36 Disorders of Heme Biosynthesis

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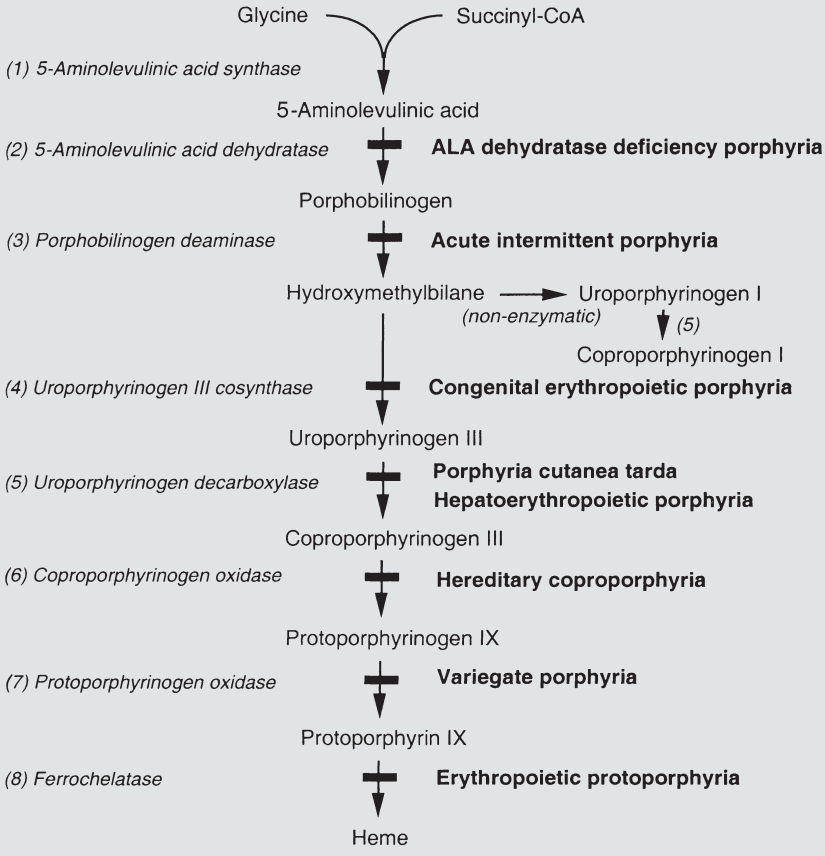
The Heme Biosynthetic Pathway

Heme (iron protoporphyrin), a metalloporphyrin with iron as the central metal atom, is the prosthetic group for many hemoproteins. It is produced mainly in the bone marrow (for hemoglobin), and in the liver (for cytochrome P450 enzymes). The pathway (◘ Fig. 36.1) consists of eight enzymes; the first and last three are mitochondrial, the other four cytosolic.

The first enzyme of the pathway, 5-aminolevulinic acid synthase (ALAS), has a housekeeping form (termed ALAS1), and an erythroid form (termed ALAS2) encoded by a separate gene on the X chromosome. ALAS1 is especially active in liver, where it is subject to negative feedback by heme, and induced by a variety of drugs, steroids and other chemicals that also induce cytochrome P450 enzymes [1, 2]. ALAS2 is induced by heme and erythropoietin but not by the factors that induce liver cytochrome P450 enzymes. This explains why such factors are important determinants of the clinical expression in hepatic porphyrias but not in erythropoietic porphyrias.

Mutations of ALAS2 are found in X-linked sideroblastic anemia. Mutations in genes for the other seven enzymes are found in the porphyrias. Deficiency of hepatic uroporphyrinogen decarboxylase, which occurs in porphyria cutanea tarda, can develop in the absence of a mutation of its gene.



◘ **Fig. 36.1.** Pathway of heme biosynthesis. Intermediates and enzymes of the heme biosynthetic pathway are listed. *ALA*, 5-aminolevulinic acid; *CoA*, coenzyme A. The porphyrias caused by the various enzyme deficiencies (indicated by *solid bars* across the arrows) are given in *bold*

X-linked sideroblastic anemia is due to a deficiency of the erythroid form of the first enzyme in the heme biosynthetic pathway, 5-aminolevulinic acid synthase. Characteristics of the disease are variable, but typically include adult onset anemia, ineffective erythropoiesis with formation of ring sideroblasts, iron accumulation and pyridoxine responsiveness.

Porphyrias are metabolic disorders due to deficiencies of other enzymes of this pathway, and are associated with striking accumulations and excess excretion of heme pathway intermediates and their oxidized products. Symptoms and signs of the porphyrias are almost all due to effects on the nervous system or skin. The three most common porphyrias, *acute intermittent porphyria*, *porphyria cutanea tarda* and *erythropoietic protoporphyria*, differ considerably from each other. The first presents with acute neurovisceral symptoms and can be aggravated by some drugs, hormones and nutritional changes, and is treated with intravenous heme and carbohydrate loading. The skin is affected in the latter two although the lesions are usually distinct and treatment is different. Porphyrias are more often manifest in adults than are most metabolic diseases. All porphyrias are inherited, with the exception of porphyria cutanea tarda, which is due to an acquired enzyme deficiency in liver, although an inherited deficiency is a predisposing factor in some cases.

36.1 X-Linked Sideroblastic Anemia

36.1.1 Clinical Presentation

Sideroblastic anemia is a variable condition and can be either acquired or inherited. Its presence is suggested by hypochromic anemia in the presence of increases in serum iron concentration and transferrin saturation. The bone marrow contains nucleated erythrocyte precursors with iron-laden mitochondria surrounding the nucleus (ring sideroblasts). Progressive iron accumulation may occur as a result of ineffective erythropoiesis, leading to organ damage.

36.1.2 Metabolic Derangement

The inherited form is due to a deficiency of the erythroid form of 5-aminolevulinic acid synthase (ALAS2). Acquired forms have been attributed to alcohol, chemotherapy and to early stages of a myelodysplastic syndrome, which might affect one or more steps in heme synthesis. However, ALAS2 mutations have not been excluded in many of these cases.

36.1.3 Genetics

X-linked sideroblastic anemia is due to mutations of the ALAS2 gene. This disorder is heterogeneous, in that multiple mutations have been described [3, 4]. Phenotypic expression is variable [5]. Point mutations may occur in the pyridoxine binding site of the enzyme, and enzyme activity may be at least partially restored and anemia corrected by high doses of this vitamin.

