46 - 428 The Porphyrias

428 The Porphyrias

TREATMENT Wilson’s Disease COPPER CHELATION The era of successful treatment of Wilson’s disease began with the use of British anti-lewisite (BAL) by a defined regimen of intramuscular injections. An orally administered alternative was d-penicillamine (Cuprimine), a free thiol that binds copper. This chelating drug does not formally correct the basic defect of impaired copper excre tion in the bile. However, it greatly enhances urinary excretion of copper and thereby corrects and prevents copper overload and its effects. Pyridoxine (vitamin B6) is usually prescribed concomitantly to counter the tendency for deficiency of this vitamin to develop during chronic penicillamine administration. PART 12 Endocrinology and Metabolism Certain individuals are intolerant of penicillamine, however, encountering significant side effects that include nephrotoxicity, hematologic abnormalities, and a distinctive rash, elastosis perforans serpiginosa (usually involving the neck and axillae). Furthermore, in some Wilson’s disease patients with neurologic presentations, peni cillamine treatment induces paradoxical worsening of neurologic status. Triethylenetetramine dihydrochloride (trientine hydrochloride [Syprine]) is a suitable alternative chelating agent with a somewhat better side effect profile. Tetrathiomolybdate (TM) is another molecule in the Wilson’s disease therapeutic armamentarium. TM forms stable tripartite complexes among albumin, copper, and itself. This drug functions both to decrease copper absorption and to reduce circulating free copper. It is fast-acting and can restore normal copper balance within several weeks compared to the several months required with other copper chelators or with zinc. Copper Chelation Treatment During Pregnancy The rate of spon taneous miscarriage is increased in pregnant women with untreated Wilson’s disease. From a benefit/risk perspective, it is important to maintain copper chelation treatment during pregnancy to prevent hepatic or neurologic relapse, as well as to lower risk of pregnancy loss. Some academic centers favor reduction of copper chelator dose during pregnancy, although if zinc monotherapy (see below) is in place at the time of conception, evidence suggests it is safe to maintain the usual daily dose. Since all anticopper medications enter breast milk, breastfeeding is not recommended for mothers with Wilson’s disease. REDUCTION OF COPPER ABSORPTION Zinc acetate (Galzin) has proven highly effective for treatment of

Wilson’s disease. The mechanism involves induction of metallothionein synthesis in intestinal epithelial cells; increased metallothionein synthe sis results in greater binding of dietary copper and thus decreased absorption. Zinc therapy has particular value in (1) young, presymp tomatic patients; (2) patients who are pregnant given the possible fetal teratogenic effects of other compounds; and (3) as maintenance therapy for patients after their initial “de-coppering” is accomplished. Zinc acetate has minimal side effects. The sole drawback is the rela tively long time (4–6 months) needed for restoration of proper copper balance when used as monotherapy in the initial stages of treatment. LIVER TRANSPLANTATION Liver transplantation is a consideration for

Wilson’s disease in advanced stages and/or when the condition is unresponsive to med ical therapy. This is generally necessary only in cases where delayed diagnosis or poor medication compliance results in irreversible hepatic damage. A recently proposed alternative for this circum stance is methanobactin, a bacterial peptide that binds copper avidly and dramatically improves mitochondrial copper overload and restores normal mitochondrial morphology in a preclinical (rat) model of advanced Wilson’s disease. GENE THERAPY In a preclinical (mouse) model of Wilson’s disease, adeno-associated virus-mediated ATP7B introduction into hepatocytes was shown to

be effective. Transduction of only 20% of hepatocytes was suffi cient to normalize copper homeostasis in the animal model. Those results potentially pave the way for viral gene therapy in Wilson’s disease patients, and clinical trials to evaluate this approach are underway. FUTURE OUTLOOK Wilson’s disease is arguably one of the best-characterized human inborn errors of metabolism from combined clinical, biochemical, and molecular perspectives, related to the detailed attention devoted to this condition. As noted, novel copper chelators are still being evalu ated, and generic formulations of established drugs are contributing to increased affordability for patients and their families. Viral gene therapy to provide working versions of ATP7B to the liver, kidney, and brain or that delivers gene-editing molecules to correct specific mutant alleles is now an emerging prospect. In addition, advances in newborn screening technology may eventually enable wider population-based screening for Wilson’s disease, which would help address lingering questions about clinical penetrance. Such future progress in newborn screening would also avert the tragedy that missed diagnoses of this eminently treatable disorder of copper transport represent. ■ ■FURTHER READING Bandmann O et al: Wilson’s disease and other neurological copper disorders. Lancet Neurol 14:103, 2015. Dev S et al: Wilson disease: Update on pathophysiology and treatment. Front Cell Dev Biol 10:871877, 2022. Gao J et al: The global prevalence of Wilson disease from nextgeneration sequencing data. Genet Med 21:1155, 2019. Kumar M et al: WilsonGen: A comprehensive clinically annotated genomic variant resource for Wilson’s disease. Sci Rep 10:9037, 2020. Lichtmannegger J et al: Methanobactin reverses acute liver failure in a rat model of Wilson disease. J Clin Invest 126:2721, 2016. Murillo O et al: Liver expression of a MiniATP7B gene results in long-term restoration of copper homeostasis in a Wilson disease model in mice. Hepatology 70:108, 2019. Sandahl TD et al: The prevalence of Wilson’s disease: An update. Hepatology 71:722, 2020. Wallace DF, Dooley JS: ATP7B variant penetrance explains differ ences between genetic and clinical prevalence estimates for Wilson disease. Hum Genet 139:1065, 2020. Robert J. Desnick, Manisha Balwani

The Porphyrias The porphyrias are metabolic disorders, each resulting from the deficiency or increased activity of a specific enzyme in the heme biosynthetic pathway (Fig. 428-1 and Table 428-1). These enzyme disorders are inherited as autosomal dominant, autosomal recessive, or X-linked traits, with the exception of porphyria cutanea tarda (PCT), which is usually sporadic (Table 428-1). The porphyrias are classified as either hepatic or erythropoietic, depending on the primary site of overproduction and accumulation of their respective porphyrin pre cursors or porphyrins (Tables 428-1 and 428-2), although some have overlapping features. For example, PCT is hepatic and presents with blistering cutaneous photosensitivity, which is typically characteristic of the erythropoietic porphyrias. The major manifestations of the acute hepatic porphyrias are neurologic, including neuropathic abdominal pain, peripheral motor neuropathy, and mental disturbances, with attacks often precipitated by dieting, certain porphyrinogenic drugs, and hormonal changes. While hepatic porphyrias are symptomatic primarily in adults, rare homozygous variants of the autosomal

dominant hepatic porphyrias

X-linked protoporphyria (XLP) X-linked sideroblastic anemia (XSLA) ALA-dehydratase Deficiency porphyria (ADP) Acute intermittent porphyria (AIP) Congenital erythropoietic porphyria (CEP) Uroporphyrinogen III synthase Uroporphyrinogen III Uroporphyrinogen I — Uroporphyrin I Porphyria cutanea tarda (PCT) Hepatoerythropoietic porphyria (HEP) Uroporphyrinogen decarboxylase Coproporphyrinogen III Hereditary coproporphyria (HCP) Coproporphyrinogen oxidase Protoporphyrinogen IX Variegate porphyria (VP) Protoporphyrinogen oxidase Protoporphyrin IX Erythropoietic protoporphyria (EPP) Ferrochelatase HEME FIGURE 428-1 The human heme biosynthetic pathway indicating in linked boxes the enzyme that, when deficient or overexpressed, causes the respective porphyria. Hepatic porphyrias are shown in yellow boxes and erythropoietic porphyrias in pink boxes. usually manifest clinically prior to puberty. In contrast, the erythro poietic porphyrias usually present at birth or in early childhood with cutaneous photosensitivity or, in the case of congenital erythropoietic porphyria (CEP), even in utero as nonimmune hydrops fetalis. Cutane ous sensitivity to sunlight results from excitation of excess porphyrins in the skin by long-wave ultraviolet light, leading to cell damage, TABLE 428-1 Human Porphyrias: Major Clinical and Laboratory Features PRINCIPAL SYMPTOMS: NV OR CP+ DEFICIENT ENZYME INHERITANCE PORPHYRIA Hepatic Porphyrias 5-ALA-dehydratasedeficient porphyria (ADP) ALAdehydratase AR NV ~5 Zn-protoporphyrin ALA, coproporphyrin III — Acute intermittent porphyria (AIP) HMB-synthase AD NV ~50 — ALA, PBG, uroporphyrin — Porphyria cutanea tarda (PCT) URODecarboxylase AD CP ~20 — Uroporphyrin, 7-carboxylate porphyrin Hereditary coproporphyria (HCP) COPRO-oxidase AD NV and CP ~50 — ALA, PBG, coproporphyrin III Coproporphyrin III Variegate porphyria (VP) PROTO-oxidase AD NV and CP ~50 — ALA, PBG, coproporphyrin III Coproporphyrin III, protoporphyrin Erythropoietic Porphyrias Congenital erythropoietic porphyria (CEP) URO-synthase AR CP 1–5 Uroporphyrin I Coproporphyrin I Erythropoietic protoporphyria (EPP) Ferrochelatase AR CP ~20–30 Protoporphyrin — Protoporphyrin X-linked protoporphyria (XLP) ALA-synthase 2 XL CP

> 100b Protoporphyrin — Protoporphyrin aType I isomers. bIncreased activity due to gain-of-function mutations in ALAS2 exon 11. Abbreviations: AD, autosomal dominant; ALA, 5-aminolevulinic acid; AR, autosomal recessive; COPRO, coproporphyrin; CP, cutaneous photosensitivity; NV, neurovisceral; PBG, porphobilinogen; PROTO, protoporphyrin; URO, uroporphyrin; XL, X-linked.

