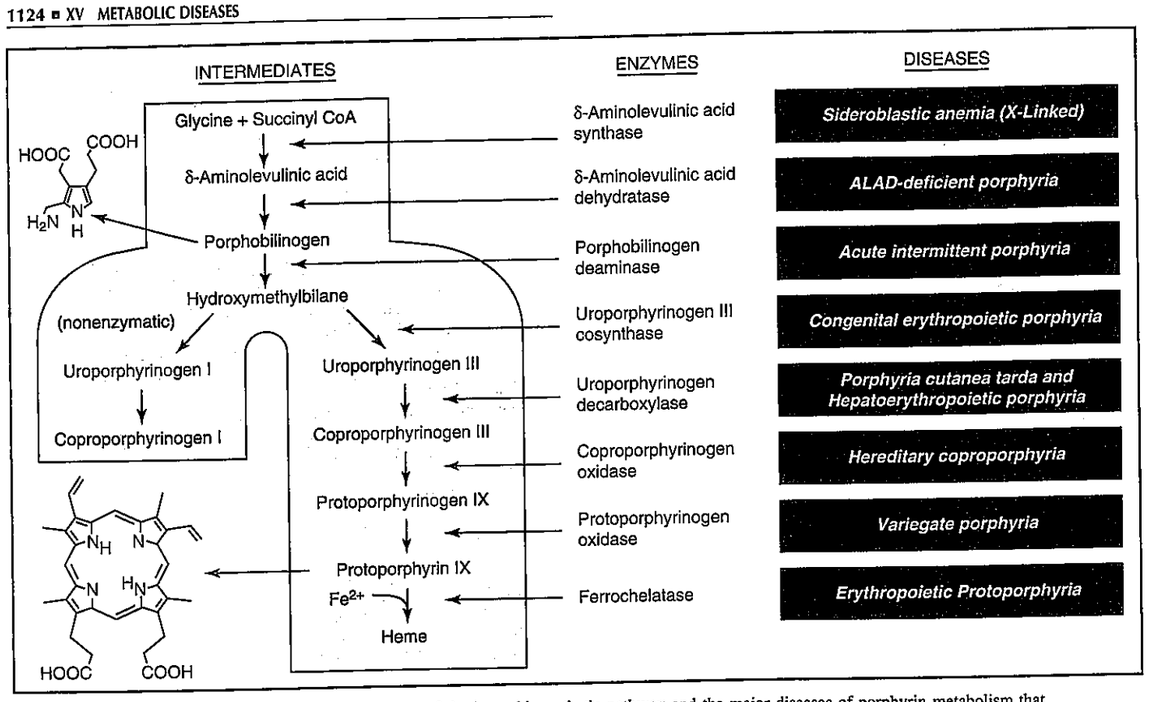

FIGURE 219–1 ■ Intermediates and enzymes of the heme biosynthetic pathway and the major diseases of porphyrin metabolism that have been associated with deficiencies of specific enzymes. The initial and last three enzymes (in red) are mitochondrial and the other four (in black) are cytosolic. Heme is synthesized from glycine and succinyl coenzyme A (CoA). Intermediates in the pathway include δ-aminolevulinic acid (an amino acid), porphobilinogen (a pyrrole), and hydroxymethylbilane (a linear tetrapyrrole). Uroporphyrinogen III cosynthase catalyzes the closure of hydroxymethylbilane, with inversion of one of the pyrroles, to form a porphyrin macrocycle, uroporphyrinogen III. (Non-enzymatic closure occurs without inversion of this pyrrole to form uroporphyrinogen I, which is not metabolized beyond coproporphyrinogen I.) The next two enzymes result in decarboxylation of six of the eight side chains of uroporphyrinogen III, with sequential formation of hepta-, hexa-, and pentacarboxyl porphyrinogens, coproporphyrinogen III, tricarboxyl porphyrinogen, and protoporphyrinogen IX. The final two enzymes catalyze the oxidation of protoporphyrinogen IX to protoporphyrin IX and the insertion of ferrous iron into the porphyrin macrocycle to form heme (iron protoporphyrin IX). With the exception of protoporphyrin IX, all porphyrin intermediates are in their reduced forms (hexahydroporphyrins or porphyrinogens). Chemical structures of two intermediates are shown.

content, which indicates that the partial deficiency of PBG deaminase does not of itself greatly impair hepatic heme synthesis or induce ALA synthase. However, when the demand for hepatic heme is increased by drugs, hormones, or nutritional factors, the deficient enzyme can become limiting for heme synthesis. Induction of hepatic ALA synthase is then accentuated and ALA and PBG accumulate in the liver and increase in plasma and urine. Excess porphyrins originate non-enzymatically from PBG or enzymatically from ALA transported to tissues other than the liver.