36.1.4 Diagnostic Tests

Hypochromic anemia with evidence of iron overload suggests this diagnosis. Ring sideroblasts in the bone marrow and pyridoxine responsiveness is further evidence. Detection of an ALAS2 mutation and demonstration of its X-linked inheritance is important for a definite diagnosis. Screening for mutations of the gene associated with hemochromatosis *(HFE)* may identify patients at greater than expected risk for iron accumulation.

36.1.5 Treatment and Prognosis

Treatment consists of administration of pyridoxine and folic acid. The starting dose of pyridoxine is 100-300 mg/day followed by a maintenance dose of 100 mg/day. Phlebotomy to remove excess iron not only prevents organ damage, which is the primary cause of morbidity in this disease, but also may increase responsiveness to pyridoxine.

36.2 Classification of Porphyrias

These metabolic disorders are due to deficiencies of heme biosynthetic pathway enzymes and characterized by accumulation and excess excretion of pathway intermediates and their oxidized products. The photosensitizing effects of excess porphyrins cause cutaneous manifestations. Neurological effects are poorly explained, but are associated with increases in the porphyrin precursors, 5-aminolevulinic acid (also known as δ-aminolevulinic acid) and porphobilinogen.

5-Aminolevulinic acid and porphobilinogen are water-soluble and are excreted almost entirely in urine, as are porphyrins with a large number of carboxyl side chains (e.g. uroporphyrin, an octacarboxyl porphyrin). Protoporphyrin (a dicarboxyl porphyrin) is not soluble in water and is excreted entirely in bile and feces. Coproporphyrin (a tetracarboxyl porphyrin) is found in both urine and bile, and its urinary excretion increases when hepatobiliary function is impaired. Most of the porphyrin intermediates are porphyrinogens (reduced porphyrins) and these undergo autooxidation if they leave the intracellular environ-

ment and are then excreted primarily as the corresponding porphyrins. 5-Aminolevulinic acid, porphobilinogen and porphyrinogens are colorless and non-fluorescent, whereas oxidized porphyrins are reddish and fluoresce when exposed to ultraviolet light [6].

The porphyrias are classified with regard to the tissue where the metabolic defect is primarily expressed (hepatic and erythropoietic porphyrias), or the clinical presentation (acute neurovisceral or cutaneous porphyrias) (◘ Table 36.1).

Acute porphyrias (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria and 5-aminolevulinic acid dehydratase porphyria) can cause acute attacks of potentially life-threatening neurovisceral symptoms (e.g. abdominal pain, neuropathy, and mental disturbances). All are associated with striking increases in 5-aminolevulinic acid, and three with increases in porphobilinogen.

Porphyrias accompanied by skin manifestations are termed *cutaneous porphyrias*. In these conditions, excitation of excess porphyrins in the skin by long-wave ultraviolet light (UV-A) leads to generation of singlet oxygen and cell damage. The two most common cutaneous porphyrias are porphyria cutanea tarda and erythropoietic protoporphyria. Variegate porphyria, and much less commonly hereditary coproporphyria, can also cause cutaneous symptoms.

Acute porphyria should be considered in patients with unexplained neurovisceral symptoms, such as abdominal pain. Diagnosis of active cases is based on measurement of porphyrin precursors and porphyrins in urine, blood and feces. Measurements of deficient enzymes and DNA methods are available for confirmation and for family studies.

36.3 Diagnosis of Porphyrias

In contrast to the nonspecific nature of symptoms, laboratory tests, if properly chosen and interpreted, can be both sensitive and specific [6]. The initial presentation determines the type of initial laboratory testing (◘ Table 36.2). In a severely ill patient with symptoms suggesting acute porphyria, it is very important to confirm or exclude this diagnosis promptly, because treatment is more successful if started soon after the onset of symptoms. Measurement of urinary porphyrin precursors (5-aminolevulinic acid and porphobilinogen) and total porphyrins is recommended when neurovisceral symptoms are suggestive of acute porphyria. Urinary porphobilinogen (and 5-aminolevulinic acid) is always markedly increased during attacks of acute intermittent porphyria but may be less increased in hereditary coproporphyria and variegate porphyria. 5-Aminolevulinic acid but not porphobilinogen is increased in 5-aminolevulinic acid dehydratase porphyria. The finding of normal levels of 5-aminolevulinic acid, porphobilinogen and total porphyrins effectively excludes all acute porphyrias as potential causes of current symptoms. Current recommendations are that all major medical centers should have capabilities for rapid screening of spot urine samples for excess porphobilinogen, and 5-aminolevulinic acid and total porphyrins be measured later on the same sample [7].

Total plasma porphyrins are increased in virtually all patients with blistering skin lesions due to porphyrias, and should be measured when a cutaneous porphyria is suspected [8, 9]. Plasma porphyrins may not be increased in all patients with the nonblistering photosensitivity found in erythropoietic protoporphyria, and measurement of erythrocyte protoporphyrin is more sensitive. Unfortunately, erythrocyte protoporphyrin is increased in many other erythrocytic disorders, and because this test lacks specificity, it does not alone confirm a diagnosis of erythropoietic protoporphyria.

Further laboratory evaluation is necessary if the initial tests are positive in order to distinguish between the different types of porphyria and establish a precise diagnosis. This is essential for management and genetic counseling.

36.4 5-Aminolevulinic Acid Dehydratase Porphyria

36.4.1 Clinical Presentation

This is the most recently described porphyria, and only 6 cases have been documented by molecular methods. Symptoms resemble those of acute intermittent porphyria, including abdominal pain and neuropathy. The disease may begin in childhood and in severe cases be accompanied by failure to thrive and anemia. Other causes of 5-aminolevulinic acid dehydratase deficiency and increased urinary 5-aminolevulinic acid need to be excluded, such as lead poisoning and hereditary tyrosinemia; these conditions can also present with symptoms resembling those in acute porphyrias.