Succinyl CoA Glycine ALA-synthase Negative feedback δ-Aminolevulinic acid ALA-dehydratase Porphobilinogen Hydroxymethylbilane synthase The Porphyrias CHAPTER 428 Hydroxymethylbilane Non-enzymatic Coproporphyrinogen I — Coproporphyrin I Negative feedback scarring, and disfigurement. Thus, the porphyrias are metabolic disor ders in which environmental, physiologic, and genetic factors interact to cause disease. Because many symptoms of the porphyrias are nonspecific, diag nosis is often delayed. Laboratory measurement of porphyrin precur sors (5′-aminolevulinic acid [ALA] and porphobilinogen [PBG]) in ENZYME ACTIVITY % OF NORMAL INCREASED PORPHYRIN PRECURSORS AND/OR PORPHYRINS ERYTHROCYTES URINE STOOL Isocoproporphyrin Uroporphyrin Ia Coproporphyrin Ia Coproporphyrin I

TABLE 428-2 Human HEME Biosynthetic Enzymes and Genes THREEDIMENSIONAL STRUCTUREc SIZE (KB) EXONSa GENE SYMBOL CHROMOSOMAL LOCATION CDNA (bp) ENZYME ALA-synthase Housekeeping ALAS1 3p21.1

M — Erythroid-specific ALAS2 Xp11.2

M

> 30 — ALA-dehydratase Housekeeping ALAD 9q32

15.9 12 (1A + 2 – 12)

C

Y Erythroid-specific ALAD 9q32

15.9 12 (1B + 2 – 12)

C — PART 12 Endocrinology and Metabolism HMB-synthase Housekeeping HMBS 11q23.3

15 (1 + 3 – 15)

C

E Erythroid-specific HMBS 11q23.3

15 (2 – 15)

C

URO-synthase Housekeeping UROS 10q26.2

10 (1 + 2B – 10)

C

H Erythroid-specific UROS 10q26.2

10 (2A + 2B – 10)

C

URO-decarboxylase UROD 1p34.1

C

H COPRO-oxidase CPOX 3q12.1

M

H PROTO-oxidase PPOX 1q23.3

5.5

M

— Ferrochelatase FECH 18q21.31

M

B aNumber of exons and those encoding separate housekeeping and erythroid-specific forms indicated in parentheses. bNumber of known mutations from the Human Gene Mutation Database (www.hgmd.org). cCrystallized from human (H), murine (M), Escherichia coli (E), Bacillus subtilis (B), or yeast (Y) purified enzyme; references in Protein Data Bank (www.rcsb.org). Abbreviations: ALA, 5-aminolevulinic acid; C, cytoplasm; COPRO, coproporphyrin; HMB, hydroxymethylbilane; M, mitochondria; PROTO, protoporphyrin; URO, uroporphyrin. Source: Reproduced with permission from KE Anderson et al: Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias, in CR Scriver: The Metabolic and Molecular Bases of Inherited Diseases. New York, NY: McGraw-Hill; 2001. the urine or porphyrins in the urine, plasma, erythrocytes, or feces is required to confirm or exclude the various types of porphyria (see below). However, a definite diagnosis requires demonstration of the specific gene defect (Table 428-3). The genes encoding all the heme biosynthetic enzymes have been characterized, permitting identifica tion of the mutations causing each porphyria (Table 428-2). Molecular genetic analyses now make it possible to provide precise heterozygote or homozygote identification and prenatal diagnoses in families with known mutations. In addition to recent reviews of the porphyrias, informative and upto-date websites are sponsored by the United Porphyrias Association (www.porphyria.org) and the European Porphyria Network (https:// porphyria.eu/). An extensive list of unsafe and safe drugs for individu als with acute porphyrias is provided at the Drug Database for Acute Porphyrias (www.drugs-porphyria.org). GLOBAL CONSIDERATIONS The porphyrias are panethnic metabolic diseases that affect individuals globally. The acute hepatic porphyrias—acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP)—are autosomal dominant disorders. The frequency of AIP, the most common acute hepatic porphyria, is ~1 in 20,000 among Caucasian individuals of Western European ancestry, and it is particularly frequent in Scandinavians, where the frequency in Sweden is ~1 in 10,000. VP is particularly frequent in South Africa, and its high prevalence (>10,000 affected patients) is in part due to a genetic “founder effect.” The auto somal recessive acute hepatic porphyria, ALA-dehydratase-deficient porphyria (ADP), is extremely rare, and <20 patients have been identi fied worldwide. The erythropoeitic protoporphyrias—CEP, erythropoietic protopor phyria (EPP), and X-linked protoporphyria (XLP)—also are panethnic. EPP is likely the most common porphyria, while CEP is very rare with about 200 reported cases worldwide. The frequency of EPP varies globally since most patients have the common low expression FECH allele, which ranges in frequency in different populations. This allele rarely occurs in Africans, is present in ~10% of the Caucasians, and is frequent (~30%) in the Japanese. The autosomal

recessive porphyrias, ADP, CEP, EPP, and hepato erythropoietic porphyria (HEP), are more frequent in regions with

GENE PROTEIN (aa) SUBCELLULAR LOCATION KNOWN MUTATIONSb high rates of consanguineous marriages. PCT, which is typically sporadic, occurs more frequently in countries in which its predispos ing risk factors such as hepatitis C and HIV are more prevalent. The reported prevalence of EPP in the Caucasian population ranges from 1 in ~75,000 to 1 in ~150,000. ■ ■HEME BIOSYNTHESIS Heme biosynthesis involves eight enzymatic steps in the conversion of glycine and succinyl-CoA to heme (Fig. 428-2 and Table 428-2). These eight enzymes are encoded by nine genes, as the first enzyme in the pathway, ALA-synthase, has two genes that encode unique housekeep ing (ALAS1) and erythroid-specific (ALAS2) isozymes. The first and last three enzymes in the pathway are located in the mitochondria, whereas the other four are in the cytosol. Heme is required for a variety of hemoproteins such as hemoglobin, myoglobin, respiratory cytochromes, and the cytochrome P450 (CYP) enzymes. Hemoglobin synthesis in erythroid precursor cells accounts for ~85% of daily heme synthesis in humans. Hepatocytes account for most of the rest, primar ily for the synthesis of CYPs, which are especially abundant in the liver endoplasmic reticulum, and turn over more rapidly than many other hemoproteins, such as the mitochondrial respiratory cytochromes. As shown in Fig. 428-2, the pathway intermediates are the porphyrin pre cursors, ALA and PBG, and porphyrins (mostly in their reduced forms, known as porphyrinogens). At least in humans, these intermediates do not accumulate in significant amounts under normal conditions or have important physiologic functions. The first enzyme, ALA-synthase, catalyzes the condensation of gly cine, activated by pyridoxal phosphate and succinyl-coenzyme A, to form ALA. In the liver, this rate-limiting enzyme can be induced by a variety of drugs, steroids, and other chemicals. Distinct nonerythroid (e.g., housekeeping) and erythroid-specific forms of ALA-synthase are encoded by separate genes located on chromosome 3p21.1 (ALAS1) and Xp11.2 (ALAS2), respectively. Defects in the erythroid gene ALAS2 that decrease its activity cause an X-linked sideroblastic anemia (XLSA). Gain-of-function mutations in the last exon (11) of ALAS2 that increase its activity cause an X-linked form of EPP, known as XLP. The second enzyme, ALA-dehydratase, catalyzes the condensa tion of two molecules of ALA to form PBG. Hydroxymethylbilane synthase (HMB-synthase; also known as PBG-deaminase) catalyzes