Most drugs that are harmful in AIP induce hepatic ALA synthase and cytochrome P-450 enzymes. Sulfonamide antibiotics are not inducers and may inhibit PBG deaminase. Reduced caloric and carbohydrate intake enhances the induction of ALA synthase in animals and in AIP can increase ALA and PBG and precipitate symptoms. Administration of carbohydrate can reduce hepatic ALA synthase and P-450 enzymes.

The mechanism of neural damage in AIP is unknown. Porphyrias and related disorders associated with increased ALA have similar neurologic manifestations. ALA is structurally analogous to γ-aminobutyric acid (GABA) and can interact with GABA receptors. However, ALA and other products of the heme pathway have not been convincingly shown to be neurotoxic. The suggestion that heme deficiency may occur in nervous tissue in these disorders is also unproved.

CLINICAL MANIFESTATIONS. Symptoms rarely occur before puberty and seldom if ever recur throughout adult life. Characteristically, attacks last for several days or longer, often require hospitalization, and are followed by complete recovery. Abdominal pain is the most common symptom, is usually steady and poorly localized, but may be cramping. Tachycardia, hypertension, restlessness, fine tremors, and excess sweating may be due to sympathetic overactivity. Other manifestations include nausea and vomiting; constipation; pain in the limbs, head, neck, or chest; muscle weakness; and sensory loss. Ileus with distention and decreased bowel sounds is common. However, increased bowel sounds and diarrhea may be seen. Because the abdominal symptoms are neurologic rather than inflammatory, tenderness, fever, and leukocytosis are generally absent or mild. Dysuria and bladder dysfunction may occur. Recurrent attacks tend to be similar in a given patient.

Peripheral neuropathy in AIP is primarily motor, results from axonal degeneration, and does not develop in all patients with acute attacks, even when abdominal symptoms are severe. Rarely, neuropathy develops apart from abdominal symptoms. Weakness most commonly begins in proximal muscles (often requiring a careful examination to detect) and more often in the arms than the legs. It can be asymmetric and focal. Tendon reflexes may be little affected or hyperactive in the early stages but are usually decreased or absent with advanced neuropathy. Cranial and sensory nerves can be affected. Progression to respiratory and bulbar paralysis and death seldom occurs unless the porphyria is not recognized, the use of harmful drugs is not discontinued, and appropriate treatment is not instituted. Sudden death, presumably from cardiac arrhythmia, may also occur.

The central nervous system can be involved. Anxiety, insomnia, depression, disorientation, hallucinations, and paranoia, which can be especially severe during acute attacks, may suggest a primary mental disorder or hysteria. Seizures may occur as an acute neurologic manifestation of AIP, as a result of hyponatremia, or secondary to causes unrelated to porphyria. Hyponatremia may be due to hypothalamic involvement and inappropriate antidiuretic hormone secretion; vomiting, diarrhea, and poor intake; or excess renal sodium loss.

After several days, an attack may resolve quite rapidly, with abdominal pain disappearing within a few hours and paresis within a few days. Attacks during the luteal phase of the menstrual cycle usually resolve with the onset of menses. Even advanced neuropathy is potentially reversible. Pain, depression, and other symptoms are sometimes chronic.

Chronic hepatic abnormalities are common in AIP, and affected patients have an increased risk of hepatocellular carcinoma (apparently not associated with hepatitis B or C). AIP may predispose to chronic hypertension and be associated with impaired renal function. The mechanisms of these associations are unknown.

PRECIPITATING FACTORS. Recognition of precipitating factors is important in management. Endogenous steroid hormones are probably most important. AIP is characterized by rarity of symptoms and excess ALA and PBG before puberty, more frequent clinical expression in women, premenstrual attacks in some women, and exacerbations after the administration of sex steroid preparations. Some patients manifest increased proportions of 5β-hydroxysteroid metabolites, which are potent inducers of hepatic ALA synthase. Recurrent cyclic attacks are troublesome in some women and occur when progesterone levels are highest. Progesterone and its metabolites are potent inducers of ALA synthase, whereas estrogens are not. Pregnancy is usually well tolerated despite high progesterone levels. Some women are more prone to attacks during pregnancy, possibly partly because of hyperemesis gravidarum and reduced caloric intake.