36.4.2 Metabolic Derangement

This disorder is due to a homozygous or compound heterozygous deficiency of 5-aminolevulinic acid dehydratase, the second enzyme in the heme biosynthetic pathway (◘ Fig. 36.1). The enzyme is markedly reduced (<5% of normal) in affected individuals, and approximately half-normal in both parents, which is consistent with autosomal recessive inheritance (◘ Table 36.1). Lead poisoning can be distinguished by showing reversal of the inhibition of 5-aminolevulinic acid dehydratase in erythrocytes by the in-vitro addition of dithiothreitol. Hereditary tyrosinemia

Table 36.1. Enzyme deficiencies and classification of human porphyrias. Classifications are based on the major tissue site of overproduction of heme pathway intermediates (hepatic vs. erythropoietic) or the type of major symptoms (acute neurovisceral vs. cutaneous), but are not mutually exclusive

Disease	Enzyme	Porphyria classifications			
		Hepatic	Erythro-poietic	Acute	Cutaneous
5-Aminolevulinic acid dehydratase porphyria	*5-Aminolevulinic acid dehydratase*	? X		X	
Acute intermittent porphyria	*Porphobilinogen deaminase*[1]	X		X	
Congenital erythropoietic porphyria	*Uroporphyrinogen III cosynthase*		X		X
Porphyria cutanea tarda[2]	*Uroporphyrinogen decarboxylase*	X			X
Hepatoerythropoietic porphyria	*Uroporphyrinogen decarboxylase*	X	X		X
Hereditary coproporphyria	*Coproporphyrinogen oxidase*	X		X	X
Variegate porphyria	*Protoporphyrinogen oxidase*	X		X	X
Erythropoietic protoporphyria	*Ferrochelatase*		X		X

[1] This enzyme is also known as hydroxymethylbilane synthase, and formerly as uroporphyrinogen I synthase.
[2] Inherited deficiency of uroporphyrinogen decarboxylase is partially responsible for familial (type 2) porphyria cutanea tarda.

type 1 leads to accumulation of succinylacetone (2,3-dioxoheptanoic acid, a structural analog of 5-aminolevulinic acid and a potent inhibitor of the dehydratase, ► Chap. 18). Other heavy metals and styrene can also inhibit 5-aminolevulinic acid dehydratase.

36.4.3 Genetics

All well-documented cases were unrelated, and most had different mutations. Immunological studies to date have indicated that most mutant alleles produce a defective enzyme protein [10].

36.4.4 Diagnostic Tests

Characteristic findings include increases in urinary 5-aminolevulinic acid and coproporphyrin and erythrocyte zinc protoporphyrin, normal or slightly increased urinary porphobilinogen, and a marked decrease in erythrocyte 5-aminolevulinic acid dehydratase. Other causes of 5-aminolevulinic acid dehydratase deficiency must be excluded and the diagnosis confirmed by DNA studies [10]. The increase in urinary coproporphyrin (mostly isomer III) is probably due to metabolism of 5-aminolevulinic acid via the heme biosynthetic pathway in tissues other than the liver. Coproporphyrin III also increases in normal subjects after loading with exogenous 5-aminolevulinic acid [11]. Erythrocyte zinc protoporphyrin content is also increased, as in other homozygous cases of porphyria.

36.4.5 Treatment and Prognosis

There is little experience in treating this porphyria. In general, the approach is the same as in acute intermittent porphyria. Heme therapy was effective in most cases. It is prudent to avoid drugs that are harmful in other acute porphyrias.

36.5 Acute Intermittent Porphyria

36.5.1 Clinical Presentation

Symptoms appear during adult life and are more common in women than in men. Acute attacks of neurovisceral symptoms and signs are the most common presentation, although subacute and chronic manifestations can also occur. Attacks usually last for several days or longer, often require hospitalization, and are usually followed by complete recovery. Severe attacks may be much more prolonged and are sometimes fatal, especially if the diagnosis is delayed. Abdominal pain, the most common symptom, is usually steady and poorly localized, but is sometimes crampy. Tachycardia, hypertension, restlessness, fine tremors, and excess sweating suggest sympathetic overactivity. Nausea, vomiting, constipation, pain in the limbs, head, neck or chest, muscle weakness and sensory loss are also common. Dysuria, bladder dysfunction and ileus, with abdominal distention and decreased bowel sounds, may occur. However, increased bowel sounds and diarrhea are sometimes seen. Because the abdominal symptoms are neurological

rather than inflammatory, tenderness, fever and leukocytosis are characteristically mild or absent. A peripheral neuropathy that is primarily motor can develop, and is manifested by muscle weakness that most often begins proximally in the upper extremities. It may progress to involve all extremities, respiratory muscles and even lead to bulbar paralysis. Tendon reflexes may be little affected or hyperactive in early stages, but are usually decreased or absent with advanced neuropathy. Muscle weakness is sometimes focal and asymmetric. Cranial and sensory nerves can be affected. Advanced motor neuropathy and death are rare unless porphyria is not recognized and appropriate treatment not instituted. Seizures may occur as an acute neurological manifestation of acute porphyrias, as a result of hyponatremia, or due to other causes unrelated to porphyria. Hyponatremia can be due to electrolyte depletion from vomiting or diarrhea, poor intake, renal sodium loss, or inappropriate antidiuretic hormone secretion. Persistent hypertension and impaired renal function may occur over the long term. Chronic abnormalities in liver function tests, particularly transaminases, are common, although few patients develop significant hepatic impairment. The risk of hepatocellular carcinoma is increased in this and other acute porphyrias, as well as in porphyria cutanea tarda [6, 12, 13].

36.5.2 Metabolic Derangement

Acute intermittent porphyria (AIP) is due to mutations that lead to loss of activity of porphobilinogen deaminase (also known as hydroxymethylbilane synthase and formerly as uroporphyrinogen I synthase), the third enzyme in the heme biosynthetic pathway (◘ Fig. 36.1, ◘ Table 36.1). Inheritance is autosomal dominant, and the residual ~50% enzyme activity is mostly due to enzyme produced from the normal allele. Most heterozygotes remain asymptomatic with normal levels of urinary porphyrin precursors. When the disease is clinically expressed, accumulation of heme pathway intermediates in liver leads to increased excretion primarily in urine.

Apparently, the partial deficiency of porphobilinogen deaminase does not of itself greatly impair hepatic heme synthesis. However, when drugs, hormones, or nutritional factors increase the demand for hepatic heme, the deficient enzyme can become limiting. Induction of hepatic ALAS1 is then accentuated and 5-aminolevulinic acid and porphobilinogen accumulate. Excess porphyrins originate nonenzymatically from porphobilinogen, and perhaps enzymatically from 5-aminolevulinic acid transported to tissues other than the liver.

