TABLE 429-3 PROGNOSTIC INDEX OF NAZER

Laboratory Measurement	Normal Value	Score (in Points) 0	1	2	3	4
Serum bilirubin[a]	0.2–1.2 mg/dL	<5.8	5.8–8.8	8.8–11.7	11.7–17.5	>17.5
Serum aspartate aminotransferase	10–35 IU/L	<100	100–150	151–200	201–300	>300
Prolongation of prothrombin time (sec)	—	<4	4–8	9–12	13–20	>20

[a]If hemolysis is present, serum bilirubin cannot be used as a measure of liver function until the hemolysis subsides.

Source: Modified from H Nazer et al: Gut 27:1377, 1986; with permission from BMJ Publishing Group.

the total serum copper. Each 10 mg/L (1 mg/dL) of ceruloplasmin contributes 0.5 μmol/L (3 μg/dL) of serum copper. The normal serum free copper value is 1.6–2.4 μmol/L (10–15 μg/dL); the level is often as high as 7.9 μmol/L (50 μg/dL) in untreated Wilson's disease. With treatment, the serum free copper should be <3.9 μmol/L (<25 μg/dL).

Zinc treatment does not require monitoring of blood or urine for toxicity. Its only significant side effect is gastric burning or nausea in ~10% of patients, usually with the first morning dose. This effect can be mitigated if the first dose is taken an hour after breakfast or if zinc is taken with a small amount of protein. Because zinc mainly affects stool copper, 24-h urine copper can be used to reflect body loading. The typical value in untreated symptomatic patients is >3.1 μmol (>200 μg) per 24 h. This level should decrease during the first 1–2 years of therapy to <2.0 μmol (<125 μg) per 24 h. A normal value (0.3–0.8 μmol [20–50 μg]) is rarely reached during the first decade of therapy and should raise concern about overtreatment (copper deficiency), the first sign of which is anemia and/or leukopenia.

GLOBAL CONSIDERATIONS

The age of onset of clinical disease may be considerably younger in India and the Far East; in these regions, onset often occurs in children at only 5 or 6 years of age. The incidence of the disease may be increased in certain populations as a result of founder effects. For example, in Sardinia, the incidence may be 1 in 3000. In countries where penicillamine, trientine, and zinc acetate (as Galzin) are not available or are unaffordable, zinc salts such as gluconate or sulfate provide an alternative treatment option.

430 The Porphyrias

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The porphyrias are metabolic disorders, each resulting from the deficiency of a specific enzyme in the heme biosynthetic pathway (Fig. 430-1 and Table 430-1).These enzyme deficiencies are inherited as autosomal dominant, autosomal recessive, or X-linked traits, with the exception of porphyria cutanea tarda (PCT), which usually is sporadic (Table 430-1). The porphyrias are classified as either *hepatic* or *erythropoietic*, depending on the primary site of overproduction and accumulation of their respective porphyrin precursors or porphyrins (Tables 430-1 and 430-2), although some have overlapping features. For example, PCT, the most common porphyria, 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 drugs, and hormonal changes. While hepatic porphyrias are symptomatic primarily in adults, rare homozygous variants of the autosomal dominant hepatic porphyrias usually manifest clinically prior to puberty.

In contrast, the erythropoietic 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. Cutaneous sensitivity to sunlight results from excitation of excess porphyrins in the skin by long-wave ultraviolet light, leading to cell damage, scarring, and disfigurement. Thus, the porphyrias are metabolic disorders in which environmental, physiologic, and genetic factors interact to cause disease.

Because many symptoms of the porphyrias are nonspecific, diagnosis is often delayed. Laboratory measurement of porphyrin precursors (5′-aminolevulinic acid [ALA] and porphobilinogen [PBG]) or porphyrins in 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 430-3). The genes encoding all the heme biosynthetic enzymes have been characterized, permitting identification of the mutations causing each porphyria (Table 430-2). 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 up-to-date websites are sponsored by the American Porphyria Foundation (*www.porphyriafoundation.com*) and the European Porphyria Initiative (*www.porphyria-europe.org*). An extensive list of unsafe and safe drugs for individuals with acute porphyrias is provided at the Drug Database for Acute Porphyrias (*www.drugs-porphyria.com*).

GLOBAL CONSIDERATIONS

The porphyrias are panethnic metabolic diseases that affect individuals around the globe. 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, with a frequency of ~1 in 10,000 in Sweden. VP is particularly frequent in South Africa, where its high prevalence (>10,000 affected patients) is in part due to a genetic "founder effect." The autosomal recessive acute hepatic porphyria, ALA dehydratase-deficient porphyria (ADP), is very rare, and less than 20 patients have been identified worldwide.

The erythropoietic protoporphyrias—CEP, erythropoietic protoporphyria (EPP), and X-linked protoporphyria (XLP)—also are panethnic. EPP is the most common porphyria in children, whereas CEP is very rare, with about 200 reported cases worldwide. The frequency of EPP varies globally because most patients have the common low expression *FECH* mutation that varies in frequency in different populations. It rarely occurs in Africans, is present in about 10% of whites, and is frequent (~30%) in the Japanese.

The autosomal recessive porphyrias—ADP, CEP, EPP, and hepatoerythropoietic porphyria (HEP)—are more frequent in regions with high rates of consanguineous unions. PCT, which is typically sporadic, occurs more frequently in countries in which its predisposing risk factors such as hepatitis C and HIV are more prevalent.

HEME BIOSYNTHESIS

Heme biosynthesis involves eight enzymatic steps in the conversion of glycine and succinyl-CoA to heme (Fig. 430-2 and Table 430-2).