TABLE 428-3 Diagnosis of Acute and Cutaneous Porphyrias SECOND-LINE TESTING IF FIRST-LINE TESTING IS POSITIVE: TO INCLUDE: URINE (U), PLASMA (P), AND FECAL (F) PORPHYRINS; FOR ACUTE PORPHYRIAS, ADD RED BLOOD CELL (RBC) HMB-SYNTHASE; FOR BLISTERING SKIN LESIONS, ADD P AND RBC PORPHYRINS FIRST-LINE TEST: ABNORMALITY POSSIBLE PORPHYRIA SYMPTOMS Neurovisceral Spot U: ↑↑ALA and normal PBG ADP U porphyrins: ↑↑, mostly COPRO III P and F porphyrins: normal or slightly ↑ RBC HMB-synthase: normal Spot U: ↑↑PBG AIP U porphyrins: ↑↑, mostly URO and COPRO P and F porphyrins: normal or slightly ↑ RBC HMB-synthase: usually ↓ “ HCP U porphyrins: ↑↑, mostly COPRO III P porphyrins: normal or slightly ↑ (↑ if skin lesions present) F porphyrins: ↑↑, mostly COPRO III “ VP U porphyrins: ↑↑, mostly COPRO III P porphyrins: ↑↑ (characteristic fluorescence peak at neutral pH) F porphyrins: ↑↑, mostly COPRO and PROTO Blistering skin lesions P: ↑ porphyrins PCT and HEP U porphyrins: ↑↑, mostly URO and heptacarboxylate porphyrin P porphyrins: ↑↑ F porphyrins: ↑↑, including increased isocoproporphyrin RBC porphyrins: ↑↑ zinc PROTO in HEPa “ HCP and VP See HCP and VP above. Also, U ALA and PBG: may be ↑ “ CEP RBC and U porphyrins: ↑↑, mostly URO I and COPRO I F porphyrins: ↑↑; mostly COPRO I Nonblistering photosensitivity P: porphyrins usually ↑ EPP RBC

porphyrins: ↓↓, mostly free PROTO U porphyrins: normal F porphyrins: normal or ↓, mostly PROTO P: porphyrins usually ↑ XLP RBC porphyrins: ↑↑, approximately equal free and zinc PROTO U porphyrins: normal F porphyrins: normal or ↑, mostly PROTO aNonspecific increases in zinc protoporphyrins are common in other porphyrias. Abbreviations: ADP, 5-ALA-dehydratase-deficient porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinic acid; CEP, congenital erythropoietic porphyria; COPRO I, coproporphyrin I; COPRO III, coproporphyrin III; EPP, erythropoietic protoporphyria; F, fecal; HCP, hereditary coporphyria; HEP, hepatoerythropoietic porphyria; ISOCOPRO, isocoproporphyrin; P, plasma; PBG, porphobilinogen; PCT, porphyria cutanea tarda; PROTO, protoporphyrin IX; RBC, erythrocytes; U, urine; URO I, uroporphyrin I; URO III, uroporphyrin III; VP, variegate porphyria; XLP, X-linked protoporphyria. Source: Data from KE Anderson et al: Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med 142:439, 2005. the head-to-tail condensation of four PBG molecules by a series of deaminations to form the linear tetrapyrrole, HMB. Uroporphyrinogen III synthase (URO-synthase) catalyzes the rearrangement and rapid cyclization of HMB to form the asymmetric, physiologic, octacarboxyl ate porphyrinogen, uroporphyrinogen (URO'gen) III. The fifth enzyme in the pathway, uroporphyrinogen decarboxylase (URO-decarboxylase), catalyzes the sequential removal of the four car boxyl groups from the acetic acid side chains of URO'gen III to form coproporphyrinogen (COPRO'gen) III, a tetracarboxylate porphy rinogen. This compound then enters the mitochondrion via a specific transporter, where COPRO-oxidase, the sixth enzyme, catalyzes the decarboxylation of two of the four propionic acid groups to form the two vinyl groups of protoporphyrinogen (PROTO'gen) IX, a decarbox ylate porphyrinogen. Next, PROTO-oxidase oxidizes PROTO'gen to protoporphyrin IX by the removal of six hydrogen atoms. The product of the reaction is a porphyrin (oxidized form), in contrast to the pre ceding tetrapyrrole intermediates, which are porphyrinogens (reduced forms). Finally, ferrous iron is inserted into protoporphyrin IX to form heme, a reaction catalyzed by the eighth enzyme in the pathway, FECH (also known as heme synthase or protoheme ferrolyase). ■ ■REGULATION OF HEME BIOSYNTHESIS Regulation of heme synthesis differs in the two major heme-forming tissues, the liver and erythron. In the liver, the concentration of "free" heme regulates the synthesis and mitochondrial translocation of the

CONFIRMATORY TEST: ENZYME ASSAY AND/OR MUTATION ANALYSIS Rule out other causes of elevated ALA; ↓↓RBC ALA-dehydratase activity (<10%); ALA-dehydratase mutation analysis HMB-synthase mutation analysis The Porphyrias CHAPTER 428 Measure RBC HMB-synthase: normal activity COPRO-oxidase mutation analysis Measure RBC HMB-synthase: normal activity PROTO-oxidase mutation analysis RBC URO-decarboxylase activity: half-normal in familial PCT (~20% of all PCT cases); substantially deficient in HEP URO-decarboxylase mutation analysis: mutation(s) present in familial PCT (heterozygous) and HEP (homozygous) ↓↓ RBC URO-synthase activity (<15%) URO-synthase mutation analysis FECH mutation analysis ALAS2 mutation analysis housekeeping form of ALA-synthase 1. Heme represses the synthesis of the ALA-synthase 1 messenger RNA (mRNA) and interferes with the transport of the enzyme from the cytosol into mitochondria. Hepatic ALA-synthase 1 is increased by many of the same chemicals that induce the CYP enzymes in the endoplasmic reticulum of the liver. Because most of the heme in the liver is used for the synthesis of CYP enzymes, hepatic ALA-synthase 1 and the CYPs are regulated in a coordinated fashion, and many drugs that induce hepatic ALAsynthase 1 also induce CYP gene expression. The other hepatic heme biosynthetic enzymes are presumably expressed at constant levels, although their relative activities and kinetic properties differ. For example, normal individuals have high activities of ALA-dehydratase but low activities of HMB-synthase, the latter

being the second ratelimiting step in the pathway. In the erythron, novel regulatory mechanisms allow for the produc tion of the very large amounts of heme needed for hemoglobin synthe sis. The response to stimuli for hemoglobin synthesis occurs during cell differentiation, leading to an increase in cell number. In contrast, the erythroid-specific ALA-synthase 2 is expressed at higher levels than the housekeeping enzyme, and erythroid-specific control mechanisms regulate other pathway enzymes as well as iron transport into erythroid cells. Separate erythroid-specific and nonerythroid or “housekeeping” transcripts are known for the first four enzymes in the pathway. As noted above, housekeeping- and erythroid-specific ALA-synthases are encoded by genes on different chromosomes, but for each of the

Cytoplasm Mitochondria SUCCINYL COA COO CH CH2 C CoAS O ALA-synthase COO CH2 CH2 C=O H-C-NH H δ-Aminolevulinic acid B6 CoASH CO2 H H-C-NH2 COO PART 12 Endocrinology and Metabolism Glycine Feedback repression Vi CH3 CH3 Vi N N Fe N N CH3 CH3 Pr Pr Heme 2H Ferrochelatase Fe2+ CH3 Vi Vi CH3 N N H H N N CH3 CH Pr Pr Protoporphyrin IX 6H PROTO-oxidase Vi CH Vi CH3 N N COPRO-oxidase H H H H 2CO2 2H N N CH3 CH Coproporphyrinogen III Protoporphyrinogen IX Pr Pr FIGURE 428-2 The heme biosynthetic pathway showing the eight enzymes and their substrates and products. Four of the enzymes are localized in the mitochondria and four in the cytosol. next three genes in the pathway, both erythroid and nonerythroid transcripts are transcribed by alternative promoters from their single respective genes (Table 428-2). ■ ■CLASSIFICATION OF THE PORPHYRIAS As mentioned above, the porphyrias can be classified as either hepatic or erythropoietic, depending on whether the heme biosynthetic inter mediates that accumulate arise initially from the liver or developing erythrocytes, or as acute or cutaneous, based on their clinical mani festations. Table 428-1 lists the porphyrias, their principal symptoms, and major biochemical abnormalities. Three of the five hepatic porphyrias—AIP, HCP, and VP—usually present during adult life with acute attacks of neurologic manifestations and elevated levels of one or