Most drugs that are harmful to patients with this and other acute hepatic porphyrias are known to have the capacity to induce the synthesis of cytochrome P450 enzymes and ALAS1 in the liver [2].

36.5.3 Genetics

More than 200 different mutations of the porphobilinogen deaminase gene have been identified in unrelated families [14]. The gene has two promoters, one of which is erythroid-specific. Erythroid-specific and housekeeping forms of this enzyme are derived from the same gene by alternative splicing of two primary transcripts. Most mutations in AIP lead to a deficiency of both isozymes. Mutations located in or near the first of the 15 exons in this gene can impair the synthesis of the housekeeping form but not the erythroid-specific form of porphobilinogen deaminase. Homozygous cases of acute intermittent porphyria are extremely rare, but should be suspected particularly if the disease is active early in childhood [15].

36.5.4 Diagnostic Tests

A substantial increase in urinary porphobilinogen is a sensitive and specific indication that a patient has either acute intermittent porphyria, hereditary coproporphyria or variegate porphyria (◘ Table 36.2). A kit is available for the rapid detection of porphobilinogen at concentrations greater than 6 mg/l with a color chart for semiquantitative estimation of higher levels [16]; this enables major medical centers to provide for rapid in-house testing for these disorders [7]. Porphobilinogen remains increased between attacks of acute intermittent porphyria and becomes normal only after prolonged latency. Fecal total porphyrins are generally normal or minimally increased in acute intermittent porphyria, and markedly increased in the other two conditions. Total plasma porphyrins are charactistically increased in variegate porphyria, as discussed later, but are normal or only slightly increased in acute intermittent porphyria. Urinary porphyrins, and particularly coproporphyrin is generally more increased in hereditary coproporphyria and variegate porphyria. Urinary uroporphyrin can be increased in all of these disorders, especially when porphobilinogen is increased.

Decreased erythrocyte porphobilinogen deaminase helps to confirm a diagnosis of acute intermittent porphyria. However, falsely low activity may occur if there is a problem with processing or storing the sample. The erythrocyte enzyme is not deficient in all patients because some mutations of the porphobilinogen deaminase gene only reduce the housekeeping form of the enzyme. Furthermore, erythrocyte porphobilinogen deaminase has a wide normal range (up to 3-fold) that overlaps the range of patients with acute intermittent porphyria.

Measuring erythrocyte porphobilinogen deaminase is very useful for detecting asymptomatic carriers, if it is known that the propositus has a deficiency of the erythrocyte enzyme. Urinary porphobilinogen should also be measured when relatives are screened for this porphyria.

Table 36.2. First-line laboratory tests for screening for porphyrias and second-line tests for further evaluation when initial testing is positive

Testing	Symptoms suggesting porphyria	
	Acute neurovisceral symptoms	Cutaneous photosensitivity
First-line	Urinary 5-aminolevulinic acid, porphobilinogen and total porphyrins[1] (quantitative; random or 24 h urine).	*Blistering skin lesions*: Total plasma porphyrins[2] *Nonblistering*: Erythrocyte porphyrins[3]
Second-line	Total fecal porphyrins[1] Erythrocyte porphobilinogen deaminase Total plasma porphyrins[2]	Urinary 5-aminolevulinic acid, porphobilinogen and total porphyrins[1] Total fecal porphyrins[1]

[1] Fractionation of urinary and fecal porphyrins is usually not helpful unless the total is increased.
[2] The preferred method is by direct fluorescence spectrophotometry.
[3] Erythrocyte porphyrins are generally expressed as protoporphyrin, however the method detects other porphyrins as well. This test lacks specificity, because erythrocyte protoporphyrin is increased in many erythrocytic disorders.

Identification of the specific mutation in a known case enables the same mutation to be detected in relatives, most of whom are likely to be asymptomatic and can then be advised to take precautions to avoid exacerbating the disease.

36.5.5 Treatment and Prognosis

Intravenous hemin (heme arginate or hematin) is considered specific therapy for acute attacks because it represses hepatic ALAS1, and markedly reduces levels of 5-aminolevulinic acid and porphobilinogen. Severe attacks, with features such as nausea, vomiting, motor weakness and hyponatremia should be treated initially with hemin. Carbohydrate loading, usually accomplished by intravenous administration of 10% glucose, also has some repressive effect on ALAS1, but is much less effective. Glucose may be started initially until hemin is obtained. Heme arginate is the preferred form of hemin [17]. Degradation products of hematin (heme hydroxide) commonly cause phlebitis at the site of infusion and a transient anticoagulant effect. In countries where heme arginate is not available, hematin can be reconstituted with human albumin to stabilize the heme as heme albumin, which confers many of the advantages of heme arginate [18].

The standard regimen for hemin is 3–4 mg per kg body weight infused intravenously once daily for 4 days. Treatment of a newly diagnosed patient should be started only after a marked increase in urinary porphobilinogen is demonstrated using a rapid and reliable method. Recurrent attacks can be diagnosed on clinical grounds, since porphobilinogen remains elevated in most AIP patients between attacks, and the presenting signs and symptoms are often similar from one attack to the next. A longer course of treatment is seldom necessary if treatment is started early. Efficacy is reduced and recovery less rapid when treatment is delayed and neuronal damage is more advanced. Heme therapy is not effective for chronic symptoms of acute porphyrias [19].

Most acute attacks are severe enough to require hospitalization for administration of intravenous hemin and observation for neurological complications and electrolyte imbalances. Narcotic analgesics are commonly required for abdominal, back or extremity pain, and small doses of a phenothiazine are useful for nausea, vomiting, anxiety, and restlessness. Chloral hydrate can be administered for insomnia. Diazepam in low doses is safe if a minor tranquilizer is required, although it needs to be kept in mind that benzodiazepines have some inducing effect on hepatic heme synthesis and may act in an additive fashion to other inducing influences. Bladder distention may require catheterization.

Carbohydrate loading can be tried instead of hemin for mild attacks. At least 300 g daily is recommended, and >500 g daily may be more effective. Carbohydrate can sometimes be given orally. However, nausea, vomiting and ileus usually prevent this approach. More complete parenteral nutrition should be considered for patients when oral intake is not possible for more than several days.