Drugs remain important as causes of AIP attacks. Published information is insufficient to allow most drugs to be classified as definitely harmful or safe. The major drugs known to be harmful or safe in the acute porphyrias are listed in Table 219–3. Barbiturates and sulfonamides are the most notorious. Benzodiazepines are much less hazardous. Some drugs may exacerbate porphyria cutanea tarda (PCT) but not acute porphyrias (see below). Advice can be sought from a center with experience in porphyria with regard to the use of drugs.

Reduced caloric intake, usually instituted in an effort to lose weight, is a common cause of attacks. Attacks are also provoked by intercurrent infections, major surgery, and other conditions. Cigarette smoke contains chemicals that can induce hepatic heme synthesis and may predispose to attacks. Attacks are almost always due to two or more factors acting in an additive fashion. Probably for this reason, (1) drugs may produce attacks in adults but are rarely reported to do so in children with PBG deaminase deficiency, (2) anticonvulsants do not produce attacks in some PBG deaminase–deficient subjects, and (3) barbiturate anesthetics more frequently exacerbate porphyria if symptoms are present before anesthetic exposure.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS. AIP and other acute

Table 219–1 ■ ENZYMES OF THE HEME BIOSYNTHETIC PATHWAY AND CLASSIFICATION AND INHERITANCE OF DISEASES ASSOCIATED WITH THEIR DEFICIENCIES*

ENZYME	CHROMOSOMAL LOCATION	DISEASE	INHERITANCE	CLASSIFICATIONS OF PORPHYRIAS			
				Hepatic	Erythropoietic	Acute	Cutaneous
ALA synthase							
Erythroid	Xp11.21	Sideroblastic anemia	X-linked recessive				
Non-erythroid	3p21	None known					
ALA dehydratase	9q34	δ-Aminolevulinic acid dehydratase–deficient porphyria (ADP)	Autosomal recessive	?X		X	
Porphobilinogen deaminase†	11q24.1 —> q24.2	Acute intermittent porphyria (AIP)	Autosomal dominant	X		X	
Uroporphyrinogen III cosynthase	10q25.2 —> q26.3	Congenital erythropoietic porphyria (CEP)	Autosomal recessive		X		X
Uroporphyrinogen decarboxylase	1p34	Porphyria cutanea tarda‡ (PCT)	Autosomal dominant	X			X
		Hepatoerythropoietic porphyria (HEP)	Autosomal recessive	X	X		X
Coproporphyrinogen oxidase	3q12	Hereditary coproporphyria (HCP)	Autosomal dominant	X		X	X
Protoporphyrinogen oxidase	1q22 or 23	Variegate porphyria (VP)	Autosomal dominant	X		X	X
Ferrochelatase	18q21.3 or 22	Erythropoietic protoporphyria (EPP)	Autosomal dominant		X		X

*The most precise classification is according to the specific enzyme deficiencies. Other classifications based on the major tissue site of overproduction of heme pathway intermediates (hepatic versus erythropoietic) or the type of major symptoms (acute neurovisceral versus cutaneous) are useful but not precise or mutually exclusive.
†This enzyme is also known as hydroxymethylbilane synthase and formerly as uroporphyrinogen I synthase.
‡Inherited deficiency of uroporphyrinogen decarboxylase is partially responsible for the familial (type II) form.

Table 219–2 ■ THREE MOST COMMON HUMAN PORPHYRIAS AND MAJOR DIFFERENTIATING FEATURES

DISORDER	INITIAL SYMPTOMS	EXACERBATING FACTORS	MOST IMPORTANT SCREENING TESTS	TREATMENT
Acute intermittent porphyria	Neurovisceral (acute)	Drugs (mostly P-450 inducers), progesterone, dietary restriction	Urinary porphobilinogen	Heme, glucose
Porphyria cutanea tarda	Blistering skin lesions (chronic)	Iron, alcohol, estrogens, hepatitis C virus, halogenated hydrocarbons	Plasma (or urine) porphyrins	Phlebotomy, low-dose chloroquine
Erythropoietic protoporphyria	Painful skin and swelling (mostly acute)		Plasma (or erythrocyte) porphyrins	β-Carotene