COO– COO CH2 CH2 CH2 ALA-dehydratase H NH2 — CH2 N H2O H Porphobilinogen HMBsythase 4NH3 Ac Pr Pr Ac N N H H H H H N N Ac Pr Pr Ac Hydroxymethylbilane H2O UROsynthase Pr Ac Pr Ac N N H H H H N N Ac Ac Pr Pr Uroporphyrinogen III URODecarboxylase 4H 4CO2 Pr CH3 Pr CH3 N N H H H H N N CH3 CH3 Pr Pr both of the porphyrin precursors, ALA and PBG, and are thus classi fied as acute hepatic porphyrias. Patients with ADP have presented in infancy and adolescence and typically have elevated ALA with normal or slightly elevated PBG levels. The fifth hepatic disorder, PCT, pres ents with blistering skin lesions. HCP and VP also may have cutaneous manifestations similar to PCT. The erythropoietic porphyrias—CEP, EPP, and XLP—are charac terized by elevations of porphyrins in bone marrow and erythrocytes and present with cutaneous photosensitivity. The skin lesions in CEP resemble PCT but are usually much more severe, whereas EPP and XLP cause a more immediate, severe, painful, and nonblistering type of photosensitivity. EPP is the most common porphyria to cause symptoms before puberty. About 20% of EPP patients develop minor

abnormalities of liver function, with up to ~5% developing hepatic complications that can lead to liver failure requiring liver transplanta tion. XLP has a clinical presentation similar to EPP causing photosen sitivity and liver disease. ■ ■DIAGNOSIS OF PORPHYRIA A few specific and sensitive first-line laboratory tests should be used whenever symptoms or signs suggest the diagnosis of porphyria (Table 428-3). If a first-line test is significantly abnormal, more com prehensive testing should follow to establish the type of porphyria, including the specific causative gene mutation.

Acute Hepatic Porphyrias An acute hepatic porphyria should be suspected in patients with neurovisceral symptoms after puberty. Symptoms include acute abdominal pain, nausea, vomiting, tachy cardia, hypertension, and motor neuropathy. As these symptoms are common, other causes should be ruled out. The diagnosis is made by measuring urinary porphyrin precursors (ALA and PBG) in a spot sample of urine (Fig. 428-2). Urinary PBG is always increased during acute attacks of AIP, HCP, and VP and is not substantially increased in any other medical condition. Therefore, this measurement is both sensitive and specific. Results from spot (single-void) urine specimens are highly informative because very substantial increases in PBG are expected during acute attacks of porphyria. A 24-h collection is unnec essary. The same spot urine specimen should be saved for quantitative determination of ALA, PBG, and creatinine, in order to confirm the qualitative PBG result and also to detect patients with ADP. Urinary porphyrins may remain increased longer than porphyrin precursors in HCP and VP. Therefore, it is useful to measure total urinary por phyrins in the same sample, keeping in mind that urinary porphyrin increases are often nonspecific. Measurement of urinary porphyrins alone should be avoided for screening, because these may be increased in disorders other than porphyrias, such as chronic liver disease, and misdiagnoses of porphyria can result from minimal increases in uri nary porphyrins that have no diagnostic significance. Measurement of erythrocyte HMB-synthase is not useful as a first-line test. Moreover, the enzyme activity is not decreased in all AIP patients, a borderline low normal value is not diagnostic, and the enzyme is not deficient in other acute porphyrias. More extensive testing is justified when an initial test is positive. A substantial increase in PBG may be due to AIP, HCP, or VP. These acute porphyrias can be distinguished by measuring urinary porphy rins (using the same spot urine sample), fecal porphyrins, and plasma porphyrins. Assays for COPRO-oxidase or PROTO-oxidase are not available for clinical testing. More specifically, mutation analysis by sequencing the genes encoding HMB-synthase, COPRO-oxidase, and PROTO-oxidase will detect almost all disease-causing mutations and is diagnostic even when the levels of urinary ALA and PBG have returned to normal or near normal. Cutaneous Porphyrias Blistering skin lesions due to porphyria are virtually always accompanied by increases in total plasma por phyrins. A fluorometric method is preferred, because the plasma porphyrins in VP are mostly covalently linked to plasma proteins and may be less readily detected by high-performance liquid chromatog raphy (HPLC). The normal range for plasma porphyrins is somewhat increased in patients with end-stage renal disease. Although a total plasma porphyrin determination will usually detect EPP and XLP, an erythrocyte protoporphyrin determination is more sensitive. Increases in erythrocyte protoporphyrin occur in many other conditions. Therefore, the diagnosis of EPP must be confirmed by showing a predominant increase in free protoporphyrin rather than zinc protoporphyrin. In XLP, both free and zinc protoporphyrin are markedly increased. Interpretation of laboratory reports can be difficult, because the term free erythrocyte protoporphyrin sometimes actually represents zinc protoporphyrin. The various porphyrias that cause blistering skin lesions can be differ entiated by measuring porphyrins in urine, feces, and plasma. The por phyrias should be confirmed by genetic testing and the demonstration of the causative pathogenic variant. It is often difficult to diagnose or “rule

out” porphyria in patients who have had suggestive symptoms months or years in the past and in relatives of patients with acute porphyrias, because porphyrin precursors and porphyrins may be normal. In those situations, detection of the specific gene mutation in the index case can make the diagnosis and facilitate the diagnosis and genetic counseling of at-risk relatives. With the increased access and accuracy of genetic testing, this often precedes secondary biochemical testing in clinical practice. Consultation with a specialist laboratory and physician will assist in selecting the

heme biosynthetic gene or genes to be sequenced.

THE HEPATIC PORPHYRIAS Markedly elevated plasma and urinary concentrations of the porphyrin precursors, ALA and/or PBG, which originate from the liver, are espe cially evident during attacks of neurologic manifestations of the four acute porphyrias—ADP, AIP, HCP, and VP. In PCT, excess porphyrins also accumulate initially in the liver and cause chronic blistering of sun-exposed areas of the skin. The Porphyrias CHAPTER 428 ■ ■ALA-DEHYDRATASE-DEFICIENT PORPHYRIA ADP is a rare, autosomal recessive, acute hepatic porphyria caused by a severe deficiency of ALA-dehydratase activity. To date, there are only a dozen documented cases, some in children or young adults, in which specific gene mutations have been identified. These affected homozy gotes had <10% of normal ALA-dehydratase activity in erythrocytes, but their clinically asymptomatic parents and heterozygous relatives had about half-normal levels of activity and did not excrete increased levels of ALA. The frequency of ADP is unknown, but the frequency of heterozygous individuals with <50% normal ALA-dehydratase activity was ~2% in a screening study in Sweden. Because there are multiple causes for deficient ALA-dehydratase activity, it is important to con firm the diagnosis of ADP by mutation analysis. Clinical Features The clinical presentation depends on the amount of residual ALA-dehydratase activity. Four of the documented patients were male adolescents with symptoms resembling those of AIP, including abdominal pain and neuropathy. One patient was an infant with more severe disease, including failure to thrive beginning at birth. The earlier age of onset and more severe manifestations in this patient reflect a more significant deficiency of ALA-dehydratase activity. Another patient developed an acute motor polyneuropathy at age 63 that was associated with a myeloproliferative disorder. He was heterozygous for an δ-aminolevulinic acid dehydratase (ALAD) mutation that presumably was present in erythroblasts that underwent clonal expansion due to the bone marrow malignancy. Diagnosis All patients had significantly elevated levels of plasma and urinary ALA and urinary coproporphyrin (COPRO) III; ALAD activities in erythrocytes were <10% of normal. Hereditary tyrosinemia type 1 (fumarylacetoacetase deficiency) and lead intoxica tion should be considered in the differential diagnosis because either succinylacetone (which accumulates in hereditary tyrosinemia and is structurally similar to ALA) or lead can inhibit ALA-dehydratase, increase urinary excretion of ALA and COPRO III, and cause manifes tations that resemble those of the acute porphyrias. Heterozygotes are clinically asymptomatic and do not excrete increased levels of ALA but can be detected by demonstration of intermediate levels of erythrocyte ALA-dehydratase activity or a specific mutation in the ALAD gene. To date, molecular studies of ADP patients have identified 12 pathogenic mutations, including missense mutations, splice-site mutations, and a two-base deletion in the ALAD gene (Human Gene Mutation Data base; www.hgmd.org). The parents in each case were not consanguine ous, and the index cases had inherited a different ALAD mutation from each parent. Prenatal diagnosis of this disorder is possible by determi nation of ALA-dehydratase activity and/or gene mutations in cultured chorionic villi or amniocytes. Treatment The treatment of ADP acute attacks is similar to that of AIP (see below). The severely affected infant referred to above was sup ported by hyperalimentation and periodic blood transfusions but did not respond to intravenous hemin and died after liver transplantation.