Abdominal pain may disappear within hours, and paresis begin to improve within days. Muscle weakness due to severe motor neuropathy may gradually resolve, but there may be some residual weakness.

Treatment of seizures is problematic, because almost all anticonvulsant drugs can exacerbate acute porphyrias. Bromides, gabapentin and probably vigabatrin can be given safely [20]. β–Adrenergic blocking agents may control tachycardia and hypertension in acute attacks of porphyria, but do not have a specific effect on the underlying pathophysiology [19].

An allogeneic liver transplant in a woman with severe, recurrent attacks of acute intermittent porphyria led to complete biochemical and clinical remission [21]. This experience supports the role of hepatic overproduction of

porphyrin precursors in causing the neurological manifestations, but is not sufficient evidence for broad application of hepatic transplantation for acute porphyrias [7].

Identification and correction of precipitating factors such as certain drugs, inadequate nutrition, cyclic or exogenous hormones (particularly progesterone and progestins), and intercurrent infections can hasten recovery from an attack and prevent future attacks. Frequent cyclic attacks occurring in some women during the luteal phase of the cycle when progesterone levels are highest can be prevented by administration of a gonadotropin-releasing hormone analogue to prevent ovulation [22].

With prompt treatment of acute attacks and precautions to prevent further attacks, the outlook for patients with acute porphyrias is usually excellent. Fatal attacks have become much less common [12]. However, some patients continue to have attacks in the absence of identifiable precipitating factors. Some develop chronic pain and other symptoms, and may become addicted to narcotic analgesics. Such patients need to be followed closely because there is often coexistent depression and an increased risk of suicide.

36.6 Congenital Erythropoietic Porphyria (Gunther Disease)

36.6.1 Clinical Presentation

This is usually a severe disease with manifestations noted soon after birth, or even in utero. But clinical expression is variable and is determined in part by the degree of enzyme deficiency. Cutaneous features resemble those in porphyria cutanea tarda but in most cases are much more severe. Lesions include bullae and vesicles on sun-exposed skin, hypo- or hyperpigmented areas, hypertrichosis, and scarring. The teeth are reddish brown (erythrodontia) because of porphyrin deposition, and may fluoresce when exposed to long-wave ultraviolet light. Porphyrins are also deposited in bone. Hemolysis is almost invariably present and results from the markedly increased erythrocyte porphyrin levels, and is accompanied by splenomegaly. Life expectancy is often shortened by infections or hematological complications. There are no neurological manifestations.

Congenital erythropoietic porphyria can present in utero as nonimmune hydrops [23]. When this is recognized, intrauterine transfusion is possible, and after birth severe photosensitivity can be prevented by avoiding phototherapy for hyperbilirubinemia. Rarely, the disease develops in adults, and is associated with a myeloproliferative disorder.

36.6.2 Metabolic Derangement

This rare disorder is due to a severe deficiency of uroporphyrinogen III cosynthase, the fourth enzyme of the heme synthesis pathway (◘ Fig. 36.1, ◘ Table 36.1). Hydroxymethylbilane (the substrate of the deficient enzyme) accumulates and is converted nonenzymatically to uroporphyrinogen I, a nonphysiological intermediate, which cannot be metabolized to heme. Therefore, uroporphyrin, coproporphyrin and other porphyrins accumulate in bone marrow, plasma, urine, and feces. Porphyrin accumulation in erythroid cells results in intramedullary and intravascular hemolysis, which leads to increased erythropoiesis. As a result, heme synthesis is actually increased in spite of the inherited enzyme deficiency, in order to compensate for porphyrin-induced hemolysis. Although the porphyrins that accumulate in this disease are primarily type I porphyrin isomers, type III isomers are also increased.

36.6.3 Genetics

Congenital erythropoietic porphyria is an autosomal recessive disorder. Patients have either homozygous or compound heterozygous mutations of the uroporphyrinogen III cosynthase gene. Like other porphyrias, this disease is genetically heterogeneous, and many different mutations have been identified [24]. Parents and other heterozygotes display intermediate deficiencies of the cosynthase. The disease can be diagnosed in utero by porphyrin measurements and DNA methods. Expansion of a clone of erythroid cells that carry a uroporphyrinogen III cosynthase mutation often accounts for adult-onset cases.

36.6.4 Diagnostic Tests

Erythrocyte and plasma porphyrins are markedly increased and usually consist mostly of uroporphyrin I. Coproporphyrin and even zinc protoporphyrin may be increased in erythrocytes. Porphyrins in urine are primarily uroporphyrin I and coproporphyrin I, and in feces mostly coproporphyrin I. Porphyrin precursors are not increased. The diagnosis should be confirmed by finding a marked deficiency in uroporphyrinogen III cosynthase activity and by mutation analysis.

36.6.5 Treatment and Prognosis

Protection of the skin from sunlight is essential. Minor trauma can lead to denudation of fragile skin. Bacterial infections should be treated promptly to prevent scarring and mutilation. Improvement in hemolysis has been reported after splenectomy. Oral charcoal may be helpful by

increasing fecal excretion of porphyrins. High level blood transfusions and hydroxyurea may be effective by suppressing erythropoiesis and porphyrin synthesis [25, 26]. Bone marrow or stem cell transplantation is effective current therapy, and gene therapy may eventually be possible [27, 28].

36.7 Porphyria Cutanea Tarda

36.7.1 Clinical Presentation

This is the most common and readily treated form of porphyria and is manifested primarily by chronic, blistering skin lesions, especially on the backs of the hands, forearms, face and (in women) the dorsa of the feet. Neurological effects are not observed. Sun-exposed skin is also friable, and minor trauma may precede the formation of bullae or cause denudation of the skin. Small white plaques (milia) may precede or follow vesicle formation. Hypertrichosis and hyperpigmentation are also noted. Thickening, scarring and calcification of affected skin may be striking, and is referred to as pseudoscleroderma. Skin lesions are indistinguishable clinically from all other cutaneous porphyrias, except for erythropoietic protoporphyria (► later discussion). In pseudoporphyria, skin lesions resemble porphyria cutanea tarda but porphyrins are not significantly increased; presumably other photosensitizers are responsible.

