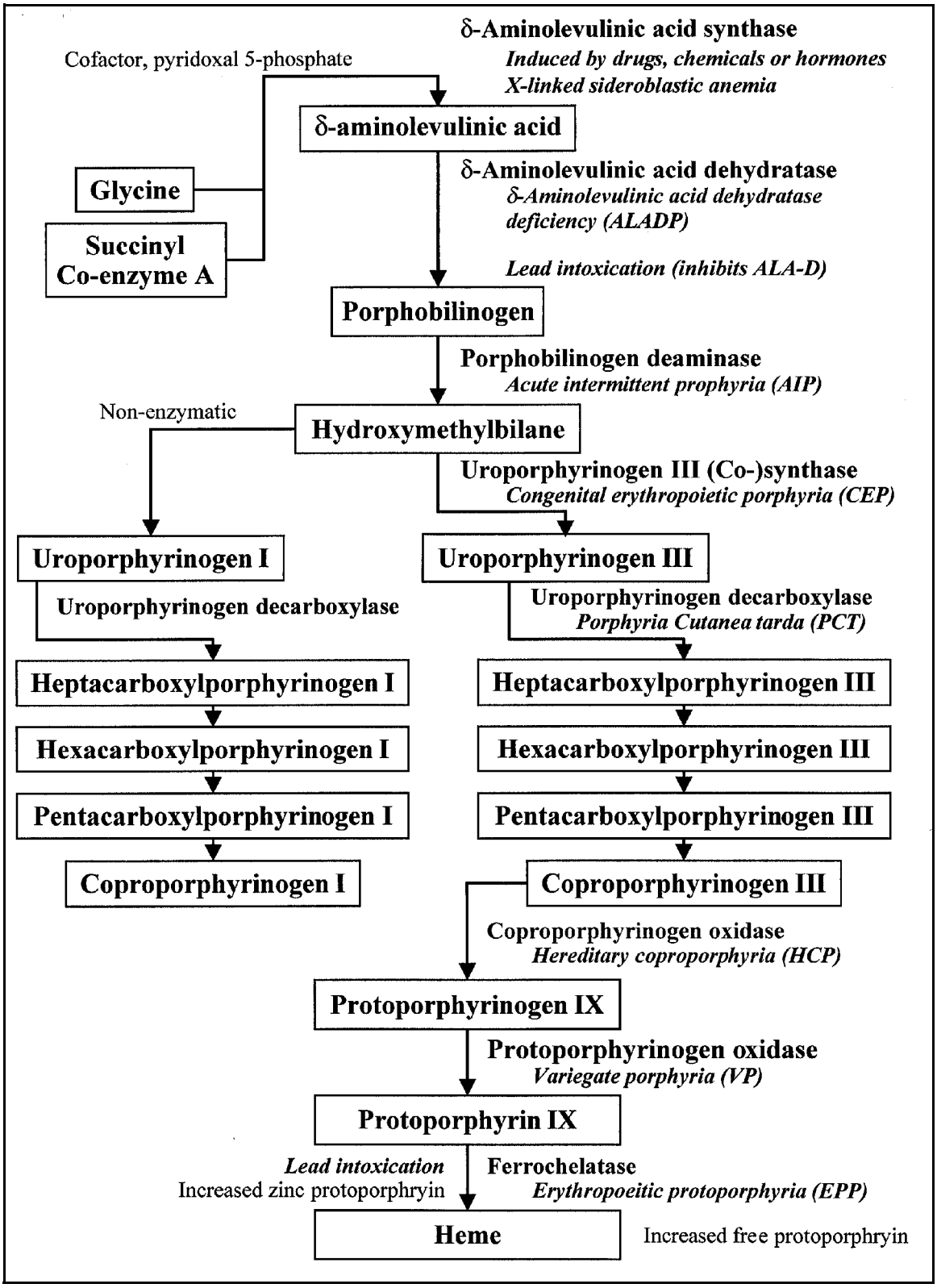
Acquired Porphyria: Accumulation of porphyrins and porphyrin precursors in blood and tissue can be caused by a variety of toxic substances; probably most of the recognized cases have been caused by ingestion of lead. Heavy metals, halogenated aromatic hydrocarbons, and drugs can suppress enzymes involved in porphyrinogen metabolism, leading to the accumulation of intermediates. Enzymes known to be suppressible by these compounds include aminolevulinic acid dehydratase, Pbg deaminase, Upg decarboxylase, and ferrochelatase. Usually, acquired or "intoxication" porphyria results in increased erythrocyte protoporphyrin, increased urinary excretion of δ-ALA and Pbg, and increased fecal excretion of protoporphyrin. In addition, increased urinary excretion of porphyrins can occur. Coproporphyrinuria has been observed in many cases of intoxication with industrial chemicals and waste by-products. Also, intoxication porphyria can mimic porphyria cutanea tarda in terms of both clinical signs and increased urinary excretion of uroporphyrin and heptacarboxylporphyrin; this form of porphyria occurs when the toxin interferes with the production of or function of Upg decarboxylase.

Symptomatic and pathological expression of the porphyrias is provoked by environmental stresses and/or physiologic factors that biochemically impact the characteristic diminished enzyme activities of the heme-forming system. The needs for avoidance of these environmental factors and for minimizing risks for potentially lethal acute episodes mandate the identification of persons with porphyriagenic genes — persons with active porphyria and persons with latent traits not yet provoked into symptomatic or pathologic status (mainly first degree relatives of persons with diagnosed porphyria).