■ ■ACUTE INTERMITTENT PORPHYRIA This hepatic porphyria is an autosomal dominant condition resulting from the half-normal level of HMB-synthase activity. The disease is widespread but is especially common in Scandinavia and Great Britain. Clinical expression is highly variable, and activation of the disease is often related to environmental or hormonal factors, such as drugs, diet,

and steroid hormones. Attacks can be prevented by avoiding known precipitating factors. Rare homozygous dominant AIP also has been described in children (see below).

Clinical Features Induction and increased expression of the ratelimiting hepatic gene ALAS1 in heterozygotes who have half-normal HMB-synthase activity is thought to underlie the acute attacks in AIP. The disorder remains latent (or asymptomatic) in the great majority of those who are heterozygous for pathogenic HMBS mutations, and this is almost always the case prior to puberty. In patients with no history of acute symptoms, porphyrin precursor excretion is usually normal, suggesting that half-normal hepatic HMB-synthase activity is sufficient and that hepatic ALA-synthase activity is not increased. However, under conditions where heme synthesis is increased in the liver, half-normal HMB-synthase activity may become limiting, and ALA, PBG, and other heme pathway intermediates may accumulate and be excreted in the urine. Common precipitating factors include endogenous and exogenous steroids, porphyrinogenic drugs, alcohol ingestion, and low-calorie diets, usually instituted for weight loss. PART 12 Endocrinology and Metabolism The fact that AIP is almost always latent before puberty suggests that adult levels of steroid hormones are important for clinical expression. Symptoms are more common in women, suggesting a role for estrogens or progestins. Premenstrual attacks are probably due to increasing endogenous progesterone during the luteal phase of the menstrual cycle. Acute porphyrias are sometimes exacerbated by exogenous steroids, including oral contraceptive preparations containing proges tins. Surprisingly, pregnancy is usually well tolerated, suggesting that beneficial metabolic changes may ameliorate the effects of high levels of progesterone. Extensive lists of unsafe and safe drugs are available on websites sponsored by the United Porphyria Association (www

.porphyria.org) and the European Porphyria Network (https://por phyria.eu/), and at the Drug Database for Acute Porphyrias website (www.drugs-porphyria.org). Reduced intake of calories and carbohy drate, as may occur with illness or attempts to lose weight, can also increase porphyrin precursor excretion and induce attacks of porphyria. Studies in a knockout AIP mouse model indicate that the hepatic ALAS1 gene is regulated, in part, by the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). Hepatic PGC-1α is induced by fasting, which in turn activates ALAS1 transcription, resulting in increased heme biosynthesis. This finding suggests an important link between nutritional status and the attacks in acute porphyrias. Attacks also can be provoked by infections, surgery, and ethanol. Because the neurovisceral symptoms rarely occur before puberty and are often nonspecific, a high index of suspicion is required to make the diagnosis. The disease can be disabling but is rarely fatal. Abdomi nal pain, the most common symptom, is poorly localized but may be associated with cramping, ileus, abdominal distention, and decreased bowel sounds. However, increased bowel sounds and diarrhea may occur. Abdominal tenderness, fever, and leukocytosis are usually absent or mild because the symptoms are neurologic rather than inflammatory. Nausea; vomiting; constipation; tachycardia; hyperten sion; mental symptoms; pain in the limbs, head, neck, or chest; muscle weakness; sensory loss; dysuria; and urinary retention are characteris tic. Tachycardia, hypertension, restlessness, tremors, and excess sweat ing are due to sympathetic overactivity. The peripheral neuropathy is due to axonal degeneration (rather than demyelinization) and primarily affects motor neurons. Significant neuropathy does not occur with all acute attacks; abdominal symptoms are usually more prominent. Motor neuropathy affects the proximal muscles initially, more often in the shoulders and arms. The course and degree of involvement are variable and sometimes may be focal and involve cranial nerves. Deep tendon reflexes initially may be nor mal or hyperactive but become decreased or absent as the neuropathy

advances. Sensory changes such as paresthesia and loss of sensation are less prominent. Progression to respiratory and bulbar paralysis and death occurs especially when the diagnosis and treatment are delayed. Sudden death may result from sympathetic overactivity and cardiac arrhythmia. Mental symptoms such as anxiety, insomnia, depression, disorienta tion, hallucinations, and paranoia can occur in acute attacks. Seizures can be due to neurologic effects or to hyponatremia. Treatment of seizures is difficult because most antiseizure drugs can exacerbate AIP (clon azepam may be safer than phenytoin or barbiturates). Hyponatremia results from hypothalamic involvement and inappropriate vasopressin secretion or from electrolyte depletion due to vomiting, diarrhea, poor intake, or excess renal sodium loss. When an attack resolves, abdominal pain may disappear within hours, and paresis begins to improve within days and may continue to improve over several years. Homozygous dominant AIP (HD-AIP) is a rare form of AIP in which patients inherit HMBS mutations from each of their heterozy gous parents and, therefore, have very low (<2%) enzyme activity. The disease has been described in a Dutch girl, two young British siblings, and a Spanish boy. In these homozygous affected patients, the disease presented in infancy with failure to thrive, developmental delay, bilat eral cataracts, and/or hepatosplenomegaly. Urinary ALA and PBG concentrations were markedly elevated. All of these patients' HMBS mutations (R167W, R167Q, and R172Q) were in exon 10 within five bases of each other. Studies of the brain magnetic resonance images (MRIs) of children with homozygous AIP have suggested damage primarily in white matter that was myelinated postnatally, while tracks that myelinated prenatally were normal. Most children with homozygous AIP die at an early age. Recently, later-onset HD-AIP was described in an adult with leukoencephalopathy. Diagnosis ALA and PBG levels are substantially increased in plasma and urine, especially during acute attacks. For example, urinary PBG excretion during an attack is usually 50–200 mg/24 h (220–880 µmol/

24 h) (normal, 0–4 mg/24 h [0–18 µmol/24 h]), and urinary ALA excre tion is 20–100 mg/24 h (150–760 µmol/24 h) (normal, 1–7 mg/24 h

[8–53 µmol/24 h]). Because levels often remain high after symptoms resolve, the diagnosis of an acute attack in a patient with biochemically proven AIP is based primarily on clinical features. Excretion of ALA and PBG decreases over a few days after intravenous hemin adminis tration or in a day after subcutaneous givosiran (see below). A normal urinary PBG level before hemin effectively excludes AIP as a cause for current symptoms. Fecal porphyrins are usually normal or minimally increased in AIP, in contrast to HCP and VP. Most AIP heterozygotes with no history of symptoms have normal urinary excretion of ALA and PBG and are classified as "latent" or "asymptomatic heterozy gotes." Patients can also have high levels of urinary PBG and ALA with no clinical symptoms. These patients may have a previous history of an acute attack and are classified as asymptomatic high excretors (ASHE) or chronic high excretors (CHE). Therefore, the detection of the family's HMBS mutation will diagnose heterozygous asymptomatic family members. A urinary ALA and PBG will diagnosis CHE patients who may have a higher risk of an attack if they experience a precipitat ing factor such as administration of a porphyrinogenic drug. Patients with HMBS mutations in the initiation of translation codon in exon 1 and in the intron 15′-splice donor site have normal enzyme levels in erythrocytes and deficient activity only in nonerythroid tis sues. This occurs because the erythroid and housekeeping forms of HMB-synthase are encoded by a single gene, which has two promot ers. Thus, the enzyme assay may not be diagnostic, and genetic testing should be used to confirm the diagnosis. More than 550 HMBS mutations have been identified in AIP, including missense, nonsense, AND splicing lesions, insertions, and deletions, with

most mutations found in only one or a few families (Human Gene Mutation Database, www.hgmd.org). The prenatal diag nosis of a fetus at risk can be made by analysis of the familial mutation in cultured amniotic cells or chorionic villi. However, this is seldom done because the prognosis of individuals with HMBS mutations is generally favorable.