Multiple susceptibility factors for porphyria cutanea tarda are commonly identified in an individual patient. A normal or increased amount of hepatic iron is a requirement for the disease. Others include moderate or heavy alcohol intake, hepatitis C infection, estrogen use and smoking. Infection with HIV is a less common association. There are geographic differences in the association with hepatitis C; in some locations more than 80% of patients are infected with this virus.

A large outbreak of this porphyria occurred in eastern Turkey in the 1950s from ingestion of wheat that was intended for planting, and had been previously treated with hexachlorobenzene as a fungicide. Porphyria cutanea tarda has been reported after exposure to other chemicals including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin). These halogenated polycyclic aromatic hydrocarbons induce an experimental porphyria in laboratory animals that biochemically closely resembles human porphyria cutanea tarda. Such toxic exposures are not evident in most human cases of sporadic porphyria cutanea tarda [29, 30].

36.7.2 Metabolic Derangement

This porphyria is caused by a profound deficiency of hepatic uroporphyrinogen decarboxylase, the fifth enzyme of the heme biosynthetic pathway (◘ Fig. 36.1, ◘ Table 36.1). Sporadic (type 1) and familial (types 2 and 3) forms of the disease have been described. These do not differ substantially in terms of clinical features or treatment. In all cases, a specific inhibitor of hepatic uroporphyrinogen decarboxylase, which has not yet been characterized, is generated from an intermediate of the heme biosynthetic pathway by an iron-dependent oxidative mechanism. Certain cytochrome P450 enzymes and low levels of ascorbic acid and carotenoids may contribute to this oxidative process within hepatocytes. The prevalence of HFE mutations is increased [30]. Individuals with type 2 disease from birth have half the normal enzyme activity and are therefore more susceptible to developing a more profound enzyme deficiency in the liver [29].

Patterns of excess porphyrins in this disease are complex and characteristic. Uroporphyrinogen, (an octacarboxyl porphyrinogen) undergoes a sequential, four-step decarboxylation to coproporphyrinogen (a tetracarboxyl porphyrinogen). Uroporphyrinogen and the hepta-, hexa-, and pentacarboxyl porphyrinogens accumulate. To complicate the porphyrin pattern further, pentacarboxyl porphyrinogen can be metabolized by coproporphyrinogen oxidase to a tetracarboxyl porphyrinogen termed isocoproporphyrinogen. These porphyrinogens accumulate first in liver, are mostly oxidized to the corresponding porphyrins, and then appear in plasma and are excreted in urine, bile and feces. Successful treatment may require some time before the massive porphyrin accumulations in liver are cleared.

36.7.3 Genetics

Porphyria cutanea tarda results from a liver-specific, apparently acquired deficiency of uroporphyrinogen decarboxylase. No mutations in this gene have been found in sporadic (type 1) porphyria cutanea tarda. The amount of hepatic uroporphyrinogen decarboxylase protein in type 1 disease, as measured immunochemically, is normal, as might be expected with an inhibitor of the enzyme.

An inherited partial deficiency of this enzyme contributes in type 2, which accounts for approximately 20% of patients with porphyria cutanea tarda. In these cases erythrocyte uroporphyrinogen decarboxylase is approximately 50% of normal in erythrocytes, and this feature is inherited as an autosomal dominant trait affecting all tissues. Type 2 becomes clinically manifest when hepatic uroporphyrinogen decarboxylase becomes profoundly inhibited, as in type 1. A number of mutations of the uroporphyrinogen decarboxylase gene have been identified in type 2 disease. Cases classified as type 3 disease, which are rare, have normal erythrocyte uroporphyrinogen decarboxylase activity but one or more relatives also have the disease. A genetic defect has not been clearly identified in type 3, and it is

possible that these cases are not fundamentally different from type I [29].

36.7.4 Diagnostic Tests

Blistering skin lesions are found in all cutaneous porphyrias, except erythropoietic protoporphyria. Skin histopathology is not specific and does not establish a diagnosis of porphyria cutanea tarda or exclude pseudoporphyria. It is important to differentiate these conditions by laboratory testing before starting therapy.

Plasma porphyrins are increased in all patients with blistering skin lesions due to porphyria. The fluorescence spectrum of plasma porphyrins can readily distinguish variegate porphyria and erythropoietic protoporphyria from porphyria cutanea tarda (◘ Table 36.2). The diagnosis is best confirmed by increased total urinary porphyrins with a predominance of uroporphyrin and heptacarboxyl porphyrin. Total fecal porphyrins are usually less increased than in hereditary coproporphyria and variegate porphyria. In porphyria cutanea tarda, an increase in the proportion of fecal isocoproporphyrin, which can be expressed as a ratio to coproporphyrin, is distinctive.

36.7.5 Treatment and Prognosis

Repeated phlebotomy is standard treatment at most centers, although low-dose hydroxychloroquine (or chloroquine) is also effective. Patients are also advised to discontinue alcohol, estrogens, iron supplements, and other contributing factors. Phlebotomies remove iron and stimulate erythropoiesis, and utilization of storage iron for hemoglobin formation gradually reduces the serum ferritin to a target range of 15–20 ng/ml. This can usually be achieved by removal of only 5–6 units (450 ml each) of blood at 1–2 week intervals. Further iron depletion is of no additional benefit and may cause anemia and associated symptoms. Many more phlebotomies may be needed in patients who have marked iron overload, which is likely to be due to familial hemochromatosis. The plasma or serum porphyrin level falls somewhat more slowly than ferritin, and may not yet be normal when the target ferritin level is reached.

With treatment the activity of hepatic uroporphyrinogen decarboxylase gradually increases to normal. After remission, ferritin can return to pretreatment values without recurrence, in most cases. Postmenopausal women who have been treated for porphyria cutanea tarda can usually resume estrogen replacement without recurrence. Relapses seem to be more common in patients who resume alcohol intake, but will respond to further phlebotomies.

A low dose of hydroxychloroquine (100 mg twice weekly) or chloroquine (125 mg twice weekly) for several months gradually removes excess porphyrins from the liver. This is a suitable alternative when phlebotomy is contraindicated or difficult, and is preferred at some centers. Standard doses of these 4-aminoquinolines exacerbate photosensitivity and cause hepatocellular damage, and should not be used. Both may produce retinal damage, although this risk is very low, and may be lower with hydroxychloroquine than chloroquine. The mechanism by which these drugs remove porphyrins from the liver in this condition is not known [31]. This treatment is not effective in other porphyrias [19].