The following table should be helpful for categorizing patients as a preliminary guide to the selection of appropriate diagnostic tests.

Type	Prevalence Among Porphyric Persons	Dermopathy	Neuropathy	Other Indicators
Aminolevulinic acid dehydratase deficiency porphyria (ADP) RBC δ-ALA dehydratase deficiency	Very rare	None	Mild to severe	Intermittent fever, hypertension
Acute intermittent porphyria (AIP) RBC Pbg deaminase deficiency	Among most prevalent	None	Mild to severe	Intermittent fever, hypertension
Congenital erythropoietic porphyria (CEP)	Very rare	Very severe, mutilating; evidence in infancy	Possibly	Pink, red, or violet urine staining diapers
Porphyria cutanea tarda (PCT)	Among most prevalent	Mild to severe	Not usually	Siderosis
Coproporphyria (CP)	Among most prevalent	20-30% of cases; mild to severe	Mild to severe	Intermittent fever, hypertension
Variegate porphyria (VP)	Among most prevalent	Present in 75-80% of all cases	Mild to severe	Intermittent fever, hypertension
Protoporphyria (PP)	Quite rare	Mild to severe	Not usually	Abnormal liver function tests; gallstones
Acquired porphyria	Among most prevalent	In some cases, not in others	Usually	Variable; intermittent fever, hypertension

The physiologic formation and transformation of the porphyrinogens in human cells proceeds by the following steps.



The porphyrinogens of series III are precursors to heme, and the isomeric porphyrinogens of series I are metabolic by-products with no known physiologic function. Porphyrins are by-products formed by nonenzymatic oxidations of the porphyrinogens.

Pbg and the porphyrinogens with 8, 7, 6, 5, and 4 carboxyl units are excreted in the urine. Normally, the urinary porphyrinogens consist mostly of Upg and coproporphyrinogen and only small amounts of the other porphyrinogens. After renal excretion, the porphyrinogens are oxidized to the corresponding porphyrins within a few hours. The porphyrins are excreted mainly in the bile; and possibly, a portion of the porphyrinogens is excreted via this route.

With the exception of AIP, the porphyrias are characterized by accumulation of porphyrinogens and porphyrins in tissues and increased excretion of porphyrinogens and porphyrins. AIP may be characterized by episodes of increased production and urinary excretion of δ-ALA and Pbg. As shown in the table, each of the several known forms of porphyria is caused by or potentiated by an abnormally low activity of 1 of the several enzymes involved in porphyrinogen metabolism.

Condition	Mode of Inheritance	Enzyme Defect	Prominent Site(s) of Metabolic Expression
Aminolevulinic acid dehydratase deficiency porphyria (ADP)	Autosomal recessive	Aminolevulinic acid dehydratase	Liver and probably erythroid cells
Acute intermittent porphyria (AIP)	Autosomal dominant	Porphobilinogen deaminase	Liver and probably erythroid cells
Congenital erythropoietic porphyria (CEP)	Autosomal recessive	Uroporphyrinogen III cosynthase	Erythroid cells
Porphyria cutanea tarda (PCT)	Autosomal dominant	Uroporphyrinogen decarboxylase	Liver and possibly erythroid cells
Hereditary coproporphyria (HCP)	Autosomal dominant	Coproporphyrinogen oxidase	Liver and possibly erythroid cells
Variegate porphyria (VP)	Autosomal dominant	Protoporphyrinogen oxidase	Liver and possibly erythroid cells
Erythropoietic porphyria (EPP)	Autosomal dominant	Ferrochelatase	Erythroid cells and probably hepatocytes
Acquired porphyria	Not inherited	Variable and often multiple	Liver and erythroid cells

The following table is a guide for the ordering of tests to establish diagnoses of porphyrias and to establish the specific type of any individual case.

Suspected Porphyria	Recommended Tests
Acute intermittent porphyria (AIP)	During acute episodes, analysis of urine Pbg, urine porphyrins, and urine δ-ALA. Erythrocyte Pbg deaminase (uroporphyrinogen I synthase) and erythrocyte δ-ALA dehydratase may be particularly useful in family studies.
Congenital erythropoietic porphyria (CEP)	Urine porphyrins, erythrocyte porphyrins with fractionation, fecal porphyrins, and uroporphyrinogen III cosynthase in RBCs
Porphyria cutanea tarda (PCT)	Urine, fecal, and plasma porphyrins; uroporphyrinogen decarboxylase in RBCs
Coproporphyria (CP)	Fecal porphyrins; urine Pbg, δ-ALA, and porphyrins; erythrocyte Pbg deaminase and δ-ALA dehydratase may be necessary to differentiate from AIP
Variegate porphyria (VP)	Fecal porphyrins; urine Pbg, δ-ALA, and porphyrins; erythrocyte Pbg deaminase and δ-ALA dehydratase may be necessary to differentiate from AIP
Erythropoietic porphyria (EPP)	Erythrocyte porphyrins with protoporphyrins fractionation and fecal porphyrins
Acquired porphyria	*Erythrocyte porphyrins; urine Pbg, δ-ALA, and porphyrins; fecal porphyrins; δ-ALA dehydratase, Pbg deaminase, and/or uroporphyrinogen decarboxylase in RBCs may be necessary
(Pbg, porphobilinogen; δ-ALA, delta-aminolevulinic acid)	
*In some cases, the quantitation of erythrocyte zinc protoporphyrin should be included to distinguish acquired porphyria from protoporphyria.	