TREATMENT Acute Intermittent Porphyria During acute attacks, narcotic analgesics may be required for abdominal pain, and phenothiazines are useful for nausea, vom iting, anxiety, and restlessness. Chloral hydrate can be given for insomnia, and benzodiazepines are probably safe in low doses if a minor tranquilizer is required. Carbohydrate loading, usually with intravenous glucose (at least 300 g daily), may be effective in milder acute attacks of porphyria (without paresis, hyponatremia, etc.) if hemin or givosiran (see below) is not available. Intravenous hemin was approved by the U.S. Food and Drug Administration (FDA) in 1984 to treat acute attacks and has been used effectively as a firstline therapy for acute attacks. The standard regimen is 3–4 mg/kg per d of heme, in the form of lyophilized hematin (Panhematin, Recordati Rare Diseases), heme albumin (hematin reconstituted with human albumin), or heme arginate (Orphan Europe), infused daily for 4 days or longer to reduce the pain. Heme arginate and heme albumin are chemically stable and are less likely than hematin to produce phlebitis or an anticoagulant effect. Recovery depends on the degree of neuronal damage and usually occurs in days, if therapy is started early. Recovery from severe motor neuropathy may require months or years. Identification and avoidance of incit ing factors can hasten recovery from an attack and prevent future attacks. Inciting factors are usually multiple, and removal of one or more hastens recovery and helps prevent future attacks. Frequent attacks that occur during the luteal phase of the menstrual cycle may be prevented with a gonadotropin-releasing hormone ana logue, which prevents ovulation and progesterone production, or by prophylactic hematin or givosiran administration. In 2019, a hepatocyte-targeted RNA interference (RNAi) therapy, givosiran (Givlarri, Alnylam Pharmaceuticals), was approved by the FDA and the European Medicines Agency (EMA) for the treatment of the acute hepatic porphyrias. Givosiran, a monthly subcutane ous injection of 2.5 mg/kg, is designed to silence the expression of hepatic ALAS1 mRNA and was initially shown in clinical trials to markedly reduce ALA and PBG levels in CHE patients and in patients with recurrent attacks. In a phase 3 trial in acute hepatic porphyria patients with recurrent attacks, the RNAi therapy sig nificantly reduced the frequency of acute attacks, decreased hemin utilization, and improved daily pain scores. The long-term risk of hypertension and chronic renal disease is increased in AIP; a number of patients have undergone suc cessful renal transplantation. Studies have shown that up to 59% of symptomatic AIP patients will develop chronic kidney disease. The PEPT2 receptor polymorphic genotype affects the severity and prognosis of porphyria-associated kidney disease with the high affinity polymorphic PEPT2 *1 allele and the PEPT2 genotypes *1*1 and, to a lesser degree, *1*2 associated with decreasing kidney function. Chronic, low-grade abnormalities in liver function tests are common, and the risk of hepatocellular carcinoma is increased. Hepatic imaging is recommended at least every 6 months for early detection of these tumors. Other long-term complications include neuropathy, fatigue, chronic pain, nausea, depression, and/ or anxiety. Orthotopic liver transplantation (OLT) has been effective in patients with severe, disabling, intractable attacks that are refrac tory to hemin therapy. Reports from both the United Kingdom and the United States show a marked improvement with no subsequent attacks, an improvement in the neuropathic manifestations, and normalization of the urinary PBG and ALA levels after liver trans plantation. OLT is associated with morbidity and mortality and should be considered a treatment of last resort in these patients. In addition, patients who already have advanced

neuropathy are considered poor risks for transplantation. Of note, the effectiveness of givosiran in such patients has not been described. Some patients with both recurrent attacks and end-stage renal disease have ben efitted from combined liver and kidney transplantation.

Liver-directed gene therapy has proven successful in the pre vention of drug-induced biochemical attacks in a murine model of human AIP, and clinical trials of adeno-associated virus vector (AAV)-HMBS gene transfer were carried out over a decade ago. Although the therapy was safe, there was essentially no biochemi cal evidence of its effectiveness, nor did it prevent recurrent attacks in the treated patients. Recent advances have led to FDA-approved gene-editing/gene therapies for genetic disorders and may lead to future treatments and/or cures for the acute hepatic and erythro poietic porphyrias.

The Porphyrias CHAPTER 428 ■ ■PORPHYRIA CUTANEA TARDA PCT, the most common of the porphyrias, can be either sporadic (type 1) or familial (type 2) and can also develop after exposure to halogenated aromatic hydrocarbons. Hepatic URO-decarboxylase is deficient in all types of PCT, and for clinical symptoms to manifest, this enzyme deficiency must be substantial (~20% of normal activity or less). Its deficiency is currently attributed to generation of an URO-decarbox ylase inhibitor in the liver, which forms a uroporphomethene in the presence of iron and under conditions of oxidative stress. The majority of PCT patients (~80%) have no UROD mutations and are said to have sporadic (type 1) disease. PCT patients heterozygous for UROD muta tions have the familial (type 2) PCT. In these patients, inheritance of a UROD mutation from one parent results in half-normal enzymatic activity in liver and all other tissues, which is a significant predispos ing factor, but is insufficient by itself to cause symptomatic PCT. As discussed below, other genetic and environmental factors contribute to susceptibility for both types of PCT. Because penetrance of the genetic trait is low, many patients with familial (type 2) PCT have no family history of the disease. HEP is an autosomal recessive form of porphyria due to the inheritance of two pathogenic UROD mutations resulting in the marked systemic deficiency of URO-decarboxylase activity with clinical symptoms in childhood. Clinical Features Blistering skin lesions that appear most commonly on the backs of the hands are the major clinical feature (Fig. 428-3). These rupture and crust over, leaving areas of atrophy and scarring. Lesions may also occur on the forearms, face, legs, and feet. Skin friability and small white papules termed milia are common, especially on the backs of the hands and fingers. Hypertrichosis and hyperpigmentation, especially of the face, are especially troublesome in women. Occasion ally, the skin over sun-exposed areas becomes severely thickened, with scarring and calcification that resembles systemic sclerosis. Neurologic features are absent. A number of susceptibility factors, in addition to inherited UROD mutations in type 2 PCT, are recognized clinically and can affect management. These include hepatitis C, HIV, excess alcohol, elevated FIGURE 428-3 Typical cutaneous lesions in a patient with porphyria cutanea tarda. Chronic, crusted lesions resulting from blistering due to photosensitivity on the dorsum of the hand of a patient with porphyria cutanea tarda. (Used with permission from Dr. Karl E. Anderson.)

iron levels, and estrogens. The importance of excess hepatic iron as a precipitating factor is underscored by the finding that the incidence of the common hemochromatosis-causing mutations, hemochroma tosis gene (HFE) mutations p.C282Y and p.H63D, are increased in patients with types 1 and 2 PCT (Chap. 426). Excess alcohol is a longrecognized contributor, as is estrogen use in women. HIV is probably an independent but less common risk factor that, like hepatitis C, does not

cause PCT in isolation. Multiple susceptibility factors that appear to act synergistically can be identified in individual patients. PCT patients characteristically have chronic liver disease and some times cirrhosis and are at risk for hepatocellular carcinoma. Various chemicals can also induce PCT; an epidemic of PCT occurred in eastern Turkey in the 1950s as a consequence of wheat contami nated with the fungicide hexachlorobenzene. PCT also occurs after exposure to other chemicals, including di- and trichlorophenols and 2,3,7,8-tetrachlorodibenzo-(p)-dioxin (TCDD, dioxin).

PART 12 Endocrinology and Metabolism Diagnosis Porphyrins are increased in the liver, plasma, urine, and stool. The urinary ALA level may be slightly increased, but the PBG level is normal. Urinary porphyrins consist mostly of uro porphyrins and heptacarboxylate porphyrin, with lesser amounts of coproporphyrin and hexa- and pentacarboxylate porphyrins. Plasma porphyrins are also increased, and fluorometric scanning of diluted plasma at neutral pH can rapidly distinguish VP and PCT (Table 428-3). Isocoproporphyrins, which are increased in feces and sometimes in plasma and urine, are diagnostic for hepatic URODecarboxylase deficiency. Type 2 PCT and HEP can be distinguished from type 1 by finding decreased URO-decarboxylase in erythrocytes. URO-decarboxylase activity in liver, erythrocytes, and cultured skin fibroblasts in type 2 PCT is ~50% of normal in affected individuals and in asymptomatic heterozygous family members. In HEP, the URO-decarboxylase activity is markedly deficient, with typical levels of 3–10% of normal. Over 150 mutations have been identified in the UROD gene (Human Gene Muta tion Database; www.hgmd.org). Of the mutations listed in the database, ~65% are missense or nonsense, and ~8% are splice-site mutations. Many UROD mutations have been identified in only one or two families. TREATMENT Porphyria Cutanea Tarda Alcohol, estrogens, iron supplements, and, if possible, any drugs that may exacerbate the disease should be discontinued, but this step does not always lead to improvement. A complete response can almost always be achieved by the standard therapy, repeated phlebotomy, to reduce hepatic iron. A unit (450 mL) of blood can be removed every 1–2 weeks. The aim is to gradually reduce excess hepatic iron until the serum ferritin level reaches the lower limits of normal. Because iron overload is not marked in most cases, remission may occur after only five or six phlebotomies; however, PCT patients with hemochromatosis may require more treatments to bring their iron levels down to the normal range. To document improvement in PCT, it is most convenient to follow the total plasma porphyrin concentration, which becomes normal some time after the target ferritin level is reached. Hemoglobin levels or hematocrits and serum ferritin should be followed closely to prevent development of iron deficiency and anemia. After remis sion, continued phlebotomy may not be needed. Plasma porphyrin levels are followed at 6- to 12-month intervals for early detection of recurrences, which are treated by additional phlebotomy. An alternative when phlebotomy is contraindicated or poorly tolerated is a low-dose regimen of chloroquine or hydroxychlo roquine, both of which complex with the excess porphyrins and promote their excretion. Small doses (e.g., 125 mg chloroquine phosphate twice weekly) should be given, because standard doses can induce transient, sometimes marked increases in photosensi tivity and hepatocellular damage. Studies indicate that low-dose hydroxychloroquine is as safe and effective as phlebotomy in PCT.