36.8 Hepatoerythropoietic Porphyria

36.8.1 Clinical Presentation

This rare disease is clinically similar to congenital erythropoietic porphyria and usually presents with red urine and blistering skin lesions shortly after birth. Mild cases may present later in life and more closely resemble porphyria cutanea tarda. Concurrent conditions, such as viral hepatitis, may accentuate porphyrin accumulation.

36.8.2 Metabolic Derangement

Hepatoerythropoietic porphyria is the homozygous form of familial (type 2) porphyria cutanea tarda, and is due to a substantial deficiency of uroporphyrinogen decarboxylase. Intermediate deficiencies of the enzyme are found in the parents, as expected for an autosomal recessive disorder (◘ Fig. 36.1, ◘ Table 36.1). The disease has features of both hepatic and erythropoietic porphyrias.

36.8.3 Genetics

This porphyria results from a homozygous or compound heterozygous state for mutations of the gene encoding uroporphyrinogen decarboxylase. The disease is genetically heterogeneous. Mutations found in this disease generally result in marked decreases in uroporphyrinogen decarboxylase activity, but some activity remains, so heme formation can occur [30].

36.8.4 Diagnostic Tests

The excess porphyrins found in urine, plasma and feces are similar to those in porphyria cutanea tarda. In addition, erythrocyte zinc protoporphyrin is increased, as in a number of other autosomal recessive porphyrias. This finding probably reflects an earlier accumulation of uroporphyrinogen in erythroblasts, which after completion of hemoglobin synthesis is metabolized to protoporphyrin.

Erythrocyte porphyrins in congenital erythropoietic porphyria are usually mostly uroporphyrin I and coproporphyrin I, but in some cases there is a predominance of zinc protoporphyrin. Hepatoerythropoietic porphyria is differentiated from congenital erythropoietic porphyria also by excess isocoproporphyrins in feces and urine, and by decreased erythrocyte uroporphyrinogen decarboxylase activity. It is important to document the diagnosis by molecular methods.

36.8.5 Treatment and Prognosis

Therapeutic options are essentially the same as in congenital erythropoietic porphyria.

36.9 Hereditary Coproporphyria and Variegate Porphyria

36.9.1 Clinical Presentation

These disorders can present with acute attacks that are identical to those in acute intermittent porphyria. However, unlike the latter disease, variegate porphyria and more rarely hereditary coproporphyria may cause blistering skin lesions that are indistinguishable from those of porphyria cutanea tarda. Symptoms are most common after puberty. Factors that exacerbate acute intermittent porphyria are important in both of these porphyrias. Variegate porphyria is particularly common in South Africa where most cases are descendants of a couple who emigrated from Holland and arrived in Cape Town in 1688 [32]. In rare homozygous cases of these porphyrias clinical manifestations begin in childhood.

36.9.2 Metabolic Derangement

Hereditary coproporphyria and variegate porphyria result from approximately 50% deficiencies of coproporphyrinogen oxidase and of protoporphyrinogen oxidase, respectively, which are the sixth and seventh enzyme of the heme biosynthetic pathway (◘ Fig. 36.1, ◘ Table 36.1). In hereditary coproporphyria there is marked accumulation of coproporphyrin III (derived from autooxidation of coproporphyrinogen III), and urinary porphyrin precursors and uroporphyrin are increased particularly in association with acute attacks. Similar abnormalities are seen in variegate porphyria, but in addition protoporphyrin (derived from autooxidation of protoporphyrinogen) is increased in feces (and bile), and plasma porphyrins are increased. Protoporphyrinogen has been shown to inhibit porphobilinogen deaminase, which along with induction of hepatic ALAS1, may account for the increase in porphyrin precursors during acute attacks, at least in variegate porphyria.

36.9.3 Genetics

Both of these porphyrias are autosomal dominant conditions. Homozygous cases are rare. Genetic heterogeneity is a feature of both. As expected, a single mutation (R59W) accounts for the many descendants with variegate porphyria in South Africa, which is an example of the founder effect [32].

36.9.4 Diagnostic Tests

Urinary 5-aminolevulinic acid and porphobilinogen are increased during acute attacks of these porphyrias, although the increases may be less and more transient than in acute intermittent porphyria. Urinary coproporphyrin increases may be more prominent and prolonged. However, coproporphyrinuria is a highly nonspecific finding. It can be seen in many medical conditions, especially when hepatic or bone marrow function is affected.

A marked, isolated increase in fecal coproporphyrin (especially isomer III) is distinctive for hereditary coproporphyria. Fecal coproporphyrin and protoporphyrin are about equally increased in variegate porphyria. An increase in fecal pseudo-pentacarboxyl porphyrin, which is a dicarboxyl porphyrin derived from protoporphyrin, is also diagnostically useful in variegate porphyria.

Increased plasma porphyrins and a fluorescence spectrum of plasma porphyrins (at neutral pH) is characteristic and very useful for rapidly distinguishing variegate porphyria from the other porphyrias. This is at least as sensitive as fecal porphyrin measurement for detecting variegate porphyria, although not as sensitive as a reliable assay for lymphocyte protoporphyrinogen oxidase or mutation analysis [33, 34].

Reliable assays for protoporphyrinogen oxidase and coproporphyrinogen oxidase in cultured fibroblasts or lymphocytes are available only in a few research laboratories. Erythrocytes cannot be used to measure these mitochondrial enzymes, because mature erythrocytes do not contain mitochondria. As in other porphyrias, identification of a mutation in an index case facilitates detection of relatives who carry the same mutation.

36.9.5 Treatment and Prognosis

Acute attacks are treated as in acute intermittent porphyria (▶ above). Cutaneous symptoms are more difficult to treat, and therapies that are effective for porphyria cutanea tarda (phlebotomy and low-dose hydroxychloroquine) are not effective in these conditions. Protection from sunlight is important.