Hepatic imaging can diagnose or exclude complicating hepatocel lular carcinoma. Treatment of PCT in patients with end-stage renal disease is facilitated by administration of erythropoietin. Because hepatitis C virus (HCV) is a common precipitating factor causing PCT, the recent development of oral direct-acting antivirals for HCV has proven effective as a first primary

treatment in HCV-infected PCT patients. ■ ■HEREDITARY COPROPORPHYRIA HCP is an autosomal dominant hepatic porphyria that results from the half-normal activity of COPRO-oxidase. The disease presents with acute attacks, as in AIP. Cutaneous photosensitivity also may occur, but much less commonly than in VP. HCP patients may have acute attacks and cutaneous photosensitivity together or separately. HCP is less common than AIP and VP. Homozygous dominant HCP and har deroporphyria, a biochemically distinguishable variant of HCP, present with clinical symptoms in children (see below). Clinical Features HCP is influenced by the same factors that cause attacks in AIP. The disease is latent before puberty, and symptoms, which are virtually identical to those of AIP, are more common in women. HCP is generally less severe than AIP. Blistering skin lesions are identical to PCT and VP and begin in childhood in rare homozygous cases. Diagnosis COPRO III is markedly increased in the urine and feces in symptomatic patients and often persists, especially in feces, when there are no symptoms. Urinary ALA and PBG levels are increased (but less than in AIP) during acute attacks but may revert to normal more quickly than in AIP when symptoms resolve. Plasma porphyrins are usually normal or only slightly increased, but they may be higher in cases with skin lesions. The diagnosis of HCP is readily confirmed by increased fecal porphyrins consisting almost entirely of COPRO III, which distinguishes it from other porphyrias. Although the diagnosis can be confirmed by measuring COPROoxidase activity, the assays for this mitochondrial enzyme are not avail able and require cells other than erythrocytes. To date, >95 mutations have been identified in the CPOX gene, ~70% of which are missense or nonsense (Human Gene Mutation Database; www.hgmd.org). Detec tion of a CPOX mutation in a symptomatic individual permits the identification of asymptomatic family members. TREATMENT Hereditary Coproporphyria Neurologic symptoms are treated as in AIP (see above). Phlebotomy and chloroquine are not effective for the cutaneous lesions. ■ ■VARIEGATE PORPHYRIA VP is an autosomal dominant hepatic porphyria that results from the deficient activity of PROTO-oxidase, the seventh enzyme in the heme biosynthetic pathway, and can present with neurologic symptoms, photosensitivity, or both. VP is particularly common in South Africa, where 3 of every 1000 whites have the disorder. Most are descendants of a couple who emigrated from the Netherlands to South Africa in 1688. In other countries, VP is less common than AIP. Rare cases of homozygous dominant VP, presenting in childhood with cutaneous symptoms, also have been reported. Clinical Features VP can present with skin photosensitivity, acute neurovisceral crises, or both. In two large studies of VP patients, ~60% had only skin lesions, 20% had only acute attacks, and ~20% had both. Acute attacks are identical to those in AIP and are precipitated by the same factors as AIP (see above). Blistering skin manifestations are similar to those in PCT but are more difficult to treat and usually are of longer duration. Homozygous VP is associated with photosensitiv ity, neurologic symptoms, and developmental disturbances, including growth retardation, in infancy or childhood; all cases had increased

erythrocyte levels of zinc protoporphyrin, a characteristic finding in all homozygous porphyrias so far described. Diagnosis Urinary ALA and PBG levels are increased during acute attacks but may return to normal more quickly than in AIP. Increases in fecal protoporphyrin and COPRO III and in urinary COPRO III are more persistent. Plasma porphyrin levels also are increased, particu larly when there are cutaneous lesions. VP can be distinguished rapidly from all other porphyrias by examining the fluorescence emission spectrum of porphyrins in plasma since VP has a unique fluorescence peak at neutral pH. Assays of PROTO-oxidase activity in cultured fibroblasts or lym phocytes are not widely available. Over 215 mutations have been identified in the PPOX gene from unrelated VP patients (Human Gene Mutation Database; www.hgmd.org). The missense mutation

encoding p.R59W is the common mutation in most South Africans with VP of Dutch descent. Five missense mutations were common in English and French VP patients; however, most mutations have been found in only one or a few families. TREATMENT Variegate Porphyria Acute attacks are treated as in AIP, and hemin should be started early in most cases. Givosiran has proven effective in clinical tri als for patients with recurrent attacks. Other than avoiding sun exposure, there are few effective measures for treating the skin lesions. β-Carotene, phlebotomy, and chloroquine are not helpful. THE ERYTHROPOIETIC PORPHYRIAS In the erythropoietic porphyrias, excess porphyrins from bone marrow erythrocyte precursors are transported via the plasma to the skin and lead to cutaneous photosensitivity. ■ ■X-LINKED SIDEROBLASTIC ANEMIA XLSA results from the deficient activity of the erythroid form of ALAsynthase (ALA-synthase 2) and is associated with ineffective erythro poiesis, weakness, and pallor. Clinical Features Typically, males with XLSA develop refractory hemolytic anemia, pallor, and weakness during infancy. They have secondary hypersplenism, become iron overloaded, and can develop hemosiderosis. The severity depends on the level of residual erythroid ALA-synthase activity and on the responsiveness of the specific muta tion to pyridoxal 5′-phosphate supplementation (see below). Peripheral blood smears reveal a hypochromic, microcytic anemia with striking anisocytosis, poikilocytosis, and polychromasia; the leukocytes and platelets appear normal. Hemoglobin content is reduced, and the mean corpuscular volume and mean corpuscular hemoglobin concentra tion are decreased. Patients with milder, later-onset disease have been reported recently. Diagnosis Bone marrow examination reveals hypercellularity with a left shift and megaloblastic erythropoiesis with an abnormal matura tion. A variety of Prussian blue–staining sideroblasts are observed. Levels of urinary porphyrin precursors and of both urinary and fecal porphyrins are normal. The activity of erythroid ALA-synthase 2 is decreased in bone marrow, but this enzyme is difficult to measure in the presence of the normal ALA-synthase 1 housekeeping enzyme. Definitive diagnosis requires the demonstration of loss-of-function mutations in the erythroid ALAS2 gene, of which >120 have been identified. Treatment The severe anemia may respond to pyridoxine supple mentation. This cofactor is essential for ALA-synthase activity, and mutations in the pyridoxine binding site of the enzyme have been found in several responsive patients. Cofactor supplementation may make it possible to eliminate or reduce the frequency of transfusions.

Unresponsive patients may be transfusion dependent and require che lation therapy.

■ ■CONGENITAL ERYTHROPOIETIC PORPHYRIA CEP, also known as Günther’s disease, is an autosomal recessive dis order. It is due to the markedly deficient, but not absent, activity of URO-synthase and the resultant accumulation of URO I and COPRO I isomers. CEP is associated with hemolytic anemia and cutaneous lesions. Clinical Features Severe cutaneous photosensitivity typically begins from birth. The skin over light-exposed areas is friable, and bullae and vesicles are prone to rupture and infection. Skin thickening, focal hypo- and hyperpigmentation, and hypertrichosis of the face and extremities are characteristic. Secondary infection of the cutaneous lesions can lead to disfigurement of the face and hands. Porphyrins are deposited in teeth and in bones. As a result, the teeth are brownish and fluoresce on exposure to long-wave ultraviolet light. Hemolysis is due to the marked increase in erythrocyte porphyrins and leads to spleno megaly. Adults with a milder later-onset form of the disease also have been described, including late-onset patients with myelodysplasias. The Porphyrias CHAPTER 428 Diagnosis URO and COPRO (mostly type I isomers) accumulate in the bone marrow, erythrocytes, plasma, urine, and feces. The pre dominant porphyrin in feces is COPRO I. The diagnosis of CEP can be confirmed by demonstration

of markedly deficient URO-synthase activity and/or by the identification of specific mutations in the UROS gene. The disease can be detected in utero by measuring porphyrins in amniotic fluid and URO-synthase activity in cultured amniotic cells or chorionic villi or by the detection of the family's specific gene mutations. Molecular analyses of the mutant alleles from unrelated patients have revealed the presence of >65 mutations in the UROS gene, including six in the erythroid-specific promoter of the UROS gene. Genotype/phenotype correlations can predict the severity of the disease. The CEP phenotype may be increased by the presence of exon 10 variants in the erythroid-specific ALA-synthase 2, mutations that typically cause XLP. One mutation (p.Arg216Trp) in GATA1, encod ing the X-linked erythroid-specific transcription factor GATA binding protein 1 (GATA1), has been identified in two individuals with CEP who both also had other hematologic abnormalities. TREATMENT Congenital Erythropoietic Porphyria Transfusion-dependent patients require periodic transfusions for anemia. Chronic transfusions of sufficient fresh packed erythro cytes to suppress erythropoiesis are effective in reducing porphyrin production but result in iron overload. Oral iron chelation is recom mended. Splenectomy may reduce hemolysis and decrease transfu sion requirements. Protection from sunlight and from minor skin trauma is essential to avoid/minimize cutaneous blistering. Com plicating bacterial infections should be treated promptly. Recently, non-transfusion-dependent patients have been treated by periodic phlebotomies to decrease iron levels, thereby decreasing erythro poiesis and porphyrin accumulation. This approach has not been evaluated in clinical trials to date. Bone marrow and hematopoi etic stem cell transplantation has proven curative in transfusiondependent children, providing the rationale for future stem cell gene therapy. ■ ■ERYTHROPOIETIC PROTOPORPHYRIA EPP is an autosomal recessive disorder resulting from the deficient activity of FECH, the last enzyme in the heme biosynthetic pathway. As noted above, EPP is likely the most common porphyria with onset typically in early childhood. EPP patients have FECH activities as low as 15–30% of normal in lymphocytes and cultured fibroblasts. Proto porphyrin IX accumulated in bone marrow reticulocytes and circulat ing erythrocytes is released into the plasma and then is taken up in the

liver where it is excreted in the bile and feces. Plasma protoporphyrin IX taken up by the vascular cells in the skin is photoactivated on exposure to sunlight causing phototoxic cellular damage and excru ciatingly painful nonblistering phototoxicity. In most symptomatic patients (>95%) with this disorder, a deleterious mutation in one FECH allele was inherited with the relatively common (~10% of Caucasians) intronic 3 (IVS3) variant (IVS3–48T>C) on the other allele; together, they result in the low expression of the normal enzyme. In ~2% of EPP families, two FECH deleterious mutations have been found.

XLP is a less common condition with the same phenotype in affected males, including increased erythrocyte protoporphyrin IX levels resulting from gain-of-function mutations in the last exon of the erythroid-specific form of 5-aminolevulinate-synthase 2 (ALAS2). These mutations delete or alter the ALAS2 C-terminal amino acids, resulting in its increased activity and the subsequent accumulation of protoporphyrin IX. Manifestations in female heterozygotes with XLP can range from asymptomatic to as severe as their affected male relatives. The variation in the presence and severity of manifestations in XLP heterozygotes results primarily from random X-chromosomal inactivation. XLP accounts for ~2–10% of cases with the EPP pheno type in Europe and North America. Rare patients with EPP symptoms and elevated erythrocyte protoporphyrin IX levels do not have muta tions in FECH or ALAS2 on genetic testing. In an affected family with EPP symptoms and accumulation of protoporphyrin IX, an autosomal dominant mutation was found in human

CLPX, a modulator of heme biosynthesis. PART 12 Endocrinology and Metabolism Clinical Features In EPP and male XLP patients, skin photosen sitivity, which differs from that in other cutaneous porphyrias, usually begins in early childhood. The initial symptoms on sun exposure consist of tingling, stinging, itching, or heat/burning sensations on the exposed skin occurring within <10 to 30 min of exposure in >60% of patients; most will have these prodromal symptoms within an hour of sun exposure. The prodromal symptoms are the “warning signal” to get out of the sun, thereby avoiding a severe incapacitating painful attack that can last from 2–5 days. Photosensitivity is associated with substantial elevations in erythrocyte protoporphyrin IX and occurs only in patients with genotypes that result in FECH activities below ~35% of normal. Vesicular lesions are uncommon. Redness and swell ing develop after prolonged sun exposure and resemble angioedema (Fig. 428-4). Pain symptoms may seem out of proportion to the visible FIGURE 428-4 Erythema and edema of the hands due to acute photosensitivity in a 10-year-old boy with erythropoietic protoporphyria. (Reproduced with permission from P Poblete-Gutiérrez et al: The porphyrias: clinical presentation, diagnosis and treatment. Eur J Dermatol 16:230, 2006.)

skin involvement. Chronic skin changes may include lichenification, leathery pseudovesicles, labial grooving, and nail changes. Severe scar ring is rare, as are pigment changes, friability, and hirsutism. Unless hepatic or other complications develop, protoporphyrin IX levels and symptoms of photosensitivity tend to remain remarkably stable over many years in most patients. Factors that exacerbate the hepatic por phyrias play no role in EPP or XLP. The primary source of excess protoporphyrin is the bone marrow ery throid cells. In EPP patients, erythrocyte protoporphyrin IX is free (not complexed with zinc) and is mostly bound to hemoglobin. In plasma, protoporphyrin IX is bound to albumin. Hemolysis and anemia are absent or usually mild. Although EPP is an erythropoietic porphyria, up to 27% of EPP patients may have minor abnormalities of liver function, and in ~2–5% of these patients, the accumulation of protoporphyrins causes chronic liver disease that can progress to liver failure requiring transplantation. Protoporphyrin IX is insoluble, and excess amounts form crystalline structures in liver cells (Fig. 428-4) and can decrease hepatic bile flow. Studies in the mouse model of EPP have shown that the bile duct epi thelium may be damaged by toxic bile, leading to biliary fibrosis. Thus, rapidly progressive liver disease appears to be related to the cholestatic effects of protoporphyrins and is associated with increasing hepatic protoporphyrin IX levels due to impaired hepatobiliary excretion and increased photosensitivity. The hepatic complications also are often characterized by increasing levels of protoporphyrins in erythrocytes and plasma as well as severe abdominal and back pains, especially in the right upper quadrant. Gallstones composed at least in part of pro toporphyrin IX occur in some patients. Hepatic complications appear to be higher in EPP due to two pathogenic FECH mutations and in males with XLP. Diagnosis A substantial increase in erythrocyte protoporphyrin IX, which is predominantly free and not complexed with zinc, is the hallmark of EPP. Protoporphyrin levels also are variably increased in bone marrow, plasma, bile, and feces. Erythrocyte protoporphyrin IX concentrations are increased in other conditions such as lead poison ing, iron deficiency, various hemolytic disorders, all homozygous forms of other porphyrias, and sometimes even in acute porphyrias. In all these conditions, however, in contrast to EPP, protoporphyrin IX is complexed with zinc. Therefore, after an increase in erythrocyte protoporphyrin IX is found in a suspected EPP patient, it is impor tant to confirm the diagnosis by an assay that distinguishes free and zinc-complexed protoporphyrin. Erythrocytes in EPP also exhibit red fluorescence under fluorescence microscopy at 620 nm. Urinary levels of porphyrins and porphyrin precursors are normal. FECH activity in cultured lymphocytes or fibroblasts is decreased (<30% of normal mean). DNA diagnosis by mutation analysis is recommended to detect the causative FECH mutation(s) and/or the

presence of the IVS3–48T>C low expression allele. To date, >235 mutations have been identified in the FECH gene, many of which result in an unstable or absent enzyme protein (null alleles) (Human Gene Mutation Database; www.hgmd.org). In XLP, the erythrocyte protoporphyrin levels appear to be higher than in EPP, and the proportions of free and zinc protoporphyrin IX may reach 50%. XLP accounts for ~2% of patients with the EPP phenotype in Western Europe. Recent studies show that ~10% of North American patients with the EPP phenotype have XLP. TREATMENT Erythropoietic Protoporphyria Avoiding sunlight exposure and wearing clothing designed to provide protection for conditions with chronic phototoxicity are essential. Various other treatments, including oral β-carotene and cimetidine, have proven of little benefit. Afamelanotide, an α-melanocyte-stimulating hormone (MSH) analogue that

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