36.10 Erythropoietic Protoporphyria

36.10.1 Clinical Presentation

Erythropoietic protoporphyria is the third most common porphyria. Cutaneous symptoms begin in childhood, and are generally much more prominent than objective changes by examination. Symptoms such as burning, itching, erythema, and swelling can occur within minutes of sun exposure, and the diffuse edema of sun-exposed areas may resemble angioneurotic edema. Other more chronic skin changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes. In contrast to other cutaneous porphyrias, blistering, milia, friability, and chronic skin changes such as scarring and hypertrichosis are not prominent. There is no fluorescence of the teeth and no neuropathic manifestations. Mild anemia with hypochromia and microcytosis is noted in some cases.

The severity of the symptoms is remarkably stable over time. Drugs that exacerbate hepatic porphyrias are not known to worsen this disease, although they are generally avoided as a precaution. Gallstones containing protoporphyrin may also develop. Some patients develop liver disease, which can progress rapidly to death from hepatic failure. This complication is accompanied by marked deposition of protoporphyrin in liver and increased levels in plasma and erythrocytes. A motor neuropathy may further complicate the course of liver decompensation in this disease, and is unexplained [35].

36.10.2 Metabolic Derangement

The inherited deficiency of ferrochelatase, the eighth and last enzyme in the heme biosynthetic pathway (◘ Fig. 36.1, ◘ Table 36.1) leads to increases in protoporphyrin in bone marrow, circulating erythrocytes, plasma, bile, and feces in this disease. Ferrochelatase is deficient in all tissues, but the deficient enzyme is rate-limiting for protoporphyrin metabolism primarily in bone marrow reticulocytes, which are the primary source of the excess protoporphyrin. Circulating erythrocytes and perhaps the liver contribute smaller amounts. Excess protoporphyrin is transported in plasma and excreted in bile and feces.

Erythrocyte protoporphyrin is mostly chelated with zinc in normal erythrocytes as well as in many other conditions where protoporphyrin in increased (e.g. lead poisoning, iron deficiency, and homozygous forms of porphyria). Formation of both heme and zinc protoporphyrin is catalyzed by ferrochelatase. Protoporphyrin accumulates mostly as free protoporphyrin in protoporphyria, because this enzyme is deficient. Free protoporphyrin diffuses more readily from erythrocytes into plasma than does zinc protoporphyrin, most of which remains in the erythrocyte for its full life span. Therefore, primarily reticulocytes and young circulating erythrocytes fluoresce when observed under long wave ultraviolet light.

Protoporphyrin is excreted in bile and may undergo enterohepatic circulation. Liver protoporphyrin content is not increased in uncomplicated protoporphyria. But large amounts of protoporphyrin derived primarily from the bone marrow can cause cholestasis and severe liver failure in some patients with protoporphyria.

36.10.3 Genetics

Many different mutations in the ferrochelatase gene have been identified in protoporphyria, and most express little or no ferrochelatase. The pattern of inheritance is best described as autosomal dominant, in that the primary inherited determinant of the disease in most families is a severe, disabling ferrochelatase mutation. As proposed in 1984, and supported by recent molecular evidence, most patients with clinically manifest disease have also inherited a normal, weakly expressed ferrochelatase allele [36-38]. This polymorphic allele, which expresses an aberrantly spliced mRNA that is subject to rapid degradation, is found in ~10% of normal Caucasians, and has no consequence in the absence of a mutant ferrochelatase allele that results in little or no enzyme activity [38]. Therefore, ferrochelatase activity is only 10-25% of normal in patients with manifest disease, rather than the expected ~50% for autosomal dominant inheritance, and many heterozygotes in a family have higher enzyme activity and no increase in erythrocyte protoporphyrin. Autosomal recessive inheritance, with two disabling mutations has been documented in a few families, where at least one of the two mutant ferrochelatase alleles expresses some enzyme activity [35].

36.10.4 Diagnostic Tests

The most sensitive screening test for this disorder is a determination of erythrocyte protoporphyrin, which under most circumstances is the predominant porphyrin in erythrocytes. This test lacks specificity because standard assays reflect all porphyrins that might be increased in many diseases, including free protoporphyrin (in protoporphyria), zinc protoporphyrin (in iron deficiency, lead poisoning, most homozygous cases of porphyria, and many other erythrocyte disorders), and very rarely uroporphyrin I and coproporphyrin I (in congenital erythropoietic porphyria). To gain specificity for protoporphyria, an increased erythrocyte protoporphyrin result is followed by a determination whether the protoporphyrin is free or complexed with zinc, using a simple ethanol extraction method.

The plasma porphyrin concentration is almost always increased, but less so than in other cutaneous porphyrias. Moreover, the excess protoporphyrin in plasma in this con-

dition is particularly sensitive to light exposure, which may increase the chance of a falsely normal measurement. It is especially important to shield plasma samples from light if protoporphyria is suspected. The fluorescence spectrum of plasma porphyrins at neutral pH can distinguish erythropoietic protoporphyria from other porphyrias.

Total fecal porphyrins may be normal or increased in protoporphyria, with a predominance of protoporphyrin. Urinary porphyrins and porphyrin precursors are normal, unless the patient has liver impairment, in which case urinary porphyrins (especially coproporphyrin) may increase. Hepatic complications of the disease are often preceded by increasing levels of erythrocyte and plasma protoporphyrin, abnormal liver function tests, marked deposition of protoporphyrin in liver cells and bile canaliculi, and increased photosensitivity.

36.10.5 Treatment and Prognosis

Photosensitivity is managed by avoidance of sunlight. Oral β-carotene and cysteine improve tolerance to sunlight in some patients, perhaps by quenching singlet oxygen or free radicals. β-Carotene seems to be more effective in erythropoietic protoporphyria than in other cutaneous porphyrias. Cholestyramine may reduce protoporphyrin levels by interrupting its enterohepatic circulation. Iron deficiency, caloric restriction, and drugs or hormone preparations that impair hepatic excretory function should be avoided.

Treatment of liver complications is difficult. Transfusions or heme therapy may suppress erythroid and hepatic protoporphyrin production. Liver transplantation is sometimes required, but there is some risk that the new liver will also accumulate excess protoporphyrin and develop impaired function [39]. Operating room lights have produced severe skin and peritoneal burns in some patients with protoporphyria, liver failure, and marked increases in erythrocyte and plasma protoporphyrin concentrations. A patient with erythropoietic protoporphyria who underwent bone marrow transplantation for leukemia experienced complete remission of the porphyria [40]. Therefore, there is potential benefit from bone marrow replacement and gene therapy in this and other erythropoietic porphyrias [35].

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